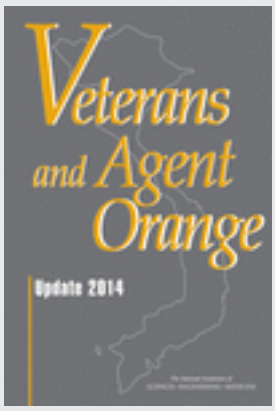

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Veterans and Agent Orange

Update 2014

Committee to Review the Health Effects in
Vietnam Veterans of Exposure to Herbicides
(Tenth Biennial Update)

Board on the Health of Select Populations

Institute of Medicine

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COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF EXPOSURE TO HERBICIDES (TENTH BIENNIAL UPDATE)

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of the independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following for their review of the report:

Cande V. Ananth, Columbia University
Frederick R. Appelbaum, Fred Hutchinson Cancer Research Center
Margit L. Bleecker, Center for Occupational and Environmental Neurology
Linda S. Birnbaum, National Institute of Environmental Health Sciences and National Toxicology Program
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David Strogatz, Bassett Research Institute

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Grace Wahba, University of Wisconsin–Madison

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen **by Kristine M. Gebbie,** Flinders University School of Nursing and Midwifery, Australia. She was responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

This is the Tenth Biennial Update of the *Veterans and Agent Orange* (*VAO*) series. This update focuses on the relevant scientific studies published from September 30, 2012, through September 30, 2014, that is, after the literature considered in *Update 2012*. A series of biennial updates has been completed by the National Academy of Sciences (NAS) as mandated in Public Law 102-4 to respond to the concerns and opinions voiced by Vietnam veterans and their families, and to inform the Department of Veterans Affairs and other stakeholders on the evidence regarding possible associations between exposure to chemical compounds contained in herbicides used in Vietnam and health effects, and to identify areas in which the scientific data were insufficient or inadequate to evaluate possible associations.

To accomplish its task, the Institute of Medicine (IOM) established a committee of 14 members representing a wide array of expertise to evaluate the newest scientific evidence and to integrate its findings with the totality of the evidence reviewed in *VAO* and updated in *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012*. A link to the experience and expertise of previous committees was provided by recruiting six members from committees responsible for earlier updates. The committee operated under the assumption that (unless there is new congressional action) this will be the final update in the IOM VAO series.

The committee sought the most accurate information and advice from the widest possible array of knowledgeable sources. In keeping with National Academies of Sciences, Engineering, Medicine's procedures, the committee met in a series of closed sessions in which members freely examined, characterized, and weighed the strengths and limitations of the scientific evidence. The committee

also convened three open meetings to provide an opportunity for veterans and veterans service organizations, researchers, policy makers, and other interested parties to present their views and concerns, review their independent research procedures and findings, and exchange information directly with the committee. The scheduling of these meetings was widely disseminated through targeted invitations to veterans' organizations and to other organizations known to have an interest in this issue**.** The insights gained during open sessions into the health problems experienced by Vietnam veterans were of great value to the committee. The committee also benefited from the input provided concerning B-cell neoplasms by Daniel Persky and Lisa Rimsza of the University of Arizona, Elaine Jaffe of the National Cancer Institute and members of the National Cancer Institute's InterLymph Project, Annaclaire De Roos, Martha Linet, and Lindsay Morton.

The committee is most grateful to Mary Paxton and Jennifer Cohen, who skillfully and elegantly served as study co-directors for this project and who shared with the committee their valuable experiences and insights from shepherding the production of previous VAO reports. The excellent work of IOM staff members Heather Chiarello, Nicole Freid, and Frederick (Rick) Erdtmann is also acknowledged and appreciated. Thanks are also extended to Julie Wiltshire, who handled the finances for the project; Robert Pool, who provided editorial assistance; and Daniel Bearss and Genevia Chamblee, who conducted database searches and helped with compiling and accessing reference materials.

The committee is pleased with its final product and optimistic that the recommendations contained in its report will help establish a path forward in continuing to meet our responsibility to Vietnam veterans and to veterans of all conflicts.

Kenneth S. Ramos, *Chair*
Committee to Review the Health Effects
in Vietnam Veterans of Exposure to
Herbicides (Tenth Biennial Update)

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Abbreviations and Acronyms

2,4-D	2,4-dichlorophenoxyacetic acid
2,4-DCP	2,4-dichlorophenol
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4,5-TCP	2,4,5-trichlorophenol
2,4,5-TP	2-(2,4,5-trichlorophenoxy) propionic acid, Silvex
ACC	US Army Chemical Corps
ACS	American Cancer Society
AD	Alzheimer disease
ADM	adrenomedullin
ADMS 3	second-generation Gaussian atmospheric-dispersion model/ software
ADVA	Australia Department of Veterans' Affairs
AFHS	Air Force Health Study (also referred to as the "Ranch Hand Study")
AGDISP	US Forest Service's Agricultural Division
AGS	a stomach-cancer cell line
AHR	aryl hydrocarbon receptor
AHRE	AHR-responsive element of the canonical DNA recognition motif of the AHR/ARNT complex, also referred to as the dioxin-responsive element (DRE) or the xenobiotic-responsive element (XRE)
AHS	US Agricultural Health Study
AIHW	Australian Institute of Health and Welfare

AL amyloidosis	amyloid light-chain amyloidosis in which the amyloid in deposits in various organs and tissues consists of antibody light chains
ALL	acute lymphocytic leukemia
ALS	amyotrophic lateral sclerosis (Lou Gehrig's disease)
ALT	alanine aminotransferase
AML	acute myeloid leukemia (previously called "acute myelogenous leukemia")
AO	Agent Orange, often loosely used to refer to all herbicides sprayed by the US military in Vietnam
AOVS	CDC Agent Orange Validation Study
ARNT	aryl hydrocarbon nuclear translocator
ARVN	Army of the Republic of Vietnam
ATSDR	Agency for Toxic Substances and Disease Registry
β	beta is the slope of a statistical model; a value of 0 corresponds to no effect
B[a]P	benzo[a]pyrene
BIRLS	VA's Beneficiary Identification Records Locator Subsystem
BLS	Bureau of Labor Statistics, US Department of Labor
BMD	bone mineral density
BMI	body mass index
BWIS	Baltimore–Washington Infant Study
CALUX	chemical-activated luciferase gene expression bioassay, a test for determination of dioxin-like activity in tissue samples
CARDIA	Coronary Artery Risk Development in Young Adults cohort
CAS number	number generated by the *Chemical Abstracts Service* that serves as unique identifier for every chemical
CATI	computer-assisted telephone interview
CB	chronic bronchitis
CC	case control
CCSPH	Cross-Canada Study of Pesticides and Health
CDC	US Centers for Disease Control and Prevention
CDD	chlorinated dibenzo-*p*-dioxin
CDF	chlorinated dibenzofuran
CDVA	Australian Commonwealth Department of Veterans' Affairs
CER	Swedish Cancer-Environment Register
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas cohort
CI	confidence interval, as defined by lower upper confidence (LCL) and upper confidence limits (UCL)

CIH	Commonwealth Institute of Health
CLL	chronic lymphocytic leukemia (now regarded as same disease as small lymphocytic leukemia [SLL] and designated by some as CLL/SLL)
CML	chronic myeloid leukemia
CNS	central nervous system
COI	chemical(s) of interest to VAO series (TCDD, 2,4,5-T, 2,4-D, picloram, or cacodylic acid)
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase
cPLA2	cytosolic phospholipase A2
CPS	Current Population Survey
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CVD	cardiovascular disease
CYP---	cytochrome P450 (specific members of this family of metabolizing enzymes are indicated by a number-letter-number suffix)
DEET	N,N-diethyl-meta-toluamide
DHEA	dehydroepiandrosterone
DIT	developmental immunotoxicity
dl	dioxin-like
dL	deciliter
DLBCL	diffuse large B-cell lymphoma
DLC	dioxin-like compound (or chemical)
DMA	dimethyl arsenic acid
DMA^{III}	dimethyl arsenic acid of valence 3
DMA^{V}	dimethyl arsenic acid of valence 5; form of arsenic found in cacodylic acid
DMBA	dimethylbenzanthracene
$DMMTA^{V}$	dimethylmonothioarsinic acid
DNA	deoxyribonucleic acid
DOD	US Department of Defense
DOHaD	developmental origins of health and disease
DRE	dioxin-responsive element, recognition motif of the AHR/ARNT complex (also called AHRE or XRE)
DTH	delayed-type hypersensitivity, a cell-mediated immune response
DXA	dual-energy x-ray absorption

E4	specific EOI score for potential exposure of ground troops to AO or other military herbicides generated by Stellman model
EA	early antigen
EBV	Epstein Barr virus
ECG	electrocardiography
EDC	endocrine-disrupting chemical
EEG	electroencephalography
EF	ejection fraction
EFED	Environmental Fate and Effects Division
EOI	exposure opportunity index, any metric of possible exposure
EPA	US Environmental Protection Agency
EPILYMPH study	a multi-center case-control study on lymphoma aetiology conducted in 22 centers of six European countries (six centers in Germany, two in Italy, four in Spain, six in Ireland, three in France, and one in the Czech Republic)
ER	estrogen receptor
EU	European Union
FAO/UNEP	Food and Agriculture Organization, United Nations Environment Programme
$FEF_{25–75}$	forced midexpiratory flow
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FYD	fetal Yusho disease
g	gram
GAO	US Government Accountability Office
GD	gestation day
GERD	gastroesophageal reflux disease
GGT	γ-glutamyltransferase
GHC	Group Health Cooperative (University of Washington)
GI	gastrointestinal
GIS	geographic information system
HCH	β-hexachlorocylohexane
HCL	hairy-cell leukemia
HDL	high-density lipoprotein
HERBS	Herbicide Reporting System
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma (previously referred to as Hodgkin's disease [HD] in VAO series)
HPV	human papilloma virus

HR	hazard ratio
HRGC	high-resolution chromotography
HRMS	high-resolution mass spectrometry
HSC	hematopoietic stem cell
HT	hypertension
IARC	International Agency for Research on Cancer
ICD-#	*International Classification of Diseases, Revision #* (# = version current for records being abstracted)
ICD-#-CM	*International Classification of Diseases, Revision* #, *Clinical Modification*
IgE	immunoglobulin E
IGF	insulin-like growth factor
IHD	ischemic heart disease
IL	interleukin
IL1RA	interleukin 1 receptor antagonist
IMT	intima-media thickness of arterial walls
InterLymph	International Lymphoma Epidemiology Consortium
IOM	Institute of Medicine
IU	international unit
IUGR	intrauterine growth retardation
IVRT	isovolumic relaxation time
JEM	job–exposure matrix
kg	kilogram
KVHS	Korean Veteran Health Study
L	liter
LATIN study	an international, multi-center case-controlled study of aplastic anemia and agranulocytosis in Latin American countries
LBW	low birth weight
LDL	low-density lipoprotein
LH	luteinizing hormone
LHC	lymphohematopoietic cancer
LN	lymphoid neoplasm
LOD	limit/level of detection
LPS	lymphoproliferative syndrome
LVMI	left ventricular mass index
MCPA	2-methyl-4-chlorophenoxyacetic acid
MCPB	4-(4-chloro-2-methylphenoxy) butanoic acid

MCPP	2-(2-methyl-4-chlorophenoxy) propionic acid or Mecoprop
MDS	myelodysplastic syndrome
MEG	magnetoencephalography
MIH	molar incisor hypomineralization
MIP	macrophage-inflammatory protein
ml	milliliter
MLR	mixed lymphocyte response
MMA^{III}	monomethyl arsonic acid of valency 3
MNU	N-methyl-N-nitrosourea
MoBa	Norwegian Mother and Child Cohort Study
MOS	month of service
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSWI	municipal solid-waste incinerator
n	number of study participants
na	not applicable
NaOH	sodium hydroxide
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NBDPS	US National Birth Defects Prevention Study
NCHS	CDC National Center for Health Statistics
NCI	National Cancer Institute
NCIDB	Korean National Cancer Incidence Database
NDI	National Death Index
NER	nucleotide excision repair
NewGeneris	Newborns and Genotoxic Exposure Risks cohort
ng	nanogram (10^{-9} gram)
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NK cells	natural killer cells
NLS	nuclear-localization signal
nM	nanomolar
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NOS	not otherwise specified
nr	not reported
NRC	National Research Council
ns	not statistically significant (usually refers to $p < 0.05$)
NTIS	National Technical Information Service

NTP	National Toxicology Program
NVVLS	National Vietnam Veterans Longitudinal Study (follow-up study based on sample in NVVRS)
NVVRS	National Vietnam Veterans Readjustment Study
NZIC	New Zealand Institute of Chemistry
OC	organochlorine
OCDD	octachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8,9-OCDD is the only dioxin congener that has eight chlorine atoms)
OFFHS	Ontario Farm Family Health Study
Operation PACER IVY	1972 operation of the US Air Force that removed Agent Orange from South Vietnam and stored it on Johnston Atoll
Operation PACER HO	1977 operation of the US Air Force that incinerated the Agent Orange stored at Johnston Atoll aboard the Dutch-owned ship M/T Vulcanus
OR	odds ratio
ORH	Operation Ranch Hand
OSCAR	Osteoporosis Cadmium as a Risk Factor cohort
p	p-value; probability of the observed result or one more extreme under null hypothesis
PAH	polycyclic aromatic hydrocarbon
PBPK model	physiologically based pharmacokinetic model
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDD/Fs	polychlorinated dioxins and furans combined
PCDF	polychlorinated dibenzofuran
PCMR	proportionate cancer mortality ratio
PCP	pentachlorophenol
PCT	porphyria cutanea tarda
PD	Parkinson disease
pg	picogram (10^{-12} gram)
picloram	4-amino-3,5,6-trichloropicolinic acid
PIVUS	Prospective Study of the Vasculature in Uppsala Seniors
PKC	protein kinase C
PL	Public Law
PM	proportionate mortality
PMR	proportional mortality ratio
PNS	peripheral nervous system
POLAIR	Gaussian plume model for dioxin concentrations
POP	persistent organic pollutant
ppb	parts per billion (ng/g)
ppm	parts per million (µg/g = mg/kg)

ppt	parts per trillion (pg/g)
PSA	prostate-specific antigen
PTD	preterm delivery, premature birth at less than 259 days (37 weeks) gestation
PTSD	posttraumatic stress disorder
PUR	California's Pesticide Use Reporting system
RANTES	**r**egulated on **a**ctivation, **n**ormal *T*-cell–**e**xpressed, and **s**ecreted
RAST	radioallergosorbent
RDD	random-digit dialing
RNA	ribonucleic acid
RR	relative risk (also called "risk ratio")
RWT	relative wall thickness
SAB	spontaneous abortion
SCE	sister-chromatid exchange
SD	standard deviation
SDTF	Spray Drift Task Force
SEA	Southeast Asia
SEER	NCI's Surveillance, Epidemiology, and End Results
SGA	small for gestational age
SHBG	steroid hormone binding globulin
SIDS	Sudden Infant Death Syndrome
SIR	standardized incidence ratio
SLE	systemic lupus erythematosus
SMR	standardized mortality ratio
SNP	single-nucleotide polymorphism
SR	sex ratio
STS	soft-tissue sarcoma
SWAP	Sawmill Workers Against Poisons
SWHS	Seveso Women's Health Study
T_3	triiodothyronine
T_4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCP	trichlorophenol
TEF	toxicity equivalency factor, potency of a dioxin-like compound (DLC) relative to TCDD
TEQ	(total) toxic equivalent (formerly "toxicity equivalent quotient"), cumulative toxic potency, sum of TEFs for a mixture of PCDDs, PCDFs, and PCBs

tetraCDD	tetrachlorodibenzo-*p*-dioxin, any of the 22 dioxin congeners that have four chlorine atoms, including TCDD as defined above
TGF	transforming growth factor
TNF	tumor necrosis factor
TPA	tetradeconoyl phorbol acetate
TRF	teacher report form
TSH	thyroid-stimulating hormone
TTP	time-to-pregnancy
TWA	time-weighted average
UFW	United Farm Workers of America
UGI	upper gastrointestinal tract
UMHS	Upper Midwest Health Study
UNEP	United Nations Environmental Programme
UNICEF	United Nations Children's Fund (also known as United Nations International Children's Emergency Fund)
US	United States
USDA	US Department of Agriculture
UV	ultraviolet radiation
VA	US Department of Veterans Affairs; previously, Veterans Administration
VAO	Veterans and Agent Orange (refers to series of IOM committees and reports; italicized *VAO*, refers to the initial comprehensive review, published in 1994)
VES	Vietnam Experience Study
VOC	volatile organic compound
VV	Vietnam veteran
VVFS	Australian Vietnam Veteran Family Study
WBC	white blood cell
WC	waist circumference
WHO	World Health Organization
WISC-R	Wechsler Intelligence Scale for Children (revised edition)
XRE	xenobiotic-responsive element, recognition motif of the AHR/ARNT complex (also called DRE or AHRE)

Summary

From 1962 to 1971, the US military sprayed herbicides over Vietnam to strip the thick jungle canopy that could conceal opposition forces, to destroy crops that those forces might depend on, and to clear tall grasses and bushes from the perimeters of US base camps and outlying fire-support bases. Mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid made up the bulk of the herbicides sprayed. The herbicide mixtures used were named according to the colors of identification bands painted on the storage drums; the main chemical mixture sprayed was Agent Orange, a 50:50 mixture of 2,4-D and 2,4,5-T. At the time of the spraying, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic form of dioxin, was an unintended contaminant generated during the production of 2,4,5-T and so was present in Agent Orange as well as some other formulations sprayed in Vietnam. It is important to recognize that Agent Orange is not synonymous with TCDD or dioxin.[1]

Complaints from returning Vietnam veterans about their own health and that of their children combined with emerging toxicologic evidence of adverse effects of phenoxy herbicides and TCDD from animal studies and some positive findings from epidemiologic studies resulted in sustained controversy for many years. In 1991, because of continuing uncertainty about long-term health effects of the sprayed herbicides in Vietnam veterans, Congress passed Public Law (PL)

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

102-4, the Agent Orange Act of 1991. This legislation directed the Secretary of Veterans Affairs to ask the National Academy of Sciences (NAS) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various components of those herbicides, including TCDD. The legislation also instructed the Secretary to ask the NAS to conduct updates every 2 years for 10 years from the date of the first report to review newly available literature and draw conclusions from the overall evidence.

In response to the first request, the Institute of Medicine (IOM) convened a committee, whose conclusions the IOM published in 1994 in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (*VAO*). The work of later committees resulted in the publication of biennial updates (*Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004*) and of focused reports on the scientific evidence regarding type 2 diabetes, acute myeloid leukemia in children, and the latent period for respiratory cancers.

Enacted in 2002, PL 107-103, the Veterans Education and Benefits Expansion Act of 2001, mandated that the *VAO* biennial updates continue through 2014. *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* were published under that legislation. The current update presents this committee's review of peer-reviewed scientific reports concerning associations between health outcomes and exposure to TCDD and other chemicals in the herbicides used in Vietnam that were published between October 1, 2012, and September 30, 2014, and the committee's integration of this information with the previously established evidence database.

CHARGE TO THE COMMITTEE

The Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Tenth Biennial Update) was assembled to produce the final report mandated by PL 102-4 and PL 107-103. It was asked to "determine (to the extent that available scientific data permit meaningful determinations)" the following regarding associations between specific health outcomes and exposure to TCDD and other chemicals present in herbicides used by the military in Vietnam:

A) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;
B) the increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
C) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease. [PL 102-4, Section 3 (d)]

In addition, the committee for *Update 2014* was asked to address the specific question of whether all neurodegenerative diseases with Parkinson-like symptoms should be considered service-related under the association identified between Parkinson disease and herbicide exposure by the committee for *Update 2006*. As for all previous updates, the committee was instructed to recommend additional scientific studies and research initiatives to resolve areas of continuing scientific uncertainty.

Judicial history and the congressional mandate, quoted above, dictated that the committee's statement of task be framed in terms of "association" between exposure and health outcomes. This and all prior committees fully recognized that an association does not establish a causal relationship and that the rigor of the evidentiary database needed to support a finding of statistical association is weaker than that needed to establish causality. Nonetheless, any positive evidence supporting a causal relationship would enhance the conviction that an observed statistical association is reliable. Such scientific evidence, of course, would include any information assembled in relation to plausible biologic mechanisms as directed in Article C. In accordance with its charge, the committee examined outcome measures commonly used to evaluate statistical associations while assessing the adequacy of control for bias and confounding and the likelihood that an observed association could be explained by chance. The committee also assessed evidence of biologic plausibility derived from laboratory findings in cell culture or animal models. In particular, associations found to have multiple supportive lines of evidence were interpreted as having stronger scientific support for reflecting causal effects.

In conducting its study, the present committee operated independently of the US Department of Veterans Affairs (VA) and other government agencies. The committee was not asked to make and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. This report provides scientific information for the Secretary of Veterans Affairs to consider as VA exercises its responsibilities to Vietnam veterans. The committee was not charged to focus on broader issues, such as the potential costs of compensation for veterans or policies regarding such compensation.

COMMITTEE'S APPROACH TO ITS CHARGE

Following the pattern established by prior VAO committees, the present committee concentrated its review on epidemiologic studies to fulfill its charge of assessing whether specific human health effects are associated with exposure to at least one of the herbicides sprayed in Vietnam or to TCDD. The committee also considered controlled laboratory investigations that provided information on whether a scientifically relevant association between the chemicals of interest and a given effect is biologically plausible.

The process of evaluation of the evidence presumes neither the presence nor the absence of association for any particular health outcome. Over the sequence

of reviews, evidence of various degrees of association, lack of association, or persistent indeterminacy with respect to a wide array of disease states has accrued. For many conditions, however, particularly those that are very uncommon, any association with the chemicals of interest has remained unaddressed in the medical research literature. For these conditions, unless the condition is logically subsumed under a broader disease category that has been evaluated, the committee remains neutral, abiding by the maxim that "absence of evidence is not evidence of absence."

In accordance with Congress's mandated presumption of herbicide exposure of all Vietnam veterans, VAO committees have treated Vietnam-veteran status as a proxy for some herbicide exposure when no more specific exposure information is available. To anticipate health conditions associated with aging that might differentially affect Vietnam veterans and to obtain additional information potentially relevant to the evaluation of health effects in Vietnam veterans, the committees have reviewed studies of other groups potentially exposed to the constituents present in the herbicide mixtures used in Vietnam (2,4-D, 2,4,5-T, TCDD, cacodylic acid, and picloram). In addition to retrieving articles identified on the basis of keywords specifying the chemicals and chemical classes of interest, literature searches for the earliest reports in the VAO series were structured to retrieve all studies of several occupational groups, including chemical, agricultural, pulp and paper, sawmill, and forestry workers. To the extent that studies of those workforces were recovered in new searches directed at particular agents of exposure, they have continued to be incorporated into the database. Some occupational and environmental cohorts that received exceptionally high exposures—such as the International Agency for Research on Cancer (IARC) and Seveso cohorts discussed in this report—are now well characterized and have produced a stream of informative results. The Agricultural Health Study, a continuing prospective cohort study of agricultural populations with specific information on the chemicals of interest, has also been steadily contributing new findings to the database. As the information in the database on populations that had established exposures to the chemicals of interest has grown, VAO committees have come to depend less on data from studies that yielded nonspecific exposure information and have been able to focus more on findings of studies that have refined exposure specificity. With advancing age, the Vietnam veterans themselves are now able to provide substantial information on chronic health conditions directly.

Tables on individual health outcomes contain the results of epidemiologic studies that have been evaluated over the entire series of VAO reports. The results for a particular endpoint are grouped by study population to emphasize and clarify the relationships among successive publications based on repeated study of particular exposed populations. Studies of cohorts have been ordered to reflect the hierarchic nature of many of the study populations—for example, the group of workers in the Dow Chemical Company plant in Midland, Michigan, are one of several cohorts making up the National Institute for Occupational Safety and

Health (NIOSH) cohort, which in turn is one of the many international cohorts making up the IARC cohort—with citations indicating the source of particular results presented in the final column. The exposure of interest in each study population is noted in the tables to facilitate judgments about when consistency might be expected among populations that experience the same exposure. Unless case-control studies are nested within study populations that have been investigated with cohort or cross-sectional design protocols, case-control studies are gathered in a separate section at the end of the results tables, because they may investigate both occupational and environmental factors as potential risk factors for a specific health outcome.

The original legislation, PL 102-4, did not provide a list of specific diseases and conditions suspected of being associated with herbicide exposure. Such a list was developed on the basis of diseases and conditions that had been mentioned in the scientific literature or in other documents identified through the original *VAO*'s extensive literature searches. The *VAO* list has been augmented in response to literature reporting assessments of additional health endpoints for association with exposure to the chemicals of interest, requests by VA, and concerns of Vietnam veterans.

The information that the present committee reviewed was identified through a comprehensive search of relevant databases, including databases covering epidemiologic, biologic, medical, toxicologic, chemical, historical, and regulatory information. More than 7,600 potentially relevant citations were identified during searches of literature published between the date of the literature cut-off for *Update 2012* and the current update deadline, that is, between October 1, 2012, and September 30, 2014. After the citation abstracts were screened for relevance, about 1,100 were retained for closer consideration. Ultimately, about 70 papers on epidemiologic studies and several score of toxicologic studies and exposure evaluations contributed new information to this updated review. Additional information came from veterans and other interested people who testified at public hearings and offered written submissions.

To determine whether there is a scientifically relevant association between exposure and a health outcome, epidemiologists estimate the magnitude of an appropriate measure (such as the relative risk or the odds ratio) that describes the relationship between exposure and disease in a defined population or group. In evaluating the strength of the evidence linking herbicide exposure with a particular outcome, the committee considered whether such estimates of risk might not be consistent with a causal association (because of confounding, chance, or bias related to errors in selection and measurement) or might be an indication of a true associations. Although not required, data supporting biologic plausibility can strengthen confidence that an association is not spurious and are presented in each of the sections. In this regard, it is important to note that while the biologic plausibility for a particular effect has been considered sufficient evidence of association by several international review boards, the Agent Orange Act requires

that a finding of association be supported by epidemiologic evidence. It has been the practice of all VAO committees to evaluate all studies according to the same criteria and then to weight findings of similar strength and validity equivalently, whether or not the study subjects are Vietnam veterans, when drawing conclusions. The committee recognizes that an absolute conclusion about the absence of association might never be attained, because, as is generally the case in science, studies of health outcomes after herbicide exposure cannot demonstrate that a purported outcome is impossible, only that it is statistically improbable.

EVIDENCE REVIEWED BY THE COMMITTEE

The sections below summarize new epidemiologic information evaluated in this update and integrated with that previously assembled. The epidemiologic studies have been divided, both here and in the health-outcome chapters, into four categories—Vietnam-veteran, occupational, environmental, and case-control—depending on the population addressed and the study design.

Vietnam-Veterans Studies

With interest in posttraumatic stress disorder (PTSD) renewed by recent military engagements, almost all recent studies concerning the impact of deployment on Vietnam veterans have addressed psychological endpoints. However, psychological endpoints are not within the scope of VAO, and therefore no conclusions about them are presented in these reports. The Vietnam veterans themselves are advancing in age and are therefore able to provide substantial information on chronic health conditions directly. Nonetheless, the intensity of research on physical health outcomes in this target population seems to have been waning in recent years. While no comprehensive new information on male US Vietnam veterans was published during the review period, several new publications were available on other groups of Vietnam veterans—from Australia, Korea, and New Zealand, plus women in the US military. It is noteworthy that the very large and comprehensive epidemiology study of Korean Vietnam veterans made use for the first time of the Exposure Opportunity Index (EOI) model developed with the encouragement of earlier VAO committees. Estimates of potential herbicide exposure were calculated for each veteran on the basis of military records of the movements of the individual service units merged with a model of location and time of US herbicide spray missions reconstructed from the records of Operation Ranch Hand. At this late date, there is no standard to which the EOI scores generated for this cohort could be compared for verification or validation, but the committee was pleased to have the opportunity to review the results obtained based on the use of individualized exposure estimates.

In addition, several studies based on samples gathered at VA medical centers have appeared (details provided in Chapter 14). It is gratifying to learn that VA

has been interested in mobilizing resources to support research on health outcomes in Vietnam veterans. Future efforts should emphasize that Agent Orange exposures abstracted from a patient's VA medical records are not definitive and therefore undue confidence should not be placed on these results.

Occupational Studies

The literature search for this update found a study on just one new occupational cohort exposed to the chemicals of interest, but the study population was so small that mortality results could be presented for only three types of cancer. A few other publications provided additional information on previously studied populations, primarily participants in the Agricultural Health Study and subcohorts of the IARC cohort.

Environmental Studies

This committee reviewed a considerable number of studies of the effects of environmental exposures to the chemicals of interest. Most involved measurements of compounds with dioxin-like activity in blood samples for association with various health outcomes. Several new publications of this sort were generated from the data of the US National Health and Nutrition Examination Surveys, the Seveso Woman's Health Study, and the Prospective Investigations of the Vasculature in Uppsala Seniors. A multitude of cohorts of mother–child birth pairs have been established internationally, and they are generating reports on various aspects of child growth and development in conjunction with levels of dioxin-like compounds in maternal blood during gestation, cord blood, or maternal milk.

Case-Control Studies

Additional articles evaluating exposures to pesticides and phenoxy herbicides in particular came from the Cross-Canada Study of Pesticides and Health, which focuses on lymphoid neoplasms, and from the National Birth Defects Prevention Study. Four new separate case-control studies also addressed lymphohematopoietic conditions in relation to the chemicals of interest, while a final case-control study was concerned with male infertility.

THE COMMITTEE'S CONCLUSIONS

Health Outcomes

In *Update 2014* (as listed in Table S-1), the committee changed the categorization of three health outcomes and clarified the breadth of the previous finding of "limited or suggestive" evidence of an association for Parkinson disease. The

TABLE S-1 Summary of *Tenth Biennial Update* of Findings on Vietnam-Veteran, Occupational, and Environmental Studies Regarding Scientifically Relevant Associations Between Exposure to Herbicides and Specific Health Outcomes[a]

Sufficient Evidence of an Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.[b] For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, then there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Soft-tissue sarcoma (including heart)
* Non-Hodgkin lymphoma
* Chronic lymphocytic leukemia (including hairy cell leukemia and other chronic B-cell leukemias)
* Hodgkin lymphoma
Chloracne

Limited or Suggestive Evidence of an Association

Epidemiologic evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.[b] For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Laryngeal cancer
Cancer of the lung, bronchus, or trachea
Prostate cancer
Cancer of the urinary bladder (category change from Inadequate or Insufficient in *Update 2012*)
* Multiple myeloma
* AL amyloidosis
Early-onset peripheral neuropathy
Parkinson disease (including Parkinsonism and Parkinson-like syndromes) (category clarification from *Update 2012*)
Porphyria cutanea tarda
Hypertension
Ischemic heart disease
Stroke
Type 2 diabetes (mellitus)
Hypothroidism (category change from Inadequate or Insufficient in *Update 2012*)

Inadequate or Insufficient Evidence to Determine an Association

The available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes that were explicitly reviewed:

TABLE S-1 Continued

Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)
Cancers of the pleura, mediastinum, and other unspecified sites in the respiratory system and intrathoracic organs
Esophageal cancer
Stomach cancer
Colorectal cancer (including small intestine and anus)
Hepatobiliary cancers (liver, gallbladder, and bile ducts)
Pancreatic cancer
Bone and joint cancer
Melanoma
Non-melanoma skin cancer (basal-cell and squamous-cell)
Breast cancer
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
Renal cancer (kidney and renal pelvis)
Cancers of brain and nervous system (including eye)
Endocrine cancers (thyroid, thymus, and other endocrine organs)
Leukemia (other than chronic B-cell leukemias, including chronic lymphocytic leukemia and hairy cell leukemia)
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than after paternal exposure to TCDD, which appears *not* to be associated)
Neonatal or infant death and stillbirth in offspring of exposed people
Low birth weight in offspring of exposed people
Birth defects in offspring of exposed people (category change from Limited or Suggestive in *Update 2012* for spina bifida)
Childhood cancer (including acute myeloid leukemia) in offspring of exposed people
Neurobehavioral disorders (cognitive and neuropsychiatric)
Neurodegenerative diseases, excluding Parkinson disease
Chronic peripheral nervous system disorders
Hearing loss
Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
Gastrointestinal, metabolic, and digestive disorders (changes in hepatic enzymes, lipid abnormalities, and ulcers)
Kidney disease
Immune system disorders (immune suppression, allergy, and autoimmunity)
Circulatory disorders (other than hypertension, ischemic heart disease, and stroke)
Endometriosis
Disruption of endocrine function (other than hypothyroidism) (category modification from *Update 2012*)
Eye problems
Bone conditions

This committee used a classification that spans the full array of cancers. However, reviews for nonmalignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. *By default, any health outcome on which no epidemiologic information has been found falls into this category.*

continued

TABLE S-1 Continued

Limited or Suggestive Evidence of *No* Association

Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to a component of the herbicides of interest and the outcome. A conclusion of "no association" is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. *In addition, the possibility of a very small increase in risk at the exposure studied can never be excluded.* There is limited or suggestive evidence of *no* association between exposure to the herbicide component of interest and the following health outcome:

Spontaneous abortion after paternal exposure to TCDD

[a]*Herbicides* indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from occupational, environmental, and veteran studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.

[b]Evidence of an association is strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.

*The committee notes the consistency of these findings with the biologic understanding of the clonal derivation of lymphohematopoietic cancers that is the basis of the World Health Organization classification system (Campo et al., 2011; see table at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109529/table/T1, accessed December 2, 2015).

specific birth defect spina bifida was moved from the "limited or suggestive" category back into the "inadequate or insufficient" category with all other birth defects. Bladder cancer and hypothyroidism were moved to the "limited or suggestive" category from their previous positions in the default "inadequate or insufficient" category; findings from the reports on the cohort of Korean veterans who served in Vietnam provided the impetus for the committee to scrutinize the previously assembled evidence on these two conditions.

Bladder Cancer

Assessment of the full body of evidence on bladder cancer had also been encouraged by representatives of Vietnam veterans, who asserted that the recognized effect of inorganic arsenic should apply for these veterans because of their presumed exposure to the organic arsenical cacodylic acid, which constituted a relatively small portion of the herbicides sprayed in Vietnam. The toxicologic information regarding exposure to methylated forms of arsenic indicate these metabolites of inorganic arsenic are potentially carcinogenic, but literature searches have not identified any publications concerning epidemiologic investigations of a possible role for direct exposure to cacodylic acid in the development of bladder or any other cancers. As such, any cacodylic acid in the herbicide mix could not be assumed to be responsible for the two-fold increase in mortality from bladder cancer observed in those Korean veterans whose movements while in Vietnam

indicated high potential for herbicide exposure as compared to those with low potential for exposure. Among the previously reviewed epidemiology studies concerning bladder cancer and exposure to the chemicals of interest, the most comprehensive pooled analyses of workers who produced dioxin-contaminated phenoxy herbicides was published by IARC in 1997. It reported a modest increase in mortality from bladder cancer that was not extreme enough to be considered significant by usual statistical standards. The committee noted, however, a distinct pattern of elevated mortality from bladder cancer among worker groups updated for mortality after their earlier findings were incorporated in the IARC analysis. Considering that bladder cancer is predominantly a cancer of old age, it is plausible that such suggestive findings would only become apparent as the cohorts became older.

Hypothyroidism

In addition to the notable increase in the prevalence of hypothyroidism associated with estimates of potential herbicide exposure individually modeled for the large cohort of Korean veterans who served in Vietnam, consistent supporting evidence was seen in several other publications new to this update. In the Agricultural Health Study, hypothyroidism among male pesticide applicators was found to be significantly associated with exposure to each of the phenoxy herbicides analyzed, and for 2,4-D, the most commonly used of these, and a dose–response relationship was observed with intensity of use. A new report from the Seveso Women's Health Study found an inverse relationship between total thyroxine levels and serum TCDD levels measured in 1996 in women who were younger than 40 years of age at the time of the industrial accident, but not with their serum TCDD levels in 2008. In addition to these highly relevant new findings, several reports of inverse relationships of dioxin-like polychlorinated biphenyls with thyroid hormones in environmentally exposed populations were added to the existing evidence, which was largely consistent with reduced thyroid activity.

Spina Bifida

The birth defect spina bifida has been in the "limited or suggestive" category of association for the children of all Vietnam veterans since *Update 1996*. The original *VAO* committee concluded that there was little and inconsistent evidence for an association between paternal exposure and birth defects in general. At the time of the first VAO update, the only additional information the committee had to consider was a publication from the Air Force Health Study (AFHS) noting more cases of spina bifida among the Operation Ranch Hand personnel than in the control group. Data gathering for the AFHS was completed in 2002, but no additional cases of spina bifida have been reported in that study population. Since *Update 1996*, no new analyses of the birth defect data from the AFHS or any

other study finding increased rates of spina bifida among children of men exposed to the chemicals of interest have become available. It has long been challenging to hypothesize feasible biologic mechanisms by which paternal exposure might generate adverse effects in offspring, and, since *Update 1996*, epigenetic modification has increasingly been considered a possible mode of action by which paternal exposure to toxic agents might produce such effects. To date, however, epigenetic research has addressed paternal exposure only to a very limited extent and has demonstrated transmission of harm from father to offspring only in the circumstance where the father himself was exposed in utero, when his mother was directly exposed. As yet, however, it has not been convincingly established that harm to offspring may arise from paternal exposures experienced as an adult. Because biologic plausibility remains uncertain for paternal transmission following adult exposure (as would be the case for Vietnam veterans), this committee deemed that the "limited or suggestive" category is inappropriate for the children of male Vietnam veterans. On the other hand, epigenetic research has further strengthened certainty that maternal exposures have the potential to alter the development of offspring. For the chemicals of interest, however, there are no supportive epidemiologic results for increases specifically in spina bifida among the children of exposed women. Consequently, spina bifida in the offspring of Vietnam veterans has been moved to the category of "inadequate or insufficient" evidence of an association with herbicide exposure along with all other types of birth defects. (This is only the second time that a VAO committee has demoted a health outcome to a weaker category of association than it had been in before; the first instance was the move of porphyria cutanea tarda from the "sufficient" category to the "limited or suggestive" category by the committee for *Update 1998*.)

Conditions with Parkinson-like Symptoms

VA charged this committee to address the specific question of whether various conditions with Parkinson-like symptoms should be considered covered under the assignment of Parkinson disease to the "limited or suggestive" category of association with herbicide exposure. The committee noted that the diagnostic standards for this condition cannot be assumed to have been uniform in the epidemiologic studies that are the basis for this association or in the claims submitted by veterans, so there is no rational basis for an exclusion of those with Parkinson-like symptoms from the service-related category denoted as Parkinson disease. To exclude a claim for a condition with Parkinson-like symptoms, the onus should be on VA on a case-by-case basis to definitively establish the role of a recognized etiologic factor other than the herbicides sprayed in Vietnam.

The changes in classification made by the committee for *Update 2014* are indicated in boldface in Table S-1.

The above conclusions and the decision not to modify any other findings from earlier VAO committees were made after the present committee weighed

the strengths and limitations of the epidemiologic evidence reviewed in this report and in previous VAO reports. Although the studies published since *Update 2012* are the subject of detailed evaluation in this report, the committee drew its conclusions in the context of the entire body of literature. The contribution of recent publications to the evidence database was substantial, but the committee did not weigh these findings more heavily merely because they were new. Epidemiologic methods and analytic capabilities have improved, but many of the recent studies were particularly useful for this committee's purpose also because they produced results in terms of serum TCDD concentrations or the amount of exposure to dioxin-like chemicals. Of course, observations on the health of our population of primary concern, Vietnam veterans, are increasingly informative as they age.

Table S-1 defines four categories of association and gives criteria for assigning health outcomes to them. On the basis of its evaluation of case-control studies and studies of veteran, occupational, and environmentally exposed populations, the committee allocated particular health outcomes to categories of relative certainty of association with exposure to the herbicides that were used in Vietnam or to any of their components or contaminants (with no intention of specifying particular chemicals). The committee notes that experimental data related to the biologic plausibility of conditions statistically associated with exposure to Agent Orange have gradually emerged since the beginning of this series of VAO reports and that these findings can inform decisions about how to categorize the degree of association of individual conditions; Table S-1 includes a footnote to this effect.

As mandated by PL 102-4, the distinctions among categories are based on statistical association, and not on strict causality. The committee was directed to review the scientific data, not to recommend VA policy; therefore, the conclusions reported in Table S-1 are not intended to imply or suggest policy decisions. The conclusions are related to the associations between exposure and outcomes in human populations, not to the likelihood that any individual's health problem is associated with or caused by the herbicides in question.

Risk in Vietnam Veterans

There have been numerous health studies of Vietnam veterans, but most have been hampered by relatively poor measures of exposure to herbicides or TCDD and by other methodologic problems. Exposures were not intentionally monitored during the Vietnam War, but there have been concerted efforts over the nearly 50 years since the end of the conflict to reconstruct the herbicide exposures experienced by US veterans during their service in Vietnam. Nonetheless, we remain completely out of range of the ideal of having reliable estimates of the intensity and duration of every soldier's exposure to each of the five chemicals of interest, and with the passage of time, it has become increasingly unlikely that even semiquantitative group estimates will ever be obtained.

Because of its international reputation as an exceptionally toxic substance and the fact that it is retained in tissues long after exposure, measurement of TCDD has been the object of considerable technological advance. Unfortunately, as sampling techniques became much more sensitive and somewhat more affordable, the blood levels of TCDD remaining after many half-life cycles in even highly exposed Vietnam veterans have become increasingly indistinguishable from those of the general population. It is also very challenging to extrapolate back with confidence from measured serum TCDD levels to what original exposure levels would have been, even with continually refined, physiologically based pharmacokinetic models.

The encouragement of VAO committees and substantial resources have gone into the development of an exposure opportunity model built using detailed records of the herbicide spraying mission conducted in Vietnam. Exposure estimates derived by merging this exposure opportunity model with temporal records of movement by individual military units could then serve as input to epidemiologic investigations of health outcomes available on an individual basis. An important aspect of this update has been reviewing the application of this exposure opportunity model in the comprehensive studies of disease incidence and mortality in a very large population of Korean men who are veterans of the Vietnam War. Regrettably, American service records needed to apply this exposure estimation model to individual American Vietnam veterans have not been located.

In light of those challenges, many conclusions regarding associations between exposure to the chemicals of interest and disease have been based on studies of people exposed in various occupational and environmental settings rather than on studies of Vietnam veterans. More recent studies of health consequences in the maturing veterans themselves, however, have generated more informative findings than were available to earlier VAO committees.

The committee believes that there is sufficient evidence to reach general or qualitative conclusions about associations between herbicide exposure and health outcomes, but the lack of adequate exposure data on Vietnam veterans themselves makes it difficult to estimate the degree of increased risk of disease in Vietnam veterans as a group or individually. Without information on the extent of herbicide exposure of Vietnam veterans and quantitative information about the dose– and time–response relationships for each health outcome in humans, estimation of the risks experienced by veterans exposed to the chemicals of interest during the Vietnam War is not possible.

Because of those limitations, only general assertions can be made about the risks to Vietnam veterans, depending on the category of association into which a given health outcome has been placed. If there were "limited or suggestive evidence of *no* association" between herbicide exposure and a health outcome, then the evidence would suggest that no increased risk of the outcome in Vietnam veterans was attributable to exposure to the chemicals of interest (at least given the conditions, exposures, and lengths of observation covered by the studies

reviewed). Even qualitative estimates are not possible when there is "inadequate or insufficient" evidence of an association. For outcomes categorized as having "sufficient" or "limited or suggestive" evidence of an association with herbicide exposure, the lack of exposure information on Vietnam veterans prevents the calculation of precise risk estimates.

The present committee agrees with the assessment of previous committees that it is not now possible to derive quantitative estimates of any increased risks of various adverse health effects that Vietnam veterans may have experienced in association with exposure to the herbicides sprayed in Vietnam. Given the amount of time that has passed since the Vietnam era, it is extremely unlikely that the situation will improve.

COMMITTEE RECOMMENDATIONS

The IOM has been asked to make recommendations concerning the need, if any, for additional scientific studies to resolve continuing scientific uncertainties about the health effects of the herbicides used in Vietnam and their contaminants. Although advances have been made over the past several years in understanding the health effects of exposure to the herbicides used in Vietnam and to TCDD, as well as in elucidating the mechanisms that underlie the effects, there are still subjects on which increased knowledge could be useful.

The committee again notes that the earlier investment in establishing cohorts of exposed populations can continue to produce useful findings with continued study; the NIOSH, Seveso, AFHS, and US Army Chemical Corps (ACC) cohorts all merit continuing follow-up or more comprehensive analysis. Longitudinal analyses of cancers, cardiovascular, and reproductive outcomes represented in the complete database assembled in the course of the AFHS are especially important, and further research using the valuable assemblage of biological samples is encouraged. The committee was disappointed that the anticipated results from the investigation into the relationship of herbicide exposure during the Vietnam War with hypertension and chronic obstructive pulmonary disease (COPD) in ACC veterans were not yet ready for evaluation. The committee is encouraged that VA is completing plans for a survey of the present health status of Vietnam veterans and has provided several suggestions about how this large effort could generate more useful findings.

As summarized in greater detail in Table S-2, this committee recommends that VA continue to query its own medical databases more actively to identify potential associations between Vietnam service and specific health outcomes, particularly outcomes that are so specific that they are infrequently addressed in epidemiology studies. Cohort studies often do not have enough cases to break out risk for particular types of cancer in a given organ, as is the case for squamous cell carcinomas of the head and neck. For such relatively uncommon conditions, a case-control approach would be recommended, but only rarely do such studies

TABLE S-2 Suggested Activities to Follow Completion of the Veterans and Agent Orange Report Series Mandated by the Agent Orange Act

OVERSIGHT OF LONG-TERM HEALTH STATUS OF DEPLOYED SERVICE MEMBERS

A single overarching body is needed to review all deployment-related issues of veteran's health regularly and in a uniform fashion. (Numerous points concerning appointment of members and other procedural matters would need to be addressed in advance.)

Very careful review of evidence concerning whether **paternal exposure** to any toxicant has definitively been demonstrated to result in abnormalities in even the first generation of offspring.

Careful assessment of the risks to offspring that may arise from **maternal exposure** is also merited given the greatly increased number women now serving in the military.

DATA COLLECTION

Department of Defense (DOD) should create and maintain **rosters of individuals deployed** on every mission.

DOD should create and maintain a **matrix of potentially toxic exposures** by time and location for every deployment.

DOD's collection of **biological specimens** should be expanded to occur at regular intervals for all service members, as well as before and after deployments. Storage should be established on a permanent basis, with samples being accessible to researchers.

Documentation of vaccination and other **medical procedures performed during service** need to be included in the records of each service person, and automatically transferred to VA upon discharge from the military.

DATA MANAGEMENT

DOD and VA databases should be linked to systematically identify, record, and/or monitor trends in diseases of soldiers and veterans for evaluation of possible associations with military service deployments.

VA should routinely (probably quarterly) obtain **frequency distributions of health conditions treated at its medical facilities** for participants in each deployment in contrast to those observed among their non-deployed contemporaries.

It would be worthwhile to conduct similar monitoring of VA claims data even though it might be less objective than treatment records and does not have an obvious comparison group.

EPIDEMIOLOGIC STUDIES

Air Force Health Study (AFHS)

Comprehensive **longitudinal analysis** of the AFHS data collected in the six intensive medical-cycle examinations (particularly concerning medical interventions, **cancer** incidence, mortality, **birth defects** in veterans' offspring) making use of the available exposure data.

Use AFHS samples for study of epigenetic changes and definition of biomarkers of exposure and effect. (See Table 14-4 from the recent report of the Committee on the Management of the Air Force Health Study Data and Specimens [IOM, 2015])

Dedicated funding should be continued for focused analyses by independent investigators.

TABLE S-2 Continued

Army Chemical Corps (ACC)
Analysis and release of findings gathered by following up on the ACC mortality study to assemble clinical information on morbidity associated with **COPD** and **hypertension.**

Vietnam Era-Health Evaluation Retrospective Observational Study (VE-HEROeS)
VA should continue epidemiologic studies (morbidity and mortality) of Vietnam veterans, especially as this population grows older and the incidence of many health outcomes increases with age.
Clinical examination and collection of biologic specimens from a subsample would provide a basis for establishing the reliability of self-reported information and deepen the value of hypotheses that could be explored.
Foster **cooperation with veterans' service organizations** in conducting studies.

Other Epidemiology Goals
Pursue development of protocols that could feasibly and efficiently investigate **paternal transmission** of adverse effects to offspring at birth or manifesting with maturation that have sufficient power for convincing findings. The logistics of attempting to detect adverse effects in the grandchildren of Vietnam veterans would be considerably more challenging.
Design a study to focus on specific manifestations in humans of dioxin exposure and **compromised immunity**, which has been so clearly demonstrated in animal models.

TOXICOLOGIC RESEARCH
Foster investigation of epigenetic changes in both somatic tissues and germ cells and during gestation.
Without sophisticated and specific **markers of environmentally induced epigenetic activity**, epidemiologic investigations will not be able to distinguish the mechanisms inducing any observed adverse health effects in exposed people or their offspring.
Fully investigate whether **paternally transmitted adverse effects** occur in animal models.
Continue exploration of the constellation of effects involved with the **metabolic syndrome**, which appear to represent a node of dioxin-related conditions.
Explore the role of **B-cell responses** to dioxin-like activity.
Resolve whether toxicology results for direct exposure to organic arsenic compounds are applicable to human exposure to such compounds.

assess exposure to include the chemicals of interest to VAO committees. Consideration of the experience of VA's own patients might also provide insight into the role of exposures unique to military service in common conditions that are recognized to have a multitude of contributing etiologic factors. Moreover, if a perceived conflict of interest exists for VA in surveying its own databases, it is recommended that an external advisory group be formed to determine the best mechanism for mining the information so that these medical databases can be available for external study.

As in previous years, this committee recommends the pursuit of additional research in toxicology. The development of animal models of neurologic outcomes and of various chronic health conditions and their progression would be useful for understanding the possible contributions of the chemicals of interest to compromising the health of aging Vietnam veterans. Specifically, determining the mechanism by which dioxin-like chemicals induce B-cell cancers and how such exposure alters the susceptibility to obesity and components of metabolic syndrome would fill important knowledge gaps. Health problems, such as metabolic syndrome, COPD, and measurement of biomarkers of immune or inflammatory disease, merit study in human populations.

There is a growing body of evidence from animal models that TCDD can induce epigenetic changes, a mechanism that may contribute to health problems in both the veterans and their children. Vietnam veterans have been concerned for decades that wartime exposures may cause harm in their offspring, but there remain extremely limited data on the risk that paternal exposure to xenobiotics in general, and the VAO chemicals of interest in particular, may pose for future generations. Although animal studies have shown epigenetic modifications to be passed along through the male germline, as yet, this has only been the result of perinatal exposure (in utero and by lactation) in which the exposed parent is the mother. The perinatal period clearly represents a period of susceptibility for impacts on the development of both male and female fetuses and on their germlines, but this exposure scenario is not relevant for the offspring of male Vietnam veterans who were adults when the exposure of concern would have taken place. Consequently, this committee continues to recommend that laboratory research be conducted to characterize TCDD's potential for inducing epigenetic modifications and for producing adverse outcomes in offspring specifically following exposure of adult males. Because the biological plausibility of paternal transmission of adverse effects remains to be established, effort should be invested in the development of epidemiologic protocols to address the logistical challenge of tracing adverse effects in the adult children and grandchildren of Vietnam veterans that are sufficiently robust to detect any actual effect associated specifically with exposures experienced by male veterans.

It is the committee's conviction that work needs to be undertaken promptly to resolve questions regarding several health outcomes, such as COPD, tonsil cancer, melanoma, Alzheimer disease, and paternally transmitted effects in offspring. Creative analysis of VA's own data resources and further work on cohorts that have already been established may well be the most effective way to address those outcomes and to gain a better understanding of the role of herbicide exposure in development of stroke, prostate cancer, and Parkinson disease in Vietnam veterans.

1

Introduction

The Agent Orange Act of 1991—Public Law (PL) 102-4, enacted February 6, 1991, and codified as Section 1116 of Title 38 of the United States Code—directed the Secretary of Veterans Affairs to ask the National Academy of Sciences (NAS) to conduct an independent comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to herbicides used during military operations in Vietnam. The herbicides picloram and cacodylic acid were to be addressed, as were chemicals in various formulations that contain the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Agent Orange refers specifically to a 50:50 formulation of 2,4-D and 2,4,5-T, which was stored in barrels identified by an orange band, but the term has come to often be used more generically to refer to all the herbicides sprayed by the US military in Vietnam.[1] 2,4,5-T contained the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, commonly referred to as "dioxin," which is referred to in this report as TCDD to represent a single—and the most toxic—congener of the tetrachlorodibenzo-*p*-dioxins (tetraCDDs). It should be noted that TCDD and Agent Orange are not the same. The NAS was also asked to recommend, as appropriate, additional studies to resolve continuing scientific uncertainties related to health effects and herbicide exposures and to comment on particular programs mandated in the law. The original legislation called for biennial reviews of newly available information for a period of 10

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

years, which was subsequently extended to 2014 by the Veterans Education and Benefits Expansion Act of 2001 (PL 107-103). This report is the final update mandated by PL 107-103.

In response to the request from the US Department of Veterans Affairs (VA), the Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine convened the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. The results of the original committee's work were published in 1994 as *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994). Successor committees formed to fulfill the requirement for updated reviews produced *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), *Update 2004* (IOM, 2005), *Update 2006* (IOM, 2007), *Update 2008* (IOM, 2009), *Update 2010* (IOM, 2011a), and *Update 2012* (IOM, 2014).

In 1999, VA asked the IOM to convene a committee to conduct an interim review of type 2 diabetes associated with exposure to any of the chemicals of interest (COIs) and this effort resulted in the report *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*, hereafter referred to as *Type 2 Diabetes* (IOM, 2000). In 2001, VA asked the IOM to convene a committee to conduct an interim review of childhood acute myelogenous leukemia (AML, now preferably referred to as acute myeloid leukemia) associated with parental exposure to any of the COIs. The committee's review of the literature, including literature available since the review for *Update 2000*, was published as *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans*, hereafter referred to as *Acute Myelogenous Leukemia* (IOM, 2002). In PL 107-103, passed in 2001, Congress directed the Secretary of Veterans Affairs to ask the NAS to review "available scientific literature on the effects of exposure to an herbicide agent containing dioxin on the development of respiratory cancers in humans" and to address "whether it is possible to identify a period of time after exposure to herbicides after which a presumption of service-connection" of the disease would not be warranted; the result of that effort was *Veterans and Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer*, hereafter referred to as *Respiratory Cancer* (IOM, 2004).

In conducting their work, the committees responsible for those reports operated independently of VA and other government agencies. They were not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. The reports were intended to provide evidence-based assessments of the scientific information available for the Secretary of Veterans Affairs to consider as VA exercises its responsibilities to Vietnam veterans. This VAO update and all previous VAO reports are freely accessible on line at the National Academies Press's website (http://www.nap.edu).

CHARGE TO THE COMMITTEE

In accordance with PL 102-4, the committee was asked to "determine (to the extent that available scientific data permit meaningful determinations)" the following regarding associations between specific health outcomes and exposure to TCDD and other chemicals in the herbicides used by the military in Vietnam:

A) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;
B) the increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
C) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease. [PL 102-4, Section 3(d)]

In addition to the request for the committee to prioritize areas for future research, which always has come with the work statement for each VAO committee, VA asked the committee for this update to address the specific question of whether service-relatedness for Parkinson disease should be interpreted to extend to all neurodegenerative diseases with Parkinson-like symptoms.

The committee notes that, as a consequence of congressional and judicial history, both its congressional mandate and the statement of task focus the target of evaluation on the "association" between exposure and health outcomes, although biologic mechanisms and causal relationships are also mentioned as part of the evaluation in Article C. As applied technically and thoroughly addressed in a report on decision making (IOM, 2008a) and in the section "Evaluation of the Evidence" in Chapter 2 of *Update 2010* (IOM, 2011a), the criteria for causation do not themselves constitute a set checklist, but are more stringent than those for association. The unique mandate of VAO committees to evaluate association rather than causation means that the approach delineated in the IOM report on decision making (IOM, 2008a) is not applicable here. The rigor of the evidentiary database required to support a finding of statistical association is weaker than that required to support causality. Importantly, positive findings on any of the indicators for causality would strengthen a conclusion that an observed statistical association is reliable. In accordance with its charge, the committee examined a variety of indicators appropriate for the task, including factors commonly used to evaluate statistical associations, such as the adequacy of control for bias and confounding and the likelihood that an observed association could be explained by chance, and it assessed evidence concerning biologic plausibility derived from laboratory findings in cell culture or animal model systems. As such, a full array of indicators was used to categorize the strength of the evidence. In particular,

associations supported by multiple indicators were interpreted as having stronger scientific support.

A VA representative delivered the charge to the committee at an open session of the committee's first meeting, and afterward the open session continued with brief presentations by other members of the public. It has been the practice of VAO committees to conduct open sessions, not only to gather additional information from people who have particular expertise on points that arise during deliberations, but also especially to listen to individual Vietnam veterans and others who are concerned about aspects of their health experience that may be service-related. Open sessions were held during the first three of the committee's five meetings, and the agendas and the issues raised are presented in Appendix A. The comments and information provided by the public were used to identify information gaps in the literature regarding specific health outcomes of concern to Vietnam veterans.

THE CURRENT POPULATION OF VIETNAM VETERANS

In this last update in the series of reports mandated by PL 102-4 and PL 107-103, the committee wanted to make note of the number of Vietnam veterans who are still living and thus still possibly at higher risk than the general public for health consequences arising from their potential herbicide exposure in Vietnam. As discussed at some length in the original report in this series (IOM, 1994), there has been substantial dispute about exactly how many US military personnel actually served in Vietnam, with estimates ranging from 2.6 to 4.3 million (see Table 3-2 in *VAO*). The estimates vary in part because of various ranges of dates being used to define the Vietnam era and whether consideration is limited to those serving literally in Vietnam or includes those serving in the Vietnam theater of operations (Laos, Cambodia, Vietnam, and the surrounding waters). Whether female Vietnam veterans are included has little impact on the total, however, because only 5,000 to 8,000 women are thought to have served in Vietnam. In contrast to the situation for the Australian and South Korean militaries, there is no comprehensive or official roster of US Vietnam veterans, which in turn has impeded the conduct of epidemiology studies and made it difficult to track the survival of the population that is the focus of these reports.

The Bureau of Labor Statistics (BLS), one of the five sources cited in *VAO*'s Table 3-2, has generated a succession of estimates of the number of male deployed and non-deployed Vietnam-era veterans in the civilian population from its Current Population Surveys (CPSs). The estimated age distributions of these two populations from the CPS of 1990 were presented in *VAO*'s Table 3-3. Since then, BLS characterized veterans in the civilian population from responses to the CPSs of 1995, 1999, 2001, and 2014, and the results for Vietnam-era veterans are presented in Table 1-1. Regrettably for this report, BLS regarded the number of Vietnam-era veterans estimated to be alive in the most recent CPS to be too small

TABLE 1-1 Age Distributions of Deployed and Non-Deployed Male Veterans of Vietnam Era (August 1964–April 1975) in Civilian Population Over Series of Current Population Surveys (CPSs) from Bureau of Labor Statistics (BLS) (numbers in thousands)

Year of Birth	Year of CPS Survey Age at Time of Survey	Deployed to Vietnam Theater N (%)		Non-Deployed N (%)	
	1990				
	All Ages	3,852		7,938	
1956 and after	**≤ 34**	32	(0.1)	133	(1.6)
1955–1951	**35–39**	369	(9.4)	1,109	(13.8)
1950–1946	**40–44**	1,676	(43.1)	3,031	(37.6)
1945–1941	**45–49**	1,090	(28.0)	2,301	(28.5)
1940–1936	**50–54**	280	(7.2)	675	(8.4)
1935–1926	**55–64**	322	(8.3)	511	(6.3)
1925 and before	**≥ 65**	83	(2.1)	178	(2.2)
	1995				
	All Ages	3,811		7,903	
1960–1951	**35–44**	614	(16.1)	1,719	(21.8)
1950–1941	**45–54**	2,615	(68.6)	5,106	(64.6)
1940–1931	**55–64**	445	(11.7)	855	(10.8)
1930 and before	**≥ 65**	137	(3.6)	223	(2.8)
	1999[a]				
	All Ages	4,109		8,116	
1964–1955	**35–44**	119	(2.9)	470	(5.8)
1954–1945	**45–54**	2,534	(61.7)	4,928	(60.7)
1944–1935	**55–64**	2,131	(51.9)	2,188	(27.0)
1934 and before	**≥ 65**	326	(7.9)	529	(6.5)
	2001				
	All Ages	4,046		8,007	
1966–1951	**35–44**	34	(0.8)	153	(1.9)
1956–1941	**45–54**	2,049	(50.9)	4,139	(51.7)
1946–1931	**55–64**	1,581	(39.1)	3,164	(39.5)
1936 and before	**≥ 65**	382	(9.4)	551	(6.9)
	2014[b]				
	All Ages	2,691		6,579	
1959–1955	**55–59**[b]	498	(7.6)		
1954–1950	**60–64**[b]	1,576	(24.0)		
1949 and before	**≥ 65**[b]	4,505	(68.5)		

[a]BLS could not specify any change in methodology between 1995 and 1999 that would account for the increases in the estimated totals for both deployed and non-deployed Vietnam-era veterans in the civilian population, so the committee assumes that the increase is due to a large number of retirements from the military during that period.

[b]Because of decreasing totals, age brackets were not calculated separately for deployed and non-deployed Vietnam veterans.

SOURCES: BLS, 1990, 1995, 1999, 2001, 2014.

to permit estimating the age distributions separately for deployed and non-deployed veterans, but the total number of surviving deployed veterans represented 29.0 percent of living male Vietnam-era veterans. The comparable proportion had been 32.7 percent in the 1990 CPS and 28.1 percent and 24.5 percent in earlier estimates of DOD (1976) and VA (1985), respectively, suggesting that deployed and non-deployed Vietnam-era veterans have not experienced dramatically different mortality rates.

CONCLUSIONS OF PREVIOUS VETERANS AND AGENT ORANGE REPORTS

Health Outcomes

VAO, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Type 2 Diabetes*, *Acute Myelogenous Leukemia*, *Respiratory Cancer*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* contain detailed reviews of the scientific studies evaluated by the committees and their implications for cancers, reproductive and developmental effects, neurologic disorders, and other health effects.

The original *VAO* committee addressed the statutory mandate to evaluate the association between herbicide exposure and individual health conditions by assigning each of the health outcomes under study to one of four categories on the basis of the epidemiologic evidence reviewed. The categories were adapted from the ones used by the International Agency for Research on Cancer in evaluating evidence of the carcinogenicity of various substances (IARC, 1977). Successor VAO committees adopted the same categories, and these are described below.

The question of whether the committee should be considering statistical association rather than causality has been debated. In legal proceedings that predated passage of the legislation that mandated the VAO series of reviews, *Nehmer v. United States Department of Veterans Affairs* found that

> the legislative history, and prior VA and congressional practice, support our finding that Congress intended that the Administrator predicate service connection upon a finding of a significant statistical association between dioxin exposure and various diseases. We hold that the VA erred by requiring proof of a causal relationship. [712 F. Supp. 1404, 1989]

The committee believes that the categorization of strength of evidence as shown in Table 1-2 is consistent with that court ruling. In particular, the ruling does not preclude the consideration of the factors usually assessed in determining a causal relationship (Hill, 1965; IOM, 2008a) as indicators of the strength of scientific evidence of an association. In accordance with the court ruling, the

committee was not seeking proof of a causal relationship, but any information that supports a causal relationship, such as a plausible biologic mechanism as specified in Article C of the charge to the committee, would also lend credence to the reliability of an observed association. An understanding of causal relationships is the ultimate objective of science, whereas the committee's goal of assessing statistical association is an intermediate point along the continuum between no association and causality.

The categories, the criteria for assigning a particular health outcome to a category, and the health outcomes that have been assigned to the categories in past updates are discussed below. Table 1-2 summarizes the conclusions of *Update 2012* regarding associations between health outcomes and exposure to the herbicides used in Vietnam or to any of their components or contaminants. That integration of the literature through September 2012 served as the starting point for the current committee's deliberations. The categories of association concern the occurrence of health outcomes in human *populations* in relation to chemical exposure. As such, the categorizations do not address the likelihood that any one *individual's* health problem is associated with, or caused by, the chemicals in question.

Health Outcomes with Sufficient Evidence of an Association

For a health outcome to be placed in the category "health outcomes with sufficient evidence of an association," a positive association between herbicides and the outcome must be observed in epidemiologic studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regarded evidence from several studies that satisfactorily addressed bias and confounding and that showed an association that is consistent in magnitude and direction to be sufficient evidence of an association. Experimental data supporting biologic plausibility strengthen evidence of an association, but are not a prerequisite and are not enough to establish an association without corresponding epidemiologic findings.

The original *VAO* committee found sufficient evidence of an association between exposure to herbicides and three cancers—soft-tissue sarcoma, non-Hodgkin lymphoma, and Hodgkin lymphoma—and two other health outcomes, chloracne and porphyria cutanea tarda (PCT). After reviewing all the literature available in 1995, the committee responsible for *Update 1996* concluded that the statistical evidence still supported that classification for the three cancers and chloracne, but that the evidence of an association with PCT warranted its being placed in the category of limited or suggestive evidence of an association with exposure.

As the committee responsible for *Update 2002* began its work, VA requested that it evaluate whether chronic lymphocytic leukemia (CLL) should be considered separately from other leukemias. That committee concluded that CLL could

TABLE 1-2 Summary of *Ninth Biennial Update* of Findings on Vietnam-Veteran, Occupational, and Environmental Studies Regarding Scientifically Relevant Associations[a] Between Exposure to Herbicides and Specific Health Outcomes[b]

Sufficient Evidence of an Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.[c] For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, then there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Soft-tissue sarcoma (including heart)
Soft-tissue sarcoma (including heart)
* Non-Hodgkin lymphoma
* Chronic lymphocytic leukemia (including hairy cell leukemia and other chronic B-cell leukemias)
* Hodgkin lymphoma
Chloracne

Limited or Suggestive Evidence of an Association

Epidemiologic evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.[b] For example, a well-conducted study with strong findings in accordance with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Laryngeal cancer
Cancer of the lung, bronchus, or trachea
Prostate cancer
* Multiple myeloma
* AL amyloidosis
Early-onset peripheral neuropathy
Parkinson disease
Porphyria cutanea tarda
Hypertension
Ischemic heart disease
Stroke (category change from *Update 2010*)
Type 2 diabetes (mellitus)
Spina bifida in offspring of exposed people

Inadequate or Insufficient Evidence to Determine an Association

The available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes that were explicitly reviewed:

Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)

TABLE 1-2 Continued

Cancers of the pleura, mediastinum, and other unspecified sites in the respiratory system and intrathoracic organs
Esophageal cancer
Stomach cancer
Colorectal cancer (including small intestine and anus)
Hepatobiliary cancers (liver, gallbladder, and bile ducts)
Pancreatic cancer
Bone and joint cancer
Melanoma
Non-melanoma skin cancer (basal-cell and squamous-cell)
Breast cancer
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
Urinary bladder cancer
Renal cancer (kidney and renal pelvis)
Cancers of brain and nervous system (including eye)
Endocrine cancers (thyroid, thymus, and other endocrine organs)
Leukemia (other than chronic B-cell leukemias, including chronic lymphocytic leukemia and hairy cell leukemia)
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than after paternal exposure to TCDD, which appears *not* to be associated)
Neonatal or infant death and stillbirth in offspring of exposed people
Low birth weight in offspring of exposed people
Birth defects (other than spina bifida) in offspring of exposed people
Childhood cancer (including acute myeloid leukemia) in offspring of exposed people
Neurobehavioral disorders (cognitive and neuropsychiatric)
Neurodegenerative diseases, excluding Parkinson disease
Chronic peripheral nervous system disorders
Hearing loss
Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
Gastrointestinal, metabolic, and digestive disorders (changes in hepatic enzymes, lipid abnormalities, and ulcers)
Immune system disorders (immune suppression, allergy, and autoimmunity)
Circulatory disorders (other than hypertension, ischemic heart disease, and stroke)
Endometriosis
Disruption of thyroid homeostasis
Eye problems
Bone conditions

This committee used a classification that spans the full array of cancers. However, reviews for nonmalignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. *By default, any health outcome on which no epidemiologic information has been found falls into this category.*

continued

TABLE 1-2 Continued

Limited or Suggestive Evidence of *No* Association
Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to a component of the herbicides of interest and the outcome. A conclusion of "no association" is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. *In addition, the possibility of a very small increase in risk at the exposure studied can never be excluded.* There is limited or suggestive evidence of *no* association between exposure to the herbicide component of interest and the following health outcome:

Spontaneous abortion after paternal exposure to TCDD

[a]This change in wording was made to emphasize the scientific nature of the VAO task and procedures and reflects no change in the present committee's criteria from those used in previous updates.

[b]*Herbicides* indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from occupational, environmental, and veteran studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.

[c]Evidence of an association is strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.

*The committee notes the consistency of these findings with the biologic understanding of the clonal derivation of lymphohematopoietic cancers that is the basis of the World Health Organization classification system (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109529/table/T1, accessed December 2, 2015).

be considered separately and, on the basis of the epidemiologic literature and the etiology of the disease, placed CLL in the "sufficient" category. In response to a request from VA, the committee for *Update 2008* affirmed that hairy-cell leukemia belonged in the category of sufficient evidence of an association along with the related conditions CLL and chronic B-cell lymphomas.

Health Outcomes with Limited or Suggestive Evidence of an Association

In the category of "health outcomes with limited or suggestive evidence of an association," the evidence must suggest an association between exposure to herbicides and the outcome considered, but the evidence can be limited by the inability to rule out chance, bias, or confounding confidently. The coherence of the full body of epidemiologic information, in light of biologic plausibility, is considered when the committee reaches a judgment about association for a given outcome. Because the VAO series has a number of agents of concern whose toxicity profiles are not expected to be uniform—specifically, four herbicides and TCDD—apparent inconsistencies can be expected among study populations that have experienced different exposures. Even for a single exposure, a spectrum

of results would be expected, depending on the power of the studies, inherent biological relationships, and other study design factors.

The committee responsible for *VAO* found limited or suggestive evidence of an association between exposure to herbicides and three categories of cancer: respiratory cancers (after individual evaluations of laryngeal cancer and of cancers of the trachea, lung, or bronchus), prostate cancer, and multiple myeloma. The *Update 1996* committee added three health outcomes to the list: PCT, acute and subacute peripheral neuropathy (indicated as early-onset transient peripheral neuropathy after *Update 2004* and then re-specified as simply early-onset peripheral neuropathy after *Update 2010*), and spina bifida in children of veterans. Initially, transient peripheral neuropathies had not been addressed in *VAO*, because they are not amenable to epidemiologic study. In response to a VA request, however, the *Update 1996* committee reviewed those neuropathies and based its determination on case histories. A combination of a 1995 report of birth defects among the offspring of veterans who served in Operation Ranch Hand and results of earlier studies of neural-tube defects in the children of Vietnam veterans (published by the Centers for Disease Control and Prevention) led the *Update 1996* committee to distinguish spina bifida from other reproductive outcomes and to place it in the "limited or suggestive evidence" category.

After the publication of *Update 1998,* the committee responsible for *Type 2 Diabetes*, on the basis of its evaluation of newly available scientific evidence and the cumulative findings of research that had been reviewed in previous VAO reports, concluded that there was limited or suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant TCDD and type 2 diabetes (mellitus).

The committee responsible for *Update 2000* reviewed the material in earlier reports and the newly published literature and determined that there was limited or suggestive evidence of an association between exposure to herbicides used in Vietnam or the contaminant TCDD and AML in the children of Vietnam veterans. After the release of *Update 2000*, the researchers for one of the reviewed studies discovered an error in their published data. The committee for *Update 2000* was reconvened to re-evaluate the previously reviewed and new literature regarding AML, and it produced *Acute Myelogenous Leukemia*, which reclassified AML in children from "limited or suggestive evidence of an association" to "inadequate or insufficient evidence to determine an association."

After reviewing the data reviewed in previous VAO reports and recently published scientific literature, the committee responsible for *Update 2006* determined that there was limited or suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant TCDD and hypertension. Amyloid light-chain (AL) amyloidosis was also moved to the category of "limited or suggestive evidence of an association," primarily on the basis of its close biologic relationship with multiple myeloma.

With a bit more consistent epidemiologic data augmented by an increased understanding of the mechanisms that new toxicology research had offered, the committee for *Update 2008* was able to resolve the *Update 2006* committee's lack of consensus and moved ischemic heart disease into the limited or suggestive category, joining hypertension. New studies of Parkinson disease that yielded findings of an association with the specific herbicides of interest were deemed to move the evidence to the category of limited or suggestive.

The committee for *Update 2012* determined that there was limited or suggestive evidence of an association of stroke with exposure to the herbicides used in Vietnam. A new finding of a strong association between serum concentrations of dioxin-like chemicals and the risk of stroke complemented earlier observations in important veteran, occupational, and environmental cohorts to make a compelling set of positive evidence.

Health Outcomes with Inadequate or Insufficient Evidence to Determine an Association

By default, any health outcome is in the category of "health outcomes with inadequate or insufficient evidence to determine an association" before enough reliable scientific data have accumulated to promote it to the category of sufficient evidence or limited or suggestive evidence of an association or to move it to the category of limited or suggestive evidence of *no* association. In this category, the available studies may have inconsistent findings or be of insufficient quality or statistical power to support a conclusion regarding the presence of an association. Such studies might have failed to control for confounding factors or might have had inadequate assessment of exposure.

The cancers and other health effects so categorized in *Update 2012* are listed in Table 1-2, but several health effects have been moved into or out of this category since the original *VAO* committee reviewed the evidence then available. Skin cancers were moved into this category in *Update 1996* when inclusion of new evidence no longer supported its classification as a condition with limited or suggestive evidence of *no* association. Similarly, the *Update 1998* committee moved urinary bladder cancer from the category of limited or suggestive evidence of *no* association to this category; in that case, although there was no evidence that exposure to herbicides or TCDD was related to urinary bladder cancer, newly available evidence weakened the evidence of *no* association. The committee for *Update 2000* had split off AML in the offspring of Vietnam veterans from other childhood cancers and put it into the category of suggestive evidence but a separate review, as reported in *Acute Myelogenous Leukemia*, found errors in the published information and returned it to this category with other childhood cancers. In *Update 2002*, CLL was moved from this category to join Hodgkin and non-Hodgkin lymphomas in the category of sufficient evidence of an association.

The committee responsible for *Update 2006* moved several cancers (of the brain, stomach, colon, rectum, and pancreas) from the category of limited or suggestive evidence of *no* association into this category partly because of some changes in evidence since they were originally placed in the "*no* association" category but primarily because that committee had concerns about the lack of information on all five COIs and each of these cancers.

Health Outcomes with Limited or Suggestive Evidence of *No* Association

The original *VAO* committee defined the category "health outcomes with limited or suggestive evidence of no association" for health outcomes for which several adequate studies covering the "full range of human exposure" were consistent in showing *no* association with exposure to herbicides at any concentration and had relatively narrow confidence intervals. A conclusion of "*no* association" is inevitably limited to the conditions, exposures, and observation periods covered by the available studies, and the possibility of a small increase in risk related to the magnitude of exposure studied can never be excluded. However, a change in classification from inadequate or insufficient evidence of an association to limited or suggestive evidence of *no* association would require new studies that correct for the methodologic problems of previous studies and that have samples large enough to limit the possible study results attributable to chance.

The original *VAO* committee found a sufficient number and variety of well-designed studies to conclude that there was limited or suggestive evidence of *no* association between the exposures of interest and a small group of cancers: gastrointestinal tumors (colon, rectum, stomach, and pancreas), skin cancers, brain tumors, and urinary bladder cancer. The *Update 1996* committee removed skin cancers and the *Update 1998* committee removed urinary bladder cancer from this category because the evidence no longer supported a conclusion of *no* association. The *Update 2002* committee concluded that there was adequate evidence to determine that spontaneous abortion is *not* associated with paternal exposure specifically to TCDD; the evidence on this outcome was deemed inadequate for drawing a conclusion about an association with maternal exposure to any of the COIs or with paternal exposure to any of the COIs other than TCDD. No changes in this category were made in *Update 2000* or *Update 2004*. The *Update 2006* committee removed brain cancer and several digestive cancers from this category because of a concern that the overall paucity of information on picloram and cacodylic acid made it inappropriate for those outcomes to remain in this category. This left the finding of evidence of *no* association between paternal exposure to TCDD and spontaneous abortion as the sole entry in this category.

Determining Increased Risk in Vietnam Veterans

The second part of the committee's charge was to determine, to the extent permitted by available scientific data, the increased risk of disease among people exposed to herbicides or the contaminant TCDD during service in Vietnam. Previous reports pointed out that most of the many health studies of Vietnam veterans were hampered by relatively poor measures of exposure to herbicides or TCDD and by other methodologic problems. Most of the evidence on which the findings regarding associations are based, therefore, comes from studies of people exposed to TCDD or herbicides in occupational and environmental settings rather than from studies of Vietnam veterans. The committees that produced *VAO* and the updates found that the body of evidence was sufficient for reaching conclusions about statistical associations between herbicide exposures and health outcomes but that the lack of adequate data on Vietnam veterans themselves complicated the consideration of the second part of the charge.

The evidence of herbicide exposure among the various groups studied suggests that although some had documented high exposures (such as participants in Operation Ranch Hand and Army Chemical Corps personnel), most Vietnam veterans had lower exposures to herbicides and TCDD than did the subjects of many occupational and environmental studies (see Figure 1-1 from Pirkle et al., 1995). However, individual veterans who had very high exposures to herbicides

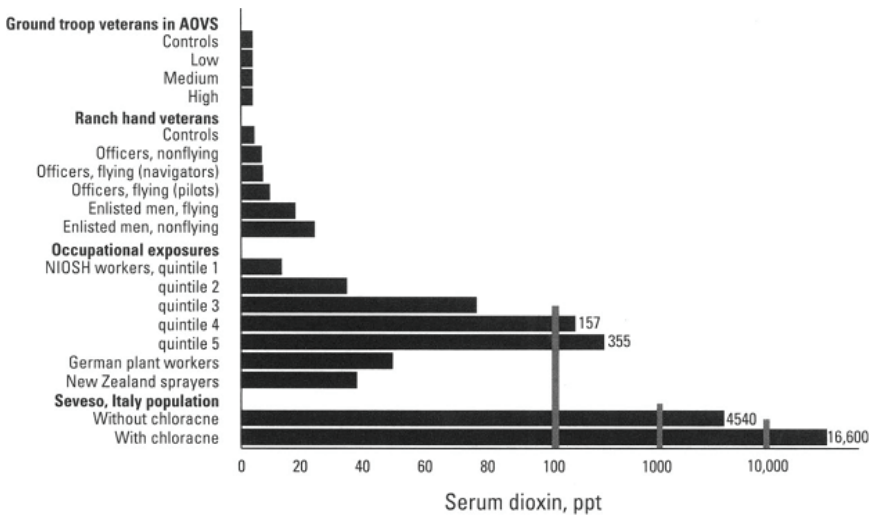


FIGURE 1-1 Median serum TCDD levels in various study populations.
SOURCE: Pirkle et al., 1995.
NOTE: AOVS = CDC Agent Orange Validation Study (CDC, 1989a); NIOSH, National Institute for Occupational Safety and Health.

could have risks approaching those described in the occupational and environmental studies.

Estimating the magnitude of risk of each particular health outcome among herbicide-exposed Vietnam veterans requires quantitative information about the dose–time–response relationship for the health outcome in humans, information on the extent of herbicide exposure among Vietnam veterans, and estimates of individual exposure. The committees responsible for *VAO* and the updates have concluded that in general it is impossible to quantify the risk posed to veterans by their exposure to herbicides in Vietnam. Statements to that effect were made for each health outcome in *VAO* (IOM, 1994) and in every update through *Update 2004*. The committee responsible for *Update 2006* chose to eliminate the repetitive restatements in favor of the following general conclusion: "At least for the present, it is not possible to derive quantitative estimates of the increase in risk of various adverse health effects that Vietnam veterans may have experienced in association with exposure to the herbicides sprayed in Vietnam." The committees responsible for later updates and the current committee have all opted to retain the modification in the formatting of the health outcomes sections.

After decades of research, the challenge of estimating the magnitude of potential risk posed by exposure to the COIs remains intractable. The requisite information is still not available despite concerted efforts to use modeling to reconstruct likely exposure from records of troop movements and spraying missions (Stellman and Stellman, 2003, 2004; Stellman et al., 2003a,b), to extrapolate from agricultural models of drift associated with spraying (Ginevan et al., 2009a; Teske et al., 2002), to measure serum TCDD in individual veterans (Kang et al., 2006; Michalek et al., 1995), and to model the pharmacokinetics of TCDD clearance (Aylward et al., 2005a,b; Cheng et al., 2006; Emond et al., 2004, 2005, 2006). There is still uncertainty about the specific agents that may be responsible for a particular health effect. Even if one accepts an individual veteran's serum TCDD concentration as the optimal surrogate for overall exposure to Agent Orange and the other herbicide mixtures sprayed in Vietnam, not only is it nontrivial to make this measurement but the hurdle of accounting for biologic clearance and extrapolating to the proper timeframe remains. Prior committees have thought it unlikely that additional information or more sophisticated methods would become available to permit any sort of quantitative assessment of Vietnam veterans' increased risks of particular adverse health outcomes that are attributable to exposure to the chemicals associated with herbicide spraying in Vietnam.

The committee for this final update in the VAO series was pleased to have the opportunity to evaluate a set of papers (Yi, 2013; Yi and Ohrr, 2014; Yi et al., 2013a,b, 2014a,b) that reported the results of applying the Exposure Opportunity Index (EOI) model (Stellman and Stellman, 2003, 2004; Stellman et al., 2003a,b), which was developed with the encouragement of earlier VAO committees, to a large cohort of Korean veterans who served in the Vietnam War. The findings appear quite coherent, but this committee notes that there is no objective standard

by which estimates generated by the EOI model can be validated. This means that exposure estimation for the investigation of health outcomes in Vietnam veterans will remain a hurdle unlikely to be resolved in a fashion that will permit the conduct of epidemiology studies with greatly improved appraisals of association specifically linked to herbicide exposure.

Existence of a Plausible Biologic Mechanism or Other Evidence of a Causal Relationship

Toxicology data form the basis of the committee's response to the third part of its charge—to determine whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and a health effect. A separate chapter summarizes toxicology findings on the chemicals of concern. In *VAO* and its updates before *Update 2008*, a considerable amount of detail was provided about individual newly published toxicology studies; the current committee concurs with the decision made by the committee for *Update 2008* that it is more informative for the general reader to provide integrated toxicologic profiles for the COIs by interpreting the underlying experimental findings. In addition, when specific toxicologic findings pertinent to a particular health outcome are available, they are discussed in the chapter reviewing the epidemiologic literature on that condition. The current committee has continued the effort to refine this approach in order to make the chapter on toxicologic information more accessible to lay readers and to make more clear its relevance to epidemiologic findings.

In *VAO* and updates before *Update 2006*, this topic was discussed in the conclusions section for each health outcome after a statement of the committee's judgment about the adequacy of the epidemiologic evidence of an association of that outcome with exposure to the COIs. As noted in *Update 2006*, the degree of biologic plausibility itself influences whether the committee perceives positive findings to be indicative of a pattern or the product of statistical fluctuations. To provide the reader with a more logical sequence, the committee responsible for *Update 2006* placed the biologic-plausibility sections between the presentation of new epidemiologic evidence and the synthesis of all the evidence; this in turn led to the ultimate statement of the committee's conclusion. The later committees have agreed with that change and have continued to arrange the sections in that fashion.

ORGANIZATION OF THIS REPORT

The remainder of this report is organized into 14 chapters. Chapter 2 briefly describes the considerations that guided the committee's review and evaluation of the scientific evidence. Chapter 3 addresses exposure-assessment issues. Chapter

4 summarizes the toxicology data on the effects of 2,4-D, 2,4,5-T and its contaminant TCDD, cacodylic acid, and picloram; the data contribute to the consideration of the biologic plausibility of health effects in human populations. Chapter 5 characterizes the relevant new epidemiologic literature published during this update period, providing the study design, exposure measures, health outcomes reported, and population studied. Chapter 6 offers a cumulative overview of the study populations that have generated findings (in some instances presented in dozens of separate publications) reviewed in the VAO report series. In addition to showing where the new literature fits into this compendium of previous publications on Vietnam veterans, occupational cohorts, environmentally exposed groups, and case-control study populations, Chapter 6 includes a description and critical appraisal of the approaches used in the design, exposure assessment, and analysis in these studies.

The committee's evaluation of the epidemiologic literature and its conclusions regarding the associations between exposures and the particular health outcomes that might be manifested long after exposure to the COIs are presented in the chapters that follow. In *Update 2010*, three short-term responses presumptively associated with herbicide exposure (early-onset peripheral neuropathy, chloracne, and PCT) were moved from the body of the report to Appendix B because they develop shortly after exposure and are unlikely to arise for the first time decades after the exposed people left Vietnam. A new feature adopted in *Update 2012* was the placement of a summary of the finding for each health outcome at the beginning of the chapter.

Chapter 7, the first of the chapters evaluating epidemiologic evidence concerning particular health outcomes, addresses immunologic effects and discusses the reasons for what might be perceived as a discrepancy between a clear demonstration of immunotoxicity in animal studies and a paucity of epidemiologic studies with similar findings. Its placement in the report reflects the committee's belief that immunologic changes may constitute an intermediate step in the generation of distinct clinical conditions, as discussed in subsequent chapters.

Chapter 8 discusses issues related to the possible overall carcinogenic potential of the COIs, particularly TCDD, and then assesses, in order of their codes in the *International Classification of Diseases* (ICD), the available epidemiologic evidence on specific types of cancer, which are regarded as individual disease states that might be found to be service related.

In *Update 2012*, what had previously been one chapter on reproductive and developmental effects was partitioned into two chapters, and this report follows that pattern. The first of the two, Chapter 9, addresses reproductive problems that may have been manifested in the veterans themselves: reduced fertility, pregnancy loss, or gestational issues (low birth weight or preterm delivery). The second, Chapter 10, focuses on problems that might be manifested in veterans' children at birth (traditionally defined as birth defects) or later in their lives

(childhood cancers, plus a broad spectrum of conditions for which impacts from parental exposures have been posited) or even in later generations.

Chapter 11 addresses neurologic disorders. Chapter 12 deals with a set of conditions related to cardiovascular and metabolic effects, which were gathered into a separate chapter by the committee for *Update 2010* on the basis of their apparent interrelationship in the emerging medical phenomenon known as "metabolic syndrome." Chapter 13 now contains the residual "other health outcomes" about which epidemiologic results related to the chemicals of interest have been encountered in the course of this series of VAO reports: respiratory disorders, gastrointestinal problems, kidney disease (new in this report), thyroid homeostasis and other endocrine disorders, eye problems, and bone conditions.

A summary of the committee's findings and its research recommendations are presented in Chapter 14. In this last update mandated by PL 102-4 and PL 107-103, the committee also discusses how best to monitor the possibility of additional health outcomes associated with herbicide exposure. In the interest of minimizing unnecessary repetition, for the first time in this series of updates, the citations for all chapters have been merged into a single reference list that follows all the chapters.

2

Evaluating the Evidence

This chapter outlines the approach used by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Tenth Biennial Update) and its predecessors to evaluate the available scientific evidence. A more complete description is found in Chapter 5 of *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*,[1] hereafter referred to as *VAO* (IOM, 1994).

OVERVIEW

Throughout its evolution, the committee has aimed to employ a methodologically sound evaluation process that is comprehensive, informative, and transparent. This has been achieved by the use of a systematic process of evaluation used over many years, one that has been consistent despite the fact the participating members of the committee have changed over time. This process of evaluation is depicted in Figure 2-1 below.

DEFINE THE EVALUATION PARAMETERS

This section describes the primary evaluation parameters used by the committee. This includes the choice and measurement of health outcomes of concern,

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

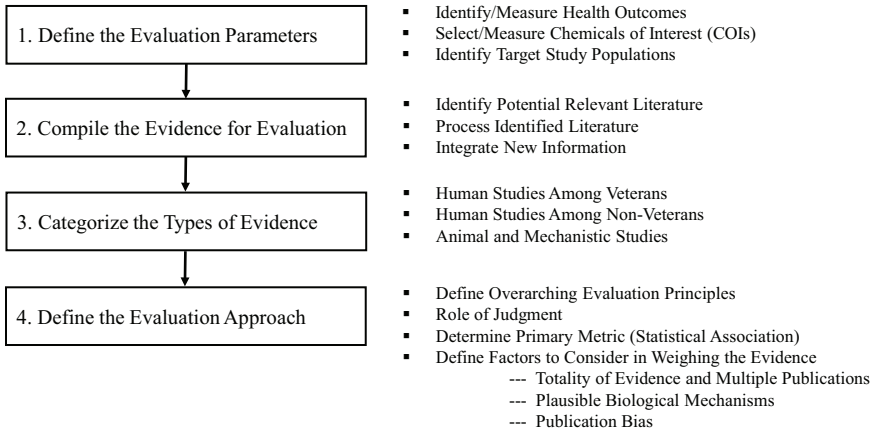


FIGURE 2-1 Process employed for evaluating the evidence.

the choice and measurement of chemicals of interest (COIs), and the target populations to be reviewed in the evaluation process.

Choice and Measurement of Health Outcomes

As discussed in Chapter 1, the committee was charged with summarizing the strength of the scientific evidence concerning associations between exposure to various herbicides and contaminants during service in the Vietnam War and individual diseases or other health outcomes. However, Public Law 102-4, which mandated the committee's work, did not specify any particular health outcomes suspected of being associated with herbicide exposure. Such a list of outcomes was developed on the basis of diseases and conditions addressed in the scientific literature identified through the original *VAO* committee's extensive literature searches. The list has been amended in the VAO updates to include additional outcomes reported upon in new publications, to requests from the US Department of Veterans Affairs (VA) and various veterans' service organizations, and to concerns of Vietnam veterans and their families. Comments received at public hearings and in written submissions from veterans and other interested persons have been valuable in identifying issues to be pursued to greater depth in the scientific literature.

Although the increased risks of various psychological conditions, including but not limited to posttraumatic stress disorder (PTSD), among veterans of all US conflicts have always been of scientific and public health concern, such conditions have not been considered by VAO committees. In continuing this practice the current committee notes two underlying principles:

- First, military service alone, including deployment and service in Vietnam, confers a range of potentially traumatic psychological exposures, which may be expected to increase the risk of developing PTSD and related psychological comorbidities. To illustrate, the prevalence of PTSD is more than twice as high for operational infantry units exposed to direct combat than it is in general population samples (Kok et al., 2012). Given the known relationship between combat exposure and an increased risk of mental health conditions, a synthesis of the literature would not provide the opportunity to identify any potential adverse effects on mental health outcomes caused by exposure to the COIs that may occur independently of psychological effects accrued through military service.
- Second, from reviewing the vast toxicology literature related to the COIs, it is clear that there is a dearth of reports that address potential associations and mechanistic explanations of how exposure to the COIs experienced during military service in Vietnam could conceivably influence the risk of developing mental health conditions. This applies specifically to an overall absence of published evidence as to how dioxin/2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure could be etiologically implicated in the development of PTSD and related psychological comorbidities.

Thus, in aggregate, the health outcomes that the committee has focused on include cancers of all types, cardiovascular and metabolic outcomes, immune system disorders, neurological disorders (excluding psychological conditions), a range of other chronic health outcomes, and fertility and gestational effects. The primary focus of the evaluation was on adverse outcomes in the veterans themselves, but a targeted evaluation was also conducted to look for potential adverse health effects in offspring of Vietnam veterans.

Because any effect of Agent Orange in individuals or groups of veterans is evaluated in terms of disease or medical outcome, the committee paid particular attention to disease classification as it assembled pertinent data from various investigations related to a particular outcome in preparation for integrating the information. The researchers who conducted the studies that the committee reviewed faced the same challenge in interpreting the available documentation when assigning diagnostic labels to given subjects and then grouping the labels for analysis.

Pathologists, clinicians, and epidemiologists use several classification systems, including the *International Classification of Diseases* (ICD): the *International Classification of Diseases, 9th Revision* (ICD-9); the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM); and the *International Classification of Diseases for Oncology*. The 10th revision of ICD (ICD-10) is currently used to classify mortality information. Most of the subjects investigated in the studies cited in the VAO updates were diagnosed under earlier systems, and most of the articles report results in accordance with

ICD-9 if they use ICD codes at all, so VAO committees have retained the use of ICD-9. ICD codes are a hierarchic system for indicating type of disease and site. For example, ICD-9 162 specifies cancers of the lung, trachea, or bronchus; 162.2, cancer of a main bronchus; 162.3, cancer of an upper lobe; 162.4, cancer of a middle lobe; and 162.5, cancer of a lower lobe.

For a patient to receive a correct cancer diagnosis, careful determination of the extent of disease is necessary, and a biopsy of the tissue must be analyzed with microscopy, often with special immunohistochemical stains and more recently genetic testing, to confirm a clinical impression. Many of the epidemiologic studies reviewed by VAO committees have not used the ICD approach to classification of disease and have relied instead on clinical impression alone. Death-certificate diagnoses are notoriously inaccurate if the certificates are completed by medical officers who are not familiar with the decedents' medical history (Smith Sehdev and Hutchins, 2001). Self-reported diagnoses, which are obtained from survey questionnaires, often are partially or completely inaccurate; for instance, a patient may report having been treated for stomach cancer when the correct diagnosis was gastric adenocarcinoma, gastric lymphoma, pancreatic cancer, large bowel cancer, or peritoneal cancer.

Many epidemiologic studies report disease outcome by organ system. For instance, the term "digestive system" may be used for conditions that are benign or malignant and that affect the esophagus, stomach, liver, pancreas, small bowel, large bowel, or rectum. Therefore, if a report indicated that a cohort has an increased incidence of digestive system cancers, then it would be unclear whether the association was attributable to excess cases of esophageal, gastric, hepatic, pancreatic, or intestinal cancers or to some combination thereof. Such generalization is complicated by the fact that the cause of cancer may differ between anatomic sites. For instance, there are strong associations between *Helicobacter pylori* infection and gastric cancer, between smoking and squamous cell carcinoma of the esophagus, and between chronic hepatitis B infection and hepatic cancer. Furthermore, a single site may experience a carcinogenic response to multiple agents, while the same agent may cause cancer at multiple sites.

The committee recognizes that outcome misclassification is a possibility when recording of a diagnosis with a specific ICD code is used as the means of entering an observation into an analysis, but this system has been refined over many decades and is virtually universally used and understood, in addition to being exhaustive and explicit. Therefore, this and previous VAO committees have opted to use the ICD system as an organizing tool. Although the groupings of cancer sites for which conclusions about association have been presented may correspond more closely with National Institute for Occupational Safety and Health or National Cancer Institute Surveillance Epidemiology and End Results categories (see Appendix C), the underlying ICD codes provide the most exactitude. In this report, ICD codes appear almost exclusively in the introductory sections of health-outcome discussions (particularly for cancers) to specify precisely what outcome

the committee is addressing and, when possible, in the results table to indicate exactly what the primary researchers believed they were investigating. (See Appendix C for cancer groupings with corresponding ICD-9 and ICD-10 codes.)

Rare diseases, such as hairy-cell leukemia and tonsil cancer, are difficult to study because it is difficult to accumulate enough cases to permit analysis. Often, the result is that the observed cases are included in a broader, less specific category. Thus, epidemiologic data may not be available for assessing whether a particular rare disease is associated with Agent Orange exposure. In some instances, such as chronic lymphocytic leukemia and amyloid light-chain (AL) amyloidosis, VAO committees have reached conclusions on the basis of the data available and the etiology of the disease. Through systematic application of the hierarchic nature of the ICD coding system, committees intend to draw, for every type of cancer, an explicit conclusion about the adequacy of available evidence to support an association between herbicide exposure and that type of cancer. For nonmalignant conditions, the diversity of disease processes involved makes the use of broad ICD ranges less useful, but, because VAO committees could not possibly address every rare nonmalignant disease, they do not draw explicit conclusions about diseases that are not discussed. Thus, the category of "inadequate or insufficient evidence to determine an association" is the default or starting point for any health outcome; if a condition or outcome is not addressed specifically, then it will be in this category.

In general, VAO committees have not considered case reports, case series, or other published studies that lacked control or comparison groups. An exception was made, however, in the case of early-onset peripheral neuropathy, for which a considerable number of case reports associated with high dioxin exposure were available. These were accepted for review because the rapid appearance and frequently transient nature of the condition impose methodologic constraints that might have precluded the application of standard epidemiologic techniques. Clinical follow-up of many of these cases ultimately demonstrated that dioxin-associated acute peripheral neuropathy is not necessarily transient. A subsequent deviation from this rule was made in considering the toxicokinetic information gathered by monitoring Victor Yushchenko (President of Ukraine, 2005–2010) following his TCDD poisoning in 2004 while campaigning.

The committee is aware of the concerns of some veterans about the role of herbicide exposure in the occurrence of multiple health outcomes, such as multiple cancers, in a given person. Little research has been done to address whether the rate of concurrence is greater than would be expected by chance. Simultaneous analysis of multiple health outcomes could potentially provide more insight into whether the chemicals of interest cause multiple health effects, into competing risks among various health outcomes, and into the interactive effects of health outcomes. Addressing health conditions individually has remained challenging, however, and, at present, methods have not been developed to identify with any confidence patterns among multiple health outcomes associated with a single exposure.

Choice and Measurement of COIs

Mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid made up the bulk of the herbicides sprayed in Vietnam. At the time of the spraying, TCDD (a form of dioxin) was an unintended contaminant in the production of 2,4,5-T and so it was present in Agent Pink, Agent Green, Agent Purple, Agent Orange, and Agent Orange II, which all contained 2,4,5-T. It is important to note that TCDD and Agent Orange are not the same. Databases have been searched for the names of those compounds, their synonyms and abbreviations, and their Chemical Abstracts Service (CAS) numbers. The evidence indicates that a single protein, the aryl hydrocarbon receptor (AHR), mediates essentially all the toxicity of TCDD, so "aryl hydrocarbon receptor" also was used as a keyword.

It is well accepted that any TCDD or herbicide effect may be diluted somewhat in studies of Vietnam veterans because some of the veterans may not have been exposed or may have been exposed only at low concentrations. The problem is exacerbated in studies in which exposure is defined in terms of occupation (even on the basis of a full job history). Exploratory studies based on linking to a one-time statement of occupation (for example, on a death certificate or in a census) are thought to be of little use even when a job–exposure matrix is used to "convert" standardized job codes into specific exposures. Not only is there uncertainty about whether all members of a sample have been exposed to one of the COIs unless detailed personal monitoring and industrial-hygiene work have been performed but also for most occupational categories there is considerable certainty that the workers were exposed to many other potentially toxic agents as well. Thus, such studies may well minimize the effects of exposure to TCDD or the herbicides of interest while yielding misleading indications of health problems resulting from other exposures.

For cacodylic acid and picloram, the search terms were the chemical names, synonyms, and CAS numbers of these herbicides. It should be noted that cacodylic acid, or dimethyl arsenic acid of valence 5 (DMA^V), is an organic form of arsenic. In addition to being synthesized as a herbicide, DMA^V is a metabolite of inorganic arsenic exposure in humans. DMA^V was long thought to be a biologically inactive metabolite, but accruing evidence suggests that methylated forms, such as monomethyl arsenic acid of valence 3 (MMA^{III}) (Aposhian et al., 2000) and perhaps DMA^{III} and DMA^V (Cohen et al., 2006), are responsible for some of the adverse effects of inorganic arsenic. This committee considered the available toxicologic information on DMA very carefully in assessing its contribution to the biologic plausibility of an association of various health outcomes with exposure to the herbicides used in Vietnam. It could not, however, accept the hypothesis that direct exposure to DMA^V would necessarily result in the same adverse health effects as would exposure to toxic concentrations of inorganic arsenic. Therefore, as in prior VAO reports, the epidemiologic literature on the

health effects of inorganic arsenic was not considered relevant for the VAO task. Further details on the effects of inorganic arsenic can be found in recent reviews (IARC, 2012a; NRC, 2013).

With the structural representation at hand in Figure 2-2, one can readily see the basis of an assertion heard repeatedly from individual Vietnam veterans that "benzene is contained in TCDD." Indeed, the two rings at the ends of the three-ring structure constituting the basic structure of dioxin compounds, to which chlorine molecules or other chemical radicals can be attached, do have the molecular structure of a single benzene molecule, and the "dibenzo-dioxin" in TCDD's chemical name does mean that the molecule is a benzene-substituted dioxane. The benzene ring structure is a basic building block of a vast number of organic compounds, both industrial (such as polyaromatic hydrocarbons, the phenoxy herbicides, picloram, and polychlorinated biphenyls [PCBs]) and natural (such as estradiol, a hormone present in both men and women). However, the biologically active compound benzene does not emerge from dioxin, whose three-ring structure is extremely stable and resistant to metabolism.

Interaction or synergism among the COIs or in combination with other agents is another theoretical concern. The committee was not charged with attributing effects to specific COIs, and joint effects among them should be adequately identified by the committee's approach. The combinations of the chemicals with other agents that might lead to problems are virtually infinite, and hence, not feasible for systematic and comprehensive evaluation. Real-life experience, as investigated with epidemiologic studies, effectively integrates any results of exposure to a target substance in combination with other substances that may be etiologically relevant.

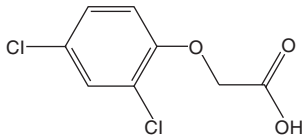
Thus, in aggregate, the primary COIs evaluated by the committee with respect to potential associations with adverse health outcomes among Vietnam veterans are 2,4-D, 2,4,5-T, picloram, cacodylic acid, and TCDD. As explained above, inorganic arsenic and benzene were not considered as relevant service-related exposures among Vietnam veterans and thus were not evaluated in relation to their potential risk of adverse health outcomes.

Exposure Assessment of COIs

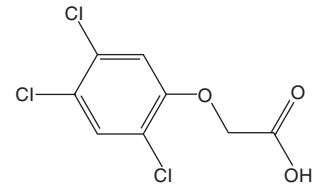
Much of the evidence that VAO committees have considered has been drawn from studies of populations that were not in Vietnam during the period when Agent Orange and other herbicides were used as defoliants. The most informative of those studies were well-documented investigations of occupational exposures to TCDD or specific herbicides, such as 2,4-D and 2,4,5-T. In many other studies, TCDD exposure was combined with exposures to an array of "dioxin-like" compounds, and the herbicides were often analyzed as members of a functional class; this is less informative for the committee's purposes than individual results on a specific compound. In the real-world situations investigated in epidemiologic

Phenoxy Herbicides

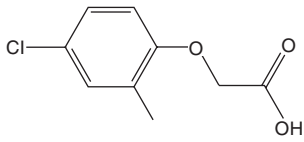
2,4-D [94-75-7]



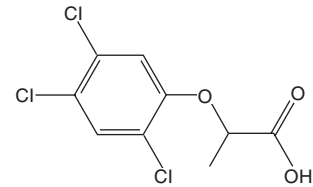
2,4,5-T [93-76-5]



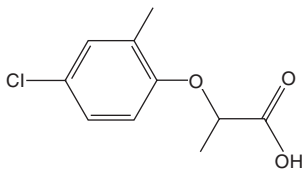
MCPA [94-74-6]



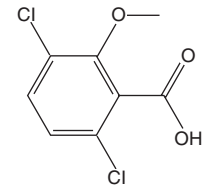
Silvex [93-72-1]



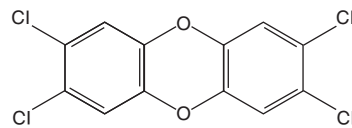
MCPP [93-65-2]



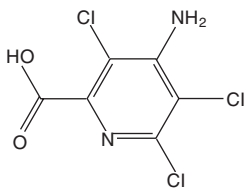
Dicamba [1918-00-9]



2,3,7,8-TCDD [1746-01-6]



Picloram [1918-02-1]



Cacodylic Acid [75-60-5]

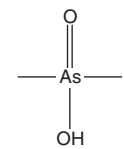


FIGURE 2-2 Chemical structures and CAS numbers for specific chemicals of interest.

studies, exposure to multiple possibly toxic chemicals is the rule rather than the exception; for example, farmers and other agricultural populations are likely to be exposed to insecticides, fungicides, and herbicides. In its examination of these epidemiologic studies, the committee looked for evidence of health effects that are associated with the specific compounds in the defoliants used in Vietnam and sought consideration of and adjustment for other possibly confounding exposures.

The quality of exposure information in the scientific literature reviewed by this and previous VAO committees varies widely. Some studies relied on interviews or questionnaires to determine the extent and frequency of exposure. Such self-reported information, which has the potential for recall bias, generally carries less weight than do more objective measures of exposure. The strength of questionnaire-based information as evidence of exposure is enhanced to the extent that the information can be corroborated or validated by other sources. Written records of chemical purchase or production can provide one type of objective information. Even more useful are scientific measurements of exposure. In some occupational studies, for example, workers wear air-sampling instruments that measure the concentration of a contaminant in each worker's breathing zone. Measurement of chemicals or their products in biologic specimens, such as blood and urine, can provide reliable indications of exposure for specific periods. Studies that categorize exposure from well-documented environmental sources of contaminants can be useful in the identification of exposed populations, but their results may be inaccurate if people with different magnitudes of exposure are assigned to the same general category of exposure. Studies that explore environmental exposure and disease frequency in regional populations (such as in states and counties) are known as ecologic studies. Most ecologic studies are considered preliminary or "hypothesis-generating" studies because they lack information on exposures and disease on an individual basis and are unable to address potential confounding factors.

Chapter 3 of this update addresses issues related to exposure estimation in more detail. The agent of interest may be assessed with various degrees of specificity. For instance, any of the four herbicides in question could be individually measured, and phenoxy herbicides would be a useful broader category for 2,4,5-T and 2,4-D; but a report of findings in terms simply of "herbicides" is only marginally informative, and results stated in terms of "pesticides" are too vague to be useful. For a given COI, the measure of exposure may be increasingly imprecise—for example, concentrations in target tissue, serum concentrations, cumulative exposure, possible exposure, and so on down to merely a report of service in a job or industry category. Those approaches can address complexities in specificity, duration, and intensity of exposure with various degrees of success. All may provide some information about an association with a COI, but this committee has determined that the investigation of associations between an exposure of concern and most health outcomes has reached the stage where some

characterizations of exposure are too nonspecific to promote insight. For health outcomes with little evidence, a somewhat less stringent criterion would apply so that no possible signal of an association would be overlooked.

Identification of Target Study Populations

Because Vietnam veterans are the target population of the charge to the VAO committees, studies of these veterans (serving in any of the armed forces, American or otherwise) have always been accorded considerable weight in the committees' deliberations, whether or not an estimation of exposure to herbicide-related substances has been attempted. The characterization of exposure in studies of the veterans was extremely uncommon at the time of the original *VAO* report, and the Vietnam veterans' own ages were still below the ages at which many chronic illnesses are manifested. Consequently, the original committee made extensive efforts to consider several groups known or thought to have potentially higher and better-characterized exposure to TCDD or phenoxy herbicides than the Vietnam veterans themselves—both occupational exposure (for example, chemical-production, paper and pulp, sawmill, tannery, waste-incinerator, railroad, agricultural, and forestry workers) and environmental exposure (for example, residents of Quail Run, Seveso, Times Beach, and Vietnam).

Successive committees have been able to concentrate more on those studies that explicitly addressed the exposures specified by the charge. Some occupational and environmental cohorts that received exceptionally high exposures (such as the International Agency for Research on Cancer and Seveso cohorts) are now well characterized and have produced a stream of informative results. The Agricultural Health Study, a continuing prospective cohort study of agricultural populations with specific information on the COIs, has contributed a steady stream of information to the database. Most important, the Vietnam veterans themselves are advancing in age and, when studied, are capable of directly providing substantial information on chronic health conditions and, in some study populations, information related to serum TCDD concentrations. The committee for *Update 2006* decided that doing exhaustive searches on job titles, occupations, or industries in order to identify additional study populations that had possible, but not specifically characterized, exposure to the COIs was no longer an efficient means of augmenting the evidence database in that the citations such searches would yield were more likely to be those with information about a health outcome at the expense of considerable uncertainty about exposure.

The previous and current committees followed the *Update 2006* committee's practice of performing more circumscribed searching. As the information in the database on populations that had established exposure to the COIs has grown, VAO committees have become less dependent on data from studies that had nonspecific exposure information and have been able to focus more on the findings of studies that had refined exposure specificity. In recognition of the more pivotal

role that findings drawn directly from Vietnam veterans were able to play in its decisions, the committee for *Update 2008* reordered its consideration of populations. For each health outcome, studies of Vietnam veterans, the target population of the VAO series, are addressed first and occupational and environmental studies are addressed second. The committee's exact criteria concerning exposure specificity are presented at the end of Chapter 3.

Thus, study populations considered by the committee included Vietnam veterans (US and otherwise), who are presumed to have been exposed to all the COIs, plus cohorts believed to have been occupationally or environmentally exposed to at least one of the COIs. Although Vietnam veterans constitute the source population of interest, the committee has taken into account the potential for more precise quantification and evaluation of the risks of adverse health outcomes associated with the COIs in better characterized cohorts (i.e., occupational and environmental cohorts). As illustrated by Figure 1-1 in Chapter 1, when the rather limited collection of serum TCDD levels gathered from exposed populations are compared, it is found that the median TCDD levels in veterans who had worked in Operation Ranch Hand were higher than those measured in their own comparison group or in ground troops, both of which had median levels in the range of contemporaneous background (unitary ppt range), but about an order of magnitude less than herbicide production workers, who in turn had levels about two orders of magnitude less than individuals who resided near the Seveso industrial explosion. Including these more highly exposed populations had the additional advantage that epidemiologic studies of them were likely to have greater statistical power to detect any adverse effects that might occur.

Mechanistic and toxicology studies of the COIs are not core evidence in the overall evaluation of the potential associations between the COIs and health outcomes specific to Vietnam veterans, but they are considered for the potential insight they may provide into biologic plausibility.

COMPILATION OF EVIDENCE FOR EVALUATION

This section describes the manner in which potentially relevant literature was identified, how such literature was screened and processed, and how the new information that was identified has been integrated with previous information evaluated by the committee.

Identification of Potentially Relevant Literature

This report concentrates on the evidence published after the completion of work on *Veterans and Agent Orange: Update 2012* (IOM, 2014). Relevant new contributions to the literature made during the period October 1, 2012–September 30, 2014, were sought. The information that the committee used was compiled through a comprehensive electronic search of public and

commercial databases—biologic, medical, toxicologic, chemical, historical, and regulatory—that provide citations of the scientific literature. In addition, the reference lists of some review and research articles, books, and reports were examined for potentially relevant articles.

The specific search terms used by the committee directly parallel the target COIs defined above, but they were also purposely broad so as to be exhaustive in terms of identifying all relevant literature. The search strategy included the chemical names, synonyms, and CAS numbers of the specific COIs—2,4-D, 2,4,5-T, TCDD, cacodylic acid, and picloram (see Figure 2-2 for chemical structures and CAS numbers)—and the more generic terms involved with this project: Vietnam veteran, Agent Orange, aryl hydrocarbon receptor, dioxin, herbicide, and phenoxy. Results on other specific phenoxy herbicides are also of interest: 2-methyl-4-chlorophenoxyacetic acid (MCPA) and 2-(2-methyl-4-chlorophenoxy) propionic acid (MCPP or Mecoprop) are structurally similar to 2,4-D, while 2-(2,4,5-trichlorophenoxy) propionic acid (2,4,5-TP or Silvex) have structures analogous to 2,4,5-T (see Figure 2-2). Although the benzoate herbicide dicamba (2-methoxy-3,6-dichlorobenzoic acid) is not always categorized with the phenoxy herbicides, it has structural similarities with this class, and measures of its association with various adverse health outcomes have been factored into the evidence.

Because some PCBs and polychlorodibenzofurans (PCDFs) have dioxin-like biologic activity, studies of populations exposed to PCBs or PCDFs were reviewed when the results were presented in terms of toxic equivalents (TEQs). Findings related only to exposure to the diverse chemical families of pesticides were considered too nonspecific for inclusion in the evidence database that was used to draw conclusions about associations. (An ancillary analysis conducted during the preparation of *Update 2008* determined that the term "pesticide" did not identify any relevant citations that were not picked up by more specific terms, so it was eliminated from the searches conducted since this reduced considerably the number of extraneous hits to be culled.)

Processing of Identified Publications

The search strategy was devised to ensure that abstracts of all potentially relevant articles were subjected to closer screening, but it also resulted in the identification of a large number of nonrelevant studies. The searches produced in excess of 7,600 "hits," including some studies that were identified more than once. It was evident from the abstracts of most of the cited articles that they did not address health effects in association with exposure to the COIs; for example, many of the cited studies investigated the efficacy of herbicides in killing weeds. All studies that discussed health effects were considered if the search-related information (title, abstract, and keywords) indicated that any of the herbicides of interest (or any of their components) may have been investigated. For each of

the more than 800 potentially relevant citations ultimately identified, a copy of the entire article was obtained online and reviewed more thoroughly by the committee for determination of whether it should be included in the report. For the present update, very few documents of interest had to be retrieved as hard copies from library sources.

In large part, the included reports are peer-reviewed journal articles, but generally available and formally published government studies (particularly those investigating health effects in Vietnam veterans) are also included under the assumption that they have been carefully reviewed. In practice, the articles are generally in English, but VAO committees have obtained translations for crucial ones that were not in English, as in the case of reports of a study of Korean veterans of the Vietnam War (Kim HA et al., 2003; Kim JS et al., 2003) when *Update 2004* was produced.

TCDD, the 2,3,7,8-chlorinated congener of dioxin, is the most potent of the polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans, and biphenyls, so it is presumed to be the most problematic of the dioxin-like chemicals contaminating the phenoxy herbicides used in Vietnam. However, our concern is not limited to that congener. In non-laboratory settings—for example, in epidemiologic studies—exposures occur not only to TCDD but also to mixtures of dioxins, dibenzofurans, and PCBs, which vary in their degree of chlorination. The concept of toxic equivalency has been developed primarily to permit an overarching estimation of oral exposure and risk from environmentally persistent chemicals that have structural similarities to PCDDs and PCDFs that bind the AHR, induce the same spectrum of effects, and bioaccumulate in the food chain (van den Berg et al., 2006). A toxicity equivalency factor (TEF) is an estimate of the dioxin-like potency of an individual congener relative to the toxicity of TCDD. TEQs are often used to estimate the cumulative toxic potency of mixtures as the sum of TEFs weighted by the concentrations of the corresponding congeners in the mixture; this total is denoted as the mixture's TEQ in terms of dioxin-like activity. That approach is often taken in epidemiologic studies that focus on PCBs. Many epidemiologic studies of PCBs have been recovered in VAO literature searches although they were not specifically sought. Because dioxin-like and non–dioxin-like PCB congeners are found together in environmental mixtures and are known to mediate toxicity by various mechanisms, the relative contribution of dioxin-like PCBs to an individual health outcome can be difficult to determine. Therefore, evidence from epidemiologic studies of PCB exposure has been retained only for results that concerned specific dioxin-like congeners or that were reported in terms of TEQs. Although all studies reporting TEQs based on PCBs were reviewed, those studies that reported TEQs based only on mono-ortho PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given very limited consideration because mono-ortho PCBs typically contribute less than 10 percent of the total TEQs, based on the World Health Organization's revised TEFs of 2005 (La Rocca et al., 2008; van den Berg et al., 2006).

The committee for *Update 2008* investigated what pesticides are used in greenhouses and determined that greenhouse workers are not likely to be exposed to herbicides, particularly those of interest for VAO committee deliberations (Czarnota, 2004; Neal, 2006; University of Connecticut, 2006). Results on such populations (Abell et al., 2000, on fertility; Hansen et al., 1992, on cancers in female workers) were retroactively excluded from the evidence database considered in *Update 2008*, and no new citations of studies of such workers have been retained. Further consultation (email in Public Access File, November 12, 2012) with Helle Raun Andersen, an Associate Professor at the University of Southern Denmark and a researcher on a series of epidemiologic studies of reproductive effects among greenhouse workers, confirmed for the current committee the lack of herbicide exposure among such workers.

Integration of New Information

More than 70 articles on epidemiologic studies and several dozen toxicology studies contributed new information to the present update. New evidence on each health outcome was reviewed in detail. The committee's conclusions, however, are based on the accumulated evidence, not just on recently published studies. In a considerable number of instances over the course of the VAO reports, single study populations have generated multiple entries for a given health outcome. Before *Update 2010*, the procedure had been to enter new results into the summary results tables in groups corresponding to the VAO update in which the study first appeared, so it has been difficult to recognize which findings are based on the experience of the same set of people.

The current committee has continued the revisions begun by the committee for *Update 2010* in organizing the tables of cumulative results on health outcomes in such a way as to make the interrelationships more evident for its own deliberations and for the reader. For example, as part of its effort to achieve an integrated picture of how a health outcome is manifested in a given study population, the committee chose to move the citations to the far right of the findings so as to put less emphasis on individual publications. The reported findings on a given condition from a particular study population have been gathered and presented in reverse chronologic order so that the most mature set of statistics appears first. In many instances, that will also represent the most informative set of data—the set that has the greatest power to demonstrate an adverse effect in the population in question. For some health problems, particularly those common in old age, the toxic effect associated with an external factor may be to cause a disease to manifest sooner. In such situations, the evidence of an association with an exposure may consist of a wave of diagnoses in younger people, and the prevalence will equalize with that in the control group as the populations age. The committee therefore decided that it could not retain only the most recent findings when considering the experience of a given study population.

The cohorts themselves have been ordered in the tables to reflect the overarching cohorts of which they are subgroups. The exposure of interest in each cohort is explicitly noted in the tables in order to facilitate judgments about when consistency might be expected among populations that experience the same exposure. This should minimize misapprehensions that there are inconsistencies if two excellent studies of groups exposed to different COIs have incongruent findings.

Primary findings, otherwise known as primary data analyses, are the specific type of evidence that the committee endeavors to integrate in drawing its conclusions. Reanalyses (without the incorporation of additional information), pooled analyses, reviews, and so on, may be discussed in conjunction with primary results or in synthesis sections on a given health outcome, but they are not themselves part of the evidence dataset. Nonetheless, well-conducted meta-analyses and literature syntheses can be informative to committee members in providing a broad framework in which to evaluate individual studies among a large body of literature.

CATEGORIZATION OF TYPES OF EVIDENCE

This section describes the manner in which the vast literature reviewed over many years has been categorized. With such a substantial literature base to review, a general categorization scheme was important for considering the relative contribution of individual studies. The committee's general approach to the evaluation of scientific evidence corresponds closely to the approach developed by the original *VAO* committee as delineated in detail in Chapter 5 of *VAO*. The committee had three specific tasks: to determine whether there is a statistical association between exposure to the herbicides used in Vietnam and health outcomes, to determine the increase in risk of effects among Vietnam veterans, and to determine whether plausible biologic mechanisms provide support for a causal relationship with a given health outcome. Scientifically relevant associations between exposures to the COIs and specific health outcomes are determined through an analysis of available epidemiologic studies that is informed by an understanding of the toxicology of the chemicals and their exposure pathways.

In general, human studies conducted among Vietnam veterans were considered to be of greatest relevance to the committee's charge. However, in many such studies, the characterization of exposure to the COIs was imprecise and was better characterized in human studies conducted among non-veterans, such as within occupational and environmental cohorts. Thus, in examining the literature in totality, there was continuous assessment of the specificity of the target population of interest (Vietnam veterans) as well as the specificity of the measurement of COIs. Animal and mechanistic studies were also considered as potentially relevant, but were reviewed in the context of biological plausibility, rather than as direct evidence for or against a statistical association between the COIs and health outcomes among Vietnam veterans. Similarly, in reaching their conclusions,

VAO committees consider the nature of the exposures, the nature of the health outcomes, the populations exposed, and the quality of the evidence examined.

Human Studies Among Vietnam Veterans

The committee reviewed all available published studies of Vietnam veterans, who are all presumed to have been exposed to the COIs as a result of military service in Vietnam. Because studies of Vietnam veterans address the very population of concern to the legislation that mandated the present review, any demonstrations of increased incidence of particular health outcomes among them are of unquestionable pertinence in drawing conclusions.

It is difficult to quantify risk when exposures of a population have not been accurately measured. Relatively recent serum TCDD concentrations are available only for subgroups enrolled in the Air Force Health Study (AFHS) (the Ranch Hand veterans and Southeast Asia comparison subjects) and from VA's study of deployed and non-deployed members of the Army Chemical Corps. Pharmacokinetic models, with their own set of assumptions, must be applied in order to extrapolate from contemporary readings and obtain presumably accurate estimates of original exposure of Vietnam-era veterans. The absence of reliable measures of Vietnam veterans' exposure to the COIs limits the committee's ability to quantify the risks of specific diseases in this population.

Although serum TCDD measurements are available in only a small portion of Vietnam-era veterans, the observed distributions of these most reliable measures of exposure make it clear that they cannot be used as a standard for partitioning veterans into discrete exposure groups, such as service on Vietnamese soil, service in the Blue Water Navy, and service elsewhere in Southeast Asia. For example, many TCDD values observed in the comparison group from the AFHS exceeded US background concentrations and overlapped considerably with those of the Ranch Hand subjects.

As explained in Chapter 1, the committee for *Update 2006* decided to make a general statement about its continuing inability to precisely determine exposure to the COIs quantitatively, rather than to reiterate a disclaimer in the concluding section for every health outcome, and the present committee has retained that approach.

Human Studies Among Non-Veterans

The committee reviewed studies among non-veteran populations that might have been exposed to the COIs. These other populations that factored into the committee's evaluation included cohorts of workers in chemical production and agriculture as well as populations residing near sites of environmental contamination. The committee believes that studies of such non-veteran subjects can help in the assessment of whether the COIs are associated with particular

health outcomes. As noted above in describing the literature search, studies of non-veteran subjects were identified because one of the COIs was specified by the original researchers as presenting a possible toxic exposure rather than on the basis of occupational definitions. Some of the studies provide stronger evidence about health outcomes than do studies of veterans because the exposures were measured sooner after occurrence and were more thoroughly characterized than has been the case in most studies of veterans. Furthermore, in the studies of workers in chemical-production plants, the magnitude and duration of exposure to the chemicals were generally greater, so the likelihood that any possible health consequence would be manifested was greater. The studies were often large enough to examine health risks among groups of people that had different levels of exposure, so dose–response relationships could be investigated. The general practice of VAO committees in determining the strength and validity of findings has been to evaluate all studies, whether or not their subjects were Vietnam veterans, according to the same criteria.

Animal and Mechanistic Studies

Animal models used as surrogates for the study of a human disease must reproduce, with some degree of fidelity, the manifestations of the disease in humans. However, a given effect of an exposure in an animal species does not necessarily establish its occurrence in humans, nor does an apparent absence of a particular effect in animals mean that the effect could not occur in humans. In addition to possible species differences, many factors affect the ability to extrapolate results from animal studies to health effects in humans. For example, animals used in experimental studies are most often exposed to purified chemicals, not to mixtures. Even if herbicide formulations or mixtures are used, the conditions of exposure might not realistically reproduce the human exposures that occur in the field. Furthermore, Vietnam veterans were exposed to other agents—such as tobacco smoke, insecticides, therapeutics, drugs, diesel fumes, and alcohol—that may increase or decrease the ability of chemicals in herbicides to produce a particular adverse health outcome. Few, if any, studies either in humans or in experimental animals have examined those interactions. Thus, the results from animal studies are principally useful for evaluating biologic plausibility.

As discussed in Chapter 4, TCDD is thought to be responsible for many of the toxic effects of the herbicides used in Vietnam. Attempts to establish correlations between the effects of TCDD on experimental systems and their effects on humans are particularly difficult because there are well-known species-, sex-, and outcome-specific differences in susceptibility to TCDD toxicity. Some data indicate that humans might be more resistant than other species to TCDD's toxic effects (Ema et al., 1994; Moriguchi et al., 2003); other data suggest that, for some outcomes, human sensitivity could be the same as or greater than that of some experimental animals (DeVito et al., 1995). Differences in vulnerability

may also be affected by variations in the rate at which TCDD is eliminated from the body. (See Chapter 4 for details on the toxicokinetics of TCDD.) Although degree of susceptibility is generally thought to be an inherent biological response, it can be influenced by life stage, past history, co-exposures, etc.

It is important to account for TCDD's mode of action in considering species and strain differences. There is a consensus that most of the toxic effects of TCDD involve interaction with the AHR, a protein that binds TCDD and some other aromatic hydrocarbons with high affinity, although it is now recognized that the AHR performs actions other than just those of a transcriptional enhancer, such as having a role in rapid signal transduction. The formation of an active complex that involves the intracellular receptor, the ligand (the TCDD molecule), and other proteins is followed by an interaction of the activated complex with specific sites on DNA. This specific interaction can alter the expression of genes involved in the regulation of cellular processes.

The development of mice that lack the AHR has helped to establish a definitive association between the AHR and TCDD-mediated toxicity. The affinity of TCDD for the AHR is species- and strain-specific, and responses to the binding of the receptor vary among cell types and developmental stages. In addition, genetically based differences in the properties of the AHR are known to exist in human populations (Zhou et al., 2009), as they are in laboratory animals, so there are genetically based differences in people's responses to TCDD, leading to some people having an intrinsically greater risk of toxic effects from TCDD exposure and others having less risk.

Although studying AHR biology in transformed human cell lines minimizes the inherent error associated with species extrapolations, caution must be exercised because it is still not clear to what extent toxicity is affected by the transformation itself or by the conditions under which cell lines are cultured in vitro. Furthermore, humans have AHR with differing affinities for dioxin, so a single transformed human cell line will not accurately reflect the spectrum of responses observed in the entire human population.

DEFINE THE EVALUATION APPROACH

This section describes the manner in which the committee reviewed all of the evidence it compiled and synthesized in rendering its conclusions on the relationships between the COIs and health outcomes among Vietnam veterans. This includes the overarching evaluation principles that the committee employed and the role of judgment, the use of statistical association as the primary evaluation metric, and the methodological factors that were considered, such as multiple publications on the same study cohort, plausible biological mechanisms, and publication bias.

Define Overarching Evaluation Principles

The VAO committees began their evaluation by assuming neither the presence nor the absence of an association between exposure and any particular health outcome. Over the series of reviews, the committee accrued evidence of various degrees of association, lack of association, or persistent indeterminacy concerning a wide array of disease states. However, for many conditions, particularly uncommon ones, associations with the COIs have remained unaddressed in the medical research literature; for these, the committee remains neutral, understanding that "absence of evidence is not evidence of absence."

An issue related to evidence evaluation that was of concern for the *Update 2006* committee was the evidence category of "*no* association." That committee determined that a conclusion of *no* association would require substantive evidence of such a lack of effect for all of the COIs. Given the paucity of available information on cacodylic acid and picloram, either positive or negative for virtually all health outcomes, such a conclusion would seem suspect even if substantial evidence uniformly supported a finding of *no* association both with exposure to the phenoxy herbicides and with exposure to TCDD. Later committees have concurred in that determination and adopted a similar approach to the placement of health outcomes in this category.

When all the available epidemiologic evidence has been evaluated, it is presumed that Vietnam veterans are at increased risk for a specific health outcome if there is evidence of a positive association between one or more of the COIs and the outcome. The best measure of potency for the quantification of risk to veterans would be the rate of the outcome in exposed Vietnam veterans compared with the rate in non-exposed veterans, adjusted for the degree to which any other factors that differ between exposed and non-exposed veterans might influence those rates. Conley and Heerwig (2012) have noted, however, that selection of service members for deployment itself may introduce elements of bias due to consideration of additional factors and application of even more stringent criteria than necessary for enlistment, which translate into the deployed being somewhat healthier than or in some other way differing from those not selected. In any event, in the absence of actual measures of exposure, VAO committees have regarded comparisons between deployed and non-deployed Vietnam-era veterans as most relevant for their purposes. A dose–response relationship established in another human population that was suitably adjusted for such factors would be similarly suitable.

The committee concluded that it would be inappropriate to use certain quantitative techniques, such as meta-analysis, to combine individual study results into a single summary measure of statistical association. The committee reached that conclusion because of the many differences among studies in their definitions of exposure, health outcomes considered, criteria for defining study populations, corrections for confounding factors, and degree of detail in reporting the results. An appropriate use of meta-analysis requires more methodologic consistency

among studies, especially in the definition of exposure, than is present in the literature that the committee reviewed (Egger et al., 2002; Petitti, 2000). A detailed discussion of the results of individual studies in appropriate categories (Vietnam-veteran, occupational, or environmental exposure; and exposure to Agent Orange or equivalent dioxin-contaminated phenoxy herbicides, to dioxin, to phenoxy herbicides without dioxin contamination, to cacodylic acid, or to picloram) with a thorough examination of each study's strengths and weaknesses is fully informative without making unfounded assumptions of homogeneity.

Role of Judgment

This committee's process for reaching conclusions about statistical associations involved more than a formulaic application of quantitative procedures to the assembled evidence. First, the committee had to assess the relevance and validity of individual reports. Then, it had to evaluate the possible influences of measurement error, selection bias, confounding, and chance on the reported results. Next, the committee integrated all the evidence within and among diverse fields of research. Finally, the committee based its conclusions on consensus reached within the committee. These aspects of the committee's review required thoughtful consideration of alternative approaches at several points and could not be accomplished by adherence to a narrowly prescribed formula.

The realized approach, as described here, has been determined to a large extent by the nature of the exposures, of the health outcomes, and of the resulting evidence available for examination; for that reason, it has evolved during the course of the work of this and previous VAO committees. The quantitative and qualitative procedures underlying the present review have been made as explicit as possible, but ultimately the conclusions about association expressed in this report are based on the committee's collective judgment. The committee has endeavored to express its judgments as clearly and precisely as the data allow.

In delivering the charge to the committee for *Update 2010*, VA's representative requested that for health outcomes found to have some evidence supporting statistical association, the committee delineate how well each of the factors that make up the so-called Bradford Hill criteria for causality (Hill, 1965) had been satisfied. It was thought that having a scientific perspective on the extent to which those factors, in addition to biologic plausibility, were met would facilitate the Secretary of Veterans Affairs in making a policy decision concerning the presumptive relationship of any new health outcome to exposure to the herbicides used by the military in Vietnam.

The committee for *Update 2010* was uniformly and strongly of the opinion that the execution of a checklist of the Hill criteria would not be an appropriate approach for fulfilling its charge, and the current committee is in complete agreement with the decision of that committee, as was the committee for *Update 2012*. The list of issues that Hill discussed is not a definitive set of factors to

be addressed in evaluating whether a collection of evidence supports causality. The nine aspects of a statistical association noted by Hill (1965) to contribute to a finding of causality—strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment, and analogy—vary in the importance that might be assigned to them, but none is sufficient by itself, and only temporality (that the cause precedes the effect) is necessary. Philosophers of science have established that a set of sufficient criteria for causality does not exist (Rothman and Greenland, 1998). Citing Weed and Gorelick (1996) and Holman et al. (2001), Rothman et al. (2008) noted that "epidemiologists have *not* agreed on a set of causal criteria or on how to apply them [emphasis in original]. . . . The typical use of causal criteria is to make a case for a position for or against causality that has been arrived at by other, unstated means." The establishment of causality is not an absolute or discrete (or necessarily permanent) state. The Hill criteria have often been used as a point of reference in addressing the subject of causation in evaluating possible environmental harms, but even in theoretical and optimal circumstances scientists have not derived a definitive algorithm for establishing causality. The extent to which a relationship is judged to be causal entails many subjective elements involving the universe of information considered and the weight accorded to each evidentiary component considered. Furthermore, with regard to chronic diseases, causality is rarely limited to a single factor.

For those reasons, the committee for *Update 2010* did not adopt the suggestion to perform what in effect would be a checklist approach to distilling the evidence concerning underlying causality for any observed statistical association between a human health effect and exposure to the components of the herbicides sprayed in Vietnam. The current committee also interprets its charge to be to summarize the scientific evidence for consideration by the Secretary, whose role is to make the policy decision of whether a contribution of herbicide exposure to the occurrence of an adverse health effect is likely enough to merit recognition as a presumptive condition.

Define Primary Metric (Statistical Association)

The primary metric used by the committee in synthesizing all its evidence and rendering its conclusions on the potential health effects of the COIs among Vietnam veterans is statistical association. The issues that arise in determining whether a valid statistical association exists are detailed in Chapter 5 of *VAO*. Since the work of that first committee, the primary relevant evidence for consideration has come from epidemiologic studies—investigations in which large groups of people are studied to identify an association between exposure to a COI and the occurrence of particular health outcomes. Subsequent committees have not modified the criteria set by the original *VAO* committee, but the committee for *Update 2012* added the clarification that the object of its evaluation was to be "scientifically relevant association" in order to clarify that the strength

of evidence evaluated, based on the quality of the scientific studies reviewed, was a fundamental component of the committee's deliberations to address the imprecisely defined legislative target of "statistical association."

Epidemiologists estimate associations between exposure and outcome in a specific population or group in terms of relative risk by using such measures as a standardized mortality ratio, odds ratio, rate ratio, or hazard ratio. Those measures indicate the magnitude of a difference in the rate of an outcome between two populations. For example, if the rate in an exposed population is twice the rate in a non-exposed population, then the relative risk is 2. Similarly, if the odds of a health outcome are 1:20 in an exposed population but 1:100 in a non-exposed population, the odds ratio is 5. In this report, both *relative risk* (also called *risk ratio*) and *odds ratio* are used to represent the association between exposure and adverse outcome. Both measures are often reported in prospective cohort studies. Case-control studies usually report odds ratios and cannot report relative risk because the sampling fraction of the population that is represented by the control group is usually not available in these studies. However, it is possible for case-control studies to provide unbiased estimates of relative risk. For rare diseases with low rates in both the exposed group and the control group, odds are approximately identical with the risk, so an odds ratio is approximately identical with a relative risk. That is,

$$odds = risk/(1 - risk),$$

so that when *risk* is close to zero, $(1 - risk)$ is close to 1, and therefore, *odds* will be close to *risk*. An estimated relative risk or odds ratio greater than 1 indicates a positive association; in this case, it is more likely that the outcome will be seen in exposed people than in non-exposed people. A relative risk or odds ratio between zero and 1 indicates a negative or inverse association; the outcome is less likely in exposed people. A relative risk or odds ratio of 1 suggests the absence of association, which is usually the null hypothesis to be tested. A statistically significant association is one that would be unlikely to occur by chance—that is, if the null hypothesis is true. (Chapters 7–13 contain tables of results abstracted from the studies that provide evidence on individual health outcomes. Because the distinction between *risk* and *odds* is of little consequence in the deliberations of VAO committees, the column labeled "Estimated Risk" presents findings without specifying the precise nature of the reported statistic.)

Determining whether an estimated association between an exposure and an outcome represents a real relationship requires careful scrutiny because there can be more than one explanation for an estimate. *Bias* is a distortion of the measure of association that results from flawed selection in the assembly of the study population or from an error in the measurement of studied characteristics. *Confounding* is a distortion of the measure of association that can arise from factors related both to exposure and to outcome; awareness of this possibility permits

collection of the ancillary data that could permit statistical adjustment to reduce the problem or to take such an influence into account when evaluating the import of data that have already been collected and analyzed. *Chance* is the degree to which an estimated association might vary randomly among different samples of the population studied. The width of a *confidence interval* is used to quantify the likely statistical variability of an exposure–disease association, but it does not incorporate the quantification of distortions that may arise from the systematic problems mentioned above. Even when a relative risk or standardized mortality ratio substantially exceeds a value of 1, a conclusion regarding increased risk must be qualified when the confidence interval is wide. In drawing conclusions, the committee examined the most thoroughly adjusted quantitative estimates of association, judged whether an adjustment for any crucial confounders was lacking, and evaluated the potential influences of bias and chance. In integrating the findings of various studies, the committee considered the degree of statistical significance associated with every estimated risk (a reflection of the magnitude of the observed effect and the power of the study designs) and took note of whether dose–response relationships were evident with increasing exposure rather than simply tallying the "significant" and "nonsignificant" outcomes as dichotomous items of evidence. The committee also considered whether controlled laboratory investigations provide information consistent with the chemicals of interest being associated with a given effect and perhaps causally linked to it.

In pursuing the question of statistical association, the committee recognized that an absolute conclusion about the absence of association is unattainable. As in science generally, studies of the health effects associated with herbicide exposure cannot demonstrate that a purported effect is impossible or could never occur, but only that it is statistically improbable. Any instrument of observation, even an excellent epidemiologic study, is limited in its resolving power. In a strict technical sense, therefore, the absence of an association between even one chemical and a health outcome cannot be proved. Convincingly demonstrating the lack of a particular effect of all five of the COIs simultaneously would be a daunting effort, especially in light of the paucity of information concerning picloram and cacodylic acid. The present committee therefore endorses the decision by the committee for *Update 2006* to reclassify several types of cancer that had been classified since *VAO* (1994) as having "suggestive evidence of *no* association" with "exposure to herbicides" into this default category of inadequate or insufficient evidence for any conclusion about association to be drawn for a specific health outcome.

Define Factors to Consider in Weighing the Evidence

Totality of Evidence and Multiple Publications

VAO committees wanted to be clear in indicating what evidence is factored into their conclusions. The practice in the VAO reports has been to augment the

results table for a given health outcome with any additional publications considered in the current update in the categories of Vietnam-veteran, occupational, or environmental studies. The inclusion of sequential sets of results from follow-ups of a study population has the potential to create the appearance of a greater weight of evidence than is warranted, so *Update 2006* and *Update 2008* used italicized citations in results tables to indicate that results had been superseded. The committee for *Update 2010* did not want to convey the notion that earlier findings were of no importance. In an effort to compile a comprehensive and comprehensible picture of the history of each study population, the committee for *Update 2010* decided to abandon the sequential entries by update that had been used in the results tables since *Update 1996*. The format adopted in *Update 2010* for the results tables was a refinement of the cohort-based approach that had been introduced in *Update 2006* for cardiovascular diseases. To make it easier for the reader to locate the discussion of the characteristics of particular study populations and the attributes of the publications based on them, the order of studies in the results tables corresponds to their presentation in Chapter 6. The main categorization of veteran, occupational, and environmental cohort studies and case-control studies has been retained in both instances. In an effort to provide a coherent picture of the occurrence over time of a specific health outcome in a given study population, the current committee has shifted its emphasis away from individual publications by moving the citation that was the source of a particular finding to the rightmost column in the results tables.

Plausible Biologic Mechanisms

Chapter 4, "Information Related to Biologic Plausibility," previously called "Toxicology," details the experimental basis of the assessment of biologic plausibility or the extent to which an observed statistical association in epidemiologic studies is consistent with other biologic or medical knowledge. Does the observation of a particular health effect make sense on the basis of what is known about how the chemicals in question act at the tissue, cellular, or molecular level? The relationship between a particular exposure and a specific human health outcome is addressed in the context of research on the effects of the chemicals on biologic systems and of evidence from animal studies.

Chapter 4 presents an integrated toxicity profile of each of the COIs without providing detailed commentary on each possibly relevant toxicology article published in the update period. Experimental information pertinent to a particular health outcome is now presented immediately after the epidemiologic evidence on that outcome in the "Biologic Plausibility" sections on individual health outcomes (see Chapters 7–13).

A positive statistical association between an exposure and an outcome does not necessarily mean that the exposure is the cause of that outcome. Data from toxicology studies may support or conflict with a hypothesis that a specific

chemical can contribute to the occurrence of a particular disease. Many toxicology studies are conducted with laboratory animals so that variables, including the amount and duration of exposure, can be controlled precisely. Studies that use isolated cells in culture also can elucidate how a chemical alters cellular processes. The objectives of those toxicology studies are to determine what toxic effects are observed at different exposure levels and to identify the mechanisms by which the effects are produced. Ultimately, the results of the toxicology studies should be consistent with what is known about the human disease process if they are to support a conclusion that the development of the disease was influenced by an exposure.

Animal studies and in vitro studies with human cells and cell lines provide links that are important for understanding the underlying biochemical mechanisms associated with toxicity induced by xenobiotics (exogenous chemicals). In some cases, however, toxic effects that are not detected in humans are observed in animal studies. Many factors may contribute to differences between the results of controlled animal studies and the effects observed in humans. The following are among the most important:

- **Physiologic differences.** Laboratory animals are not miniature humans. Depending on the biologic process under investigation, a particular test species may match the human system more closely and so be a better experimental model.
- **Magnitude of exposure.** As is often the case for toxicologic studies of any chemical, TCDD exposure used for animal studies has been many orders of magnitude higher than Vietnam veterans are likely to have received during military service, although the ultimate body burdens may not be as divergent.
- **Duration of exposure.** Although TCDD is a persistent organic pollutant, animal studies seldom examine the chronic low-level exposure that occurs over a period of years or even many months.
- **Timing of exposure.** It is well known that many organ systems are highly susceptible to xenobiotic exposure during critical stages of development, such as gestation; the response of some systems (such as the immune system) may also depend on the timing of the exposure to antigens relative to the timing of the exposure to xenobiotics such as TCDD.
- **The route of exposure.** The route of exposure by which an exogenous agent enters an organism may influence the nature of any toxic response elicited. The outcomes of animal studies may be perturbed by the delivery of treatment doses by "unnatural" routes of exposure such as a bolus by gavage or intraperitoneal injection, but the route of exposure does not seem to be a major reason that the results of epidemiology studies may not agree with the findings of controlled studies for the COIs considered in the VAO series.

- **Genetic constitution and expression.** The etiologies of most diseases in humans and in animals are likely to be influenced by numerous genes and to involve complex gene–environment interactions, and preliminary evidence suggests that TCDD can induce epigenetic modifications of an organism's DNA that may alter future expression of the genome.
- **Sex differences.** There are well-known differences between male and female animals (including humans) in susceptibility to xenobiotic exposures, some of which are modified by sex steroids.
- **Prior and recurring exposures to multiple sources.** Humans are exposed to xenobiotics from multiple sources throughout their lifetimes.
- **Complex mixtures.** Most xenobiotic exposures occur in complex mixtures; the makeup of these mixtures can heavily influence the ultimate toxic effects. In addition to the dietary modulation of responses to other exposures of both humans and animals, human metabolism is perturbed by dietary supplements, prescription and over-the-counter pharmaceuticals, and other factors (such as cigarette smoking and ambient pollution).
- **Stress.** Stress—of known or unknown origin—is a well-known modifier of human disease responses (such as immune responses); stress is an ever-present variable that is difficult to assess or control for in epidemiologic studies because there is substantial individual variation in response to it (Cohen et al., 2007a).

The absence of evidence of biologic plausibility from toxicology studies does not rule out the possibility of a biologic relationship. In fact, cases in which the epidemiologic evidence is strong, but toxicologic support is lacking, often drive new toxicology research. As noted in *VAO*, not only is information on biologic plausibility one of the primary elements in the oft-cited list of factors that have rather imprecisely become known as the Bradford Hill (1965) criteria for causality (previously discussed), but also insights about biologic processes inform whether an observed pattern of statistical association might be interpreted as the product of more than error, bias, confounding, and chance. The committee used toxicologic information in that fashion and placed the information before its synthesis and conclusion in order to provide readers with a more coherent argument for its ultimate conclusion about the adequacy of the available evidence to support the existence of a particular association.

Publication Bias

Depending on the results that have been obtained, some studies are more likely to be published than others. That is the concept of "publication bias," which has been documented in biomedical research (Song et al., 2000; Stern and Simes, 1997). Most commonly, bias can be introduced when studies whose hypotheses are supported by statistically significant results or that are otherwise deemed

favorable by their authors are selectively submitted for publication. In addition, papers with "interesting findings" may be of more interest to journal editors and reviewers and thus be more likely to be accepted for publication after submission. Conversely, "negative" studies, in which the hypotheses being tested are not supported by the study findings, often go unpublished. Investigators employed by industry may be inhibited from submitting findings that have potential legal or economic ramifications.

Thus, conclusions about the associations between exposure and outcome that are based solely on published results could be subject to bias. Despite that, the committee does not believe that its conclusions have been unduly affected by publication bias, for two reasons: The extensive publicity surrounding the possibility of health effects associated with the herbicides used in Vietnam has created considerable pressure to publish all findings on the subject, and the many published studies assembled and reviewed contain among their results the full range of possible statistical associations, from convincingly negative through indeterminate to strongly positive.

3

Exposure to the Herbicides Used in Vietnam

The assessment of human exposure continues to be a key element in addressing two of the charges that guide the work of this committee. This chapter first presents background information on the military use of herbicides in Vietnam from 1961 to 1971 with a review of our knowledge about the exposures of those who served in Vietnam and of the Vietnamese population to the herbicides and to the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, which is referred to in this report as TCDD (and commonly referred to as dioxin) and is the most toxic congener of the tetrachlorodibenzo-*p*-dioxins. Two modeling approaches to estimating exposure of ground troops to herbicides are presented. The fact that they lead to quite different conclusions demonstrates the difficulties of assessing exposure in the complex environment that characterized Vietnam during the period of interest. The application of one of these models in an epidemiologic context is discussed in considerable detail. The chapter concludes by reviewing several key methodologic issues in human population studies: disease latency, possible misclassification based on exposure, and the exposure specificity required for the scientific evaluation of study results.

The exposure of human populations can be assessed in a number of ways, including the use of historical information, questionnaires and interviews, measurements in environmental media, and measurements in biologic specimens. Researchers often rely on a mixture of qualitative and quantitative information to derive such estimates (Armstrong et al., 1994; Checkoway et al., 2004). The most basic approach compares members of a presumably exposed group with the general population or with a nonexposed group; this method of classification offers simplicity and ease of interpretation. A more refined method assigns each study subject to an exposure category—such as high, medium, or low exposure—and

calculates the disease risk for each group separately and then compares that with the risk for a reference or non-exposed group; this method can identify the presence or absence of an exposure–response trend. In some cases, more detailed information is available for quantitative exposure estimates that can be used to construct what are sometimes called exposure metrics. The metrics integrate quantitative estimates of exposure intensity (such as the chemical concentration in air or the extent of skin contact) with exposure duration to produce an estimate of cumulative exposure. Exposure can also be assessed by measuring chemicals and their metabolites in human tissues. Such biologic markers of exposure integrate absorption from all exposure routes, but their interpretation requires knowledge of pharmacokinetic processes. All of those exposure-assessment approaches have been used in studies of Vietnam veterans.

MILITARY USE OF HERBICIDES IN VIETNAM

The military use of herbicides in Vietnam took place from 1962 through 1971. Tests conducted in the United States and elsewhere that were designed to evaluate defoliation efficacy were used to select specific herbicides (IOM, 1994; Young and Newton, 2004). Four compounds were used in the herbicide formulations in Vietnam: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 4-amino-3,5,6-trichloropicolinic acid (picloram), and dimethylarsinic acid (DMA or cacodylic acid). The chemical structures of those compounds are presented in Chapter 2 (see Figure 2-1). These herbicides were used to defoliate inland hardwood forests, coastal mangrove forests, cultivated lands, and zones around military bases. A National Resource Council committee estimated the amount of herbicides sprayed from helicopters and other aircraft by using records gathered from August 1965 through February 1971 (NRC, 1974). That committee calculated that about 18 million gallons (about 69 million liters) of herbicide were sprayed over about 3.6 million acres (about 1.5 million hectares) in Vietnam during that period. The amount of herbicides sprayed on the ground to defoliate the perimeters of base camps and fire bases and the amount sprayed by Navy boats along river banks were not estimated.

A revised analysis of spray activities and of the exposure potential of troops emerged from a study overseen by a committee of the Institute of Medicine (IOM, 1997, 2003b,c). That work yielded new estimates of the amounts of military herbicides used in Vietnam from 1961 through 1971 (Stellman et al., 2003a). The investigators reanalyzed the original data sources that were used to develop herbicide-use estimates in the 1970s and identified errors that inappropriately removed spraying missions from the dataset. They also added new data on spraying missions that took place before 1965. Finally, a comparison of procurement records with spraying records found errors that suggested that additional spraying had taken place but had gone unrecorded at the time. The new analyses led to a revision of the estimates of the amounts of the agents applied, as indicated

TABLE 3-1 Military Use of Herbicides in Vietnam (1961–1971)

Code Name	Chemical Constituents[a]	Concentration of Active Ingredient[a]	Years Used[a]	Amount Sprayed	
				VAO Estimate[b]	Revised Estimate[a]
Pink	60% *n*-butyl ester, 40% isobutyl ester of 2,4,5-T	961–1,081 g/L acid equivalent	1961, 1965	464,817 L (122,792 gal)	50,312 L sprayed; 413,852 L additional on procurement records
Green	*n*-butyl ester of 2,4,5-T	—	1961, 1965	31,071 L (8,208 gal)	31,026 L on procurement records
Purple	50% *n*-butyl ester of 2,4-D, 30% *n*-butyl ester of 2,4,5-T, 20% isobutyl ester of 2,4,5-T	1,033 g/L acid equivalent	1962–1965	548,883 L (145,000 gal)	1,892,733 L
Orange	50% *n*-butyl ester of 2,4-D, 50% *n*-butyl ester of 2,4,5-T	1,033 g/L acid equivalent	1965–1970	42,629,013 L (11,261,429 gal)	45,677,937 L (could include Agent Orange II)
Orange II	50% *n*-butyl ester of 2,4-D, 50% isooctyl ester of 2,4,5-T	910 g/L acid equivalent	After 1968	—	Unknown; at least 3,591,000 L shipped
White	Acid weight basis: 21.2% triisopropanolamine salts of 2,4-D, 5.7% picloram	By acid weight, 240 g/L 2,4-D, 65 g/L picloram	1966–1971	19,860,108 L (5,246,502 gal)	20,556,525 L
Blue powder	Cacodylic acid (dimethylarsinic acid) sodium cacodylate	Acid, 65% active ingredient; salt, 70% active ingredient	1962–1964	—	25,650 L
Blue aqueous solution	21% sodium cacodylate + cacodylic acid to yield at least 26% total acid equivalent by weight	Acid weight, 360 g/L	1964–1971	4,255,952 L (1,124,307 gal)	4,715,731 L
Total, all formulations	—	—	—	67,789,844 L (17,908,238 gal)	76,954,766 L (including procured)

[a]Based on Stellman et al., 2003a.
[b]Based on data from MRI, 1967; NRC, 1974; Young and Reggiani, 1988.

in Table 3-1. The new research effort estimated that about 77 million liters were applied, about 9 million liters more than the previous estimate.

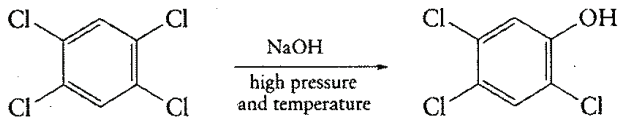
Herbicides were identified by the color of a band on 55-gallon shipping containers and were called Agent Pink, Agent Green, Agent Purple, Agent Orange, Agent White, and Agent Blue. Agent Green and Agent Pink were used in 1961 and 1965, and Agent Purple in 1962–1965. Agent Orange was used in 1965–1970, and a slightly different formulation (Agent Orange II) probably was used after 1968. Agent White was used in 1966–1971. Agent Blue was used in powder form in 1962–1964 and as a liquid in 1964–1971. Agent Pink, Agent Green, Agent Purple, Agent Orange, and Agent Orange II all contained 2,4,5-T and were contaminated to some extent with TCDD. Agent White contained 2,4-D and picloram. Agent Blue (powder and liquid) contained cacodylic acid. The chlorinated phenoxy acids 2,4-D and 2,4,5-T persist in soil for only a few weeks; picloram is much more stable, persisting in soil for years; and cacodylic acid is nonvolatile and stable in sunlight (NRC, 1974). More details on the herbicides used are presented in the initial IOM report, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*,[1] referred to as *VAO* (IOM, 1994).

TCDD IN HERBICIDES USED IN VIETNAM

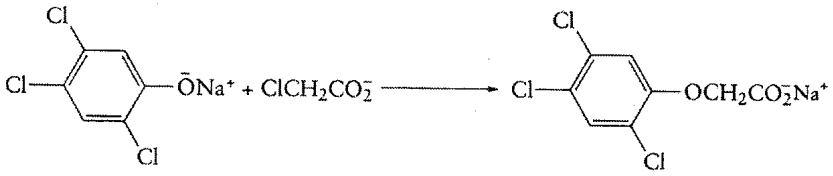
TCDD is formed during the manufacture of 2,4,5-T in the following manner: trichlorophenol (2,4,5-TCP), the precursor for its synthesis, is formed by the reaction of tetrachlorobenzene and sodium hydroxide (see Figure 3-1a); 2,4,5-T is formed when 2,4,5-TCP reacts with chloroacetic acid (see Figure 3-1b); small amounts of TCDD are formed as a byproduct of the intended main reaction (see Figure 3-1b) when a molecule of 2,4,5-TCP reacts with the tetrachlorobenzene stock (see Figure 3-1c) instead of with chloroacetic acid. In each step in the reaction, a chlorine atom is replaced with an oxygen atom, and this leads to the final TCDD molecule (NRC, 1974). In the class of compounds known as polychlorinated dibenzo-*p*-dioxins (PCDDs), 75 congeners can occur, depending on the number and placement of the chlorine atoms. Cochrane et al. (1982) noted that TCDD had been found in pre-1970 samples of 2,4,5-TCP. Other PCDDs—2,7-dichloro-dibenzo-*p*-dioxin and 1,3,6,8-tetrachloro-dibenzo-*p*-dioxin—were measured in the same samples. The concentration of TCDD in any given lot of 2,4,5-T depended on the manufacturing process (FAO/UNEP, 2009; Young et al., 1976).

The manufacture of 2,4-D is a different process: Its synthesis is based on dichlorophenol, a molecule formed from the reaction of phenol with chlorine

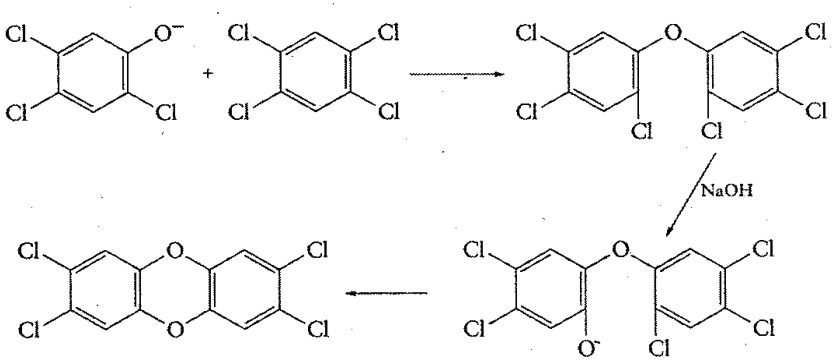
[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.



a. Trichlorophenol, the precursor for the synthesis of 2,4,5-T, is formed by the reaction of tetrachlorobenzene and sodium hydroxide (NaOH).



b. The herbicide 2,4,5-T is formed when a reactive form of trichlorophenol (2,4,5-trichlorophenoxide) reacts with chloroacetic acid.



c. TCDD is formed when a molecule of trichlorophenol reacts with its own precursor, tetrachlorobenzene. Two intermediate steps are shown in this diagram. At each step, an oxygen–carbon bond forms as a chlorine atom is released. This reaction does not occur in the synthesis of 2,4-D because precursors with adjacent chlorines are not used in its production.

FIGURE 3-1 TCDD formation during 2,4,5-T production.

(NZIC, 2009). Neither tetrachlorobenzene nor trichlorophenol is formed during this reaction, so TCDD is not normally a byproduct of the manufacturing process. However, other, less toxic PCDDs have been detected in pre-1970 commercial-grade 2,4-D (Cochrane et al., 1982; Rappe et al., 1978; Tosine, 1983). Cochrane et al. (1982) found multiple PCDDs in isooctyl ester, mixed butyl ester, and dimethylamine salt samples of 2,4-D. It has also been noted that a cross-contamination of 2,4-D with 2,3,7,8-TCDD occurred in the operations of at least one major manufacturer (Lilienfeld and Gallo, 1989).

TCDD concentrations in individual herbicide shipments were not recorded, but they were known to vary from batch to batch and between manufacturers. TCDD concentrations in stocks of Agent Orange remaining after the conflict, which either had been returned from South Vietnam or had been procured but not shipped, ranged from less than 0.05 ppm to almost 50 ppm and averaged 2–3 ppm in two sets of samples (NRC, 1974; Young et al., 1978). In 1974, domestic manufacturing standards for 2,4,5-T required that TCDD not be present at over 0.05 ppm (NRC, 1974).

Originally, data from Young and Gough were used to estimate the amount of TCDD in the various herbicide formulations (Gough, 1986; Young, 1992; Young et al., 1978). Young et al. (1978) estimated that Agent Green, Agent Pink, and Agent Purple—which all were used early in the program (through 1965)—contained 16 times the mean TCDD content of the Agent Orange formulations used in 1965–1970, which had mean TCDD concentrations estimated at 2 ppm. Gough (1986) estimated that about 167 kg of TCDD were sprayed in Vietnam from 1962 to 1970.

Later analysis by researchers at Columbia University benefited from access to military spray records that had not been available earlier, and it resulted in substantial revisions of the estimates (Stellman et al., 2003a). The investigators were able to incorporate newly found data on spraying in the early period of the war (1961–1965) and to document that larger volumes of TCDD-containing herbicides were used in Vietnam than had been estimated previously. They also found the earlier estimates of TCDD contamination in the herbicide formulations to be low, noting that the original estimates were based on samples whose concentrations were at the lower end of the distribution. The researchers concluded that the mean TCDD concentration in Agent Orange was closer to 13 ppm than to the earlier estimate of 3 ppm. They therefore proposed 366 kg of TCDD as a plausible estimate of the total amount of TCDD applied in Vietnam during 1961–1971.

EXPOSURE OF VIETNAM VETERANS

Determining the exposures of US military personnel who served in Vietnam has been perhaps the greatest challenge in the study of the health effects associated with herbicides and TCDD. Some military personnel stationed in cities or

on large bases may have received little or no herbicide exposure, whereas troops who moved through defoliated areas soon after treatment may have been exposed through soil contact, drinking water, or bathing. In most cases it is not possible to make reliable estimates of the magnitude and duration of such exposures because of the lack of contemporaneous chemical measurements, the lack of a full understanding of the movement and behavior of the defoliants in the environment, and the lack of records of individual behaviors and locations. Consequently, most studies have focused on populations that had well-defined tasks that brought them into contact with the agents. It is believed that the subjects of those studies, primarily Air Force personnel involved in fixed-wing aircraft spraying activities (often referred to as Operation Ranch Hand [ORH]) and members of the US Army Chemical Corps (ACC), may have had among the highest exposures. As described below, the exposures of ground troops are difficult to define, so this group has not been studied as intensively. As illustrated by Figure 1-1 in Chapter 1, the median TCDD levels in veterans who had worked in Operation Ranch Hand were higher than those measured in their own comparison group or in ground troops, which both had median levels in the unitary ppt range of contemporaneous background levels, but about an order of magnitude less than herbicide production workers, who in turn had levels about two orders of magnitude less than individuals who resided near the site of the industrial explosion in Seveso, Italy (Pirkle et al., 1995).

In accordance with Congress's mandated presumption of herbicide exposure of all Vietnam veterans, VAO committees have treated Vietnam-veteran status as a proxy for some herbicide exposure when more specific exposure information is not available.

Exposure of Herbicide Handlers

Military personnel who came into direct contact with the herbicidal chemicals through mixing, loading, spraying, and clean-up activities had relatively high exposures to them. The US Environmental Protection Agency refers to such personnel as pesticide handlers and provides special guidance for preventing or minimizing their exposure during those activities in its worker-protection standard for pesticides (EPA, 1992). The number of US military personnel who handled herbicides directly is not known precisely, but two groups have been identified as high-risk subpopulations among veterans: Air Force personnel involved in ORH and members of the ACC who used hand-operated equipment and helicopters to conduct smaller-scale operations, including defoliation around special-forces camps; clearing of the perimeters of airfields, depots, and other bases; and small-scale crop destruction (NRC, 1980; Thomas and Kang, 1990; Warren, 1968). Additional units and individuals handled or sprayed herbicides around bases or lines of communication; for example, Navy river patrols were reported to have used herbicides to clear inland waterways, and engineering personnel used

herbicides to remove underbrush and dense growth in constructing fire-support bases. The latter groups have not been the subject of epidemiologic studies. The herbicides used in Vietnam were not thought to present an important human health hazard at the time, so few precautions were taken to prevent the exposure of personnel (GAO, 1978, 1979); that is, military personnel did not typically use chemical-protective gloves, coveralls, or protective aprons, so substantial skin exposure almost certainly occurred in these populations in addition to exposure by inhalation and incidental ingestion (such as by hand-to-mouth contact).

The Air Force personnel who participated in ORH were the first Vietnam-veteran population to receive special attention with regard to herbicide exposure. In the Air Force Health Study (AFHS), job and work history, biomarkers, and the health outcomes of members of this Ranch Hand cohort were contrasted with Air Force personnel who had served elsewhere in Southeast Asia during the Vietnam era. The AFHS began in 1979 (IOM, 2006a). The exposure index that was initially proposed relied on military spray records for the TCDD-containing herbicides (Agent Orange, Agent Purple, Agent Pink, and Agent Green); these records also helped identify the members of the cohort. The subjects were further characterized by military occupation, and the exposure in the cohort and the comparison group was evaluated by measurements of TCDD in blood (serum) samples drawn in 1987 or later. A general increase in serum TCDD was detected in people whose jobs involved more frequent handling of herbicides, but there was no clear demarcation between the distributions of serum TCDD concentrations in the Ranch Hand subjects and those in the comparison group (AFHS, 1991a). Several methods for estimating the herbicide exposure of members of the cohort were developed on the basis of questionnaires, and they focused on such factors as the number of days of skin exposure, the percentage of skin area exposed, and the concentration of TCDD in the different herbicidal formulations (Michalek et al., 1995). Analyses of the AFHS data have typically relied on serum TCDD concentration as the primary exposure metric for epidemiologic classification (Kern et al., 2004; Michalek et al., 2001a, 2003; Pavuk et al., 2003). Pavuk et al. (2014) examined the serum concentrations of several other dioxins and dioxin-like compounds (i.e., PCDDs, polychlorinated dibenzofuran [PCDFs], and polychlorinated biphenyls [PCBs]) in serum samples gathered in 2002 from 777 ORH participants and 1,173 Air Force veterans in the comparison group. While the median TCDD levels were more than twice as high in the ORH subjects as in the comparison veterans (5.0 and 2.2 pg/g, respectively), no substantial differences were found between these groups for the other compounds. When contrasted with the serum levels measured in men in their age range during the 2001–2002 cycle of NHANES, the concentrations of the ORH subjects were similar except for TCDD, which demonstrated the specificity of the dioxin exposure experienced from contact in Vietnam with military herbicides. (Although serum TCDD measurements in 2002 were still sufficiently elevated to distinguish exposed and unexposed veterans at the group level, with the passage of several

more TCDD half-lives of about 7 years, newly drawn serum samples will cease to be useful metrics for assessing health outcomes in surviving Vietnam veterans, occupational cohorts, or Seveso residents. Factors influencing TCDD's half-life are discussed in Chapter 4 along with Table 4-1, which documents the variability in TCDD half-life observed in various circumstances.)

Members of the ACC performed herbicide-spraying operations on the ground and by helicopter and were thereby involved in the direct handling and distribution of Agent Orange and other herbicides in Vietnam. They were not identified for detailed study of health effects related to herbicide exposure until the late 1980s (Thomas and Kang, 1990). An initial feasibility study recruited Vietnam veterans and non-deployed Vietnam-era veterans from within the ACC (Kang et al., 2001). Blood samples collected from 50 Vietnam veterans in 1996 showed an association between veterans reporting having sprayed herbicides and higher serum TCDD concentrations; this finding was confirmed in a follow-up study of a larger fraction of the cohort (Kang et al., 2006). Modeling efforts (Ross et al., 2015a,b) have also found that higher exposures were probably experienced by those involved with mixer, loader, and applicator activities than by bystanders because of the fact that those in the first group were generally in closer proximity to and had more frequent contact with the herbicides.

Other veteran populations may also have been involved in handling herbicides although probably to a small degree. As discussed in Young (2009), for example, in 1971 the US Department of Defense (DOD) initiated Operation PACER IVY, which was responsible for removing stocks of Agent Orange from Vietnam to Johnston Island in the central Pacific Ocean. Operation PACER IVY was the responsibility of the 7th Air Force with assistance from Ranch Hand units and the ACC. PACER IVY procedures included the identification of unused herbicides, the transport of the identified herbicides to a central location in Vietnam for relabeling, and, for about half of the barrels, re-drumming before shipment. Potential Agent Orange hot spots included central PACER IVY locations, such as Du Nang, Bien Hoa, and to a small extent Phu Cat and Nha Trang airbases (Young, 2006). Although this is not certain, exposures of Allied troops from PACER IVY may have been low because most of the relabeling, repackaging, and handling of Agent Orange during PACER IVY was overseen and conducted by Chinese contractors, local Vietnamese, and the Vietnamese military. However, there were spills of Agent Orange in the de- and re-drumming and storage areas, which contaminated surrounding soils and asphalt (Young, 2009), and these have been suggested as possible sources of exposure. Other possible points of contamination for Vietnam-era veterans include defoliation tests conducted in South Vietnam as part of Project AGILE; ports in New Orleans, Louisiana; Baltimore, Maryland; Seattle, Washington; Mobile, Alabama; and Gulfport, Mississippi, which served as embarkation points for shipping of Agent Orange to Vietnam; storage locations on Johnston Island, where contamination could have occurred from re-drumming and maintenance of drums that contained Agent Orange; and

at-sea incineration of Agent Orange as part of Operation PACER HO (Young, 2009). Because the Army of the Republic of Vietnam (ARVN) was responsible for handling, transport, and storage of herbicides from the time it was delivered to Vietnam until it was loaded onto Ranch Hand aircraft, the herbicide exposures of Allied troops during these procedures may have been negligible.

Exposure of Ground Troops

In light of the widespread use of herbicides in Vietnam for many years, it is reasonable to assume that many military personnel were inadvertently exposed to the chemicals of concern. In surveys of Vietnam veterans who were not part of the Ranch Hand or ACC groups, 25 to 55 percent said that they believed they had been exposed to herbicides (CDC, 1989b). That belief has been supported by government reports (GAO, 1979) and reiterated by veterans and their representatives in testimony to the VAO committees over the years.

In contrast with those reports and veteran testimony, Young and colleagues provide evidence in a series of papers that is consistent with the veterans having received minimal exposures to herbicides (Young et al., 2004a,b). They used data from unpublished military records and environmental-fate studies to argue that ground troops had little direct contact with herbicide sprays and that TCDD residues in Vietnam had low bioavailability. They also argued that direct exposures of ground troops were relatively low because herbicide-spraying missions were carefully planned, and spraying occurred only when friendly forces were not in the target area.

To resolve the issue, numerous attempts were made in the 1980s to characterize the herbicide exposures of people who served as ground troops in Vietnam (CDC, 1988a; Erickson et al., 1984a; NRC, 1982; Stellman and Stellman, 1986; Stellman SD et al., 1988a). Those efforts combined self-reports of contact with herbicides or military service records with aerial-spray data to produce an Exposure Opportunity Index (EOI). For example, Erickson et al. (1984a) created five exposure categories based on military records in order to examine the risks of birth defects among the offspring of veterans. Those studies were conducted carefully and provided reasonable estimates based on available data, but there were no means of testing the validity of the estimates available at the time.

The search for a validation method led to the development of exposure biomarkers in veterans. Initial studies measured concentrations of dioxin in adipose tissue of veterans (Gross et al., 1984; Schecter et al., 1987). A study sponsored by the New Jersey Agent Orange Commission was the first to link dioxin concentrations in adipose tissue to dioxin concentrations in blood (Kahn et al., 1988). At the same time, the Centers for Disease Control (now the Centers for Disease Control and Prevention) undertook what came to be called the Agent Orange Validation Study, measuring TCDD in the serum portion of blood from a relatively large sample of Vietnam veterans and other Vietnam-era veterans (CDC,

1989a). The study did not find a statistically significant difference in mean serum TCDD concentrations between the groups: The mean values in each group were about 4 parts per trillion (ppt), and only two Vietnam veterans had concentrations greater than 20 ppt (CDC, 1988a). A review of a preliminary report of the work by an advisory panel established through the IOM concluded that the long lag between exposure and the serum measurements (about 20 years) called into question the accuracy of exposure classification based on serum concentrations. The panel concluded that estimates based on troop locations and herbicide-spraying activities might be more reliable indicators of exposure than serum measurements (IOM, 1987).

The report of the first *VAO* committee (IOM, 1994) proposed further work on exposure reconstruction and the development of a model that could be used to categorize exposures of ground troops. The committee cautioned that serum TCDD measurements should not be regarded as a "gold standard" of exposure, that is, as a fully accurate measure of herbicide exposure. Efforts to develop exposure-reconstruction models for US Vietnam veterans are discussed later in this chapter.

One other effort to reconstruct exposure was reported by researchers in the Republic of Korea who developed an exposure index for Korean military personnel who served in Vietnam (Kim JS et al., 2001, 2003). The exposure index was based on herbicide-spray patterns in military regions in which Korean personnel served during 1964–1973, time–location data on the military units stationed in Vietnam, and an exposure score derived from self-reported activities during service. The researchers were not successful in an attempt to validate their exposure index with serum dioxin measurements.

Exposure of Personnel Who Had Offshore Vietnam Service

US Navy riverine units are known to have used herbicides while patrolling inland waterways (IOM, 1994; Zumwalt, 1993), and it is generally acknowledged that estuarine waters became contaminated with herbicides and dioxin as a result of shoreline spraying and runoff from spraying on land, particularly in heavily sprayed areas that experienced frequent flooding. Thus, military personnel who did not serve on land could have been among those exposed to the chemicals during the Vietnam conflict. In recent years, there has been concern about dioxin exposure among personnel who served offshore but within the territorial limits of the Republic of Vietnam. It has been hypothesized that in addition to possibly experiencing drift from herbicide-spray missions, personnel on those ships that converted seawater by distillation may have been exposed via drinking water. Those concerns were heightened by findings from an Australian study (Muller et al., 2002) that showed that TCDD could be enriched in a simulation of the potable-water distillation process that was used on US Navy and Royal Australian Navy ships during the Vietnam War era. The National Academies convened the Blue Water Navy Vietnam Veterans and Agent Orange Exposure Committee

to address that specific issue; its report (IOM, 2011b) found that information to determine the extent of exposure experienced by Blue Water Navy personnel was inadequate, but that there were possible routes of exposure.

EXPOSURE OF THE VIETNAMESE POPULATION

As summarized by Constable and Hatch (1985), Vietnamese researchers have made a number of attempts to characterize the herbicide exposure of residents of Vietnam in the process of trying to assess adverse reproductive outcomes. Some researchers compared residents of the South with residents of the unsprayed North, and others endeavored to compare South Vietnamese people who lived in sprayed and unsprayed villages as determined by observed defoliation. To evaluate reproductive outcomes, the pregnancy outcomes of North Vietnamese women married to veterans who had served in South Vietnam were compared with those of women whose husbands had not. In some cases, records of herbicide spraying have been used to refine exposure measurements. In assessing infant mortality, Dai et al. (1990) considered village residents to have been exposed if an herbicide mission had passed within 10 km of the village center and classified exposure further by length of residence in a sprayed area and the number of times that the area reportedly had been sprayed.

Armitage et al. (2015) used the US Forest Service's Agricultural Dispersion (AGDISP), an aerial dispersion, to compare the distributions on the forest canopy and in the soil that would be expected following herbicide spraying in South Vietnam. Results were coupled with a chemical fate and transport model and with additional models considering dermal exposure via direct overspray and long-term dietary exposures. The investigators concluded that highly elevated exposures to the people in the upland forests of South Vietnam were not common.

A small number of studies have provided information on TCDD concentrations in Vietnamese civilians who were exposed during the war (Schecter et al., 1986, 2002, 2006). Dwernychuk et al. (2002) emphasized the need to evaluate dioxin contamination around former air bases in Vietnam. Those researchers collected environmental and food samples, human blood, and breast milk from residents of the Aluoi Valley of central Vietnam. The investigators identified locations where relatively high dioxin concentrations remained in soil or water systems. Soil dioxin concentrations were particularly high around former airfields and military bases where herbicides were handled. Fish harvested from ponds in those areas were found to contain high dioxin concentrations. Dwernychuk (2005) elaborated on the importance of "hot spots" as important locations for future studies and argued that herbicide use at former US military installations was the most likely cause of the hot spots. Other hot spots that have been identified include depots of chemical defoliants, airbases used for defoliant spray missions, and areas where chemical defoliants were used extensively. The Vietnamese population has since inhabited the areas in and around many former airbases and

depots, which have become the focus of studies of environmental contamination and bioaccumulation. Considering results of modeling exercises quantifying the dispersion and extent of exposure, Armitage et al. (2015) similarly emphasize hot spots as locations of higher potential exposure to TCDD as compared with areas primarily affected by aerial spraying only. The Bien Hoa Air Base, which is considered a hot spot because of the use of chemical defoliants around the base, was the focus of a study that examined dioxin contamination in soils in Vietnam (Mai et al., 2007). The study found high soil concentrations but did not estimate the exposures of people who lived in the vicinity of the bases. More recently, Hoang et al. (2014) reported that dioxin total toxic equivalent (TEQ) levels in eggs of poultry raised by the Vietnamese population currently living on the former Bien Hoa airbase were found to exceed the adult exposure guideline set forth by the World Health Organization (WHO) by two-fold and the child guideline by five-fold. In Thau Thien-Hue Province, a region affected by defoliant spraying, Banout et al. (2014) reported that although dioxin and furan (PCDD/PCDF) concentrations were below the WHO recommended guideline for dioxin TEQ in sediments, the concentrations in the muscle and liver of the poultry raised in the region exceeded the WHO guidelines for dioxin content per unit fat mass.

Publications reviewed in earlier updates have reported environmental concentrations and human body burdens of dioxins in various areas throughout Vietnam (Brodsky et al., 2009; Feshin et al., 2008; Hatfield Consultants, 2009a,b,c; Nhu et al., 2009; Saito et al., 2010; Tai et al., 2011). They have found pervasive exposure to dioxins more than a half-century after the Vietnam War. Dioxin concentrations in breast milk reflect the residence location of the mothers, with levels and TEQs being elevated in areas where herbicides sprayed during the war and tending to be still higher in areas where herbicides were stored. Phu Cat airbase, a hot spot in South Vietnam, has recently been the focus of several studies examining dioxin levels in human sera and breast milk and corresponding levels of steroid hormones. In 16 mother–baby pairs from Phu Cat airbase compared to 10 pairs from Kim Bang, Manh et al. (2013) reported significantly higher concentrations of salivary cortisol, cortisone, and dehydroepiandrosterone (DHEA) in primiparous mothers and of dioxin TEQs in their milk. The associations between dioxin TEQ levels in mothers' breast milk and salivary hormone levels were non-linear: The relationship was U-shaped for estradiol, and an inverted U-shape for cortisol, cortisone, and DHEA. The two groups did not differ significantly in the concentrations of four other salivary steroid hormones (androstenedione, estradiol, progesterone, or testosterone). In men, however, Sun et al. (2014) reported no correlation between serum dioxin TEQ and steroid hormones for either those who had lived in and around the Phu Cat airbase for 50 years or more or those who had lived in the unsprayed Kim Bang district of Ha Nam Province in North Vietnam. Manh et al. (2014) reported a correlation between proximity of residence to Phu Cat airbase and serum dioxin levels among men. When contrasting men from Kim Bang who had spent time in South Vietnam

during or after the war to those who had not, however, Manh et al. (2014) found no significant differences in serum dioxin levels between the two groups. These findings imply a greater body burden of dioxin exists in those currently living in the vicinity of the Phu Cat airbase than remains in those who spent time in areas that had been the target of herbicide spraying.

The above studies are not directly relevant to the present committee's task, but they may prove useful in future epidemiologic studies of the Vietnamese population and in the development of risk-mitigation policies.

MODELS FOR CHARACTERIZING HERBICIDE EXPOSURE

The development of a means of characterizing the exposure of individual Vietnam veterans has long been a prime objective for use in refining epidemiologic investigations of health outcomes in this population. Serum TCDD levels might have been a very useful proxy for harmful exposures to all the components of the herbicides used by the US military in Vietnam. As analytic methods for TCDD have become much more sensitive and somewhat less costly with the passage of time, body burdens in even quite highly exposed individuals by now would have decreased to such an extent over many half-lives that newly gathered samples would be minimally informative. The consideration of records detailing the herbicide spray missions has provided another approach to deriving individual-specific exposure estimates. Two models—a proximity-based EOI model and an aerial spray distribution model (explained and contrasted below)—have been proposed for estimating the exposure of Vietnam veterans. Until this update, neither had actually been applied in an epidemiologic investigation. The use of the EOI model in studying health consequences in a large cohort of Korean veterans who participated in the Vietnam War is assessed in the final portion of this section.

Exposure Opportunity Index Model

The IOM, following up on the recommendations contained in the original *VAO* report (IOM, 1994), issued a request for proposals seeking individuals and organizations to develop historical exposure-reconstruction approaches suitable for epidemiologic studies of the herbicide exposure of US veterans during the Vietnam War (IOM, 1997). The request resulted in the project Characterizing Exposure of Veterans to Agent Orange and Other Herbicides in Vietnam. The project was carried out under contract by a team of researchers in Columbia University's Mailman School of Public Health. The Columbia University project integrated various sources of information concerning spraying activities and information on the locations of military units assigned to Vietnam, all compiled into a database. The resulting EOI model (Stellman and Stellman, 2003) generates individualized estimates (EOI scores) of the exposure potential of troops serving in Vietnam.

Mobility factor analysis, a technique used for studying troop movement, was developed for use in reconstructing herbicide-exposure histories. The analysis is a three-part classification system for characterizing the location and movement of military units in Vietnam. It comprises a mobility designation (stable or mobile), a distance designation (usually in kilometers) to indicate how far a unit might travel in a day, and a notation of the modes of travel available to the unit (by air, by water, or on the ground by truck, tank, or armored personnel carrier). A mobility factor was assigned to every unit that served in Vietnam.

The data were combined into a geographic information system (GIS) for Vietnam. Herbicide-spraying records were integrated into the GIS and linked with data on military-unit locations to derive individual EOI scores. The results are the subject of reports by the contractor (Stellman and Stellman, 2003) and the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam (IOM, 2003b,c). A summary of the findings on the extent and pattern of herbicide spraying (Stellman et al., 2003a), a description of the GIS for characterizing exposure to Agent Orange and other herbicides in Vietnam (Stellman et al., 2003b), and an explanation of the EOI model based on that work (Stellman and Stellman, 2004) have been published in peer-reviewed journals. In those publications the researchers have argued that it is feasible to conduct epidemiologic investigations of veterans who served as ground troops during the Vietnam War. The IOM later issued a report that examined the feasibility of using the EOI model developed by Columbia University (IOM, 2008b). The report concluded that "despite the shortcomings of the exposure assessment model in its current form and the inherent limitations in the approach, the committee agreed that the model holds promise for supporting informative epidemiologic studies of herbicides and health among Vietnam veterans and that it should be used to conduct studies" (p. 2).

AgDRIFT-based Model

As an alternative to the EOI model, Ginevan et al. (2009a) proposed the use of the AgDRIFT Tier III forestry model for estimating the deposition of herbicides via aerial spraying. Hewitt et al. (2002a) presented the history of AgDRIFT's development as a model to describe deposition and drift patterns resulting from spraying from fixed wing aircraft and helicopters. The National Aeronautics and Space Administration (NASA) sponsored the initial development of the model's computational approach. The Forest Service of the US Department of Agriculture (USDA) and the US Army oversaw its refinement into the AGDISP model. The final development of AgDRIFT occurred under a cooperative agreement between the Spray Drift Task Force (SDTF) (i.e., a consortium of chemical companies formed in 1990), the US Environmental Protection Agency (EPA), and the USDA. Hewitt et al. (2002b) discussed the Lagrangian modeling of physical properties (such as droplet size, wind speed and direction, and equipment

design) factored into the models and validation efforts that ultimately resulted in the AgDRIFT model.

The AgDRIFT model can provide, among other things, ground and foliar deposition estimates derived from application information such as aircraft speed and altitude, nozzle characteristics, and droplet evaporation and environmental parameters such as canopy density, canopy roughness, and crosswind speed (Ginevan et al., 2009a). AgDRIFT outputs are then used to estimate dermal exposure through both direct deposition and post-application transfer from foliage. Exposures resulting from contact with soil and dust, and through the inhalation route, are considered negligible and are not included. Ginevan et al. (2009a) claim that the resulting estimates are more accurate and more appropriate for estimating aerial herbicide exposure than those from the EOI model because they are quantitative in nature, unlike the EOI model, which was designed to provide rank-ordered exposures.

Comparison and Validation of EOI and AgDRIFT-based Models

Until the current update, the position of earlier committees has been that exposure to herbicides experienced by US troops in Vietnam could not be determined with any certainty. Because the EOI and AgDRIFT models have both been proffered as solutions for estimating the extent of herbicide exposure in Vietnam, a summary of the efforts to compare and validate these models is included in this update. Overall, the committee recognizes that there is little consensus as to how accurate a model should be in order for it to be useful. The necessary accuracy likely differs depending on the application and the implications of using modeled estimates, and validation under one set of assumptions may not indicate validation under a different set of conditions. Furthermore, there is no standard against which these models could now be validated.

In support of validation of the AgDRIFT model, Ginevan et al. (2009a) pointed to Bird et al. (2002) and asserted justification for the use of this model in estimating the exposure to herbicides in Vietnam. Bird et al. concluded that the AgDRIFT model reasonably predicted average field deposition levels of herbicides when compared with 161 low-flight (< 10 m) aerial field trials collected over three field studies by the SDTF. However, the model under predicted mean deposition levels in the near-field and overpredicted at far-field distances. In a peer review of the collection of the SDTF field studies, several critiques emerged on the data used for validation. Several of the reviews that were requested by the Environmental Fate and Effects Division (EFED) of EPA's Office of Pesticide Programs praised the efforts and agreed that the resulting data represented the state of the art at the time, but they also concluded that there were several missed opportunities to collect data that represent real-world conditions in agricultural settings (Akesson, 1997; EFED, 1997; Fox, 1997; Kirk, 1997; Mulchi, 1997; Zhang et al., 1997). These conditions and suggestions included a broader array

of atmospheric stability classes, deposition on vegetation and canopies rather than relatively bare ground, an experimental design to capture airborne spray and the full extent of the drift plume, adequate methods to estimate dermal and inhalation exposure to non-target organisms, measurement of post-application volatilization and other fate and transport phenomena (for example, spray flux, lift off, attachment to water vapor), and larger field applications.

Perhaps a more appropriate scenario applicable to Vietnam includes high-flight (> 10 m) forestry applications, which are briefly referenced in Bird et al. (2002). Several of these analyses, however, were carried out using the preceding AGDISP or the Forest Service's near-wake model, which, similar to AgDRIFT, incorporates AGDISP computations (Teske et al., 2002). Testing the near-wake model against 17 aerial spray trials over mixed oak forest, Anderson et al. (1992) found that the model adequately predicted the ensemble average over a large number of spray applications but that it was less successful in predicting values from individual runs and could not replicate the wider variability of measured deposition. In evaluating computational methods for aircraft wake effects, Rafferty and Bowers (1993) compared results from near-wake and AGDISP models to deposition measurements from 15 trials in two field programs. When examining trials over a mixed conifer forest, they found areas of over prediction and under prediction similar to other studies, and only about 10 to 15 percent of modeled values fell within a factor of two of the observed measurements. Additionally, the study uncovered the importance of deposition sampling methods. Statistical differences were found between two difference sampling methods (i.e., spot count and manganese analysis) that were used simultaneously on the same trials. This difference in measuring deposition further complicates attempts at comparing modeled and observed values. Finally, when testing the near-wake model against 12 field tests, Richardson et al. (1995) found that although overall predictions showed good correlation with ground deposition measured to a distance of 300 m, modeled values generally underpredicted measured values (i.e., by a range of 3.3 to 27.0 when measured as the maximum ratio between prediction and measurement), and the model had trouble predicting the location of peak deposition.

It is difficult to judge whether these evaluations are currently appropriate in light of the improvements in AgDRIFT over the years and the various versions used in validation attempts over time. Additionally, while several field studies have been used to test the modeled ground deposition results of AgDRIFT, there do not appear to have been any tracer or field studies to validate the composite model relating deposition to human exposure estimates.

Discrepancies between the modeled AgDRIFT deposition estimates and scores from the EOI model, when applied to similar time points for Vietnam-era exposures, were reported by Ginevan et al. (2009a). For example, the AgDRIFT model predicted a much smaller area under the spray path and herbicide concentrations that are several orders of magnitude lower than EOI estimates for the same set of sample flight paths. The differences between the two exposure

estimation methods were particularly pronounced at points distant from the spray path, with AgDRIFT predicting herbicide exposures up to 20 orders of magnitude lower than the EOI model at a location 4 km away from the flight-path centerline.

In their response to the Ginevan et al. (2009b) critique of the EOI model, Stellman and Stellman (2013) questioned the validity of most, if not all, of Ginevan's calculations of EOI scores, citing errors regarding the use of "incorrect data and its fundamentally incorrect and negative interpretations." The Stellmans noted that Ginevan et al. compared raw EOI scores to log-transformed EOI scores. As a result, the variability in raw EOI scores on the flight line was potentially artificially high, but the log-transformed scores produced reasonable values that varied within 10 percent around the mean for each spray mission. The Stellmans also stated that the use of raw EOI scores leads to a host of other incorrect assertions and theories, such as "an incorrect score of 60,791 for one point, when the true score is zero in our [the EOI] system" (p. 2).

Given the lag time since herbicide exposures in Vietnam took place and the lack of direct exposure measurements from that era, it is neither possible to fully validate either the AgDRIFT or EOI models, nor to ascertain the accuracy and precision of estimates from either model or the claims of either Stellman and Stellman (2013) or Ginevan et al. (2009a,b). In addition, because the intent and outcomes of the two models differ substantially, the model results and interpretation would likely differ. The EOI model, for example, predicts potential exposure to troops on the basis of military data on spray history and troop locations. The AgDRIFT model, in contrast, predicts ground concentrations and their spatial dispersion with additional equations extending dispersion to the fraction deposited on skin and transferred from foliage; however, by design, the AgDRIFT model does not consider troop-location data.

The issue of Allied troop presence during spraying is one of the central issues in the debate regarding the use of the EOI model. The EOI model relied on actual military data on spray history and troop locations, which, as pointed out by both Stellman and Stellman (2004) and Young (2009), are limited in their spatial and temporal resolution and accuracy. The accuracy of the records with regard to missions flown, mission locations, and number of gallons sprayed, and other important information was examined by MITRE Corporation (Heizer, 1971). MITRE reported that about 2 percent of the records were missing data, 6 percent of the records had serious transcription or measurement errors, and 23 percent of the records that had complete data were off by 50 percent in the reported distance sprayed (Young, 2009). However, the overall quality of the data was found to be good, and it could be improved with adjustments, as performed by Stellman et al. (2003a,b) and others (ESG, 1985; NRC, 1974). Whether the adjustments improved the quality of the military data is not known. However, the troop movement information in the GIS database compiled by Stellman et al. (2003a,b) for the EOI model was compiled with the assistance of the US Armed Services Center for Research of Unit Records with presumably limited potential

for information bias. These data account for locations and changes in locations of approximately 80 percent of Army troops and most Air Force and Navy personnel during the Vietnam era (IOM, 2003b).

Exposure Estimation in Korean Veterans Health Study

Military personnel of the Republic of Korea served in Vietnam during 1964–1973. Since *Update 2012*, the committee reviewed several publications from a large epidemiological study of more than 114,000 Korean Vietnam veterans, four of which described how the exposure metrics used were derived (Yi et al., 2013a,b, 2014a,b). This study cohort, referred to here as the "Korean study," is much larger in scope than any of the other published epidemiological studies conducted among Vietnam veterans. The results of a very large set of health outcomes examined in the Korean study are discussed in subsequent chapters of this report. Exposures to herbicides and their contaminants were estimated using an EOI method developed by Stellman et al. (2003a). This model produced a set of EOI scores, as summarized below, based on the descriptions provided by Yi et al. (2013a,b, 2014a,b). Although the IOM (2008b) acknowledged that it was not feasible to directly validate the accuracy of exposure assignments developed by the EOI method, the committee encouraged efforts to quantify the degree of accuracy and to incorporate those estimates into sensitivity analyses. The Korean study, unfortunately, did not provide information on whether the influence of uncertainty on estimated associations between the EOI metric and specific health outcomes had been evaluated.

The Korean study investigators used a number of methods to estimate potential exposure to herbicides during Vietnam service. First, a self-report perceived exposure index was used to query Korean veterans as to how they might have been exposed to herbicides in Vietnam (Yi et al., 2013a,b). Study participants were asked to respond "yes," "no,'" or "do not know" to questions regarding perceived exposure to herbicides. The survey results showing the distribution of perceived herbicide exposure among the Korean veterans are presented in Table 3-2. These self-reported perceived exposures are not directly comparable to the objective EOI scores, which were designed to assess the exposure opportunity that would result from unintended proximity to herbicide spraying and not the direct result of duties that required handling or applying herbicides (IOM, 2008b). The perceived herbicide exposure estimates were highly correlated with the health outcomes in Yi et al. (2013a), indicating the possibility of recall bias.

Because concerns about potential inaccuracy or recall bias in self-reports of exposure and disease, as well as empirical observations of inconsistencies when such data are compared to more objective metrics of exposure potential, the committee expressed considerable concern about findings based on self-report exposure and outcome data in the Korean study (Yi, 2013; Yi et al., 2013a).

TABLE 3-2 Distribution of Perceived Herbicide Exposure Among 114,562 Korean Vietnam Veterans[a]

2 Groups	Exposure Questions	4 Groups	Prevalence
High	1. Sprayed herbicides	High	16.1%
	2. Handled herbicide spray equipment		
	3. Present during herbicide spraying	Moderate	35.7%
	4. Got herbicide on skin or clothing		
Low	5. Walked through sprayed area	Low	13.2%
	6. Exposed in other ways (not listed above)		
	Answered "no" to all six questions	None	34.9%

[a]Exposures assigned based on their self-reported responses to a postal survey.
SOURCE: Adapted from Yi et al., 2013a.

In the second method, an objective EOI score of exposure potential was calculated for each veteran based on the proximity of the veteran's military unit to herbicide sprayed areas. The Korean investigators obtained locations and calendar date histories for the military units represented in their cohort and provided this information to the Stellman group to use as input to obtain EOI scores from its model, which consolidates all the temporal and spatial information gathered from the original military records on the herbicide spray missions conducted in Vietnam. The investigators classified the resulting EOI scores using two- and four-group categorizations, and multiple aggregations of military units, as summarized in Tables 3-3 and 3-4.

The Korean study aggregated military units at two levels in the development of EOI scores: the larger brigade/division level and the smaller battalion/company level. According to Yi et al. (2013a), the Vietnam post locations and the tactical and operational areas were identified at the battalion level and higher through

TABLE 3-3 Distribution of EOI Scores on Two-Level Scale in Epidemiology Studies Among Korean Vietnam Veterans[a]

Exposure Category ($\log_{10}$ EOI score)	Yi et al. (2014a)[b] Division/Brigade or Battalion/Company (n = 111,726)[d]	Yi et al. (2014b)[c] Division/Brigade (n = 180,251)[e]
Low (< 4.0)	62.0%	52.4%
High (≥ 4.0)	38.0%	47.6%

[a]Details of the Two-level exposure classification is described in Ohrr et al. (2006, publication in Korean).
[b]Battalion/company level EOI score assigned for combat units only.
[c]The overall range of log EOI scores in Yi et al. (2014b) is 0.0–5.8.
[d]Yi et al. (2014a), 111,726 veterans analyzed for disease prevalence.
[e]Yi et al. (2014b), 180,251 veterans analyzed for cancer outcomes.

TABLE 3-4 Distribution of EOI Scores on Four-Level Scale[a]

Exposure Category (log_{10} EOI score)	Yi et al. (2013a) Division/ Brigade (n = 96,126)[b]	Yi et al. (2013a) Battalion/ Company (n = 96,126)	Yi et al. (2014a) Division/ Brigade or Battalion/ Company[c] (n = 111,726)[d]	Yi et al. (2014b) Division/ Brigade (n = 180,251)[e]
None (< 0.1)	20.1%	26.1%	30.9%	25.2%
Low (0.1 ≤ EOI < 4.0)	28.2%	33.1%	31.2%	27.2%
Med (4.0 ≤ EOI < 5.0)	31.1%	21.5%	20.1%	28.3%
High (≥ 5.0)	20.6%	19.3%	17.9%	19.3%

[a]Details of the Four-level exposure classification is described in Ohrr et al. (2006, publication in Korean).

[b]Yi et al. (2013a), 96,126 veterans analyzed for self-reported disease prevalence. Log (EOI score) mean and range not reported.

[c]Battalion/company level EOI score assigned for combat units only.

[d]Yi et al. (2014a), 111,726 veterans analyzed for disease prevalence. Log (EOI score) mean 2.6 ± 2.2 (range 0.0–6.2).

[e]Yi et al. (2014b), 180,251 veterans analyzed for cancer outcomes. Log (EOI score) range 0.0–5.8.

records review. Because veterans also reported the specific battalion/company in which they served while in Vietnam, this presumably finer unit level was also used in estimating EOI scores. However, no information regarding the validity and reliability of the company-level spatial coordinates relative to military records was provided. The rationale for the two- and four-level exposure categories is explained in more detail only in a Korean-language paper (Ohrr et al., 2006), but the distributions of EOI scores are similar across the Korean study publications (see Tables 3-3 and 3-4) regardless of military unit aggregation. However, the committee noted that proportion of veterans in the "high" exposure category may be too large for optimal detection of associations between exposure and adverse health conditions. Stated another way, the "high" exposure individuals may be too similar to the lower categories, thereby diluting the strength of the associations. An exposure classification that put only the top 10 or 15 percent in the "high" category would perhaps have been better for the purpose of identifying adverse health effects due to exposure.

In summary, the recent Korean study overcame significant logistical challenges in applying the EOI model to a large-scale epidemiologic study of a broad spectrum of health effects. The Korean researchers did not refine the EOI model for the influence of environmental fate and transport between spraying of the herbicides and possible exposure of ground troops, as recommended by the IOM in 2008. Nor were the results subjected to sensitivity testing for variability arising from the parameter values selected and other sources of uncertainty in the exposure assessment method. Nonetheless, compared to the severe constraints on exposure assessment in previous studies of this population of ultimate interest,

this first application of the EOI model represents a "more accurate, if still imperfect, method to increase the specificity of exposure classification" for observing the association between herbicide exposure and health effects among Vietnam veterans (IOM, 2008b, p. 84).

In conclusion, the committee acknowledges that there are undoubtedly sources of error in the EOI method for modeling herbicide exposures of Vietnam veterans, but there is no indication of systematic bias in rank ordering of exposure scores developed by this method. Given that nondifferential misclassification of exposure would bias measures of association toward the null, observed statistically significant relationships between EOI scores and health effects are likely to be real.

METHODOLOGIC ISSUES IN EXPOSURE ASSESSMENT

The focus here is on several key methodologic issues that complicate the development of accurate estimates of exposure of the Vietnam-veteran population and the other study populations discussed in this report: The latent period between exposure and disease, exposure misclassification, and exposure specificity.

Latency

The temporal relationship between exposure and disease is complex and often difficult to define in studies of human populations. Many diseases do not appear immediately after exposure. Cancers, for example, might not appear for many years after exposure. The time between a defined exposure period and the occurrence of disease is often referred to as a latent period (IOM, 2004). Exposures can be brief (sometimes referred to as acute exposures) or protracted (sometimes referred to as chronic exposures). At one extreme, an exposure can be the result of a single event, as in an accidental poisoning. At the other extreme, a person exposed to a chemical that is stored in the body may continue to experience "internal exposure" for years even if exposure from the environment has ceased. The determination of the proper timeframe for duration of exposure constitutes a challenge to exposure scientists.

Misclassification

Exposure misclassification in epidemiologic studies can affect estimates of risk. A typical situation is in a case-control study in which the reported measurement of exposure of either group or both groups can be misclassified. The simplest situation to consider is the binary case in which the exposure is classified into just two levels, for example, "ever exposed" versus "never exposed." If the probability of exposure misclassification is the same in both cases and controls (that is, nondifferential), then it can be shown that the estimated association

between disease and exposure is biased toward the null value; in other words, one would expect the true association to be stronger than the observed association. However, if the probability of misclassification is different between cases and controls, then a bias in the estimated association can occur in either direction, and the true association might be stronger or weaker than the observed association.

The situation in which exposure is classified into more than two levels is somewhat more complicated. Dosemeci et al. (1990) demonstrated that in that situation the slope of a dose–response trend is not necessarily attenuated toward the null value even if the probability of misclassification is the same in the two groups of subjects being compared; the observed trend in disease risk among the several levels of exposure may be either an overestimate or an underestimate of the true trend. Greenland and Gustafson (2006) discussed the effects of exposure misclassification on the statistical significance of the result and demonstrated that if one adjusts for exposure misclassification when the exposure is represented as a binary variable, the resulting association is not necessarily more significant than in the unadjusted estimate. That result remains true even though the observed magnitude of the association (for example, the relative risk) might be increased.

Even progressing beyond discrete exposure categories, some continuous exposure metrics can be problematic from the perspective of misclassification. It is often noted that continuous measures of an exposure variable carry more information per observation than do those that are partitioned into categories at basically arbitrary cut points. Despite their continuous nature, however, measurements of serum TCDD levels have decreasing utility for epidemiologic research as they are derived from samples drawn longer and longer after the exposure in question occurred. The variance of the underlying exposed and non-exposed groups has increased to the extent that two overlapping populations can no longer be distinguished, effectively leading to an increase in misclassification.

The committee has been concerned about the strong possibility that the degree of misclassification associated with a particular exposure assignment convention employed in several recent publications (Ansbaugh et al., 2013; Li et al., 2013; Qureshi et al., 2013) may be vastly underappreciated by even the researchers using it. Over the past few years, VAO literature searches have identified publications concerning various health outcome authored by researchers affiliated with the VA medical care delivery system. The analyses in question used exposure categories assigned on the basis of a variable in a patient's electronic medical record indicating whether the individual was "exposed to Agent Orange." Its presence in VA's medical records system conveys a degree of authenticity that the committee strongly suspects is unmerited. From the vagueness of what the committee could learn about how this variable is populated, it remains unclear whether the source of this information is deployment status, entry on the Agent Orange Registry, the veteran's self-report, a physician's observation that the patient has a condition presumed to be service-related, results of serum TCDD measurements performed on some patients, or some other criteria. At any rate,

none of these approaches represents a reliable method of determining whether an individual was truly exposed to herbicides (above some unspecified level) or for uniform application to all veterans using the VA medical system, who themselves are a self-selected subset of veterans. The committee has no reason to believe VA has access to some previously unrecognized means of definitively establishing whether a given veteran was truly exposed to herbicides in Vietnam. The committee is concerned that these publications misrepresent (perhaps unintentionally) the reliability of the underlying exposure metric.

Specificity

The incorporation of the findings of studies of persons exposed to components of the herbicides sprayed in Vietnam requires some decisions about their relative contributions to the VAO project's evidentiary database. Only a few herbicidal chemicals were used as defoliants during the Vietnam conflict: esters and salts of 2,4-D and 2,4,5-T, cacodylic acid, and picloram in various formulations. Many scientific studies reviewed by the committee report exposures to broad categories of chemicals rather than to those specific chemicals. The categories are presented in Tables 3-5 and 3-6 with their relevance to the committee's charge. The information in these tables has helped to guide the committee's evaluation of epidemiologic studies. Earlier VAO committees did not address the issue of exposure specificity in exactly this manner. The committee for *VAO* and the first several updates gave more weight to results that were based on job title (for example, "farmer" with

TABLE 3-5 Current Committee Guidance for the Classification of Exposure Information in Epidemiologic Studies That Focus on the Use of Pesticides or Herbicides, and Relevance of the Information to the Committee's Charge to Evaluate Exposures to 2,4-D and 2,4,5-T (Phenoxy Herbicides), Cacodylic Acid, and Picloram

Specificity of Exposure Reported in Study	Additional Information	Relevance to Committee's Charge
Pesticides	Chemicals of interest were not used, or there was no additional information	Not relevant
	Chemicals of interest were used	Limited relevance
Herbicides	Chemicals of interest were not used	Not relevant
	There was no additional information	Limited relevance
	Chemicals of interest were used	Relevant
Phenoxy herbicides	—	Highly relevant
2,4-D or 2,4,5-T	—	Highly relevant
Cacodylic acid[a]	—	Highly relevant
Picloram	—	Highly relevant

[a]None of the epidemiologic studies reviewed by the committee to date has specified exposure to cacodylic acid.

TABLE 3-6 Current Committee Guidance for the Classification of Exposure Information in Epidemiologic Studies That Focus on Exposure to Dioxin-Like Chemicals and Relevance of the Information to the Committee's Charge

Specificity of Exposure Reported in Study	Additional Information	Relevance to Committee's Charge
Dioxin-like chemicals	Exposure to PCBs or polychlorinated dibenzofuran (PCDFs)	Limited relevance
Dioxin-like chemicals	Results expressed in terms of (total) toxic equivalent (TEQs) or concentrations of individual congeners recognized as having dioxin-like activity[a]	Highly relevant
TCDD or mixture of PCDDs	Established on the basis of environmental sampling or work histories	Highly relevant
TCDD or mixture of PCDDs	Concentrations in tissues of a subset of participants (preferably soon after exposure)	Very highly relevant
TCDD or mixture of PCDDs	Concentrations in tissues of individual participants (preferably soon after exposure)	Most informative

[a]The values of toxic equivalency factors for individual dioxin-like chemicals, which are weighted by concentration and summed to derive TEQs are presented in Table 4-2.
NOTE: PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent.

no additional information) than have the committees for the past five updates, but entirely excluded findings from the Yusho and Yucheng PCDF and PCB poisonings, whereas recent committees have considered studies that analyzed for dioxin-like PCDF and PCB congeners and expressed the results in terms of TEQs. Studies that report TEQs based only on mono-ortho PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189), however, have been given only limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the revised WHO Toxicity Equivalency Factor (TEF) scheme of 2005 (La Rocca et al., 2008; van den Berg et al., 2006). A 2013 joint WHO and United Nations Environment Programme evaluation concluded that there was sufficient evidence for the inclusion of brominated analogues of the dioxin-like compounds in the WHO TEF scheme (van den Berg et al., 2013). Classifications schemes for PCB congeners have also been evaluated in terms of gene expression (Warner et al., 2012). Recent studies of dioxin-like compounds have investigated systemic distribution of the congeners in rodents and differences in their relative effect potencies (van Ede et al., 2013a,b, 2014) and relative effect potencies in human thyroid responses (Trnovec, 2014; Trnovec et al., 2013).

Many studies have examined the relationship between exposure to "pesticides" and adverse health outcomes, while others have used the category of "herbicides" without identifying specific chemicals. A careful reading of a scientific report often reveals that none of the chemicals of interest (COIs) (that is, those used in Vietnam, as delineated above) contributed to the exposures of the study population, so such studies could be excluded from consideration. But in many cases, the situation is more ambiguous. For example, reports that define exposure in the broad category of "pesticides" with no further information have little relevance to the committee's charge to determine associations between exposures to herbicides used in Vietnam and adverse health outcomes. Reports that define exposure in the more restricted category of "herbicides" are of greater relevance but are still of little value unless it is clear from additional information that an exposure to one or more of the herbicides used in Vietnam occurred in the study population. Possibilities include: if a published report indicates that the COIs were among the pesticides or herbicides used by the study population, if the lead author of the report has been contacted and has indicated that the COIs were among the chemicals used, if the COIs are used commonly for the crops identified in the study, or if the COIs are used commonly for a specific purpose, such as the removal of weeds and shrubs along highways.

Among the various chemical classes of herbicides that have been identified in published studies reviewed by the committee, phenoxy herbicides, particularly 2,4-D and 2,4,5-T, are directly relevant to the exposures experienced by US military forces in Vietnam. On the basis of the assumption that compounds with similar chemical structure may have analogous biologic activity, information on the effects of other chemicals in the phenoxy herbicide class—such as 2-(2,4,5-trichlorophenoxy) propionic acid (Silvex), 2-methyl-4-chlorophenoxyacetic acid, 2-(2-methyl-4-chlorophenoxy) propionic acid (Mecoprop), and 3,6-dichloro-2-methoxybenzoic acid (dicamba)—has been factored into the committee's deliberations with somewhat less weight. The very few epidemiologic findings on exposure to picloram or cacodylic acid have been regarded as highly relevant. The committee has decided to include many studies that report on unspecified herbicides in the health-effects sections, and the results of these studies have been entered into the health-outcome–specific tables; however, these studies tend to contribute little to the evidence considered by the committee. The many studies that provide chemical-specific exposure information are believed to be far more informative for the committee's purposes.

A similar issue arises in the evaluation of studies that document exposure to dioxin-like compounds. Most "dioxin" studies reviewed by the committee have focused on TCDD, but TCDD is only one of a number of PCDDs. The committee recognizes that in real-world conditions exposure to TCDD virtually never occurs in isolation and that there are hundreds of similar compounds to which humans might be exposed, including other PCDDs, PCDFs, and PCBs. Human exposure to TCDD is almost always accompanied by an exposure to one or more of the

other compounds. The literature on the other compounds, particularly PCBs, has not been reviewed systematically by the committee except for those reports in which TCDD was identified as an important component of the exposure or the risks of health effects were expressed in terms of TEQs, which are the sums of toxicity equivalence factors for individual dioxin-like compounds as measured by activity with the aryl hydrocarbon receptor (AHR). The committee took that approach for two reasons. First, the exposure of Vietnam veterans to substantial amounts of the other chemicals, relative to exposure to TCDD, has not been documented. Second, the most important mechanism for TCDD toxicity involves its ability to bind to and activate the AHR. Many of the other chemicals act by different or multiple mechanisms, so it is difficult to attribute toxic effects after such exposures specifically to TCDD. Furthermore, people's environmental exposures to dioxin-like chemicals and their non-dioxin–like counterparts are to mixtures of components that tend to correlate, so it is not surprising that specific chemicals measured in a person's serum also tend to correlate; this means that it will be difficult for epidemiologic studies to attribute any observed association to a particular chemical configuration (Longnecker and Michalek, 2000). Analyses in terms of TEQs circumvent that problem to some extent.

4

Information Related to Biologic Plausibility

The committee reviewed all the relevant experimental studies of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 4-amino-3,5,6-trichloropicolinic acid (picloram), dimethylarsinic acid (DMA, also called cacodylic acid), and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) that have been published since *Update 2012* (IOM, 2014), and it has incorporated the findings into this chapter when it is appropriate and into the biologic-plausibility sections of Chapters 7–13 when they are of consequence for particular health outcomes. For each substance, this chapter includes a review of toxicokinetic properties, a brief summary of the toxic outcomes investigated in animal experiments, and a discussion of underlying mechanisms of action as illuminated by in vitro studies. The final section of this chapter discusses complicating factors in extrapolating findings from laboratory experimentation to humans and two emerging subjects in molecular and biologic science that provide novel insights into the potential mechanisms of xenobiotic-induced disease, which may thereby establish greater biologic plausibility for various toxic responses being associated with exposure to the herbicides sprayed in Vietnam.

The establishment of biologic plausibility through laboratory studies strengthens the evidence of a cause–effect relationship between herbicide exposure and health effects reported in epidemiologic studies, and thus supports the existence of the less stringent relationship of association, which is the target of this committee's work. Experimental studies of laboratory animals or cultured cells make it possible to observe the effects of herbicide exposure under highly controlled conditions, which is difficult or impossible to do in epidemiologic studies. The conditions that are controlled include the genetic differences among people, the frequency and magnitude of exposure, exposure to other chemicals,

and preexisting health conditions, all of which can be controlled in a laboratory animal study.

Once a chemical contacts the body, it becomes subject to the processes of absorption, distribution, metabolism, and excretion. The combination of those four biologic processes determines the concentration of the chemicals in the various tissues and organs in the body and how long each organ or tissue is exposed to it and thus influences its pharmacologic and possibly toxic activity.

The absorption of a substance in an organism normally takes place by uptake into the bloodstream from mucous surfaces, such as the intestinal walls of the digestive tract during ingestion. Low solubility, chemical instability in the stomach, and an inability of the substance to permeate the intestinal wall can all reduce the extent to which the substance is absorbed after being ingested. The solubility of a chemical in fat and its hydrophobicity influence the pathways by which it is absorbed, its relative potential to be metabolized (structurally transformed), and ultimately whether it persists in the body or is excreted. Absorption is a critical determinant of a chemical's bioavailability, that is, the fraction of it that reaches the systemic circulation. In addition to ingestion, the routes of exposure experienced by humans are inhalation (entry via the airways) and dermal exposure (entry via the skin). Animal studies may involve additional routes of exposure that are not ordinarily encountered by humans, such as intravenous or intraperitoneal injection, in which a chemical is injected into, respectively, the bloodstream or the abdominal cavity.

Distribution refers to the movement of a substance from the site of entry to the tissues and organs where it may have its ultimate effect or be sequestered. Distribution takes place most commonly via the bloodstream.

Metabolism is the process by which a foreign substance is chemically modified when it enters an organism. For many environmental toxicants, this process takes place largely in the liver via the action of enzymes, including cytochrome P450s, which catalyze the oxidative metabolism of many chemicals. As metabolism occurs, the parent chemical is converted into new chemicals called metabolites, which are often more water-soluble (polar) and thus more readily excreted. When the resulting metabolites are pharmacologically or toxicologically inert, metabolism has deactivated the administered dose of the parent chemical and thus reduced its effects on the body. Metabolism may, however, generate a chemical that is more potent or more toxic than the parent compound. Excretion is the removal of substances or their metabolites from the body, most commonly in urine or feces, whereas elimination applies to the disappearance of the parent molecule from the bloodstream. The rate of excretion of a chemical from the body is often limited by the rate of metabolism of the parent chemical into more water-soluble, readily excreted metabolites. Excretion is often incomplete, especially in the case of chemicals that resist biotransformation, and incomplete excretion results in the accumulation of foreign substances that can adversely affect biologic functions. Elimination is referred to as "first-order" when its rate is directly proportional to

TABLE 4-1 Estimates of TCDD Half-Life in Humans and Animals

Reference	Half-Life[a]	Confidence Interval	Comment
Human studies:			
Leung et al., 2006	0.4 year		Breastfed infants, 0–1 year after exposure
Aylward et al., 2005a			Toxicokenetic model estimates for exposures:
	< 3 years		> 10,000 pg/g of serum lipid
	> 10 years		< 50 pg/g of serum lipid
Emond et al., 2005			PBPK model based on 10 Ranch Hand veterans:
	Weeks		40,000 pg/g of serum lipid
	>10 years		138 pg/g of serum lipid
Flesch-Janys et al., 1996	7.2 years		Adult males, Boehringer cohort
Geusau et al., 2002	1.7 years[b]		0–3 years after exposure: Adult female 1, 144,000 pg/g of serum lipid
	3.4 years[b]		Adult female 2, 26,000 pg/g of serum lipid
Kumagai and Koda, 2005	1.1–2.3 years		Adult male, incinerator workers, 0–1.3 years after exposure
Michalek et al., 2002	0.34 year[b]		Adult males, Seveso cohort, 0–3 months after exposure
	6.9 years		3–16 years after exposure
	9.8 years		Adult females, Seveso cohort, 3–16 years after exposure
	7.5 years		Adult males, Ranch Hands, 9–33 years after exposure
Needham et al., 1994	7.8 years	7.2–9.7 years	Adults, Seveso cohort
Pirkle et al., 1989	7.1 years	5.8–9.6 years	Adult males, Ranch Hands, 9–23 years after exposure
Milbrath et al., 2009	7.2 years		Reference half-life for 48.7-year-old
Sorg et al., 2009	15.4 months		Victor Yushchenko: TCDD at 108,000 ppt lipid
Animal studies:			*Monkeys*
Neubert et al., 1990	73.7 days	60.9–93.8 days	single injection
			Mice
DeVito and Birnbaum, 1995	15 days		female B6C3F1
Gasiewicz et al., 1983	11 days[c]		C5BL/6J
	24.4 days[c]		DBA/2J
	12.6 days[c]		B6D2F1/J
Koshakji et al., 1984	20 days		male ICR/Ha Swiss

continued

TABLE 4-1 Continued

Reference	Half-Life[a]	Confidence Interval	Comment
			Rats
Emond et al., 2006			Inducible elimination PBPK model estimates:
	10 days		10^3 µg/kg acute treatment
	75 days		10^{-3} µg/kg acute treatment
Hurst et al., 1998	8 days		Pregnant female Long-Evans, excretion from liver
Pohjanvirta and Tuomisto, 1990	21.9 days		Male Han/Wistar, resistant strain
Viluksela et al., 1996	20.2 days		Long-Evans, TurkuAB strain
	28.9 days[d]		Long-Evans, Charles River strain
Weber et al., 1993	16.3 ± 3.0 days		Male Sprague-Dawley

[a]Half-lives of TCDD in humans based on measurement of TCDD in serum samples.

[b]Shorter half-lives measured in humans during first months after exposure or in severely contaminated persons consistent with nonlinear elimination predicted by physiologically based pharmacokinetic (PBPK) models (for example, Carrier et al., 1995). Greater half-life in females attributed to greater BMI index.

[c]Total cumulative excretion of ^{3}H-TCDD–derived radioactivity.

[d]Attributed to differences in dilution due to different growth rates.

the amount of chemical then in the body, which also means that the chemical's half-life is independent of dose. A half-life is defined as the time required for the plasma concentration or the amount of a chemical in the body to be reduced by half. The half-life of TCDD in humans varies with body mass index (BMI), age, sex, and concentration in the body and has been found to vary from 0.4 to more than 10 years (see Table 4-1).

Collectively, the routes and rates of absorption, distribution, biotransformation or metabolism, and excretion of a toxic substance make up the *toxicokinetics* (or *pharmacokinetics* for chemicals used as pharmaceutical agents) of the substance. Those processes determine the amount of a particular substance or metabolite that reaches specific organs or cells and that persists in the body. Understanding the toxicokinetics of a chemical is useful for assembling a valid reconstruction of a human exposure, but it is most important in assessing the risk of effects from exposure to a chemical by determining the concentration of the active chemical in target tissues. The principles involved in toxicokinetics are similar from chemical to chemical, although the degree to which different processes influence distribution depends on the structure and other inherent properties of a particular chemical. Thus, the lipophilicity or hydrophobicity of a chemical and its structure influence the pathways by which it is metabolized and whether it persists in the body or is excreted. The degree to which different toxicokinetic processes influence the toxic potential of a chemical depends on

metabolic pathways, which often differ among species. For that reason, attempts at extrapolation from experimental animal studies to human exposures must be done extremely carefully.

Many chemicals were used by the US armed forces in Vietnam. The nature of the substances themselves was discussed in detail in Chapter 4 of the original *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (*VAO*) report (IOM, 1994). Four herbicides documented in military records were of particular concern and are examined here: 2,4-D, 2,4,5-T, picloram, and cacodylic acid. This chapter also examines TCDD, the most toxic congener of the tetrachlorodibenzo-*p*-dioxins (tetraCDDs), also commonly referred to as dioxin, which is a contaminant of 2,4,5-T. Considerably more information is available on TCDD than on the herbicides themselves. Other contaminants present in 2,4-D and 2,4,5-T are of less concern. Except as noted, the laboratory studies of the chemicals of concern used pure compounds or formulations; the epidemiologic studies discussed in later chapters often tracked exposures to mixtures.

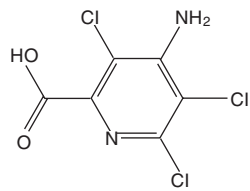
PICLORAM

Chemistry

Picloram (Chemical Abstracts Service Number [CAS No.] 1918-02-1; see chemical structure in Figure 4-1) was used with 2,4-D in the herbicide formulation Agent White, which was sprayed in Vietnam. It is also used commonly in Australia in a formulation that has the trade name Tordon 75D®. Tordon 75D contains several chemicals, including 2,4-D, picloram; a surfactant, diethyleneglycolmonoethyl ether; and a silicone defoamer. A number of studies of picloram used such mixtures as Tordon formulations or other mixtures of 2,4-D and picloram that are similar to Agent White.

Toxicokinetics

The original *VAO* committee reviewed studies of the toxicokinetics of picloram. Studies of animals showed a rapid absorption through the gastrointestinal



4-amino-3,5,6-trichloropicolinic acid

FIGURE 4-1 Structure of picloram.

tract and a rapid elimination of picloram as the unaltered parent chemical in urine. Nolan et al. (1984) examined the toxicokinetics of picloram in six healthy male volunteers who were given a single oral dose of 0.5 or 5.0 mg/kg or a dermal dose of 2.0 mg/kg. Picloram was rapidly absorbed in the oral study and rapidly excreted unchanged in urine. More than 75 percent of the dose was excreted within 6 hours, and the remainder with an average half-life of 27 hours. On the basis of the quantity of picloram excreted in urine in the dermal study, the authors noted that only 0.2 percent of the picloram applied to the skin was absorbed. Because of its rapid excretion, picloram has low potential to accumulate in humans.

In general, the literature on picloram toxicity continues to be sparse. Studies of humans and animals indicate that picloram is rapidly eliminated as the parent chemical. Studies of animals indicate that picloram is sparingly toxic at high doses.

Toxicity Profile

The original *VAO* committee reviewed studies of the carcinogenicity, genotoxicity, acute toxicity, chronic systemic toxicity, reproductive and developmental toxicity, and immunotoxicity of picloram. In general, there is some evidence of carcinogenicity in some rodent models but not in other species (NCI, 1978). Because of some concern that contaminants in the picloram (in particular, hexachlorobenzene) might be responsible for the carcinogenicity, picloram itself has not been established as a chemical carcinogen.

Studies conducted by the Environmental Protection Agency (EPA) (1988) yielded no evidence that picloram is a genotoxic agent. Picloram is considered a mild irritant; it has produced erythema in rabbits only at high doses. The available information on the acute toxicity of picloram is paltry. Some neurologic effects—including hyperactivity, ataxia, and tremors—were reported in pregnant rats exposed to picloram at 750 or 1,000 mg/kg (Thompson et al., 1972).

Chronic Systemic Toxicity

Several studies have reported various effects of technical-grade picloram on the livers of rats. In the carcinogenicity bioassay conducted by Stott et al. (1990), treatment-related hepatomegaly, hepatocellular swelling, and altered tinctorial properties were noted in the central regions of the liver lobules in the groups exposed at 60 and 200 mg/kg per day. Males and females exposed at the 200 mg/kg dose had higher liver weights than controls. The no-observed-effect level (NOEL) was 20 mg/kg per day, and the lowest observed-effect level was 60 mg/kg per day for histologic changes in centrilobular hepatocellular tissues. According to EPA (1988), hexachlorobenzene (a contaminant of technical-grade picloram at 197 ppm) was probably not responsible for the hepatic effects. Gorzinski and

colleagues (1987) also reported a dose-related increase in liver weights, hepatocellular hypertrophy, and changes in centrilobular tinctorial properties in male and female F344 rats exposed to picloram at 150 mg/kg per day and higher in the diet for 13 weeks. In a 90-day study, cloudy swelling in the liver cells and bile duct epithelium occurred in male and female F344 rats given 0.3 percent or 1.0 percent technical picloram in the diet (EPA, 1988). Hepatic effects have also been reported in dogs exposed to picloram: Increased liver weights were reported in beagles that received 35 mg/kg per day or more in the diet for 6 months (EPA, 1988). No other effects of chronic exposure to picloram have been reported.

Reproductive and Developmental Toxicity

The reproductive toxicity of picloram was evaluated in a two-generation study; however, few animals were evaluated, and no toxicity was detected at the highest dose tested, 150 mg/kg per day (EPA, 1988). Some developmental toxicity was produced in rabbits exposed to picloram by gavage at 400 mg/kg per day on gestation days (GDs) 6–18. Fetal abnormalities were forelimb flexure, fused ribs, hypoplastic tail, and omphalocele, each occurring in a single litter (John-Greene et al., 1985). Some maternal toxicity was observed at that dose, however, and EPA concluded on the basis of the sporadic nature of the findings that the malformations were not treatment related (EPA, 1988). No teratogenic effects were produced in the offspring of rats given picloram by gavage at up to 1,000 mg/kg per day on GDs 6–15, but the occurrence of bilateral accessory ribs was significantly increased (Thompson et al., 1972).

Immunotoxicity

Studies of the potential immunotoxicity of picloram have included dermal sensitization in humans and rodent immunoassays. In one study, 53 volunteers received nine 24-hour applications of 0.5 mL of a 2 percent potassium picloram solution on the skin of both upper arms. Each volunteer received challenge doses 17–24 days later. The formulation of picloram (its potassium salt) was not a skin sensitizer or an irritant (EPA, 1988). In a similar study, a 5 percent solution of picloram (M-2439, Tordon 101 formulation) produced a slight dermal irritation and a sensitization response in six of the 69 volunteers exposed. When the individual components of M-2439—picloram, triisopropanolamine (TIPA) salt, and 2,4-D TIPA salt—were tested separately, no sensitization reaction occurred (EPA, 1988). Tordon K+, but not technical-grade picloram, was also found to be a skin sensitizer in guinea pigs (EPA, 1988). CD1 mice exposed to Tordon 202C (94 percent 2,4-D and 6 percent picloram) had no consistent adverse effects on antibody responses (Blakley, 1997), but the lack of a consistent response may be due to the fact that CD1 mice are outbred.

Mechanisms

No well-characterized mechanisms of toxicity for picloram are known.

CACODYLIC ACID

Chemistry

Arsenic (As) is a naturally occurring element that exists in a trivalent form (As^{+3} or As^{III}) and a pentavalent form (As^{+5} or As^{V}). See Figure 4-2 for the chemical structures of selected arsenic-containing compounds; sodium arsenite, which contains As^{III}, is generally considered to be the most toxic of these arsenic compounds. Arsenic is commonly present in drinking-water sources that are associated with volcanic soils and can reach high concentrations (over 50 ppb). Numerous human health effects have been attributed to drinking-water exposure, particularly bladder, skin, and lung cancers and vascular diseases. Arsenic exists

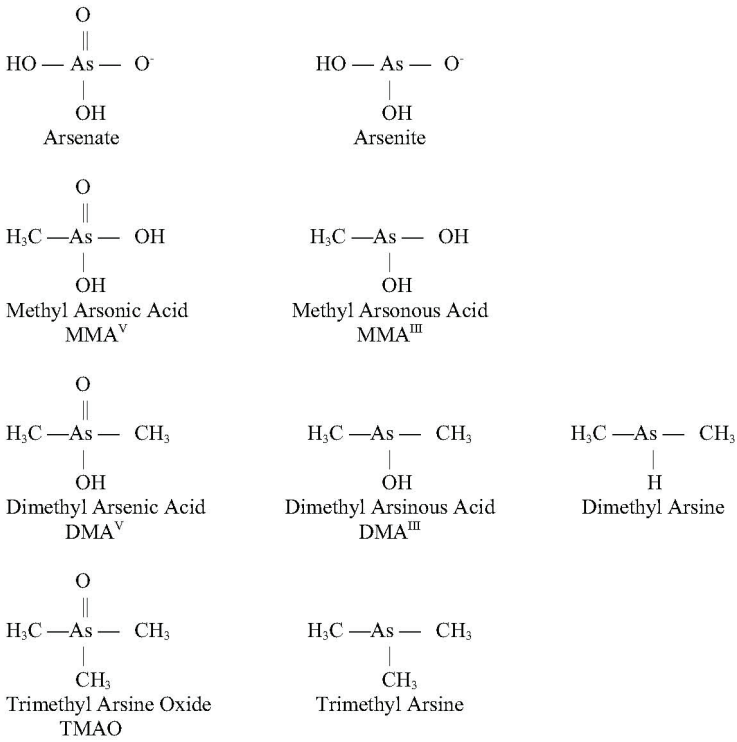


FIGURE 4-2 Structures of selected arsenic-containing compounds.

in both inorganic and organic (including methylated) forms and is readily metabolized in humans and other species, and inorganic arsenic can be converted to organic forms. Although organic forms can be converted into inorganic forms by microorganisms in the soil, there is no evidence that this can occur in humans or other vertebrate species (Cohen et al., 2006).

The arsenic in cacodylic acid (CAS No. 75-60-5) has a valence of +5. Cacodylic acid (also known as dimethylarsinic acid [DMA^V] by its more standard chemical name) was the form of arsenic used in Agent Blue, one of the mixtures used for defoliation in Vietnam. DMA^V made up about 30 percent of Agent Blue. Agent Blue was chemically and toxicologically unrelated to Agent Orange, which consisted of phenoxy herbicides contaminated with dioxin-like compounds.

Potential cacodylic acid exposure of Vietnam veterans would have involved direct exposure to exogenous DMA^V, rather than exposure to inorganic arsenic, which would have led to endogenous formation of MMA^V and MMA^{VIII} and then DMA^V, as shown in Figure 4-3. The old hypothesis that methylation of inorganic arsenic was a detoxifying mechanism has been dispelled by newer studies. Direct treatment of laboratory animals with these metabolic products has demonstrated them to be linked to increased incidence of cancers and non-cancer health outcomes, but there are no studies of health effects in humans following direct exposure to DMA that could provide epidemiologic evidence of association for DMA as required by the Agent Orange Act. It cannot be assumed, particularly given the

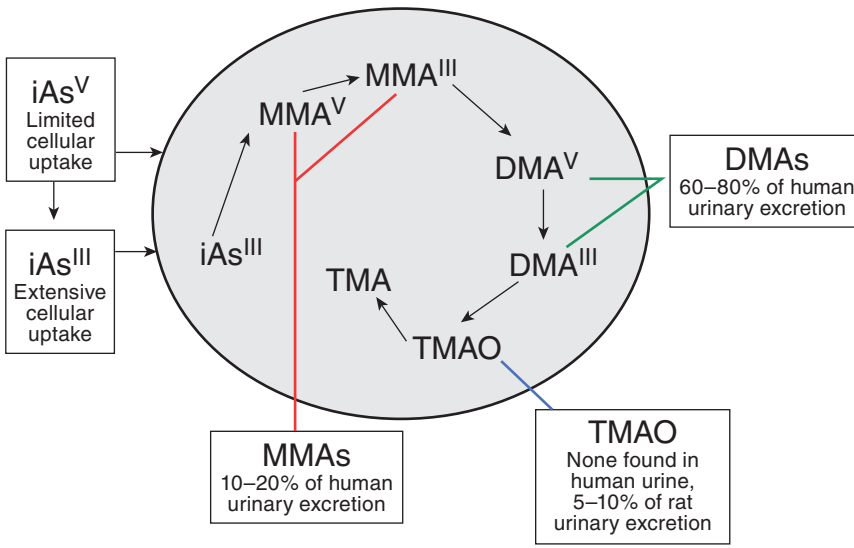


FIGURE 4-3 General pathways of arsenic metabolism after exposure to inorganic arsenic (IAs).
SOURCE: Adapted with permission from Cohen et al., 2006.

apparent lack of endogenous demethylation, that direct exposure to DMA would be equivalent to exposure to inorganic arsenic. Consequently, VAO committees have considered and reviewed toxicologic studies in which animals were directly exposed to DMA, but the extensive literature on the health effects of exposure to inorganic arsenic (including the epidemiologic research, animal experiments, and mechanistic studies) has been regarded as not primarily pertinent to DMA exposure and has not been considered. For information about effects of inorganic arsenic exposure, the reader is referred to recent reviews (IARC, 2012a; NRC, 2013).

Toxicokinetics

Investigations of its metabolism and disposition have generally found DMA^V to be rapidly excreted and mostly unchanged in the urine of most animal species after systemic exposure (Cohen et al., 2006; Suzuki et al., 2010). However, rats differ from most other mammals (including humans) in that a larger percentage (10 percent) of DMA^V binds to hemoglobin in red blood cells, which leads to a considerably longer half-life in blood (Cui et al., 2004; Suzuki et al., 2004). The binding of DMA^V to hemoglobin is 10 times higher in rats than in humans (Lu et al., 2004). Chronic exposure of normal rat hepatocytes to DMA^V results in decreased uptake and increased excretion, so that over time they developed resistance to its cytotoxic effects (Kojima et al., 2006); the tolerance was mediated by the induction of glutathione-*S*-transferase activity and of multiple-drug–resistant protein expression. Adair et al. (2007) examined the tissue distribution of DMA in F344 rats after drinking-water exposure to DMA for 14 days and found that it was extensively metabolized to trimethylated forms that may play a role in toxicity. In a study of DMA treatment of Wistar rats for 10 weeks, the metabolism to trimethylated forms was far less apparent, and the tissue distribution of DMA and trimethylated metabolites was strikingly different (Liu et al., 2015). Thus, there may be differential effects of exposure duration or rat strains, or both, in DMA distribution and metabolism.

A physiologically based pharmacokinetic (PBPK) model of intravenous and ingested DMA^V has been developed on the basis of mouse data (Evans et al., 2008). Similar models have been developed for humans on the basis of exposure to inorganic arsenic (El-Masri and Kenyon, 2008), but these models have limited relevance for assessing potential harm to Vietnam veterans who are presumed to have been directly exposed to DMA^V.

Although epidemiologic studies of direct exposure to DMA^V are not available, investigations into the relationship between health outcomes and the metabolic profiles of humans exposed to inorganic arsenic provide some insight into the roles of the individual metabolites in producing adverse outcome. An increased incidence of urothelial cancer (bladder, kidney, renal pelvis, ureter, and urethra combined) among people exposed to high levels of inorganic arsenic

in drinking water was found in those who generate more MMA^V and less DMA^V endogenously (Huang SK et al., 2008). Also, lower risk of arsenical skin lesions was associated with evidence of higher arsenic methylation capacity in people in areas of high arsenic exposure via the drinking water (Zhang et al., 2014a,b) and smelter workers (Wen et al., 2012). These results could suggest that elevated cumulative levels of urinary MMA^V may be causally associated with increased risk of inorganic arsenic-induced adverse health outcomes, but they could also imply that complete methylation of inorganic arsenic to DMA^V and resulting enhanced excretion are relatively protective.

Toxicity Profile

This section discusses the toxicity associated with organic forms of arsenic, most notably DMA^V because it is the active ingredient in Agent Blue. The toxicity of inorganic arsenic is not considered relevant to veteran exposures to Agent Blue.

Neurotoxicity

Kruger et al. (2006) found that both DMA^{III} and DMA^V significantly attenuated neuronal ion currents through *N*-methyl-D–aspartate receptor ion channels, whereas only DMA^V inhibited ion currents through α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. The data suggest that those methylated forms of arsenic may have neurotoxic potential.

Immunotoxicity

Previous studies have shown that a low concentration of DMA^V (10^{-7} M) could increase the proliferation of human peripheral blood monocytes after their stimulation with phytohemagglutinin, whereas it took a high concentration (10^{-4} M) to inhibit release of interferon-γ. This suggested that various immunomodulatory effects of DMA^V have their own concentration specificity (Di Giampaolo et al., 2004).

Skin Toxicity

In a recent evaluation of the effects of topical exposure of pregnant mice to DMA (valence not stated) on the skin of the dams and offspring (Kim E et al., 2012), no effects were observed in offspring, but the exposure did increase skin thickness in the area of application and alter the expression of apoptosis-related genes (Bcl-2, Bad, caspase-12). The results suggested that transient DMA exposure can be a skin irritant and produce dermatitis.

Genotoxicity and Carcinogenicity

DMA^{III} and DMA^{V} are genotoxic and increase oxidative stress and cause DNA damage, particularly aneuploidy, but they are, such as inorganic arsenic species, poor mutagens (Rossman and Klein, 2011). Gómez et al. (2005) demonstrated that DMA^{III} induces a dose-related increase in DNA damage and oxidative stress in Jurkat cells. DMA^{III} was considerably more potent than DMA^{V} in inducing DNA damage in Chinese hamster ovary cells (Dopp et al., 2004), which was associated with a greater uptake of DMA^{III} into the cells. An additional study showed that DMA^{V} permeates membranes poorly, but when forced into cells by electroporation it can induce DNA damage (Dopp et al., 2005). Similarly, an analysis of arsenical dimethylated metabolites in human bladder cancer cells found dimethylmonothioarsinic acid ($DMMTA^{V}$) and DMA^{III} to be the most toxic and DMA^{V} to be less toxic in terms of DNA damage (Naranmandura et al., 2011). DNA damage from $DMMTA^{V}$ was shown to be related to the accumulation of reactive oxygen species and down-regulation of p53 and p21 (DNA repair proteins); these processes were mediated in part through intracellular conversion of $DMMTA^{V}$ to DMA^{V} and DMA^{III} (Naranmandura et al., 2011). Thus, although extracellular DMA^{V} has little toxic effect in cells because of its low uptake, intracellular DMA^{V} can be highly toxic. Gene-expression profiling of bladder urothelium after chronic exposure to DMA^{V} in drinking water showed significant increases in genes that regulate oxidative stress (Sen et al., 2005), whereas hepatic gene-expression profiling showed that DMA^{V} exposure induced changes consistent with oxidative stress (Xie et al., 2004). In vivo, DMA^{V}-induced proliferation of the urinary bladder epithelium could be attenuated with the antioxidant *N*-acetylcysteine (Wei et al., 2005). Arsenicals, including DMA, also interfere with certain DNA repair mechanisms, both base- and nucleotide-excision repair, and may thereby act as co-carcinogens enhancing the effect of other genotoxic carcinogens (Rossman and Klein, 2011). In fact, DMA is a stronger inhibitor of nucleotide-excision repair than inorganic arsenic (Shen et al., 2008).

DMA^{III} and DMA^{V} are carcinogenic. Cancers have been induced in the urinary bladder, kidneys, liver, thyroid glands, and lungs of laboratory animals exposed to high concentrations of DMA. In a 2-year bioassay of F344/Crl rats fed a diet containing 40 or 100 ppm DMA^{V}, the females consuming the highest dose (100 ppm) developed urothelial carcinomas and papillomas in the bladder, and males and females at both dose levels (40 and 100 ppm) developed hyperplastic nonneoplastic changes in the bladder (Arnold et al., 2006). Wei et al. (2002) exposed male F344/DuCrj rats to DMA via the drinking water and found statistically significant incidences of bladder hyperplasia and transitional cell papillomas and carcinomas at doses of 50 and 100 ppm. Similarly, Wang A et al. (2009) found that exposure of F344 rats to DMA^{V} in drinking water at 1, 4, 40, or 100 ppm resulted in a change in the urinary bladder epithelium, but there were no changes in DNA repair capacity. In another study, Cohen et al. (2007b) exposed

F344 rats to DMA^V in the diet for 2 years and found an increase in bladder tumors in those receiving 100 ppm; the researchers postulated that trimethylated forms of arsenic may be responsible for bladder cancer in rats. Direct intravesical administration of 90 mg/kg DMA^V to female adult rats resulted in increased bromodeoxyuridine labeling in urothelial cells, indicating DNA damage, weak neutrophil infiltration, and the proliferation of urothelial epithelium mediated through modest increases in oxidative-stress indexes (Takahashi et al., 2011). Increased urothelial cell proliferation was also found following DMA exposure via the drinking water (Wei et al., 2002). It is noteworthy that co-treatment with an antioxidant, N-acetylcysteine, worsened the DMA^V-induced bladder injury rather than ameliorating it as expected, suggesting that the carcinogenic mechanism of DMA^V is more complicated than simple production of oxidative stress. In the mouse lung, DMA^V acts as a tumor initiator (Yamanaka et al., 2009) and as a tumor promoter (Mizoi et al., 2005). DMA^V can also act as a complete carcinogen, inducing lung tumors in susceptible strains of mice, including those with deficient DNA-repair activity (Hayashi et al., 1998; Kinoshita et al., 2007). In F344/DuCrj rats treated with a mixture of carcinogens for 4 weeks, subsequent exposure to DMA (not indicated whether this was DMA^{III} or ^{V}) via the drinking water for 24 weeks caused tumor promotion in the urinary bladder, kidney liver, and thyroid gland but inhibited the induction of tumors of the nasal passages (Yamamoto et al., 1995). In a similarly designed experiment, DMA (not indicated whether this was DMA^{III} or ^{V}) was found to be a bladder tumor promotor after treatment with the bladder carcinogen *N*′-butyl-*N*′-(4-hydroxybutyl) nitrosamine (Wanibuchi et al., 1996). Yamanaka et al. (2009) suggested that DMA^{III} can act as a tumor promoter through the formation of a DMA^{III} radical after the reduction of DMA^V. Recent studies have also found that oral exposure of adult mice to 200 ppm DMA^V in addition to fetal arsenic exposure can act as a promoter of renal and hepatocellular carcinoma, markedly increasing tumor incidence beyond that produced by the fetal arsenic exposure alone (Tokar et al., 2012). These findings emphasize how multiple life events can contribute to an adverse health outcome in which adult DMA^V exposure triggered an otherwise dormant disease.

Mechanisms

Oxidative stress is a common theme that runs through the literature on the mechanisms of action of arsenic, particularly with regard to cancers in animals, although some studies have suggested that methylated arsenicals (MMA^{III} and DMA^{III}) can induce aneuploidy in mammalian cells at concentrations below those required to produce oxidative stress after in vitro exposure (Kligerman and Tennant, 2007) and that oxidative stress can be induced at non-cytotoxic concentrations (Rossman and Klein, 2011). Other studies have shown that mice that are deficient in enzymes associated with repair of oxidative DNA damage are highly susceptible to induction of tumors, particularly lung tumors, by DMA^V (Kinoshita

et al., 2007). The chemical reaction of arsenicals with thiol groups in sensitive target tissues, such as red blood cells and kidneys, may also be a mechanism of action of organic arsenicals (Naranmandura and Suzuki, 2008).

Cohen et al. (2007b) postulated that cytotoxicity-induced regenerative cell proliferation in the urothelium is a major factor in the carcinogenicity of DMA to the rat bladder, and indeed urothelial cell proliferation is increased following DMA exposure (Takahashi et al., 2011; Wei et al., 2002). However, whether this can be taken to indicate that there is a dose threshold for DMA carcinogenicity remains uncertain in view of the above mentioned in vitro data from Kligerman and Tennant (2007) and Rossman and Klein (2011). There may also be epigenetic effects involved in DMA carcinogenicity, as suggested by a study in humans in which there was a significant association between global DNA methylation and urinary DMA levels (Tellez-Plaza et al., 2014).

The variation in the susceptibility of various animal species to tumor formation caused by inorganic and organic arsenic is thought to depend heavily on differences in metabolism and distribution. Thus, genetic differences may play an important role. Numerous investigators have examined potential human susceptibility factors and gene polymorphisms that may increase a person's risk of cancer and other diseases induced by arsenicals (Aposhian and Aposhian, 2006; Hernandez et al., 2008; Huang SK et al., 2008; Huang YK et al., 2008; McCarty et al., 2007; Meza et al., 2007; Steinmaus et al., 2007, 2010), but as yet polymorphisms that may contribute to a person's susceptibility to DMA-induced cancers or tissue injury have not been identified.

Summary

DMA is genotoxic and carcinogenic in certain animal models and in vitro assays, including studies in human cells, and it interferes with DNA repair mechanisms and has epigenetic effects that may be involved in gene damage and carcinogenesis. However, it is not clear whether these effects would also occur in humans directly exposed to DMA.

PHENOXY HERBICIDES: 2,4-DICHLOROPHENOXY ACID AND 2,4,5-TRICHLOROPHENOXYACETIC ACID

Chemistry

2,4-D (CAS No. 94-75-7) is an odorless crystalline powder that, when pure, is white in color (see Figure 4-4); it may appear yellow when phenolic impurities are present. The melting point of 2,4-D is 138°C, and the free acid is corrosive to metals. It is soluble in water and in a variety of organic solvents (such as acetone, alcohols, ketones, ether, and toluene). 2,4,5-T (CAS No. 93-76-5) is an odorless, white to light-tan solid with a melting point of 158°C. 2,4,5-T is noncorrosive

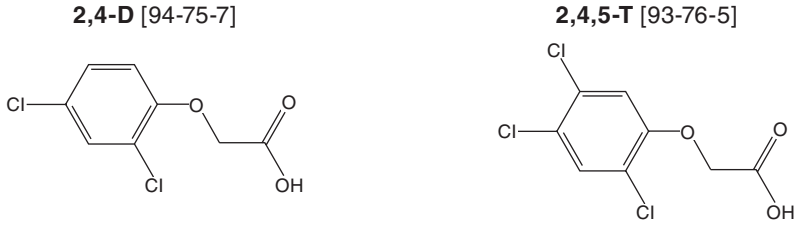


FIGURE 4-4 Structures of 2,4-D and 2,4,5-T.

and is soluble in alcohol and water. It reacts with organic and inorganic bases to form salts and with alcohols to form esters.

Uses of 2,4-D and 2,4,5-T

2,4-D has been used commercially in the United States since World War II to control the growth of broadleaf plants and weeds on range lands, lawns, golf courses, forests, roadways, parks, and agricultural land; it remains a widely used herbicide approved for use by the European Union and EPA. Formulations include 2,4-D amine and alkali salts and esters, which are mobile in soil and readily absorbed through the leaves and roots of many plants. Like 2,4-D, 2,4,5-T was developed and marketed as a herbicide during World War II. However, the registration for 2,4,5-T was canceled by EPA in 1978 when it became clear that it was contaminated with TCDD during the manufacturing process. It is recognized that the production of 2,4-D also involves the generation of some dioxin contaminants, even some with dioxin-like activity, but the fraction of TCDD is comparatively very small, as discussed in Chapter 3 in conjunction with Figure 3-1, which describes the chemistry leading to TCDD contamination during the manufacture of 2,4,5-T from tricholophenol.

The herbicidal properties of 2,4-D and 2,4,5-T are related to the chemical's ability to mimic the plant growth hormone indole acetic acid. They are selective herbicides in that they affect the growth of only broadleaf dicots (which include most weeds) and do not affect monocots, such as wheat, corn, and rice.

Toxicokinetics

Several studies have examined the absorption, distribution, metabolism, and excretion of 2,4-D and 2,4,5-T in animals and humans. Data on both compounds are consistent among species and support the conclusion that the absorption of oral or inhaled doses is rapid and complete. A recent study indicates that 2,4-D can bind to innate intestinal, intracellular lipid-binding proteins, which may be how these compounds move through columnar absorptive epithelial cells from the intestines to systemic distribution (Carbone and Velkov, 2013). Absorption

through the skin is much lower but may be increased with the use of sunscreens or alcohol (Brand et al., 2002; Pont et al., 2004). After absorption, 2,4-D and 2,4,5-T are distributed widely in the body but are eliminated quickly, predominantly in unmetabolized form in urine (Sauerhoff et al., 1977), but 2,4,5-trichlorophenol and 2,4-dichlorophenol have been identified as trace metabolites in urine. The half-life of single doses of 2,4-D or 2,4,5-T in humans has been estimated to be about 18–23 hours and is highly dependent on urinary pH (Gehring et al., 1973; Kohli et al., 1974; Sauerhoff et al., 1977; WHO, 1984). Hines et al. (2003) found that concentrations of 2,4-D and its metabolites in the urine of herbicide applicators—that is, those who apply the herbicides—were consistent with 2,4-D urinary half-life estimates of 13–40 hours in humans.

Toxicity Profile

The toxicity database on 2,4-D is extensive,[1] whereas the available data on the toxicity of purified 2,4,5-T, independent of its contamination by TCDD, are sparse. TCDD is much more toxic than 2,4,5-T, and much of the toxicity attributed to 2,4,5-T in early studies was later shown to be caused by the TCDD contaminant. The following summary therefore focuses on 2,4-D toxicity, and information on pure 2,4,5-T is added when it is available.

After a single oral dose, 2,4-D is considered to produce moderate acute toxicity with an LD_{50} (dose lethal to 50 percent of exposed animals) of 375 mg/kg in rats, 370 mg/kg in mice, and from less than 320 to 1,000 mg/kg in guinea pigs. Rats and rabbits have dermal LD_{50}s of 1,500 mg/kg and 1,400 mg/kg, respectively. 2,4,5-T itself also produces moderate acute toxicity, with oral LD_{50}s of 389 mg/kg in mice and 500 mg/kg in rats. Death from acute poisoning with 2,4-D or 2,4,5-T has been attributed to the ability of the chemicals to uncouple oxidative phosphorylation, a vital process used by almost all cells in the body as the primary means of generating energy. After exposure to a high dose, death due to multiple organ failure can occur rapidly. Studies in rats, cats, and dogs indicate that the central nervous system is the principal target organ for acute 2,4-D toxicity in mammals and suggest that the primary site of action is the cerebral cortex or the reticular formation (Arnold et al., 1991; Dési et al., 1962a,b). Based on case reports, neurotoxicity in humans is the predominant effect of acute inhalation and oral exposure to 2,4-D; symptoms include stiffness of the arms and legs, lack of coordination, lethargy, anorexia, stupor, and coma. 2,4-D is also an irritant of the gastrointestinal tract, causing nausea, vomiting, and diarrhea.

Chronic exposure to 2,4-D at relatively high concentrations has been shown to produce a variety of toxic effects, including hepatic and renal toxicity, neurotoxicity, and hematologic changes. A NOEL of 2,4-D of 1 mg/kg was identified

[1]See http://toxnet.nlm.nih.gov, search on "2,4-D" or "2,4,5-T," accessed July 24, 2015.

for renal toxicity in rats (Hazleton Laboratories America, 1986). Exposure to 2,4-D was associated with reduced survival and decreased growth rates of offspring of mothers fed high doses during pregnancy, which were associated with maternal toxicity (Munro et al., 1992). Charles et al. (2001) found 2,4-D did not affect fertility or produce teratogenic effects in the offspring of rats or rabbits gavaged with doses lower than 90 mg/kg/day, which caused overt maternal toxicity. A recent one-generation study in which rats were fed diets containing 2,4-D (females: up to 40 mg/kg/day; males: up to 45 mg/kg/day) from 4 weeks before breeding through 3 weeks of lactation confirmed these results, and furthermore found that even at the highest exposure there is no evidence of interaction with the androgen, estrogen, or steroidogenesis pathways in the pups (Marty et al., 2013). Other studies, however, suggest that exposure to 2,4-D does have an impact on the male reproductive system (Alves et al., 2013; Joshi et al., 2012). Exposure of adult male rats to 2,4-D at doses as low as 150 mg/kg for 30 days resulted in a reduction in the weight of the testes, prostate, epididymis, and seminal vesicles and a reduction in sperm density (Joshi et al., 2012). Alves et al. (2013) show that the exposure of rat Serotoli cells in culture at 10 μM 2,4-D resulted in alterations in cellular metabolism linked to effective spermatogenesis, which could be a mechanism that would reduce sperm density. Mazhar et al. (2014) treated pregnant rats by gavage on GDs 1–19 with 100 mg/kg/day 2,4-D alone or administered with 100 mg/kg/day of the antioxidant vitamin E. Morphological and skeletal defects and low birth weight were observed in the fetuses of dams treated only with 2,4-D, but not in those whose mothers were also treated with vitamin E, thereby suggesting that 2,4-D exposure elicits fetotoxicty through inducing oxidative stress. In vitro exposure of human erythrocytes to 2,4-D caused changes in antioxidant enzyme activity as well as increased protein carbonyls, also indicating induction of oxidative stress (Bukowska, 2003). Similar changes were observed in the liver of exposed rats (Tayeb et al., 2010, 2013). Immunotoxicity of 2,4-D has been reported in a small number of studies, including a few studies of 2,4-D applicators showing both immunosuppression (Faustini et al., 1996) and immuno-stimulation (Figgs et al., 2000; Holland et al., 2002). At high doses that produced clinical toxicity in experimental animals, a suppression of the antibody response was observed, whereas other measures of immune function were normal. The immunotoxicity of 2,4,5-T has not been evaluated in laboratory animals.

The carcinogenicity of 2,4-D and 2,4,5-T has been studied in rats, mice, and dogs after exposure in their food, direct placement in their stomachs, or exposure of their skin. Early studies in mice (NTIS, 1968) and rats (Hansen et al., 1971) found little to suggest tumor induction when animals were treated with 2,4-D by gavage or subcutaneously. Hazelton Laboratories of America (1986, 1987) conducted a series of studies in rats and mice, which all had negative results except one that found an increased incidence of brain tumors in male rats—but not female rats—that received the highest dose of 45 mg/kg/day 2,4-D in their feed.

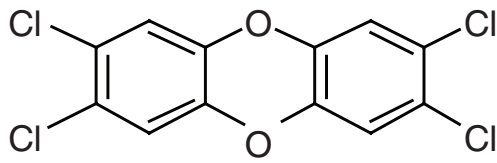
The occurrence of malignant lymphomas in dogs kept as pets was reported to be higher when owners reported that they used 2,4-D on their lawns than when they did not (Hayes et al., 1991, 1995), but detailed reanalysis did not confirm this finding (Kaneene and Miller, 1999). A controlled study that used dogs exposed to 2,4-D in the laboratory had negative results. Timchalk (2004) suggested that dogs are not relevant for comparative evaluation of human health risk attributable to 2,4-D exposure, because they excrete 2,4-D less efficiently than rats or humans. Given the degree of variability observed in humans (Hines et al., 2003), however, the canine information might be applicable for some people.

2,4-D is not metabolized to reactive intermediates capable of interacting with DNA, and the evidence supports the conclusion that 2,4-D is not a genotoxic carcinogen. However, Sandal and Yilmaz (2011) found that lymphocytes from smokers show genotoxic damage after exposure to 2,4-D, whereas lymphocytes from non-smokers do not, which suggests that although 2,4-D may not be a carcinogen, it may influence the activity of known carcinogens.

2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN

Chemistry

TCDDs are polychlorinated dibenzo-*p*-dioxins that have a triple-ring structure consisting of two benzene rings connected by an oxygenated ring with four attached chlorine atoms; in the case of the dioxin congener of greatest concern, 2,3,7,8-TCDD (commonly called simply TCDD), the chlorine atoms are attached at the 2, 3, 7, and 8 positions of the benzene rings (see Figure 4-5). The chemical properties of TCDD include a molecular weight of 322, a melting point of 305–306°C, a boiling point of 445.5°C, and a log octanol–water partition coefficient of 6.8 (National Toxicology Program substance profile). It is very lipophilic or fat soluble, is virtually insoluble in water (19.3 ng/L), and is soluble in organic solvents, such as benzene and acetone. It has been suggested that volatilization of dioxin from water may be an important mechanism of transfer from the aqueous to the atmospheric phase (EPA, 2004); however, because of its very low water solubility, most TCDD is bound to sediments and particulate matter.



2,3,7,8-tetrachlorodibenzo-*p*-dioxin

FIGURE 4-5 Chemical structure of TCDD.

Toxicokinetics

The disposition of TCDD (which includes its absorption, distribution, biotransformation, and excretion) have been extensively studied in humans and a number of other animal models in the past 30 years. Given the plethora of data, this section highlights and summarizes only key findings.[2]

TCDD is absorbed into the body rapidly but is eliminated slowly. Because it is very lipophilic, resistant to biotransformation, and slowly eliminated, the concentration of TCDD in the lipid fraction of blood serum is thought to be in dynamic equilibrium with that in the lipid fraction in other tissue compartments. Thus, the lipid-adjusted blood serum concentration of TCDD is used to estimate total body burdens; at high TCDD concentrations, however, the liver sequesters some of the dioxin, so a lipid adjustment that ignores the hepatic fraction would underestimate the total body burden. The exposure of humans to TCDD is thought to occur primarily via the mouth, skin, and lungs. In laboratory animals, oral administration of TCDD has been shown to result in absorption of 50 to 93 percent of the administered dose (Nolan et al., 1979; Rose et al., 1976). Similarly, a study performed in a 42-year-old man found that 87 percent of the oral dose was absorbed (Poiger and Schlatter, 1986). Dermal absorption appears to be dose-dependent: Lower absorption occurs at higher doses (Banks and Birnbaum, 1991). Studies performed in vitro with tissues isolated from humans indicate that human skin may not be readily penetrable (Weber et al., 1991). The varied and complex environmental matrices make environmental exposures difficult to quantify. Animal studies have demonstrated that the presence of soil or lipophilic agents dramatically reduces dermal absorption of TCDD: Application in an activated carbon–water paste essentially eliminates absorption in contrast with the absorption of the pure compound dissolved in solvents. Oral bioavailability of TCDD and related compounds also depends on the matrix: Contaminated breast milk and food products have much higher bioavailability than soil-bound or sediment-bound TCDD, and activated carbon essentially blocks oral bioavailability (Olson, 2012).

After ingestion and gastrointestinal absorption, TCDD associates primarily with the lipoprotein fraction of the blood and later partitions into the cellular membranes and tissues (Henderson and Patterson, 1988). TCDD is distributed to all compartments of the body; the amounts differ from organ to organ, but most studies indicate that the primary distribution of TCDD is in the liver and adipose tissues. For example, in a human volunteer it was found that 135 days after ingestion 90 percent of TCDD was in fat (Poiger and Schlatter, 1986), and TCDD persists in adipose tissue in the rhesus monkey (Bowman et al., 1989). The

[2]A more exhaustive review and support documents may be accessed at http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=366&tid=63, http://www.epa.gov/ncea/pdfs/dioxin/nas-review, or http://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1024, accessed July 24, 2015.

distribution and elimination of TCDD depend on the tissue examined, the time that has elapsed since exposure, total exposure, and other factors. For example, the concentration of cytochrome P450 1A2 (CYP1A2) in the liver is increased by TCDD (Poland et al., 1989). Direct binding of TCDD to CYP1A2 is thought to result in the sequestration of TCDD in the liver and to inhibit its distribution to other tissues. The importance of CYP1A2 concentrations for the toxic actions of TCDD has also been demonstrated in several laboratory situations; for instance, CYP1A2-knockout mice were more susceptible than wild-type mice to TCDD immunotoxicity (Smialowicz et al., 2008), and maternal hepatic CYP1A2 was found to sequester TCDD and protect mouse fetuses against TCDD-induced teratogenesis (Dragin et al., 2006). In addition, the distribution of TCDD is age dependent, as shown by studies in which young animals displayed the highest concentration of TCDD in the liver and aged animals the highest concentrations in kidneys, skin, and muscle (Pegram et al., 1995). Finally, the rate of elimination of TCDD, particularly after low exposures, depends heavily on the amount of adipose tissue mass (Aylward et al., 2005a; Emond et al., 2005, 2006).

In laboratory animals, TCDD is metabolized slowly. It is eliminated primarily in feces as both the parent chemical and its more polar metabolites. However, elimination appears to be dose dependent; at low doses, about 35 percent of the administered dose of TCDD was detected in the feces; at higher doses, about 46 percent was observed (Diliberto et al., 2001). The dose-dependent occurrence of TCDD metabolites in the feces is thought to be due to the increased expression of metabolizing enzymes at higher doses and to hepatic sequestration, which makes dioxins more available for metabolism.

Milbrath et al. (2009) conducted a comprehensive review of studies that reported the congener-specific elimination rates of TCDD and related compounds and analyzed the relationships between the apparent half-lives of the compounds as a function of age, body fat, smoking status, and breastfeeding. In infants (under 2 years old), the compounds have a reported half-life of 0.4 year (Leung et al., 2006), and in adults, a half-life of 7.2 years (Milbrath et al., 2009). Aging results in an increase in and redistribution of body fat and lipophilic chemicals that alters their rate of elimination (Van der Molen et al., 1996). Human studies of the Ranch Hand cohort have consistently found a similar relationship between an increasing half-life of TCDD and an increasing BMI (Michalek and Tripathi, 1999; Michalek et al., 1992, 1996). Smoking and breastfeeding are associated with promoting the elimination of TCDD and, in the case of breastfeeding, exposing infants through breast milk. Polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke are capable of inducing CYP1A1, 1A2, and 1B1, which in turn may increase the rate of metabolism and subsequent elimination of TCDD. A 30 percent decrease in TCDD plasma half-life has been associated with smoking (Flesch-Janys et al., 1996).

Special Case of the Poisoning of Victor Yushchenko

In 2004 Victor Yushchenko, a candidate for the presidency of the Ukraine, was poisoned with TCDD. It led to severe chloracne and a blood serum TCDD concentration of 108,000 ppt (pg/g lipid), which was about 50,000 times as great as that in the general population at the time. The incident provided an opportunity to assess the toxicokinetics of TCDD after what was apparently a single large exposure. Serum and fat analysis of TCDD supports the first-order elimination half-life of 15.4 months in Yushchenko, and the similar decay curves confirmed that TCDD was in equilibrium between serum lipids and subcutaneous fat (Sorg et al., 2009). That is much shorter than the 7.2-year reference half-life reported by Milbrath et al. (2009) and supports the dose-dependent elimination of TCDD, which is associated with the induction of potential TCDD-metabolizing enzymes (CYP1A1, 1A2, and 1B1) in very high TCDD exposures. Two metabolites of TCDD (2,3,7-trichloro-8-hydroxydibenzo-*p*-dioxin and 1,3,7,8-tetrachloro-2-hydroxydibenzo-*p*-dioxin) were detected in Yushchenko's feces, serum, and urine but not in his fat or skin. Over a 12-month period, about 38 percent of the TCDD-derived material was eliminated as metabolites (95 percent in feces, 5 percent in urine) and 62 percent as parent chemical. The metabolite:TCDD ratio in the blood serum was about one-fiftieth of that in the feces; this supports the conclusion that the metabolites were not originally ingested with TCDD (Sorg et al., 2009). The very slow metabolism of TCDD has been previously reported in laboratory animal models (Gasiewicz et al., 1983; Olson, 1986; Olson et al., 1980; Poiger and Schlatter, 1979) and in humans (Wendling et al., 1990). It is also noteworthy that the structures of the human metabolites are the same as previously reported in the rat and dog (Poiger et al., 1982; Sawahata et al., 1982). A continued analysis of Yushchenko's condition has revealed putative metabolomic and transcriptomic biomarkers that may prove useful for predicting health effects in populations with significant TCDD exposures (Jeanneret et al., 2014; Saurat et al., 2012).

In light of the variables discussed above and the effect of differences in physiologic states and metabolic processes, which can affect the mobilization of lipids and possibly of compounds stored in them, complex PBPK models have been developed to integrate exposure dose with organ mass, blood flow, metabolism, and lipid content in order to predict the movement of toxicants into and out of each organ. A number of modeling studies have been performed recently in an effort to understand the relevance of animal experimental studies to the exposures that occur in human populations (Aylward et al., 2005a,b; Beaudouin et al., 2010; Emond et al., 2005).

Toxicity Profile

Effects on Tissues and Organs of Laboratory Animals

The effects of TCDD in laboratory animals have been observed in a number of species (rats, mice, guinea pigs, hamsters, monkeys, cows, and rabbits) after the administration of a variety of doses and after periods that represent acute exposures (less than 24 hours), subchronic exposures (1 day–3 months), and chronic exposure (more than 3 months). Some differences have been observed between species, particularly with respect to the degree of sensitivity, but in general the effects observed are qualitatively similar. Relatively high exposures of TCDD affect a variety of organs and result in organ dysfunction and death. The lethal toxicity of TCDD waries widely among animal species; the oral LD_{50} of the chemical varies from 1 µg/kg in guinea pigs to 5,000 µg/kg in hamsters. The developing fetus, however, is especially vulnerable to TCDD exposure, and there is only about a 10-fold variability in fetal lethal potency among these species (Kransler et al., 2007; Peterson et al., 1993; Poland and Knutson, 1982). One characteristic of TCDD exposure is a wasting syndrome that includes the loss of adipose and muscle tissue and severe weight loss, but the specific mechanisms of lethality remain unknown. In most rodents, exposure to TCDD leads to hepatic enlargement, the presence of hepatic lesions, and impaired hepatic function. The thymus is also sensitive. Finally, in both humans and nonhuman primates, TCDD exposure results in chloracne and associated dermatologic changes. As will be discussed in more detail in Chapters 7–13, studies performed in animal models have indicated that exposure to TCDD adversely affects the heart, the skin, and the immune, endocrine, and reproductive systems and increases the incidence of cancers of the liver, skin, thyroid, adrenal cortex, hard palate, nasal turbinates, tongue, and respiratory and lymphatic systems (ATSDR, 1998; Barouki et al., 2012; Birnbaum, 1994; Huff et al., 1994; Knerr and Schrenk, 2006). When TCDD has been administered to pregnant animals, birth defects—such as cleft palate, malformations of the reproductive organs of male and female progeny, and abnormalities in the cardiovascular, pulmonary, endocrine, skeletal, and nervous systems—have been observed. Of course, effects arising from perinatal exposure are not in question for Vietnam veterans themselves, but this activity is of concern with respect to their offspring. The developmental origins of health and disease are discussed in more detail in Chapter 10.

Effects on Enzymes, Hormones, and Receptors in Laboratory Animals and Cultured Cells

In addition to adversely affecting the ability of specific organs to fulfill their normal physiologic roles, TCDD has been found to alter the function and expression of essential proteins, particularly a number of enzymes. The enzymes

that are most affected by TCDD are ones that act on or metabolize xenobiotics and hormones, often by changing the chemicals' polarity (water solubility), and thus promoting the elimination of the metabolites. Among the enzymes affected by TCDD, the best studied is CYP1A1, which metabolizes some xenobiotics. In laboratory animals, exposure to TCDD commonly results in an increase in CYP1A1 in most tissues; CYP1A1 therefore is often used as a marker of TCDD exposure. Related enzymes whose levels are also increased with TCDD exposure include CYP1B1 and CYP1A2, which together with CYP1A1 are capable of biotransforming some procarcinogens to potentially mutagenic and carcinogenic metabolites.

In addition to CYP1A1 and CYP1A2, TCDD can affect other enzymes that metabolize hormones, such as thyroid hormones, retinoic acid, testosterone, estrogens, and adrenal steroids. Those hormones transmit their signals by interacting with specific proteins called receptors and in this manner initiate a chain of events in many tissues of the body. For example, the binding of the primary female sex hormone, estrogen, to the estrogen receptor promotes the formation of breasts and the thickening of the endometrium, regulates the menstrual cycle, and influences brain development. Exposure to TCDD can increase the metabolism of estrogen and thus lead to a decrease in the amount of estrogen available for binding and activating the estrogen receptor. The ultimate effect of TCDD is an interference with all the bodily functions that are regulated by estrogens. Similarly, the actions of TCDD on the adrenal steroids can adversely affect their ability to regulate glucose tolerance, insulin sensitivity, lipid metabolism, body weight, vascular function, and cardiac remodeling. In addition to changing the amount of hormone present, TCDD has been found to interfere with the ability of receptors to fulfill their role in transmitting hormone signals. Those actions of TCDD on enzymes and hormone receptors are thought to underlie, in part, the observed developmental and reproductive effects and cancers that are hormone responsive.

Effects on Paths of Cellular Differentiation

The broad spectrum of TCDD effects on hormone and growth factor systems, cytokines, and other signal-transducer pathways indicates that TCDD is an extremely powerful growth dysregulator (Birnbaum, 1994). Research performed primarily in cultured cells has shown that TCDD can affect the ability of cells to undergo such processes as proliferation, differentiation, and apoptosis. During the proliferation process, cells grow and divide. When cells are differentiating, they are undergoing a change from less specialized to more specialized. Cellular differentiation is essential for an organism to mature from a fetal to an adult state. In the adult, proper differentiation is required for the normal functioning of the body, for example, in maintaining a normally responsive immune system. The processes of controlled cell death, such as apoptosis, are similarly important during development of the fetus and are necessary for normal physiologic functions

in the adult. Apoptosis is a way for the body to eliminate damaged or unnecessary cells. The ability of a cell to undergo proliferation, differentiation, and apoptosis is tightly controlled by an intricate network of signaling molecules that allows the body to maintain the appropriate size and number of all the specialized cells that form the fabric of complex tissues and organs. Any disruption of the network that alters the delicate balance of cell fate can have severe consequences, including impairment of the function of the organ because of the absence of specialized cells. Alternatively, the presence of an excess of some kinds of cells can result in the formation and development of tumors. Thus, the ability of TCDD to disrupt the normal course of a specific cell to proliferate, differentiate, or undergo apoptosis is thought to underlie (at least in part) its adverse effects on the immune system and the developing fetus and its ability to promote the formation of some cancers.

Mechanisms

TCDD binds and activates the aryl hydrocarbon receptor (AHR) in the cells of virtually every tissue in the body. The ability of TCDD to bind to the AHR with high affinity is necessary—but not sufficient—to produce most of the adverse effects associated with TCDD exposure, including those from direct TCDD binding to and activation of the AHR and later alterations in the expression of TCDD-regulated genes as well as to those signaling pathways altered through interactions with the AHR pathway (Poland and Knutson, 1982; Safe, 1990; Schmidt and Bradfield, 1996; Whitlock, 1990).

The AHR functions as a ligand-activated nuclear transcription factor. Upon binding of agonists (ligands), such as TCDD, the AHR forms a heterodimer with a structurally related protein called AHR nuclear translocator (ARNT). The dimeric complex binds to core DNA sequences called xenobiotic-responsive elements (XREs) or dioxin-responsive elements (DREs) in the promotor region of responsive genes and enhances the transcription of those genes. Many of the AHR-regulated genes encode drug-metabolizing enzymes, such as CYP1A1, CYP1A2, CYP1B1, and a variety of phase II conjugating enzymes. Although the up-regulation of these enzymes is a sensitive biomarker of exposure to TCDD and in part contributes mechanistically to some of the adverse effects of TCDD, the tissue-, species-, time-, and dose-specific modulation (increase or decrease) of many genes is thought to contribute to the wide array of toxic responses to TCDD exposure (Black et al., 2012; Boverhof et al., 2006; Ovando et al., 2006, 2010; Perdew, 2008; Puga et al., 2009; Schneider et al., 2014).

AHR Signaling Pathways

The primary and most intensely studied pathway by which TCDD elicits biologic responses is depicted in Figure 4-6. In the absence of a bound ligand,

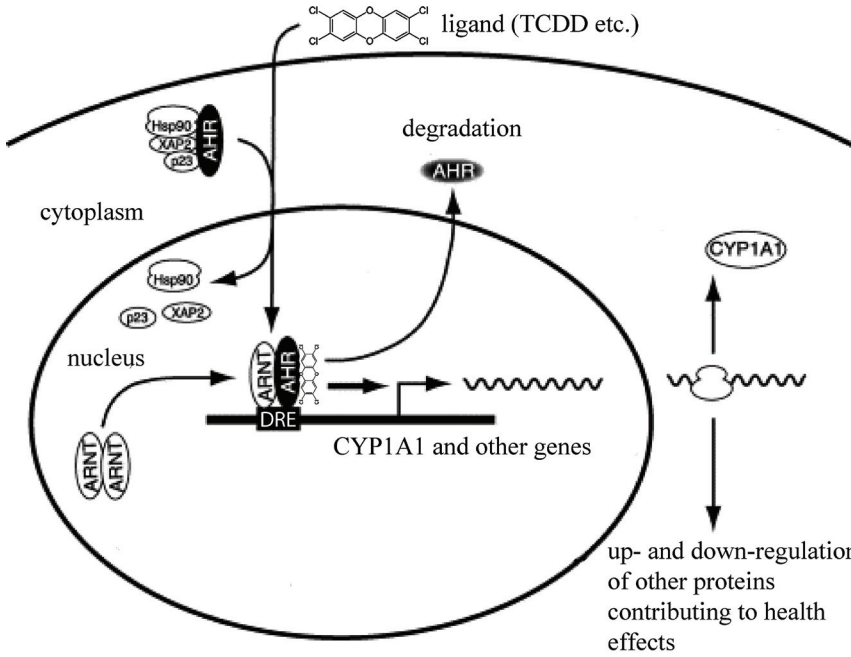


FIGURE 4-6 Mechanism of gene induction and repression after AHR activation by TCDD.

the inactive AHR is retained in the cytoplasm of the cell in a complex consisting of two molecules of the heat-shock protein Hsp90, one molecule of prostaglandin E synthase 3 (p23) (Kazlauskas et al., 1999), and one molecule of the immunophilin-like protein hepatitis B virus X-associated protein 2 (XAP2) (Petrulis et al., 2003), previously identified as either AHR-interacting protein (AIP; Ma and Whitlock, 1997) or AHR-associated protein 9 (ARA9; Carver and Bradfield, 1997). The hsp90 dimer–p23 complex plays multiple roles in the protection of the AHR from proteolysis, maintaining it in a conformation that makes it accessible to ligand binding at the same time that it prevents the premature binding of ARNT (Carver et al., 1994; Pongratz et al., 1992; Whitelaw et al., 1993). XAP2 interacts with the carboxyl terminus of hsp90 and with the AHR nuclear-localization signal (NLS), a short amino acid domain that targets the receptor for interaction with nuclear-transport proteins. The binding of XAP2 blocks such an interaction, preventing the inappropriate trafficking of the receptor into the nucleus (Petrulis et al., 2003).

The binding of ligands (such as TCDD) induces the release of XAP2 and the exposure of the NLS and leads to the binding of nuclear-import proteins and

translocation of the cytosolic complex into the nucleus (Davarinos and Pollenz, 1999; Song and Pollenz, 2002). Once in the nucleus, Hsp90, p23, and XAP2 dissociate from the AHR, which allows the binding of ARNT (Hoffman et al., 1991; Probst et al., 1993). The activated AHR–ARNT heterodimeric complex is then capable of directly or indirectly interacting with DNA by binding to recognition sequences in the regulatory region of responsive genes (Dolwick et al., 1993; Probst et al., 1993).

The canonical DNA recognition motif of the AHR–ARNT complex is referred to as the AHR-responsive element (AHRE, also referred to as the DRE or the XRE, for dioxin- or xenobiotic-response element, respectively). This element is found in the promoter region of AHR-responsive genes and contains the core sequence 5′-GCGTG-3′ (Shen and Whitlock, 1992), which is part of a more extensive consensus-binding sequence, 5′-T/GNGCGTGA/CG/CA-3′ (Lusska et al., 1993; Yao and Denison, 1992). The AHR–ARNT complex binds to the AHRE core sequence in such a manner that ARNT binds to 5′-GTG-3′ and AHR binds to 5′-TC/TGC-3′ (Bacsi et al., 1995; Swanson et al., 1995). A second type of element, termed AHRE-II, 5′-CATG(N6)C[T/A]TG-3′, has been shown to be capable of acting indirectly with the AHR–ARNT complex (Boutros et al., 2004; Sogawa et al., 2004). The end result of the process is the recruitment of the transcriptional machinery associated with RNA polymerase II and the initiation of differential changes in the expression of the genes bearing the AHR–ARNT recognition motif. Many of the genes code for proteins responsible for detoxification reactions directed at the elimination of the ligand. Research suggests that posttranslational modifications in histone proteins may modify the response (Hestermann and Brown, 2003; Schnekenburger et al., 2007).

In addition to the widely accepted view that the actions of TCDD are mediated by the binding of the activated AHR–ARNT dimer to AHREs on DNA, which results in altered gene expression (see Figure 4-6), more recent studies suggest that a "nongenomic" pathway within the cytoplasm also contributes to the toxic effects of TCDD, as reviewed by Matsumura (2009). The TCDD-mediated activation of AHR within the cytoplasm does not involve binding to ARNT or DNA and appears to contribute to rapid inflammatory responses associated with TCDD (Sciullo et al., 2008). In several cell lines, the activation of protein kinase C (PKC) and the later activation of the serine phosphorylated form of cytosolic phospholipase A2 (cPLA2) takes place within 15 min of TCDD exposure (Dong and Matsumura, 2008; Park et al., 2007). It is proposed that within the cytoplasm, the TCDD-mediated activation of AHR leads to a rapid increase in intracellular Ca^{2+}, plus activation of cPLA2, protein kinases, and pro-inflammatory proteins, such as cyclooxygenase (COX-2) (Matsumura, 2009). This pathway and other alternative mechanisms of TCDD-mediated AHR activation have also been reviewed by Denison et al. (2011) and Perdew (2008).

AHR Physiology

The vertebrate AHR is presumed to have evolved from its counterpart in invertebrates, in which it serves a ligand-independent role in normal development processes. The ancestral function of the AHR appears to be the regulation of specific aspects of embryonic development, it having acquired the ability to bind xenobiotic compounds only during vertebrate evolution (Hahn, 2001). The invertebrate AHR also functions as a transcription factor and binds to the same dimerization partner (ARNT) and DNA-response elements as the vertebrate protein, but it does not respond to any of the environmental ligands recognized by the vertebrate receptor. Instead, it regulates diverse developmental processes that are independent of exogenous ligand exposure, such as neuronal differentiation during worm development in *Caenorhabditis elegans* (Huang et al., 2004; Qin and Powell-Coffman, 2004) or normal morphogenesis of legs, antennae, and bristles in *Drosophila melanogaster* (Adachi-Yamada et al., 2005; Céspedes et al., 2010). In developing vertebrates, the AHR seems to play a role in cellular proliferation and differentiation and, in keeping with this role in invertebrates, also has a developmental role in craniofacial, pulmonary, renal, cardiovascular, and reproductive tract morphogenesis and blood cell differentiation (Birnbaum et al., 1989; Fernandez-Salguero et al., 1997; Lahvis et al., 2005). Other potential functional roles of the AHR include reproduction, innate immunity, tumor suppression, and blood-pressure regulation (Fujii-Kuriyama and Kawajiri, 2010).

The clearest adaptive physiologic response to AHR activation is the induction of xenobiotic-metabolizing enzymes involved in detoxification of toxic ligands. Evidence of that response, which was described above, was first observed in conjunction with the induction of *Cyp1a1*, which resulted from exposure to PAHs or TCDD and was directly related to the activation of the AHR signaling pathway (Israel and Whitlock, 1983, 1984). Because of the presence of the AHRE motif in their gene promoters, other metabolizing genes were tested and found to be induced by AHR ligands, which led to the identification of a so-called AHR gene battery of phase I and phase II detoxification genes that code for the drug-metabolizing enzymes CYP1A1, CYP1A2, CYP1B1, NQO1, ALHD3A1, UGT1A2, and GSTA1 (Nebert et al., 2000). Presumably, vertebrates have evolved those enzymes to detect a wide array of foreign, potentially toxic chemicals, represented in the wide variety of substrates that the AHR is able to bind to and whose biotransformation and elimination it is able to facilitate.

A potential complication of the adaptive responses elicited by AHR activation is the induction of a toxic response. Toxicity may result from the adaptive response itself if the induction of metabolizing enzymes results in the production of toxic metabolites. For example, the PAH benzo[a]pyrene (B[a]P), an AHR ligand, induces its own metabolism and detoxification by the AHR-dependent signaling mechanism described earlier, but paradoxically becomes bioactivated to a toxic metabolite in several tissues by a metabolism that depends on CYP1A1 and CYP1B1

activity (Harrigan et al., 2004). A second potential source of AHR-mediated toxicity may be aberrant changes in global gene expression beyond those observed in the AHR gene battery. The global changes in gene expression may lead to deleterious changes in cellular processes and physiology. Microarray and other transcriptomic analyses have proved invaluable in understanding and characterizing that response (Boverhof et al., 2006; Martinez et al., 2002; Ovando et al., 2006, 2010; Puga et al., 2000, 2004; Takeda et al., 2012; Vezina et al., 2004).

Endogenous AHR functions likely involve interaction with endogenous ligands that activate specific physiological processes. Several chemicals and chemical classes have been identified as putative endogenous ligands including equilenin, indigoids, 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester, leukotrienes, heme metabolites, arachidonic acid metabolites, tryptophan metabolites, and ultraviolet (UV) photoproducts of tryptophan (Guyot et al., 2013; Nguyen and Bradfield, 2008). The tryptophan catabolite and AHR ligand kynurenine has been identified as a tumor promoter that suppresses antitumour immune responses and promotes tumour-cell survival and motility (Opitz et al., 2011). The tryptophan UV photoproduct 6-formylindolo[3,2-b]carbazole (FICZ) is a high affinity AHR ligand, an inducer of CYP1A1 (Wei et al., 1998), and a substrate for CYP1A1 (Wincent et al., 2012). This autoregulatory loop maintains endogenous low levels of FICZ that influence circadian rhythms, responses to UV light, homeostasis associated with pro- and anti-inflammatory processes, and genomic stability (Wincent et al., 2012). FICZ has been shown to reduce the inflammatory response in skin inflammation models (Di Meglio et al., 2014) and enhances NK cell control of tumors (Shin et al., 2013).

It is clear that the AHR is an essential component of the toxicity of dioxin and of dioxin-like chemicals (DLCs). Homozygous deletion of the AHR in mice leads to a phenotype that is resistant to the toxic effects of TCDD and to the carcinogenic effects of B[a]P (Fernandez-Salguero et al., 1996; Lahvis and Bradfield, 1998; Schmidt et al., 1996). The AHR knockout mice, however, have other phenotypic effects, including reduced liver size, hepatic fibrosis, and cardiovascular abnormalities. AHR knockout rats also demonstrate resistance to the toxic effects of TCDD, and, in contrast to mice, display pathological alterations to the urinary tract in the absence of TCDD (Harrill et al., 2013). Hence, it is likely that dioxin has effects that are due to the disruption of endogenous AHR functions and that are unrelated to the intrinsic toxicity of some of its ligands.

Definition of Dioxin-Like Compounds, Toxic Equivalence Factor, and Toxic Equivalents

TCDD has the highest affinity for the AHR, but many other chemicals have dioxin-like properties: They have similar chemical structures, have similar physiochemical properties, and cause a common battery of toxic responses because of their relatively high affinity for the AHR. Because of their hydrophobic nature and

TABLE 4-2 World Health Organization Toxicity Equivalence Factors (TEFs) for Dioxin-Like Chemicals (values revised as of 2005)

Chemical	TEF
Chlorinated dibenzo-*p*-dioxins	
2,3,7,8-TCDD	1.0
1,2,3,7,8-PeCDD	1.0
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OctoCDD	0.0003
Chlorinated dibenzofurans	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,7,8,9-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OctoCDF	0.0003
Non-*ortho*-substituted PCBs	
PCB 77—3,3′,4,4′-tetraCB	0.0001
PCB 81—3,4,4′,5-tetraCB	0.0003
PCB 126—3,3′,4,4′,5-pentaCB	0.1
PCB 169—3,3′,4,4′,5,5′-hexaCB	0.03
Mono-*ortho*-substituted PCBs	
PCB 105—2,3,3′,4,4′-pentaCB	0.00003
PCB 114—2,3,4,4′,5-pentaCB	0.00003
PCB 118—2,3′,4,4′,5-pentaCB	0.00003
PCB 123—2′,3,4,4′,5-pentaCB	0.00003
PCB 156—2,3,3′,4,4′,5-hexaCB	0.00003
PCB 157—2,3,3′,4,4′,5′-hexaCB	0.00003
PCB 167—2,3′,4,4′,5,5′-hexaCB	0.00003
PCB 189—2,3,3′,4,4′,5,5′-heptaCB	0.00003

NOTE: CB, chlorinated biphenyl; CDD, chlorinated dibenzo-*p*-dioxin; CDF, chlorinated dibenzofuran; PCB, polychlorinated biphenyl.
SOURCE: Adapted from van den Berg et al., 2006.

resistance to metabolism, these chemicals persist and bioaccumulate in the fatty tissues of animals and humans. Although there are several hundred polychlorinated, polybrominated, and mixed polychlorinated-polybrominated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls, only a relatively small number of congeners of these chemical classes display dioxin-like activity. Only 17 polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans with chlorine at the 2, 3, 7, and 8

positions and a few of the coplanar polychlorinated biphenyls that are often measured in environmental samples are recognized as being DLCs.

In the context of risk assessment, these polychlorinated–polybrominated dibenzo-*p*-dioxin, polychlorinated dibenzofuran, and biphenyl DLCs are commonly found as complex mixtures when detected in environmental media and biologic tissues or when measured as environmental releases from specific sources. That complicates the human health risk assessment that may be associated with exposures to varied mixtures of DLCs. To address the problem, the concept of toxic equivalence has been elaborated by the scientific community, and the toxic equivalence factor (TEF) has been developed and introduced to facilitate the risk assessment of exposures to those chemical mixtures. On the most basic level, TEFs compare the potential toxicity of each DLC found in a mixture with the toxicity of TCDD, the most toxic member of the group. The procedure involves assigning individual TEFs to the DLCs on the basis of in vivo and in vitro potency relative to TCDD, which is assigned a TEF of 1.0. The DLCs have been assigned TEFs ranging from 0.00001 to 1.0 by the World Health Organization (WHO) (van den Berg et al., 2006, as summarized in Table 4-2). Interim TEF values have been established for brominated congeners by the most recent (2011) joint WHO–UNEP (UN Environment Programme) meeting to evaluate the WHO TEF scheme. The recommendation is to use the TEF of the corresponding chlorinated congener as an interim TEF value for brominated congeners for human risk assessment (van den Berg et al., 2013).

When several chemicals are present in a mixture, the toxicity of the mixture is estimated by multiplying the TEF of each DLC in the mixture by its mass concentration and summing the products to yield the TCDD toxic equivalents (TEQs) of the mixture. In that approach to assessing the dioxin-like activity of a complex real-world mixture of DLCs, an environmental or biologic specimen with a 100-ppt (100-pg/g) TEQ is toxicologically equivalent to 100-ppt TCDD. There are two accepted specialized methods for assessing the DLCs in a complex biologic or environmental specimen: One involves analytic chemistry that quantifies specific DLCs (high-resolution gas chromatography–mass spectroscopy), and the other is a reporter-gene biologic screen that assesses dioxin-like activity due to binding to the AHR in a transformed cell line (CALUX, EPA method 4435). Epidemiologic studies discussed in this and other updates assess exposure by reporting the specific concentration of TCDD in a specimen or by expressing dioxin-like activity in a complex mixture in units of TEQs.

Carcinogenic Classification

EPA and the International Agency for Research on Cancer (IARC), a branch of WHO, have defined criteria to classify the potential carcinogenicity of chemicals on the basis of the weight of scientific evidence from animal, human, epidemiologic, mechanistic, and mode-of-action studies. EPA classified TCDD as a

"probable human carcinogen" in 1985 and as "carcinogenic to humans" in a 2003 reassessment. In 1998 the IARC panel of experts concluded that the weight of scientific evidence supported the classification of dioxin as a class I carcinogen, that is, as "carcinogenic to humans." Four years later the US National Toxicology Program upgraded its classification to "known to be a human carcinogen." In 2006 a panel of experts convened by the National Research Council to evaluate the EPA reassessment concluded that TCDD was "likely to be carcinogenic to humans"; this designation reflected the revised EPA *Guidelines for Carcinogen Risk Assessment* made public in 2005.

Genotoxicity

Genotoxicity refers to a deleterious action that affects the integrity of a cell's DNA. Genotoxic substances are known to be potentially mutagenic or carcinogenic. Although TCDD is carcinogenic in humans and laboratory animals, it is generally classified as nongenotoxic and nonmutagenic (Wassom et al., 1977). There is no evidence of covalent binding of TCDD or its metabolites to DNA (Poland and Glover, 1979). TCDD does interact with DNA through a receptor-mediated pathway that involves the initial binding of TCDD to the AHR, binding of the activated receptor complex to DREs on DNA and later alterations in the expression of TCDD-regulated genes, and altered signaling of the biologic pathways that interact with the AHR signal-transduction mechanism (Poland and Knutson, 1982; Safe, 1990; Schmidt and Bradfield, 1996; Whitlock, 1990). TCDD, 2,4,5-T, and 2,4-D were not mutagenic in *Salmonella typhimurium* with or without the addition of liver metabolic-activation enzymes (Blevins, 1991; Mortelmans et al., 1984). TCDD-induced cytogenetic damage in laboratory mice showed no increase in the frequencies of sister-chromatid exchanges, chromosomal aberrations, or micronuclei in the bone marrow cells of either C57Bl/6J or DBA/2J mice after the administration of a single high dose of TCDD—up to 150 µg/kg (Meyne et al., 1985). TCDD did not alter the frequency or the spectrum of mutations in male and female Big Blue transgenic rats (Thornton et al., 2001). There is one report of a positive result with TCDD in a test that measured the induction of chromosomal deletions resulting from intrachromosomal recombination in mouse embryos in vivo (Schiestl et al., 1997).

In summary, although TCDD does have some genotoxic activity, the vast majority of studies did not detect mutagenic activity of TCDD in a variety of in vitro and in vivo short-term tests.

Epigenetic Activity

Chromosomes contain the genetic material of an organism and are composed of both DNA and proteins called histones. Interactions between DNA

and histones regulate the accessibility of DNA to binding factors that activate or suppress gene transcription. This interaction is controlled by chemical modifications of the DNA (generally methylation) and histones (such as sulfation and acetylation), which are maintained by enzymatic processes. These modifications are considered "epigenetic" because they control the function of genes without changing the coding sequence. TCDD has been demonstrated to cause changes to the epigenetic marks on the chromosomes, potentially altering the function of numerous genes. Below is a brief summary of the epigenetic effects of TCDD. More detailed information about epigenetic mechanisms in general can be found later in this chapter, particularly concerning somatic modifications in an individual, and again in Chapter 10 with respect to effects that may affect offspring of an exposed organism.

The exposure of rodents has been shown to result in the methylation of DNA in the adult rodents' tissues—sperm, mammary tissue, and a number of other solid tissues (Papoutsis et al., 2013; Somm et al., 2013). Developmental exposure to TCDD has been shown in rodents to alter DNA methylation in preimplantation embryos (Wu et al., 2014). The effects on DNA methylation were found to persist in rats for three generations following maternal exposure to TCDD and so could essentially be considered permanent and heritable (Manikkam et al., 2012a). When Olsvik et al. (2014) fed female zebrafish TCDD in their diet prior to breeding, they found no change in the level of DNA methylation throughout the genomes of them or their embryos, but altered methylation was identified by probes for the promoter regions of a number of specific genes with corresponding marked elevations in the expression of CYP1A1 and CYP1B1 in the mothers and embryos (Olsvik et al., 2014). To date, however, there have not been publications reporting on the persistence of methylation or other epigenetic modifications in the offspring of males exposed to TCDD as adults.

Other Toxic Outcomes

Chloracne is a signature effect of high exposure to TCDD and DLCs in some species and in humans who are sensitive.

There is an extensive body of evidence from experimental studies in animal-model systems that TCDD, other dioxins, and several DLCs are immunotoxic (Kerkvliet, 2009). Although the available evidence on dioxin immunotoxicity in humans is scant, mechanistic considerations support the notion that chemical alterations of immune function would cause adverse health outcomes because of the critical role that the immune system plays in general protection—fighting off infection and eliminating cancer cells at early stages. Because of those considerations, the chemicals are potential immunotoxicants.

Similarly, reproduction and embryonic development clearly are targets of TCDD, other dioxins, and DLCs; it is found consistently that the adverse effects are more prevalent during fetal development than in the adult. Although data

on those effects in humans are practically nonexistent, some good data are now emerging on the developmental effects of DLCs in humans (Mocarelli et al., 2008). Human and animal studies have revealed other potential health outcomes, including cardiovascular disease, hepatic disease, thyroid dysfunction, lipid disorders, neurotoxicity, and metabolic disorders, such as diabetes.

A number of effects of TCDD exposure in vitro appear to be independent of AHR-mediated transcription and in at least one instance perhaps independent of AHR itself. Guo et al. (2004) showed that TCDD induced expression of transforming growth factor-α and other genes involved in extracellular matrix deposition in cells from mice that had homozygous ablation of the *Ahr* gene. Studies have shown that TCDD can mobilize calcium from intracellular sources and increase calcium imported from the culture medium (Puga et al., 1995). Mitochondrial oxidative stress has been shown to be induced when calcium is mobilized (Senft et al., 2002). Calcium mobilization by TCDD may have an important effect on signal-transduction mechanisms that control gene expression, inasmuch as several proto-oncogenes, such as *c-fos*, are activated by calcium changes.

Summary of Biologic Plausibility That TCDD Induces Adverse Effects in Humans

Mechanistic studies in vitro and in laboratory animals have characterized the biochemical pathways and types of biologic events that contribute to the adverse effects of exposure to TCDD. For example, much evidence indicates that TCDD, acting via the AHR in partnership with ARNT, alters gene expression. Receptor binding may result in release of other cytoplasmic proteins that alter the expression or activity of other cell-regulatory proteins. Mechanistic studies also indicate that many other cellular-component proteins contribute to the gene-regulatory effect and that the response to TCDD exposure involves a complex interplay between genetic and environmental factors. Comparative data from animal and human cells in vitro and from tissues suggest a strong qualitative similarity among species in their response to TCDD, and this further supports the applicability to humans of the generalized model of initial events in response to dioxin exposure.

Biochemical and biologic responses to TCDD exposure are considered adaptive or simply reflective of exposure and not adverse in themselves if they take place within the normal homeostatic ranges of an organism. However, they may exceed normal physiologic boundaries or constitute early events in a pathway that leads to damage in sensitive members of the population. In the latter case, the response is toxic and would be expected to cause an adverse health effect. Those generalizations about dose–response and individual variability are central to establishing *biologic plausibility*, which in the case of TCDD largely relies on extrapolation from animal studies to human risks.

OVERARCHING TOXICOLOGIC ISSUES RELATED TO THE CHEMICALS OF INTEREST

Limitations of Extrapolating Results of Laboratory Studies to Human Responses

In some instances, the toxic responses identified in laboratory-animal and cell-culture studies are not detected in epidemiologic studies after human exposure to the same chemicals. Although animal and cell-culture studies provide important links to understanding the biochemical and molecular mechanisms associated with toxicity induced by xenobiotics, many factors must be considered in extrapolating their results to human disease and disease progression. The following are key factors that might limit the ability of laboratory studies to predict human responses completely and accurately.

- **Magnitude and duration of exposure** In many instances, animal and cell-culture studies are conducted at higher exposures and for shorter durations than are typical in human exposures. For example, the concentrations of TCDD used in animal studies can be many times higher than was typical in the TCDD exposures of Vietnam veterans during their military service. In addition, TCDD is a persistent organic pollutant, and this results in human exposure that occurs over a lifetime, whereas animal studies seldom examine chronic low-level exposure that occurs over a period of many months or years, except those that evaluate chronic toxicity or carcinogenicity. Animal studies that establish a measurement of body burden over a specific period provide the best potential for extrapolation to humans.
- **Toxicokinetics** The toxicokinetics—absorption, distribution, metabolism, and excretion—of xenobiotics can vary widely between laboratory animals and humans. As shown in Table 4-1, the biologic half-life of TCDD varies from 8 to 29 days in rats and mice to about 7 years in humans even though the drug-metabolizing enzymes—including cytochrome P450 1A1, 1A2, and 1B1—are up-regulated or induced via TCDD-mediated activation of the AHR in both rat and human liver (Black et al., 2012).
- **Timing of exposure** Many organ systems are more susceptible to xenobiotic exposure during critical stages of development, differentiation, or function—such as during gestation or in the face of another external challenge (for example, antigens, smoking, dietary salt, and fat)—than at other times. Therefore, the response of some systems (such as the immune or cardiovascular systems) may depend on the timing of exposure relative to the other challenges.
- **Exposure composition** Most animal and cell-culture studies involve exposure to single chemicals or a well-defined mixture, but most human exposures are to complex mixtures from multiple sources, so it is difficult

to definitively attribute any observed effects to a particular component of the environment.

- **Difference in AHR affinity** The binding affinity of AHR for TCDD differs between species (discussed in Okey et al., 2005). Many of the strains of mice used for toxicologic studies harbor a high-affinity AHR allele (AHR^b), and these mice exhibit greater sensitivity to hepatic CYP1A induction, immunosuppression, birth defects, and other responses than do strains that carry the low-affinity allele (AHR^d). Such a simple allelic difference in AHR affinity has not been observed in humans, and the TCDD-binding affinity of the AHR found in most humans more closely resembles the low-affinity mouse AHR^d allele. Nonetheless, Nebert et al. (2004) reported that some people have TCDD-binding affinity that is 12 times higher than that in others. Thus, although humans are generally considered less sensitive on the basis of an AHR that has low TCDD-binding affinity, this assumption may not apply to everyone.
- **Complex disease etiology and environment** The etiology of human diseases is highly influenced by genetics, environmental factors, and gene–environment interactions; these factors can be protective as well as deleterious. In addition to the chemical of interest, the environmental factors that commonly influence human responses include diet, prescription and over-the-counter pharmaceuticals, cigarette smoking, alcohol consumption, physical activity, and stress. Stress (not to be confused with oxidative stress) produced via known or unknown sources is a well-known modifier of human disease responses (for example, immune and cardiovascular responses). Furthermore, stress is an ever-present variable that is difficult to assess or control for in epidemiologic studies because there is substantial individual variation in response to it (Cohen et al., 2007a). In contrast, laboratory studies are often conducted with inbred strains of animals and under tightly controlled experimental conditions, thus possibly underestimating or overestimating the potential contribution of a single chemical exposure to disease development. On the other hand direct cause-and-effect relationships are more easily established in animal studies because of their standardization.
- **Sex differences** There are well-known differences in susceptibility to xenobiotic exposures between male and female animals, some of which are modified by sex steroids. For example, female Sprague Dawley rats are significantly more responsive to the hepatotoxic (neoplastic and non-neoplastic) effects of TCDD than are males of the same strain (Kociba et al., 1978).

Epigenetics

Epigenetics is the term used to describe the mechanisms that regulate gene expression and genomic stability, but that involve no changes in DNA sequence.

The epigenetic marks on DNA and bound histones are mitotically stable because they are maintained every time a cell divides. The totality of epigenetics marks in each cell, termed the line epigenome, creates and maintains the identity and function of the cell type (Christensen and Marsit, 2011; Cortessis et al., 2012; Skinner et al., 2010).

Conrad Waddington coined the term "epigenetics" in the 1940s to describe environment–gene interactions that alter biologic traits (Waddington, 1940, 1953, 1956). It was not until the 1970s, however, that the first molecular epigenetic factor was described: DNA methylation, the chemical addition of a methyl group to DNA (Holliday and Pugh, 1975). In the 1980s, the role of DNA methylation in modifying gene expression—turning genes on and off—was established (Chen and Riggs, 2005). In the 1990s, the chemical modification of histone proteins associated with DNA was shown to also modify gene expression, thus establishing a second molecular epigenetic mechanism (Turner, 1998). In the early 2000s, various small noncoding RNA molecules were shown to regulate DNA activity (Sato et al., 2011). Around 2005, the first mapping of the yeast epigenome was conducted (Pokholok et al., 2005). Since that time the mapping of cell-specific human epigenomes has accelerated under the National Institutes of Health Epigenomics Roadmap and the ENCODE projects, and more than 100 have been identified (Kundaje et al., 2015). The studies show that epigenetic marks act together in an exquisitely choreographed fashion to control cellular differentiation and the cellular ability to interact with, process, and initiate events and to respond to the signals and needs of the individual and local tissue environment.

Today, the processes recognized as epigenetic mechanisms are DNA methylation (Chen and Riggs, 2005; Holliday and Pugh, 1975), histone modification (Turner, 1998), alterations in chromatin structure (Murr, 2010), and modulation of expression by some micro RNA molecules (Valeri et al., 2009). DNA methylation is the addition of a methyl group onto specific nucleotides. In mammals it occurs mostly at cytosine nucleotides that are adjacent to guanine nucleotides, but it can also occur at cytosine nucleotides followed by other bases in embryonic cells and brain cells (Lister et al., 2013). Methylation of DNA in the promoter region of the gene can reduce the expression of the adjacent gene. Other modulations of DNA include hydroxymethylation (which is prominent in stem cells and brain cells), formylcytosine, and carboxylcytosine (Cheng et al., 2014; Song et al., 2013). Histones are the proteins that bind and form complex structures with DNA called nucleosomes in which DNA is wrapped around the histone core. The combination of DNA and histones is called chromatin. Chemical modifications of histones, such as methylation and acetylation, can alter the histone structure and modify gene expression by attracting protein complexes that can stimulate or repress transcription, in part by changing nucleosome spacing (Reid et al., 2009; Zhang and Pradhan, 2014). The most recently recognized epigenetic factor consists of small noncoding RNA molecules that can associate with mRNA and regulate gene expression.

The interaction of all those epigenetic processes creates the epigenome, which has a critical role in regulating gene expression (Christensen and Marsit, 2011; Cortessis et al., 2012; Skinner et al., 2010). The variation that is possible in the epigenome is startling: The histone proteins that control chromatin configurations have dozens of possible modifications, and there are upwards of 50 million nucleotides in the DNA where methylation can occur and participate in regulating the cellular state. That implies that trillions of configurations of the epigenome are possible, though expression of about half of all genes is common to all cells. Epigenetic marks are erased and re-established at two times during the life cycle, shortly after fertilization and during gametogenesis to allow gamete-specific epigenomes to be converted to cell-specific epigenomes and vice versa (Dean, 2014).

Environmental epigenetics is the study of how environmental factors—such as nutrition, toxicants, and stress—alter epigenetic programming. In particular, it provides a molecular mechanism—other than mutations in the DNA itself—by which environmental factors can influence disease etiology (Jirtle and Skinner, 2007; Szyf, 2007). The role of epigenetics in disease etiology has been shown for cancers and a number of other diseases (Christensen and Marsit, 2011; Cortessis et al., 2012; Skinner et al., 2010). In addition, exposure to environmental factors at critical times of development when epigenomes are shifting has the ability to alter epigenetic programming and to cause changes in gene expression because these are times when epigenomes are evolving rapidly as stems cell differentiate into more mature cell types (Skinner et al., 2010). Hence, immune responses, fetal development, and gamete formation are important examples of physiological processes whose functioning can be affected by environmentally induced epigenetic changes.

New investigative tools and a more refined understanding of the epigenetic process have given rise to active research on the nature of the relationship between environmental exposure to epigenetically active agents and the occurrence of diverse disease states, including cancers, reproductive-developmental problems, immune dysregulation, diabetes, obesity, and psychiatric illnesses (Brookes and Shi, 2014). The committee sought to review data on the potential relationship of the exposures of interest with adverse epigenetic effects in the directly exposed veterans in an attempt to find evidence linking the exposures to disease processes that might have been mediated epigenetically. We also sought to review relevant data on female veterans and male veterans separately inasmuch as the epigenetic consequences of exposures could be different, particularly in the case of adverse reproductive outcomes.

A relevant example is that the in vitro exposure of preimplantation embryos to TCDD alters the DNA methylation of imprinted genes (Wu et al., 2004). Similar results were obtained more recently when several solid tissues and sperm DNA were analyzed in adult male mice exposed to TCDD in utero (Somm et al., 2013). In utero exposure to TCDD was also shown to cause DNA methylation

and reduced expression of the *BRCA1* (breast cancer) gene in mammary tissue in adult female offspring (Papoutsis et al., 2013). More generally, studies of the developmental origins of health and disease have shown that early-life exposures or environmental influences can be associated with the onset of disease much later in life (Barker et al., 2010). These early developmental alterations in the epigenome provide a molecular mechanism by which environmental exposures of female veterans can have effects on their children into adulthood.

Most epigenetic modifications occur in somatic cells and are heritable only within the altered cell line, thereby having the potential to generate effects in the exposed individual, but not in that individual's offspring. The possibility exists, however, of epigenetic transgenerational inheritance, which involves the environment promoting a stable alteration in the germ line that is transmitted to later generations (Schmidt, 2013; Skinner, 2014; Skinner et al., 2010; Wei et al., 2015). Manikkam et al. (2012b) have shown that the exposure of pregnant female rats to TCDD at critical times of development of the germ line (when epigenetic programming is being established) can lead to abnormalities in the third-generation offspring, including kidney disease and changes in the ovaries and sperm of the offspring. There are few data on possible male-mediated heritable effects of TCDD or other environmental compounds. The sparse data include the results of studies of lead, a known developmental toxicant. Lead exposure can alter semen quality in males (Alexander et al., 1996) and has been shown to induce paternally mediated developmental toxicity in rats (Anjum et al., 2011); this demonstrates that male-mediated effects on reproduction can be induced by reproductive toxicants. It has been suggested that environmental exposures can result in reduced fertility (Guerrero-Bosagna and Skinner, 2014; Paoloni-Giacobino, 2014). However, a serious need exists for additional study of the question, particularly of the effects of the compounds of interest to this committee.

In summary, the ability of epigenetic mechanisms to regulate gene expression coupled with the interaction of the epigenome and the environment might underlie the ability of xenobiotic exposure to contribute to disease development and the potential for offspring to inherit the effects of the disrupted epigenetic processes.

Developmental Immunotoxicity

A second emerging field in the biologic sciences that may provide insight into the mechanism of xenobiotic-induced disease is developmental immunotoxicity (DIT), the study of the disruption of the developing immune system by xenobiotic exposure. The developing immune system is among the most sensitive physiologic targets of prenatal and childhood environmental insult. The sensitivity is due, in part, to the novel processes of gene rearrangement, somatic-cell selection, and immune-cell distribution that are required to produce a security system that can effectively protect not only the child but also the aging adult

against external challenges without itself producing immune-mediated chronic disease. To produce that security system, the immune system, as it matures, must coordinate steps that result in highly specialized immune cells that are capable of self-versus-non-self-recognition and that are tailored to the specialized functional environments of different tissues and organs (such as brain, lungs, skin, liver, gastrointestinal tract, and reproductive tract). A disruption of immune development can place the integrity of the organism at risk.

Among the known risk factors for DIT are various chemicals including heavy metals, some pesticides, industrial solvents such as trichloroethylene, and polychlorinated biphenyls. The adverse outcomes of DIT may become apparent soon after exposure or can emerge much later in life (Gascon et al., 2013). Often, childhood or adult infections can trigger the appearance of DIT-associated immune problems that were established earlier in life (Dietert, 2009). DIT-induced alterations can also contribute to myriad health problems related to dysfunction or pathologic conditions in virtually any tissue or organ. Chemicals, drugs, infectious agents, and physical and emotional stressors can act synergistically and increase the risk of DIT. Not everyone is at identical risk for DIT. People who have particular genotypes may be at increased risk for specific chemical-induced DIT on the basis of heritable factors that affect metabolism or immune vulnerability.

The heightened sensitivity of the developing immune system is due to the existence of critical developmental windows of vulnerability during which environmental interference with key steps of immune maturation can change the entire course of immune development and result in later-life immune dysfunction and an increased risk of disease. The events programmed for these critical developmental windows have several basic features:

- They are necessary, usually one-time events of early development, with no equivalents in adults.
- They lock in building blocks on which additional maturational events rely.
- If they do not occur both on time and efficiently, the ramifications are usually profound, prolonged, and irreversible.

Examples of critical windows of immune vulnerability and the chemicals that can cause disruptions have been described in several reviews (Dietert and Dietert, 2008; Dietert and Piepenbrink, 2006; Dietert et al., 2000; Holsapple et al., 2003; Landreth, 2002) and include

- The process of the seeding of immune cells in tissues where they grow into resident populations.
- The selection process of thymocytes in the thymus to distinguish nonself from self during the development of acquired immunity.
- The maturation of macrophage populations in the lung, in the brain, and elsewhere.

- The maturation of dendritic cells to provide balanced immune responses.
- The initial development, expansion, and seeding to the periphery of t-regulatory cell populations.

The increased sensitivity of the fetal, neonatal, and juvenile immune systems compared with the immune system of an adult can be manifested as a sensitivity to lower doses of chemical exposure than doses that affect the adult, a greater persistence of the immune problems that follow exposure than are seen in adults, a broader array of immune problems than are experienced by adults, and greater likelihood that a second later-life chemical exposure or environmental stressor will trigger an unexpected immune problem.

It is important to note that disruption of immune maturation is not the only route for DIT. Early-life chemical exposure may affect the status of genes (the epigenome) in such a way that their pattern of expression in later life is affected and thereby alter immune functional capacity. Such changes in gene status that affect immune status could occur in the exposed generation (for people exposed in utero or during childhood), or they could carry through one or more additional generations as a result of true epigenetic alterations.

5

Epidemiologic Studies: Compendium of New Publications

The continuing effort to evaluate and integrate epidemiologic studies pertinent to the possible health effects of the chemicals of interest (COIs)—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 4-amino-3,5,6-trichloropicolinic acid (picloram), and dimethyl arsenic acid (DMA or cacodylic acid)—has involved the review of thousands of publications over successive reports (the original retrospective report, nine updates prior to the current report, and three short reports on single issues, as delineated in Chapter 1). The search strategy used to identify these publications is described in Chapter 2, along with explanations of the various refinements that have been employed since the initial volume in this series was prepared.

This chapter tabulates publications of primary epidemiologic research that appeared in the period from October 1, 2012 (the closing date for inclusion in *Update 2012* [IOM, 2014]), through September 30, 2014, as a compendium of the new information on human health outcomes considered by the present committee. In this chapter and later chapters, epidemiologic studies are organized into categories according to the populations being studied (Vietnam veterans, occupational populations other than Vietnam veterans, and nonoccupational populations affected by environmental exposures) or by study design (case-control). The various study designs (the most relevant being cohort, case-control, and cross-sectional) have strengths and weaknesses that influence their potential to contribute evidence considered in the health-outcomes chapters.

Design information on populations that are the subject of multiple references in this and earlier *Veterans and Agent Orange* (VAO) reviews—including new studies of populations that have been studied previously and studies of new

populations that had multiple health outcomes—is provided in the next chapter "Epidemiology Studies: Background on Multiply Referenced Populations," along with committee commentary. This integrative approach has been taken to avoid repeating design information in multiple health-outcomes chapters and to make evident to the reader the extensive degree of interrelationship among many of the published analyses that have been reviewed in the course of the VAO series. (Design information on the studies of new populations that involve single health outcomes is provided in the various health-outcomes chapters.)

In addition to reviewing studies involving exposures to the specific COIs listed previously, this and earlier VAO committees have considered studies that examined compounds chemically related to the herbicides used in Vietnam, such as 2-(2-methyl-4-chlorophenoxy) propionic acid, hexachlorophene, and chlorophenols, particularly 2,4,5-trichlorophenol. Some publications did not indicate the specific herbicides or polychlorinated biphenyls (PCBs) with dioxin-like toxic actions to which study participants were exposed or the magnitude of exposure; those limitations were considered when the committee weighed the relevance of each publication, as detailed in Chapter 2. The committee considers studies of exposure to PCBs and other dioxin-like compounds (DLCs) informative if their results were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of specific congeners of DLCs. The available details of the exposure assessment and the use of the resulting data in analyses are discussed in Chapter 3, which follows the same sequence to categorize the study populations.

NEW EPIDEMIOLOGIC PUBLICATIONS

The new epidemiologic publications reviewed by the committee for this update are listed in Tables 5-1, 5-2, and 5-3. The conditions listed in the "Health Outcomes Reported" columns are indicative of the chapters in which the new publications are considered. Note, however, that studies assessing the occurrence of various cancers after exposure scenarios that are temporally comparable with exposure during military service are discussed in Chapter 8, which addresses cancer outcomes as applicable to the veterans themselves. Studies of childhood cancers in relation to parental exposure to the COIs are discussed in Chapter 10, which addresses possible adverse effects in veterans' offspring. Cancer studies that consider *only* childhood exposure are not considered relevant to the committee's charge.

Publications Reporting a Single Health Outcome in New Populations

The new publications reporting a single health outcome in populations not studied previously are listed in Table 5-1 with an indication of the outcomes. Descriptions and critiques of the designs of the studies are provided in the sections of the report that discuss the results related to particular health outcomes. The

TABLE 5-1 Publications Reporting a Single Health Outcome in New Populations

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Studies of Vietnam Veterans				
Ansbaugh et al., 2013	Cohort	"Agent Orange" as per US Department of Veterans Affairs designation	Prostate cancer	2,720 veterans referred to the Portland Veterans Affairs Medical Center
Li Q et al., 2013	Cohort	Dioxin-TEQ levels measured in abdominal subcutaneous fat	Prostate cancer, biochemical recurrence after radical prostatectomy	93 Vietnam veterans who underwent radical prostatectomy, median of 5.3 yrs of post-operative follow-up
Environmental Studies				
Delvaux et al., 2014	Cohort	EDCs, including dioxin (TEQs) and non-dl PCBs in cord blood	Prenatal exposure to EDCs and body composition at 7–9 years of age	Flemish children; part of the Flemish Environment and Health Study
Ferguson et al., 2012	Cohort	POPs in serum (including dl-PCBs 77, 105, 118, 156, 170, 180)	Reproductive hormones	Male partners (aged 18–51), in subfertile couples seeking infertility evaluation and treatment at Massachusetts General Hospital (01/2000–05/2003)
Gauthier et al., 2014	Cross-sectional	OCDD and dl-PCBs (including PCBs 105, 118, 156, 157, 189)	Fasting plasma levels (pg/ml) from non-diabetic, obese, post-menopausal women	"Metabolically healthy" vs 40 "metabolically abnormal" women from Montreal, categorized on the basis of insulin sensitivity
Hansen et al., 2014	Cohort	PCB congeners (including dl-PCBs 118, 156, 170, 180)	Asthma in offspring to mothers exposed to POPs	965 women; 20-year follow-up to the Danish Fetal Origins 1988–1989 Cohort in Aarhus, Denmark

continued

TABLE 5-1 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Kim et al., 2013	Cross-sectional	PCB congeners	Free t_3, total T_3, free T_4, total T_4, TSH	138 pregnant women from 5 Korean hospitals
Medehouenou et al., 2014	Cohort	OC pesticides and PCBs measured in plasma, including dl-PCBs 105, 118, and 156	Dementia	Canadian Study of Health and Aging, a national cohort study of Canadians 65+ years of age
Nakamoto et al., 2013	Cross-sectional	PCDD/Fs, dl-PCBs, and total dioxins in blood	History of disease, including asthma, atopic dermatitis, allergic rhinitis, hypertension, hyperlipidemia, diabetes, gout, thyroid and kidney disease, gastric ulcer	Japanese men (1,063) and women (1,021), aged 15–76 yrs, from general population
Sioen et al., 2013	Cohort	dl-compounds (including total of PCDD/Fs and dl-PCBs	Prenatal exposure and behavior problems at 7–8 years of age	Flemish Mother–New-Born Cohort)
Spector et al., 2014	Cross-sectional and longitudinal associations	PCBs (dl-PCBs 105, 118, 156 combined)	Immune function in postmenopausal women	109 post-menopausal overweight women enrolled in the Physical Activity for Total Health study, 1998–2000
Tai et al., 2013	Cohort	Dioxin in breast milk	Neurodevelopment in infants birth to 4 months old	216 mother-infant pairs living near the Da Nang airport in Vietnam
Valera et al., 2013a,b	Cohort	dl-PCB 105	Hypertensive status	Inuit adults from Quebec and Greenland
Wohlfahrt-Veje et al., 2014	Cohort	PCDDs, furans, and biphenyls in breast milk	Exposures to dl chemicals in breast milk and early growth and serum IGF1	Copenhagen Mother Child Cohort of Growth and Reproduction; Danish children (born 1997–2001)

TABLE 5-1 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Winneke et al., 2014	Cohort	TEQs from maternal blood during gestation and milk within 3 weeks of birth	Behavioural sexual dimorphism in school-age children	Duisburg Cohort; 232 pregnant women 09/2000–10/2002 in Duisburg, Germany
Case-Control Studies				
Cocco et al., 2012	Case-control	Pesticides (including 2,4-D, phenoxys, chlorophenols, organochlorines)	Lymphoma	Participants in the EPILYMPH case-control study in six European countries (1998–2003)
Glass et al., 2012	Case-control	Phenoxy herbicides	ALL	Parental occupational exposures and ALL in Australia
Metayer et al., 2013	Case-control	Pesticides, including 2,4-D	ALL	Northern California Childhood Leukemia Study

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; ALL, acute lymphoblastic lymphoma; dl, dioxin-like; EDC, endocrine-disrupting chemical; OC, organochloride; OCDD, octachlorodibenzo-*p*-dioxin; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; POP, persistent organic pollutant; TEQ, (total) toxic equivalent; TSH, thyroid-stimulating hormone.

publications in this table include a mix of study designs and focus principally on individual types of cancer as the primary health outcome of interest.

Publications Reporting Multiple Health Outcomes in New Populations

The new publications reporting multiple health outcomes in populations not studied previously are listed in Table 5-2 with a list of outcomes that were investigated. Comprehensive discussions of the designs of the studies are presented in Chapter 6, organized according to the type of study population. For *Update 2014*, six publications were identified from a new, exceptionally large epidemiological study of more than 114,000 Korean Vietnam War veterans. This study cohort is much larger in scope than all of the other published epidemiological studies conducted among Vietnam veterans. It provides results for a very large set of health outcomes, including rare conditions, as well as information on both non-fatal outcomes and cause-specific mortality. The results for new publications reporting multiple health outcomes in populations not studied previously, with

TABLE 5-2 Publications on Multiple Health Outcomes in New Study Populations

Author	Study Design	Exposure Measures(s) Having Results	Health Outcome(s) Reported	Study Population
Studies of Vietnam Veterans				
McBride et al., 2013	Cohort	Service in Vietnam during Vietnam War	Mortality and cancer experience (1988–2008)	New Zealand Vietnam war veterans
Yi, 2013	Cohort	Service in Vietnam during the Vietnam War	Cancer incidence 1992–2003; all cancers and full spectrum individually	KVHS–Korean Vietnam veterans identified using the Korea National Cancer Incidence Database
Yi and Ohrr, 2014	Cohort	AO exposure using GIS-based model	Cancer incidence 1992–2003; all cancers and full spectrum individually	KVHS–Korean Vietnam veterans identified using the Korea National Cancer Incidence Database
Yi et al., 2014a	Cohort	AO exposure using GIS-based model	Disease prevelance, full spectrum individually	KVHS–Korean Vietnam veterans identified using Korean National Health Insurance Health claim data, January 2000–September 2005
Yi et al., 2014b	Cohort	AO exposure using GIS-based model	Morbidity and mortality from individual cancers and various diseases	KVHS–Korean Vietnam veterans with cause of death reported 1992–2005
Occupational Studies				
Wang et al., 2013	Cohort	PCDDs/PCDFs	Lung, liver, and stomach cancer, individually	Workers from an automobile foundry factory in Hubei province in China
Environmental Studies				
Papadopoulou et al., 2013a	Cohort	Dietary intake of dioxins and dl-compounds	Maternal diet and birth size	Mothers enrolled in Norwegian Mother and Child Cohort Study

TABLE 5-2 Continued

Author	Study Design	Exposure Measures(s) Having Results	Health Outcome(s) Reported	Study Population
Papadopoulou et al., 2013b	Cohort	dl activity in maternal blood samples at time of delivery and anogenital distance in newborns and infants	Anogenital distance in newborns and children	Mothers and newborns enrolled in European NewGeneris Cohort
Papadopoulou et al., 2014	Cohort	dl activity in maternal blood samples at time of delivery	Association between maternal diet and birth outcome	Mothers enrolled in European NewGeneris Cohort
Vafeiadi et al., 2013	Cohort	In utero exposure to dioxin and dl-compounds	In utero exposure to dioxin and dl-compounds and anogenital distance	Subset of mother–Child cohorts from NewGeneris Cohort
Vafeiadi et al., 2014	Cohort	dl activity in cord blood and maternal blood samples at time of delivery	dl activity in blood and birth weight, gestational age, and head circumference,	Mothers and newborns enrolled in European NewGeneris Cohort

NOTE: AO, Agent Orange; dl, dioxin-like; GIS, geographic information system; KVHS, Korean Veterans Health Study; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran.

comments related to their reliability or limitations, appear in the appropriate outcome-specific sections of Chapters 7–13.

New Publications on Previously Studied Populations

The new publications on previously studied populations are listed in Table 5-3. The new publications are reviewed in the context of the history of publications on the same populations to take into account the fact that they are not presenting entirely new evidence, but rather enhancing a picture that has been emerging for many years.

A number of long-term studies of populations exposed to the COIs are of particular importance to the VAO project. The disease experiences of those populations are updated with the passage of time. Placing each new publication into its historical context helps the committee combine the evidence from various publications appropriately and take into consideration the interdependence of related publications. Such clusters of studies are useful in describing the course of a population's response to an exposure, and joint consideration of an entire body

TABLE 5-3 Publications on Previously Studied Populations

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Studies of Vietnam Veterans				
Kang et al., 2014	Retrospective cohort	US military service in Vietnam or near Vietnam	Mortality 1965–2010; all cancers and specific (brain, breast, cervical, ovarian, pancreatic, respiratory, uterine), diabetes mellitus, heart disease, circulatory disease, respiratory disease, and nervous system disease	US women who served in Vietnam or near-Vietnam vs non-Vietnam veteran peers in the US
ADVA, 2014a,b	Cohort	Vietnam veteran families	Study overview, pregnancy and birth defect outcomes	Vietnam veteran sons and daughters
ADVA, 2014c	Cohort	Vietnam veteran families	Mortality patterns	Vietnam veteran families
Occupational Studies				
Goldner et al., 2013	Cohort	50 specific herbicides, including 2,4-D, 2,4,5-T, and 2,4,5-TP	Association between thyroid disease and use of insecticides, herbicides, and fumigants/ fungicides	AHS (male private pesticide applicators)
Rinsky et al., 2013	Cohort	Specific pesticides, inluding 2,4-D	Stroke mortality	AHS (male private pesticide applicators)
Saberi Hosnijeh et al., 2013a (same group as Saberi Hosnijeh et al., 2012a)	Cohort	TCDD	Serum metabolomics pertubations	Subcohort of IARC (Dutch phenoxy herbicide workers)
Saberi Hosnijeh et al., 2012b	Cohort	TCDD	Changes in lymphocyte subsets	Subcohort of IARC (Dutch phenoxy herbicide workers)
Starling et al., 2014	Cohort	Pesticides (including 2,4,5-T)	Diabetes	AHS (wives of farmers)

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Environmental Studies				
Bouchard et al., 2014	Cross-sectional	PCB congeners	Cognitive function	NHANES (1999–2002)
Chevrier et al., 2014	Cohort	Serum TCDD concentrations	Thyroid hormone levels	SWHS (Seveso women 0–40 yrs old at time of accident; follow-up April 2008–December 2009)
Eskenazi et al., 2014	Cohort	Serum TCDD concentrations	Bone density and structure	SWHS (Seveso women 0–40 yrs old at time of accident; follow-up 2008)
Everett and Thompson, 2014	Cross-sectional	Dioxins and dl-PCBs (including dl-PCBs 81, 105, 118, 126, 156, 157, 167) in blood samples	Diabetes nephropathy	NHANES (1999–2004)
Gallagher et al., 2013	Cross-sectional	dl-PCBs	Serum antinuclear antibodies	NHANES (2003–2004)
Krieg, 2013	Cross-sectional	Pesticide metabolites in urine after 2,4-D exposure	Cognitive function	NHANES III
Lin et al., 2012	Cross-sectional	PCDDs, PCDFs, dl-PCBs (dl-PCBs 81, 105, 118, 126, 156, 157, 167, 169, 189) in serum	Cause-specific mortality through 2006 for all-causes, all cancers, and CVD	NHANES (1999–2004)
Lind et al., 2013	Cross-sectional	POPs (including dl-PCBs 105, 118, 126, 156, 157, 169, 189)	Life-time weight change	PIVUS seniors (2001–2004)
Pahwa P et al., 2012a	Cohort	Herbicides	Chronic bronchitus	Saskatchewan Rural Health Study
Peters et al., 2014	Cross-sectional	dl-PCBs (dl-PCBs 81, 118, 126, 189)	Blood pressure	NHANES (1999–2008)

continued

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
ten Tusscher et al., 2014 (same cohort as Patandin et al., 1998)	Cohort	Pre-, peri-, and postnatal exposure to dioxin	Neurodevelopmental retardation	Amsterdam–Zaandam cohort; children born 1987–1991
Turunen et al., 2012	Cohort	PCDDs, PCDFs, PCBs	C-reactive protein (an indicator of inflammation)	Finnish fisherman and their wives
Warner et al., 2013	Cohort	Serum TCDD concentrations	Diabetes, metabolic syndrome, obesity	SWHS (Seveso women 0–40 yrs old at time of accident; follow-up April 2008–December 2009)
Wesselink et al., 2014	Cohort	Serum TCDD concentrations	Pregnancy outcomes	SWHS (Seveso women 0–40 yrs old at time of accident; follow-up 2008–2009)
Case-Control Studies				
Carmichael et al., 2013	Case-control	Pesticides (including 2,4-D, MCPA, cacodylic acid)	Hypospadias	NBDPS
Carmichael et al., 2014	Case-control	Pesticides (including 2,4-D)	Selected congenital birth defects	NBDPS
Kachuri et al., 2013	Case-control	Pesticides (including 2,4-D)	Multiple myeloma	CCSPH
Navaranjan et al., 2013	Case-control	Herbicides, phenoxy herbicides	Hodgkin lymphoma	CCSPH
Pahwa P et al., 2012b	Case-control	Pesticides (including phenoxys, 2,4-D, MCPA)	Multiple myeloma	CCSPH
Shaw et al., 2014	Case-control	2,4-D	Early pregnancy and risk of gastroschisis	NBDPS

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Yang et al., 2014	Case-control	2,4-D	Neural tube defects and orofacial clefts	NBDPS

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; AHS, Agricultural Health Study; CCSPH, Cross-Canada Study of Pesticides and Health; CVD, cardiovascular disease; dl, dioxin-like; IARC, International Agency for Research on Cancer; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NBDPS, National Birth Defects Prevention Study; NHANES, National Health and Nutrition Examination Survey; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; PIVUS, Prospective Study of the Vasculature in Uppsala Seniors; POP, persistent organic pollutant; SWHS, Seveso Women's Health Study; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

of research on a population may yield insights into relationships with potential confounding factors.

Many groups potentially exposed to the COIs have been monitored periodically, including the cohorts of the International Agency for Research on Cancer (IARC) and the National Institute for Occupational Safety and Health (NIOSH); residents of Seveso; and Ranch Hand and Army Chemical Corps personnel. For the sake of completeness, the discussions of specific health outcomes and the associated cumulative-results tables in Chapters 7–13 include references to publications discussed in previous VAO reports and to new publications. In drawing its conclusions, the committee combined the evidence in new publications and the evidence synthesized in the most recent update (*Update 2012*), taking into account the interdependence of related publications. For the present update, several relevant studies of dioxin-like compounds and a range of health outcomes were identified from serum samples collected from the federally funded National Health and Nutrition Examination Survey (NHANES).

Individual researchers who belong to research consortia that are evaluating cohorts in large multicenter studies (such as the IARC and NIOSH cohort studies) sometimes publish reports based on the subsets of study participants that they themselves are monitoring. The VAO committees consider all reports that have been published, including those based on entire cohorts and those based on subcohorts. In drawing its conclusions, the committee factored in both types of studies, taking into consideration the interdependence among related studies. In particular, some subcohort studies have access to information not available for the entire cohort, such as data on individual serum TCDD concentrations and personal information that can be used to adjust for confounders of concern. Furthermore, even when the analyses based on an entire cohort would include data on a subcohort as a subset, the reports on the subcohort might provide additional information on the consistency of the relationships among subcohorts, such as

whether there are important subcohort-by-exposure interaction effects, when these issues were not considered in the full-cohort studies. As long as the structures of the study populations are recognized, VAO committees have been less concerned about over-weighting unstable positive findings on small subgroups or giving "repeated consideration" to duplicative results than would be the case if a quantitative meta-analysis were being undertaken.

Many of the cohorts that have contributed to the cumulative findings of the VAO committees are no longer being followed; however, the cohorts' histories are briefly recapitulated in the body of this report. Additional background information can be found in earlier reports in this series. The subjects of the new epidemiological studies identified include female US Vietnam veterans as well as Australian, Korean, and New Zealand veterans who served in Vietnam. These studies are augmented with a wealth of new data from civilian populations exposed to the COIs along with herbicides and pesticides with mechanistic and toxic properties similar to the COIs.

6

Epidemiologic Studies: Background on Multiply Referenced Populations

This chapter presents study-design information on populations of Vietnam veterans, occupational cohorts, and environmentally exposed groups that have been reported on repeatedly, often for many health outcomes, as well as case-control studies that have generated multiple publications relevant to the *Veterans and Agent Orange*[1] (VAO) series. One-time reports on given study populations that addressed only single health outcomes are not discussed in this chapter.

In drawing its conclusions, the committee synthesized the evidence from studies that have gathered data and published results over an extended period of time, taking into account the interdependence among related studies. In particular, if new results are based on updating or adding subjects to previously studied populations or concern a subset of original study populations, then this synthesis considers the redundancy among studies while recognizing that separately reported information can impart new relevance to other data on a study population. The design information provided in this chapter links repeated studies and clarifies their interdependence.

This chapter also provides design information on studies involving multiple health outcomes in order to avoid repetition in the health-outcomes chapters (Chapters 7–13). Some of the populations have been studied previously and reviewed in previous VAO publications (thus, these populations are multiply referenced both over time and among health outcomes), and others have not been

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

addressed in other VAO publications. The procedures used to identify relevant literature on health effects in human populations in conjunction with exposure to the chemicals of interest (COIs) are provided in Chapter 2. The details of the exposure assessments conducted within individual studies are presented in this chapter, whereas generic issues of exposure assessment are discussed in Chapter 3 along with the special challenges involved in characterizing and reconstructing the herbicide exposures of Vietnam veterans.

In *Update 2010*, the committee undertook a major change in the formatting of the tables of cumulative results on the health outcomes that was aimed at making relationships among publications more evident for its own deliberations and for the reader. The prior practice had been to insert findings from new publications in the results tables at the beginning of the sections on veteran, occupational, and environmental studies and so to create bands of studies reviewed in individual updates. Since *Update 2010*, however, the reported findings on a given condition from a particular study population described in any of the VAO reports are gathered and presented in reverse chronologic order in order to provide the full history of the study of each endpoint in each group studied. The current update has attempted to shift the focus further to the total picture presented by a study population by clustering related findings and shifting the citations that were the source of particular results to the far right of the results tables. For instance, all incidence findings on the Seveso cohort over the successive follow-up periods are grouped first, and they are followed by all the analogous mortality findings, even when that means separating various sorts of results from the same publication.

Within the three general types of exposure that cohorts or cross-sectional study populations may have experienced, the order of the study populations (Vietnam veterans, occupationally exposed workers, and environmentally exposed people) roughly reflects the degree of importance attributed to the information generated. Because of substantial differences in the nature and intensity of their exposures, the occupational-study populations have been partitioned into those involved in the production of herbicides and other industrial products contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and those involved in occupational use of the herbicides of interest. In *Update 2012* this entailed splitting the findings on cohorts of sprayers from those on cohorts of production workers in the large International Agency for Research on Cancer (IARC) cohort of phenoxy herbicide workers.

The studies of subgroups are presented after those on an overarching cohort. For example, when first reported (Saracci et al., 1991), the original IARC Cohort of Phenoxy Herbicide Workers was composed of 20 cohorts in 10 countries that had been studied separately. When the mortality in those workers was followed up (Kogevinas et al., 1997), they were augmented with 16 additional cohorts—4 German study populations and 12 groups of workers studied separately in US manufacturing facilities—which together make up the independently studied National Institute for Occupational Safety and Health (NIOSH) cohort. To simplify

the location of underlying information on study populations, the discussion of the study populations in this chapter follows the order in which the findings on each population are presented in the results tables for each health outcome.

The initial review section below on Vietnam veterans covers studies conducted in the United States by the Air Force, the Centers for Disease Control and Prevention (CDC), the Department of Veterans Affairs (VA), the American Legion, and individual states; it also covers studies of Australian, New Zealand, and South Korean Vietnam veterans. The section "Occupational Studies" covers studies of workers other than Vietnam veterans exposed occupationally to the COIs and dioxin-like compounds, including production workers, agriculture and forestry workers (including herbicide and pesticide applicators), and paper and pulp workers. The section "Environmental Studies" covers studies of populations exposed to the COIs and dioxin-like compounds from nonoccupational sources, including the general population, such as the National Health and Nutrition Examination Survey cohort, and people who had unusually high exposures because of industrial sources in their residential neighborhoods, such as the residents of Seveso, Italy; southern Vietnam; suburban Taichung, Taiwan; Chapaevsk, Russia; and Times Beach, Missouri. This chapter ends with a section that addresses the publications that are based on repeatedly mentioned case-control study populations; the case-control studies that assessed Vietnam-veteran status, however, are included in the section on veteran studies, and nested case-control studies are presented in conjunction with the cohorts from which they were derived.

Because of the breadth of literature reviewed in this chapter, Figure 6-1 provides the reader with a comprehensive overview of the individual study populations reviewed.

VIETNAM-VETERAN STUDIES

Studies of Vietnam veterans who might have been exposed to herbicides, including Agent Orange, have been conducted in the United States at the national and state levels and in Australia, South Korea, and New Zealand. Exposures have been defined in various ways, and health outcomes have been evaluated with reference to various comparison or control groups. This section is organized primarily by research sponsor because it is more conducive to a methodologic presentation of the studies. The specificity of exposure spans a wide range from the individual exposures of Ranch Hand and Army Chemical Corps (ACC) personnel, as reflected in serum TCDD measurements, to the use of service in Vietnam as a surrogate for TCDD exposure in some studies.

Several comparison groups have been used for veteran cohort studies: Vietnam veterans who were stationed in areas where herbicide-spraying missions were unlikely to have taken place; Vietnam-era veterans who were in the military at the time of the conflict but did not serve in Vietnam; veterans who served in

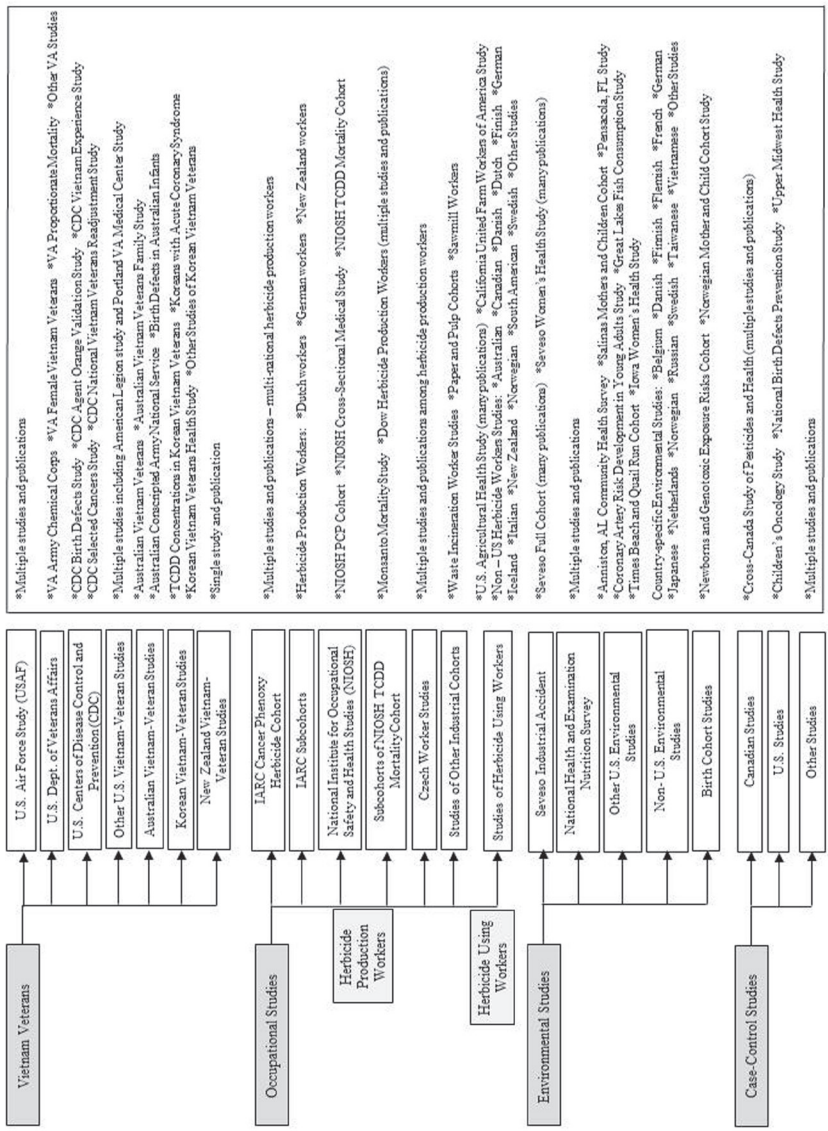


FIGURE 6-1 Overview of the individual study populations reviewed by the committee.

other wars or conflicts, such as the Korean War and World War II; and various state and national populations.

In all studies of Vietnam veterans, whether or not the study participants were American, the study participants are the target population of the committee's charge, and they are assumed to have had a higher probability of exposure to the COIs than people who did not serve in Vietnam, whether or not their individual exposures are characterized beyond the mere fact that they were deployed to Vietnam.

The publication period considered in the present update included the examination of a range of health outcomes among Vietnam veterans with service history from the United States, as well as countries outside the United States. This included a long-term mortality analysis conducted among US female Vietnam veterans (Kang et al., 2014), a 20-year mortality and cancer incidence study among New Zealand Vietnam veterans (McBride et al., 2013), and six publications from an exceptionally large cohort of approximately 120,000 Korean veterans (Yi, 2013; Yi and Ohrr, 2014; Yi et al., 2013a,b, 2014a,b). For the Korean Vietnam veteran studies, multiple methods of exposure ascertainment were used, including self-report perceived exposure to herbicides and an objective geography-based exposure opportunity model. Similarly, multiple methods of health outcome ascertainment were used, including veteran self-report and a review of data from the Korean Cancer Incidence Database, the Korea National Health Insurance system, and death records from the National Statistical Office. The committee carefully considered the strengths and limitations of the different methods of exposure and health outcome ascertainment in synthesizing the evidence from the large Korean Veteran study. In addition, a series of four publications was reviewed looking at Australian Vietnam veterans (ADVA, 2014a,b,c,d), but the focus of these publications was on the family members of Australian veterans, and many health outcomes of these family members are not central to the charge of the committee (e.g., mental health and social functioning). Thus, minimal consideration was given to the new evidence from these publications.

US Air Force Health Study

Reports and findings from the US Air Force Health Study (AFHS) have provided important information that was incorporated into the previous VAO reports and continue to play an important role in the committee's assessment of the overall evidence for the current report. The data-gathering phase of this study is complete, but VAO committees have remained interested in having the opportunity to review additional publications that provide longitudinal analysis of the vast amount of information assembled and to make use of the collection of preserved biologic samples. As yet, such comprehensive summarizations of findings from the AFHS have not materialized, but the current committee is glad to note that the samples are being used in research even though the questions investigated do not necessarily address health outcomes in these Vietnam-era veterans themselves (IOM, 2015).

Major defoliation activities in Vietnam were conducted by Air Force personnel as part of Operation Ranch Hand (ORH). Veterans who took part in the defoliation activities became the first subpopulation of Vietnam veterans to receive special attention with regard to herbicides exposure and have become known as the Ranch Hand cohort within the AFHS. To determine whether exposure to herbicides, including Agent Orange, had adverse health effects, the Air Force made a commitment to Congress and the White House in 1979 to conduct an epidemiologic study of Ranch Hand personnel (AFHS, 1982). The results of biologic-marker studies of Ranch Hand personnel have been consistent with their being exposed, as a group, to TCDD. When the Ranch Hand cohort was classified by military occupation, a general increase in serum TCDD was detected in people whose jobs involved more frequent handling of herbicides (AFHS, 1991b). This provides a strong rationale for close examination of this study cohort.

The exposure index initially proposed in the AFHS relied on military records of spraying of TCDD-containing herbicides (Agent Orange, Agent Purple, Agent Pink, and Agent Green) as reported in the Herbicide Reporting System (HERBS) tapes for the period starting in July 1965 and on military procurement records and dissemination information for the period before July 1965. In 1991 the exposure index was compared with the results of the Ranch Hand serum-TCDD sampling conducted on personnel years after their service in Vietnam. The exposure index and the TCDD body burden correlated weakly.

Michalek et al. (1995) developed several indexes of herbicide exposure of members of the Ranch Hand cohort and tried to relate them to the measurements of serum TCDD from 1987 to 1992. Self-administered questionnaires completed by veterans of ORH were used to develop three indexes of herbicide or TCDD exposure: The number of days of skin exposure, the percentage of skin area exposed, and the product of the number of days of skin exposure, the percentage of skin exposed, and a factor for the concentration of TCDD in the herbicide. A fourth index, which used no information gathered from individual study participants, was calculated by multiplying the volume of herbicide sprayed during a person's tour of duty by the concentration of TCDD in herbicides sprayed in that period and then dividing the product by the number of crew members in each job specialty at the time.

Each of the four indexes tested was significantly related to serum TCDD although the models explained only 19 to 27 percent of the variability in serum TCDD concentrations. Days of skin exposure had the highest correlation. Military job classification (for example, Ranch Hand combat troops, Ranch Hand administrators, Ranch Hand flight engineers, and Ranch Hand ground crew), which is separate from the four indexes, explained 60 percent of the variability in serum TCDD. When the questionnaire-derived indexes were applied within each job classification, days of skin exposure added statistical significance, but not substantially, to the variability explained by job alone.

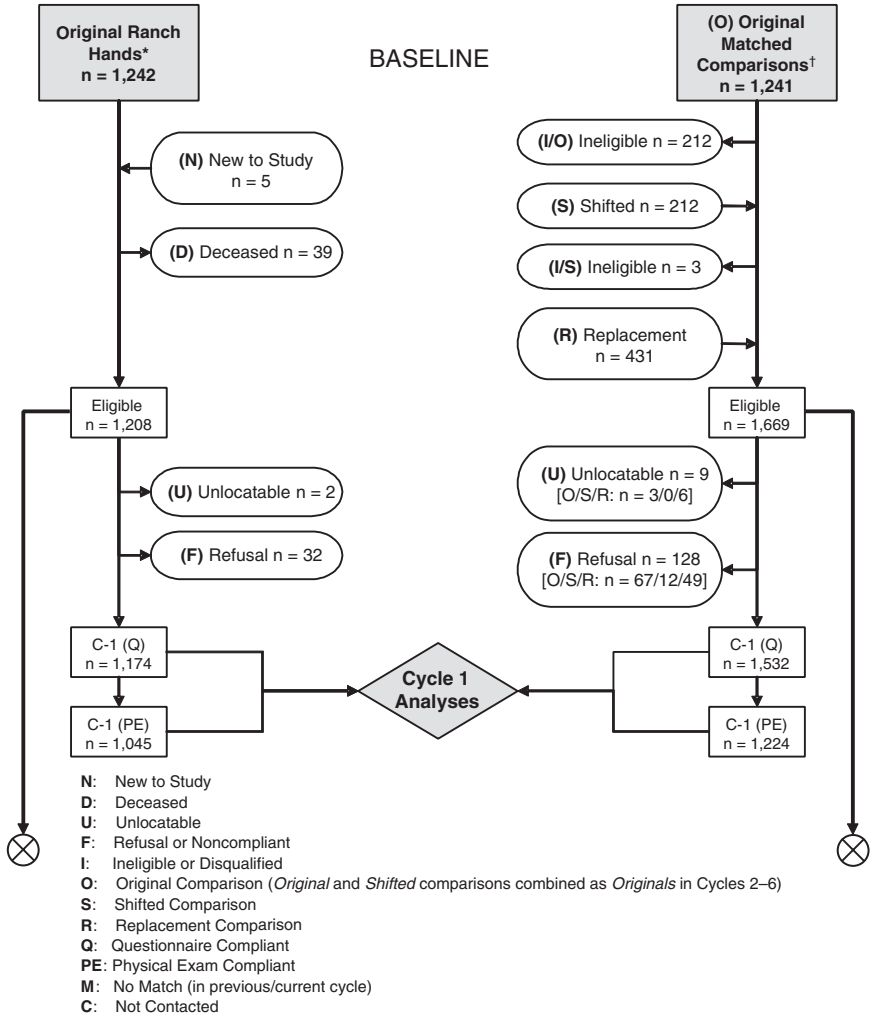
As depicted in Figure 6-2, a retrospective matched-cohort study design was used to examine morbidity and mortality; follow-up was scheduled to continue until 2002. Records from the National Personnel Records Center and the US Air Force Human Resources Laboratory were searched and cross-referenced to identify all Ranch Hand personnel (AFHS, 1982; Michalek et al., 1990). A total of 1,269 participants were originally identified (AFHS, 1983). A control population of 24,971 C-130 crew members and support personnel assigned to duty in Southeast Asia (SEA) but not occupationally exposed to herbicides (AFHS, 1983) was selected from the same data sources. Control participants were individually matched for age, type of job (based on Air Force specialty code), and race (white or not white) to control for possible differences in the development of chronic disease that may relate to age, race, or educational and socioeconomic status. To control for the many potential confounders related to the physical and psychophysiologic effects of combat stress and the SEA environment, Ranch Hands were matched to control participants who performed similar combat or combat-related jobs (AFHS, 1982). Rank also was used as a surrogate of exposure. Alcohol use and smoking were included in the analysis when they were known risk factors for the outcome of interest.

Ten matches formed a control set for each exposed participant. For the mortality study, the intent was to follow each exposed participant and a random sample of half each participant's control set for 20 years in a 1:5 matched design. The morbidity component of follow-up consisted of a 1:1 matched design; the first control was randomized to the mortality-ascertainment component of the study. If a control was noncompliant, then another control from the matched "pool" was selected; controls who died were not replaced.

The baseline physical examination occurred in 1982, and examinations took place in 1985, 1987, 1992, 1997, and 2002. Morbidity was ascertained through questionnaires and physical examination, which emphasized dermatologic, neurobehavioral, hepatic, immunologic, reproductive, and neoplastic conditions. Some 1,208 Ranch Hands and 1,668 comparison participants were eligible for the baseline examination. Initial questionnaire response rates were 97 percent for the exposed cohort and 93 percent for the nonexposed; baseline physical-examination responses were 87 percent and 76 percent, respectively (Wolfe et al., 1990). Deaths were identified and reviewed by using US Air Force Military Personnel Center records, the VA Beneficiary Identification Record Locator Subsystem (BIRLS), and the Internal Revenue Service database of active Social Security numbers. Death certificates were obtained from the appropriate health departments (Michalek et al., 1990).

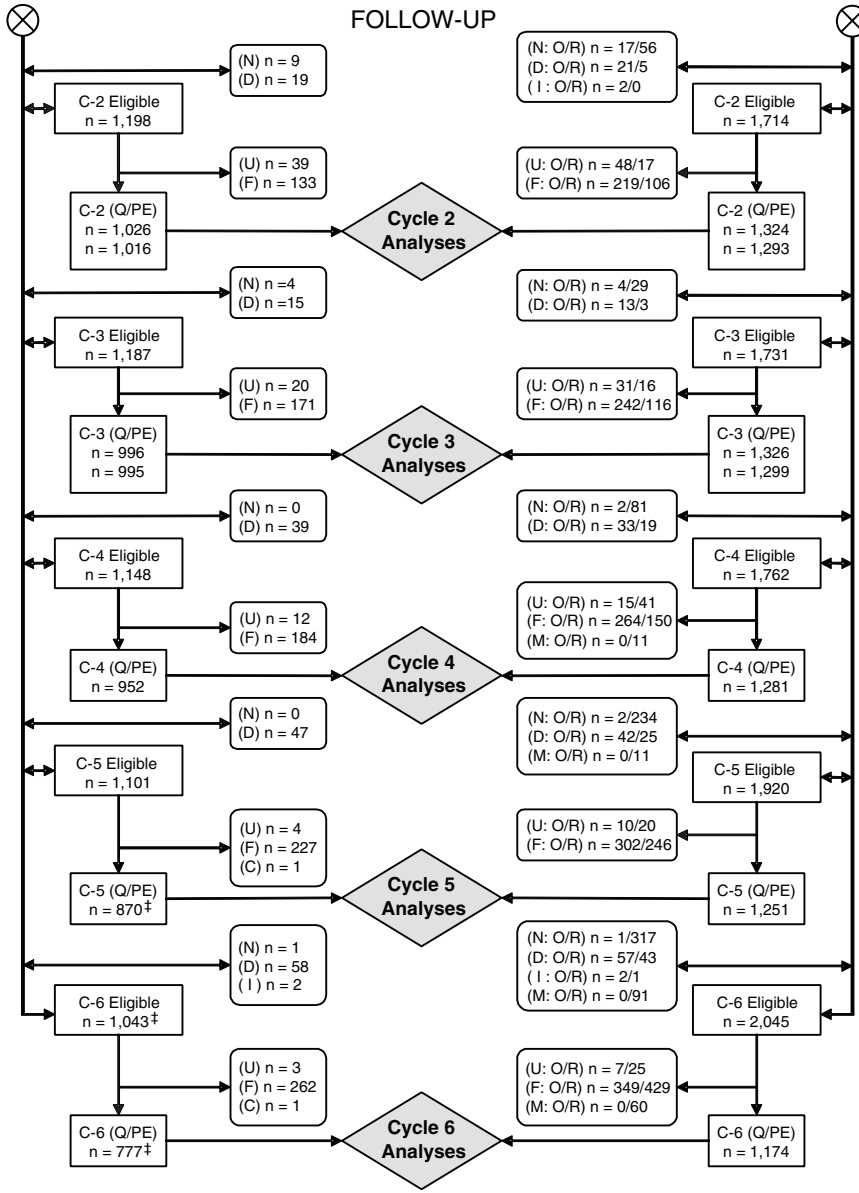
Ranch Hands were divided into three categories on the basis of their potential exposure:

- *Low potential.* Pilots, copilots, and navigators. Exposure was primarily through preflight checks and spraying missions.



* Total does not reflect the 22 Ranch Hands known at the Baseline to have been killed in action.
† One Ranch Hand (Black officer) remained unmatched to a comparison.
‡ Numbers of eligible and participating Ranch Hands reflect AFHS reports (AFHS, 2000 & 2005) and not the numbers that would be expected—Cycle 5, PE: n = 869; Cycle 6, Eligible n = 1,042, PE: n = 776—from reported changes in the study population recorded in AFHS reports.

FIGURE 6-2 Flowchart of procedures followed and participant involvement in the Air Force Health Study.
NOTE: Flowchart numbers reflect what was known to Air Force Health Study (AFHS) investigators at any given cycle according to AFHS reports and do not reflect corrections made to earlier cycles due to the identification of misclassified subjects in later cycles. Identical study population counts vary on occasion within and across cycle reports. Thus,



this reconstruction should be considered a general overview of AFHS population dynamics. Eligibility in any cycle reflects eligibility in a previous cycle, and not compliance in a previous cycle, corrected for between-cycle newly identified or deceased subjects.
SOURCES: AFHS, 1984a, 1987, 1990, 1995, 2000, 2005c.

- *Moderate potential.* Crew chiefs, aircraft mechanics, and support personnel. Exposure could occur by contact during de-drumming and aircraft loading operations, onsite repair of aircraft, and repair of spray equipment.
- *High potential.* Spray-console operators and flight engineers. Exposure could occur during operation of spray equipment and through contact with herbicides in the aircraft.

Ostensibly, the AFHS was designed to answer exactly the question that the VAO project is asking, but the nature of the "exposed" (Ranch Hand veterans) and "comparison" (SEA veterans) groups and the evolving practices of VAO committees in endeavoring to fulfill the intention of their congressional mandate make interpretation less straightforward.

Results have been published for baseline morbidity (AFHS, 1984a), baseline mortality (AFHS, 1983), and for reproductive outcomes (AFHS, 1992; Michalek et al., 1998a; Wolfe et al., 1995). Mortality updates have been published for 1984–1986, 1989, and 1991 (AFHS, 1984b, 1985, 1986, 1989, 1991b). An interim technical report updated cause-specific mortality in Ranch Hands through 1993 (AFHS, 1996). Michalek et al. (1998b) and Ketchum and Michalek (2005) reported on 15-year and 20-year follow-up of post-service mortality, respectively, in veterans of ORH, updating an earlier cause-specific mortality study by Michalek et al. (1990). Comparisons presented in the voluminous reports on the follow-up examinations of 1984, 1987, 1992, 1997, and 2002 cited as AFHS (1987, 1990, 1995, 2000, 2005) have been deemed not useful for the purposes of the VAO reviews because of the prevalence or cross-sectional nature of the data on only those in the cohort who were still alive and participated in a particular examination.

Blood samples for determination of serum TCDD concentrations were drawn at the periodic examinations conducted in 1982 from 36 Ranch Hands (Pirkle et al., 1989), in 1987 from 866 Ranch Hands (AFHS, 1991a), in 1992 from 455 Ranch Hands (AFHS, 1995), and in 1997 from 443 Ranch Hands (AFHS, 2000). For veterans whose TCDD was not measured in 1987 but was measured later, the later measurement was extrapolated to 1987 by using a first-order kinetics model with a constant half-life of 7.6 years. Analyses of the serum TCDD readings were included in the report on the 1987 follow-up examination (AFHS, 1991a), and other Ranch Hand publications have addressed the relationship between serum TCDD and reproductive hormones (Henriksen et al., 1996); diabetes mellitus, glucose, and insulin (Henriksen et al., 1997); skin disorders (Burton et al., 1998); infant death (Michalek et al., 1998a); sex ratios (Michalek et al., 1998c); skin cancers (Ketchum et al., 1999); insulin, fasting glucose, and sex-hormone-binding globulin (Michalek et al., 1999a); immunologic responses (Michalek et al., 1999b); diabetes mellitus (Longnecker and Michalek, 2000; Steenland et al., 2001); cognitive function (Barrett et al., 2001); hepatic abnormalities (Michalek

et al., 2001b); peripheral neuropathy (Michalek et al., 2001c); hematologic results (Michalek et al., 2001a); psychologic functioning (Barrett et al., 2003); correlations between diabetes and TCDD elimination (Michalek et al., 2003); thyroid function (Pavuk et al., 2003); cancer incidence (Akhtar et al., 2004; Pavuk et al., 2005); insulin sensitivity (Kern et al., 2004); prostate cancer (Pavuk et al., 2006); serum testosterone and risk of benign prostate hyperplasia (Gupta et al., 2006a); and diabetes and cancer incidence (Michalek and Pavuk, 2008). All of the VAO updates, *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (IOM, 2000), and *Veterans and Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer* (IOM, 2004) discussed the reports and papers that address the cohort in more detail.

The tendency of the AFHS researchers to use differing cutpoints and population definitions for analogous analyses suggests that they used a posteriori selection in a fashion that influenced the results. For example, Michalek and Pavuk (2008) allude to the commonly held assumption that Agent Orange was more heavily contaminated earlier in the war as the motivation for making various temporal partitions in their analyses, but the choices were not consistent. For cancers, service in 1968 or before was considered to fall in the critical exposure period, whereas days of spraying were counted through 1967 and the variable for "days of spraying" was assigned the value "low" or "high" by partitioning the resulting distribution at 30 days. For diabetes, however, service in 1969 or before was regarded as being in the critical exposure period, and the variable "days of spraying" was split into "low" and "high" at 90 days or more, with no specification of the period over which the counting was done.

The AFHS is perceived by many to be the central piece of research for decision making by the VAO committees, but it also has important limitations that all VAO committees have had to consider. A prior Institute of Medicine (IOM) report, *Disposition of the Air Force Health Study* (IOM, 2006b), which was undertaken by another IOM committee as the AFHS was approaching the end of its data-gathering phase, effectively described the limitations of the AFHS and was quoted in extensive detail in *Updates 2006* and *2008*. In summary, VAO committees have recognized the following features as the primary strengths and limitations of the AFHS:

- The AFHS is one of the most pertinent studies for the VAO reviews, with a study population that was directly exposed to the COIs in the Vietnam War theater.
- It can be argued that the AFHS population is not representative of the entire population of Vietnam veterans, so its findings might not be generalizable to all Vietnam veterans.
- The AFHS might be underpowered for detecting small effects, especially rare outcomes, because of its relatively small sample. Therefore, its

findings are vulnerable to false negatives (failure to detect an important association). This also raises questions about the stability of positive findings; this is somewhat less of a problem if they are repeated over examination cycles, although the results of the examination cycles themselves are not fully independent repetitions.

- For AFHS analyses that used non-AFHS Vietnam veterans as the comparison group, the comparison group might also have been exposed to the COIs although the exposure was likely to be substantially higher in the AFHS group than in the comparison group. Therefore, the comparison is not an ideal exposed-versus-unexposed comparison but rather a high-exposure-versus-low-exposure comparison. The exposure in the comparison group might also make the study findings vulnerable to false negatives if the exposure differential between the AFHS group and the comparison group was not large enough to allow an association between exposure and outcome to be detected. However, that problem does not affect the validity of positive findings.

Only one new report from the AFHS (Pavuk et al., 2014) was identified in the current literature review. In this report, serum concentrations of dioxin-like compounds (i.e., polychlorinated dibenzo-*p*-dioxins [PCDDs], polychlorinated dibenzofurans [PCDFs], polychlorinated biphenyls [PCBs]) in addition to TCDD were analyzed from samples collected in 2002 from 777 ORH subjects and 1,173 in the comparison group. In addition, the results were compared with serum samples from 436 age- and gender-matched adults from the National Health and Nutrition Examination Survey (NHANES). The main findings showed that median serum TCDD levels were more than two times higher in the ORH veterans compared to both the Air Force control veterans and the NHANES comparison group. However, the absolute values of serum TCDD levels, as well as the group differences in median serum TCDD levels, were substantially lower than results from prior serum samples collected in 1987. For the other dioxin-like compounds, the concentrations in 2002 were similar in all three groups. These data demonstrate the unique TCDD signature experienced from herbicide exposure in Vietnam and indicate that, over time, the elimination rate is higher than the ongoing intake rate from background exposure to TCDD in both groups of Air Force veterans.

US Department of Veterans Affairs

VA Army Chemical Corps Cohort

The study of members of the US ACC was conducted by VA, whose other research efforts on Vietnam veterans are discussed together below. The ACC study is discussed immediately after the discussion of the AFHS because of the

importance that VAO committees have attributed to it. Like the Ranch Hand personnel, members of the ACC were involved directly in handling and distributing herbicides in Vietnam. Because the ACC personnel were expected to have been highly exposed to herbicides, VAO committees recommended studying this important group of Vietnam veterans (IOM, 1994) and later encouraged the publication of the study's findings (IOM, 2004). The availability of serum TCDD concentrations in a subset of this cohort of Vietnam veterans has made its findings particularly useful in appraising possible associations with various health outcomes.

ACC troops performed chemical operations on the ground and by helicopter and were thereby involved in the direct handling and distribution of herbicides in Vietnam. The ACC population was belatedly identified for the study of health effects related to herbicide exposure (Thomas and Kang, 1990). In an extension, Dalager and Kang (1997) compared mortality among veterans of the ACC specialties, including Vietnam veterans and non-Vietnam veterans. The results of an initial feasibility study were reported by Kang et al. (2001). The researchers recruited 565 veterans: 284 Vietnam veterans and 281 non-Vietnam veterans as controls. Blood samples were collected in 1996 from 50 Vietnam veterans and 50 control veterans, and 95 of the samples met CDC standards of quality assurance and quality. A comparison of the entire Vietnam cohort with the entire non-Vietnam cohort showed that the geometric mean TCDD concentrations did not differ significantly ($p = 0.6$). Of the 50 Vietnam veterans sampled, an analysis of the questionnaire responses indicated that those who reported spraying herbicides had higher TCDD concentrations than did those who reported no spraying activities. The authors concluded that Agent Orange exposure was a likely contributor to TCDD concentrations in Vietnam veterans who had a history of spraying herbicides.

Kang et al. (2006) reported the findings of the main study. A health survey of 1,499 Vietnam veterans and 1,428 non-Vietnam veterans was administered by telephone. Exposure to herbicides was assessed by analyzing serum specimens from a sample of 897 veterans for dioxin. Veterans who reported spraying herbicides had significantly higher TCDD serum concentrations than did Vietnam veterans and other veterans who did not report herbicide spraying. The final analysis compared Vietnam-veteran sprayers with Vietnam-veteran nonsprayers in the entire study population.

Having determined the vital status of the ACC personnel through 2005, Cypel and Kang (2010) presented results on mortality from the following causes: cancers (oral and pharyngeal, digestive, respiratory, prostate, testicular, skin, brain, and lymphopoietic [leukemia]), diabetes, circulatory (hypertension and cerebrovascular), respiratory conditions (pneumonia, influenza, and chronic obstructive pulmonary disease), and cirrhosis of the liver. The study compared 2,872 ACC personnel who served in Vietnam with 2,737 ACC personnel who did not serve in

Vietnam, using survival analysis that controlled for race, age at entry into follow-up, rank, and duration of military service. It also compared 662 ACC personnel who served in Vietnam and reported spraying herbicides with 811 who did not serve in Vietnam and did not report spraying, controlling for additional covariates obtained in the telephone survey—body mass index (BMI) and smoking status. Mortality in both cohorts was also compared with the expected mortality in US males. Concerns were raised that the findings in Cypel and Kang (2010) regarding respiratory diseases were not adjusted for smoking status, which was probably an important confounding factor for respiratory diseases, in the analyses based on the entire ACC cohort that compared those who served in Vietnam with those who did not. (The subcohort analyses that compared sprayers with nonsprayers were adjusted for smoking status.)

The primary strengths and limitations of the ACC studies are similar to those of the AFHS. No new ACC studies were reported during the current review period.

VA Female US Vietnam-Veteran Cohort

Although estimates vary, 5,000 to 7,000 US women are believed to have served in Vietnam after volunteering for military service (Thomas et al., 1991). The vast majority of them served as combat nurses—mostly in the Army Nurse Corps—but some also served with the Women's Army Corps and the Air Force, Navy, and Marine Corps (Spoonster-Schwartz, 1987; Thomas et al., 1991).

In 1986, Public Law (PL) 99-972 was enacted. It required that an epidemiologic study be conducted to examine the long-term adverse health effects on female Vietnam veterans caused by their exposure to traumatic experiences, exposure to such herbicides as Agent Orange or other chemicals or medications, or any similar experience or exposure during such service. The first study that VA conducted to assess mortality in female Vietnam veterans was by Thomas et al. (1991). No comprehensive record of female personnel who served in Vietnam in 1964–1972 existed, so the researchers gathered military service data from each branch of the armed forces to conduct the mortality study through December 31, 1987. Female Army and Navy personnel were identified from morning reports and muster rolls of hospitals and administrative support units where women were likely to have served. Military personnel were identified as female by their names, leaving open the possibility that some women may have been inadvertently excluded from the analysis. Women who served in the Air Force and Marine Corps were identified through military records. The combined roster of all female personnel from the military branches was considered by the researchers to be generally complete. A comparison group consisted of female veterans who were identified through the same process as the female Vietnam veterans but had not served in Vietnam during their military service. Demographic information and information on overseas tours of duty, unit assignments, jobs, and principal duties

were abstracted from military records. Mortality information was obtained from VA's BIRLS, the Social Security Administration, the Internal Revenue Service, the National Death Index (NDI), and military personnel records. When women whose service in the military fell outside the period of interest, whose records were lacking data, or who served in SEA but not in Vietnam were excluded, the analysis included 132 deaths among 4,582 female Vietnam veterans and 232 deaths among 5,324 comparison veterans who served in the military from July 4, 1965, to March 28, 1973. Cause-specific mortality was derived for Vietnam veterans and comparison veterans and compared with mortality in US women with adjustments for race, age, and calendar period. Dalager et al. (1995a) updated mortality in the original cohort until December 31, 1991, using the same study protocol as Thomas et al. (1991). After updating the mortality figures and adjusting the existing cohort on the basis of new information about the study groups based on the inclusion criteria, 4,586 Vietnam veterans and 5,325 comparison veterans were included in the final analyses (Dalager et al., 1995a).

VA also published studies of pregnancy outcomes and gynecologic cancers—namely, neoplasms of the cervix, uterus, and ovary—in US female Vietnam veterans (Kang et al., 2000a,b). Army veterans were identified from a list obtained by the US Army and Joint Services Environmental Support Group; computerized lists were also provided by the Air Force, Navy, and Marine Corps. Military-service data were abstracted from personnel records. Of 5,230 eligible veterans, 4,390 whose permanent tour of duty included service in Vietnam were alive on January 1, 1992. From a pool of 6,657 potential control participants whose military units did not serve in Vietnam, 4,390 veterans who were alive on January 1, 1992, were randomly selected as controls. After exclusion of 250 veterans and 250 nonveterans who participated in a pilot study, an attempt was made to locate the remaining 4,140 veterans in each group. Various location strategies were used, and fewer than 5 percent (370) were not located; another 339 were deceased. A full telephone interview was conducted on 6,430; 775 refused (13 percent of Vietnam veterans and 17 percent of non-Vietnam veterans), and another 366 completed only a short written questionnaire. A questionnaire was administered on demographic background, general health, lifestyle, menstrual history, pregnancy history, pregnancy outcomes, and military experience, including nursing occupation and combat exposure. Information on pregnancy risks and complications—including smoking, infections, medications, exposure to X-rays, occupational history, and exposure to anesthetic gases, ethylene oxide, herbicides, and pesticides—was collected for each pregnancy. In Kang et al. (2000a), the first pregnancy after the beginning of Vietnam service was designated as the index pregnancy of each woman. For the comparison group, the first pregnancy after July 4, 1965, was used as the index pregnancy of each woman. Odds ratios (ORs) were calculated for the reproductive history and pregnancy outcomes. The study analyzed data on 3,392 Vietnam and 3,038 non-Vietnam veterans and on 1,665 Vietnam and 1,912 non-Vietnam veteran index pregnancies. In Kang et al.

(2000b), a self-reported history of gynecologic cancers (defined by the authors as cancers of the breast, ovary, uterus, and cervix) was collected. The authors attempted to "retrieve hospital records on all reported cancers as far back as 30 years." Of records successfully found, 99 percent of the breast cancers and 90 percent of all cancers were confirmed. The authors did not provide data on validation of the three sites other than the breast, but they stated that Vietnam status was not associated with verification of outcome.

After the publications by Kang et al. (2000a,b), Congress passed PL 106-419, which provides compensation for children of female Vietnam veterans who are born with birth defects unrelated to an existing familial disorder, to a birth-related injury, or to a fetal or neonatal infirmity with a well-established cause. Eighteen birth defects are covered by the legislation, including cleft lip or palate, congenital heart disease, hypospadias, neural-tube defects, and Williams syndrome. A complete list of covered birth defects can be found in Section 3.815 of the legislation.

Cypel and Kang (2008) conducted a mortality study of female Vietnam veterans and compared their mortality with that in a control group of women who were in military service but did not participate in the Vietnam War. Non-Vietnam veterans were selected randomly from among female veterans who never served in Vietnam and were matched to the Vietnam veterans according to rank and military occupation.

Since *Update 2012*, Kang and colleagues (2014) have updated total and cause-specific mortality analyses of female US Vietnam-era veterans through December 31, 2010. Vital status was obtained from multiple sources including the VA BIRLS Death File, the Social Security Administration Death Master File, and the National Center for Health Statistics National Death Index (NDI). For deaths that occurred before 1992, the cause of death was ascertained from official death certificates. For deaths occurring on or after January 1, 1992, cause of death information was obtained from NDI Plus, which provides cause of death codes by the *International Classification of Diseases* (ICD) system. Underlying causes of death were formally assigned by a qualified nosologist.

This retrospective cohort study consisted of three study groups of female Veterans who served during the Vietnam era when combat operations occurred (July 4, 1965, through March 28, 1973). This included 4,734 female veterans who served in Vietnam, 2,062 female veterans who served near Vietnam, and a non-deployed US cohort of 5,313 female veterans. Mortality comparisons were made with the non-deployed US cohort as well as with the US general population (women) adjusted for age, race, and calendar year. Of the total sample of 12,109 female veterans, 2,743 (23 percent) were deceased by the study end date of December 31, 2010. Importantly, the cause of death information was available for 96.2 percent of the total cohort.

Cause-specific mortality results are presented in the individual chapters addressing specific disease outcomes. However, to summarize, the adjusted total

mortality rate was statistically lower in the female Vietnam veterans group than in the US cohort of female veterans as well as in the US general population. Similar results were reported for heart disease mortality, with the Vietnam veterans group having a lower rate, whereas rates of cancer mortality were approximately equal between the female Vietnam veterans group and both the US cohort of female veterans and the US general population. However, among nurses only (approximately two-thirds of the study cohort), higher adjusted mortality rates for pancreatic and brain and other nervous system cancers were reported for the female Vietnam veterans group. Whereas all reports from the female US Vietnam-veterans cohort provide direct information on the health and mortality status of female military personnel who served in Vietnam, results must be taken in the context of limitations. Specifically, female veterans likely experienced low herbicide exposure because they were not involved in applying herbicides or engaged in direct combat, and had in-country tours of duty that were generally 1 year in length and at fixed locations that were away from known defoliated areas. In summary, this analysis does not provide evidence in support of female Vietnam veterans being at higher risk of total and cause-specific mortality compared with non-Vietnam female veterans and the US general population. The suggestion of higher rates of mortality from pancreatic and brain and other nervous system cancers among nurse Vietnam veterans should be cautiously interpreted given the study's limitations and the large number of causes of mortality examined.

VA Proportionate-Mortality Cohort

Among the earliest reports on Vietnam veterans was a proportionate-mortality study by Breslin et al. (1988). The participants were men who had served as ground troops in the US Army or Marine Corps at any time from July 4, 1965, through March 1, 1973. A list of 186,000 Vietnam-era veterans who served in the Army or Marine Corps and were reported deceased as of July 1, 1982, was assembled from VA's BIRLS; of these, 75,617 names were randomly selected from the list for inclusion in the study. The information extracted from the selected military records included the places, dates, and branch of military service; date of birth; sex; race; military occupation specialty codes; education level; type of discharge; and confirmation of service in Vietnam. Additional information was extracted on veterans who served in SEA, including the first and last dates of service in SEA, the military unit, and the country where the veteran served. For the final sample of 52,253 Army and Marine Corps veterans, the cause of death was ascertained from death certificates or Department of Defense Report of Casualty forms for 51,421 men, including 24,235 who served in Vietnam and 26,685 men who did not serve in SEA; 501 deaths were excluded from the final analyses because service in SEA was in a country other than Vietnam or the location of military service was unknown. Each veteran's cause of death was coded by a nosologist who used the 8th revision of the *International Classification of Diseases*.

On the basis of the proportionate-mortality study (Breslin et al., 1988), Burt et al. (1987) conducted a nested case-control study of non-Hodgkin lymphomas (NHLs) with controls selected from among the cardiovascular-disease deaths. In a follow-up of the Breslin et al. study, Bullman et al. (1990) compared cause-specific proportionate mortality in 6,668 Army I Corps Vietnam veterans—veterans who served in the northernmost part of South Vietnam in a combat zone designated as Military Region I by the US military—with that in 27,917 Army Vietnam-era veterans who had not served in Vietnam. The subjects studied by Bullman et al. included the study population identified by Breslin et al. and an additional 9,555 Army Vietnam-era veterans whose deaths were identified after the BIRLS mortality data were extended through December 31, 1984. Similarly, Watanabe et al. (1991) updated the Vietnam-veteran mortality experience reported by Breslin et al. (1988) by extending the follow-up from January 1, 1982, to December 31, 1984. An additional 11,325 deceased Army and Marine Vietnam-era veterans were identified from the period and included in the study. The study population for Watanabe et al. consisted of 62,068 military veterans, of whom 29,646 served in Vietnam and 32,422 never served in SEA. Proportionate-mortality ratios were calculated for three referent groups: branch-specific (Army and Marine Corps) non-Vietnam veterans, all non-Vietnam veterans combined, and the US male population. A third follow-up proportionate-mortality study (Watanabe and Kang, 1996) used the veterans from Breslin et al. (1988) and Watanabe et al. (1991) and included an additional 9,040 randomly selected Vietnam-era veterans who died from July 1, 1984, through June 30, 1988. The final study included 70,630 veterans—33,833 who had served in Vietnam and 36,797 who never served in SEA—and the analyses were performed with the same referent groups described previously (Watanabe et al., 1991).

Other VA Studies

VA also conducted studies that focused on specific health outcomes, using data from VA's Agent Orange Registry (AO Registry), a computer database containing health information on Vietnam veterans who voluntarily undergo examinations in a VA hospital. The AO Registry was set up in 1978 to monitor those health complaints or problems of Vietnam veterans that could be related to herbicide exposure during their military service in Vietnam. The examinations consist of an exposure history, a medical history, laboratory tests, and an examination of the body systems most commonly affected by toxic chemicals. As of September 30, 2012, the AO Registry contained information on 573,088 initial examinations (an increase of 119,019 since 2008) and 65,758 follow-up evaluations, for a total of 638,846 examinations (VA, 2012). Updated statistics on the AO Registry were not reported in the next issue of VA's *Agent Orange Newsletter* (VA, 2015).

Using early data from the AO Registry, Bullman et al. (1991) examined the risk of posttraumatic stress disorder (PTSD) in a case-control study of veterans

who had received medical examinations from January 1983 through December 1987. The final analyses included 374 PTSD cases and 373 controls whose military records were used to verify Vietnam service, Military Occupational Specialty Codes (MOSCs), primary duties, military branch, dates of Vietnam service, medals, awards, and disciplinary actions for each veteran. Of note, as described in Chapter 2, PTSD and other mental health conditions were not formally evaluated by more recent VAO committees. Similarly, Bullman et al. (1994) studied the risk of testicular cancer by using the AO Registry health records of veterans who received medical examinations from March 1982 through January 1991. The final analyses in that study included 97 testicular-cancer cases and 311 controls. A surrogate metric for herbicide exposure was developed by using the branch of service, combat MOSCs, geographic area of service in Vietnam, location of military units in relation to herbicide-spraying missions, and the length of time between spray missions and military operations in sprayed areas.

Watanabe and Kang (1995) compared postservice mortality in Vietnam veterans in the Marine Corps with that in Vietnam-era marines who did not serve in Vietnam. All of the study participants were on active duty during 1967–1969 and were followed from their discharge date or from the date of the US military withdrawal from Vietnam until their date of death or December 31, 1991, whichever came first. The final study population included 10,716 Vietnam and 9,346 non-Vietnam veteran marines.

Kang et al. (1991) conducted a case-control study that compared dioxin and dibenzofuran concentrations in the adipose tissue of 36 Vietnam veterans with those in 79 non-Vietnam veterans and a sample of US men born in 1936–1954. All tissue samples were archived specimens from the US Environmental Protection Agency National Human Adipose Tissue Survey and had been collected by hospitals and medical examiners from men who died from external causes or surgical procedures. Military service—branch of service, MOSC, and geographic service location in Vietnam, if applicable—was researched and verified with military records. Controls were matched by birth year and sample collection year (± 2 years), and the final analyses were adjusted by age and BMI.

Dalager et al. (1991) examined NHL in male Vietnam veterans in a hospital-based case-control study. Study participants were identified via inpatient discharge records from VA medical centers for the fiscal years 1969–1985. The cases were veterans identified as having a malignant lymphoma and a birth date from 1937 through 1954. The controls were veterans identified from VA medical-center discharge records and were matched by hospital, discharge date, and birth date. The locations and dates of each veteran's military service were verified by using military records. A surrogate herbicide exposure opportunity was also developed for each Vietnam veteran according to the veteran's branch of service, combat experience, and the geographic location of the military unit assignment. The final analysis included 201 cases and 358 controls. Another study by Dalager et al. (1995b) examined the association between Hodgkin lymphoma (HL) and

Vietnam service. It used the same method as the 1991 Dalager et al. study; the analysis included 283 HL cases and 404 controls.

VA has evaluated specific health outcomes, including case-control studies of soft-tissue sarcomas (STSs) (Kang et al., 1986, 1987), testicular cancer (Bullman et al., 1994), and lung cancer (Mahan et al., 1997). It also has conducted a study of self-reported physical health (Eisen et al., 1991) and PTSD (Goldberg et al., 1990) in monozygotic twins who served during the Vietnam era.

VA has examined other outcomes in Vietnam veterans: PTSD (Bullman et al., 1991; True et al., 1988), suicide and motor-vehicle crashes (Bullman and Kang, 1996; Farberow et al., 1990), and tobacco use (McKinney et al., 1997). The studies have been included for completeness, but the outcomes that they address are outside the purview of this committee. *VAO* and *Update 1998* discuss them in detail; most did not deal with exposure to herbicides specifically, and the exposure to "combat" was evaluated as the risk factor of interest.

US Centers for Disease Control and Prevention Studies

Surveys of US Vietnam veterans who were not part of the Ranch Hand or ACC groups indicated that 25 to 55 percent believed that they were exposed to herbicides (CDC, 1989b; Erickson et al., 1984a,b; Stellman and Stellman, 1986). Several attempts have been made to estimate the exposures of Vietnam veterans who were not part of the Ranch Hand or ACC groups. CDC has undertaken a series of studies to examine various health outcomes in Vietnam veterans as directed by Congress in the Veterans Health Programs Extension and Improvement Act of 1979 (PL 96-151) and the Veterans' Health Care, Training, and Small Business Loan Act of 1981 (PL 97-72).

CDC Birth-Defects Study

The first of these CDC studies was a case-control interview study of birth defects in the offspring of men who served in Vietnam (Erickson et al., 1984a,b). In 1983 the US government asked CDC to conduct a study of possible long-term health effects in Vietnam veterans exposed to herbicides. The CDC Agent Orange study (CDC, 1985) attempted to classify veterans' service-related exposures to herbicides. This involved determining the proximity of troops to herbicide spraying by using military records to track troop movement and using the HERBS tapes to locate herbicide-spraying patterns. The CDC birth-defects study developed an exposure-opportunity index to score herbicide exposure (Erickson et al., 1984a,b).

CDC Agent Orange Validation Study

In 1987, CDC conducted the CDC Agent Orange Validation Study (AOVS) to test the validity of the various indirect methods used to estimate the exposure

of ground troops to herbicides in Vietnam. The study measured serum TCDD in a nonrandom sample of Vietnam veterans and in Vietnam-era veterans who did not serve in Vietnam (CDC, 1988a). Vietnam veterans were selected for the study on the basis of the number of herbicide hits that they were thought to have experienced, given the number of days on which their company was within 2 km and 6 days of a recorded herbicide-spraying event. Blood samples were obtained from 66 percent of 646 Vietnam veterans and from 49 percent of the eligible comparison group of 97 veterans. More than 94 percent of those whose serum was obtained had served in one of five battalions.

The median serum TCDD in Vietnam veterans in 1987 was 4 parts per trillion (ppt) (range, under 1 to 45 ppt). Only two veterans had concentrations above 20 ppt. The "low" exposure group consisted of 298 Vietnam veterans, the "medium" exposure group 157 veterans, and the "high" exposure group 191 veterans. The distribution of TCDD measurements was nearly identical with that in the control group of 97 non-Vietnam veterans. The CDC validation study concluded that study participants could not be distinguished from controls on the basis of serum TCDD. In addition, neither record-derived estimates of exposure nor self-reported exposure to herbicides could predict Vietnam veterans with currently high serum TCDD (CDC, 1988b, 1989b). The report concluded that it was unlikely that military records alone could be used to identify a large number of veterans who might have been heavily exposed to TCDD in Vietnam.

CDC Vietnam Experience Study

Using exposure estimates from the AOVS, CDC conducted the CDC Vietnam Experience Study (VES), a historical cohort study of the health experience of Vietnam veterans (CDC, 1989a). The study was divided into three parts: physical health, reproductive outcomes and child health, and psychosocial characteristics (CDC, 1987, 1988a,c,d, 1989a). Using VES data, CDC examined postservice mortality (through 1983) in a cohort of 9,324 US Army veterans who served in Vietnam and in 8,989 Vietnam-era Army veterans who served in Germany, Korea, or the United States (Boyle et al., 1987; CDC, 1987). Another study (O'Brien et al., 1991) combined the mortality and interview data to identify all veterans who had NHL. To evaluate whether self-reported assessment of exposure to herbicides influences the reporting of adverse health outcomes, CDC designed a study of VES participants (Decoufle et al., 1992). In a follow-up of CDC's VES cohort, Boehmer et al. (2004) reported findings on mortality from 1965 through 2000.

The serum TCDD measurements in Vietnam veterans also suggested that the exposure to TCDD in Vietnam was substantially lower, *on average*, than that of persons exposed as a result of the industrial explosion in Seveso or that of the heavily exposed occupational workers who have been the focus of many of the studies evaluated by the present committee. The assessment of *average*

exposure does not preclude subgroups of Vietnam veterans from having had heavy exposures.

CDC Selected Cancers Study

CDC undertook the CDC Selected Cancers Study (CDC, 1990a) to investigate the effects of military service in Vietnam and of exposure to herbicides on the health of American veterans, specifically the risk of developing NHL (CDC, 1990b), STS and other sarcomas (CDC, 1990c), HL (CDC, 1990d), and nasal, nasopharyngeal, and primary liver cancers (CDC, 1990d).

CDC National Vietnam Veterans Readjustment and Longitudinal Studies

The CDC National Vietnam Veterans Readjustment Study investigated primarily psychological outcomes. It is now being updated to become the National Vietnam Veterans Longitudinal Study (NVVLS). The literature search for *Update 2014* identified an additional peer-reviewed article based on data gathered during the original study (Currier and Holland, 2012), which addressed psychologic outcomes in association with combat trauma and bereavement. To date (9 months after the cut-off date for this update), the only publications arising from the new NVVLS effort have been a press release (Abt Associates, 2014) associated with a conference presentation, a non-peer-reviewed article prepared by the VA contractors for the newsletter of the Vietnam Veterans of America (Schlenger and Corry, 2015), and an article addressing the protocols and methods used in NVVLS (Schlenger et al., 2015).

Other US Vietnam-Veteran Studies

Ansbaugh et al. (2013) conducted a historical cohort analysis of 2,720 veterans who were referred to the Portland Veterans Affairs Medical Center and underwent an initial prostate biopsy. Prior exposure to herbicides was crudely classified as "yes" or "no" within the electronic medical record system in a variable called "AO exposure" and yielded an overall prevalence of 7.5 percent. In a multiple logistic regression analysis, herbicide exposure (compared to no exposure) was associated with an estimated 1.52 higher odds of prostate cancer (all subtypes), including OR estimates of 1.24 for low-grade prostate cancer, 1.75 for high-grade prostate cancer, and 2.10 for the detection of prostate cancer with Gleason scores of 8 or higher. The reliability of the medical record variable classified as "yes" or "no" is unknown in this cohort and is considered to be a methodological concern by the committee.

Clemens et al. (2014) reviewed the clinical characteristics of 100 consecutive male patients with Fitzpatrick skin types I though IV who enrolled in the AO Registry at the Veterans Affairs Hospital of Washington, DC, between August 2009

and January 2010. Because by design all participants were selected on the basis of presumably having been exposed to herbicides and having been diagnosed with non-melanotic invasive skin cancers, the committee deemed this analysis of no value with respect to examining the relationships between the COIs.

Qureshi et al. (2013) reanalyzed cases of veterans diagnosed with Barrett's esophagus and veteran controls who have been previously assembled at the VA Medical Center in Houston, Texas, for the role of occupational pesticide exposure as a risk factor. The committee deemed this study to be of no value to its charge because it neither distinguished the types of pesticides examined nor considered the subjects' deployment status or exposure to military herbicides as potential risk factors.

In a published abstract by Srinivas et al. (2012), demographic, clinical, and pathology data were compared between Vietnam-era and non-Vietnam-era veterans with NHL. Beyond the inadequately detailed information presented and its lack of peer review, the committee deemed this study of no value to its charge because it was unrelated to the development of NHL in relation to service in Vietnam.

American Legion Study

The American Legion, a voluntary service organization for veterans, conducted a cohort study of the health and well-being of Vietnam veterans who were members. Studies examined physical health and reproductive outcomes, social–behavioral consequences, and PTSD in veterans who had served in SEA and elsewhere (Snow et al., 1988; Stellman JM et al., 1988; Stellman SD et al., 1988b). No additional studies have been published on the cohort.

State Studies

Several states have conducted studies of Vietnam veterans, most of which have not been published in the scientific literature. *VAO* and *Update 1996* reviewed studies of veterans of Hawaii (Rellahan, 1985), Iowa (Wendt, 1985), Maine (Deprez et al., 1991), Massachusetts (Clapp, 1997; Clapp et al., 1991; Kogan and Clapp, 1985, 1988; Levy, 1988), Michigan (Visintainer et al., 1995), New Jersey (Fiedler and Gochfeld, 1992; Kahn et al., 1988, 1992a,b,c), New Mexico (Pollei et al., 1986), New York (Greenwald et al., 1984; Lawrence et al., 1985), Pennsylvania (Goun and Kuller, 1986), Texas (Newell, 1984), West Virginia (Holmes et al., 1986), and Wisconsin (Anderson et al., 1986a,b). Chamie et al. (2008) examined the association between herbicide exposure and prostate cancer in all Vietnam-era veterans using the VA health system in northern California; the reliability of this study of about 13,000 men is limited by its reliance on self-reported exposure status and by the exclusion of prostate cases diagnosed

before 1998, when computerized records became available. No additional state studies have been published.

Additional studies have examined health outcomes that included spontaneous abortion (Aschengrau and Monson, 1989) and adverse outcomes late in pregnancy in spouses of Vietnam veterans (Aschengrau and Monson, 1990). After a published study indicated a potential association between testicular cancer in dogs and their service in Vietnam (Hayes et al., 1990), Tarone et al. (1991) conducted a case-control study of testicular cancer in male veterans. VAO summarized those studies, and no additional studies have been published on these study populations.

Australian Vietnam-Veteran Studies

Over many years the Australian government has commissioned studies to follow health outcomes in two sets of Australian veterans who served in Vietnam.

Australian Vietnam Veterans

The Australian Vietnam-veterans study population corresponds to the cohort defined by the "Nominal Roll of Vietnam Veterans," which lists Australians who served on land or in Vietnamese waters from May 23, 1962, to July 1, 1973, including military and some nonmilitary personnel of both sexes. People who served in any branch of service in the defense forces and citizen military forces (such as diplomatic, medical, and entertainment personnel) were considered. The comprehensive studies, however, are limited to male members of the military, and most of the analyses focus on men in the defense forces—the Army (41,084), the Navy (13,538), and the Air Force (4,570). An investigation looked into the possibility of an association between Vietnam service and cancer incidence (ADVA, 2005a) by comparing diagnoses from 1982 to 2000 among male Vietnam veterans with those in the general population of Australia. The results in this report supersede those in the report of the Australian Department of Veterans' Affairs (CDVA 1998a). Morbidity in all female Vietnam veterans had been studied in an earlier report (CDVA, 1998b). Additional case-control studies of the incidence of adrenal gland cancers, leukemias, and NHL were conducted in this population (AIHW, 1999, 2000, 2001).

A related report (ADVA, 2005b) considered the causes of death of men in all branches of service through 2001. The numbers of deaths were 4,045 in the Army, 1,435 in the Navy, and 686 in the Air Force. The mortality experience of military personnel serving in Vietnam was compared with that of the general population of Australia and reported by branch of service. The findings of this study supersede those in the report on mortality from 1980 to 1994 (CDVA, 1997a). There had been several earlier studies of mortality among Australian Vietnam veterans

(CIH, 1984a,b,c; Crane et al., 1997a,b; Evatt, 1985; Fett et al., 1987a,b; Forcier et al., 1987).

Australian Vietnam Veterans Family Study (VVFS)

Since *Update 2012*, the Australian Department of Veterans' Affairs has published four large volumes that summarize the results of studies conducted among family members of Vietnam-era veterans (ADVA, 2014a,b,c,d). The first volume (2014a) provided an overview of the entire effort, which consisted of several studies of the veterans' family members. The second (ADVA, 2012b) assessed the health of the family members with more emphasis placed on the details of psychological and social wellbeing, rather than adverse impacts on physical health. The third (ADVA, 2014c) investigated mortality among members of the veterans' families, while the final volume (ADVA, 2014d) discussed qualitative information gathered in the course of the entire study. Although responses were collected on spouses and partners of the veterans, the analyses focused upon outcomes reported by the children of the veterans. The wide range of outcomes examined for the family members themselves included mental health outcomes, pregnancy and birth defect outcomes, physical health, social functioning, and mortality. The purpose of this study was to better understand the long-term impacts of service on the health and welfare of the families of Australian Vietnam veterans.

From the roster of Australian Vietnam veterans, more than 10,000 Australians who had served in the Vietnam War were randomly selected and contacted, along with their family members, for potential participation in the study. The Vietnam veterans who were identified and ultimately selected included 3,940 who were randomly selected and 2,569 who self-selected into the study based on media publications announcing that the study would be conducted.

The primary comparison group consisted of family members of non-deployed Vietnam-era personnel, meaning family members of Australian veterans who served from 1962 through 1975, but were not deployed to Vietnam. This included the identification and selection of 3,967 randomly selected veterans and 418 who self-selected in the study. Thus, there were far more Australian Vietnam veterans than Australian Vietnam-era veterans who self-selected into the study, and the percentage of the Vietnam veterans who self-selected was much higher than the percentage of Vietnam-era veterans who self-selected. In total, the family members of Vietnam veterans included 2,199 sons and daughters, of which 1,385 were investigated for pregnancy and birth defect–related outcomes.

The VAO series has considered comparisons of deployed and non-deployed groups to cover potential exposure to all the COIs, and thus the most relevant measures for their task (in the absence of specific exposure information). Such constrasts, however, also cover all aspects of the deployment experience, and in this set of Australian studies there was considerably more concern about psychological effects on the veterans (especially PTSD) and their secondary impact on

the veterans' family members, which would not be expected to be an effect of herbicide exposure.

The VVFS has conducted some analyses among all study participants, as well as some analyses stratified by type of enrollment (random versus self-selected). The committee fully recognized potential reporting biases that may have emanated from the self-selected cohort, and thus it placed considerably more weight on results derived for the randomly selected cohort, as did the researchers themselves.

Australian Conscripted Army National Service

The Australian Conscripted Army National Service study population is a subset of the veterans considered in the overall Australian Vietnam Veterans study group. The 19,240 conscripted male Army veterans deployed to Vietnam ("National Service" veterans) were compared with 24,729 non-deployed counterparts ("National Service non-veterans"). This comparison between contemporaries who had been sufficiently healthy to enter the service provided a means of adjusting for a possible "healthy-warrior" effect. The results on death and cancers in the Australian conscripted Army National Service veterans (ADVA, 2005c) supersede those of earlier internal comparisons of deployed and non-deployed Vietnam War–era National Service veterans (CIH, 1984a; Crane et al., 1997b; Fett et al., 1987a,b). Those government-sponsored studies of Australian Vietnam veterans did not characterize the veterans' exposure to the herbicides sprayed in Vietnam beyond the fact that they had served on land or in Vietnamese waters from May 23, 1962, through July 1, 1973. It is the convention of VAO committees to regard Vietnam veterans in general as being more likely to have received higher exposures to the COIs than the general public, but it would have been informative to validate that assumption by gathering biomarkers of exposure, such as serum measurements, in a sample of Australian Vietnam veterans.

Update 2000 had moved the occurrence of acute myeloid leukemia in offspring of Vietnam veterans into the limited or suggestive category of association primarily on the basis of findings reported by the Australian Institute of Health and Welfare (AIHW, 2000) but rescinded in a revised report (AIHW, 2001). The reversal of the conclusion on this matter by the committee for *Update 2000* is discussed in *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans* (IOM, 2002).

Sample of 1,000 Australian Vietnam Veterans

O'Toole et al. (1996a,b,c) studied a broad spectrum of health issues in a random sample of 1,000 Australian Vietnam veterans (both regular enlisted and conscripted Army National Service members) selected from Australia's comprehensive roster of 57,643 service members deployed to Vietnam. In wave 1,

conducted in 1990–1993, 641 members of the sample were located and interviewed. In wave 2, conducted in 2005–2006, O'Toole et al. (2009) obtained responses from 450 (51.4 percent of those not known to have died); 391 responded to both waves. The Australian Bureau of Statistics' National Health Survey was administered in both waves with the collection of additional data on combat experience, PTSD, and general psychiatric status. The veterans' self-reported health status was compared with that of the general male Australian population gathered during the government's administration of the same survey in 1989–1990 and 2004–2005; it is not clear that this instrument was administered to the two groups under comparable conditions. The low response rates make the findings vulnerable to nonresponse bias and the use of self-report measures of health conditions might be of low validity and subject to recall bias. The committee for *Update 2010* was skeptical about the reliability of the nearly uniform findings of statistically increased prevalence of nearly 50 health conditions. O'Toole et al. (2010) reported on the mortality in the sample through 2004 as related to previously gathered information on psychosocial factors that are not within the scope of VAO reviews. It is of interest, however, that they found that 11.7 percent of the veterans in the sample had died by the end of 2004.

Case-Control Study of Birth Defects in Australian Infants

The Australian government sponsored a case-control study of 8,517 infants with congenital anomalies born in 1966–1979 at 34 hospitals in New South Wales, Victoria, and in the Australian Capital Territory matched by period of birth, mother's age, hospital, and means of hospital payment to live-born infants without diagnosed birth defects (Donovan et al., 1983, 1984; Evatt, 1985). The fathers of both groups were identified and their names compared to the roster of men who had served in the Australian Army in 1962–1972; additional means of verification were used to determine whether the child's father was in the Army during this interval (329 cases and 338 controls) and also whether he was deployed to Vietnam (127 cases and 123 controls). After adjustments were made for maternal age, infant sex, multiple births, and father's place of birth, conditional logistic regression was used to compare the Vietnam veterans (National Service or regular Army) to other era veterans and to all other fathers for all birth anomalies and for seven diagnostic groups.

Korean Vietnam-Veteran Studies

Study of TCDD Concentrations in Korean Vietnam Veterans

Military personnel of the Republic of Korea served in Vietnam from 1964 through 1973. Kim et al. (2001) attempted to use serum dioxin concentrations to validate an index for estimating group exposure. The study involved 720 veterans

who served in Vietnam and 25 veterans who did not. The exposure index was based on herbicide-spraying patterns in military regions in which Korean personnel served, time–location data on the military units stationed in Vietnam, and an exposure score derived from self-reported activities during service. A total of 13 pooled samples were submitted to CDC for serum dioxin analyses. One analytic sample was prepared from the pooled blood of the 25 veterans who did not serve in Vietnam. The remaining 12 samples were intended to correspond to 12 exposure categories; each was created by pooling blood samples from 60 veterans. The 12 exposure categories ultimately were reduced to four exposure groups, each representing a quartile of 180 Vietnam veterans but characterized by only three serum TCDD measurements.

The paper by Kim et al. (2001) reported highly significant Pearson correlation coefficients and results of multiple logistic-regression analysis. The statistical analyses apparently were based on the assignment of the pooled serum dioxin value to each person in the exposure group and thereby inflated the true sample size. The multiple regression analysis evaluated such variables as age, BMI, and consumption of tobacco or alcohol. In a later report on the same exposure groups and serum dioxin data, the authors corrected their analysis (Kim JS et al., 2003). A correlation was observed between serum dioxin concentrations and ordinal exposure categories, but the correlation was not statistically significant. The authors attributed the lack of statistical significance to the small sample size, and they noted that the data exhibited a distinct monotonic upward trend; the average serum dioxin concentrations were 0.3, 0.6, 0.62, 0.78, and 0.87 picograms per gram (pg/g) (lipid-adjusted) for, respectively, exposure categories 0 through 4. The decision to pool blood samples from a large number of persons in each exposure set (Kim et al., 2001) greatly reduced the power of the validation study. Instead of 180 samples in each of the final exposure categories, the pooled analysis produced only three samples in each category. The lipid-adjusted serum TCDD concentrations in the 12 pooled samples from Vietnam veterans ranged from 0.25 to 1.2 pg/g, whereas the single sample from the non-Vietnam veterans contained 0.3 pg/g. The narrow range of results makes the biologic relevance of any differences questionable.

Thus, it appears that there was not a clear separation between Korean Vietnam veterans and non-Vietnam veterans. Furthermore, the range of mean values in the four Vietnam-veteran exposure categories was narrow, and all concentrations were relatively low (less than 1 pg/g). The relatively low serum dioxin concentrations observed in the 1990s in those people are the residual of substantially higher initial concentrations, as has been seen in other Vietnam-veteran groups. However, the concentrations reported in the Korean-veterans study are significantly lower than those reported in American Vietnam veterans in the 1988 CDC AOVS, which was nonetheless unable to distinguish Vietnam veterans from non-Vietnam veterans on the basis of serum dioxin (CDC, 1988b). The Korean authors were able to construct plausible exposure categories based on military

records and self-reporting, but they were unable to validate the categories with serum dioxin measurements.

Study of Role of Vietnam Service in Recovery of Koreans with Acute Coronary Syndrome

JB Kim et al. (2012) reported on the association between exposure to TCDD and recovery outcomes (hypertension, hyperlipidemia, and the rate and severity of major adverse coronary events) in men who presented with acute coronary syndrome (obstruction of coronary arteries and chest pain) from 2004 through 2009 at Gwangju Veterans Hospital. The age range was limited to 50–70 years to reflect the current age of Korean veterans of the Vietnam War. There were 251 patients: 121 were Vietnam veterans (assumed to have been exposed to TCDD), and 130 were not. Medical records were reviewed to determine a variety of cardiovascular recovery outcomes. T-tests, chi-square tests, and logistic regression were used to determine whether measures of recovery differed between the acute coronary patients who had served in Vietnam and those who did not. The study findings are not informative about associations between TCDD and acute coronary syndrome itself, as the researchers allege.

Korean (Vietnam) Veterans Health Study

The committee identified six publications from an exceptionally large epidemiological study of more than 180,000 Korean Vietnam veterans that have appeared since *Update 2012*. This study cohort, denoted herein as the "Korean study," is much larger in scope than all of the other published epidemiological studies conducted among Vietnam veterans. The Korean study provides results for a very large set of health outcomes, including rare conditions, as well as information on both non-fatal outcomes and cause-specific mortality. Consequently, the synthesis of results from the Korean study by the committee members had the potential to substantially influence (i.e., update) conclusions drawn from previous updates.

The research methodology employed in the Korean study was very carefully evaluated by the committee. This was done so that across all health outcomes, committee members would weigh the results from the Korean study in a consistent manner and appropriately take into account the respective strengths and limitations from this large body of data.

For the Assessment of the Potential Exposure to Herbicides For the assessment (referred to imprecisely in the Yi articles as Agent Orange), multiple methods were employed by the Korean study investigators. Responses to six questions on a postal survey were used to derive a four-tiered categorization of self-perceived herbicide exposure (Yi et al., 2013a). The initial four-tier scale

(high, moderate, low, and none) was further compressed into simply "high" or "low" for many analyses (see Table 3-2 in Chapter 3 for the quantitative distributions). An objective index of potential herbicide exposure was calculated for each veteran based on the proximity of their military unit to herbicide-sprayed areas. The model, developed by Stellman et al. (2003b), included herbicide exposure opportunity scores, which accounted for location histories of military units and calendar dates in which spraying occurred. The Korean study investigators classified these quantitative exposure data using two-group and four-group categorizations, the details of which are presented in Tables 3-3 and 3-4 in Chapter 3.

For the Assessment of the Health Outcomes of Interest There were multiple methods used. First, veterans were asked to indicate (self-report) all current and physician-diagnosed diseases. The diseases were classified into seven groups of diseases; cancers, circulatory diseases, respiratory diseases, digestive diseases, neuromuscular diseases, endocrine diseases, and other diseases. Within the major disease groups, self-reporting was further provided for 17 cancers (including stomach cancer, liver cancer, and lung cancer), 13 circulatory diseases (including hypertension, myocardial infarction, and angina), five respiratory diseases (including chronic bronchitis and emphysema), six digestive diseases (including central nervous system disorders and peripheral neuropathy), three endocrine diseases (including diabetes and hypothyroidism), and four other diseases (including renal failure and skin disease).

Second, incidence data of individual types of cancer experienced by Korean Vietnam veterans were obtained from the Korean Cancer Incidence Database (1992–2003) and classified by use of ICD, tenth revision (ICD-10).

Third, prevalent cases of individual disease conditions were identified by extraction of claims data from the Korea National Health Insurance system during the period January 1, 2000, to September 30, 2005, along with medical care covered directly by the Korean government through the Veterans Health Service during the same period. Health outcomes examined included the prevalence of endocrine diseases (E00–E90), neurologic diseases (G00–G99), circulatory diseases (I00–I99), respiratory diseases (J00–J99), and digestive diseases (K00–K93).

Fourth, deaths of Korean Vietnam veterans and the underlying causes of their deaths were ascertained by use of the 1992–2005 death records of the National Statistical Office. Causes of death were classified according to the ICD-10. This included all-causes of death, 15 chapter diseases, 23 specific cancers, and 36 specific causes of death other than cancer.

Using these multiple methods for exposure classification and health outcome ascertainment, associations between metrics of herbicide exposure potential and health outcomes were derived. First, in some analyses, the health experiences of Korean Vietnam veterans, given their exposure status, was compared to the health status of age-matched adults in the Korean general population. This method is known as an

"external" control group. Second, some analyses were performed among Korean Vietnam veterans with the lowest herbicide exposure classification serving as the comparison group. This method is known as an "internal" control group.

The above variations in exposure assessment, health outcome ascertainment, and source of comparator (reference) group have significant implications for the appropriate interpretation of results from the Korean study. In considering these variations, the committee noted the following methodological principles and empirical observations:

1. Whereas self-reported exposure may be reliable and valid in some research circumstances, it is generally considered less reliable and valid than objectively obtained estimates of exposure (Zajacova and Dowd, 2011). The potential for recall bias is of particular concern and the likelihood of it occurring increases with the length of time from potential exposure to the incidence of disease.
2. For ascertaining health outcome data, objective sources (e.g., a cancer registry or health claims system) are generally preferred over self-report outcome data, assuming that the objective source of outcome data is largely comprehensive.
3. For mortality analyses, the estimation of relative risk (and the corresponding confidence interval) may be more prone to bias when an external control group is used (e.g., general population) than when an internal control group is used (Monson, 1990). This may be due to the "healthy soldier" effect. That is, service members upon entry into military service are generally healthy, whereas the general population will always include some individuals of poor health. This healthy soldier effect can also apply to the risk of development of non-fatal outcomes, such as individual types of cancer.
4. The concern over the healthy soldier effect is not present when an internal control group is used instead of the general population (external control group). Similarly, the examination of cancer incidence will not suffer from a potential healthy soldier effect when an internal control group is used so long as the veteran groups are similar or adjusted for potential confounding variables, such as military rank.
5. Relative risk estimates that are only slightly above (e.g., 1.1) or below (e.g., 0.9) the null value of 1.0 may achieve statistical significance, yet be more liable to reflect bias (e.g., selection, confounding) and be of less clinical significance than relative risk estimates of larger magnitude.

Conclusions When reviewing results within and across publications from the Korean study, given its considerable variability in methods of exposure assessment, outcome ascertainment, and selection of control group, the committee members adhered to the following guidelines:

1. Very limited overall weight was afforded to self-reported exposure data and self-reported health-outcomes data compared to objective measurements of the chemicals and health outcomes of interest.
2. More weight was given to the relative risk estimates of mortality and cancers derived from the use of an internal control group than from the use of the general population in order to minimize concern about a healthy soldier effect.
3. Less weight was afforded to statistically significant associations close to the null value (e.g., ranging from 0.9 to 1.1) than to those further from the null in order to account for differences of questionable clinical significance arising from this large study's statistical power and to allow for modest selection bias and confounding.

Brief reviews of individual publications on the Korean Veteran study are presented below.

In Yi (2013), a total of 185,265 Korean men, who had served in Vietnam from 1964 to 1973 and who were alive in 1992, were followed for cancer incidence from 1992 to 2003 and for mortality through 2005. Cancer diagnoses were ascertained via linkage with the Korean National Cancer Incidence Database, whereas cancer deaths were identified using the National Statistical Office records during the follow-up of this cohort. Age-adjusted incidence and standardized incidence ratios (SIRs) were calculated using the Korean male population during 1992 to 2003 as the reference population (Yi, 2013). The overall cancer incidence in Vietnam veterans was not higher than in the general male population, although there were exceptions across the very long list of types of cancer examined. Specifically, Vietnam veterans and military rank subcohorts experienced a higher incidence of several cancers, including prostate cancer, T-cell lymphoma, lung cancer, bladder cancer, kidney cancer, and colon cancer, than the general population. This study did not examine cancer incidence and cancer mortality in terms of herbicide exposure during military service in Vietnam.

In Yi et al. (2013a), the associations between perceived self-report herbicide exposure and a wide range of self-reported diseases were reported for 114,562 Korean Vietnam veterans. For an estimation of potential herbicide exposure, a six-item perceived exposure index was used to query Korean veterans as to how they might have been exposed to herbicides in Vietnam. Veterans were categorized as having either "low" or "high" perceived exposure, and similarly, classified using four categories of perceived exposure defined as "none," "low," "moderate," or "high." In addition, herbicide exposure was objectively estimated for individual veterans based on the proximity of their military units to herbicide sprayed-areas by use of the exposure opportunity model developed by Stellman et al. (2003b). Using this method, veterans were again classified using two-group and four-group exposure categorizations. All disease outcomes were based on self-report and classified into seven groups of diseases: cancers, circulatory

diseases, respiratory diseases, digestive diseases, neuromuscular diseases, endocrine diseases, and other diseases. Subtypes of disease were reported for each disease condition. The committee's concern about the reliability of self-reported exposure and health data are illustrated by the fact that the use of such data in Yi et al. (2013a) uniformly yielded highly significant statistical associations across an exhaustive spectrum of disease conditions, while the use of the objective (Stellman) method of exposure classification and documented reports of adverse health outcome in the later publication on this population produced more variable results. The observation of inconsistencies when theoretically more reliable measures of health and exposure were analyzed reinforced the committee's concern about the findings based on self-report in the Korean study.

Yi et al. (2013b) examined the serum levels of TCDD in 102 of these Korean Vietnam veterans with several purposes:

1. to assess their use as a potential objective tool for herbicide exposure;
2. to determine their correlation to self-reported exposure (six item questionnaire); and
3. to evaluate how they related to age, BMI, and smoking.

Serum sample were collected in 2002 along with information from a health examination. For the objective assessment of herbicide exposure, Exposure Opportunity Indices (EOIs) were derived from a model (Stellman et al., 2003b) based on the proximity of the veterans' military units to areas of herbicide spraying. From this model, veterans were classified as low versus high exposure or in four categories consisting of none, low, moderate, or high exposure. The serum TCDD concentrations among the Korean Vietnam veterans were lower than those reported in other studies of Korean and US Vietnam veterans, and such concentrations were not associated with herbicide exposure indices or with age, BMI, or smoking. The net value of this study is the observation that the assessment of serum levels of TCDD among veterans long after service in Vietnam (e.g., 40 years or more) may be of very limited value as a metric for herbicide exposure unless individuals were exposed to very high levels during military service.

In Yi and Ohrr (2014), the incidence of cancer was examined among 180,251 Korean Vietnam veterans from 1992 through 2003. As opposed to classifying exposure by self-report, this analysis used the EOIs from the Stellman model. The incidence of cancer was determined through a review of records from the Korea National Cancer Incidence Database (NCIDB). Overall, the veterans classified with "high" exposure had a small yet statistically significant higher risk of cancer than the veterans classified with "low" exposure (adjusted hazard ratio [HR] = 1.08, 95% confidence interval [CI] 1.03–1.13). Compared to low exposure, high herbicide exposure appeared to be most related to an elevated risk of cancers of the mouth, salivary glands, stomach, and small intestine. The objective

classification of both herbicide exposure and cancer incidence is considered a strength of this study versus other publications from this cohort with analyses based on self-report data.

Yi et al. (2014a) looked for associations between herbicide exposure and the prevalences of a wide range of disease conditions. Herbicide exposure was objectively estimated by the use of the opportunity exposure index developed by Stellman et al. (2003b). The prevalence of disease outcomes, specifically, those pertaining to the endocrine, nervous, circulatory, respiratory, and digestive systems, was determined through a review of claims data from the Health Insurance Review and Assessment Service of Korea from January 1, 2000, to September 30, 2005. Overall, and compared to "low" exposure," "high" herbicide exposure was associated with a significantly higher prevalence of hypothyroidism, autoimmune thyroiditis, other endocrine gland disorders including pituitary gland disorders, amyloidosis, and Alzheimer disease. The objective classification of both herbicide exposure and disease prevalence is considered a strength of this study versus other reports from the Korean study that were based on self-report data.

Finally, Yi et al. (2014b) analyzed cause-specific mortality in 180,639 Korean Veteran veterans in terms of the objective exposure metrix. The EOIs were used as the basis for two characterizations of herbicide exposure: As "low" versus "high" and per unit increased based on a log-transformed scale. The incidence of mortality and cause of death were ascertained by the use of death records from the National Statistical Office for the period 1992–2005. The long-term risk of mortality was elevated slightly—yet was statistically significant—for veterans with high herbicide exposure (HR = 1.10, 95% CI 1.07–1.14). The hazard ratio for high exposure was also slightly elevated for cancer mortality (HR = 1.13, 95% CI 1.07–1.19), with the highest cause-specific cancer mortality estimates being observed for thyroid cancer (HR = 11.31, 95% CI 1.33–96.55), chronic myeloid leukemia (HR = 7.91, 95% CI 1.67–37.52), small intestine cancer (HR = 2.88, 95% CI 1.00–8.82), and bladder cancer (HR = 2.04, 95% CI 1.17–3.55). The objective classification of both herbicide exposure and cause-specific mortality is considered a strength of this study versus other analyses of this cohort based on self-report data.

Other Studies of Korean Vietnam Veterans

Epidemiologic studies have also looked at immunotoxicologic outcomes (Kim HA et al., 2003) and skin and general disease patterns (Mo et al., 2002) in Korean Vietnam veterans who were exposed to herbicides during the Vietnam War.

New Zealand Vietnam-Veteran Studies

McBride et al. (2013) followed 2,783 male veterans from New Zealand who served in Vietnam between 1964 and 1972. Their status with respect to cancer incidence and mortality were determined from 1988 through 2008. This cohort comprised 84 percent of all 3,322 Vietnam veterans from New Zealand who had survived service in Vietnam. Standardized incidence and mortality ratios (SIRs and SMRs, respectively) were generated by comparing the observed incident cases and deaths in this cohort with the corresponding expected numbers of new cases and deaths rates from the general male population of New Zealand. For all-cause mortality, the Vietnam veterans had significantly lower mortality than the New Zealand general population (SMR = 0.85, 95% CI 0.77–0.94). On the other hand cancer mortality and incidence overall were similar between Vietnam veterans and the New Zealand general population, and heart disease mortality was non-significantly lower in Vietnam veterans (SMR = 0.84, 95% CI 0.69–1.02). In contrast, New Zealand Vietnam veterans appeared to be at higher risk of cancers of the head and neck (SMR = 2.20, 95% CI 1.09–3.93) and oral cavity, pharynx, and larynx as well as of incident chronic lymphoid leukemia than the New Zealand general population. Although the follow-up of this cohort was long (20 years), the study did not have information on cancer incidence and mortality in the time period immediately after the service (i.e., between 1972 and 1988). It also lacked an internal comparison group and information on potential confounding factors including smoking, drinking habits, and human papilloma virus status were not available, which limits the interpretation of the data, particularly regarding incident cancers.

OCCUPATIONAL STUDIES

Several occupational groups in the United States and elsewhere have been exposed to the COIs. Exposure characterization in studies of these groups varies widely in the metric used, the extent of detail, confounding by other exposures, and whether individual, surrogate, or group (ecologic) measures are used. Some studies use job titles as broad surrogates of exposure; others rely on disease-registry data.

The committee reviewed many epidemiologic studies of occupationally exposed groups for evidence of an association between exposure to TCDD or to the herbicides used in Vietnam—primarily the phenoxy herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)—and health risks. TCDD is an unwanted byproduct of 2,4,5-T production but not of 2,4-D production. Other contaminants, including other dioxins (such as 1,3,6,8-tetrachlorodibenzo-*p*-dioxin) have been reported at low concentrations in 2,4-D, but those identified do not have the toxicity of TCDD (ATSDR, 1998; Huston, 1972; Norström et al., 1979). In reviewing the studies, the committee

considered two types of exposure separately: exposure to 2,4-D or 2,4,5-T and exposure to TCDD from 2,4,5-T or other sources. That separation is necessary because some health effects could be associated with an exposure to 2,4-D or 2,4,5-T in the absence of substantial TCDD exposure. After recognition of the problem of dioxin contamination in phenoxy herbicides, production conditions were modified to minimize contamination, but the use of the products most subject to containing specifically TCDD (2,4,5-T and Silvex) was banned. As a result, the study participants exposed to phenoxy herbicides only after the late 1970s would not be assumed to have been at risk for exposure to TCDD.

The distinction is particularly important for workers in agriculture and forestry, including farmers and herbicide appliers, whose exposure is primarily the result of mixing, loading, and applying herbicides. In addition to those occupational groups, the committee considered studies of occupational exposure to dioxins, focusing on workers in chemical plants that produced phenoxy herbicides or chlorophenols, which tend to be contaminated with PCDDs. Waste-incineration workers were also included in the occupation category because they can come into contact with dioxin-like compounds while handling byproducts of incineration. Other occupationally exposed groups included were pulp-and-paper workers exposed to dioxins through bleaching processes that use chlorinated compounds and sawmill workers exposed to chlorinated dioxins, which can be contaminants of the chlorophenates used as wood preservatives.

Studies of Herbicide Production Workers

International Agency for Research on Cancer Phenoxy Herbicide Cohort

A multisite study by IARC involved 18,390 production workers and phenoxy herbicide sprayers working in 10 countries (Saracci et al., 1991). The full cohort was established by using the International Register of Workers Exposed to Phenoxy Herbicides and Their Contaminants. Twenty cohorts were combined for the analysis: one each in Australia, Austria, Canada, Finland, and Sweden; two each in Denmark, Italy, the Netherlands, and New Zealand; and seven in the United Kingdom. There were 12,492 production workers and 5,898 sprayers in the full cohort.

Questionnaires were constructed for workers who were manufacturing chlorophenoxy herbicides or chlorinated phenols and for herbicide sprayers and were completed with the assistance of industrial hygienists. Information from production records and job histories was examined when available. Workers were classified as exposed, probably exposed, with unknown exposure, or nonexposed. The exposed-workers group (13,482) consisted of all those known to have sprayed chlorophenoxy herbicides and all who had worked in particular aspects of chemical production. Two subcohorts (totaling 416) had no job titles available but worked in chemical-production facilities that were likely to produce TCDD

exposure, so they were deemed probably exposed. Workers with no exposure information (541) were classified as of unknown exposure. Nonexposed workers (3,951) were those who had never been employed in parts of factories that produced chlorophenoxy herbicides or chlorinated phenols and had never sprayed chlorophenoxy herbicides. Two nested case-control studies were undertaken with the IARC cohort to evaluate the relationship between STSs and lymphomas (Kogevinas et al., 1992, 1995). Kogevinas et al. (1993) presented the information available on the subcohort of 701 women who were occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins included in 11 of the cohorts in seven of the countries; nine deaths and 29 incident cancer cases were reported (too few to tabulate results).

An expanded and updated analysis of the IARC cohort with an emphasis on cancer mortality was published in 1997 (Kogevinas et al., 1997). The researchers added herbicide production workers in 12 plants in the United States (the NIOSH cohort) and four plants in Germany. The 21,863 male and female workers exposed to phenoxy herbicides or chlorophenols were classified in three categories of exposure to TCDD or higher-chlorinated dioxins: those exposed (13,831), those not exposed (7,553), and those with unknown exposure (479). Several exposure metrics were constructed for the cohort—years since first exposure, duration of exposure (in years), year of first exposure, and job title—but detailed methods were not provided. The overall results were for mortality in 1939–1992, but for some of the subcohorts follow-up had begun as late as 1975, and at the time of publication, mortality in some had been tracked only through 1983. For non-neoplastic causes of death, Vena et al. (1998) repeated the grouped statistics for all phenoxy-herbicide workers in the updated IARC cohort (as previously presented in Kogevinas et al., 1997) and provided results partitioned according to whether the workers had the potential for exposure to TCDD and more highly chlorinated dioxin contaminants.

No new studies of the IARC cohort have been published since *Update 1998*.

International Agency for Research on Cancer Subcohorts

In addition to the NIOSH cohort and its component subcohorts (discussed below), several of the subcohorts that make up the IARC cohort have generated independent reports that have been evaluated separately by VAO committees to garner additional insights, such as the results associated with TCDD concentrations measured in various subjects: Austrian production workers (Jäger et al., 1998; Neuberger et al., 1998, 1999), British production workers (Coggon et al., 1986, 1991), Danish production workers (Lynge, 1985, 1993), Dutch production workers (Boers et al., 2010, 2012; Bueno de Mesquita et al., 1993; Hooiveld et al., 1998), German production workers (Becher et al., 1996; Flesch-Janys, 1997; Flesch-Janys et al., 1995; Manz et al., 1991), and New Zealand production workers (McBride et al. 2009a,b; Smith et al., 1981, 1982; 't Mannetje et al.,

2005). Several of the component cohorts have not been the subject of any separate publications: Australian herbicide sprayers, Canadian herbicide sprayers, Finnish production workers, two cohorts of Italian production workers, and Swedish production workers. The international production-worker cohorts are discussed below in alphabetical order, followed by the NIOSH cohort and its subcohorts. The section on studies of herbicide-using workers, which follows the discussion of all the production-worker studies, includes consideration of the separate reports on the New Zealand herbicide sprayers.

Boehringer–Ingelheim Cohort in Hamburg As first reported by Manz et al. (1991), workers in the Boehringer–Ingelheim plant in Hamburg had high potential for TCDD exposure because of the production of trichlorophenol (TCP) and 2,4,5-T from 1951 to 1954 and from 1957 to 1984. The hiatus was motivated by a chloracne outbreak, and production recommenced when a process that resulted in less TCDD contamination became available. The cohort consisted of 1,184 men and 399 women who had been employed for at least 3 months from 1952 through 1984. Vital status of all but 46 workers (2.9 percent) through 1989 was established; 313 deaths were observed in the men and 54 in the women. Detailed results were reported only for the men. Mortality from all causes did not differ from what would be predicted by rates for West Germany (SMR = 1.00, 95% CI 0.89–1.12); compared with what was probably a more appropriate occupational cohort of Boehringer gas workers, however, mortality from all causes (only through 1985 because of the limitations of available information) was significantly higher (SMR = 1.34, 95% CI 1.18–1.51). The risk of death from all cancers was marginally higher than the West German rates (SMR = 1.24, 95% CI 1.00–1.52) and more definitively so compared with the gas workers (SMR = 1.39, 95% CI 1.10–1.75).

Flesch-Janys et al. (1995) updated the cohort's vital status through 1992 and added a quantitative exposure assessment based on blood or adipose-tissue measurements of PCDDs and PCDFs. The authors estimated the maximum PCDD and PCDF exposures for 190 workers with a first-order kinetics model, half-lives with an elimination study of 48 workers in the cohort, and background concentrations in the German population. They then regressed the estimated maximum PCDD and PCDF exposures of the workers against the length of time that they worked in each production department in the plant. The working-time weights were then used with work histories of the remainder of the cohort to estimate the PCDD and PCDF exposure of each person at the end of his or her exposure. Those values were used to estimate TCDD doses in the population. (At this the stage of updating, the Hamburg cohort was discussed with three other German cohorts by Becher et al., 1996, and became a subcohort of the IARC phenoxyherbicide cohort as updated by Kogevinas et al., 1997.)

Manuwald et al. (2012) updated the mortality experience of 1,191 men and 398 women in the Hamburg cohort. Subjects entered the cohort on the date of

their first employment in the plant, and vital status was sought through 2007; the loss to follow-up was only 3.2 percent. SMRs calculated relative to the population of Hamburg showed that death from all causes was slightly higher in men (698 deaths, SMR = 1.14, 95% CI 1.06–1.23); the increase in mortality was significant in the entire cohort (SMR = 1.08, 95% CI 1.01–1.16), but not in women (180 deaths, SMR = 0.91, 95% CI 0.78–1.05). Similarly, mortality from all malignant neoplasms was slightly higher in men (226 cancer deaths, SMR = 1.14, 95% CI 1.06–1.23), and the increase in mortality was significant in the entire cohort (SMR = 1.33, 95% CI 1.18–1.49) but not in women (65 cancer deaths, SMR = 0.91, 95% CI 0.78–1.05). The individual cumulative exposure was estimated from work history on the basis of company records, and the intensity of TCDD exposure in workplaces was based on previous analyses of serum and fat-tissue dioxin concentrations. Cochran–Armitage trend tests on quartiles of cumulative exposure were conducted for deaths from all causes, all malignancies, breast cancer, cancers of digestive organs, respiratory cancers, and circulatory diseases.

BASF Ludwigshafen Plant Workers Involved in Accident Cleanup (This group was not in the IARC cohort.) An accident on November 17, 1953, during the manufacture of TCP in a BASF plant in Germany, resulted in the extreme exposure of some workers to TCDD. *VAO*, *Update 1996*, *Update 1998*, and *Update 2000* summarized studies of those workers, including a mortality study of persons initially exposed or later involved in cleanup (Thiess et al., 1982), an update and expansion of that study (Zober et al., 1990), and a morbidity follow-up (Zober et al., 1994). In addition, Ott and Zober (1996a) and Zober et al. (1997) examined cancer incidence and mortality in workers exposed to TCDD after the accident or during reactor cleanup, maintenance, or demolition. No new studies have been published on these workers since *Update 2000.*

Dutch Production Workers The two Dutch subcohorts of the IARC cohort consist of 2,106 male workers employed in two manufacturing factories producing and formulating chlorophenoxy herbicides: 2,4,5-T in factory A from 1955 through 1985 and 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2-(2-methyl-4-chlorophenoxy)propionic acid (Mecoprop, MCPP), and 2,4-D in factory B from 1965 through 1986. Accordingly, members of both subcohorts had potential exposure to phenoxy herbicides, but only those in factory A would have been exposed to TCDD. Contamination with the TCDD congener of dioxin in Factory A was exacerabated in 1963 by an explosion due to an uncontrolled reaction in an autoclave where 2,4,5-T was synthesized from 2,4,5-TCP that released dioxins with an exceptionally high concentration of TCDD. In factory B, the main products were 2,4-D and MCPP, which suggests that it is unlikely that there was significant exposure to TCDD. The study populations were defined as all workers who worked in factory A during 1955–1985 or factory B during 1965–1986. Bueno de Mesquita et al. (1993) reported on their mortality experience through 1985.

Hooiveld et al. (1998) updated the mortality experience (1955–1991) of the production workers in these two Dutch chemical factories. On the basis of an assumption of first-order TCDD elimination with an estimated half-life of 7.1 years, the measured TCDD concentrations were extrapolated to the time of maximum TCDD exposure of a group of 47 workers. A regression model was then used to estimate, for each cohort member, the effect on estimated maximum TCDD exposure attributable to exposure as a result of the accident, the duration of employment in the main production department, and the time of first exposure (before or after 1970).

Boers et al. (2010) conducted a third follow-up of cause-specific mortality (cancer and non-cancer) through 2006 for the 2,106 male workers employed in factories A and B, accumulating 65,087 person-years, with 567 deaths observed. The sample loss was minimal (< 1 percent lost to follow-up, < 5 percent emigrated). Death certificates obtained by linkage to Statistics Netherlands were used to ascertain the cause-specific mortality, including various cancers, endocrine or blood diseases, nervous system, ischemic heart disease, other heart disease, cerebrovascular diseases, respiratory diseases, digestive diseases, and genitourinary diseases. Exposure to chlorophenoxy herbicides was determined on the basis of the type of work experience (such as production versus office) and the involvement in the accident of 1963 in factory A (factory A: 539 exposed, 482 non-exposed; factory B: 411 exposed, 626 non-exposed). TCDD measures taken in 1993 support that exposure classification: The highest mean TCDD concentrations were found in workers involved in the 1963 accident (1,841.8 ppt) and those who worked in main production (608.2 ppt), whereas concentrations in non-exposed workers were much lower (7.6 ppt). Cox proportional-hazards models with attained age as the time scale were used to assess the hazard ratios for exposed versus nonexposed workers. The exposure to phenoxy herbicides and dioxins was expected to be different between factory A and factory B, and the factories were therefore analyzed separately. Further nested case-control studies were conducted for the factory A cohort by using all cancer cases (112) and three controls per case matched on age and employment period; the analysis used conditional logistic regression.

Boers et al. (2012) conducted more detailed dose–response analyses of the updated mortality data on the cohorts reported in Boers et al. (2010). From May 2007 to September 2008, blood was drawn for the determination of plasma TCDD concentrations in a systematically selected subsample of 187 workers (101 in factory A, 86 in factory B). Serum concentrations measured in the workers in factory B (geometric mean = 0.4 ppt) confirmed they had not experienced TCDD exposures above background. The combination of linear regression on the log-transformed serum results and the workers' work-history details was used to derive a model to predict current TCDD concentrations in the entire cohort. A first-order, one-compartment kenetic model with the half-life of TCDD estimated to be 7.1 years was used to estimate each person's concentration when he left

employment in factory A or B (presumably the time of maximum cumulative exposure). There were considerable individual differences from the previously assigned exposure groups, but overall the exposures predicted by the empirical model had a high rank correlation (Spearman's r = 0.79) with the exposure statuses used in previous analyses. A Cox proportional-hazards model was used to assess exposure–outcome relationships on the basis of the predicted exposures as a time-varying covariate. To allow for latency, a 1-year lag was used for non-cancer endpoints and a 10-year lag for cancer outcomes. The log-linear TCDD model was applied to the workers in factory A only and to the entire cohort, including workers from factory B, who had been exposed only to phenoxy herbicides as confirmed by the serum samples from the 86 factory B subjects who had only background concentrations of TCDD.

Saberi Hosnijeh et al. (2011) examined the association between TCDD exposure and outcomes, including humoral immunity (serum immunoglobulin and complement factor concentrations) and atopic diseases (self-reported asthma, hay fever, eczema, and allergy) in a subsample of 153 workers, including 45 who had TCDD exposure in factory A, matched individually with a non-exposed comparison group consisting of 39 in factory A and 69 in factory B. TCDD exposure was characterized by using exposure status (exposed versus non-exposed), current serum concentration, and serum concentration at the time of the last exposure as derived by Boers et al. (2012). Logarithmic transformation was used for both TCDD and immune-marker concentrations. Statistical analyses were conducted with t tests, chi-square tests, and linear regression. Similarly, Saberi Hosnijeh et al. (2012a) examined the association between TCDD exposure and serum concentrations of 16 cytokines, 10 chemokines, and 6 growth factors from the blood plasma samples taken in 2007 and 2008 from workers in factory A only (47 with high exposure, 38 with low exposure).

Since *Update 2012*, Saberi Hosnijeh et al. (2012b, 2013a,b) have published three additional studies based on the serum samples drawn from the Dutch cohort in 2007–2008. These studies examined immunological and metabolic parameters that may relate etiologically to some adverse health outcomes, including cancers and heart disease. In Saberi Hosnijeh et al. (2012b), changes in cell counts and lymphocyte subsets were compared between the 47 workers with high-TCDD-exposure and the 38 with low-TCDD-exposure from Factory A. Saberi Hosnijeh et al. (2013a) addressed plasma levels of CD27, CD30, and interleukin 1 receptor antagonist (IL1RA) from this same set of workers; these proteins regulate immune function and have been found to be involved in lymphopoeitic neoplasms. Similarly, in Saberi Hosnijeh et al. (2013b), serum metabolites measured in this set of serum samples by ultra-high pressure liquid chromatography and mass spectrometry were the focus of similar analyses.

Rather than being the type of health outcomes that VAO committees assess for association with herbicide exposure, the measures considered in these studies of the Dutch production workers provide information on biologic plausibility for

health outcomes involving immune response and B-cell neoplasms. Interpretation of results is complicated for these analyses of endpoints measured nearly four decades after TCDD exposure on the basis of the current TCDD level and the maximum TCDD level based on back-extrapolation. The analyses also did not take into account potential intervening exposures.

German Production Workers Becher et al. (1996) conducted an analysis of the four German cohorts added to the IARC cohort as of 1997: the Boehringer–Ingelheim cohort (also reported on in more detail by Manz et al., 1991, and later researchers), a cohort in the BASF Ludwigshafen plant that did not include those involved in a 1953 accident, and cohorts in a Bayer plant in Uerdingen and a Bayer plant in Dormagen. Preliminary information on the four cohorts had been published earlier (Becher et al., 1992). All the plants were involved in production of phenoxy herbicides or chlorophenols. Additional information is available only on the Boehringer–Ingelheim cohort, and the workers involved in the 1953 accident have been studied separately.

New Zealand Production Workers

The mortality status of the New Zealand cohort that was incorporated into the original IARC cohort was followed through 2000 by 't Mannetje et al. (2005). The New Plymouth plant produced phenoxy herbicides from the late 1950s through the mid-1980s. This plant also produced picloram, one of the COIs about which very little information is available. Complete employment records for 1969–1984 were available, so the study included anyone who had worked at least 1 month in that period—a cohort of 713 men and 100 women (the 1984 cohort).

Burns et al. (2010), Collins et al. (2009a), and McBride et al. (2009a,b), examined the New Zealand production-worker subcohort of the IARC cohort, which consisted of employees who worked at the Dow AgroSciences (formerly Ivon Watkins-Dow) plant in New Plymouth that manufactured diverse agrochemical products, including phenoxy herbicides. McBride et al. (2009a) conducted expanded analyses and updated previous analyses of cause-specific mortality (from both cancers and other conditions). The cohort was increased to 1,599 participants (referred to hereafter as the 1988 cohort), including a substantial number of people who had minimal opportunity for exposure, by extending the employment period for eligibility to November 1, 1988, and removing the requirement that employment lasted at least 1 month. McBride et al. (2009b) further expanded the cohort to 1,754 participants (the 2003 cohort) by further extending eligibility to anyone who worked at the site at any time until October 1, 2003. Both enlarged cohorts were followed through 2004. The New Zealand Health Information Service Mortality Collection was used to identify deaths (247 in both cohorts; there seem to have been no deaths in the increment of 155 worker who were in the 2003 cohort but not in the 1988 cohort). Exposure status was classified according to

work experience. A subsample of the 1988 cohort participated in a serum-dioxin analysis (346, 70 percent exposed).

Collins et al. (2009a) described the group's serum TCDD concentrations overall, and Burns et al. (2010) performed analyses to determine what factors might predict serum TCDD: Age, BMI, and employment history were found to be significant determinants. In particular, the exposed group had significantly ($p = 0.03$) higher concentrations (9.9 ppt) than the non-exposed group (4.8 ppt); the number of years since termination was associated significantly ($p = 0.002$) with lower TCDD; and the serum TCDD was also associated significantly ($p < 0.0001$) with predicted cumulative TCDD exposure on the basis of area-under-the-curve in a pharmacokinetic model of the accumulation and elimination of dioxins. Both studies reported SMRs that were derived by using the Occupational Cohort Mortality Analysis Program with the New Zealand population as the reference population and adjusted for age, sex, and calendar age. For the 1988 cohort, SMRs were stratified by exposure status (ever exposed and never exposed) and by predicted cumulative exposure categories. For the 2003 cohort, SMRs were reported for the entire cohort and stratified by employment duration (less than 3 months and at least 3 months) and by latency (15 years and less than 15 years of latency). For the 1988 cohort, proportional-hazards survival analysis was also used to test the association between mortality and predicted cumulative exposure categories.

The New Zealand studies have several important limitations. The sample loss was substantial: 13 percent were lost to follow-up in both cohorts, and 8 percent of the 1988 cohort and 9 percent of the 2003 cohort emigrated. If sample loss was nonrandom, then the study findings might be vulnerable to sample selection bias. In addition, the inclusion in the 2003 cohort of the employees hired as recently as 2003 is questionable. It appears that no deaths were observed in the increment between the 1988 cohort and the 2003 cohort (those hired since 1988), presumably because these participants are relatively young. The inclusion of the incremental participants might dilute the power of the study to detect the effects of TCDD exposure on health outcomes that require a long latent period; participants who have not yet "matured" through the latent period might be contributing noise rather than signal to the analyses. The committee, therefore, did not give substantial weight to the dose–response findings of McBride et al. (2009b). The serum concentrations of dioxins and furans observed in a subset of the workers in the Dow phenoxy-herbicide plant in New Zealand have been used in estimating individual exposure (Aylward et al., 2010; Collins et al., 2009a).

National Institute for Occupational Safety and Health Studies

NIOSH PCP Cohort Ruder and Yiin (2011) reported findings on mortality in 2,122 pentachlorophenol (PCP) production workers in four plants—Midland,

Michigan; Sauget, Illinois; Tacoma, Washington; and Wichita, Kansas—in the NIOSH dioxin registry. For analytic purposes, the cohort was partitioned into a subcohort of 1,402 workers (PCP-only group) who were employed only in the production of PCP, which has dioxin and furan contaminants that do not include the most toxic 2,3,7,8-TCDD congener, and a subcohort of 720 (PCP-plus-TCDD group) who also worked in TCP production and therefore had exposure to TCDD). The cohort was followed through December 31, 2005. Exposure was specified both as exposure status (exposed versus not exposed, for cohort members versus reference population) and as cumulative duration of exposure stratified into four quartiles. Statistical analyses were based on SMRs with the US population as the reference, and standardized rate ratios were used to compare workers in cumulative duration categories.

NIOSH Cross-Sectional Medical Study Before the first publication of mortality results in the main cohort, the NIOSH Cross-Sectional Medical Study gathered comprehensive medical histories, conducted medical examinations, and measured the pulmonary function of workers employed in chemical manufacturing at plants in Newark, New Jersey (1951–1969) and Verona, Missouri (1968–1972). The control participants were recruited from surrounding neighborhoods (Sweeney et al., 1989, 1993). The New Jersey plant manufactured 2,4,5-TCP and 2,4,5-T; the Missouri plant manufactured 2,4,5-TCP, 2,4,5-T, and hexachlorophene. Specific health outcomes were evaluated in the members of this subcohort, including porphyria cutanea tarda (Calvert et al., 1994), effects on pulmonary function (Calvert et al., 1991), effects on hepatic and gastrointestinal function (Calvert et al., 1992), mood (Alderfer et al., 1992), effects on the peripheral nervous system (Sweeney et al., 1993), and effects on reproductive hormones (Egeland et al., 1994). Sweeney et al. (1996, 1997/1998) reviewed and updated noncancer outcomes, including the effects on hepatic function, gastrointestinal disorders, chloracne, diabetes, and serum glucose, hormone, and lipid concentrations. The data gathered from the two plants were also examined for cardiovascular effects (Calvert et al., 1998); diabetes mellitus, thyroid function, and endocrine function (Calvert et al., 1999); immune characteristics (Halperin et al., 1998); and cancer incidence (Kayajanian, 2002). Halperin et al. (1995) investigated the relationship between serum TCDD concentrations and cytochrome P450 induction in 400 of the original 586 subjects in the cohort. Lawson et al. (2004) studied three birth outcomes—birth weight, preterm delivery, and birth defects—in the offspring of the cohort members by comparing serum TCDD concentrations with those in a reference population. TCDD exposures at conception were estimated by using physiologically based pharmacokinetic modeling (Dankovic et al., 1995; Thomaseth and Salvan, 1998).

NIOSH TCDD Mortality Cohort Since 1978, NIOSH has compiled an extensive set of data on chemical production workers potentially contaminated with TCDD in 1942–1984. More than 5,000 workers who were involved in production or maintenance in any of 12 companies were identified from personnel and payroll records; 172 additional workers identified previously by their employers as being exposed to TCDD were also included in the study cohort (Suskind and Hertzberg, 1984). The employees' possible exposure resulted from working with substances of which TCDD was a contaminant: 2,4,5-TCP, 2-(2,4,5-trichlorophenoxy) propionic acid (Silvex, 2,4,5-TP), 2-(2,4,5-trichlorophenoxy) ethyl 2,2-dichloropropionate (Erbon), *O*,*O*-dimethyl *O*-(2,4,5-trichlorophenyl) phosphorothioate (Ronnel®), and hexachlorophene. The 12 plants involved were large manufacturing sites of major chemical companies, so many of the participants were potentially exposed to many other compounds, some of which could be toxic and carcinogenic. The NIOSH cohort was added to the IARC cohort as of the 1997 publication by Kogevinas et al.

Exposure status was determined initially through a review of process operating conditions, employee duties, and analytic records of TCDD in industrial-hygiene samples, process streams, products, and waste (Fingerhut et al., 1991). Occupational exposure to TCDD-contaminated processes was confirmed by measuring serum TCDD in 253 cohort members. The duration of exposure, defined as the number of years worked in processes contaminated with TCDD, was used as the primary exposure metric in the study. The use of duration of exposure as a surrogate for cumulative exposure was based on a correlation (Pearson correlation efficient, 0.72) between log-transformed serum TCDD and the number of years worked in TCDD-contaminated processes. The duration of exposure of individual workers was calculated from work records, and exposure-duration categories were created: Less than 1 year, 1 to less than 5 years, 5 to less than 15 years, and 15 years and longer. In some cases, information on the duration of exposure was not available, so a separate metric, duration of employment, was defined as the total time that each worker was employed at the study plant. Fingerhut et al. (1991) used the exposure measures in assessing mortality through 1987.

A follow-up study (Steenland et al., 1999) examined the association between TCDD exposure and cause of death through 1993; it examined specific health outcomes, including cancers (all and site-specific), respiratory disease, cardiovascular disease (CVD), and diabetes. The researchers used a more refined exposure assessment than did previous analyses; it excluded workers whose records were inadequate to determine duration of exposure, and this reduced the number of study participants to a subcohort of 3,538 workers (69 percent of the overall cohort). The exposure assessment for the subcohort was based on a job–exposure matrix (JEM) that assigned each remaining worker a quantitative exposure score for each year of work (Piacitelli and Marlow, 1997).

No new studies on the entire NIOSH cohort were published during the current review period.

Subcohorts of the NIOSH TCDD Mortality Cohort

Monsanto The NIOSH study cohort (Fingerhut et al., 1991) included employees of the Monsanto facility in Nitro, West Virginia, which produced 2,4,5-T in 1948–1969. Zack and Suskind (1980) examined the mortality experience of the 121 men who had chloracne associated with an unintentional release that occurred on March 8, 1949. Other studies considered mortality and other health outcomes in additional workers involved in numerous aspects of 2,4,5-T production at the Monsanto plant (Collins et al., 1993; Moses et al., 1984; Suskind and Hertzberg, 1984; Zack and Gaffey, 1983). The Monsanto studies were discussed in more detail in *VAO*. No additional studies on those participants alone have been published; they have since been followed as part of the NIOSH and IARC cohorts.

Dow 2,4-D Production Workers CJ Burns et al. (2011) have reported on cancer incidence in 2,4-D production workers in the Dow Midland plant. The exposed cohort consisted of 1,316 men who worked in 2,4-D operations from 1945 through 1994 and who were alive on January 1, 1985, when the Michigan statewide cancer registry was initiated. Exposure was considered both as a category (exposed [cohort members] versus non-exposed [reference population]) and as a cumulative variable estimated as (job-specific exposure estimate) × (duration on the job) summed over all jobs held since 1945. Workers were stratified into three categories according to their estimated cumulative exposure. The cohort was followed in 1985–2007. Cancer incidence was ascertained from the Michigan statewide cancer registry and data linked to Arizona and Ohio, states where cohort members might reside. Three nested cohorts were used for statistical analyses in order to address potential problems with data that were missing because of migration outside the three states with data linkage. Cohort 1 consisted of the entire exposed cohort (1,316 who had 25,267 person-years of follow-up). Cohort 2 required Michigan residency; follow-up was terminated when a person was known to not be a Michigan resident, either because company records showed a permanent non-Michigan address or a death certificate showed a state other than Michigan as the state of residency (1,256 who had 23,354 person-years). Cohort 3 had a more stringent residency requirement; follow-up was terminated when a person was no longer known to be a Michigan resident (1,108 who had 18.897 person-years). For Cohort 2, people of unknown residency status were assumed to remain Michigan residents and were included in the follow-up; for Cohort 3, such people were assumed to be nonresident and were excluded. Standardized incidence ratios were derived for all three cohorts with Michigan white males as the reference population; Fisher's exact confidence interval was used to characterize

the uncertainty. For Cohort, 2 additional analyses were conducted by using the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) registry population and a regional population as the reference populations and by stratifying the cohort according to cumulative duration and cumulative exposure categories.

There are concerns that the study findings might be biased, for several reasons. First, the study cohort might be healthier than the general population being used as the reference population. Second, the lack of a latent period in the study design might lead to an attenuation effect on the risk estimates; this is similar to the Villeneuve and Steenland (2010) criticism of the Dow–Midland mortality study reported in Collins et al. (2009b). Third, Cohort 2, which was the researchers' focus in the study, might be vulnerable to an attenuation effect because of the uncertainty in residency status. For the present VAO review, the results on Cohort 3 are considered the least subject to bias and hence the most reliable, although this smallest group is subject to the most variability; consistency in results among the three cohorts is considered confirmatory.

All Dow TCP-Exposed Workers TCP was produced in Dow's facility in Midland, Michigan, from 1942 to 1979, and 2,4,5-T was produced there from 1948 to 1982. The cohort of TCP workers who were potentially exposed specifically to TCDD is one of the eight cohorts in the NIOSH cohort of dioxin-exposed US workers that were entered into the IARC phenoxy herbicides cohort.

Collins et al. (2009b) updated the vital status through 2003 of 1,615 people who worked with TCP or 2,4,5-T from 1942 through 1982; 58,743 person-years were accumulated, and 662 deaths were observed. SMRs for cause-specific mortality in the cohort—with and without the overlap of 196 people with the PCP cohort in Collins et al. (2009c)—were calculated by using the US population as the reference population and using the Occupational Mortality Analysis Program.

Dow PCP Production Workers This set of people were engaged in the manufacture of PCP from 1937 to 1980 in the same plant where the TCP cohort worked. Unlike TCP, PCP did not contain TCDD, but it did contain other highly chlorinated dioxin congeners, and 20 percent of the PCP workers had suffered from chloracne. Those who had no TCDD exposure are not in the IARC or NIOSH cohorts. This group is one of four cohorts included in NIOSH's PCP cohort (Fingerhut et al., 1984; Ruder and Yiin, 2011).

Dow has tracked a cohort of its manufacturing workers who were exposed to PCP (Ramlow et al., 1996). The exposure assessment evaluated the available industrial-hygiene and process data, including recollections from employees about processes and jobs, information about changes in processes and engineering controls, measurements from surface wipes, and exposure monitoring data from area sampling and personal breathing zones. Jobs in the "flaking/prilling/

packaging area" were determined to have a higher potential exposure because of dermal exposure to airborne PCP; the industrial-hygiene data suggested a difference of about a factor of 3 between the areas of highest and lowest potential exposure. An estimated exposure-intensity score of 1–3 (from lowest to highest potential exposure intensity) was assigned to each job. Information concerning the use of personal protective equipment was deemed to be unreliable. For each participant, cumulative PCP and TCDD exposure indexes were calculated by multiplying the duration of each exposed job by its estimated exposure intensity and then summing across all exposed jobs.

Collins et al. (2009c) conducted a mortality study of the Dow PCP production workers with the accrual of years at risk starting at the beginning of 1940. The cohort was followed for up to 64 years. Although the date of closure of the follow-up was not provided explicitly, it appears that the cohort was followed through 2003, as were the TCP workers (Collins et al., 2009b). The cohort consisted of 773 PCP workers; 27,035 person-years were accumulated, and 370 deaths were observed. SMRs for the PCP cohort (with and without the overlap of 196 people in the TCP cohort) were given for cause-specific mortality with the US population as the referent population. Proportional-hazards survival analysis was also used to assess the association between mortality and predicted cumulative exposure as total toxic equivalent (TEQ) to TCDD.

Dow TCDD-Exposed Production Workers Dow conducted a study of 204 workers engaged in the production of 2,4,5-T (Ott et al., 1980) and another study of 61 TCP manufacturing workers who had chloracne (Cook et al., 1980). Industrial hygienists developed a JEM that ranked employee exposures as low, moderate, or high on the basis of available air-monitoring data and professional judgment. The matrix was merged with employee work histories to assign an estimate of exposure to each job. A cumulative dose was then developed for each of the 878 employees by multiplying the representative 8-hour time-weighted average (TWA) exposure value for each job by the number of years in the job and then adding the products for all jobs. A 2,4-D TWA of 0.05 mg/m^3 was used for low, 0.5 mg/m^3 for moderate, and 5 mg/m^3 for high exposure. The exposure estimates do not appear to have taken into account the role of dermal exposure in the facilities. It is not clear to what extent the use of air measurements alone can provide accurate classification of workers into low-, moderate-, and high-exposure groups. Biologic monitoring of 2,4-D apparently was not included in the study.

Bond et al. (1983) investigated potential exposure to TCDD and morbidity in the sets of workers reported on by Cook et al. (1980) and Ott et al. (1980). Potential TCDD exposure and reproductive outcomes were studied in the offspring of 930 men who worked with chlorophenol from 1939 through 1975 (Townsend et al., 1982). Dow employees who had a diagnosis of chloracne or who were classified as having chloracne on the basis of a clinical description were followed

prospectively for mortality (Bond et al., 1987). There was a succession of mortality studies of workers involved in 2,4-D production in several of the plants (Bloemen et al., 1993; Bond et al., 1988; Burns et al., 2001), which also were conducted with the same exposure-assessment procedures.

Dow assembled a large cohort at the Midland, Michigan, plant (Bond et al., 1989a; Cook et al., 1986, 1987). The exposure to TCDD in the cohort was characterized on the basis of chloracne diagnosis (Bond et al., 1989b). Within the cohort, a subcohort study of women (Ott et al., 1987) and a case-control study of STS (Sobel et al., 1987) were conducted. The Dow cohorts have been followed as part of the NIOSH and IARC cohorts since 1991 and 1997, respectively.

Bodner et al. (2003) published a 10-year follow-up of the work of Cook et al. (1986), comparing the mortality experience of 2,187 male Dow workers who were potentially heavily exposed to dioxin before 1983 with that of the NIOSH and IARC cohorts. Dow researchers have published a study of serum dioxin concentrations measured in 2002 in former chlorophenol workers (Collins et al., 2006). Most of the workers in the study were included in the NIOSH and IARC cohorts. The authors used their data to estimate worker exposure at the time of exposure termination by using several pharmacokinetic models. They concluded that their findings were consistent with those of other studies that reported high serum dioxin concentrations in chlorophenol workers after occupational exposure.

Since *Update 2012*, Aylward et al. (2013) examined the elimination rates of dioxin congeners in former chlorophenol workers from Midland, Michigan. This study examined blood samples from 56 former chlorophenol workers in 2004–2005, and then re-sampled in 2010. The purpose of this analysis was to estimate half-life reductions for TCDD TEQs, which, in aggregate, were 9.3 years for the dioxin congeners analyzed. This analysis is informative with respect to estimating elimination rates over time for the COIs as the Vietnam-veteran cohort continues to age.

Czech Worker Studies

Several studies of Czech workers have been reviewed by VAO committees. The original committee reviewed a 10-year follow-up study of 55 men in Czechoslovakia who were exposed to TCDD during the production of 2,4,5-T (Pazderova-Vejlupková et al., 1981). The exposure occurred because of excessive temperature and pressure in the production process over an extended period (1965–1968) rather than as a consequence of a major release at a single time. More than 80 workers were affected, but the researchers provided little information about those who were not included in the study. Researchers observed several disorders in the workers, including chloracne, metabolic disturbances, abnormal results of glucose-tolerance tests, evidence of a mild hepatic lesion, nervous system focal damage, and psychologic disorders. In a 30-year follow-up, Pelclová et al. (2001, 2002) examined biochemical, neuropsychologic, neurologic,

and lipid-metabolism abnormalities in the surviving Czech cohort. Previous VAO committees concluded that there were a number of methodologic problems: selection bias; a lack of control for confounding by educational achievement, tobacco use, or alcohol use; the use of self-reported symptoms; and the lack of an objective measure of exposure. In 2004 Pelclová and colleagues (2007) compared the vascular function of 15 exposed workers with that of 14 healthy male health care workers who had no history of occupational exposure to TCDD. Urban et al. (2007) evaluated the same set of workers, looking at overall health effects. Further details on those studies were given in *Update 2006* and *Update 2008*.

Pelclová et al. (2009) reported on an update on the exposed cohort that was based on the examination and testing of 11 participants in a follow-up visit in 2008. The testing included an internal and a neurologic examination; an eye fundus examination; tests for TCDD in plasma, thyroid-stimulating hormone, and testosterone and serum lipids; ultrasonography of the carotid artery; a nerve-conduction study; electroencephalography; visual-evoked potential; a Lanthony test of acquired visual impairment; single-photon emission computed tomography of the brain; a neuropsychologic examination (eight consented); and carbohydrate-deficient transferrin, an index of long-term alcohol consumption. The mean TCDD concentration remained high (274 pg/g of blood lipids), with a wide dispersion (53–756 pg/g) among the 11 participants. The prevalences of health conditions were compared with those in the general male population of comparable age. Paired t tests and F tests were used to test for changes in the assessments obtained repeatedly during follow-up visits; Spearman's rank correlation coefficient was used to test the association between health outcomes (such as color-vision impairment) and risk factors (such as concentrations of TCDD and carbohydrate-deficient transferring). This study has important limitations. With a low retention rate (11 participants of the original cohort of 80), the study findings are vulnerable to nonresponse bias. No description of the sample loss was given, even regarding the loss of four participants from the 2004 follow-up reported in Pelclová et al. (2007). The comparison with the prevalence in the male population of comparable age is important in the interpretation of the study findings, but no description of the comparison group is given beyond citations of its (presumed) sources. Pelclová et al. (2011) have reported on further comparisons of markers of oxidative or nitrosative stress and inflammation in plasma, urine, and exhaled breath condensate of the 11 exposed workers studied previously in Pelclová et al. (2009) compared with 16 health care workers (7 men, 9 women). This study has limitations similar to those in Pelclová et al. (2009). In particular, the mixed-sex comparison group might not be appropriate for the all-male cohort of exposed people.

Jeanneret et al. (2014) described the use of a metabolomic strategy to determine metabolic patterns related to dioxin effects in humans, including the discovery of predictive subsets of biologically meaningful and clinically relevant

compounds. This was based on blood samples taken from 11 of these Czech workers in 2011. The analysis also incorporated results of samples drawn from Victor Yushchenko, who was poisoned in September 2004. While academically of interest with respect to a better future understanding of the molecular events related to dioxin toxicity, this work was not specifically informative to the charge of the committee.

Studies of Other Industrial Cohorts

Chinese Automobile Foundry Workers

Wang and colleagues (2013) followed a cohort of 3,529 workers who worked at least 1 year between January 1, 1980, and December 31, 1985, in an automobile foundry factory located in Hubei province in China to determine the concentrations and characteristics of PCDD/Fs (including 2,3,7,8-TCDD) found in the workers and to evaluate the chemicals' association with mortality from all causes, all cancers, and lung, liver, and stomach cancers individually. The follow-up period was from January 1, 1980, through December 31, 2005, and for all deceased subjects during this period the cause of death was collected through medical records from local or regional hospitals. When compared to the general population, all-cause mortality was similar, yet cancer mortality overall and mortality for several specific types of cancer was higher in the automobile factory workers.

Other Chemical Plants

Several studies have reviewed the health outcomes in UK chemical workers exposed to TCDD as a result of an industrial accident in 1968 (Jennings et al., 1988; May, 1982, 1983), 2,4-D production workers in the former Soviet Union (Bashirov, 1969), 2,4-D and 2,4,5-T production workers in the United States (Poland et al., 1971), white men employed at a US chemical plant that manufactured flavors and fragrances (Thomas, 1987), and US chemical workers engaged in the production of PCP, lower-chlorinated phenols, and esters of chlorophenoxy acids (Hryhorczuk et al., 1998). The long-term immunologic effects of TCDD were examined in 11 industrial workers involved in production and maintenance operations in a German chemical factory that produced 2,4,5-T (Tonn et al., 1996), and immunologic effects were studied in a cohort of workers formerly employed at a German pesticide-producing plant (Jung et al., 1998). *VAO*, *Update 1998*, and *Update 2000* detailed those studies. Garaj-Vrhovac and Zeljezić (2002) conducted a study of workers occupationally exposed to a complex mixture of pesticides (atrazine, alachlor, cyanazine, 2,4-D, and malathion) during their production.

Waste-Incineration Worker Studies

A study in Japan examined the association between serum-dioxin concentrations (TEQ values for PCDDs, PCDFs, and coplanar polychlorinated biphenyls) and oxidative DNA-damage markers in municipal waste–incineration workers (Yoshida et al., 2006).

A Korean study evaluated immunologic and reproductive toxicity (DNA damage and sperm quality) in 31 waste-incineration workers and 84 control participants (Oh et al., 2005). Rather than measuring serum dioxin, both studies inferred the dioxin exposure of individual workers on the basis of dioxin concentrations in air and estimated the exposures to polycyclic aromatic hydrocarbons by analyzing two urinary metabolites, 1-hydroxypyrene and 2-naphthol.

No studies of waste-incineration workers relevant to the COIs have been published since *Update 2006*.

Paper-and-Pulp Cohorts

Workers in the paper-and-pulp industry can be exposed to TCDD and other dioxins that can be generated by the bleaching process during the production and treatment of paper and paper products. *VAO* described mortality studies of pulp and paper–mill workers potentially exposed to TCDD in five mills in Washington, Oregon, and California (Robinson et al., 1986) and in a New Hampshire mill (Henneberger et al., 1989); studies of vested members of the United Paperworkers International Union (Solet et al., 1989); and studies of cancer incidence in male paperworkers in Finland (Jappinen and Pukkala, 1991). Rix et al. (1998) studied cancer incidence through 1993 in 11,130 male and 3,232 female workers employed at three Danish paper mills at any time from 1943 through 1990.

IARC Paper-and-Pulp Cohort *Update 2006* reviewed a collaborative study of cancer mortality (McLean et al., 2006) led by IARC that was composed of cohorts in 11 countries and had follow-up through 1990 to 1996 (depending on the country). The pooled data included several cohorts that had been evaluated individually in *VAO* and its updates before 2006. For departments in each company, industrial-hygiene experts estimated exposure to 27 agents over time. The 60,468 pulp and paper–industry workers employed from 1920 through 1996 were assigned to the "nonvolatile organochlorines" (potential contamination with TCDD assumed) group (58,162) and the "volatile organochlorines" group (60,468). The entire cohort was portioned into apparently overlapping groups for "volatile" and "nonvolatile" organochlorines on the basis of detailed job–exposure matrices developed for each of the 27 chemicals at the department level in each mill for time periods between 1920 and 1996, and these populations were then subdivided for analyses into sets that "ever" or "never" had exposure to the chemicals on the

basis of job titles. Only the results for those in the main category with potential exposure to the nonvolatile agents are relevant to the VAO task.

Sawmill Workers Sawmills use PCP (which has some contamination with dioxins but not the TCDD congener) as a fungicide, so the exposures experienced are more like "herbicide-use" than those encountered in herbicide production or in pulp-and-paper processes. Workers in sawmills might have been exposed to pentachlorophenates, which are contaminated with higher-chlorinated PCDDs (Cl_6–Cl_8), or to tetrachlorophenates, which are less contaminated with higher-chlorinated PCDDs. Wood is dipped into those chemical preservatives and then cut and planed in the mills. Most exposure is dermal, but some exposure can occur by inhalation (Hertzman et al., 1997; Teschke et al., 1994).

McLean et al. (2009) studied serum dioxin concentrations in 94 former sawmill workers in New Zealand who were classified as exposed (71) or non-exposed (23) according to their work history. In addition, the serum dioxin test results on 23 former sawmill workers in Sawmill Workers Against Poisons (SWAP) were provided for the study. A semi-quantitative estimate of exposure intensity was also developed by using a PCP exposure algorithm that incorporated the participants' job titles and specific work tasks: Mixing of PCP solutions, cleaning sludge, and spraying. Serum concentrations of PCDDs and PCDFs were analyzed; the total TEQ was calculated by using the World Health Organization (WHO) toxic equivalence factors (TEFs) (van den Berg et al., 2006). The mean concentrations in exposed workers were higher than those in the non-exposed: 1,2,3,6,7,8-hexachlorodibenzodioxin, 1,2,3,4,6,7,8-heptachlorodibenzodioxin, and octachlorodibenzodioxin concentrations were two to three times higher and the WHO TEQs about 40 percent higher (13.67 pg/g versus 9.56 pg/g). The congener profiles in serum were consistent with those in PCP solutions, and dioxin concentrations increased with both the employment duration and estimated exposure intensity. The averages in the SWAP members were two to three times those in the exposed study participants (37.74 pg/g).

Studies of Herbicide-Using Workers

Various methods have been used to estimate the occupational exposure of agricultural workers to herbicides or TCDD. The simplest method derives data from death certificates, cancer registries, or hospital records (Burmeister, 1981), in which information on "usual occupation" is used to construe likely exposure to the COIs. Although such information is relatively easy to obtain, it does not provide information on the duration or the intensity of the exposure, and it cannot be used to determine whether a worker was exposed to a specific agent. In some studies of agricultural workers, an examination of the differences between occupational practices has allowed the identification of subsets of workers who were likely to have had higher exposures (Hansen et al., 1992; Musicco et al.,

1988; Ronco et al., 1992; Vineis et al., 1986; Wiklund, 1983; Wiklund and Holm, 1986; Wiklund et al., 1988a). In other studies, the county of residence was used as a surrogate for exposure, and agricultural censuses of farm production and chemical use were relied on for characterizing the exposures in individual counties (Blair and White, 1985; Cantor, 1982; Gordon and Shy, 1981), exposure was estimated on the basis of the number of years of employment in a specific occupation as a surrogate for exposure duration, or information on herbicide use at each farm was used as a surrogate of its operator's exposure (Morrison et al., 1992; Wigle et al., 1990). Still others used self-reported information on exposure that recounted direct handling of a herbicide, whether it was applied by a tractor or a hand-held sprayer, and what types of protective equipment or safety precautions were used (Hoar et al., 1986; Zahm et al., 1990). A set of studies validated the self-reported information with written records, signed statements, or telephone interviews with co-workers or former employers (Carmelli et al., 1981; Woods and Polissar, 1989).

Forestry and other outdoor workers, such as highway-maintenance workers, are also likely to have been exposed to herbicides and other chemicals. The exposure of those groups has been classified by using approaches similar to those noted above for agricultural workers—for example, using the number of years employed, job category, and occupational title.

The original *VAO* committee and the update committees up to the committee for *Update 2006* were satisfied with exposure characterizations as nonspecific as "usual occupation" on a death certificate or "current occupation" from a census. With the passage of time, however, exposure assessments in epidemiology studies have been increasingly exact in both specificity and amount, and this has led the members of the more recent updates to establish stricter criteria for accepting exposure as sufficiently specific for results to be added to the evidentiary database. The current committee now seeks results expressed in terms of the five chemicals of interest for this project or their analogues, and it regards classification based only on job title as inadequate; restriction by the investigators to "herbicide" exposure is considered specific enough only to provide supporting evidence. According to the policy established by the Agent Orange Act of 1991, studies of Vietnam veterans are presumed to involve relevant exposure, as are studies of workers at a particular plant during a period when it is known to have been producing phenoxy herbicides or other chemicals recognized as having been contaminated with TCDD.

American Herbicide-User Studies

Agricultural Health Study

The US Agricultural Health Study (AHS) is a prospective investigation of cohorts of private pesticide applicators (farmers), their spouses, and commercial

pesticide applicators in Iowa and North Carolina, with a total of 89,658 participants, including 57,311 applicators (82 percent of those seeking licensing) and 32,347 spouses (75 percent of all spouses). The applicators are predominantly but not exclusively male, and the spouses are predominantly but not exclusively female. The AHS is sponsored by the NCI, the Environmental Protection Agency, and the National Institute of Environmental Health Sciences. Enrollment in the study was offered to applicants for applicator certification in Iowa and North Carolina. The project's website (www.aghealth.org) provides many details about the study, including a specification of which pesticides were the subject of information gathered from the enrollment forms and mailed questionnaires (Alavanja et al., 1994).

In phase I (1993–1997), the enrollment form for both commercial (8.6 percent) and private (largely farmers) applicators asked for details on the use of 22 pesticides (10 herbicides, including 2,4-D; 9 insecticides; 2 fungicides; and 1 fumigant) and yes–no responses as to whether 28 other pesticides (8 herbicides, including 2,4,5-T and Silvex, 2,4,5-TP; 13 insecticides; 4 fungicides; and 3 fumigants) had ever been used.

A subset of 24,034 applicators also completed and mailed back a take-home questionnaire. The questionnaire asked for details about use of the 28 pesticides with yes–no information on the enrollment form and for yes–no responses as to whether 108 other pesticides (34 herbicides, including organic arsenic, which would cover cacodylic acid; 36 insecticides; 29 fungicides; and 9 fumigants) had ever been "frequently" used. Dosemeci et al. (2002) published an algorithm designed to characterize the personal exposures of that population. Weighting factors for the key exposure variables were developed from the literature on pesticide exposure. This quantitative approach has the potential to improve the accuracy of exposure classification for the cohort but has not yet been used in published epidemiologic studies.

The 42 percent response rate for the take-home questionnaire was rather low. Although no pronounced differences in demographics, medical histories, or farming practices were found between those who completed the questionnaire and those who did not (Tarone et al., 1997), selection bias might compromise the validity of studies based on the questionnaire because of differences that might not have been captured in the enrollment form.

Phase II was a 5-year follow-up conducted in 1999–2003. Computer-assisted telephone interviews (CATIs) were completed by 60,138 participants. The interviews specified "pesticides" in general to include herbicides. They asked about specific pesticides on individual crops; for several crops, only if atrazine or 2,4-D was specified was a participant asked whether it had been used alone or as part of the manufacturer's mixture. A full pesticide list was not posted on the website with the follow-up questionnaire. In addition, dietary histories were completed by 35,164 respondents, and buccal-cell samples were gathered from 34,810 participants. The rate of response to the phase II survey—67 percent overall and 63

percent of the original cohort of 55,748 male applicators—was modest and leaves some room for selection bias to compromise the validity of studies based on the survey. In phase III (2005–2010), responses to an updated CATI were provided by 43,426 participants.

Numerous reports on the AHS cohort have been considered in earlier updates. All have developed pesticide-exposure estimates or exposure categories from self-administered questionnaires. Using various subsets of the study population, they have addressed a variety of health outcomes: doctor visits resulting from pesticide exposure (Alavanja et al., 1998), chemical predictors of wheeze (Hoppin et al., 2002), prostate cancer incidence (Alavanja et al., 2003, 2005), lung cancer incidence (Alavanja et al., 2004), reproductive effects (Farr et al., 2004, 2006), cancer risk in the 21,375 children of pesticide appliers born in 1975 or later (Flower et al., 2004), mortality (Blair et al., 2005a), morbidity (Alavanja et al., 2005; Blair et al., 2005b), rheumatoid arthritis (De Roos et al., 2005a), breast-cancer incidence (Engel et al., 2005), neurotoxicity of chronic exposure to modest amounts of pesticides (Kamel et al., 2005), and prevalence of wheeze (Hoppin et al., 2006a). Three additional publications have discussed pesticide-use patterns in the population (Hoppin, 2005; Hoppin et al., 2006b; Kirrane et al., 2004; Samanic et al., 2005). The AHS questionnaire collected detailed information regarding herbicide use; 2,4-D was the most commonly reported herbicide. Kamel et al. (2007a) evaluated questionnaire responses from more than 18,000 AHS participants, who listed a variety of neurologic symptoms, including memory and concentration problems. Another study by Kamel et al. (2007b) evaluated Parkinson disease (PD) in participants in the AHS. WJ Lee et al. (2007) analyzed incident colorectal cancers diagnosed in AHS participants in 1993–2005. Associations with self-reported exposures to 50 pesticides (including 2,4-D, 2,4,5-T, and 2,4,5-TP) were studied. Samanic et al. (2006) reported on the incidence of all cancers combined and selected individual cancers in male pesticide applicators in the AHS particularly with respect to reported exposures to the benzoic acid herbicide dicamba (3,6-dichloro-2-methoxybenzoic acid), which has been used in combination with other herbicides, such as 2,4-D. Montgomery et al. (2008) discussed the relationship between self-reported incidence of diabetes and pesticide and herbicide exposure in 31,787 licensed pesticide applicators and their spouses. Saldana et al. (2007) reported on the cross-sectional relationship between pesticide and herbicide exposure and a history of gestational diabetes in the wives of licensed applicators. Of 11,273 women asked about their pregnancies closest to enrollment, 506 (4.5 percent) reported gestational diabetes. Hoppin et al. (2006c) evaluated participants who experienced wheeze, Hoppin et al. (2007b) evaluated farmer's lung (hypersensitivity pneumonitis), Hoppin et al. (2007a) and Valcin et al. (2007) evaluated chronic bronchitis, and Hoppin et al. (2008) evaluated atopic and nonatopic asthma in women.

Andreotti et al. (2009) conducted a case-control analysis of pancreatic cancer in participants who completed the enrollment form (93 incident cases in 64

applicators and 29 spouses and 82,503 cancer-free controls). The ever-use of 24 chemicals and the intensity-weighted lifetime days—(lifetime exposure days) × (exposure intensity score)—of 13 chemicals were assessed. Risk estimates were calculated by using unconditional logistic regression for various exposures and controlling for age, smoking, and diabetes.

Hoppin et al. (2009) reported on pesticide use and 127 cases of allergic and 314 cases of nonallergic adult-onset asthma in 19,704 male private applicators in the AHS who were at least 20 years old and who completed both the enrollment form and the take-home questionnaire with full information on smoking, asthma history, age, BMI, and high pesticide-exposure events. The researchers excluded 487 female applicators with 19 cases of asthma because of the small sample. Logistic regression was used to evaluate the association between farming exposures and adult-onset asthma, allowing for separate associations with allergic and nonallergic asthma and adjusting for age, state (Iowa or North Carolina), smoking status (current, past, or never), and BMI. For each of 48 pesticides, the exposure status was specified as ever-use versus never-use. Further analyses of response to exposure were conducted with a three-level specification for exposure—never used, median use or less, and greater than median use—according to the distribution for intensity-adjusted days of use for the specific pesticide. As noted previously, the findings from this study might be vulnerable to selection bias because of the low response rate (42 percent) for the take-home survey.

Mills et al. (2009) reported on the association between lifetime use of 49 pesticides and the incidence of and mortality from myocardial infarction (MI) in the AHS cohort: 476 deaths among the 54,069 male participants who completed the enrollment form and 839 nonfatal events among the 32,024 male participants who completed the phase II telephone interview. Deaths from MI, as either a primary or contributing cause, were recorded from state and national death records starting at enrollment and going through December 31, 2006. The incidence of nonfatal MI was determined on the basis of a positive response on the 5-year follow-up questionnaire to the question "Has a doctor or other health professional ever told you that you had a heart attack (or myocardial infarction)?" First MIs that occurred after enrollment were counted as incident MIs. Separate analyses for mortality and incidence were conducted by using Cox regression and adjusting for state (Iowa or North Carolina), age, and smoking status (whether or not the participant had smoked 100 cigarettes in his or her lifetime). The incidence analysis also adjusted for BMI. The analyses were conducted for each pesticide specified as ever used and as lifetime days of exposure. As noted previously, the validity of the findings for the incidence analysis might be compromised because of the modest rate of response to the phase II survey—63 percent according to the committee's calculation (35,088 respondents of 55,748 in the original cohort), reported as 70 percent in Mills et al. (2009). In particular, for incidence analyses reported in Mills et al. (2009), this survey is vulnerable to selection bias because of left truncation, that is, missing participants who died before the survey.

Goldner et al. (2010) examined the association between organochlorine exposure and thyroid disease in 19,529 female spouses in the AHS. The analysis was limited to female spouses of private applicators who completed both the take-home survey in phase I (pesticide use) and the follow-up interview in phase II (thyroid disease) and for whom there were complete data on all covariates. Thyroid-disease status (none in 14,486, hyperthyroidism in 369, hypothyroidism in 1,114, and other in 560) was ascertained from a self-reported history of physician diagnoses obtained during the phase II interviews. Logistic regression was used to estimate the association between the use of herbicides (including 2,4-D and 2,4,5-T) and insecticides and thyroid-disease status (with no disease as the reference group) with adjustments for education, age, smoking (never, past, or current), BMI, and hormone-replacement therapy (ever or never). As noted previously, the findings from this study might be vulnerable to selection bias because of the low overall rate of response to the combination of the take-home survey and the follow-up interview.

Dennis et al. (2010) reported on 150 cases of cutaneous melanoma diagnosed after enrollment in the AHS of pesticide applicators who completed both the enrollment form and the take-home questionnaire during phase I, excluding 24,704 who had a cancer diagnosis before enrollment. Cases were identified through linkage to cancer registries, state death registries, and the NDI with a cutoff date of December 31, 2005. Dichotomous measures (ever or never used) were used for arsenic pesticides (lead arsenate and inorganic and organic arsenic). Categorical measures (no, low, or high) based on intensity-weighted lifetime days of exposure were used for other chemicals, including 2,4-D, 2,4,5-T, and 2,4,5-TP. Unconditional logistic regression was used to estimate the association between melanoma and exposure with adjustments for age, sex, and other variables "as indicated" (apparently selection through an unspecified variable selection procedure), including sun exposure, tendency to burn, red hair, and BMI.

Thomas et al. (2010) reported on a monitoring study of 2,4-D and chlorpyrifos exposures in a sample of AHS participants. For 69 2,4-D applicators, the geometric mean values were 7.8 and 25 mg/L in pre-application and postapplication urine, respectively ($p < 0.05$ for the difference), and 0.37 mg/m^3 in personal air. The estimated amounts of dermal absorption through the hands (hand loading) and through total skin surface (body loading) were 0.39 mg and 2.9 mg of 2,4-D, respectively; the readings for individual applicators were correlated across these media. Glove use and the mode of application were found to be associated with the degree of exposure.

Slager et al. (2009) reported on current rhinitis in commercial pesticide applicators in the AHS (excluding private applicators, such as farmers). Of the 4,916 commercial pesticide applicators in the full AHS cohort, the 2,245 who provided information on all the variates in the analysis model constituted the sample for this investigation. Current rhinitis was ascertained with the following question in the take-home questionnaire: "During the past 12 months have you had a stuffy,

itchy, or runny nose?" Exposure to individual pesticides was specified both as a dichotomous measure (ever versus never in the preceding year) and as a categorical measure (days per year). Logistic regression was used to estimate the association between exposure and current rhinitis, with adjustments for age, education, and having grown up on a farm. As noted previously, the findings from this study might be vulnerable to selection bias because of the low rate of response to the take-home survey (46 percent by commercial applicators, slightly higher by the entire AHS cohort).

Crawford et al. (2008) reported on hearing loss in white male licensed pesticide applicators in the AHS, under the hypothesis that some pesticides are neurotoxic and could potentially affect hearing. The study sample consisted of participants who completed the enrollment form and the take-home questionnaire during phase I and the follow-up telephone interview during phase II. Hearing loss was ascertained with the following question in the phase II interview: "Do you have trouble with your hearing in one or both ears (this is without a hearing aid)?" Potential cases of hearing loss attributable to a congenital condition or to infection or injury (determined by responses to survey questions) were excluded. The analysis also excluded participants who reported never using pesticides and excluded nonwhite and female respondents. Of the 16,246 participants who completed all three surveys, 14,229 were retained in the final analysis sample. Logistic regression was used to estimate the associations between exposure and hearing loss with adjustments for state, age, and exposures to noise, solvents, and metals. The overall low rate of response (less than 30 percent) to the combination of the three surveys raises concerns about the validity of the study findings. The authors argued that there were too few nonwhites and females (1.5 percent of eligible participants) for analysis. Although it might be reasonable to consider those participants to be too few to be analyzed as subgroups, it is unclear why they needed to be excluded from the main analysis. (Limited analysis for nonwhites is mentioned in the discussion.)

Although health outcome results in the whole cohort or entire subgroups are not fully relevant for the COIs and might be regarded as of marginal interest to more recent VAO committees, Blair et al. (2005b) reported that 2,4-D is the pesticide most frequently used by the Iowa famers and is often used by the rest of the applicators. Consequently, the results on the relative rates of individual conditions seem comparable in exposure specificity with findings in production cohorts in which not all of the workers included were necessarily exposed to the COIs and may have had additional toxic exposures. Therefore, the findings on mortality from enrollment through 2000 (Blair et al., 2005a) and on cancer incidence through 2002 (Alavanja et al., 2005) have been retained in the results tables for health outcomes were added. Accordingly, mortality findings through 2007 on various causes of death (Waggoner et al., 2011) and comparisons with state populations for cancer incidence updated through 2006 (Koutros et al., 2010a) to the health-outcomes results tables. Conventional SMRs and SIRs were

calculated with adjustment for age, calendar year, race, sex, and state. In an effort to compensate for the pronounced healthy worker effect evident in the AHS cohorts, both Waggoner et al. (2011) and Koutros et al. (2010a) also calculated, in addition to conventional SMRs and SIRs, "relative" counterparts of these statistics—rSMR and rSIR, respectively. To obtain the relative rates, the standardized ratio for incidence or mortality was divided by the standardized ratio for all causes excluding it. Because even the usual SMRs and SIRs from these non-pesticide specific findings on the entire cohort are minimally informative, the committee opted not to consider the relative versions.

Waggoner et al. (2011) reported 4,880 deaths in the applicators (private and commercial) and 1,539 in the spouses, significantly fewer than expected for both (SMR = 0.54, 95% CI 0.52–0.55; and SMR = 0.52, 95% CI 0.50–0.5). Similarly, the deaths from all types of cancer were significantly lower than the state rates in both applicators (SIR = 0.61, 95% CI 0.58–0.864) and spouses (SIR = 0.65, 95% CI 0.60–0.70). Koutros et al. (2010a) found 4,316 cancer cases in the private applicators, 219 in the commercial applicators, and 1,896 in the spouses. Findings on the commercial applicators were set aside, and the cancer incidence rates in both the private applicators (SIR = 0.85, 95% CI 0.83–0.88) and the spouses (SIR = 8.2, 95% CI 0.79–0.86) were again significantly lower than expected.

Several recent AHS publications (Andreotti et al., 2012; Barry et al., 2011, 2012; Koutros et al., 2010b, 2011) reported on a nested case-control substudy that examined the relationship of pesticide exposure (including herbicides of interest, such as 2,4-D and 2,4,5-T) and of genetic markers with the risk of prostate cancer. All men eligible for inclusion in the study were white applicators who had not had any cancers other than non-melanoma skin cancers before enrollment in the AHS and who had provided a buccal-cell sample. Two controls matched on age to each case had to have been alive at the time of the case's diagnosis. The final study sample consisted of 776 prostate-cancer cases diagnosed in 1993–2004 and 1,444 controls. Although the primary focus of this substudy was the interaction between pesticide exposure and genetic markers (how pesticide exposure modified the association between genetic markers and prostate cancer), some useful information about the association between exposure to particular pesticides and prostate cancer can still be gleaned as a byproduct of the interaction analyses. Intensity-weighted lifetime exposure days are used in Andreotti et al. (2012) and Barry et al. (2011, 2012). Genotyping for an array of 26,512 single-nucleotide polymorphisms (SNPs) in 1,291 candidate genes was performed at the NCI's Core Genotype Facility. Unconditional logistic regression was used to estimate ORs and 95 percent CIs for the associations between prostate cancer and the main effect for pesticide exposure, the main effect for genetic markers, and the interaction between pesticide exposure and genetic markers, adjusted for age and state. Only Koutros et al. (2011), who reported the findings for this substudy on 1,913 SNPs in 149 candidate genes known to play a role in the metabolism of xenobiotic substrates, also adjusted for a family history of prostate cancer and

provided main effects for exposure to individual pesticides and the incidence of prostate cancer. Koutros et al. (2010b) reported the findings on 211 SNPs in the 8q24 region known to be associated with prostate cancer. Andreotti et al. (2012) reported the findings on 220 SNPs in 59 genes involved in lipid metabolism. Barry et al. (2011) reported the findings on 394 SNPs in 31 base-excision repair genes involved in repairing oxidative DNA damage that are hypothesized to be possibly important for populations exposed to pesticides or other putative oxidative stress-inducing agents. Barry et al. (2012) reported findings on 324 SNPs in 27 nucleotide excision repair (NER) genes thought to be important in repairing damage induced by putative prostate carcinogens. The false discovery rate (Benjamini and Hochberg, 1995) method is used to account for multiple comparisons involving a large number of pesticides and genetic markers.

Tanner et al. (2011) conducted a case-control study of PD in AHS participants. Suspect cases (170) were identified from self-reports and state mortality files and confirmed (115; 110 with pesticide data included in study) by a neurologist during home visits. Potential controls (644) were sampled randomly from the AHS cohort and frequency-matched about 3:1 to cases by age, sex, and state. Controls were confirmed (383; 358 with pesticide data included in study) by a neurologist or a neurologist-trained technician during home visits. CATIs were used to obtain detailed information on use, since the age of 14 years, of 31 selected pesticides expected to be possibly associated with PD (oxidative stressors and mitochondrial inhibitors) as well as key covariate information, including smoking and family history of PD. Participant characteristics were compared between cases and controls by using Fisher's exact test or Pearson's chi-square test for categorical variables and Wilcoxon's rank-sum test for continuous variables. Logistic regression was used for pesticides reported by at least 10 participants, controlling for potential confounding factors, including age, sex, state, and cigarette-smoking (ever or never).

Several recent AHS studies examined a variety of exposure issues. Blair et al. (2011) examined the effect of exposure misclassification, which is likely to occur when self-reported exposure assessment is used, on the relative risks estimated in the AHS and showed substantial attenuation toward the null. Similar results are likely for other studies that use self-reported exposure status. Coble et al. (2011) reported on an updated version of an estimation algorithm for pesticide exposure intensity, developed previously in Dosemeci et al. (2002) for the AHS, to incorporate new data obtained in two exposure-monitoring studies to modify the weighting factors used in the algorithm. Payne et al. (2012) conducted a Cox proportional-hazards regression to assess the risk posed by high pesticide exposure in the AHS cohort.

Since *Update 2012*, a large series of papers has been published from the AHS cohort. These are described briefly below, prioritizing first the health outcomes of most interest in light of evidence considered thus far by VAO committees. This includes an examination of the relationships between occupational pesticide

exposure (i.e., among pesticide applicators and their spouses) and risk of stroke, diabetes, Parkinson's-related diseases, and hypothyroidism. More details on these individual health outcomes are provided in the individual chapters concerning health outcomes of interest to the committee.

Rinsky et al. (2013) examined the relationship between self-reported pesticide use provided by the male private and commercial pesticide applicators and stroke as an underlying or contributing cause of death based on ICD-9 and ICD-10 criteria. The composite set of 50 commonly used pesticides included 2,4-D, but the set of 22 pesticides for which individual analyses of lifetime frequency and duration of use did not include 2,4-D. Although additional information about stroke and the COIs would be of considerable interest, the relevance of this publication to the VAO task is minimal.

Starling et al. (2014) conducted an analysis of 13,637 farmers' wives without a history of diabetes who reported ever personally mixing or applying any pesticides before enrollment in the AHS. At enrollment, the women were asked to report the number of years and average number of days per year that they personally mixed or applied any pesticides or herbicides. The herbicides 2,4,5-T and 2,4,5-TP were combined into a single variable because of their similar chemical structures and similar use patterns in the cohort and because both contained dioxin at some points in time. A total of 45 pesticides were examined for possible association with incident diabetes among study women over a 10-year follow-up period. With respect to the COIs, picloram, cacodylic acid, and TCDD were not examined. Analyses were adjusted for the state of residence and body mass index at enrollment. During the follow-up period, 5 percent of women reported development of diabetes. Whereas exposure assessment is based on self-report, two strengths of this analysis are that the ascertainment of exposure history included a specific examination of 2,4,5-T and 2,4,5-TP combined and that the incident development of diabetes (by self-report) was prospectively ascertained.

Kamel at el. (2014) examined the association between dietary fat intake, pesticide use, and Parkinson disease. A nested case-control design (within the AHS) was used whereby self-reported levels of dietary fat intake, specifically consumption of monounsaturated, polyunsaturated, and saturated fats, and pesticide use were compared between 89 confirmed cases of PD versus 336 control subjects frequency-matched by age, gender, and state and who did not develop PD. Dietary fat intake was assessed using the Diet History Questionnaire version I, a self-administered 144-item food frequency questionnaire developed by the NCI. Analyses were adjusted for age, gender, state, smoking, and total energy. The applicability of the analysis in addressing the committee's charge is severely limited because the study evaluated the pesticides paraquat and rotenone and pesticides similar to the Vietnam veteran COIs and also because it focused on interaction with dietary fat intake, which is not germane to the experience of Vietnam veterans.

Goldner et al. (2013) examined the association between use of 50 specific pesticides and self-reported hypothyroidism, hyperthyroidism, and "other" thyroid disease among 22,246 male pesticide applicators. The approach was very similar to earlier analyses done on females spouses (Goldner et al., 2010). The relationship between exposure and response was assessed on the basis of intensity-weighted cumulative days of use. Specifically, the exposure distribution for each pesticide was split at the median value of intensity-adjusted cumulative days of use among users to create a three-level variable categorized as no exposure (zero days of use), low exposure (median or less), or high exposure. Comparisons of the history of thyroid disease between the three groups in relation to pesticide use were adjusted for age, education, and BMI at enrollment. During follow-up, 2 percent of pesticide applicators reported a history of hypothyroidism, 1 percent reported a history of hyperthyroidism, and 1 percent reported a history of other thyroid disease. A strength of this analysis is that separate risk estimates were calculated for self-reported use of 2,4-D and 2,4,5-T, chemicals of direct interest to Vietnam veterans, and for the chemically related herbicides 2,4,5-TCP and dicamba. A significant limitation of this analysis is that the assessment of thyroid disease was based on a lifetime history of disease because thyroid disease was not reported at baseline and information on age of diagnosis was incomplete at follow-up. Thus, this analysis is based on the untested and unconfirmed assumptions that essentially all reports of thyroid disease at follow-up assessments were incident cases, and that the prevalence of thyroid disease at study entry did not differ between the pesticide exposure groups.

In addition to the recently published studies from the AHS that relate specifically to health outcomes of interest among Vietnam veterans, Hou et al. (2013) examined the relationship between self-reported lifetime pesticide-use days and intensity-weighted lifetime pesticide use (log-transformed) and relative telomere length among 1,234 cancer-free white male pesticide applicators in the AHS. For purposes of the analysis, pesticide exposure was classified into four categories consisting of none, low, medium, and high. The rationale for the investigation of telomere length is based on human epidemiologic investigations that suggest that telomere length in surrogate tissues (blood or buccal cells) may be associated with some cancers. The 48 pesticides examined were grouped into seven classes of pesticides, with one group of interest consisting of 2,4-D. A strength of this analysis is that the outcome measure, relative telomere length, is biologically based and not based on self-report. On the other hand, the direct relevance of relative telomere length to the specific outcomes of interest to Vietnam veterans is unknown, particularly because studies are inconsistent as to the extent to which telomere length reliably predicts an elevated risk of cancer development of various types. The fact that self-reported exposure to 2,4-D as a class of pesticides was included in the analysis is considered a strength of this study.

Karami et al. (2013) evaluated interactions between 41 pesticides and 152 SNPs involved in nine vitamin-D pathway genes among 776 prostate cancer cases

diagnosed between 1993 and 2004 and 1,444 male controls in a nested case-control study of Caucasian pesticide applicators within the AHS. The method of estimating pesticide exposure matched that of Hou et al. (2013) (described above) and included self-reported lifetime pesticide-use days and intensity-weighted lifetime pesticide use (log-transformed). These quantities were then grouped into three categories consisting of none, low (median level or below), and high (above the median level). The identification of nine vitamin D–associated candidate genes was done with standard genotyping methods. In supplementary analyses, main effects of 2,4-D and 2,4,5-T were examined in relation to their association with prostate cancer. Whereas the purpose of this study was to investigate pesticide and gene interactions with respect to risk of prostate cancer, strengths of this study are that main effects of some of the COIs to the Vietnam-veteran population were examined and that the occurrence of prostate cancer was based on clinical diagnoses.

In an earlier, similar analysis of the risk of prostate cancer, Barry et al. (2012) evaluated interactions between pesticide exposure among white pesticide applicators and 324 SNPs tagging 27 nucleotide excision repair genes among 776 prostate cancer cases and 1,444 male controls using a nested case-control design in the AHS. As with Karami et al. (2013), prostate cancer cases were diagnosed between the years 1993 and 2004 and after enrollment in the AHS. For exposure assessment, lifetime days and intensity-weighted lifetime days of application for each pesticide were categorized into a three-level ordinal-valued variable consisting of none, low, and high with the low and high categories distinguished by the median value among exposed controls. Whereas 2,4-D was one of the many different pesticides assessed, it was only analyzed as an interaction with the *DDB1* gene and not as a main effect. Thus, this study was deemed of very limited value to evaluating the relationship between 2,4-D and the risk of prostate cancer.

Alavanja and Bonner (2012) conducted a lengthy review of the epidemiological literature linking pesticides (including 2,4-D) to cancers in occupational studies worldwide, with a particular focus on those articles published after the release of *IARC Monograph 53 (1991): Occupational Exposures in Insecticide Applications and Some Pesticides*. Given the time span, and the fact that this paper was a review article and not a new data-based analysis, it was deemed of very little value by the committee other than the authors' conclusions on the potential relationships between occupational pesticide exposure and different types of cancer. Moreover, a very similar published review article on the same subject by Alavanja et al. (2013a) was deemed of tangential value to the committee charge, as was a corresponding letter by Gray et al. (2013) to the Alavanja et al. (2013a) review, as well as the subsequent reply to Gray et al. (2013) by Alavanja et al. (2013b).

Finally, by use of the AHS, Heltshe et al. (2012) presented methodological work on the ability to use multiple imputation to assign pesticide use values for nonresponders (missing data) in the AHS follow-up questionnaire. Although

academically of interest, the paper did not provide any meaningful evidence to evaluate with respect to the charge of the committee.

California United Farm Workers of America Study

Mills and Yang (2005) and Mills et al. (2005) analyzed lymphohematopoietic cancers and breast cancer, respectively, in nested case-control studies of Hispanic workers drawn from a cohort of 139,000 Californians who were members of the United Farm Workers of America (UFW). Estimates of exposure to specific pesticides, including 2,4-D, were developed through a linkage of the union's job histories with the California Pesticide Use Reporting Database of the state's Department of Pesticide Regulation, which has records of all agricultural applications of pesticides in the state since 1970. Vital status and cancer incidence were ascertained through a probabilistic record linkage to the California Cancer Registry for the period 1988–2001. Mills and Yang (2007) conducted a nested case-control gastric cancer study embedded in the UFW cohort and identified cases of gastric cancer newly diagnosed in 1988–2003.

No reports relevant to the COIs have been published on the California UFW population since *Update 2008*.

Other US Studies of Agricultural Workers

Studies of proportionate mortality were conducted among Iowa farmers (Burmeister, 1981) and male and female farmers in 23 states (Blair et al., 1993). Mandel et al. (2005) reported the results of urinary biomonitoring of farm families in Minnesota and South Carolina as a part of CropLife America's Farm Family Exposure Study. Curwin et al. (2005) measured 2,4-D concentrations in urine and hand-wipe samples to characterize exposures of farmers and non-farmers in Iowa.

Studies in Other Countries

Australian Herbicide-User Studies

Fritschi et al. (2005) used CATIs and occupational histories reviewed by an industrial hygienist to estimate exposures to phenoxy herbicides in an Australian study.

Canadian Herbicide-User Studies

The Ontario Farm Family Health Study (OFFHS) has produced several reports on exposure to phenoxyacetic acid herbicides, including 2,4-D. A study of male pesticide exposure and pregnancy outcome (Savitz et al., 1997) developed

an exposure metric based on self-reports of mixing or application of crop herbicides, crop insecticides, and fungicides; livestock chemicals; yard herbicides; and building pesticides. Study participants were asked whether they participated in those activities during each month, and their exposure classifications were based on activities in 3-month periods. Exposure classification was refined with answers to questions about the use of protective equipment and the specificity of pesticide use.

A related study included analysis of 2,4-D residues in semen as a biologic marker of exposure (Arbuckle et al., 1999a). The study began with 773 potential participants, but only 215 eventually consented to participation. Of the 215, 97 provided semen and urine samples for 2,4-D analysis.

The OFFHS also examined the pregnancy outcomes of stillbirth, gestational age, and birth weight (Savitz et al., 1997) and the effects of exposure to pesticides, including 2,4-D, on time to pregnancy (Curtis et al., 1999) and on the risk of spontaneous abortion (Arbuckle et al., 1999b, 2001). About 2,000 farm couples participated in the study. Exposure information was pooled from interviews with husbands and wives to construct a history of monthly agricultural and residential pesticide use. Exposure classification was based on a yes–no response for each month. Data on such variables as acreage sprayed and the use of protective equipment were collected but were not available in all cases. Other studies have used herbicide biomonitoring in a subset of the population to evaluate the validity of self-reported predictors of exposure (Arbuckle et al., 2002). Assuming that the presence of 2,4-D in urine was an accurate measure of exposure and that the results of the questionnaire indicating 2,4-D use were more likely to be subject to exposure-classification error (that is, assuming that the questionnaire results were less accurate than the results of urinalysis), the questionnaire's prediction of exposure, compared with the urinary 2,4-D concentrations, had a sensitivity of 57 percent and a specificity of 86 percent. In multivariate models, pesticide formulation, protective clothing and gear, application equipment, handling practice, and personal-hygiene practice were valuable as predictors of urinary herbicide concentrations in the first 24 hours after application was initiated.

Urinary concentrations of 2,4-D and MCPA were measured in samples from farm applicators (Arbuckle et al., 2005) and from women who lived on Ontario farms (Arbuckle and Ritter, 2005). Potential indirect sources of farm families' herbicide exposure were evaluated through wipe sampling of surfaces and samples of drinking water (Arbuckle et al., 2006). Weselak et al. (2008) examined occupational exposures and birth defects in the offspring of OFFHS participants. Spouses completed questionnaires that requested the history of pesticide use on the farm. Pregnancies resulting in birth defects were reported by the female study participants. All birth defects were combined for study analyses, and exposure was examined by pesticide class, family, and active ingredient for two 3-month periods—before and after conception.

No reports on the OFFHS relevant to the COIs have been published since *Update 2008*.

The Canadian Farm Operator Study assembled a cohort of 156,242 male farmers from 1971 Canadian census data on the provinces of Manitoba, Saskatchewan, and Alberta and linked to the national mortality database to identify deaths occurring during the period June 1971–December 1987. The cohort was also matched to the Central Farm Registers for 1966, 1976, 1981, and 1986 to gather information on reported exposures and farm practices. Information on the amount of acreage on each farm sprayed in 1970 with herbicides (without product specificity) was used as surrogate for its operator's exposure in determining the risk of specific causes of death: NHL (Morrison et al., 1994; Wigle et al., 1990), prostate cancer (Morrison et al., 1993), brain cancer (Morrison et al., 1992), multiple myeloma (Semenciw et al., 1993), and leukemia (Semenciw et al., 1994). In the one-third sample that completed the census long form, the people most likely to have been exposed (no employees or custom expenses reported) could be identified. The age at which years at risk began to accumulate for each person varied for the various causes of death assessed, which resulted in different numbers of eligible subjects. No reports on relevant health outcomes have been published on participants in this study population since *Update 1996.*

Other Canadian Studies of Agricultural and Forestry Workers Faustini et al. (1996) evaluated the immune, neurobehavioral, and lung function of residents in an agricultural area of Saskatchewan, Canada, and focused on immunologic changes in 10 farmers who mixed and applied commercial formulations that contained chlorophenoxy herbicides. Studies have been conducted in forestry workers who were potentially exposed to the types of herbicides used in Vietnam. A cohort mortality study examined men employed by a Canadian public utility (Green, 1987, 1991). Senthilselvan et al. (1992) investigated asthma's relationship to pesticide use with self-reported data gathered in a cross-sectional survey completed by 1,939 of the 2,375 male farmers approached in Saskatchewan. Mortality and reproductive effects have been studied in British Columbia sawmill workers potentially exposed to chlorophenate wood preservatives used as fungicides (Dimich-Ward et al., 1996; Heacock et al., 1998; Hertzman et al., 1997); PCP, which would be a frequently used fungicide, is expected to have dioxin and furan contamination, but the 2,3,7,8-TCDD congener is unlikely to have been present.

Danish Herbicide-User Studies

Records of the Danish Union of General Workers for 10 trade unions of gardeners were used to identify 3,156 male members on May 1, 1975; 859 women were also identified. The workers were known to be highly exposed to pesticides.

Most of the women worked in greenhouses, where herbicides are not routinely used; for the men, however, exposure was mainly to herbicides, which included the phenoxy herbicides 2,4-D, 2,4,5-T, and MCPA. Matching of union records to the Danish Central Population Registry permitted the establishment of the vital status of the entire cohort through 1984 for a determination of person-years at risk; this provided for a latent period of 10–15 years by starting accumulation when people reached the age of 30 years. Using the Danish Cancer Registry, Hansen et al. (1992) determined the cancer incidence in this cohort of Danish gardeners from 1975 to 1984 and compared it with the general Danish population and adjusted for age, sex, and calendar period.

Hansen et al. (2007) used analogous methods to extend the follow-up period for the men through 2001. The updated information was analyzed by using year of birth as a surrogate for intensity of exposure, with high exposure assumed for those born before 1915, low exposure for those born in 1934 or later, and intermediate exposure for those born in between.

Drawing from the same cohort of Danish gardeners and further stipulating that people must have been alive and living in Denmark at the beginning of 1977, Kenborg et al. (2012) established a cohort of 3,124 men who were monitored in the Danish Hospital Register for hospitalization for PD as a primary diagnosis from 1977 through 2008 and compared the results with the observed incidence of PD in all Danish men by calendar period and age group. Revisiting the Danish Cancer Registry, they also investigated the incidence of lung, larynx, and bladder cancers, which are recognized as smoking-related. The incidence of those cancers was compared by age and calendar period with the incidence in the general male Danish population, and the rates were used as a proxy for smoking frequency in the cohort. The birth cohorts defined by Hansen et al. (2007) were used again to stratify degree of exposure.

Ronco et al. (1992) studied mortality in Danish farmers. The utility of the findings was limited by their being largely unanalyzed products of linking the country's cancer registry with census records to garner information on recent occupation.

Dutch Herbicide-User Studies

A Dutch study of forestry workers exposed to 2,4,5-T investigated the prevalence of acne and hepatic dysfunction (van Houdt et al., 1983). No reports on forestry workers have been published since 2000.

Mortality from cancers and other causes in Dutch male herbicide applicators has been studied by Swaen et al. (1992, 2004).

Finnish Herbicide-User Studies

Asp et al. (1994) conducted a follow-up through 1989 on mortality and cancer morbidity in Finnish men who had applied 2,4-D and 2,4,5-T for at least 2 weeks in 1955–1971. This group of 1,971 was assembled in 1972 from records of

the four Finnish employers primarily responsible for brush removal and assessed for mortality through 1980 (Riihimaki et al., 1982) and for cancer morbidity (Riihimaki et al., 1983) through 1978.

German Herbicide-User Studies

Barthel (1981) studied cancer incidence overall mortality from 1970 through 1978 in 1,658 male agricultural plant-protection workers in the former German Democratic Republic who spent a portion of at least 5 years in 1948–1972 applying pesticides. Unlike most of the many pesticides thought to have contributed to the exposure of these workers, the phenoxy herbicides were available for use throughout this period. It was not known, however, which individuals used the COIs, so exposure characterization was not as specific as current VAO committees require for results to be considered fully relevant. Among the cancers, only lung cancer had a large enough number of cases to permit an analysis by the amount and time period of pesticide use.

Iceland Herbicide-User Studies

Using the national cancer and death registries, Zhong and Rafnsson (1996) determined cancer incidence from entry into a pesticide-using occupation through 1993 for 2,449 men and women in Iceland. A ranked listing of the amount of specific pesticides sold for agricultural use in Iceland between 1976 and 1993 was led by 2,4-D, but the listing did not specify which of these pesticides individual subjects had been exposed to, so the results of this study do not constitute fully relevant evidence according to the criteria of recent VAO committees.

Italian Herbicide-User Studies

Ronco et al. (1992) also studied the incidence of specific types of cancer in Italian farmers. The utility of the findings was limited by their being the largely unanalyzed products of linking the country's cancer registry with census records to garner information on recent occupation.

Cancer mortality in a cohort of rice growers in the Novara Province of northern Italy was investigated by Gambini et al. (1997).

A cohort of male farmers in Italy's southern Piedmont region who were licensed to use agricultural pesticides in 1970–1974 was established. The use of phenoxy herbicides in the area was reported to be twice the national average. Corrao et al. (1989) evaluated cancer incidence in 25,945 on the basis of new diagnoses from hospital admissions in 1976–1983. In a continuation of that study, Torchio et al. (1994) reported on mortality through 1986 in the 23,401 who were residents of the Piedmont area at the time of registration; the cause of death was abstracted from death certificates. The cohort was partitioned into people who

lived near arable land, those who lived near woodlands, and those who lived near mixed-use land; separate results were reported for the first two groups. No reports on this cohort have been published since 1994.

New Zealand Herbicide-User Studies

A study evaluated cancer incidence in a group of New Zealand forestry workers (Reif et al., 1989). No reports on forestry workers have been published since 2000. 't Mannetje et al. (2005) evaluated a study population that included herbicide production workers and was a subcohort of the IARC cohort.

Norwegian Herbicide-User Studies

Kristensen et al. (1997) tested whether cancers or birth defects were increased in the offspring of Norwegian farmers who worked on farms with pesticide use documented by agricultural censuses.

South American Herbicide-User Studies

Lerda and Rizzi (1991) studied the incidence of sperm abnormalities in Argentinean farmers. The utility of the findings was limited by their being the largely unanalyzed products of linking each country's cancer registry with census records to garner information on recent occupation.

Swedish Herbicide-User Studies

The Swedish Cancer-Environment Register (CER) linked the cancer cases entered in the Swedish Cancer Registry with the records of people who responded to the 1960 and 1970 national censuses, which had obtained data on current occupation. The resulting database has been used in studies that evaluated cancer mortality and farm work (Wiklund, 1983); STS and malignant lymphoma in agricultural and forestry workers (Wiklund and Holm, 1986; Wiklund et al., 1988a); and the risk of NHL, HL, and multiple myeloma in relation to occupational activities (Eriksson et al., 1992). No new studies using the Swedish CER that are relevant to the COIs have been published since the original *VAO* report.

Cancer mortality in Swedish railroad workers has been studied (Axelson and Sundell, 1974; Axelson et al., 1980). Another study examined mortality and cancer incidence in a cohort of Swedish lumberjacks (Thörn et al., 2000). Cancers in Swedish pesticide and herbicide applicators has been studied repeatedly (Dich and Wiklund, 1998; Wiklund et al., 1987, 1988b, 1989a,b).

Other Studies of Workers Using Herbicides

Other studies of the agricultural use of pesticides have not provided specific information on exposure to 2,4-D, TCDD, or other compounds relevant to Vietnam veterans' exposure (Bell et al., 2001a,b; Chiu et al., 2004; Duell et al., 2001; Garry et al., 2003; Gorell et al., 2004; Hanke et al., 2003; van Wijngaarden et al., 2003).

A series of papers from a workshop focused on methods of assessing pesticide exposure in farmworker populations (Arcury et al., 2006; Barr et al., 2006a,b; Hoppin et al., 2006b; Quandt et al., 2006). They provide a helpful review of current methodologic issues in exposure science for those populations but do not address the COIs directly.

ENVIRONMENTAL STUDIES

Industrial accidents have led to the evaluation of long-term health effects in non-worker populations that live near areas with fairly high environmental concentrations of the COIs. Effects on residents around normally performing industrial operations, such as waste incinerators, and even on people exposed only to "background" concentrations have also been studied. We note that the systematic follow-up studies that have been conducted on the Seveso population and the numerous analyses of the large database generated by the continuing US NHANES contributed prominently to the evidence base considered by VAO committees.

People's environmental exposures to dioxin-like chemicals and their non–dioxin-like counterparts are to mixtures of components that tend to correlate, so it is not surprising that specific chemicals measured in a person's serum also tend to correlate; this collinearity means that it is difficult for epidemiologic studies to attribute any observed association to a particular chemical configuration (Longnecker and Michalek, 2000). Analyses in terms of TEQs circumvent that problem, to some extent.

Environmental studies are presented below alphabetically by country.

Belgian Environmental Studies

From the Flemish Environment and Health Study (2002–2006), Delvaux et al. (2014) evaluated relationships between prenatal exposure to endocrine disrupting chemicals (EDCs, including dioxins) and anthropometric measures of height, weight, waist circumference, and skin folds at 7–9 years of age. The sample included 114 Flemish children with analyses adjusted for maternal BMI, age of the mother, smoking of mother during pregnancy, parental education level, and lipid content, and age and gender of the child. The strengths of this study include the objective measurement of dioxin TEQs from cord/blood samples at birth and the anthropometric measures of child development. Its limitations include only

its potential relevance to female Vietnam veterans with pregnancy subsequent to military service and the evaluation of anthropometric outcome measures among children with unknown long-term clinical significance.

Danish Environmental Studies

Halldorsson et al. (2009) studied the association between consumption of fatty fish, as a source of environmental exposure to dioxins and dioxin-like chemicals, and birth weight and development in 100 healthy pregnant women 25–35 years old selected from the Danish National Birth Cohort, which includes 101,046 women (Olsen et al., 2001). The 9,815 eligible women were stratified according to the frequency of fatty-fish intake (low, zero meals per month; medium, one to three; and high, more than three); 34, 33, and 33 were randomly sampled in three strata, respectively. Four standardized CATIs (at gestation weeks 12 and 30 and at 6 and 18 months postpartum) were used to collect information on parental lifestyle and health. Participants received a food-frequency questionnaire in week 25 of gestation, and two maternal blood samples were collected during routine visits to a general practitioner. The blood samples were analyzed for CALUX-TEQs in pg/g of lipid. Birth outcomes (weight, length, and head circumference) based on measures performed by the midwives who attended the births were extracted from the Danish National Birth Registry. Developmental milestones (such as sitting without support and crawling) were obtained from the telephone interviews conducted when the children were 5.7–7.0 months old. A total-development scale was derived by summing the indicators of 13 milestones. Linear mixed models (with the multiple plasma samples specified as an individual-level random effect) were used to estimate the association between CALUX-TEQ and birth weight with adjustments for gestational age, infant sex, and maternal smoking. Logistic regression was used for the association between CALUX-TEQ (dichotomized into high and low relative to the sample median) and infant development milestones, with adjustments for gestational age, duration of breastfeeding, infant age at interview, and maternal fish intake. Spearman rank correlation was used for the association between CALUX-TEQ and the total-development scale.

Wohlfahrt-Veje et al. (2014) examined the relationships between polychlorinated dibenzo-*p*-dioxins, furans, and biphenyls (PCDDs/PCDFs and PCBs), quantified as TEQs in breast milk samples, and measures of early childhood growth and serum insulin-like growth factor (IGF) levels. The sample consisted of 418 Danish children (born 1997–2001) followed longitudinally for measures of height, weight, BMI, and skinfold percentage at 0, 3, 18, and 36 months of age. Measures of IGF were obtained at 3 months. Separate estimates were provided for TCDD. The strengths of this study include an objective measurement of COIs to Vietnam veterans and anthropometric measures of infant development. Limitations include only its potential relevance to female Vietnam veterans with

pregnancy subsequent to military service and the evaluation of anthropometric outcome measures among infants with unknown long-term clinical significance.

Dutch Environmental Studies

Since *Update 2012*, de Jong et al. (2014) investigated relationships between pesticide and other occupational exposures and airwave obstruction in the Lifelines Cohort Study. The LifeLines cohort study is a multidisciplinary prospective population-based cohort study examining health and health-related behaviors of persons living in the northern region of The Netherlands. For the present analysis, the sample included 11,851 subjects who completed a baseline questionnaire and received a medical examination that included prebronchodilator spirometry to measure airway obstruction and respiratory function. Presumed exposure to pesticides (subcategories of herbicides and insecticides) was based on job title and description of current or last job held, with exposure classification made by use of the International Standard Classification of Occupations and subsequent assignment of "non-exposed," "low," and "high" exposure. Multiple linear and logistic regression models were fit with adjustment for sex, age, height, weight, current/ex-smoking, and pack-years at enrollment. Analyses were also stratified by gender and smoking status. A significant limitation of this analysis is that pesticide exposure history was based on job classification and not objective measurements, and that individual dioxin-like pesticides relevant to Vietnam veterans were not examined.

In an unrelated analysis, ten Tusscher et al. (2014) reported on relationships between prenatal and lactational dioxin exposure and a range of neurodevelopmental parameters. This included longitudinal assessment of behavior and intelligence among 41 children at ages 7–12 years, measures of behavior in adolescence at ages 14–18 among 33 children of the original group, and neurophysiological measurements done at ages 7–12 years. Assessment of neurophysiological development was based on use of magnetoencephalography (MEG) and electroencephalography (EEG). Assessment of intelligence was based on use of the Dutch version of the Wechsler Intelligence Scale for Children (WISC-R) and behavioral questionnaires, and assessment of behavior was based on the Dutch version of the Child Behavior Checklist for ages 4–18 years (CBCL 4–18) and the Teacher Report Form (TRF). In addition, current levels of dioxins and dioxin-like PCBs were measured again in adolescence at ages 14–18. Strengths of this study include objective measurement of perinatal dioxin exposure and neurophysiological development. Limitations include a particularly poor overall description of study results and direct relevance only to childbearing Vietnam veterans.

Finnish Environmental Studies

Turunen et al. (2008) studied mortality in 6,410 fishermen and their 4,260 wives in Finland in comparison with national mortality figures (standardized by sex, age, and period), assuming that the difference in mortality reflected the high consumption of contaminated fish by fishermen and their wives. A small subsample (88 fishermen and 94 wives) participated in a substudy of fish consumption and life habit and provided blood samples that were analyzed for nutrients and environmental contaminants, including dioxins and PCBs. The substudy found higher fish consumption and higher serum dioxins and PCBs in fishermen and their wives than in the general population studied in the 2000 health survey. However, the validity of the findings of the mortality study is limited by various types of confounding factors, including the possible health benefits of fish consumption by fishermen and their wives and a possible healthy-worker effect in the cases of fishermen.

Turunen et al. (2012) derived total TEQs for 17 PCDD/F and 37 PCB congeners in blood samples from 123 men and 132 women from this population of fishermen and their wives. They also measured 11 risk factors for CVD, four indicators of carotid artery plaque, and C-reactive protein (CRP), a single marker of inflammation. These variables were analyzed with respect to tertiles of overall TEQs, after adjustments for age, smoking, physical activity, dietary factors, alcohol consumption, and medications. They found that fish consumption was associated with lowered CVD risk markers, whereas consumption of high levels of dioxin-like compounds appeared to mitigate this benefit.

French Environmental Studies

Viel et al. (2000) reported on an investigation of apparent clusters of cases of STS and NHL in the vicinity of a municipal solid-waste incinerator (MSWI) in Doubs, France. The presumptive source of TCDD in the region is an MSWI in the Besançon electoral ward in western Doubs. Dioxin emissions from the incinerator were measured in international TEQ units at 16.3 ng/m^3, far in excess of the European Union (EU) standard of 0.1 ng/m^3. TCDD concentrations in cow's milk that were measured on three farms near the incinerator were well below the EU guideline of 6 ng/kg of fat, but the concentrations were highest on the farm closest to the incinerator. Floret et al. (2003) examined the same population and investigated rates of NHL in Besançon, France. Cases were identified from a cancer registry of people who had a diagnosis of NHL in 1980–1995. Viel et al. (2008a) examined the same population and reported a case-control study conducted in 434 women who had breast cancer compared with 2,170 community controls selected according to the proximity of their residence to emissions from the waste incinerator.

Viel et al. (2008b) expanded the previous work and studied the association between NHL and dioxin exposure from MSWIs in four French administrative departments (Isère, Bas-Rhin, Haut-Rhin, and Tarn), which were covered by a population-based cancer registry. (The study did not include the area of previous studies, Doubs, which is a separate administrative department.) The study was conducted with geostatistical analysis at the level of block groups, and it compared exposures and outcomes in the 2,270 block groups in the area. The block groups had an average area of 9.45 km^2. The cases considered for this study were in people 15 years old and older who had received a diagnosis of NHL during the period 1990–1999 and who were living in the study area at the time of their diagnosis. Anonymous data were extracted from cancer registries on the date of birth, sex, date of diagnosis, address at the time of diagnosis, and cancer category. The block group for each case was geocoded by using the residential address.

A second-generation Gaussian atmospheric-dispersion model (ADMS 3) was used to derive "immission" estimates (defined by the researchers as "the amount of pollutant reaching a particular location as a result of—and in contrast to—the emission coming out the chimney") for dioxins, metals, and dusts in the area near each of 13 MSWIs operating in the study area. That involved a receptor grid of 200 m that was based on emission estimates for the MSWI, plant characteristics (chimney height and diameter, emission temperature, particle size, and density), topography indicators (roughness and relief), local meteorologic conditions, and so on. For each of the 2,270 block groups, the median of all immission estimates for receptors in the block group was used as the immission for the block group. For block groups under the plumes of multiple MSWIs, the sum of the immission estimates was used. A cumulative ground-level dioxin concentration estimate was derived for each block group by using the immission estimates transformed to account for the number of years that the plant had operated and the degradation rate in the soil. Poisson regression was applied at the block-group level to assess the association between the observed number of NHL cases in each block group and the dioxin concentration (with a square-root transformation) estimated for the block group and adjusted for population density, urbanization, socioeconomic level, airborne traffic pollution, and industrial pollution.

Since *Update 2010*, Viel et al. (2011) have reported a new case-control study of NHL in a study area consisting of three electoral wards (170,000 people) that contained the Besançon MSWI. Cases (53 eligible, 34 participated) were identified from the local university hospital. Controls (34) were matched 1:1, randomly selected from blood donors living in the area matched on sex, age (± 5 years), and date of blood draw (± 1 year); five refusals were replaced. A wide spectrum of organochlorines (OCs) was measured in a fasting blood sample drawn from each participant. Exact logistic-regression models were used to assess the association between NHL and exposure measures.

Cordier et al. (2004, 2010) studied the risk of birth defects attributable to environmental dioxins released from MSWIs in the Rhône-Alpes region (Lyon

and surrounding areas) in southern France. The studies partially overlapped the areas studied by Viel et al. (2008b). All three studies included the administrative department of Isère.

Cordier et al. (2004) conducted a geostatistical analysis at the level of communities (official municipalities), studying 2,872 communities, each with fewer than 50,000 residents. Birth defects during the study period, 1988–1997, were identified from a population-based birth-defects registry (the French Central-East Registry). Seventy MSWIs operated in the study region for at least a year during the study period. Immission scores were derived using a Gaussian plume model (POLAIR) for dioxin concentrations in kilometer grids within 10 km of the plants and using plant emission estimates, chimney heights, and local meteorologic data. For each community, the immission score at the geographic point with the highest population density was used as the contemporaneous exposure index for the community. (That is a bit different from the usual practice of using the population centroid for the community.) In addition, a cumulative exposure index was derived by multiplying the contemporaneous exposure index by the number of years that the plant was in operation. A total of 194 communities were classified as exposed, and the remaining 2,678 communities were classified as non-exposed. In the exposed communities, only births after the start of the MSWI were considered in the analysis. Poisson regression was used to derive the relative risk of congenital malformations, with adjustments for the year of birth, maternal age, department of birth, population density, average family income, and (when available) local road traffic.

Cordier et al. (2010) examined the same population with a case-control study in 2001–2003, comparing 304 infants who had urinary tract birth defects with a random sample of 226 population controls that were frequency-matched for infant sex and year and district of birth. Of the 353 cases identified in the birth-defects registry, 304 were located, and 187 were interviewed. The modest response rate (53 percent of all cases, although the authors claimed a higher response rate of 62 percent, excluding 49 cases not located) may compromise the validity of the study findings. The controls were recruited through CATIs that attempted to reach 3,000 telephone numbers in the region presumed to belong to families with children; this resulted in 226 control participants after 1,989 ineligible candidates were excluded. Exposure estimates for dioxins, furans, and metals in areas near each MSWI (in 100-m grids) were derived by using Gaussian modeling software (ADMS 3) that took into account emissions, plant characteristics (chimney height and diameter, emission temperature and speed, and distribution between gaseous and particulate phases), and local meteorologic conditions. Participants were classified as exposed or non-exposed; those exposed were further classified into above or below the median. Multiple logistic regression was used to estimate the association between dioxin exposure and urinary tract birth defects with adjustments for stratification variables (child's sex and year and district of birth). Potential confounders were selected by using backward

selection, including community characteristics (population density, deprivation score, and industrial dioxin sources beside MSWIs), maternal age, parental geographic origin, educational level, employment status during pregnancy, treatment for chronic disease during the first trimester, folic acid supplementation, history of urinary tract birth defects in first-degree relatives, parity, obesity, tobacco and alcohol use during pregnancy, and environmental tobacco-smoke exposure.

Seveso, Italy

A large industrial accident that resulted in environmental exposure to TCDD was caused by an uncontrolled reaction during TCP production in Seveso, Italy, on July 10, 1976. The degree of TCDD contamination in the soil has been used extensively as a means of imputing exposures of members of the population. Three areas were defined on the basis of soil sampling: Zone A (556 people), the most heavily contaminated, from which all residents were permanently evacuated within 20 days; Zone B (3,920), an area of lower contamination that all children and women in the first trimester of pregnancy were urged to avoid during daytime; and Zone R (26,227), a region with some contamination in which the consumption of local crops was prohibited (Bertazzi et al., 1989a,b). The sample sizes differ among follow-up studies, presumably because of migration; the sample sizes given above were reported in Bertazzi et al. (1989b).

Cohort of Entire Exposed Population

Data on serum TCDD concentrations in Zone A residents have been presented by Mocarelli et al. (1990, 1991) and by CDC (1988e). In the 10 who had severe chloracne, TCDD concentrations were 828–56,000 ppt of lipid weight. In 10 without chloracne, TCDD concentrations were 1,770–10,400 ppt. TCDD was undetectable in all control participants but one. The highest of the concentrations exceeded any that had been estimated at the time for TCDD-exposed workers on the basis of backward extrapolation and a half-life of 7 years. Data on nearby soil concentrations, the number of days that a person stayed in Zone A, and whether local food was consumed were considered in evaluating TCDD. That none of those data correlated with serum TCDD suggested strongly that the important exposure was from fallout on the day of the accident. The presence and degree of chloracne correlated with TCDD. Adults seemed much less likely than children to develop chloracne after acute exposure, but surveillance bias could have affected that finding. Recent updates (Bertazzi et al., 1998, 2001) have not changed the exposure-assessment approach.

A number of studies of the Seveso population have used lipid-adjusted serum TCDD concentrations as the primary exposure metric (Baccarelli et al., 2002; Eskenazi et al., 2002a,b, 2003a, 2004; Landi et al., 2003). Fattore et al. (2003) measured the current air concentrations of PCDDs in Zones A and B and

compared them with measurements in a control area near Milan. The authors concluded that a release from PCDD-contaminated soil did not add appreciably to air concentrations in the Seveso study area. Finally, Weiss et al. (2003) collected breast milk from 12 mothers in Seveso to compare TCDD concentrations with those in a control population near Milan. The investigators reported that the TCDD concentrations in human milk from mothers in Seveso were twice as high as those in controls. The authors concluded that breastfed children in the Seveso area were likely to have higher body burdens of TCDD than children in other areas.

Several cohort studies have been conducted on the basis of the exposure categories. Seveso residents have had long-term follow-up of their health outcomes, especially cancers. Bertazzi and colleagues conducted 10-year mortality follow-up studies of adults and children who were 1–19 years old at the time of the accident (Bertazzi et al., 1989a,b, 1992), 15-year follow-up studies (Bertazzi et al., 1997, 1998), and a 20-year follow-up study (Bertazzi et al., 2001). Pesatori et al. (1998) also conducted a 15-year follow-up study to update non-cancer mortality. Consonni et al. (2008) reported on the 25-year follow-up (through 2001) vital status of residents ("present") in the Seveso area and reference territory at the time of the Seveso accident and of immigrants and newborns ("non-present") in the 10 years thereafter. Cause-specific mortality was determined for each zone, compared with that in the comparison cohort, and adjusted for presence at the accident, sex, age, and time since the Seveso accident.

In addition to a 2-year prospective controlled study of workers potentially exposed to TCDD during the cleanup of the most highly contaminated areas after the accident (Assennato et al., 1989a), studies have examined specific health effects associated with TCDD exposure in Seveso residents—chloracne, birth defects, and spontaneous abortion—as well as crude birth and death rates (Bisanti et al., 1980); the distribution of chloracne in Seveso children (Caramaschi et al., 1981); chemicals in the blood and urine of children who had chloracne (Mocarelli et al., 1986); chloracne and peripheral nervous system conditions (Barbieri et al., 1988); dermatologic and laboratory tests in a group of the children who had chloracne and in a group of controls (Assennato et al., 1989b); health status and TCDD concentrations in chloracne cases and non-cases recruited previously by Landi et al. (1997, 1998) and followed by Baccarelli et al. (2005a); hepatic enzyme–associated conditions (Ideo et al., 1982, 1985); abnormal pregnancy outcomes (Mastroiacovo et al., 1988); cytogenetic abnormalities in maternal and fetal tissues (Tenchini et al., 1983); neurologic disorders (Boeri et al., 1978; Filippini et al., 1981); cancers (Bertazzi et al., 1993; Pesatori et al., 1992, 1993); the sex ratio of offspring who were born in Zone A (Mocarelli et al., 1996); immunologic effects (Baccarelli et al., 2002); aryl hydrocarbon receptor (AHR)-dependent pathway and toxic effects of TCDD in humans (Baccarelli et al., 2004); effects of TCDD-mediated alterations in the AHR-dependent pathway in people who lived in Zones A and B (Landi et al., 2003); and NHL-related (14;18) translocation

prevalence and frequency in dioxin-exposed healthy people in Seveso (Baccarelli et al., 2006). Baccarelli et al. (2005b) reviewed statistical strategies for handling nondetectable readings or readings near the detection limit in dioxin-measurement datasets. They recommended that a distribution-based multiple-imputation method be used to analyze environmental data when substantial proportions of observations have nondetectable readings.

Baccarelli et al. (2008) reported on crude sex ratios, birth weight, and neonatal thyroid function for all births in 1994–2005 to women who were less than 18 years old at the time of the Seveso accident. Mocarelli et al. (2008) investigated TCDD's effects on reproductive hormones and sperm quality in a comparison of 135 young men exposed to TCDD by the 1976 Seveso accident with 184 age-matched healthy men who lived outside the contamination zones. Both groups were divided into three categories that reflected their ages at the time of the Seveso accident: infancy to prepuberty (1–9 years), puberty (10–17 years), and adulthood (18–26 years).

Pesatori et al. (2008) investigated the incidence of pituitary tumors in the Seveso population (804 in Zone A, 5,941 in Zone B, and 38,624 in Zone R) compared with the reference population in the surrounding, noncontaminated area (232,745). The hospital discharge-registration system of the Lombardy Region (where the study area is) was used to identify incident cases of pituitary adenoma from 1976 through 1996. All relevant medical records were reviewed to confirm the diagnosis for each case. Risk ratios and 95 percent CIs were estimated by using Poisson regression and adjusting for age, sex, and calendar period and an assumed 10-year latent period for dioxin effects. Pesatori et al. (2009) reported on cancer incidence in a 20-year follow-up of the Seveso cohort covering the period 1977–1996. The study included all participants 0–74 years old who lived in the study area (723 in Zone A, 4,821 in Zone B, 31,643 in Zone R, and 181,574 in the reference zone) at the time of the accident. Participants who moved outside the study area were traced with a success rate of greater than 99 percent (Consonni et al., 2008). Emigration was homogeneous among zones and ranged from 4.7 percent to 6.7 percent. The difference in exposure among zones was corroborated by soil TCDD measurements, serum concentrations of TCDD, and TEQs. In the absence of a regionwide cancer registry, incident cancer cases were ascertained from the 120-hospital network of the Lombardy region, where the study area is located. Original medical records were examined to identify true cases, to retrieve diagnoses as accurately as possible, and to determine the dates of occurrence. The study covered malignant tumors at any site and benign tumors of liver, bladder, and central nervous system first diagnosed after the date of the accident. For cohort members who were not hospitalized or who emigrated outside Lombardy, cancer cases were identified solely from death certificates, so nonfatal incident cases were missed. Risk ratios and 95 percent CIs for Zones A, B, and R versus the reference zone were derived by using Poisson regression and adjusting for sex, age, and period.

Mocarelli et al. (2011) have reported on the sperm quality and hormone concentrations of sons born from March 1977 to January 1984 to women exposed to dioxin in Seveso (78 invited, 39 participated) compared with men of similar age and socioeconomic status whose mothers did not live in the dioxin-contaminated areas and who were recruited from healthy volunteer permanent blood donors (123 invited, 58 participated). The exposed group was exposed both in utero (39) and perinatally through breastfeeding (21). Mothers' serum TCDD concentrations were measured by using serum samples collected in 1976–1977 and kept frozen since and extrapolated to the time of conception. The outcome measures included sperm concentration, total count, progressive motility, and total motility count based on semen samples and follicle-stimulating hormone concentration based on fasting blood sample. A general linear model was used to analyze sperm and hormone data—including exposure group, lactation class, and group × lactation interaction—adjusted for age, days in abstinence, smoking, chemical exposures, BMI, alcohol use, education level, and employment status. Scale transformations were taken on the outcome measures to achieve an approximate normal distribution and homoscedasticity. Although the study was carefully designed and implemented, the low response rate raises concerns about possible selection bias.

Seveso Women's Health Study

The Seveso Women's Health Study (SWHS) was undertaken to evaluate the association between individual serum TCDD concentrations and reproductive effects in women who resided in Seveso at the time of the 1976 accident. From a pool of 1,271 eligible women who were between infancy and 40 years old at the time of the accident, who had resided in Zone A or B, and for whom adequate serum remained from the samples collected shortly after the explosion, 981 were enrolled in the study group in 1996–1998. The fairly adequate 80 percent participation rate resulted from 17 women being lost to follow-up, 21 having died, 12 being seriously ill, and almost 250 refusing. All the women were interviewed by a nurse blinded to their exposure status, and a subset received gynecologic examinations. Medical records of those who reported ever having received a diagnosis of cancer were obtained and subjected to blind review by a pathologist. The stored samples were used for new TCDD analyses with improved analytic techniques that had become available in recent years.

As an initial step in the SWHS, Eskenazi et al. (2001) tested the validity of exposure classification by zone. Investigators measured serum TCDD in samples collected in 1976–1980 from 601 residents (97 in Zone A and 504 in Zone B). A questionnaire that the women completed in 1996–1998 included age, chloracne history, animal mortality in the vicinity, consumption of homegrown food, and the woman's location at the time of the explosion. Participants did not know their TCDD concentrations at the time of the interview, but most knew their zones of residence. Interviewers and TCDD analysts were blinded to the participants'

zones of residence. The zone of residence explained 24 percent of the variability in serum TCDD. Adding the questionnaire data improved the regression model to the point that it explained 42 percent of the variability. Those findings demonstrate a significant association between zone of residence and serum TCDD, but much of the variability in TCDD concentration is still unexplained by the models. Warner et al. (2005) compared a chemical-activated luciferase-gene expression bioassay with a high-resolution isotope-dilution gas-chromatography mass-spectrometry assay to measure PCDDs, PCDFs, and PCBs in the serum of 78 women who resided near Seveso in order to determine average total dioxin-like chemical TEQs; similar results were obtained with the two methods.

The women enrolled in the SWHS were assessed for cancer incidence during the 20 years after the accident (Warner et al., 2002). A pathologist blinded to the women's exposure status reviewed medical records of the 21 women who reported in their initial interview (conducted between March 1996 and July 1998) ever having received a diagnosis of cancer; 15 of these diagnoses were for breast cancer, so the analysis was limited to all cancers and to this cancer type. The remaining six cancers consisted of three cases of thyroid cancer, a melanoma, a kidney cancer, and an unspecified tumor. For each woman, the earliest post-accident blood samples with at least 0.5 mL remaining were analyzed for TCDD. The resulting readings were back-extrapolated to the time of the 1976 explosion, assuming a 9-year half-life, as derived from data obtained on Vietnam veterans in the AFHS (Pirkle et al., 1989). A Cox estimation of hazard ratios (HRs) was conducted by using those values and the women's ages at diagnosis or when they were interviewed for the controls, and a test for trend was conducted over four exposure categories with partitions at 10, 20, and 44 TCDD ppt; the results for both tests were marginally significant for breast cancer ($p = 0.05$ and $p = 0.07$, respectively) and slightly weaker for all cancers. A broad spectrum of possible confounders was assessed, but they had to be tested individually in the model. The small number of cases observed was a consequence of the cohort's being relatively small (981) and young at the time of interview (72 percent less than 50 years old).

Warner et al. (2011) added more than 10 years of observation on cancer incidence in the women in the SWHS, updating the borderline significant results for breast cancer published earlier (Warner et al., 2002) to cover the period from the 1976 explosion through 2009. Of the 981 women participating in the earlier study, 833 were located, alive, and willing to participate. They were reinterviewed, provided clinical measurements, and allowed access to medical records for confirmation; a subset was given bone-density tests. The average age was now 50.8 years. In the update, an additional 45 cancers had been diagnosed, for a total of 66 cases, of which 33 were breast cancers. Thyroid cancer was the next most prevalent with 7 cases, and the 15 other types of cancer observed had at most 3 cases. After adjusting for age at the time of the accident and for marital status, the risk of any cancers in association with lipid-adjusted, log-transformed

serum TCDD concentrations at the time of the accident was distinctly elevated (HR = 1.86. 95% CI 1.29–2.52). It was a small cohort, so the analyses that could be conducted were curtailed, but the availability of serum TCDD concentrations measured from blood samples gathered fairly soon after the single-substance accident (which minimizes uncertainty about what exposure had been experienced and reduces the need for back-extrapolation) contributes substantially to the value of the results.

A series of studies have examined the associations between serum TCDD and a variety of endpoints related to female reproductive functioning: menstrual cycle (Eskenazi et al., 2002a), endometriosis (Eskenazi et al., 2002b), pregnancy outcome (Eskenazi et al., 2003a), age at exposure to the accident (Eskenazi et al., 2004), age at menarche and age at menopause (Eskenazi et al., 2005), and age at menarche in women who were premenarcheal at the time of the explosion (Warner et al., 2004). Eskenazi et al. (2007) and Warner et al. (2007) examined the incidence of fibroids and ovarian function, respectively, in SWHS participants. Eskenazi et al. (2007) excluded women who had received a diagnosis of fibroids before 1976, leaving a total of 956 women for analysis. Fibroids were ascertained in 634 women by self-report, medical records, and ultrasonography. Analyses were adjusted for confounding by parity, family history of fibroids, age at menarche, current BMI, smoking, alcohol consumption, and education. Warner et al. (2007) studied menstrual function in SWHS participants who were 20–40 years old and not taking oral contraceptives; the evaluations included ultrasonography (96 women), serum hormone concentrations (87 women), and the occurrence of ovulation (203 women).

Eskenazi et al. (2010) examined the relationship between serum TCDD around the time of the accident and time to pregnancy (TTP) in 472 SWHS participants who had attempted pregnancy since the accident. In addition to other eligibility criteria for SWHS, participants were eligible for the study only if they were no more than 40 years old at the time of the accident. Nine women were excluded because of fertility-related problems, leaving 463 eligible women in the analysis sample. The main analysis was restricted to the 278 women who delivered live births that were not the results of contraceptive failure. Alternative analyses included various subsamples excluded in the main analysis. TTP for the first post-accident pregnancy was determined from responses in interviews conducted in 1996–1998 to the question "How many months did it take to become pregnant? In other words, for how many months had you been having sexual intercourse without doing anything to prevent pregnancy?" Women whose TTP was 12 months or more were classified as infertile. Initial serum TCDD concentrations at the time of the accident were measured in stored samples from 444 participants (431 collected in 1976–1977 and 13 collected in 1978–1981). For 19 participants with insufficient stored samples, new samples were collected in 1996 or 1997. For the 27 women with detectable post-1977 TCDD measurements, TCDD was back-extrapolated to 1976 using the Filser model (Kreuzer

et al., 1997). Initial serum TCDD concentrations were extrapolated to the time when each woman initiated her attempt to become pregnant; Kreuzer et al. (1997) used a toxicokinetic model for women 16 years old or younger at the time of the accident, and Pirkle et al. (1989) used a first-order kinetic model that assumed a 9-year half-life. The association between serum TCDD and TTP was assessed by using a Cox proportional-hazards model to estimate the fecundability ORs and 95 percent CIs. The association between serum TCDD and infertility was assessed by using multiple logistic regression. Both models were adjusted for maternal age, maternal smoking in the year before conception, parity, menstrual-cycle irregularity, oral-contraceptive use in the year before attempt, paternal age near the time of conception, and history of reproductive and endocrine conditions, including pelvic infection and thyroid or urogenital problems. A variety of sensitivity analyses were conducted to investigate the consistency of the study findings and to check for possible bias. Initial serum TCDD and extrapolated serum TCDD were specified as continuous variables on the logarithmic scale and as categorical variables.Since *Update 2012*, four additional publications from the SWHS were identified for review by the committee. Warner et al. (2013) reported on a total of 980 women with serum TCDD levels collected shortly after the 1976 Seveso chemical accident and with respect to future development of diabetes and the metabolic syndrome approximately 30 years after the accident. Analyses of serum TCDD levels were stratified by age at the time of the explosion (≤ 12 years versus > 12 years). A strength of this study is the prospective examination of serum TCDD levels in relation to the future development of diabetes. However, the analyses stratified by females ≤ 12 years of age are not relevant for inference with veterans who served in Vietnam.

Chevrier et al. (2014) examined TCDD concentrations collected from women in the Seveso cohort in 1976 (n = 981) and 1996 (n = 260) in relation to levels of total thyroxine, free thyroxine, free triiodothyronine, and thyroid-stimulating hormone, as measured in 1996 (n = 909) and 2008 (n = 724). Analyses were stratified by menarcheal status at the time of the Seveso explosion. A strength of this study is the biological measurement of TCDD levels at two different time points. Limitations include the fact that thyroid hormone levels (and disruption), in and of themselves, are not primary health outcomes of interest among Vietnam veterans. In addition, analyses stratified by females who were premenarche at the time of the explosion are not relevant for inference with veterans who served in Vietnam.

Eskenazi et al. (2014) examined the relationship between TCDD concentrations measured in 1996 and the bone mineral density of the spine and hip measured in 2008 by use of dual-energy X-ray absorptiometry (DXA) bone scan. Because this analysis was limited to women who were less than 20 years of age at the time of the Seveso explosion, and because bone mineral density is not a primary health outcome of interest among Vietnam veterans, this study was deemed of no practical value by the committee.

Wesselink et al. (2014) examined the risk of adverse pregnancy outcomes in relation to TCDD concentrations (1996) in the SWHS among 1,211 post–chemical explosion pregnancies through the 2008–2009 follow-up assessment. Birth outcomes examined included gestational age, pre-term delivery, and birth weight. Of note, only 35 percent of women in the analysis were age 21 or older at the time of explosion, thereby limiting inference of this work to female veterans who served in Vietnam.

Japanese Environmental Studies

From 2002 to 2006, Uemura et al. (2008a,b) assembled a stratified sample of 1,374 Japanese subjects 15–73 years old (627 men and 747 women) who represented urban, farming, and fishing areas of the entire country. The participants completed questionnaires on occupational, medical, smoking, and residential histories and height and weight. They also provided blood samples that were analyzed with isotope-dilution high-resolution gas chromatography–mass spectrometry for PCDDs, PCDFs, and dioxin-like PCBs. Uemura et al. (2008a) investigated the relationship of those chemicals with the prevalence of diabetes, defined as self-reported physician-diagnosed diabetes or the occurrence of plasma HbA1c greater than 6.1 percent as a predictor of fasting plasma glucose above 126 mg/dL. Uemura et al. (2008b) presented summary statistics on the serum concentrations of the individual chemicals in the blood of the study participants and on their distributions with respect to various demographic characteristics; the researchers also provided the results of log-transformed correlation analyses of all PCDDs and PCDFs combined, of all dioxin-like PCBs, and of total TEQ with total cholesterol, high-density lipoprotein, and triglycerides.

Uemura et al. (2009) conducted further studies of the same cohort and examined the association of body burdens of dioxins and related chemicals with the prevalence of metabolic syndrome, assessed by using a modification of the National Cholesterol Education Program Adult Treatment Panel III definition (NCEP, 2002) to accommodate the differences between Asian and Caucasian populations (Ko et al., 2005; Tan et al., 2004). In particular, participants were classified as having metabolic syndrome if they satisfied three or more of the following five criteria: BMI of at least 25 kg/m^2 (rather than abdominal waist circumference), serum triglycerides of at least 150 mg/dL, serum high-density lipoprotein (HDL) under 40 mg/dL in men or under 50 mg/dL in women, systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg or self-reported history of physician-diagnosed hypertension, and HbA1c of at least 5.6 percent (rather than fasting serum glucose) or a self-reported history of physician-diagnosed diabetes. Logistic regression was used to assess the associations between exposures (TEQs for PCDDs, PCDFs, and dioxin-like PCBs and total TEQs) and the prevalence of metabolic syndrome, both adjusted and not adjusted for age, sex, smoking and drinking habits, regional block, residential

area, and survey year. The analysis was conducted with and without prevalent diabetes cases. Further analyses were conducted for the adjusted associations of the TEQs with the five components of metabolic syndrome and the adjusted associations of the concentrations of the 16 selected congeners of which more than 75 percent of the subjects had detectable concentrations with the prevalence of metabolic syndrome.

From 2002 to 2010, Nakamoto et al. (2013) gathered fasting blood samples from a cross-sectional sample of 1,063 men and 1,201 women (aged 15–76 years), who were living in 125 areas of 45 prefectures throughout Japan and who were not occupationally exposed to dioxins (including TCDD). The full WHO 2005 set of dioxin-like PCDDs, PCDFs, and PCBs were measured in the samples and assessed in relation to a range of self-reported history of diseases including allergic diseases, hypertension, diabetes, hyperlipidemia, gout, thyroid disease, kidney disease, gastric ulcer, and gynecological disease. Multiple logistic regression models were fit to estimate the odds of reporting individual diseases by quartiles (pg/g lipid) for PCDDs/PCDFs, for PCBs, and for all dioxin-like chemicals measured. Models were adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and BMI. Strengths of this study include the relatively large sample and objective measurements of dioxins, which is directly relevant to military service in Vietnam. Limitations include the cross-sectional design, which precludes establishment of the temporal relationship between dioxin exposure and development of the diseases investigated and the fact that information on disease history was based on self-report and thus latent and undiagnosed patients may have been missed.

Yusho Disease Group

Tsukimori et al. (2012a) reported on the association between a mother's dioxin exposure and her children's birthweight among Japanese women affected by Yosho disease after an accidental exposure to rice oil contaminated with PCBs, PCDFs, and PCDDs in western Japan in 1968 that affected more than 1,900 people. Of 737 affected women officially registered with the Study Group for Yusho, 206 reported having given birth after the Yusho incident. Of them, 101 (with 190 eligible births) had their dioxin concentrations measured and participated in the mother–child study. Maternal serum concentrations of contaminants were assessed, converted into TEQs, and extrapolated to the time of delivery. Multiple linear-regression models were used to examine the association between birth weight and maternal serum contaminant concentrations, log-transformed to account for their log-normal distributions. The models adjusted for potential confounders for birth weight, including maternal age, parity, maternal smoking during pregnancy, gestation age at delivery, infant sex, duration of breast feeding, number of births, and frequency of seafood consumption.

In a follow-up analysis by Tsukimori et al. (2013), blood samples were obtained from 64 Yusho mothers who had 117 children, which included 10 with fetal Yusho disease (FYD) and 107 without FYD. Based on earlier analyses, FYD among the Yusho Disease Group was phenotypically defined as having children with low birth weight, hyperpigmentation of the gums and nails, conjunctivitis, dysplastic nails, wide fontanels, metastatic scalp calcification, diffuse dark skin pigmentation ("black baby"), and natal teeth at birth. After birth, exposed descendants also showed developmental delay, deficits on formal developmental testing, and abnormalities on behavioral assessment (Rogan et al., 1988). Maternal blood samples collected at delivery were analyzed for the presence of 7 PCDDs, 10 PCDFs, and 4 coplanar PCBs, including TCDD and by calculation of TEQs. Random effects logistic regression models were fit to estimate the odds of elevated maternal blood TEQ concentrations in relation to "black-baby" delivery versus non "black-baby" delivery. Analyses were adjusted for age at delivery, gestational age at birth, birth weight, descendant sex, and consumption of fish (times per week). This study is limited by the fact that dioxin concentrations were not measured in maternal blood at the time of delivery because the Yusho incident had taken place more than 40 years prior. In addition, the analyses are directly relevant only to childbearing Vietnam veterans.

Norwegian Environmental Studies

Stølevik et al. (2011) reported on the relationship between prenatal exposure to PCBs and increased risk of wheeze, eczema, and infections in newborns in the birth subcohort of the Norwegian Mother and Child Cohort Study. Maternal exposure to PCBs was determined from a validated food-frequency questionnaire that covered the first 4 months of pregnancy and that was adapted to include rarely eaten foods that are known to have high concentrations of PCBs and dioxins. Pregnant women were invited to enter the study in 2007–2008. The outcomes were determined through a questionnaire sent to the mothers at 1 year. Confounders in the statistical analyses were taken from the questionnaires filled out by the mothers during pregnancy and at 6 months after birth. They included previous breastfeeding, parity, history of atopy, age, smoking, education, BMI, child's sex, and others. Logistic regression with backward selection was used to fit multivariate models. There is concern about selection bias because of the low participation rate (38.5 percent).

Russian Environmental Studies

Chapaevsk

Several studies in the Samara region of Russia have identified the Middle Volga Chemical Plant (also known as SZVH or Khimprom) in Chapaevsk,

about 950 km southeast of Moscow, as a major source of TCDD pollution (Revazova et al., 2001; Revich et al., 2001). From 1967 to 1987 the plant produced γ-hexachlorocyclohexane (lindane) and its derivatives, and many of the workers experienced chloracne. Since then, it has produced various chlorinated products. Dioxins were detected in the small number of air, soil, drinking-water, and cow's-milk samples gathered in the region, but no description of how these media were sampled was given. When Revich et al. (2001) compared the samples with measurements from four other Russian cities that had industrial facilities, the TCDD concentrations observed in Chapaevsk exceeded all reported maximums. Revich et al. (2001) presented rudimentary comparisons of cancer incidence and mortality and reproductive outcomes with regional and national rates; residence in the city of Chapaevsk was used as a surrogate for exposure, and no attempt was made to create exposure categories based on factors that might have influenced the degree of TCDD exposure. The analyses of chromosomal aberrations and other cytologic indicators of genetic damage partitioned the women studied into three groups on the basis of worker status or distance of residence from the factory (Revazova et al., 2001).

Chapaevsk Children's Study Later research efforts on Chapaevsk residents have focused on quantifying the serum concentrations of dioxins and TEQs associated with furans and PCBs. Akhmedkhanov et al. (2002) reported on a convenience sample of 24 volunteers. A cohort of 499 peripubertal boys (8–9 years old in 2003–2005) and their mothers has been established as the Russian Children's Study for assessing the effect of in utero and childhood exposure on development. The information generated by this study will be relevant to VAO reports only in conjunction with effects in offspring after maternal exposure to the extent that the consequences of gestational and childhood exposure can be distinguished. To date, however, the published findings have not involved health outcomes but have been limited to detailed characterizations of serum concentrations in the boys (Burns et al., 2009) and their mothers (Humblet et al., 2010).

Swedish Environmental Studies

Prospective Study of the Vasculature in Uppsala Seniors

The Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) study recruited participants, within 2 months after their 70th birthdays, randomly from the registry of residents of the community of Uppsala, Sweden, from April 2001 to June 2004. The primary aim was to investigate CVD in an elderly population with an adjustment for sex. Of the 2,025 subjects who were invited to participate, 1,016 were included, for a participation rate of about 50 percent; 50 percent of the participants were female. All participants answered a questionnaire about

their medical history, medications, diet, and smoking habits. The burden of POPs, including several dioxin-like PCBs, was assessed from blood serum or plasma.

Salihovic et al. (2012a) reported on circulating concentrations of POPs in 992 participants with valid measurements. They found significant sex differences in the concentrations of 17 of 21 POPs; women had higher concentrations of 5 of them. An appropriate adjustment for multiple comparisons (via Holm's method) was applied. Salihovic et al. (2012b) investigated a new method for extracting POPs from human blood in the PIVUS study and found it to be robust.

DH Lee et al. (2011b) reported on the association between POPs and type 2 diabetes in the subjects of the PIVUS study. Of the 1,016 evaluated at baseline, 81 percent returned 5 years later at age 75. The cross-sectional study (baseline) included 989 of these participants, and 725 were in the prospective analysis. The additional value of POPs on top of the standard risk factors was evaluated with the C-statistic and the net reclassification index and the improved discrimination index. The cross-sectional analyses could not account for any measure of duration of exposure. The results are limited by the small number of incident diabetes cases (36), the multiple testing, and the correlation of POPs (and the ensuing difficulty of interpretating the association with diabetes).

Rönn et al. (2011) reported on the association of POPs with fat mass in the PIVUS study. Multiple imputation was used to handle missing dietary assessments. A strength of the study was its use of DXA screening to measure fat. There was considerable multiple testing without adjustment. The findings are limited by the cross-sectional design and the limited age of the participants inasmuch as age could affect the findings in several ways; the published paper could report on only one subset of findings for this age group.

Lee et al. (2012a) reported on the associations of POPs with abdominal obesity in the PIVUS study. Abdominal obesity was treated as a binary variable. The authors note concerns with residual confounding due to diet and physical activity. Furthermore, greater food consumption may lead to obesity and increased concentrations of chemicals. There could be alterations in the pharmacodynamics of POPs because of health disorders, which themselves may influence obesity.

Lee et al. (2012b) reported on the associations of POPS with stroke in the PIVUS study. Only hospital-treated strokes were considered. Ischemic and hemorrhagic strokes were not distinguished. There were 35 incident strokes during the 5 years of follow-up. Sex might be an important effect modifier, but the sample was too small to assess this. The POPs in this study may not be causally related to stroke, but rather may be associated with other, causal POPs. The study was not able to use time of stroke in a survival analysis, which would have been a more powerful analysis.

Lind et al. (2012) reported on the association of POPs with carotid atherosclerosis in the PIVUS study. Ordinal logistic regression was used to model the ordinal outcome of number of involved arteries. A Bonferroni adjustment for multiple testing was applied.

Eight publications from the PIVUS cohort that have appeared since *Update 2012* were identified for review and evaluation. None of these studies examined relationships between POPs and "primary" health outcomes of interest to the VAO committee, but rather they examined "surrogate" health outcomes, including CVD measures and risk factors (left ventricular systolic and diastolic dysfunction, left ventricular hypertrophy, carotid atherosclerosis, weight change, inflammatory markers, complement system, and oxidative stress). These studies augment previous publications from PIVUS that examined a range of indicators related to CVD and cardiovascular health. As with previous analyses from the PIVUS cohort, results are limited by the fact that participants were recruited in the 2-month period after their 70th birthday. This potentially imparts a survival bias, meaning that persons from the catchment area with very high levels of POPs may have been disproportionately excluded from the study sample. In addition, results are limited by the relative non-specificity of the POPs examined, although, the battery of congeners included octachlorodibenzo-*p*-dioxin (OCDD), which is relevant to Vietnam veterans.

Sjoberg et al. (2013a) analyzed circulating levels of POPs in relation to impairments in left ventricular systolic and diastolic function. The left ventricular ejection fraction, E/A-ratio, and isovolumic relaxation time were determined by echocardiography, and 21 POPs were analyzed in serum samples measured by high-resolution chromatography coupled to high-resolution mass spectrometry in 998 subjects from the PIVUS cohort. Results were adjusted for sex, hypertension, diabetes, smoking, hypertrophy, and BMI, and subjects with myocardial infarction or atrial fibrillation were excluded from the analysis. In addition to the limitations described above for the PIVUS cohort, this analysis is limited by its cross-sectional design.

Using a study design that was essentially identical to that in Sjoberg et al. (2013a), Sjoberg et al. (2013b) analyzed circulating levels of POPs in relation to geometric measures of the left ventricle carried out with echocardiography, including the left ventricular mass index, relative wall thickness, and groups of left ventricular hypertrophy. This analysis included 1,016 elderly adults from PIVUS with statistical adjustments for sex, blood pressure, antihypertensive treatment, diabetes, and BMI.

Lind et al. (2012) examined the relationships between circulating levels of POPs and carotid artery plaques and carotid intima-media thickness. This analysis was based on 1,016 elderly adults from PIVUS with statistical adjustment for sex, waist circumference, BMI, fasting blood glucose, systolic and diastolic blood pressure, high-density lipoprotein and low-density lipoprotein (LDL) cholesterol, serum triglycerides, smoking, antihypertensive treatment, and statin use. Estimates included TEQs for two classes of dioxin-like congeners; thus the study is of relevance to Vietnam veterans, taking into account the limitations of PIVUS described above.

In a second paper by Lind et al. (2013), a retrospective classification of the magnitude of weight change between the ages of 20 and 70 (n = 1,016) was examined relative to 16 PCBs congeners and three OC pesticides. A series of linear-regression models were fit to evaluate the relationship between the change in body weight and POP levels, with the full models adjusted for sex, BMI at 20 years of age, serum cholesterol, triglycerides, education, exercise habits, and smoking. The limitations of this analysis include the fact that body weight and height at age 20 were self-reported and potentially imprecise in terms of accuracy and that there was no assessment of dietary intake measured throughout life.

In a third PIVUS paper, circulating levels of PCBs in 1,016 participants were examined in relation to genetic variation in the genes coding for P450 enzymes (Lind et al., 2014). Whereas P450 proteins catalyze reactions involved in drug metabolism and the synthesis of cholesterol, steroids, and other lipids, the direct clinical relevance of this analysis with respect to herbicide exposure and adverse health effects among Vietnam veterans is limited.

Kumar and colleagues published three papers in 2014 that examined relationships between POPs and measures of inflammatory markers, the complement system, and oxidative stress in participants enrolled in PIVUS. In the first paper (Kumar et al., 2014a), TEQ values were calculated using seven mono- and non-ortho-substituted dioxin-like PCBs and OCDD and examined in relationship to eight inflammatory markers, including C-reactive protein (n = 996). The primary analytical method used was multiple linear regression with statistical adjustment for sex, kidney function, smoking, BMI, waist circumference, blood glucose, systolic blood pressure, high-density lipoprotein, low-density lipoprotein, triglycerides, exercise habits, and education.

The second paper by Kumar et al. (2014b) used essentially identical methods as the 2014a paper. The researchers analyzed levels of 16 PCBs and 3 OC pesticides for their association with the levels of protein complement 3 (C3), 3a (C3a), and 4 (C4) and the C3a/C3 ratio (n = 992). The analysis included TEQ values with results derived from multiple linear regression. Whereas the complement system is part of innate immune system that helps to clear pathogens from the body, the direct clinical relevance of this analysis with respect to herbicide exposure and adverse health effects among Vietnam veterans is limited.

In the third paper by Kumar et al. (2014c), which again used very similar methods, 16 PCBs and 5 OC pesticides, including values derived from TEQs, were examined in relation to plasma oxidative stress markers. The full battery of oxidative stress markers included homocysteine, reduced and oxidized glutathione, the glutathione ratio, total glutathione, oxidized LDL, oxidized LDL antibodies, conjugated dienes, baseline conjugated dienes of LDL, and total anti-oxidative capacity. As with the similar papers by Kumar et al. (2014a,b), the direct clinical relevance of these analyses with respect to military service in Vietnam is limited.

Taiwanese Environmental Studies

Taiwan Residents Around Closed PCP Factory

Chang et al. (2010) reported on the relationship between exposure to PCDDs and PCDFs and hypertension in metabolic syndrome in 1,490 non-diabetic Taiwanese who lived near a highly dioxin-contaminated area. This was a cross-sectional study (2005–2007) that accrued subjects from a health center near a deserted PCP factory. The sample consisted of about 80 percent of the invited residents of the community. Univariate analyses of the relationships among several components of metabolic syndrome were conducted, as was a principal component factor analysis, in order to identify a set of uncorrelated factors from among the components of metabolic syndrome. Multiple regression models were fitted for each component. In addition, an analysis of the association between each congener and the prevalence of metabolic syndrome was conducted. The authors list the following limitations of the study: Unknown age at first exposure to PCDDs and PCDFs and an unknown duration of exposure; a cross-sectional design that evaluated the current association; an adjustment for obesity as one element of metabolic syndrome, rather than BMI; and some arbitrary choices inherent in factor analysis. In summary, the large size of this study is a strength, but the unknown age and duration of exposure are clear weaknesses.

Chang et al. (2011a) reported on the same cross-sectional study, restricted to 1,449 non-diabetic residents (the slight decrease in sample size from the 2010 study is due to slightly different starting population sizes and to a difference of 19 diabetic people between the studies). The study aimed to investigate the joint effects of exposure to dioxins and mercury on pancreatic endocrine function. People who lived near the deserted factory were exposed to both PCDDs and PCDFs and also to mercury from eating contaminated seafood from the reservoir near the factory. In their multiple-regression models, the authors did not include PCDDs and PCDFs along with mercury simultaneously but rather included each singly. They reported the correlation of PCDDs and PCDFs with mercury to be 0.14 ($p < 0.001$), which is low, so it is not apparent why they did not fit models that included both simultaneously and perhaps even with an interaction term to assess the magnitude of the contribution of each contaminant. They did, however, fit a model that included all combinations of tertiles of exposure to each. Again, a major limitation of this study is the absence of information on the onset and duration of exposure. Furthermore, the authors note that the homeostasis model for insulin-resistance assessment is not the gold standard and that repeated testing may be needed for assessment in older people. The study did not address co-contamination with mercury.

Chang et al. (2011b) reported on the same cross-sectional study with enrollment extended to December 2009 and restricted to 914 residents who did not have CVD and who were 30–45 years old. The study aimed to investigate the

association between PCDD and PCDF exposure and continuous measures of CVD within 10 years as measured by the Framingham risk score, a formula for combining established risk factors into a single number. Mercury concentrations were not adjusted for in the models, although seafood consumption was. One limitation is the use of the Framingham score; other factors are associated with risk but were not included in the score (such as socioeconomic position, genetics, and imaging biomarkers). As in all the publications on this cohort, this one is limited by the lack of information about the onset and duration of exposure.

Chang et al. (2012) reported on the same cross-sectional study during 2006–2009 with enrollment restricted to 1,167 residents who had fasted before blood sampling and who were more than 50 years old. The study aimed to investigate the biochemical profiles of those exposed to PCDDs and PCDFs. Na-PCP, a widely used pesticide, had been used in the production process at the abandoned factory. After the factory shut down, a large quantity was improperly stored and later released into the environment. Some of the retired workers moved away from the area and were not exposed by eating seafood, whereas others remained and were exposed, alongside other local residents. Thus, there were three exposure groups of retired Na-PCP workers: those who still lived locally (23), those who lived locally but did not knowingly eat polluted fish (37), and those who moved away (96). Three control groups did not include any Na-PCP workers: Local residents who had eaten polluted fish (345), local residents who had not eaten polluted fish (666), and "background participants" in Taiwan's general population (645). The first two of the control groups made up the 1,167 in the study population. Limitations of the study include the unknown PCDD and PCDF concentrations in retired workers who moved away and knowledge about when the exposure ceased. There may be important unmeasured confounders related to which workers moved away and which ones did not.

US Environmental Studies

Anniston, Alabama, Community Health Survey

In 2003 the Agency for Toxic Substances and Disease Registry (ATSDR) funded a study of the health effects of environmental exposures on the residents of Anniston, Alabama. Anniston housed a plant that produced PCBs from 1929 to 1971; it had been owned and operated by Monsanto since 1935. Residents of Anniston were known to have high concentrations of PCBs although these have not been found to be associated with employment in the plant or with the consumption of local fish and produce. PCBs spread in Anniston via air, soil, and water movement. Before the ATSDR study, there had been minimal research into the health effects of PCBs on Anniston residents. Residents were recruited into the study through a stratified random sampling of housing units across the city, weighted by proximity to the plant and by race. Of the 1,110 who agreed

to be interviewed, 772 had blood drawn for biochemical and PCB analyses and had blood pressure measured. Of the 758 subjects who provided sufficient data to be retained in the study, 364 were taking antihypertensive medications and 394 were not.

Two methods were considered for PCB analysis: Wet-weight values and lipid-standardized values. The latter are thought to be more prone to bias, but both were considered. The two approaches make comparisons between the studies difficult. Another issue was the problem of PCB values that were below the level of detection (LOD). These variables amounted to left-censored covariates in a regression model. They were dealt with by a crude imputation of the LOD divided by the square root of 2 (Goncharov et al., 2010; Silverstone et al., 2012) or by 2 (Goncharov et al., 2011). This is highly biased, and alternative methods (such as multiple imputation) would have been preferable. It may also be a problem that the studies took different approaches.

Goncharov et al. (2010) studied the association between all PCBs and blood pressure. After adjusting for age there was a significant association between PCB concentrations and the risk of hypertension. When people on antihypertensive medications were included in the models, the associations between PCB concentrations and risk of hypertension were diluted; this could be due to an effect of the medications on PCB metabolism.

Goncharov et al. (2011) extended the 2010 report by considering the effect of PCBs on the entire range of continuous blood pressure and by investigating five PCB groups and 33 individual PCB cogeners. Only the 394 people who were not on antihypertensive medications were included in this study. The study found that serum PCB concentration is associated with blood pressure even in the normotensive range. Furthermore, the relationship is found to be strongest for ortho-substituted PCB congeners that have two or more chlorines and with some that have some dioxin-like activity. The overall concentrations of PCB's are higher in the Anniston population than in the US population overall.

Silverstone et al. (2012) examined the association between PCB exposure and diabetes in the Anniston study. Diabetes was present in 27 percent of 774 participants; 75 percent of the 27 were taking glycemic control medications. People who had pre-diabetes were identified and were excluded from some regression analyses because they were intermediate between the diabetic and normoglycemic groups. There was a non-monotonic increase in the prevalence of diabetes with high PCB congener concentrations, but some of the groups (for example, by age) were small. Women had a consistently higher likelihood of diabetes in each subset of PCBs (except the estrogenic subset). The findings suggest a low-dose PCB effect inasmuch as the ORs increased in the second quintile of PCB exposure and remained high. Advantages of this study are its adjustment for family history of diabetes and exclusion of people who had prediabetes. Lipid metabolism in people who have diabetes may affect the metabolism of PCBs.

Coronary Artery Risk Development in Young Adults Study

DH Lee et al. (2010) reported on the association between low-dose POPs and type 2 diabetes in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. Serum samples were collected at year 2 (1987–1988) and were later used to measure POPs. This was a nested case-control study in which subjects were required to be free of diabetes at years 0 and 2. From 1988 to 2006, 116 received a diagnosis of diabetes; 90 were randomly selected as cases. Controls were randomly selected from those who had not received a diagnosis of diabetes. Cases and controls were frequency-matched on BMI strata. The authors analyzed summary measures of POPs. The second summary measure selected POPs on the basis of their effect in the current study; this invalidates standard inference. The authors asserted that summary measures are useful because appropriate controls are those with globally low concentrations of POPs. Other limitations are the single measure of POPs and the age of the samples at analysis (18 years). The authors stated that the study was underpowered and that extensive statistical testing was performed.

DH Lee et al. (2011a) further investigated the 90 controls selected for the nested case-control study reported in DH Lee et al. (2010). This investigation is concerned with associations between exposure to POPs and obesity, dyslipidemia, and insulin resistance in people who are free of diabetes. The multiple comparisons are of concern, as is the small sample size.

Great Lakes Fish Consumption Study

The Great Lakes Fish Consumption Study was initiated in early 1992. Bloom et al. (2006) measured serum dioxin in New York sport fishermen as part of a study of thyroid function. A methodologic study by Petreas et al. (2004) found generally high correlations between concentrations of dioxins and related chemicals in breast and abdominal fat in the same woman; this suggested that they could be used interchangeably in epidemiologic studies. The same study, however, also found that adjusting concentrations according to lipid content rather than the weight of the fat samples is important because of the presence of nonlipid components in the samples.

In 2001–2005, 1,788 of the 4,200 people who had participated in the original study were contacted and asked for updated information on health, reproductive history, and fish consumption. Blood samples gathered from 515 of them were analyzed for the serum concentrations of various POPs, including a number of PCBs. Turyk et al. (2009) investigated whether the serum results were related to self-reported diabetes. Lambertino et al. (2011) studied the self-reported occurrences of uterine leiomyomas (benign fibroid tumors) in 580 women using the serum results from the 197 women who had provided blood samples. The exposure measure for the category "dioxin-like PCBs" consisted of the summed

concentrations of only the mono-ortho PCBs 118 and 167. Because the results were based solely on mono-ortho PCBs, which typically contribute only a small percentage to total TEQs, the findings of these publications cannot be considered conclusive.

Iowa Women's Health Study

Jones et al. (2014) analyzed data from a cohort of 37,099 Iowa women aged 55–69 years who reported their residence location (farm, rural [not a farm], population of their town) at enrollment in 1986. Incident lymphohematopoietic cancers were identified in the period 1986–2009 by linkage with the Iowa Cancer Registry. A geographic information system was used to geocode addresses and to calculate the total acreage of pasture and row crops within 750 m of homes using the 1992 National Land Cover Database. The purpose of this analysis was to estimate the cancer risk in relation to both residence location and crop acreage. This analysis was deemed to be of no value to the committee because exposure assessment was based on attributes of residence related to farming and not on specific pesticides with dioxin-like properties.

National Health and Nutrition Examination Survey

In the early 1960s, the CDC National Center for Health Statistics began the NHANES program as a means of monitoring and assessing the health and nutritional status of people of all ages living in the United States. In 1999, the survey became a continuous program that has a changing focus on a variety of health and nutrition measurements in order to meet emerging needs. A rich variety of data—demographic and socioeconomic data; dietary information; medical, dental, and physiologic assessments; and the serum concentrations of POPs, including specific congeners of dioxins, furans, and PCBs—are collected through in-person interviews, health examinations, and blood samples obtained from a nationally representative sample of adults and children in the noninstitutionalized US population. Information obtained from NHANES data is used to determine prevalences of diseases, to assess nutritional status, and to establish national standards of height, weight, and blood pressure. Researchers also conduct analyses of the NHANES data for epidemiologic studies and health-science research on serum concentrations of various compounds in association with various health outcomes.

Starting with the preparation of *Update 2008*, VAO committees began seeing a stream of publications addressing possible association of some pesticides and various individual and grouped dioxin-like chemicals with the occurrence of a variety of health outcomes as assessed by the surveys for particular temporal spans. NHANES data from 1999 to 2002 were used to evaluate relationships of the COIs with CVD (Ha et al., 2007); diabetes, the metabolic

syndrome, insulin resistance, and arthritis (Lee DH et al., 2006, 2007a,b,c); and thyroid-hormone concentrations (Turyk et al., 2007). Everett et al. (2008a) address hypertension over this time period and provided additional information for the years 2003–2004 in a subsequent commentary (Everett et al., 2008b)

Lee et al. (2008) examined the associations between serum concentrations of POPs and the prevalence of peripheral neuropathy and poor glycemic control (A1C ≥ 7.0 percent) in NHANES 1999–2002 participants who were at least 40 years old and had diabetes or impaired fasting glucose. Peripheral neuropathy was ascertained on the basis of one or more insensate sites on the foot. Diabetes was ascertained on the basis of high plasma glucose (≥ 126 mg/dL fasting or ≥ 200 mg/dL nonfasting) or on the basis of whether a person is taking insulin or an oral anti-diabetes agent. Although 49 POPs were measured, analysis was restricted to 25, of which at least 60 percent of the study participants had detectable concentrations: three PCDDs, four PCDFs, five dioxin-like PCBs, seven non–dioxin-like PCBs, and six OC pesticides. Logistic regression was used to determine the OR between each outcome (peripheral neuropathy or poor glycemic control) and each exposure to POP subclass with adjustment for age, sex, race or ethnicity, poverty, duration of diabetes, hypertension (yes or no), BMI, cigarette smoking (never, former, or current), cotinine concentration, alcohol consumption, leisure-time physical activity (vigorous, moderate, or none), and A1C (neuropathy only). For each POP subclass, a cumulative measure was derived by summing the rank scores among individual chemicals that belonged to the subclass; the cumulative measure was then categorized into tertiles. Additional analyses were conducted for individual compounds by using the correlation coefficient between the rank score for each chemical and each outcome with adjustment for the same covariates listed above.

Ha et al. (2009) examined the association between serum concentrations of POPs and the prevalence of newly diagnosed hypertension in NHANES 1999–2002 adult participants 40 years old or older. After the exclusion of 444 patients known to be hypertensive irrespective of antihypertensive medication, 165 diabetic patients, and 49 subjects whose blood-pressure values were missing, the final sample size was 524. Participants were considered to have hypertension if their systolic blood pressure was 140 mmHg or higher or if their diastolic blood pressure was 90 mmHg or higher. The analysis was restricted to 21 POPs of which at least 60 percent of study participants had detectable concentrations: Three PCDDs, three PCDFs, five dioxin-like PCBs, six non–dioxin-like PCBs, and four OC pesticides. The discrepancy from Lee et al. (2008) in the number of POPs detected is probably due to the difference in the samples used. For each POP, participants whose serum concentrations were below the limit of detection were regarded as the reference group; participants who had detectable concentrations were categorized into quartiles. A cumulative measure for each POP subclass was derived by summing the category numbers (0 for nondetectable, 1 for

detectable below the first quartile, and so on up to 4 for above the third quartile) of individual chemicals belonging to the subclass. The summary values were again categorized into quartiles. Logistic regression was used to derive adjusted ORs, which were stratified by sex and adjusted for age, race or ethnicity, poverty-income ratio, BMI, cigarette smoking (never, former, or current), cotinine, alcohol consumption, and leisure-time physical activity (vigorous, moderate, or none).

Cho et al. (2011) reported on the associations between bone mineral density (BMD) and exposures to POPs, including OC pesticides, assessed from serum samples from NHANES participants in 1999–2004 (2,769 for OC pesticide analyses and 2,565 for POP analyses). The study also examined whether the POP levels modified the association between BMD and fat mass or lean mass. All analyses were stratified by sex and age group (cutoff 50 years). General linear models were used to derive means that were adjusted for age, race or ethnicity, poverty-income ratio, fat mass, lean mass, height, smoking, physical activity, and postmenopausal hormone intake.

Elobeid et al. (2010) examined the association between POPs and obesity—BMI and waist circumference (WC)—in NHANES 1999–2002 participants (2,464 for BMI analysis and 2,448 for WC). Regression models were used to assess the association between the obesity measures and POPs, adjusted for sex, ethnicity, age, and age squared. An additional model for WC also adjusts for BMI.

Jones et al. (2011) examined the association between urinary arsenic and hypertension and blood pressure in NHANES 2003–2008 participants (4,167). Logistic-regression and linear-regression models were used for hypertension and blood pressure, respectively, adjusted for age, sex, race or ethnicity, urinary creatinine, education, BMI, and serum cotinine; models for blood pressure also adjusted for antihypertensive medication. All analyses accounted for the complex sample design of NHANES.

Since *Update 2012*, there have been several more publications based on NHANES data concerning the COIs and various health outcomes. Specifically, Lin et al. (2012) examined samples for measurement of dioxin-like chemicals from the 1999–2004 NHANES in relation to total and cause-specific (cardiovascular, cancer) mortality based on the ICD-10 system, and follow-up through 2006. The analysis was restricted to non-Hispanic whites, non-Hispanic blacks, and Mexican-American participants aged 40 years or older who provided samples for the measurement of dioxin-like chemicals. The analysis included a sample of 1,176 males and 1,185 females. The estimation of potential toxicity from exposure to dioxin-like chemicals, including PCDDs, PCDFs, and PCBs, was based on TEQs. Analyses were adjusted for age, gender, BMI, race or ethnicity, cigarette smoking, and alcohol consumption. The strengths of this study include its biological measurement of exposure to dioxin-like chemicals and the prospective assessment of mortality, which is generally believed to be reliable and accurate within NHANES.

Lee et al. (2013) evaluated associations between OC pesticides (n = 1,299) as well as PCDDs, PCDFs, and PCBs (n = 1,299) and the risk of hyperuricemia in subjects 20 years of age and older in the 2003–2004 NHANES. TEFs were calculated for dioxins and dioxin-like compounds. Hyperuricemia was defined as a blood uric acid concentration greater than 7.0 mg/dL in men and 6.0 mg/dL in women. Analyses were performed among all subjects and separately among subjects without the presence of the metabolic syndrome. The analyses were adjusted for age, race, ethnicity, and poverty income ratio. A strength of this study is the use of biological measurement of TEFs for dioxins and dioxin-like compounds. Limitations include the cross-sectional design, which does not permit the assessment of temporal effects, and the fact that hyperuricemia is a measure of disturbed metabolism, but not one of the primary health outcomes of interest specified by the committee with respect to service in Vietnam.

Everett and Thompson (2014) examined the relationship between dioxins (including TCDD) and dl-PCBs and the prevalence of diabetic nephropathy using blood samples and self-report data collected from the 1999–2004 NHANES (n = 2,588). TEQs were calculated for six different dioxins and eight dl-PCBs and analyses were stratified by subjects with and without nephropathy. Analyses were adjusted for a range of covariates including age, gender, race, ethnicity, education, poverty income ratio, fruit and vegetable consumption, physical activity, and family history of diabetes. The strengths of this study include the use of biological measurement of TEFs, including for TCDD, and the objective assessment of nephropathy by the use of urinary albumin-to-creatinine ratio. Limitations include the cross-sectional study design, and most notably, the fact that the analyses did not include a comparison group of subjects without diabetes. Thus, the analysis can only be suggestive of whether or not dioxins and dioxin-like compounds may be associated with nephropathy in the presence of diabetes, but not the development of diabetes.

Peters et al. (2014) added NHANES data for 2005–2008 to the sets for 1999–2002 and 2003–2004 previously analyzed by Everett et al. (2008a,b) for association of blood pressure with blood concentrations of dioxin-like PCBs 126 and 169 and mono-ortho PCBs 118 and 156. Using this expanded data set, they developed a model to predict blood PCB concentrations using generally available variables (age, sex, ethnicity, and blood lipid levels) as a step toward producing a structural equations model involving lead and cadmium blood levels, in addition to PCB blood concentrations for the prediction blood pressure. The PCBs metric used for this modeling effort was the total blood concentration by weight of PCBs 66, 101, 118, 128, and 187. Because this measure of PCB exposure includes only a single mono-ortho dioxin-like PCB in combination with PBC having no dioxin-like activity, this work does not augment the results previously published by Everett et al. (2008a,b) for VAO purposes.

The study population for the Priority Toxicant Reference Range Study was a subgroup of participants aged 20–59 years in NHANES III (1988–1994) established

to characterize levels of 44 environmental toxicants (including 2,4-D and its metabolite 2,4-dichlorophenol [2,4-DCP]) in urine and blood, which can be regarded as indicators of internal dose. Unlike overall NHANES samples established by rigorous statistical sampling procedures to be representative samples of the US population, this study sample is regarded as a convenient sample, because its 1,338 members had voluntarily provided an additional 20 ml of blood and had responded to an extra questionnaire during their regular NHANES medical examination.

Schreinemachers (2010) examined the association in healthy adults between exposure to 2,4-D, as indicated by its presence in urine, and biomarkers that are linked to the pathogenesis of acute myocardial infarction and type 2 diabetes, namely, serum HDL, triglycerides, total cholesterol minus HDL, insulin, C-peptide, plasma glucose, and thyroid-stimulating hormone. A sample of 727 people remained in the study after exclusion of 375 individuals without results for measurement of urinary 2,4-D and 236 more on the basis of health criteria: A history of congestive heart failure, heart attack, diabetes, thyroid disease, lupus, or cancer; a white blood cell count over 12×10^9 per liter CRP over 10 mg/dL; or glycosylated hemoglobin (HbA1c) over 8 percent. Urinary 2,4-D was detectable in 102 (14 percent), with concentrations of 1–28 mg/dL. The outcome variables were compared between participants with and without detectable urinary 2,4-D by using Wilcoxon's rank-sum test. Further analysis was conducted with linear regression, and the outcome variables were transformed to a logarithmic scale. The linear-regression models included the following explanatory variables: 2,4-D (binary), HDL (continuous, log-transformed, and included in all models except when HDL itself was the dependent variable), urinary creatinine (continuous and log-transformed), sex, age, BMI, race or ethnicity, and smoking (none, past, and active). Alcohol consumption, education, household income, and hours of fasting before a blood sample was drawn were also checked for their effects on the regression coefficient for urinary 2,4-D. The analyses were conducted on the final study sample of 727 and on two subsamples that were expected to be more susceptible: Participants who had HbA1c above the median (5.1 percent) of the total sample and participants who had thyroxine at or below the median (8.5 µg/dL) of the total sample.

Krieg (2013) performed a limited assessment of cognition in 700 adults. Twelve pesticide metabolites were measured in the urine, including two chemicals found in the urine after 2,4-D exposure: Unmetabolized 2,4-D and 2,4-DCP (Sauerhoff et al., 1977). The analysis investigated association of their concentrations with the results of three neurobehavioral tests (simple reaction time, symbol-digit substitution, and serial digit learning).

Pensacola, Florida

Karouna-Renier et al. (2007) examined health effects related to dioxins and furans in soil at a Superfund site in Pensacola, Florida, that was contaminated by

operations at a wood-treating company that operated from 1942 to 1982. In 2001 the study collected health and exposure histories and measured serum concentrations of 17 PCDD and PCDF congeners in 47 potentially exposed people who were selected nonsystematically from among former workers, their families, and residents. Logistic regression was used to predict the prevalence of health outcomes from TEQs with adjustments for age, race, sex, BMI, tobacco and alcohol use, and worker status.

Times Beach and Quail Run Cohorts

Several reports have provided information on environmental exposure to TCDD in the Times Beach area of Missouri (Andrews et al., 1989; Patterson et al., 1986), one of the incidents that heightened concerns about the health effects of dioxin. In 1971, TCDD-contaminated sludge from a hexachlorophene-production facility was mixed with waste oil and sprayed in various areas for dust control. Soil contamination in some samples exceeded 100 ppb. Among the Missouri sites with the highest soil TCDD concentrations was the Quail Run mobile-home park. Residents were considered exposed if they had lived in the park for at least 6 months during the time when contamination occurred (Hoffman et al., 1986).

Of 51 exposed participants, 87 percent had adipose-tissue TCDD concentrations below 200 ppt; however, the TCDD concentrations in 7 of the 51 were 250–750 ppt. In 128 non-exposed control participants, adipose-tissue TCDD ranged from undetectable to 20 ppt (median, 6 ppt). On the basis of a 7-year half-life, it is calculated that two study participants would have had adipose-tissue TCDD near 3,000 ppt at the time of their last exposure (Andrews et al., 1989).

Several studies evaluated health effects potentially attributable to exposure (Evans et al., 1988; Hoffman et al., 1986; Stehr et al., 1986; Stehr-Green et al., 1987; Stockbauer et al., 1988; Webb et al., 1987). Those studies were reviewed in *VAO*; no further work on the cohorts has been published.

Vietnamese Environmental Studies

Various epidemiologic studies have been conducted in the Vietnamese population exposed to the spraying that occurred during the Vietnam War. In a review paper, Constable and Hatch (1985) summarized the unpublished results of studies conducted by researchers in Vietnam. They also examined nine reports that focused primarily on reproductive outcomes (Can et al., 1983a,b; Huong and Phuong, 1983; Khoa, 1983; Lang et al., 1983a,b; Nguyen, 1983; Phuong and Huong, 1983; Trung and Chien, 1983). Vietnamese researchers later published the results of four additional studies: two on reproductive abnormalities (Phuong et al., 1989a,b), one on mortality (Dai et al., 1990), and one on hepatocellular carcinoma (Cordier et al., 1993). Ngo et al. (2006) published a meta-analysis that

addressed an association between exposure to herbicides in Vietnam and birth defects and covered some reports reviewed previously by Constable and Hatch (1985), some new Vietnam studies, and studies on US and Australian veterans who served in Vietnam.

The committee has been interested in assessments of contaminant concentrations in Vietnam attributable to the storage, distribution, and spraying of herbicides by the US military during the Vietnam War, but no studies have as yet explored associations between the measured concentrations and health outcomes.

Dioxins and PCBs were among the OC chemicals measured by Schecter et al. (2003) in food samples gathered in 2002 around Bien Hoa City, Vietnam, about 32 km north of Ho Chi Minh City (formerly Saigon). Bien Hoa City is known as a dioxin "hot spot," with a substantial leak of more than 5,000 gal of Agent Orange at the nearby Bien Hoa airbase about 30 years before the study. Marked increases in TCDD concentrations and TEQs were found in ducks, chickens, and fish, but not in pork or beef. The study concluded that food appeared to be responsible for the increase in TCDD in residents of Bien Hoa City even though the original Agent Orange contamination occurred 30 to 40 years before sampling.

Hansen et al. (2009) studied maternal serum concentrations of OC chemicals (including dioxin-like PCBs 118, 126, 156, and 169) at the time of delivery in women from two communities in southern Vietnam: Nha Trang, a coastal city about 450 km northeast of Ho Chi Minh City, and Dien Khanh, a rural district about 10 km inland from Nha Trang. Of 246 women who delivered infants in May–July 2005, 94 in Nha Trang and 95 in Dien Khanh met the study's residence requirements, agreed to participate, and provided blood specimens. Mean concentrations of the ordinarily prevalent non–dioxin-like PCB 153 were 0.15 µg/L in Nha Trang and 0.10 µg/L in Dien Khanh; other PCB congeners were low in both communities. Age and parity were the most important predictors of plasma concentrations of all chemicals, whereas the community of residence was also predictive for PCB 153. Correlations with the health status of mothers or children were not reported.

Nhu et al. (2009) examined the correlations among dioxin concentrations in soil, sediment, and breast milk in an area in Vietnam that had been sprayed with herbicide during the war, Cam Chinh commune in Quang Tri province, and a control site that was not sprayed, Cam Phuc commune in Ha Tinh province. Soil and sediment samples were taken randomly throughout Cam Chinh commune and analyzed for PCDDs and PCDFs. The spatial distribution of PCDDs and PCDFs was estimated by using log-normal kriging (Saito and Goovaerts, 2000). Breast-milk samples were taken from lactating mothers 20–40 years old who lived in two communes (86 in Cam Chinh commune and 71 in Cam Phuc commune) in September 2002–July 2003. The participants were also interviewed to collect information on personal habits, such as smoking, alcohol drinking, contraceptive-drug use, history of pesticide contact, disease history,

number of pregnancies, age at each pregnancy, and reason for pregnancy failure, if applicable. The mean dioxin concentrations in soil and breast milk in the sprayed area were significantly higher than those in the unsprayed area. There were no significant correlations between the estimated dioxin concentrations in soil obtained with the kriging method and those in breast milk. Again, no results were presented with respect to the health status of mothers or infants.

Since *Update 2012*, three relevant environmental papers from Vietnam residents were identified for review. Tai et al. (2013) studied 216 mother–infant pairs living near the Da Nang airbase, a dioxin-contaminated area in Vietnam, and relationships between the dioxin levels in breast milk and infant neurodevelopment parameters at 4 months of age. Breast-milk samples were collected from each nursing mother 1 month after giving birth in order to quantify the levels of 17 different 2,3,7,8-substituted PCDD and PCDF congeners. TEQs were calculated, including for TCDD. A neurodevelopment assessment at 4 months was based on the Bayley Scales of Infant and Toddler Development. Generalized linear models were used to compare neurodevelopment parameters across four groups of dioxin exposure: Low, mild, moderate, and high. Whereas the results of this analysis are limited by inference to childbearing female Vietnam veterans, the strengths of this study include objective measurement of dioxin contamination in a known contaminated area and use of the well-validated Bayley Scales of Infant and Toddler Development.

Sun et al. (2013) compared prostate-specific antigen (PSA) levels (2009–2011) in a cross-sectional study in men over the age of 50 years between those residing in the Phu Cat district (a presumed contamination hot spot, n = 101) and those residing in the Kim Bang district (presumed non-sprayed, n = 97). Analyses were adjusted for age and included stratification by occupation, including farmers and other non-farm occupations. Results of this study are limited by its cross-sectional design and, in particular, the relatively crude measurement of exposure assessment many years after the time when herbicide spraying would have occurred.

In a second paper by Sun et al. (2014) with similar methodology to Sun et al. (2013), serum dioxin and steroid hormone levels were compared between 48 men in the presumed hotspot area (Phu Cat district) and 36 men in the non-sprayed area (Kim Bang district). Five dioxin congeners expressed as TEQs were calculated along with nine serum steroid hormones, including testosterone, cortisol, estradiol, and others. Multiple linear-regression analyses were conducted with statistical adjustment for age, BMI, employment status, and tobacco use. The limitations of this analysis include the cross-sectional design with exposure assessment occurring many years after presumed herbicide exposure.

Other Environmental Studies

A number of additional outcomes of environmental exposure to the COIs were studied: NHL in Yorkshire, England (Cartwright et al., 1988); adverse health effects after an electric-transformer fire in Binghamton, New York (Fitzgerald et al., 1989); lymphomas and STSs in Italy (Vineis et al., 1991); cancers in Finland (Lampi et al., 1992); early-onset PD in Oregon and Washington (Butterfield et al., 1993); neuropsychologic effects in Germany (Peper et al., 1993); mortality and cancer incidence in two cohorts of Swedish fishermen whose primary exposure route was assumed to be diet (Svensson et al., 1995a); the immunologic effects of prenatal and postnatal exposure to PCB or TCDD in Dutch infants from birth to the age of 18 months (Weisglas-Kuperus et al., 1995); the effects of inhalation exposure to TCDD and related chemicals in wood preservatives on cell-mediated immunity in German daycare center employees (Wolf and Karmaus, 1995); skin cancers in Alberta, Canada (Gallagher et al., 1996); immunologic effects in hobby fishermen in the Frierfjord in southeastern Norway (Lovik et al., 1996); HL, NHL, multiple myeloma, and acute myeloid leukemia in various regions of Italy (Masala et al., 1996); NHL, HL, and chronic lymphocytic leukemia in a rural Michigan community (Waterhouse et al., 1996); cancer mortality in four northern wheat-producing US states (Schreinemachers, 2000); mortality and incinerator dioxin emissions in municipalities in Japan (Fukuda et al., 2003); the prevalence of hypertension in Taiwanese who lived near MSWIs (Chen HL et al., 2006); and adverse pregnancy outcomes in Japan on the basis of maternal residence at the time of birth (Tango et al., 2004).

Combustion records in the Zeeburg area of Amsterdam in the Netherlands were used as a surrogate for exposure to dioxins in a study of orofacial clefts (ten Tusscher et al., 2000). The location downwind or upwind of an incineration source was used to define exposed and reference groups for the study. A study of STS in the general population was conducted around the city of Mantua in northern Italy (Costani et al., 2000). Several industrial facilities are in Mantua, and residential proximity to them was presumed to result in increased TCDD exposure, but TCDD was not measured in the environment or in human tissues.

A study of dioxin exposure pathways in Belgium focused on the long-time residents of an area in the vicinity of two MSWIs (Fierens et al., 2003a). Residents near a rural incinerator had significantly higher serum dioxin concentrations than a control group (38 versus 24 TEQ pg/g of lipid). The concentrations in people who lived near the incinerators increased proportionally with intake of local-animal fat. A second study (Fierens et al., 2003b) measured the dioxin body burden in 257 people who had been environmentally exposed in order to determine whether dioxin and PCB exposures were associated with type 2 diabetes and endometriosis. No difference in body burden was found between women who had endometriosis and women in a control group, but the risk of type 2 diabetes was significantly higher in those who had higher body burdens of dioxin-like

chemicals and of PCBs. Another study of the correlation between dioxin-like chemicals in Italian and Belgian women and the risk of endometriosis used measurements of TCDD and other dioxins in blood (De Felip et al., 2004). There was no difference in the body burden between women who had endometriosis and a control group, but the serum dioxin concentrations were substantially higher in the Belgian controls than in a similar group in Italy (45 versus 18 TEQ pg/g of lipid, respectively).

Birth Cohorts

Center for the Health Assessment of Mothers and Children of Salinas Cohort Castorina et al. (2010) compared the metabolites of current-use pesticides and other precursor compounds in 538 women in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort with those in 342 pregnant women in NHANES 1999–2002. CHAMACOS (Eskenazi et al., 2003b) is a longitudinal birth-cohort study investigating the effect of in utero and postnatal environmental exposures on the health of children who live in the Salinas Valley of Monterey County, California. The study enrolled 601 pregnant women from September 1999 to November 2000 in six prenatal clinics in the largely agricultural Salinas area. Women were eligible if they were no more than 20 weeks into gestation, were at least 18 years old, were qualified to receive poverty-based government health insurance, and planned to continue receiving prenatal care in a participating clinic. Personal interviews were conducted during which information on the demographics, household characteristics, health, and occupations of CHAMACOS participants was collected. Two interviews were conducted shortly after enrollment (mean, 13 weeks of gestation; standard deviation (SD), 5.2 weeks) and later in the second trimester (mean, 26 weeks of gestation; SD, 2.6 weeks) by bilingual (English and Spanish), bicultural study staff. At each prenatal interview, spot urine samples were collected from the CHAMACOS participants and analyzed for metabolites, including organophosphorus, OC chemicals, pyrethroid pesticides, herbicides, and ethylene bisdithiocarbamate fungicides. Adequate urine samples with valid creatinine concentrations were collected from 538 (90 percent) of the 601 participants at the first sampling point and 481 (80 percent) at the second. In addition, pesticide-use data were extracted from the California pesticide use reporting data set and geocoded into square-mile units. NHANES reported concentrations of current-use pesticide metabolites measured in spot urine collected from representative samples of the US population stratified by age, sex, and racial or ethnic group (Barr et al., 2005; CDC, 2004a). The NHANES comparison group consisted of 342 pregnant women 15–50 years old, a subset of the 3,048 US residents 6–59 years old who had metabolite concentrations measured in urine samples during NHANES testing in 1999 and 2002. The public-release versions of the NHANES data sets, including demographic information and metabolite data, were used for the analyses. No sample weights

were applied to the NHANES data. Descriptive analyses were conducted on the CHAMACOS and NHANES cohorts. Metabolite concentrations were compared between the two cohorts with a Wilcoxon rank-sum test and quantile regression at the 95th percentile adjusted for demographic variables, including age, current smoking (yes or no), ethnicity, and socioeconomic status. An analysis of variance was used to compare differences in detection frequency.

Duisburg Birth Cohort Study

Winneke et al. (2014) examined the relationship between early developmental exposure to dioxins and PCBs and behavioral sexual dimorphism, meaning the expression of feminine versus masculine traits. This analysis was based on the Duisburg birth cohort study and included 232 women who had no serious complications or illnesses during pregnancy or parturition and who gave birth to a child who was born at term (weeks 38–42 of pregnancy). TEQ measures were obtained from maternal blood samples taken during weeks 28–43 of gestation and from maternal milk collected from nursing mothers during the first 3 weeks after parturition. Blood samples were analyzed for PCDD/Fs and PCBs in relation to sexually dimorphic behavior, as reported by parents through completion of the Pre-School Activities Inventory. This analysis provides insight into potential endocrine-disrupting effects of prenatal environmental exposure to dioxins and PCBs in the children of female Vietnam veterans, but the relevance of behavioral sexual dimorphism as a "health" outcome of interest is unclear.

Newborns and Genotoxic Exposure Risks (NewGeneris) Cohort

The Newborns and Genotoxic Exposure Risks (NewGeneris) project (Papadopoulou et al., 2014; Vafeiadi et al., 2014) is a prospective, population-based effort that combines information on 1,151 mother–child dyads from existing European birth cohorts:

- RHEA mother–child cohort of pregnancies gathered in Heraklion, Crete, Greece, from February 2007 to February 2008.
- INMA [Infancia y Medio Ambiente (Environment and Childhood)] mother–child cohort of singleton pregnancies from Sabadell and Barcelona, Spain, from May 2007 to March 2010.
- Norwegian Mother and Child (MoBa) cohort of full-term singleton pregnancies in Oslo and Akershus, Norway, from 2007 to 2008 (only 2 years of Norwegian effort beginning in 2002).
- Danish mother–child cohort of singleton pregnancies gathered in Copenhagen, Denmark, from December 2006 to December 2007 and from September to December 2009.

- BiB (Born in Bradford) mother–child cohort of elective Caesarian sections in Bradford, United Kingdom, from January 2008–May 2009.

For many of these dyads, information about maternal diet during pregnancy and measurements of dioxin-like chemicals in maternal serum, cord blood, and breast milk were available. Standardized food frequency questionnaires were used to estimate the amount of particular food items consumed, which were in turn combined with local estimates of item-specific dioxin, furan, and PCB concentrations to derive TEQs associated with the maternal diet. Although considerable effort has been taken to validate this approach to estimating dietary intake, for the purposes of assessing association with birth outcomes, direct measurement in the biological fluids would be a more accurate characterization of the infants' actual exposure and thus would be considered a preferable metric. Since *Update 2012*, several new papers have been identified that examined relationships between dioxins and dioxin-like compounds and birth outcomes in the NewGeneris cohort or its component subcohorts.

Anogenital distance, long used as a marker of androgen function in toxicology studies, has now been adopted in epidemiology studies as a means to assess the effects of exposures that may affect hormonally related outcomes. Papadopoulou et al. (2013b) addressed anogenital distance in 231 newborns in the Greek and Spanish subcohorts and in 476 Greek children at 1–2 years of age in light of their mothers' diets during pregnancy. To estimate gestational exposure to OC contaminants, a fat-in-diet score between 0 and 11 was derived based on the mother's self-reported frequency of consuming red meat, processed meat, fatty fish, other seafood, eggs, and high-fat dairy products. As might be expected considering the lipophilicity of these dioxin-like chemicals, the fat-in-diet scores were found to be correlated with dioxin-like activity as measured by CALUX in blood samples from 121 of the mothers. The mothers' fat-in-diet scores were regressed against anogenital distance separately by infant sex and whether the mother consumed seafood, with adjustment for the infant's birth weight and for maternal ethnicity, age, and smoking. Here again, however, direct use of the results from maternal blood samples as done by Vafeiadi et al. (2013), would be regarded as a more meaningful approach to assessing association.

Vafeiadi et al. (2013) used dioxin-like activity measured by CALUX assays in maternal blood samples collected at the time of delivery and anogenital distance. Included in the analyses were 237 newborns (119 boys and 118 girls) and 462 children aged 1–31 months (239 boys and 223 girls) each with anogenital distance measured in three ways. Regression analyses in terms of 10 pg CALUX-TEQ/g lipid with adjustment for an infant's birth weight and gestational age at birth or child's weight and age at time of examination, plus maternal ethnicity and education, were conducted separately by gender and age group

Papadopoulou et al. (2014) considered the entire NewGeneris cohort when investigating the relationship between a potentially dioxin-rich dietary pattern during pregnancy and gestational age and birth weight in 604 births. The fat-in-diet

scores were shown to be correlated with CALUX measurements in blood samples drawn from the mothers at delivery and divided into tertiles. The high and middle groups were compared to the lowest tertile for maternal education, energy intake, age, pre-pregnancy BMI, parity, smoking, and country of cohort, plus infant's gestational age and gender. This study is limited by its reliance on a self-report food-frequency questionnaire rather than on actual plasma dioxin levels, an entirely different exposure history (dietary intake) compared to the spraying of herbicides, and its relevance only to childbearing female Vietnam veterans.

Vafeiadi et al. (2014) assessed CALUX measures of dioxin-like activity in maternal and cord blood plasma samples collected at delivery in relation to birth weight, gestational age, and head circumference. Birth information and at least one CALUX result were available from 967 singleton births in the entire NewGeneris cohort. Analyses were conducted separately for cord plasma and maternal plasma and also by country. Multiple linear-regression models were fit with adjustments for a range of covariates, including country, gestational age, maternal pre-pregnancy BMI, type of delivery, and sex of the child. Moreover, effect modification was examined among subgroups of interest, including sex of the child, maternal smoking status, and pre-pregnancy BMI. Strengths of this analysis include the large, diverse sample of childbearing women and objective measures of dioxin-like activity and birth outcomes. The results are limited by their direct relevance only to childbearing female Vietnam veterans and the unknown long-term clinical significance of the birth outcomes examined.

Norwegian Mother and Child Cohort Study

In a very large analysis from the entire Norwegian Mother and Child Cohort Study (MoBa) as assembled from 2002–2008, Papadopoulou et al. (2013a) investigated birth weight, length, and head circumference in relation to the estimated intake of dioxin-like chemicals from the maternal diet. After limiting analysis to babies with gestational ages of 29–42 weeks and excluding mothers whose energy intake ($< -4{,}500$ or $> 20{,}000$ kilojoules) or weight gain during pregnancy (< -30 or > -50 kg) were deemed implausible, a total of 50,651 singleton pregnancies remained. Regression analyses were conducted separately by infant gender and seafood intake during pregnancy with adjustment for maternal age, energy intake, maternal education, pre-pregnancy BMI, parity, weight gain and smoking during pregnancy, and gestational age and sex of the child. The limitations of this study include its reliance on self-report food-frequency intake to estimate dioxin exposure and its direct relevance only to childbearing female Vietnam veterans.

Taiwanese Mother-and-Child Studies

A prospective study of healthy Taiwanese mothers and their children recruited during the mothers' pregnancy was conducted as a way to study the

associations between exposures to PCDDs, PCDFs, and PCBs and health outcomes (Chao et al., 2004, 2007; Su et al., 2010, 2012; Wang et al., 2004, 2005). The study enrolled pregnant women who had no clinical complications, were 25–35 years old, and delivered in the period December 1, 2000, to November 30, 2001 in a medical center in suburban Taichung in central Taiwan, the location of a solid-waste incinerator. Participants completed a questionnaire concerning maternal age, occupation, disease history, cigarette smoking, alcohol consumption, dietary habits, and baby's stature. Biologic samples (including placenta, umbilical cord blood, mother's venous blood, and breast milk) were collected for analysis of PCDDs, PCDFs, and PCBs. A total of 610 women were enrolled (80 percent of those invited). The placenta was collected from and the questionnaire completed by 430 participants. Of those, 250 provided sufficient venous blood for the chemical analyses. Of the 250, 175 provided adequate breast-milk samples. Wang et al. (2004) reported on PCDDs, PCDFs, and PCBs in the biologic samples and correlations among specimens. Chao et al. (2004) reported on PCDDs, PCDFs, and PCBs in breast milk and the cumulative dose derived for infants exclusively breastfed versus those formula-fed.

Wang et al. (2005) examined the association between in utero exposure to PCDDs, PCDFs, and PCBs and the thyroid and growth hormones in the newborns. The hormone concentrations were compared between infants with high- versus low-dioxin/PCB TEQ (above versus below the median) and between females (62) and males (57) by using a two-sample t test or the Mann-Whitney U test (when the distribution deviated significantly from the normal distribution assumed for the t test). Spearman's correlation was used to evaluate the association between the hormone concentrations and the PCDD, PCDF, and PCB concentrations. Further analyses were carried out with stepwise multivariate regression analysis to adjust for age and other covariates selected through the stepwise selection procedure. Wang et al. (2006) examined the association between PCDDs, PCDFs, and PCBs measured in the placenta samples and estrogens and metabolites measured in mothers' blood samples by using Pearson correlations, linear and quadratic regressions, and multivariate regression analyses.

Su et al. (2010) reported on the 2-year and 5-year follow-ups of the mother–child pairs of Wang et al. (2005). Children's anthropomorphic measures were obtained, including height, weight, BMI, head circumference, chest girth, bone age, and the ratio between bone age and chronologic age. Thyroid, sex-hormone, and growth-factor concentrations were measured in venous blood samples obtained from those children whose mothers' serum PCDD and PCDF TEQs were available. The anthropomorphic measures and the thyroid, sex-hormone, and growth-factor concentrations were compared by sex (29 and 14 males at years 2 and 5, respectively, and 41 and 27 females at years 2 and 5, respectively) and pooled across sexes; those who had high versus low in utero PCDD and PCDF concentrations ($\geq$ 15 versus $<$ 15 pg-TEQ/g of lipid) were compared with a two-sample t test or (when not normally distributed) a Wilcoxon rank-sum test.

Further analyses were conducted with multiple regression and stepwise selection for detecting factors that might affect growth or hormone concentrations. Su et al. (2012) reported on the 8-year follow-up of the same cohort in a subset of 23 boys and 33 girls, substantially more than the numbers examined in the 5-year follow-up. In addition to anthropomorphic measures used in previous waves, reproductive development (breast, genital, and armpit stages) were assessed.

CASE-CONTROL STUDIES

Cross-Canada Study of Pesticides and Health (Rare Tumors Study)

After a pilot study done for the Canadian government, McDuffie et al. (2001) initiated a full population-based case-control study of men in six Canadian provinces that addressed several fairly uncommon malignancies—HL, NHL, multiple myeloma (MM), and STS—and the relationship between their occurrence and exposure to pesticides (both occupationally and domestically). A target number of cases of each cancer type was preset for each province; cases newly diagnosed starting on September 1, 1991, were gathered from the provincial cancer registries or hospital records in Quebec until the end of 1994 or until the target number was reached. Physician consent was obtained, diagnoses were confirmed with pathology reports and preserved tissues, and consent forms and questionnaires were sent to the cases. The controls were men at least 19 years old identified in the health-insurance records of Alberta, Saskatchewan, Manitoba, and Quebec; telephone listings for Ontario; and voter lists in British Columbia. The controls were selected randomly in order to obtain a stratified age distribution matching that of the cases. The controls, too, were sent consent forms and questionnaires. People who died were dropped from the study, as were people who had Kaposi sarcoma or were HIV positive. All 1,506 controls who responded were used in comparisons for each of four cancer groups: 316 HL cases, 517 NHL cases, 342 MM cases, and 357 STS cases.

The postal questionnaire gathered standard demographic information, personal and family medical histories, employment history, smoking behavior, and basic data on pesticide exposure. The pilot study tested the reliability of self-reported pesticide use by comparison with purchase records. Any subject who reported at least 10 hours of pesticide exposure per year was asked to complete a telephone questionnaire on the details of pesticide exposure; in addition, 15 percent of the remaining subjects were randomly selected to answer the telephone survey. A conditional logistic regression stratified on age and province and adjusted for all covariates found to be associated with the outcome at the 0.05 level of significance was used to estimate ORs for specific active ingredients, including dicamba and the phenoxy herbicides 2,4-D, Mecoprop, MCPA, and diclofopmethyl. Dose–response relationships were investigated for the cumulative categories of time spent in mixing or applying particular products.

A series of publications have addressed the relationship between each of the cancers and various risk factors. Those pertaining to herbicides overall or to the particular ones of interest are as follows:

- HL—Karunanayake et al., 2012; Pahwa et al., 2003
- NHL—Hohenadel et al., 2011; McDuffie et al., 2001
- MM—P Pahwa et al., 2003, 2012b
- STS—Pahwa et al., 2003, 2011

A number of other publications arising from that data set have addressed topics somewhat more tangential to the interests of the VAO reports. For instance, McDuffie et al. (2005) and Pahwa et al. (2006) considered the possible interaction of exposure to insect repellents, particularly *N,N*-diethyl-*m*-toluamide (DEET) and phenoxy herbicides, in the genesis of the malignancies in question. McDuffie et al. (2009) examined family histories of cancers in first-degree relatives of the study participants (1,528 cases and 1,506 controls) to assess the interaction between family history and pesticide exposure. Hohenadel et al. (2011) investigated how various combinations of pesticide exposures influenced the occurrence of NHL. Ghosh et al. (2011) investigated the association of occupational exposures other than to pesticides with the occurrence of MM.

Since *Update 2012*, Pahwa M et al. (2012) analyzed data from the Cross-Canada Study of Pesticides and Health (CCSPH) population-based case-control study to examine the interactions between pesticide exposures and measures of immune suppression (asthma, allergies, hay fever) and risk of NHL. The analysis included 513 incident pathologically confirmed NHL cases diagnosed between the years 1991 and 1994 and 1,506 randomly selected controls identified from provincial health insurance records. Lifetime occupational history and pesticide use and other exposures were based on self-report, as was the diagnosis of various immunologic conditions. Multiple logistic regression models were fit with statistical adjustment for age, province of residence, respondent type (self or proxy), and diesel oil exposure. In addition, analyses were stratified by self-report of asthma, allergies, or hay fever versus non-reporting of such conditions. The limitations of this analysis include the self-report measurement of immunologic conditions and the nonspecific and crude self-report classification of pesticide use, which did not characterize exposure use by duration, intensity, or frequency. In addition, the focus of this analysis on the interaction between immunological conditions and pesticide use in relation to risk of NHL is not directly relevant to assessment of the effects of Agent Orange alone among Vietnam veterans.

In a second, similar examination of risk of HL in men from the CCSPH, Navaranjan et al. (2013) classified pesticide use into the categories of 0, 1, 2–4, and 5 pesticides and grouped by class, including herbicides, insecticides, and fungicides. The analysis included 316 HL cases and 1,506 control subjects. Multiple logistic regression models were fit with statistical adjustments for age and

province of residence. In addition, analyses were stratified by subjects younger than age 40 versus age 40 and older. The assessment of the effect of pesticide exposure also included estimates for work-related exposure and home-related exposure. As with Pahwa M et al. (2012), this study is limited by the relatively nonspecific and crude self-report classification of pesticide use. This significantly limits direct inference to the effects of herbicide exposure during military service in Vietnam.

Children's Oncology Group Study (United States)

In two related case-control studies, Chen Z et al. reported on exposure to pesticides (including herbicides) and the risk of childhood germ-cell tumors. One study focused on parental occupational exposures (Chen Z et al., 2005) and the other on parental exposures to residential pesticides and chemicals (Chen Z et al., 2006), but they are based on the same overall case-control study.

No reports from the Children's Oncology Group have been published since *Update 2008.*

National Birth Defects Prevention Study

The National Birth Defects Prevention Study (NBDPS) is a population-based case-control study conducted cooperatively by CDC and eight monitoring centers throughout the United States using a standardized study methodology (Yoon et al., 2001). Starting in October 1, 1997, the individual centers began monitoring births in their respective areas for the occurrence of more than 30 types of birth defect (excluding cases attributable to single-gene conditions or chromosomal abnormalities) for comparison with randomly selected sets of live-born babies without malformations. Information about demographics and possible exposures is abstracted from an extensive telephone interview that the mothers complete within 24 months of delivery, which raises concerns about recall bias addressed by the researchers. On the basis of the work histories, job classifications are assigned by an industrial hygienist and processed using a JEM and expert opinion used to derive occupational exposures. Bucchal samples are gathered for DNA testing from the infant and its parents.

Rocheleau et al. (2011a) reported on the association between maternal occupational pesticide exposure and the risk of hypospadias in the NBDPS. This was a case-control study with 647 cases of hypospadias and 1,496 controls with estimated delivery dates of October 1997–December 2002 identified by the surveillance centers in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas. Mothers were interviewed about their job status, which was then formally coded. Typical pesticide ratings were assigned to the job codes. The duration and confidence in the exposure were used to refine them. A complete case analysis was conducted, with some sensitivity analysis around

missingness (creation of a missing category). Most exposure was to insecticides only or to all three types of pesticide (insecticides, herbicides, and fungicides). The analysis did not include fetuses that died with hypospadias. Multiple comparisons are a concern. There was generally a low level of occupational pesticide exposure in the study population. Other exposures of the population could cause the outcome in question.

Using data from the NBDPS, Kielb et al. (2014) analyzed the occurrence of isolated craniosynostosis, gastroschisis, diaphragmatic hernia, or transverse limb deficiencies among employed women with due dates from October 1, 1997, to December 31, 2002. Cases included 871 live-born, stillborn, or electively terminated fetuses, which were compared to 2,857 live-born control infants. The odds of these musculoskeletal malformations were examined in relation to periconceptional maternal occupational exposure to insecticides, herbicides, or fungicides (classified as yes/no) for each job held during 1 month pre-conception through 3 months post-conception. Multiple logistic regression models were fit with adjustments for age, race, ethnicity, education, smoking, singleton versus multiple birth, BMI, folic acid use during pregnancy, and gravidity. The limitations of this analysis include the nonspecificity of pesticides with respect to the herbicides sprayed in Vietnam, the crude assessment of exposure history (yes/no) by self-reported occupational history, and its potential direct relevance only to childbearing female Vietnam veterans.

Several papers from the California Center of the NBDPS have been published since *Update 2012*. It has monitored deliveries in the San Joaquin Valley for 1997 to 2006 and has invested considerable effort toward developing time-specific estimates of exposure to individual pesticides by women residing in the area at the time of delivery.

Carmichael et al. (2014) evaluated 569 congenital heart defect cases (8 different types) and 785 non-malformed controls born during 1997–2006. Maternal pesticide exposure was crudely classified as "any" versus "no exposure" based on the commercial application of pesticides within a 500-meter radius of the mother's address during a 3-month periconception window. The determination of the proximity-based pesticide application exposure was based on data obtained from the California Pesticide Use Reporting (PUR) record system concerning agricultural pesticide applications occurring during the periconception intervals corresponding observation period for births. Multiple logistic regression models were fit with statistical adjustments for maternal race/ethnicity, education, age, intake of folic acid–containing supplements, alcohol, and smoking during the month before and the first 2 months of pregnancy. Exposure to individual pesticides was examined, including the dimethylamine salt of 2,4-D. Analogous investigations were conducted on neural tube defects and orofacial clefts (Yang et al., 2014) and on gastroschisis (Shaw et al., 2014). The strengths of these studies include that it was population based and that it used medically confirmed occurrences of congential heart defects and an objective geocoded source of pesticide

exposure classification. Their limitations include a crude binary classification of pesticide exposure (yes/no) rather than dose–response estimation and the very large number of statistical comparisons made without correction for potential false-positive findings.

Upper Midwest Health Study

The Upper Midwest Health Study (UMHS) was initiated by NIOSH as a population-based case-control study of cancer risk in a nonmetropolitan Midwestern US population. Several reports from the study were reviewed in previous updates. Chiu et al. (2004) and Lee et al. (2004a) conducted pooled (combined) analyses of two earlier case-control studies of NHL carried out by the UMHS in Iowa and Minnesota (Cantor et al., 1992) and Nebraska (Zahm et al., 1990). Chiu et al. (2004) examined the association of NHL with agricultural pesticide use and familial cancers, and Lee WJ et al. (2004a, 2006) looked at NHL in asthmatic people who reported pesticide exposure. Data from Nebraska (Chiu et al., 2006, based on Zahm et al., 1990, 1993), were used to identify whether there was a higher risk of subtypes of NHL. Specifically, tissue samples were analyzed according to the presence of a specific chromosomal translocation (t[14;18][q32;q21]); only 172 of 385 cases were included.

Two studies focused on pesticide use and the risk of adenocarcinomas of the stomach and esophagus (Lee et al., 2004b) and the risk of gliomas (Lee et al., 2005). The participants were white Nebraska residents over 21 years old who were identified from the Nebraska Cancer Registry and matched to controls drawn from an earlier study by Zahm et al. (1990).

The researchers evaluated farm pesticide exposure in men (Ruder et al., 2004) and women (Carreon et al., 2005) in Iowa, Michigan, Minnesota, and Wisconsin in relation to gliomas as part of the UMHS. Ruder et al. (2006) reported a follow-up of Ruder et al. (2004) that evaluated gliomas in UMHS participants. The new analyses provided no evidence of greater use of pesticides in cases than in controls, and there was no breakdown by specific agents.

Ruder et al. (2009) reported another follow-up, which had similar findings and no breakdown by specific agents.

Since *Update 2010*, Yiin et al. (2012) has reported findings from new analyses of the UMHS sample that incorporated more detailed exposure information that was not used in previous analyses, including years of use and estimated cumulative exposures to categories of pesticides, including phenoxy herbicides, and the use of specific agents, including 2,4-D and dicamba.

Other Case-Control Studies

Numerous case-control studies have been reviewed in previous updates. In 1977, case-series reports in Sweden (Hardell, 1977, 1979) of a potential

connection between exposure to phenoxyacetic acids and STS prompted several case-control investigations (Eriksson et al., 1979, 1981, 1990; Hardell, 1981; Hardell and Eriksson, 1988; Hardell and Sandström, 1979; Wingren et al., 1990). After the initial STS reports (Hardell, 1977, 1979), case-control studies of other cancer outcomes were conducted in Sweden: HL and NHL (Hardell and Bengtsson, 1983; Hardell et al., 1980, 1981; Persson et al., 1989, 1993), NHL (Hardell and Eriksson, 1999; Olsson and Brandt, 1988), nasal and nasopharyngeal carcinomas (Hardell et al., 1982), gastric cancer (Ekström et al., 1999), and primary or unspecified liver cancer (Hardell et al., 1984). To address criticism regarding potential observer bias in some of the case-control series, Hardell (1981) conducted another case-control study of colon cancer. Hardell et al. (1994) also examined the relationship between occupational exposure to phenoxyacetic acids and chlorophenols and various characteristics related to NHL—including histopathologic measures, stage, and anatomic location—on the basis of the NHL cases in a previous study (Hardell et al., 1981).

Prompted by the Swedish studies (Hardell, 1977, 1979), Smith et al. (1983, 1984) and Smith and Pearce (1986) conducted a set of case-control studies to evaluate the association between phenoxy herbicide and chlorophenol exposure and STS incidence and mortality in New Zealand. An expanded case series was collected, and additional case-control studies of exposure to phenoxy herbicides or chlorophenols and the risks of malignant lymphoma, NHL, and MM were conducted (Pearce et al., 1985, 1986a,b, 1987).

Geographic patterns of increased leukemia mortality in white men in the central part of the United States prompted a study of leukemia mortality in Nebraska farmers (Blair and Thomas, 1979). Additional case-control studies of leukemia were later conducted in Nebraska (Blair and White, 1985), in Iowa (Burmeister et al., 1982) on the basis of the cohort study of Burmeister (1981), and in Iowa and Minnesota (Brown et al., 1990). Another study investigated leukemia in association with NHL and 2,4-D in eastern Nebraska (Zahm et al., 1990).

Case-control studies have been conducted in various US populations looking for associations of herbicides with other cancers, including NHL (Cantor, 1982; Cantor et al., 1992; Hartge et al., 2005; Tatham et al., 1997; Zahm et al., 1993); MM (Boffetta et al., 1989; Brown et al., 1993; Morris et al., 1986); gastric cancer, prostate cancer, NHL, and multiple myeloma (Burmeister et al., 1983); STS, HL, and NHL (Hoar et al., 1986); NHL and HL (Dubrow et al., 1988); and STS and NHL (Woods and Polissar, 1989; Woods et al., 1987). In a subset of participants in the Hartge et al. (2005) study, De Roos et al. (2005b) studied associations between the overall TEQs of PCBs, furans, and dioxins but not TCDD alone.

Other case-control studies conducted outside the United States have addressed various cancers: STS and other cancers in the 15 regional cancer registries that constitute the National Cancer Register in England in connection with the COIs (Balarajan and Acheson, 1984); ovarian cancer in the Piedmont region of Italy (Donna et al., 1984); STS in rice weeders in northern Italy (Vineis et al.,

1986); mortality from esophageal cancer, pancreatic cancer, cutaneous melanoma, renal cancers, and brain cancer in three English counties (Magnani et al., 1987); brain gliomas in two hospitals in Milan, Italy (Musicco et al., 1988); lymphoid cancer in Milan, Italy (LaVecchia et al., 1989); primary lung cancer in pesticide users in Saskatchewan (McDuffie et al., 1990); STS and malignant lymphomas in the Victorian Cancer Registry of Australia (Smith and Christophers, 1992); oral-cancer risk in occupationally exposed workers in Sweden (Schildt et al., 1999); and renal-cell carcinoma in the Denmark Cancer Registry (Mellemgaard et al., 1994). Nanni et al. (1996) conducted a population-based case-control study, based on the work of Amadori et al. (1995), of occupational and chemical risk factors for lymphocytic leukemia and NHL in northeastern Italy.

Noncancer health outcomes have also been investigated in case-control studies: Spontaneous abortion (Carmelli et al., 1981); congenital malformations (García et al., 1998); immunosuppression and later decreased host resistance to infection in AIDS patients who had Kaposi sarcoma (Hardell et al., 1987); mortality in the US Department of Agriculture extension agents (Alavanja et al., 1988) and conservationists (Alavanja et al., 1989); PD associated with occupational risk factors (Semchuk et al., 1993); birth defects in the offspring of agriculture workers (Nurminen et al., 1994); mortality from neurodegenerative diseases associated with occupational risk factors (Schulte et al., 1996); PD associated with various rural factors, including exposure to herbicides and wood preservatives (Seidler et al., 1996); spina bifida in offspring associated with paternal occupation (Blatter et al., 1997); PD associated with occupational and environmental risk factors (Liou et al., 1997); and mortality from neurodegenerative diseases, including Alzheimer disease and presenile dementia, PD, and motor neuron disease associated with occupational factors (Park et al., 2005). Those studies have been discussed in detail in previous updates.

Orsi et al. (2009) studied the association between occupational exposures to pesticides and lymphoid neoplasms by using a hospital-based case-control study in the main hospitals of six French cities (Brest, Caen, Nantes, Lille, Toulouse, and Bordeaux) from September 2000 to December 2004. Cases were eligible if they were male, were 20 to 75 years old, were residing in the hospital's catchment area (the administrative department where the hospital is or a neighboring department), lacked a history of immunosuppression or of taking immunosuppressant drugs, and had recently received a diagnosis of any lymphoid neoplasm except acute lymphoid leukemia. The diagnoses were classified using WHO's *International Classification of Diseases for Oncology*, third edition, codes and was confirmed cytologically or histologically by a panel of pathologists and hematologists. Among the 513 eligible incident cases, 491 (96 percent) participated: 87 with HL, 244 with NHL, 56 with MMs, and 104 with lymphoproliferative syndrome (LPS). The controls were male patients from the same hospitals who had no prior history of lymphoid neoplasm (LN), were residing in the hospital's catchment area, and were not admitted to the hospital

for conditions directly related to occupation, smoking, or alcohol abuse. The controls were individually matched with the cases by hospital and age (± 3 years). Among the 501 eligible controls, 456 (91 percent) participated. Participants were given a self-administered questionnaire, had a face-to-face interview, and had a re-interview by an occupational hygienist and an agronomist when needed to collect socioeconomic and lifestyle information, personal and family medical history, residential and occupational histories, and detailed information on occupational and nonoccupational exposure to herbicides and pesticides. Dichotomous exposure measures (ever or never exposed) were constructed for each category (insecticides, fungicides, and herbicides) and for each chemical family (such as OC chemicals and phenoxy herbicides). Unconditional logistic regression was used to estimate the ORs and CIs for each outcome (all LN, NHL, HL, LPS, and MM) and chemical exposure with adjustments for age, hospital, and socioeconomic category (white-collar or blue-collar). Logistic regression was used for NHL subtypes (diffuse large B-cell lymphoma, follicular lymphoma, and other NHL) and LPS (chronic lymphocytic leukemia and hairy-cell leukemia).

Spinelli et al. (2007) conducted a population-based case-control study of histologically confirmed NHL in men and women 20 to 79 years old who lived in the greater metropolitan areas of Vancouver and Victoria, British Columbia, from 2000 through 2004. Population controls, frequency-matched to cases by 5-year age groups and area, were identified from the client registry of the provincial health care system. A random subset of controls was included in the analyses. The analyses were based on concentrations of OC and related chemicals in serum obtained from controls at the time of interview and from cases before chemotherapy. NHL patients who lost weight rapidly were excluded. Ng et al. (2010) examined SNPs in the AHR gene that were genotyped for the same study cohorts (422 NHL cases and 459 controls) to measure the association between individual SNPs, haplotypes, and the risk of NHL. Gene–environment interaction analyses were conducted for OC chemicals and AHR SNPs by using logistic regression.

Hartge et al. (2005) conducted a case-control study that used four NCI SEER registries (Detroit, Iowa, Los Angeles County, and Seattle) to look for associations between herbicides and NHL. In a subset of participants in the Hartge et al. study, De Roos et al. (2005b) studied associations between NHL and the overall TEQs of PCBs, furans, and dioxins but not TCDD alone. Colt et al. (2009) studied whether the relationship between OC exposure and NHL was modified by immune-gene variation in the SEER study participants (1,172 cases and 513 controls). The study genotyped 61 polymorphisms in 36 immune genes and examined three exposures measured in plasma and dust: to PCB 180, to OC pesticides (TEQ), and to α-chlordane. Unconditional logistic regresson was used to estimate the exposure–outcome association with stratification by genotype and adjustments for sex, age, race, education, and study region.

Firestone et al. (2005) reported on a population-based case-control study of incident PD cases in Washington state (250 cases and 388 controls). PD cases were identified in 1992–2002 at the Group Health Cooperative (GHC, a large managed-care organization) or the University of Washington. Control participants were sampled randomly from GHC enrollees who had no history of PD or other progressive neurologic disorder and were frequency-matched to cases by age, sex, GHC clinic location, and year of GHC enrollment. Participants were interviewed to obtain information on demographics, medical and occupational history, occupational and home-based pesticide use, drinking-water source, residential history, and smoking history. Both occupational exposures and residential exposures were reported. No specific COIs were reported beyond the broad category "herbicide." Unconditional logistic regression was used to estimate the association between PD and exposure with adjustments for age, sex, and smoking.

Firestone et al. (2010) provided an expanded update (404 cases and 526 controls) that extended the same recruitment protocol through 2006. The participation rates were good among eligible cases (70 percent) and modest among eligible controls (60 percent); this left some room for selection bias due to nonresponse. Only occupational exposures were reported. Exposures to specific chemicals were reported, including 2,4-D (9 exposed cases and 12 exposed controls).

7

Immune-System Disorders

Chapter Overview

Based on new evidence and a review of prior studies, the committee for Update 2014 *did not find any new significant associations between the relevant exposures and immune outcomes. Current evidence supports the findings of earlier studies that*

- *No specific diseases involving immune suppression, allergy, autoimmunity, or inflammation had sufficient evidence of an association with the chemicals of interest.*

As in *Veterans and Agent Orange: Update 2010*[1] (IOM, 2012, hereafter referred to as *Update 2010*), in this volume immune-system disorders are addressed in a separate chapter that precedes the chapters on other adverse health outcomes. In *Veterans and Agent Orange* (*VAO*) reports prior to *Update 2010—Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994), *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), *Update 2004* (IOM, 2005), *Update 2006* (IOM, 2007), and *Update 2008* (IOM, 2009)—the possible adverse health outcomes arising from disruptions of the immune system were included in the "Other Health Effects" chapter. The current

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

committee elected to revisit comprehensively the limited epidemiologic evidence concerning the association of immune disease with herbicide exposure in light of the substantial volume of toxicologic evidence of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) impairment of the immune systems of laboratory animals.

This chapter opens with an overview of the various types of health problems that can arise from the malfunctioning of the human immune system. The standard VAO sections leading to the committee's assignment of a health outcome to a category of association follow and include a new tabulation of all the immune-related epidemiologic information that has been considered in this series and a synopsis of the information that is new in this update. The next section discusses factors that may lead the immune responses of animals exposed to the chemicals of interest (COIs) to be much more pronounced than any observed to date in humans. The chapter closes with the committee's thoughts regarding research on the possibility that immune perturbations in humans function as a mechanistic step in the development of disease processes in other organ systems.

The immune system plays three important roles in the body:

1. It defends the body against infection by viruses, bacteria, and other disease-producing microorganisms, known as pathogens.
2. It defends against cancers by destroying mutated cells that might otherwise develop into tumors and by providing immunity against tumors.
3. It provides resident immune cells that are specially adapted for different tissues and organs (such as microglia in the central nervous system and Kupffer cells in the liver) that help to regulate the functional activity and integrity of those tissues.

To recognize the wide array of pathogens in the environment, the immune system relies on many cell types that operate together to generate immune responses. These cells arise from stem cells in the bone marrow, are found in lymphoid tissues throughout the body, and circulate in the blood as white blood cells (WBCs). The main types of WBCs are granulocytes, monocytes, and lymphocytes. Each type has many specialized cell populations that are responsible for specific functions connected to the production of specific mediators, such as immune hormones, cytokines, and other secreted factors. Imbalances in those specialized populations or in their level of functional activity can result in inadequate or improper immune responses, which may lead to pathologic outcomes. Diseases arising from immune dysfunction may be apparent immediately or observed only after an organism encounters an environmental challenge that causes the immune cells to respond (such as an infection).

CATEGORIES OF IMMUNE DYSFUNCTION

There are four major categories of immune dysfunction, which are not mutually exclusive: immune suppression, allergy, autoimmunity, and inflammatory

dysfunction (inappropriate or misdirected inflammation). Immune suppression usually manifests itself as an increased incidence of infections or an increased risk of neoplasatic, allergic, autoimmune, and inflammatory disorders can be manifested as diseases that affect virtually any tissue. It is often difficult to diagnose such diseases, so they may or may not be medically categorized as immune disorders.

Immune Suppression

The suppression of immune responses can reduce resistance to infectious disease and increase the risk of cancer. Infection with the human immunodeficiency virus (HIV) is a well-recognized example of an acquired immune deficiency in which a specific type of lymphocyte (CD4+ T cell) is the target of the virus. The decline in the number of CD4+ T cells after HIV infection correlates with an increased incidence of infectious diseases, including fatal opportunistic infections, and with an increased incidence of several types of cancer. The treatment of cancer patients with toxic chemotherapeutic drugs suppresses the immune system by inhibiting the generation of new WBCs by the bone marrow and blocking proliferation of lymphocytes during an immune response. Both of those examples represent severe immune suppression in which the adverse outcome is easily detected with clinical measurements.

Immune suppression can also result from exposure to chemicals in the workplace or in the environment and manifest as recurrent infections, opportunistic infections, a higher incidence of a specific category of infections, or a higher incidence of many forms of cancer. However, unless the immune suppression is severe, it is often difficult to obtain clinical evidence that directly links chemically induced changes in immune function to increases in infectious diseases or cancers, because many confounding factors can influence a person's ability to combat infection. Such confounders include age, vaccination status, the virulence of the pathogen, the presence of other diseases (such as diabetes), stress, smoking, and the use of drugs or alcohol. Therefore, immunotoxicology studies are often conducted in laboratory animals to understand the scope and mechanism of chemical-induced immune suppression. The results of such studies can be used to develop biomarkers to assess the effects in human populations. Infectious-disease models in animals can also be used to determine whether the pattern of disease changes with chemical exposure.

Allergic Diseases

The immune system sometimes responds to a foreign substance that is not pathogenic. Such immunogenic substances are called allergens. Like most immune-based diseases, allergic diseases have both environmental and genetic risk factors. Their prevalence has increased in many countries in recent decades (CDC, 2004b;

Linneberg et al., 2000; Simpson et al., 2008; Sly, 1999). Major forms of allergic diseases are asthma, allergic rhinitis, atopic dermatitis, and gastrointestinal responses. In immediate hypersensitivity, the response to some allergens, such as pollen and bee venom, results in the production of immunoglobulin E (IgE) antibodies. Once produced, IgE antibodies bind to mast cells, which are specialized cells that occur in tissues throughout the body such as lung airways, the intestinal wall, and blood-vessel walls. When a person is exposed to the allergen again, it binds to the antibodies on the mast cells and causes them to release histamine and leukotrienes, which produce the symptoms associated with an allergic response. In delayed-type hypersensitivity (DTH) reactions, also known as cell-mediated immunity, other allergens, such as poison ivy and nickel, activate allergen-specific lymphocytes (memory T-cells) at the site of contact (usually the skin) that release substances that cause inflammation and tissue damage. Some allergic responses, such as those to food allergens, may involve a combination of allergen-specific lymphocyte-driven and IgE-driven inflammation. Allergic responses may be manifested in specific tissues (such as skin, eyes, airways, and gastrointestinal tract) or may result in a system-wide response called anaphylaxis.

Autoimmune Diseases

The National Institutes of Health's Autoimmune Disease Coordinating Committee recognizes 80 different autoimmune diseases and conditions which affect the cardiovascular, respiratory, nervous, endocrine, dermal, gastrointestinal, hepatic, and excretory systems (NIH Autoimmune Diseases Coordinating Committee, 2005). These diseases affect both men and women, but most of them affect more women than men (Fairweather et al., 2008). Genetic predisposition, age, hormone status, and environmental factors, such as the presence of infectious diseases and stress, are known to affect the risk of developing autoimmune diseases, and different autoimmune diseases tend to occur in the same person and to cluster in families. The existence of some autoimmune diseases is also a risk factor for the development of other immune-related diseases, such as some types of cancer (Landgren et al., 2010).

Autoimmune disease is an example of the immune system's causing rather than preventing disease: The immune system attacks the body's own cells and tissues as though they are foreign. Inappropriate immune responses that result in autoimmune disease can be promoted by different components of the immune system (such as antibodies and lymphocytes) and can be directed against a wide variety of tissues or organs. For example, the autoimmune reaction in multiple sclerosis is directed against the myelin sheath of the nervous system; in Crohn disease, the intestine is the target of attack; in type 1 diabetes mellitus, the insulin-producing cells of the pancreas are destroyed by the immune response; and rheumatoid arthritis arises from an immune attack on the joints, although it can also involve the lung, heart, and additional organs.

More generalized forms of autoimmune diseases also occur. Systemic lupus erythematosus (SLE) is an autoimmune disease in which multiple organs are targeted by immune attack. In such a case, patients have a variety of symptoms that often occur in other diseases, which makes diagnosis difficult. A characteristic rash across the cheeks and nose and a sensitivity to sunlight are common symptoms of SLE; oral ulcers, arthritis, pleurisy, proteinuria, and neurologic disorders may also be present. Almost all people who have SLE test positive for antinuclear antibodies in the absence of drugs known to induce them. The causes of SLE are unknown, but environmental and genetic factors have been implicated. Some of the environmental factors that may trigger it are infections, antibiotics (especially those in the sulfa and penicillin groups) and some other drugs, ultraviolet radiation, extreme stress, and hormones. Occupational exposures to such chemicals as crystalline silica, solvents, and pesticides have also been associated with SLE (Cooper and Parks, 2004; Parks and Cooper, 2005).

Inflammatory Diseases

Inflammatory diseases (also referred to as auto-inflammatory diseases) make up a more recently identified category of immune-related disorders and are characterized by exaggerated, excessively prolonged, or misdirected dysfunctional inflammatory responses (usually involving immune cells). Tissue disease can result from this inappropriate inflammation, which can affect virtually any organ. Examples of the diseases and other conditions that are most often included in other disease categories but are also considered to be inflammatory diseases are coronary arterial disease, asthma, eczema, chronic sinusitis, hepatic steatosis, psoriasis, celiac disease, and prostatitis. Inflammatory diseases often occur with one another, which has resulted in the categorizing of different but linked inflammatory diseases together as a single chronic inflammatory disorder (Borensztajn et al., 2011); among these inflammatory disorders are atherosclerosis and chronic pulmonary obstructive disease. Inappropriate inflammation also appears to play a role in promoting the growth of neoplasms (Bornschein et al., 2010; Hillegass et al., 2010; Landgren et al., 2010; Porta et al., 2011; Winans et al., 2010); examples can be seen in the higher prevalence of specific cancers in patients who have such inflammatory diseases as inflammatory bowel disease (Lucas et al., 2010; Viennot et al., 2009; Westbrook et al., 2010), prostatitis (Sandhu, 2008; Wang W et al., 2009), and psoriasis (Ji et al., 2009).

Ordinarily, inflammation can be advantageous in fighting infectious diseases. It is one component of the normal host response to infection and is mediated by innate immune cells. Inflammatory responses have evolved to speed the movement of macrophages, granulocytes, and some lymphocytes to the area of infection, where they produce toxic metabolites that kill pathogens. Interactions among innate immune cells and epithelial and endothelial cells are important in regulating the magnitude of inflammation, and improperly regulated inflammation

can contribute to diseases that arise in non-lymphoid tissues, such as the lungs, skin, nervous system, endocrine system, and reproductive system.

CONCLUSIONS FROM *VAO* AND PREVIOUS UPDATES

The following comments are restricted to findings related to the immune system that occur after adult human exposures. For a discussion of potential effects on the immune system arising from early-life (such as perinatal) exposures (which would not be directly applicable to the Vietnam veterans who are the target of this report), see Chapters 4 and 9. Studies that served as the basis of prior updates of *VAO* are shown in Table 7-1.

Vietnam Veterans

A handful of the direct studies of veterans listed in Table 7-1 reported a statistically significant difference in a single immune measure (Kim HA et al., 2003; Michalek et al., 1999b). But invariably the same effect was not found in other studies of Vietnam veterans, nor was support for the effect found in epidemiologic studies of other populations. Thus, there were no consistent findings indicative of immunosuppression, increased risk of autoimmunity (usually as measured with autoantibodies), or biomarkers of atopy or allergy (such as increased IgE concentrations). Much of the focus of the studies was on measuring T4:T8 ratios. The T4:T8 ratio is an effective biomarker of the progression of HIV-induced AIDS, but the TCDD-exposure animal data indicate that it is not an immunologic index that is expected to be altered. The results of a survey of Australian Vietnam veterans (O'Toole et al., 2009) included purportedly significant increases in the prevalence of a number of conditions in which immune function may play a prominent role, but the study's methods were deemed unreliable.

Occupational Exposures

The occupational-exposure studies shown in Table 7-1 evaluated the concentrations of lymphoid populations in circulation, such as CD4, CD8 (and the ratio of the two), and natural killer (NK) cells; cell-mediated immunity (the delayed-hypersensitivity response); serum concentrations of immunoglobulins, such as IgM, IgG, and IgA; concentrations of complement, such as C3 and C4; and concentrations of cytokines, such as IL-1, IL-2, interferon-gamma, IL-4, IL-6, and tumor necrosis factor (TNF)-alpha. A few studies also included disease or condition end points, such as rheumatoid arthritis, SLE, immune suppression, and sensitivity to fungal infection. Ex vivo analyses included measures of NK activity, lymphoid mitogen-induced proliferation, and the mixed lymphocyte response (MLR) against allogeneic cells. Some studies identified one or more dioxin-related shifts in immune measures, but many reported no significant differences

TABLE 7-1 Selected Epidemiologic Studies—Immune Effects in Adult Humans (Shaded entries are new information for this update)

Study Population	**Exposure**/Results	Reference
VIETNAM VETERANS		
US Air Force Health Study—Ranch Hand veterans vs SEA veterans	**All COIs**	
Participants in 1997 examination cycle, Ranch Hands vs comparisons (incidence)	No change in surface markers for B and T cells, no change in serum Ig, no change in autoantibodies (antinuclear antibody, smooth muscle autoantibody, parietal cell autoantibody, rheumatoid factor, and monoclonal immunoglobulins), and no dose-related change in DTH response	Michalek et al., 1999b
Participants in 1987 examination cycle, Ranch Hands vs comparisons (morbidity)	No change in surface markers for B and T cells	Wolfe et al., 1990
Participants in 1985 examination cycle, Ranch Hands vs comparisons (morbidity and mortality)	No change in surface markers for B and T cells	Wolfe et al., 1985
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed	**All COIs**	
Morbidity—Deployed vs non-deployed	No differences in infections, no changes in B and T cell-surface markers, WBC counts, or circulating serum Ig	CDC, 1988b
Mortality (1965–2000)	No suggestion of excess deaths due to immune-system disorders (ICD-9 240–279, which covers endocrine, nutritional, metabolic, and immunity disorders).	Boehmer et al., 2004
US VA Cohort of Monozygotic Twins	**All COIs**	
Physical health—morbidity	Increase in skin conditions of unknown etiology, no increase in blood disorders	Eisen et al., 1991
US American Legion Cohort	**All COIs**	
Physical health and reproductive outcomes	Increase in skin conditions and arthritis	Stellman SD et al., 1988b
State Studies of US Vietnam Veterans	**All COIs**	
Michigan Vietnam Veterans (deployed vs non-deployed)	Increased mortality from infectious (including parasitic) diseases	Visintainer et al., 1995
New Jersey Agent Orange Commission	Depressed response to tetanus in DTH tests, decrease in CD4 and SmIg+ B cells	Kahn et al., 1992b
Texas Agent Orange Advisory Committee	Increase in percentage of active T rosette-forming cells	Newell, 1984
Sample of 1,000 Male Australian Vietnam Veterans–prevelance	**All COIs**	
Australian Vietnam Veterans—longitudinal cohort study of 67 conditions in randomly selected Vietnam veterans vs general population	Increase in hay fever, increases in infectious and parasitic diseases, increase in arthritis	O'Toole et al., 2009

continued

TABLE 7-1 Immune Effects in Adult Humans, continued

Study Population	**Exposure**/Results	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)	**All COIs**	
1983–1985—Australian Vietnam Veterans—longitudinal cohort study of 67 conditions in randomly selected Vietnam veterans vs general population	Increase in hay fever, increases in infectious and parasitic diseases, increase in arthritis	CDVA, 1997b
Korean Vietnam Veterans	**All COIs**	
Immunotoxicologic study	Increase in IgE and IL-4, decrease in IgG1 and IFN-gamma, no change in lymphocyte counts	Kim et al., 2003
Vietnamese Vietnam Veterans	**All COIs**	
Antinuclear and sperm autoantibodies	No change in autoantibodies to sperm, antinuclear bodies	Chinh et al., 1996
OCCUPATIONAL STUDIES		
IARC Phenoxy Herbicide Cohort—Dutch workers from 2 plants that produced and formulated chlorophenoxy herbicides (Plant A, n = 1,167; Plant B, n = 1,143).	**Chlorophenoxy herbicides:** Negative correlation between TCDD exposure and markers of humoral immunity, except perhaps for C4	Saberi Hosnijeh et al., 2011
IARC Phenoxy Herbicide Cohort— Subset of **Dutch workers** (n = 85) from 2 plants that produced and formulated chlorophenoxy herbicides (high exposure = 47, low exposure = 38); serum collected 30 yrs after exposure	**Chlorophenoxy herbicides:** General reduction in most analyte levels with the strongest effects for fractalkine, fibroblast growth factor (FGF_2), and transforming growth factor alpha (TGF-α)	Saberi Hosnijeh et al., 2012a
	High vs low: CD4/CD8 ratio increased ($p = 0.05$); no difference for other cell counts and lymphocyte subsets Decrease in B cells with increasing serum TCDD	Saberi Hosnijeh et al., 2012b
	Soluble CD27 and CD30 levels not related to TCDD levels; With exclusion of chronically ill subjects, IL1RA decreased with increasing TCDD levels	Saberi Hosnijeh et al., 2013a
IARC Phenoxy Herbicide Cohort—German production workers (2,479 workers at 4 plants, in IARC as of 1997)	**Dioxins, phenoxy herbicides**	
Cross-sectional study of 153 male workers in six chemical plants in Germany	**TCDD** (during production of TCP): DTH responses not correlated with dioxin concentration; slight decrease in IgM was reported with increasing dioxin exposure; overall lymphoid counts not different	Benner et al., 1994

TABLE 7-1 Immune Effects in Adult Humans, continued

Study Population	**Exposure**/Results	Reference
German production workers at BASF Ludwigshafen Plant—BASF cleanup workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)	**Focus on TCDD**	
138 surviving workers from a larger cohort of 254 exposed workers after an accident in a BASF TCP production facility	**TCDD:** Among 14 immune measures; regression analysis of TCDD concentration suggested marginal positive associations with IgG, IgA, C3, and C4; marginal reductions in some lymphocyte population were also reported	Ott et al., 1994
IARC Phenoxy Herbicide Cohort—German production workers at Boehringer-Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954)	**Dioxins, 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Updated and expanded evaluation of 158 workers in a German chemical plant with differing exposure studied in two trials	**TCDD** (or "TCDD toxic equivalents" from PCDD/PCDF): No differences in serum Ig or cytokine (IL1, IL6, TNF-alpha)	Neubert et al., 2000
19 highly exposed chemical workers vs 28 unexposed controls in two chemical plants in Hamburg, Germany	**TCDD** (in chemical plant): In subset of leukocytes, increase in CD8+ memory T cells and decrease in naïve T cells (CD45RA+) after TCDD exposure, as was stimulated IFN-gamma production from whole blood cultures associated with TCDD exposure	Ernst et al., 1998
192 workers in a German pesticide plant, including 29 highly exposed and 28 controls compared for immune functional tests	**TCDD** (or TEQs from PCDD/PCDF exposure): No significant changes in TCDD and lymphocyte subsets, antibody responses to vaccination, lymphocyte proliferation, or autoantibody production; decrease in chromate resistance of PHA-stimulated lymphocytes in highest exposure group	Jung et al., 1998
Comparison of 11 2,4,5-trichlorophenol production workers 20 years after exposure vs 10 unexposed age-matched workers in the same company	**TCDD:** No differences in any lymphoid subset or in mitogen-induced proliferation; TCDD exposure was associated with decreases in MLR response and in stimulation with IL-2 in vitro	Tonn et al., 1996
Examination of eight trichlorophenol production workers who developed chloracne and were re-examined 15–25 yrs after initial exposure	**TCDD:** Reduced gamma globulins in the most-exposed workers; no significant effects on T4, T8 ratios	Jansing and Korff, 1994

continued

TABLE 7-1 Immune Effects in Adult Humans, continued

Study Population	**Exposure**/Results	Reference
89 volunteers involved in decontamination work at a chemical plant in Hamburg, Germany; no control population	**TCDD** (or equivalents via PCDD/PCDF exposure): Potentially complicated by age differences among the compared groups; only subtle, clinically nonsignificant changes were seen among immune-cell surface markers in a comparison of higher exposed vs low-exposed to moderately exposed workers	Neubert et al., 1993, 1994
NIOSH Cohort (current and former workers from chemical plants in New Jersey and Missouri, 2 of the 12 plants included in the NIOSH Mortality Study)	**Dioxins, phenoxy herbicides**	
Cross-sectional study of 259 TCDD-exposed 2,4,5-trichlorophenate (and its derivatives) workers (mean serum TCDD, 223 ppt) and 243 unexposed residential controls (mean serum TCDD, 6ppt)	**TCDD** (exposure in a chemical plant): No significant changes in serum Ig or major leukocyte categories; TCDD associated with decreased circulating CD26 cells (activated T cells)	Halperin et al., 1998
1987 cross-sectional study of 281 chemical-plant workers in NJ and MO at least 15 yrs after exposure vs 260 unexposed controls	**TCDD** (as a contaminant in chemical production): Increase in TCDD associated with a decrease in CD3/Ta1 (helper lymphocytes) cells	Sweeney et al., 1997/1998
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)		
EUROPIT Study—Prospective multicenter cohort study (Bulgaria, Finland, Italy, The Netherlands) of 238 pesticide-exposed workers vs 198 unexposed workers	**Pesticide factories** (not specifically TCDD): Reduced antibody responses to hepatitis B vaccination among exposed workers carrying a specific IL-1 allele	Baranska et al., 2008
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)		
Agricultural Health Study (AHS)—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916 men), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010	**Pesticides/herbicides**	
Comparison from the AHS of 534 cases of self-reported physician-diagnosed depression vs 17,051 controls	Both high-level acute pesticide exposure (OR = 2.6, 95% CI 1.7–3.8) and cumulative pesticide exposure (OR = 1.5, 95% CI 1.2–2.0) were positively associated with increase in depression	Beseler et al., 2008

TABLE 7-1 Immune Effects in Adult Humans, continued

Study Population	**Exposure**/Results	Reference
29,074 female spouses of pesticide applicators in the AHS	Depression was significantly associated with pesticide poisoning (OR = 3.3, 95% CI 1.7–6.2) but not with lower cumulative exposure	Beseler et al., 2006
Nested case-control study of rheumatoid arthritis in agricultural families (57,000 pesticide applicators and their spouses).	No strong risk factors were identified for pesticide mixing or application or for any specific class of pesticides in the AHS of rheumatoid arthritis.	De Roos et al., 2005b
Other Studies of Herbicide-Using Workers		
Longitudinal study of 10 farmers during 1994 within 7 days before and 1–12 days and 50–70 days after exposure	**2,4-D and MCPA formulations:** Decreases in percentages of CD4, CD8, CTL, CD8-DR, and NK cells and in NK activity and mitogen-stimulated lymphoproliferation; CD4/CD8 ratio was unaltered; CD3 and CD8 percentages had recovered by the second assessment period; no significant correlations between immune changes and amount of pesticides applied	Faustini et al., 1996
ENVIRONMENTAL STUDIES		
Seveso Cleanup Workers	**TCDD**	
Prospective study using analysis of samples from 36 cleanup workers (divided into three groups based on time spent in the contamination area); pre-employment samples and samples after 9 months were analyzed for comparison with samples from 31 unexposed workers	No differences in WBC counts and platelet counts	Ghezzi et al., 1982
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)	**TCDD**	
Study of 101 chloracne cases vs 211 controls 20 years after the accident; relatively low statistical power was available because the study examined the occurrence of individual diseases	Persistent increase in TCDD in chloracne cases; younger people seemed to be more susceptible; no major trends in disease occurrence	Baccarelli et al., 2005a
Study of 62 people from a highly exposed zone and 53 from noncontaminated areas 20 yrs after the accident	Plasma concentration of TCDD was determined; multivariate regression analysis showed significant decrease in plasma IgG with increasing TCDD concentration and no changes in IgM, IgA, or C3	Baccarelli et al., 2002

continued

TABLE 7-1 Immune Effects in Adult Humans, continued

Study Population	**Exposure**/Results	Reference
45 children (3–7 yrs of age) living in exposed areas vs 45 unexposed children as controls	No differences in serum IG, mitogen responses of lymphocytes (PHA and pokeweed), or percentage of rosette-forming lymphocytes	Pocchiari et al., 1979
Times Beach (MO) Cohort	**TCDD**	
Regression analysis used for comparisons among 41 exposed people for adipose-tissue, TCDD vs immune measures; three exposed groups defined by tissue dioxin	No TCDD–DTH response relationships were reported; no change in mitogen responsiveness; some serum markers (A/G ratio and serum IgG) were affected	Webb et al., 1989
82 people in more highly contaminated areas vs 40 in low-risk exposure areas as controls	No differences in DTH response or T-cell subsets (T4/T8)	Webb et al., 1987
80 people in highly contaminated areas vs 40 controls in lower-risk areas	No differences in DTH induration or T-cell subset analysis (T4/T8)	Stehr et al., 1986
Pilot study of small numbers of people; for comparisons, people were assigned to two environmental-exposure groups: those in high-risk areas (27 men, 23 women, and 15 children) and those in low-risk areas (12 men, 10 women, and 8 children)	Multitest DTH evaluation to seven recall antigens was performed, no statistical differences were reported, and only trends were noted; no statistical differences were reported for T-cell markers (T3, T4, and T8) or mitogen-induced lymphocyte proliferation (PHA, Con A, and pokeweed mitogen), and only trends were noted	Knutsen, 1984
Quail Run Mobile Home Park (MO) Cohort	**TCDD**	
A subset of the previously anergic persons in the Stehr-Green et al. (1987) study were re-evaluated in the DTH test with a higher DTH test dose and highly trained, blinded readers	Retesting of DTH failed to produce the differences observed initially	Evans et al., 1988
Small (ill-defined) samples were used; comparisons of residents of the Quail Run Mobile Home Park with residents of St. Louis–area trailer parks as controls	DTH suppression in the exposed group was reported, but data from two of four readers were discarded; no differences in T-cell mitogen stimulation; decreases in percentages of T3, T4, and T11 cells in the exposed group	Knutsen et al., 1987
154 people in highly contaminated area vs 155 in three low–environmental-contamination areas as controls	Increase in anergy and decrease in induration for DTH in exposed group; data from some readers were excluded; decrease in percentages of T3, T4, and T11 cells, but no difference in cell number of T4/T8 ratio	Stehr-Green et al., 1987
80 people in a high–exposure risk group vs 40 controls	Decreases in DTH indurations, number of positive reactors, and percentages of T3, T4, and T11 cells in the exposed group	Andrews et al., 1986

TABLE 7-1 Immune Effects in Adult Humans, continued

Study Population	**Exposure**/Results	Reference
154 people in the exposed area vs 155 unexposed people in an uncontaminated area	Recall antigen multitest for DTH, increase in percentage of anergy and decrease in duration in exposed group; data from two of four readers were excluded	Hoffman et al., 1986
Other Environmental Studies		
Belgium (Flanders)—200 people 17–18 yrs of age in three areas of Flanders (Belgium); TEQ values were calculated from serum dioxin–like PCB concentrations, and relationships with immune measures were examined	**Dioxins and PCBs:** Decreases in eosinophil and NK-cell counts with increasing TEQ; IgE concentrations; history of upper airway allergy, and odds of a positive RAST test correlated negatively with serum TEQ; IgA concentrations correlated positively with TEQ	Van den Heuvel et al., 2002
Finland—123 men and 132 women from high–fish consumption group	**TEQ for dioxins, furans, and PCBs:** CRP was not associated with overall TEQ for men ($p = 0.29$) or women ($p = 0.94$)	Tururen et al., 2012
Germany—Cross-sectional study of 221 teachers who worked in German day-care centers treated with wood preservatives vs 189 teachers who worked in untreated facilities	**Dioxin in wood preservatives,** exposure primarily via inhalation: No effects of inhaled dioxin were seen on T4 or T8 cell numbers or on the ratio; some evidence of a dose–response relationship was seen for risk of anergy (or hypoergy) in the DTH assay	Wolf and Karmaus, 1995
Japan—1,063 men and 1,201 women without occupational dioxin exposure from 125 areas	**All WHO 2005 DLCs:** Self-reported asthma not associated with DLCs; marginal association of atopic dermatitis and allergic rhinitis with DLCs	Nakamoto et al., 2013
US (Seattle)—109 postmenopausal women tested for immune function at start and after 1 yr exercise program	**Mono-ortho PCBs 105, 118, 156:** PHA-induced T-lymphocyte proliferation decreased with PCB levels after 1 yr, but not at start; NK cytotoxicity not associated with PCBs at either time	Spector et al., 2014
US (NHANES)	**Dioxin-like PCBs**	
1,721 adults assessed for serum dioxin–like PCBs and self-reported arthritis	Association between serum dioxin–like PCBs and prevalence of arthritis particularly among women	Lee et al., 2007a
632 women and 670 men assessed for dioxin-like PCBs and serum antinuclear antibodies	In women only, TEQ for PCBs associated with positivity for antinuclear antibodies ($p < 0.001$)	Gallagher et al., 2013

continued

TABLE 7-1 Immune Effects in Adult Humans, continued

Study Population	**Exposure**/Results	Reference
CASE-CONTROL STUDIES		
Norway—blood samples from 24 Norwegian hobby fishermen were compared with those of 10 male referents as controls	**PCDD,** exposure from food: The study generally lacks experimental details; no differences in an NK cell marker or in NK activity were seen; apparently, some effects on lymphoid markers were observed but specific details are lacking	Lovik et al., 1996
Sweden—23 high consumers of fatty fish from the Baltic Sea (containing low concentrations of PCDD) vs 20 low consumers or nonconsumers of fish as controls	**PCDD,** exposure from food: Blood PCDDs were significantly different between the groups; mercury concentrations also differed; NK cells correlated negatively with blood concentrations of persistent organic chemicals; no other	Svensson et al., 1994
South Korea (Ansan)—comparison of immune measures in 31 waste-incineration workers vs 84 controls	**TCDD** (via waste incineration): Lymphoid subsets, IFN-gamma, and Ig not statistically different; decrease in IL-4 and increase in T-cell activation (measured as combined CD3 and CD69 markers) associated with TCDD exposure	Oh et al., 2005
United Kingdom (Derbyshire)—18 chemical workers in a 2,4,5-T in the Coalite Oils and Chemical, Ltd. factory exposed as a result of an industrial accident 17 yrs before study vs 15 matched controls	**TCDD:** No changes in serum Ig classes, increases in antinuclear antibodies and immune complexes, and increase in circulating NK cells (Leu7+) in exposed workers	Jennings et al., 1988
United States (California)—telephone interviews concerning environmental and occupational chemical exposures were conducted with 50 AIDS patients (with Kaposi sarcoma) and 50 homosexual men as controls	**Chemical exposures, including pesticides, and Agent Orange:** No significant differences were reported in a small study that generally lacked focus	Hardell et al., 1987

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AHS, Agricultural Health Study; CATI, computer-assisted telephone interview; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; Con A, concanavalin A; CRP, C-reactive protein; DLC, dioxin-like compound; DTH, delayed-type hypersensitivity; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; IFN-gamma, interferon-gamma; Ig, immunoglobulin; IL, interleukin; IL1RA, interleukin one receptor agonist; MCPA, methyl-4-chlorophenoxyacetic acid; MLR, mixed lymphocyte response; MO, Missouri; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; NK, natural killer; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofurans; PHA, phytohemagglutinin; RAST, radioallergosorbent; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, total toxic equivalent; TNF, tumor necrosis factor; VA, Department of Veterans Affairs; WBC, white blood cell; WHO, World Health Organization.

in the same measures. Saberi Hosnijeh et al. (2012a) reported a positive correlation between plasma TCDD concentrations and decreased levels of cytokines, chemokines, and growth factors. However, this correlation was not supported by other studies. That is particularly true of the study by Neubert et al. (2000), which measured toxicity equivalents (TEQs) for dioxin but found no immunoglobulin or cytokine alterations. In general, the various occupational-exposure findings do not provide a consistent or clear picture of alterations in immune measures that could be extrapolated to an increased risk of a single disease or even a broader category of diseases. The exception may be observations of pesticide-associated autoimmunity and immune suppression. Immune suppression was rather consistently associated with very high pesticide exposures or pesticide poisonings. However, because the studies generally concerned broad categories of pesticide exposure, their relevance to herbicide exposures in Vietnam is not clear.

Environmental Exposures

Several environmental-exposure studies reported alterations, but the findings were inconsistent among the studies (see Table 7-1). Some studies reported alterations in immune measures associated with TEQs for dioxin. For example, Van den Heuvel et al. (2002) reported that IgE, positive radioallergosorbent (RAST) tests in response to specific allergens, eosinophil counts, and NK-cell counts correlated negatively with dioxin TEQs but that IgA increased; these alterations, however, were not seen consistently in other studies. Baccarelli et al. (2002) found no changes in IgA but saw changes in IgG in the Seveso population. Svensson et al. (1994) found that NK-cell numbers were reduced with increasing concentrations of persistent organic chemicals, but Lovik et al. (1996) found no difference in NK numbers or activity. Similarly, the occupational-exposure studies (see Table 7-1) that examined NK concentrations reported the full spectrum of results: no alterations (Halperin et al., 1998), a decrease (Faustini et al., 1996), and even an increase in NK numbers (Jennings et al., 1988) in dioxin-exposed people.

As seen in Table 7-1, some early studies of the Quail Run Mobile Home Park population exposures reported that dioxin exposure was associated with a reduced cell-mediated immune response, the DTH response (Andrews et al., 1986; Hoffman et al., 1986; Knutsen et al., 1987; Stehr-Green et al., 1987). But some of those studies had technical problems in assessment and in the follow-up analyses. Dioxin-associated changes were not confirmed (Evans et al., 1988; Webb et al., 1989). In addition, several studies of the Times Beach population did not find any alteration of the DTH response in dioxin-exposed populations (Knutsen, 1984; Stehr et al., 1986; Webb et al., 1987).

Analysis of National Health and Nutrition Examination Survey (NHANES) data found that exposure to dioxin-like polychlorinated biphenyls (PCBs) was associated with an increase in self-reported arthritis (Lee et al., 2007a), but De Roos et al. (2005b) found no such association in their study.

Prior VAO updates have concluded that human data were either insufficient or inconsistent with respect to an increased risk of immunosuppression, allergic disease, or autoimmune disease.

UPDATE OF THE EPIDEMIOLOGIC LITERATURE AND HUMAN STUDIES

Vietnam-Veteran and Case-Control Studies

No new case-control studies or studies of Vietnam veterans exposed to the COIs and adverse immunologic conditions have been published since *Update 2010*.

Occupational Studies

Since *Update 2012*, several additional relevant occupational studies have been reported. In a publication reviewed in *Update 2012*, Saberi Hosnijeh et al. (2012a) examined serum cytokine concentrations in a subsample of 47 highly TCDD-exposed workers and 38 low-exposed workers selected from those in the Dutch subcohort (Bueno de Mesquita et al., 1993) of the IARC cohort who were alive in 2006 at the end of follow-up by Boers et al. (2010). Highly exposed workers were matched to low-exposed workers by factory, sex, age, and residence at the time of study. Having generated results consistent with immune suppression being associated with TCDD exposure, Saberi Hosnijeh et al. (2012b, 2013a) continued with this group to assess TCDD levels with respect to several other immunological parameters. Comparing the high- and low-exposure groups, Saberi Hosnijeh et al. (2012b) found no differences in hematologic measurements other than an increase in the CD4/CD8 lymphocyte ratio ($p = 0.05$). With adjustment for age, body mass index (BMI), drinking, smoking, medication, and chronic, inflammatory, or recent infectious disease, the WBC subsets generally decreased with increasing TCDD levels, but only for B lymphocytes was this tendency significant. Finally, Saberi Hosnijeh et al. (2013a) reported on the levels of interleukin 1 receptor agonist (IL1RA) as well as of the soluble forms of CD27 and CD30, immunomodulatory members of the TNF receptor superfamily. Here they found no association of TCDD level with CD27 or CD30; however, IL1RA was significantly decreased in those with higher TCDD levels after adjusting for concurrent chronic disease. This result is also consistent with a degree of immune system impairment being associated with high exposure to TCDD.

Environmental Studies

Several additional studies focused on immunological changes after exposure to the COIs in environmental settings. Spector et al. (2014) assessed immune

function in 109 postmenopausal women who participated in a year-long study of exercise and health in Seattle. Blood samples gathered at baseline and at 1 year were analyzed for levels of dioxin-like PCBs and tested for NK cell cytotoxicity and for phytohemagglutinin-induced T-lymphocyte proliferation. At baseline, the concentration of mono-ortho PCBs 105, 118, and 156 were not associated with lymphocyte proliferation; after a year, however, a decrease with increased levels of this set of PCBs ($p = 0.039$) was observed. No association of NK cytotoxicity with PCB levels was observed.

In a cross-sectional study of 1,063 men and 1,201 women living throughout Japan (who had not been occupationally exposed to dioxins), from 2002 to 2010, Nakamoto et al. (2013) gathered fasting blood samples for an assessment of environmental exposure to dioxin-like compounds (DLCs). Blood levels and corresponding TEQs were determined for dioxin-like polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and PCBs. A logistic regression that adjusted for age, sex, smoking habit, drinking habit, regional block, and survey year estimated the odds of self-reported histories of several allergic-like diseases by quartiles (picogram per gram [pg/g] lipid) for PCDDs/PCDFs, for PCBs, and for all DLCs. Self-reported asthma was not associated with any of these three groupings, while atopic dermatitis showed a marginally significant trend over quartiles for PCDDs/PCDFs ($p = 0.04$) and for all DLCs ($p = 0.02$), and allergic rhinitis did for PCDDs/PCDFs ($p = 0.04$), but not for all DLCs ($p = 0.14$). These results showed an association with exposure to dioxin and DLCs and a significantly decreased incidence of reported atopic dermatitis.

One study examined the link between environmental exposure to the COIs and autoimmunity. In 632 women and 670 men who participated in NHANES in 2003–2004, Gallagher et al. (2013) investigated the association of either non–dioxin-like or and dioxin-like PCBs and the levels of serum antinuclear antibodies (ANA), which are associated with autoimmune disorders. Among the women, after adjustments for mercury blood level, race, menopausal status, diet, and BMI, total TEQs for PCBs were significantly associated with positivity for ANA (intensity ≥ 3) for each higher quartile compared with the lowest and for overall trend ($p < 0.001$). This pattern was observed neither in women for non-dioxin–like PCBs nor in men for either type of PCBs.

Turunen et al. (2012) derived total TEQs for 17 PCDD/F and 37 PCB congeners in blood samples from 123 men and 132 women from a population with high fish consumption and analyzed their relationship with C-reactive protein (CRP), an indicator of inflammation. No evidence of a trend across the tertiles of overall TEQ concentration was seen for either men (0.29) or women ($p = 0.94$).

BIOLOGIC PLAUSIBILITY

There is an extensive body of evidence from experimental studies in animal-model systems indicating that TCDD, other dioxins, and several DLCs are

immunotoxic (Kerkvliet, 2009, 2012). Studies in laboratory mice show that the immunotoxicity of TCDD and DLCs depends on activation of the aryl hydrocarbon receptor (AHR). As most of the cell types involved in the immune system express the AHR, there are many potential pathways to immunotoxicity. TCDD-induced immunotoxicity is due primarily to changes in adaptive immune responses resulting in the suppression of both antibody-mediated and cell-mediated immunity. Dioxin and other AHR agonists may also reduce the clearance of infections and promote tumor growth through alterations in immune function. TCDD exposure alters macrophages and neutrophils such that it exacerbates some types of inflammation during infections and may contribute to the development of chronic inflammatory lung disease (Teske et al., 2005; Wong PS et al., 2010). Although there are many examples of dioxin and DLCs having immunosuppressive effects, these compounds also appear to influence autoimmune diseases, which are viewed as an inappropriate increase in immune function. Therefore, these compounds may be best described as immunomodulatory. Although the mechanisms of this immunomodulatory effect are not entirely clear, recently the tryptophan catabolite, kynurenine, was recognized as a ligand for the AHR and shown to function as a suppressor of allogenic T-cell proliferation (Opitz et al., 2011), providing a direct link between the AHR pathway and normal immune function.

TCDD has been shown to be a potent immunosuppressive chemical in laboratory animals and cell culture models. The relative potencies of given DLCs based on induction of hepatic enzymes—their toxicity equivalence factors (TEFs)—appear to predict the degree of immunosuppression induced (Smialowicz et al., 2008). The exposure of animals to dioxin not only suppresses some adaptive immune responses, but also has been shown to increase the incidence and severity of various infectious diseases and to increase the development of cancers (Choi et al., 2003; Elizondo et al., 2011; Fiorito et al., 2010, 2011; Head and Lawrence, 2009; Jin et al., 2010; Sanchez et al., 2010). It is consistent with its immunosuppressive effects that TCDD exposure suppresses the allergic immune response of rodents; this in turn results in decreased allergen-associated pathologic lung conditions and has been shown to suppress the development of experimental autoimmune disease (Quintana et al., 2008), to induce the suppression of autoimmune uveoretinitis (Zhang L et al., 2010), and to affect colitis (Takamura et al., 2011), arthritis (Nakahama et al., 2011), and inflammatory lung diseases, such as silicosis (Beamer et al., 2012).

Some current reports indicate that the AHR pathway plays an integral role in B-cell maturation, and that TCDD and DLC exposure may alter the B-cell and result in critical changes in the immune response (Baba et al., 2012; Sibilano et al., 2012; Simones and Shephard, 2011; Singh et al., 2011). Working with human B cells in vitro, Allan and Sherr (2010) demonstrated a new AHR-dependent mechanism by which exposure to environmental polycyclic aromatic hydrocarbons could suppress humoral immunity by blocking differentiation of B cells

into plasma cells. Recently, this finding was confirmed by data from human hemopoietic stem cells (HSCs) and knockout AHR mouse models showing that the AHR is critical in HSC maturation and differentiation (Fracchiolla et al., 2011; Singh et al., 2011a). Recently, using a novel pluripotent stem cell–based culture system, Smith et al. (2013) demonstrated that AHR expression and activity can direct human hematopoietic progenitor cell proliferation and differentiation. These data show that pluripotent hematopoietic human cells express AHR and that AHR agonists enhance erythroid differentiation, whereas antagonism of AHR favors the expansion of megakaryocyte cells. This finding is supportive of previous work indicating that B-cell activation results in increased AHR expression and that exposure of B-cells to B[a]P suppresses B-cell differentiation (Allan and Sherr, 2010). Lu H et al. (2010) demonstrated that although human B cells appeared less responsive to TCDD in increasing expression of AHR battery genes, TCDD's ability to decrease IgM production was similar in both mouse and human B cells. Data from Zhang et al. (2013) suggest that this decrease in IgM production is the result of a TCDD-mediated decrease in B-cell terminal differentiation, resulting in fewer IgM-producing cells. TCDD alters not only HSC maturation but also alters proliferation and migration in vivo and in vitro (Casado et al., 2011), which indicates that exposure may have multiple effects on immune-cell function.

Cellular immunity, mediated by the thymus and T cells, is also a target of TCDD/dioxin exposure and the AHR pathway. Early evidence indicated that dioxin and DLC alter cellular immunity, because it was observed that exposure to the chemicals resulted in thymic involution and suppressed cytotoxic T-lymphocyte activity (Hanieh, 2014). Recent attention has focused on the ability of the AHR to induce regulatory T cells, or Tregs (Kerkvliet, 2012; Marshall and Kerkvliet, 2010). Tregs have potent suppressive activity in the immune system, and their inappropriate induction by TCDD could account for much of the immune suppression. AHR activation in dendritic cells has also been shown to promote the development of Tregs by inducing tryptophan metabolism. AHR activation in B cells can directly disrupt the production of antibodies (Sulentic and Kaminski, 2011). The recent demonstration that AHR activation by TCDD leads to the development of Tregs helps explain the diversity of effects seen after exposure to TCDD (Funatake et al., 2008; Kerkvliet, 2012; Marshall et al., 2008; Quintana et al., 2008; Stockinger et al., 2011; Yamamoto and Shlomchik, 2010).

One ultimate effect of dysregulation of the immune system is an alteration of autoimmunity. Data from animal models and cell culture indicate that exposure to dioxin and DLCs alters the development of autoimmune disorders. For example, antagonism of the AHR represses the expression of cytokines and chemokines in primary human synovial fibroblasts (Lahoti et al., 2013), indicating a potential contribution to the inflammatory process of rheumatoid arthritis. Nguyen et al. (2013) have hypothesized that may occur when AHR stimulation of IL-17 production in Th17 cells overwhelms the immune suppressive effects of inhibition

of Treg differentiation. TCDD has also been shown to induce apoptosis in rabbit chondrocytes, which supports a potential role of TCDD in contributing in a novel way to arthritis (Yang and Lee, 2010). Exposure to TCDD was also shown to induce the reactivation of the latent form of the Epstein barr virus (EBV) in 19 patients with Sjogren's syndrome, an autoimmune disease, when compared to activation in 19 healthy patients (Inoue et al., 2012). Furthermore, a study of 18 people who had allergic asthma, 17 people whose asthma was controlled, and 12 controls showed that the plasma concentrations of IL-22 and the expression of the AHR in peripheral blood mononuclear cells was associated with the severity of allergic asthma; this finding strengthened the possibility that the AHR is involved in allergic asthma, thereby implying a role for dioxin exposure in this condition (Zhu et al., 2011). Thus, depending on the disease, TCDD exposure could exacerbate or ameliorate symptoms.

SYNTHESIS

Very few studies of humans and exposure to the COIs have addressed outcomes that would be considered disease states primarily due to perturbation of immune function. In the 30-year follow-up study of the Vietnam Experience Study, Boehmer et al. (2004) found no suggestion of excess deaths that could be attributed to immune-system disorders (risk ratio [RR] = 1.32, 95% confidence interval [CI] 0.50–3.47, for *International Classification of Diseases*, Revision 9 [ICD-9] 240–279, which covers endocrine, nutritional, metabolic, and immunity disorders).

Immune Suppression

One would expect exposure to substantial doses of TCDD to result in immune suppression in Vietnam veterans. However, several studies of various measures of human immune function failed to reveal consistent correlations with TCDD exposure, probably because the exposures were inadequate to produce immune suppression or because the characteristics measured were not among those most relevant with respect to biologic plausibility. No clear pattern of an increase in infectious disease has been documented in the studies of veterans exposed to TCDD or to the herbicides used in Vietnam. However, three occupational-exposure studies provide some support for the idea that exposure to TCDD may result in an altered immune response to some exposures and an increased frequency of infections. The study of a single highly exposed person (Brembilla et al., 2011) confirmed TCDD-associated changes in immune measures that may not be applicable to people whose exposure was considerably lower. Immune alteration and the frequency and duration of specific types of infections should therefore be a focus of future studies. Suppression of the immune response by TCDD might

increase the risk of some kinds of cancer in Vietnam veterans, but there is no evidence to support such an association.

Allergic and Autoimmune Diseases

Epidemiologic studies have been inconsistent with regard to TCDD's influence on IgE production in humans. No human studies have specifically addressed the influence of TCDD on autoimmune disease, but several animal studies have shown that TCDD suppresses the development of autoimmune diseases. The study of people who had allergic asthma or controlled asthma strengthened the data and suggested that the AHR (and thus dioxin exposure) is involved in the disease (Zhu et al., 2011). More studies are needed to determine the mechanism of TCDD-induced allergic and autoimmune disease, including rheumatoid arthritis.

Few effects of phenoxy herbicide or cacodylic acid exposure on the immune system have been reported in animals or humans, and no clear association between such exposure and autoimmune or allergic disease has been found. The exposure of laboratory animals to phenoxy herbicides or cacodylic acid has not been associated with immunotoxicity.

Inflammatory Diseases

Lee et al. (2007a) found a significant association between concentrations of dioxin-like PCBs and the prevalence of arthritis in women, but not in men. There is no experimental evidence to support that finding, but increased inflammatory responses could be involved. There are no other human data on the potential for dioxin or the herbicides of interest to induce dysregulation of inflammation that could contribute to an increased risk of inflammation-associated diseases.

Possible associations involving infectious or inflammation-related diseases should be a focus for the future. Examples of earlier studies whose results support the occurrence of such adverse outcomes are Baccarelli et al. (2002), Baranska et al. (2008), Beseler et al. (2008), Oh et al. (2005), O'Toole et al. (2009), Tonn et al. (1996), and Visintainer et al. (1995).

CONCLUSIONS

On the basis of the evidence reviewed here and in previous VAO reports, the present committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and any specific diseases involving immune suppression, allergy, autoimmunity, or inflammation.

TRANSLATION BETWEEN ANIMAL AND HUMAN STUDIES

Animal studies and in vitro studies with human cells and cell lines are important ways of trying to understand the underlying biologic mechanisms associated with immunotoxic and other responses to xenobiotics ("foreign" substances that do not normally occur in biologic systems). However, as discussed above, despite the vast array of data supporting the immunotoxicity of TCDD in laboratory animals, little evidence from studies of Vietnam veterans or other human populations suggests that exposure to TCDD or the herbicides of concern produce immune alterations that have directly observable and predictable functional consequences. Many factors must be considered in examining the relevance of animal and in vitro studies to human disease and disease progression, and they are discussed in Chapter 4. Here, we present the factors that are important in considering differences between the results of laboratory studies and the findings of observational epidemiologic studies.

Magnitude and Timing of Exposure

In general, the TCDD exposures used in animal studies have been orders of magnitude higher than the exposures that Vietnam veterans are likely to have received during military service. It is well known that the immune system is highly susceptible to xenobiotic exposure during critical stages of development, such as gestation, and that primary immune responses are easier to alter than secondary immune responses. In vivo studies show that exposure to antigens may be important, so the timing of antigen exposure relative to TCDD exposures may be an important variable.

Genetic Susceptibilities

Human immune diseases are likely to have complex etiologies and to be under the influence of numerous genes and gene–environment interactions (Dietert et al., 2010). Differences in AHR affinity between species may be a factor in animal-to-human extrapolation. For example, many strains of mice (AHR^b) are known to exhibit greater susceptibility of CYP1A1 induction and immune suppression than other strains (AHR^d). In contrast, a simple single-haplotype difference in susceptibility to TCDD has not been observed in humans. Rats appear to be more similar to the resistant AHR^d phenotype of mice in their sensitivity to TCDD. Indeed, it is difficult to produce immune suppression in rats with TCDD because of that, and there probably are other genetic reasons as well.

Sex Differences

There are well-known differences in susceptibility to xenobiotic exposures between male and female animals. There are probably multiple reasons for the differences, some of which may pertain to immunomodulation by sex steroids. Similarly, evidence suggests that specific immune-based health risks in humans have important sex differences. For example, women generally are much more susceptible than men to the development of several autoimmune diseases; such differences in humans may result from a combination of genetic factors and environmental exposures. One simple example of this is the fact that the gene associated with control (at least in part) of the T-regulatory immune cells (these cells can suppress some of the immune response) is located on the X chromosome. Hence, there are (at least conceptually) different mechanisms through which the immune system could be altered in men and women; the incomplete silencing of one X chromosome could alter the suppressive immune environment in women. This has ramifications for future studies. In considering the potential effects of the COIs on the immune system and the risk of disease, sex-based differences in chemically induced adverse immune outcomes need to be investigated. Future studies should ensure that—whether in animal models or in human studies—gene-specific or sex-specific immune effects are able to be evaluated with sufficient statistical power to support distinctions.

Stress

Stress is a well-known modifier of human immune responses. It is an ever-present variable that is difficult to assess or control for in epidemiologic studies. Stress, of course, is ever present in combatants and thus likely to play an important role in their immune response, which would be extremely difficult to estimate or to study.

8

Cancers

Chapter Overview

Based on new evidence and a review of prior studies, the committee for Update 2014 *determined that epidemiologic results concerning an association between exposure to the chemicals of interest (COIs) and bladder cancer had accrued to now constitute limited or suggestive evidence of an association. No other new significant associations between the relevant exposures and particular types of cancer were found. Aside from the conclusion concerning bladder cancer, current evidence supports the findings of earlier updates. Thus the current findings on cancer can be summarized as follows:*

- *There is sufficient evidence of an association with the COIs and soft tissue sarcomas and B-cell lymphomas (Hodgkin lymphoma, non-Hodgkin lymphomas, chronic lymphocytic leukemia, hairy cell leukemia).*
- *There is limited or suggestive evidence of an association between the COIs and bladder cancer; laryngeal cancer; cancers of the lung, bronchus, or trachea; prostate cancer; multiple myeloma, and amyloid light-chain (AL) amyloidosis.*
- *There is inadequate or insufficient evidence to determine whether there is* an *association between the COIs and any other specific type of cancer.*

Cancers are the second-leading cause of death in the United States. However, among men 60–75 years old, the group that includes most Vietnam veterans, the risk of dying from cancer exceeds the risk of dying from heart disease, the leading cause of death in the United States, and it does not fall to second place

until after the age of 75 years (Heron et al., 2009). About 589,430 Americans of all ages were expected to die from cancer in 2015—more than 1,500 per day. In the United States, one-fourth of all deaths are from cancer (Siegel et al., 2015).

This chapter summarizes—and presents conclusions about—the strength of the evidence from epidemiologic studies regarding associations between exposure to the COIs—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid—and various types of cancer. The committee also considers studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like chemicals (DLCs) informative if their results were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of specific congeners of DLCs. However, studies that report TEQs based only on mono-ortho PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given very limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the World Health Organization (WHO) revised toxicity equivalency factors (TEFs) of 2005 (La Rocca et al., 2008; van den Berg et al., 2006). If a new study reported on only a single type of cancer and did not revisit a previously studied population, then its design information is summarized here with its results; design information on all other new studies can be found in Chapter 6.

The objective of this chapter is to provide an assessment of whether the occurrence of various cancers in Vietnam veterans themselves may be associated with exposure they may have received during military service. Therefore, studies of childhood cancers in relation to parental exposure to the COIs are discussed in Chapter 10, which addresses possible adverse effects in the veterans' offspring. Studies that consider only childhood exposure are not considered relevant to the committee's charge.

In an evaluation of a possible connection between herbicide exposure and the risk of cancer, the approach used to assess the exposure of study subjects is of critical importance in determining the overall relevance and usefulness of findings. As noted in Chapters 3 and 6, there is great variation in the detail and the accuracy of exposure assessments among studies. A few studies used biologic markers of exposure, such as the presence of a chemical in serum or tissues; some developed an index of exposure from employment or activity records; and some used other surrogate measures of exposure, such as an individual's presence in a locale when herbicides were used. As noted in Chapter 2, an inaccurate assessment of exposure, a form of measurement error, can obscure the relationship between exposure and disease.

Each section on a type of cancer opens with background information, including data on its incidence in the general US population and known or suspected risk factors. Cancer-incidence data on the general US population are included in the background material to provide a context for consideration of the cancer risk in Vietnam veterans; the figures presented are estimates of incidence in the entire US population, not predictions for the Vietnam-veteran cohort. The data

reported are for 2008–2012 and are from the most recent dataset available (NCI, 2015). Incidence data are given for all races combined and also separately for blacks and whites. The age range of 60–74 years now includes about 80 percent of Vietnam-era veterans, and the incidences are presented for three 5-year age groups: 60–64 years, 65–69 years, and 70–74 years. The data were collected for the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute and are categorized by sex, age, and race, all of which can have profound effects on risk. For example, the incidence of prostate cancer is about 2.6 times as high in men who are 70–74 years old as in men 60–64 years old and about 75 percent higher in blacks 60–64 years old than in whites in the same age group (NCI, 2015). Many other factors can influence cancer incidence, including screening methods, tobacco and alcohol use, diet, genetic predisposition, and medical history. Those factors can make someone more or less likely than the average to contract a given kind of cancer; they also need to be taken into account in epidemiologic studies of the possible contributions of the COIs.

Each section of this chapter pertaining to a specific type of cancer includes a summary of the findings described in the previous Agent Orange[1] reports: *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994); *Veterans and Agent Orange: Update 1996*, referred to as *Update 1996* (IOM, 1996); *Update 1998* (IOM, 1999); *Update 2000* (IOM, 2001); *Update 2002* (IOM, 2003); *Update 2004* (IOM, 2005); *Update 2006* (IOM, 2007); *Update 2008* (IOM, 2009); *Update 2010* (IOM, 2011a); and *Update 2012* (IOM, 2014). That is followed by a discussion of the most recent scientific literature, a discussion of biologic plausibility, and a synthesis of the material reviewed. When it is appropriate, the literature is discussed by exposure type (service in Vietnam, occupational exposure, or environmental exposure). Each section ends with the committee's conclusion regarding the strength of the evidence from epidemiologic studies. The categories of association and the committee's approach to categorizing the health outcomes are discussed in Chapters 1 and 2.

Biologic plausibility corresponds to the third element of the committee's congressionally mandated statement of task. In fact, the degree of biologic plausibility itself influences whether the committee perceives positive findings to be indicative of an association or the product of statistical fluctuations (chance) or bias.

Information on biologic mechanisms by which exposure to TCDD could contribute to the generic (rather than tissue-specific or organ-specific) carcinogenic potential of the other COIs is summarized in Chapter 4. It distills toxicologic

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

information concerning the mechanisms by which TCDD affects the basic process of carcinogenesis; such information, of course, applies to all the cancer sites discussed individually in this chapter. When biologic plausibility is discussed in this chapter's sections on particular cancer types, the generic information is implicit, and only experimental data peculiar to carcinogenesis at the site in question are presented. A large literature indicates that carcinogenesis is a process that involves not only genetic changes but also epigenetic changes, which modify DNA and its expression without altering its sequence of bases (Johnstone and Baylin, 2010). There is increasing evidence that TCDD and the COIs may disturb cellular processes through epigenetic mechanisms (see Chapter 4), and reference to this evidence, as it applies to cancers, is included where it exists, by cancer site.

Considerable uncertainty remains about the magnitude of the risk posed by exposure to the COIs. Many of the veteran, occupational, and environmental studies reviewed by the committee did not control fully for important confounders. There is not enough information about the exposure experience of individual Vietnam veterans to permit combining exposure estimates for them with any potency estimates that might be derived from scientific research studies to quantify risk. The committee therefore cannot accurately estimate the risk to Vietnam veterans that is attributable to exposure to the COIs. The (at least currently) insurmountable problems in deriving useful quantitative estimates of the risks of various health outcomes in Vietnam veterans are explained in Chapter 1 and in the summary of this report, but the point is not reiterated for every health outcome addressed.

ORGANIZATION OF CANCER GROUPS

For *Update 2006*, the committee developed a system for addressing cancer types to clarify how specific cancer diagnoses had been grouped for evaluation by the committee and to ensure that the full array of cancer types would be considered. The organization of cancer groups follows the major and minor categories of cause of death related to cancer sites established by the National Institute for Occupational Safety and Health (NIOSH). The NIOSH groups map the full range of *International Classification of Diseases*, *9th Revision* (ICD-9) codes for malignant neoplasms (140–208). The ICD system is used by physicians and researchers to group related diseases and procedures in a standard form for statistical evaluation. Revision 10 (ICD-10) came into use in 1999 and represents a marked change from the previous four revisions that evolved into ICD-9. ICD-9 was in effect from 1979 to 1998; because ICD-9 is the version most prominent in the research reviewed in this series, it is used when codes are given for a specific health outcome. Appendix C describes the correspondence between the NIOSH cause-of-death groupings and ICD-9 codes (see Table C-1); the groupings for mortality are largely congruent with those of the SEER program for cancer incidence (see

Table C-2, which presents equivalences between the ICD-9 and ICD-10 systems). For the present update, the committee gave more attention to the WHO's classification of lymphohematopoietic neoplasms (WHO, 2008), which stresses partitioning of the disorders first according to the lymphoid or myeloid lineage of the transformed cells rather than into lymphomas and leukemias.

The system of organization used by the committee simplifies the process for locating a particular cancer for readers and facilitated the committee's identification of ICD codes for malignancies that had not been explicitly addressed in previous updates. The VAO reports' default category for any health outcome on which no epidemiologic research findings have been recovered has always been "inadequate evidence" of association with exposure to the COIs, which in principle is applicable to specific cancers. A failure to review a specific cancer or other condition separately reflects the paucity of information, so there is indeed inadequate or insufficient information to categorize an association with such a disease outcome.

BIOLOGIC PLAUSIBILITY

The studies considered by the committee that speak to the biologic plausibility of associations between exposure to the COIs and human cancers have been performed primarily in laboratory animals (rats, mice, hamsters, and monkeys) or in cultured cells.

Concerning 2,4-D, 2,4,5-T, and picloram, several studies have been performed in laboratory animals. In general, the results were negative although some would not meet current standards of cancer bioassays; for instance, there is a question whether the highest doses (generally 30–50 mg/kg) in some of the studies reached a maximum tolerated dose. It is not possible to have absolute confidence that these chemicals have no carcinogenic potential. Further evidence of a lack of carcinogenic potential is provided, however, by negative findings on genotoxic effects in assays conducted primarily in vitro. The results of such studies indicate that 2,4-D and 2,4,5-T are genotoxic only at very high concentrations.

There is evidence that cacodylic acid is carcinogenic. Studies performed in laboratory animals have shown that it can induce neoplasms of the kidney (Yamamoto et al., 1995), bladder (Arnold et al., 2006; Cohen et al., 2007b; Wang et al., 2009; Wei et al., 2002; Yamamoto et al., 1995), liver, and thyroid gland (Yamamoto et al., 1995). Treatment with cacodylic acid induced the formation of neoplasms of the lung when administered to mouse strains that are genetically susceptible to developing these tumors (Hayashi et al., 1998; Yamanaka et al., 2009). Other studies have used the two-stage model of carcinogenesis in which animals are exposed first to a known genotoxic agent and then to a suspected tumor-promoting agent; with this model, cacodylic acid has been shown to act

as a tumor-promoter with respect to lung cancer (Yamanaka et al., 1996). These studies are further discussed in Chapter 4.

Collectively, the evidence obtained from studies of TCDD indicates that a connection between human exposure to this chemical and cancers is biologically plausible, as will be discussed more fully in a generic sense below and more specifically in the biologic plausibility sections on individual cancers. Recent reviews have affirmed the well-established mechanistic roles of the aryl hydrocarbon receptor (AHR) in TCDD-induced cancers (Androutsopoulos et al., 2009; Barouki and Coumoul, 2010; Dietrich and Kaina, 2010; Murray et al., 2014; Ray and Swanson, 2009; Rysavy et al., 2013; Tsay et al., 2013). On the basis of these data, the biologic plausibility of an association between TCDD exposure and cancer has been firmly established in a mechanistic sense, and TCDD is considered a nongenotoxic carcinogen, as reviewed by Hernández et al. (2009). TCDD can disrupt circadian rhythms via the AHR, and chronic disruption of circadian rhythms is associated with an increased incidence of cancer, suggesting a potential additional pathway by which TCDD increases cancer risk (Wang C et al., 2014; Xu et al., 2013).

Studies in laboratory animals in which only TCDD has been administered have shown that it can increase the incidence of a number of neoplasms, most notably of the liver, lungs, thyroid, and oral mucosa (Kociba et al., 1978; NTP, 2006). Some studies have used the two-stage model of carcinogenesis and shown that TCDD can act as a tumor promoter and increases the incidence of ovarian cancer (Davis et al., 2000), liver cancer (Beebe et al., 1995), and skin cancers (Wyde et al., 2004). In exerting its carcinogenic effects, TCDD is thought to act primarily as a tumor promoter. In many of the animal studies reviewed, treatment with TCDD has resulted in hyperplasia or metaplasia of epithelial tissues. Work with a mouse lung cancer model suggests that in addition to increasing cell division, the tumor-promoting activity of TCDD includes decreasing apoptosis (Chen et al., 2014a). In addition, in both laboratory animals and cultured cells, TCDD has been shown to exhibit a wide array of effects on growth regulation, hormone systems, and other factors associated with the regulation of cellular processes that involve growth, maturation, and differentiation, in most cases via its interaction with AHR (Murray et al., 2014; Rysavy et al., 2013). Thus, it may be that TCDD increases the incidence or progression of human cancers through the interplay of multiple cellular mechanisms. Tissue-specific protective cellular mechanisms may also be important to the response to TCDD and may complicate our understanding of its site-specific carcinogenic effects.

As shown with long-term bioassays in both sexes of several strains of rats, mice, hamsters, and fish, there is adequate evidence that TCDD is a carcinogen in laboratory animals because it increases the incidence of tumors, including tumors at sites distant from the site of treatment, at doses well below the maximum tolerated dose (Rysavy et al., 2013). TCDD has frequently been characterized as a nongenotoxic carcinogen. TCDD is non-mutagenic because it does not produce

changes in DNA sequences, but because of the oxidative stress it produces, TCDD does have some genotoxic potential. This may contribute to its recognized activity as a potent tumor promoter and a weak initiator in two-stage initiation–promotion models for liver, skin, and lung. Early studies demonstrated that TCDD is two orders of magnitude more potent than the "classic" promoter tetradecanoyl phorbol acetate (TPA) and that its skin-tumor promotion depends on the AHR.

A number of potential pathways for TCDD carcinogenesis have been proposed. TCDD may contribute to tumor progression by inhibiting p53 regulation (phosphorylation and acetylation) triggered by genotoxic agents through the increased expression of the metastasis marker AGR2 (Ambolet-Camoit et al., 2010) and through a functional interaction between the AHR and FHL2—the "four and a half LIM protein 2," in which the LIM domain is a highly conserved protein structure (Kollara and Brown, 2009). Borlak and Jenke (2008) demonstrated that the AHR is a major regulator of c-Raf and proposed that there is cross-talk between the AHR and the mitogen-activated protein kinase signaling pathway in chemically induced hepatocarcinogenesis. TCDD inhibits ultraviolet-C radiation-induced apoptosis in primary rat hepatocytes and Huh-7 human hepatoma cells, and this finding supports the hypothesis that TCDD acts as a tumor promoter by preventing initiated cells from undergoing apoptosis (Chen et al., 2014b; Chopra et al., 2009). AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the cytokine interleukin-6, which has tumor-promoting effects in numerous tissues—including breast, prostate, and ovary—and opens up the possibility that TCDD would promote carcinogenesis in these and possibly other tissues (Hollingshead et al., 2008). In rat liver, TCDD downregulates reduced folate carrier (Rfc1) mRNA and protein, whose normal levels are essential in maintaining folate homeostasis (Halwachs et al., 2010). Reduced Rfc1 activity and a functional folate deficiency may contribute to the risk of carcinogenesis posed by TCDD exposure, perhaps via an epigenetic effect of interfering with DNA methylation levels (Davis and Uthus, 2004; Williams, 2012). Recent work has shown an interaction between the AHR and the *ADM* (adrenomedullin) oncogene in cell lines and lung tissue (Portal-Nunez et al., 2012), and AHR repression experiments in gastric and head and neck cancers suggest that AHR expression leads to increased cancer cell growth and invasion (DiNatale et al., 2012; Yin et al., 2013)

Additional in vitro work with mouse hepatoma cells has shown that activation of the AHR results in increased concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a product of DNA-base oxidation and a marker of DNA damage. The induction of cytochrome P4501A1 (CYP1A1) in these cells by TCDD or indolo(3,2-b)carbazole is associated with oxidative DNA damage (Park et al., 1996). In vivo experiments in mice corroborated those findings by showing that TCDD caused a sustained oxidative stress, as determined by measurements of urinary 8-OHdG (Shertzer et al., 2002) and involves AHR-dependent uncoupling of mitochondrial respiration (Senft et al., 2002). Mitochondrial reactive-oxygen

production depends on the AHR. Other than these observations of 8-OHdG formation and oxidative stress, there is little evidence that TCDD is genotoxic, and it appears likely that some of its mechanisms of action may involve epigenetic modifications of the genome.

Electronics-dismantling workers who experienced complex exposures, including exposure to polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDDs and PCDFs), had increased concentrations of urinary 8-OHdG, indicative of oxidative stress and genotoxicity; this cannot, however, be ascribed directly to these compounds (Wen et al., 2008). Clastogenic genetic disturbances arising as a consequence of confirmed exposure to herbicides were determined by analyzing sister-chromatid exchanges (SCEs) in lymphocytes from a group of 24 New Zealand Vietnam War veterans and 23 control volunteers (Rowland et al., 2007). The results showed a highly significant difference ($p < 0.001$) in mean SCE frequency between the group of veterans and the control group. These Vietnam War veterans also had a much higher proportion of cells with SCE frequencies above the 95th percentile than the controls (11.0 percent and 0.07 percent, respectively). A study of SCE frequencies in blood samples taken from Vietnamese women from high and moderate TCDD-sprayed areas also showed increased SCE frequencies of 2.40 per cell and 2.19 per cell, respectively, for these women compared with Vietnamese women from unexposed areas (1.48 per cell, $p < 0.001$) (Suzuki et al., 2014).

The weight of evidence that TCDD and dioxin-like PCBs make up a group of chemicals with carcinogenic potential includes unequivocal animal carcinogenesis and biologic plausibility based on mechanistic mode-of-action data. Although the specific mechanisms by which dioxin causes cancer remain to be definitively established, the intracellular factors and mechanistic pathways involved in dioxin's cancer-promoting activity all have parallels in both animals and humans. No qualitative differences have been reported to indicate that humans should be considered as fundamentally different from the multiple animal species in which bioassays have demonstrated dioxin-induced neoplasia. The International Agency on Cancer Research (IARC) has classified TCDD in group 1 as carcinogenic to humans and found the strongest evidence for carcinogenicity for all cancers combined and a positive association between exposure to TCDD and soft-tissue sarcomas, non-Hodgkin lymphomas, and lung cancer (IARC, 2012b). The combination of a positive association with TCDD exposure for these specific cancer sites no doubt contributes to the association with all cancers combined being the strongest, as reports of increased risks for several other cancers in TCDD-exposed workers and in the TCDD-exposed population in Seveso were only sporadic and not fully consistent.

Thus, the toxicologic evidence indicates that a connection of TCDD and perhaps cacodylic acid with cancer in humans is, in general, biologically plausible, but (as discussed in The Committee's View of "General" Human Carcinogens, below) it must be determined case by case whether such carcinogenic potential

contributes to an individual type of cancer. Experiments with 2,4-D, 2,4,5-T, and picloram in animals and cells have not provided a strong biologic basis for the presence or absence of carcinogenic effects.

THE COMMITTEE'S VIEW OF "GENERAL" HUMAN CARCINOGENS

To address its charge, the committee weighed the scientific evidence linking the COIs to specific individual cancer sites. That was appropriate given the different susceptibilities of various tissues and organs to cancer and the various genetic and environmental factors that can influence the occurrence of a particular type of cancer. Before considering each site in turn, however, it is important to address the concept that cancers share some characteristics among organ sites and to clarify the committee's view regarding the implications of a chemical being a "general" human carcinogen. All cancers share phenotypic characteristics: uncontrolled cell proliferation, increased cell survival, invasion outside normal tissue boundaries, and eventually metastasis. The current understanding of cancer development holds that a cell or group of cells must acquire a series of sufficient genetic mutations to progress and that particular epigenetic events must occur to accelerate the mutational process and provide growth advantages for the more aggressive clones of cells. Both genetic (mutational) and epigenetic (non-mutational) activities of carcinogenic agents can stimulate the process of cancer development.

In classic experiments based on the induction of cancer in mouse skin that were conducted more than 40 years ago, carcinogens were categorized as initiators, those capable of causing an initial genetic insult to the target tissue, and promoters, those capable of promoting the growth of initiated tumor cells, generally through non-mutational events. Some carcinogens, such as those found in tobacco smoke, were considered "whole carcinogens" or "complete carcinogens"—that is, they were capable of both initiation and promotion. Today, cancer researchers recognize that the acquisition of important mutations is a continuing process in tumors and that promoters, or epigenetic processes that favor cancer growth, enhance the accumulation of genotoxic damage, which traditionally would be regarded as initiating activity.

As discussed above and in Chapter 4, 2,4-D, 2,4,5-T, and picloram have shown little evidence of genotoxicity in laboratory studies, except at very high doses, and little ability to facilitate cancer growth in laboratory animals. However, cacodylic acid and TCDD have shown the capacity to increase cancer development in animal experiments, particularly as promoters rather than as pure genotoxic agents. Extrapolating organ-specific results from animal experiments to humans is problematic because of important differences between species in the overall susceptibility of various organs to cancer development and in organ-specific responses to particular putative carcinogens. Therefore, judgments

about the "general" carcinogenicity of a chemical in humans are based heavily on the results of epidemiologic studies, especially on the issue of whether there is evidence of an excess cancer risk at multiple organ sites. As the evaluations of specific types of cancer in the remainder of this chapter indicate, the committee finds that TCDD appears to be a multisite carcinogen. That finding is in agreement with IARC, which has determined that TCDD is a category 1 "known human carcinogen" (Baan et al., 2009; IARC, 2012b); with the US Environmental Protection Agency (EPA), which has concluded that TCDD is "likely to be carcinogenic to humans"[2]; and with the National Toxicology Program (NTP), which regards TCDD as "known to be a human carcinogen" (NTP, 2011). It is important to emphasize that the goals and methods of IARC and EPA in making their determinations were different from those of the present committee: Those organizations focus on anticipating hazards in order to minimize future exposure, whereas this committee focuses on risk after exposure. Furthermore, the recognition that TCDD and cacodylic acid are multisite carcinogens does not imply that they cause human cancer at every organ site.

The distinction between general carcinogen and site-specific carcinogen is more difficult to grasp in light of the common practice of beginning analyses of epidemiologic cohorts with a category of "all malignant neoplasms," which is a routine first screen for any unusual cancer activity in the study population rather than a test of a biologically based hypothesis. When the distribution of cancers among anatomic sites is not provided in the report of a cohort study, a statistical test for an increase in all cancers is not meaningless, but it is usually less scientifically supportable than analyses based on specific sites, for which more substantial biologically based hypotheses can often be developed. The size of a cohort and the length of the observation period often constrain the number of cancer cases that are observed and which specific types of cancer have enough observed cases to permit analysis. For instance, an analysis of the cumulative results on diabetes and cancers in the prospective Air Force Health Study (Michalek and Pavuk, 2008) produced important information summarizing previous findings on the fairly common condition of diabetes, but the cancer analysis does not go beyond "all cancers." The committee does not accept the cancer findings as an indication that exposure to herbicides increases the risk of every variety of cancer, but rather as an indication that the agent is carcinogenic to humans. The committee acknowledges that the results of the highly stratified analyses conducted suggest that the incidence of some cancers did increase in the Ranch Hand subjects, but it views the "all cancers" results as a conglomeration of information on specific cancers—most important, melanoma and prostate cancer, for which elevated results have been published (Akhtar et al., 2004; Pavuk et al., 2006)—and as meriting individual longitudinal analysis to resolve outstanding questions.

[2]See http://www.epa.gov/ttn/atw/hlthef/dioxin.html, updated January 2000, accessed September 21, 2013.

The literature search for this update identified several publications on populations with relevant exposures that included risk statistics for overall cancer incidence (McBride et al., 2013; Yi and Ohrr, 2014) or mortality (Kang et al., 2014; Lin et al., 2012; Wang et al., 2013), which were all somewhat elevated, although not necessarily significantly so. The most substantial elevation (standardized mortality ratio [SMR] = 1.70, 95% confidence interval [CI] 1.35–2.13) was seen among workers at a Chinese automobile foundry factory, where TCDD was only one of several toxic agents, but there was no consistent indication of elevated cancer risk associated with exposure to the VAO COIs specifically (Wang et al., 2013).

The committee notes that current information on overall mortality in US Vietnam veterans themselves has been elusive. Considerable confusion and alarm has arisen from Internet attribution of all of the approximately 800,000 deaths among all 9.2 million US Vietnam-era veterans to the 2.7 million who served in Vietnam (Brady, 2011; Gelman, 2013). The most recent reliable information was obtained in the 30-year update of mortality through 2000 of the deployed and era veterans in the Vietnam Experience Study (Boehmer et al., 2004), which found that mortality among the deployed veterans slightly exceeded that of their nondeployed counterparts, but was only about 9 percent. A follow-up study (O'Toole et al., 2010) of a random sample of 1,000 Australian Vietnam veterans selected from Australia's comprehensive roster of 57,643 service members deployed to Vietnam may provide a somewhat newer estimate of mortality through 2004; that study found mortality among Vietnam veterans to be 11.7 percent, which may be fairly comparable with that of their American fellows. The recent update on mortality among female US Vietnam veterans (Kang et al., 2014) stated that at the end of 2010, 20.2 percent of the deployed women in the cohort had died compared to 24.6 percent of those who remained in the United States. Because of considerable differences in mortality profiles for men and women, however, this does not provide a particularly accurate estimate for the large majority of American Vietnam veterans who are male.

The remainder of this chapter deals with the committee's review of the evidence on each individual cancer site in accordance with its charge to evaluate the statistical association between exposure and cancer occurrence, the biologic plausibility and potential causal nature of the association, and the relevance to US veterans of the Vietnam War.

A number of studies of populations that received potentially relevant exposures were identified in the literature search for this review but did not characterize exposure with sufficient specificity for their results to meet the committee's criteria for inclusion in the evidentiary database. For instance, the British Pesticide Users Health Study has followed almost 60,000 men and 4,000 women who were certified for agricultural pesticide use in Great Britain since 1987. Frost et al. (2011) reported cancer incidence and mortality in this cohort up to 2004 for the full array of anatomic sites, but exposure was defined only as being

a member of this cohort. Therefore, the cancer-specific findings of Frost et al. (2011) will not be repeatedly noted in the individual sections below. That is also the case for the mortality follow-up of Japanese Americans in the Honolulu Heart Program reported by Charles et al. (2010). Technically, this rubric would apply to the mortality and morbidity results reported by Waggoner et al. (2011) and Koutros et al. (2010a); however, because of the context provided by the extensive pesticide-specific results that have been published on individual cancers in the Agricultural Health Study (AHS) and the knowledge that 2,4-D was one of the most frequently used pesticides in this large prospective cohort, those results are presented below, but not given full evidentiary weight. Numerous cancer studies of the case-control design addressing particular cancers had exposure characterizations that were no more specific than job titles, farm residence, or pesticide exposure; therefore, their results are not regarded as fully relevant for the purpose of this review, and such studies are mentioned only in passing in a discussion of the cancer investigated.

ORAL, NASAL, AND PHARYNGEAL CANCERS

Oral, nasal, and pharyngeal cancers are found in many anatomic sites: the structures of the mouth (inside lining of the lips, cheeks, gums, tongue, and hard and soft palate—ICD-9 codes 140–145), oropharynx (ICD-9 146), nasopharynx (ICD-9 147), hypopharynx (ICD-9 148), other buccal cavity and pharynx (ICD-9 149), and nasal cavity and paranasal sinuses (ICD-9 160). Although the above cancers are classified together in the same category, the epidemiological risk factors for cancers that occur in the oral cavity and pharynx are very different from the risk factors for cancer of the nasopharynx. We now recognize that, in addition to cigarette smoking and alcohol consumption, infection with human papilloma virus (HPV), particularly alpha HPV16, is an important risk factor for squamous-cell carcinoma of the head and neck, and risk estimates are highest for cancers of the base of the tongue, tonsils, and oropharynx (collectively classified as oropharyngeal cancers) (Gillison et al. 2000; Marur et al., 2010; Oliveira et al., 2012).

The American Cancer Society (ACS) estimated that about 45,780 men and women would receive diagnoses of oral cavity or pharyngeal cancers in the United States in 2015 and that 8,650 men and women would die from these cancers (Siegel et al., 2015). Almost 90 percent of those cancers originate in the oral cavity or oropharynx. Most oral, nasal, and pharyngeal cancers are squamous-cell carcinomas. Nasopharyngeal carcinoma (NPC) is the most common malignant epithelial tumor of the nasopharynx but is relatively rare in the United States. There are three types of NPC: keratinizing squamous-cell carcinoma, nonkeratinizing carcinoma, and undifferentiated carcinoma. The average annual incidence rates reported in Table 8-1 show that men are at greater risk than women to be diagnosed with these cancers and that the incidence rates increase with age. However, because of the small number of cases, incidence rates should

TABLE 8-1 Average Annual Incidence (per 100,000) of Nasal, Oral Cavity, and Pharyngeal Cancers in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Nose, Nasal Cavity, and Middle Ear:									
Men	2.3	2.3	2.2	2.8	2.8	2.2	3.8	3.8	3.8
Women	1.3	1.3	0.8	1.5	1.5	1.3	2.1	2.2	0.9
Oral Cavity and Pharynx:									
Men	53.5	55.9	52.3	59.8	62.2	59.4	61.5	64.5	53.6
Women	15.9	16.7	13.5	19.8	21.0	16.4	24.2	25.7	18.0

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

be interpreted with caution. Tobacco and alcohol use are well-established risk factors and also contribute synergistically to the incidence of oral cavity and pharyngeal cancers, and, as mentioned above, infection with HPV is a major risk factor for oropharygeal cancers (Hashibe et al., 2007, 2009; Kreimer et al., 2013; Michaud et al., 2014; Oliveira et al., 2012). Ecological studies in the United States have shown that between 2001 and 2010 the incidence rates for cancers of the oral cavity went down (possibly because of decreasing prevalence of smoking), whereas incidence rates for oropharyngeal cancers have increased annually by 2.9 percent, which has been attributed to HPV infection (Chaturvedi et al., 2011).

Reported risk factors for nasal cancer include occupational exposure to nickel and chromium compounds (d'Errico et al., 2009; Feron et al., 2001; Grimsrud and Peto, 2006), wood dust (d'Errico et al., 2009), leather dust (Bonneterre et al., 2007), and high doses of formaldehyde (Nielsen and Wolkoff, 2010), as well as infection with Epstein–Barr virus.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COI and oral cavity, nasal, and pharyngeal cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion.

In *Update 2006*, at the request of the Department of Veterans Affairs (VA), the committee attempted to evaluate tonsil cancer cases separately, but it was able to identify only three cohort studies that provided the number of tonsil cancer cases in their study populations and concluded that the studies did not provide sufficient evidence to determine whether an association existed between exposure

to the COIs and tonsil cancer. No new published studies have offered any important additional insight into this specific question. The committee responsible for *Update 2006* recommended that VA evaluate the possibility of studying health outcomes, including tonsil cancer, in Vietnam-era veterans by using existing administrative and health-services databases. Anecdotal evidence provided to that committee suggested a potential association between the exposures in Vietnam and tonsil cancer. Increasing evidence indicating that some cancers of the oropharynx and oral cavity can have a viral (HPV) etiology is consistent with the potential mechanistic hypothesis explaining an excess of these cancers in Vietnam veterans: Immune alterations associated with herbicide exposure may have increased susceptibility to HPV infection in the oral cavity and tonsils of Vietnam veterans, thereby making them more prone to the development of squamous-cell carcinomas of these tissues. The present committee strongly reiterates the 2006, 2008, 2010, and 2012 recommendation that VA develop a strategy that uses existing databases to evaluate tonsil cancer in Vietnam-era veterans.

In *Update 2010*, Cypel and Kang (2010) reported on a follow-up study of Vietnam-era Army Chemical Corps (ACC) veterans, comparing mortality through 2005 in ACC veterans by Vietnam service. They reported a non-significant increase in oral cavity and pharyngeal cancers in the deployed cohort compared with cases in the non-deployed cohort—a result that is consistent with a prior report on mortality through 1991 (Dalager and Kang, 1997). McBride et al. (2009a) reported on mortality through 2004 in the New Zealand cohort of 1,599 workers who had been employed in manufacturing phenoxy herbicides from trichlorophenol (TCP); picloram was also produced in the plant. They reported a non-significant excess in mortality from buccal cavity and pharyngeal cancers, but there were no deaths from nasopharyngeal cancers in either group.

In *Update 2012*, several occupational cohort studies reported on cancers of the oral cavity or pharynx, but the evidence was inconsistent. Studies of workers at Dow's plant in Midland, Michigan, and in the NIOSH pentachlorophenol (PCP) cohort reported no increases in incidence (Burns CJ et al., 2011) or mortality (Ruder and Yiin, 2011) from oral cavity and pharyngeal cancers. By contrast, Manuwald et al. (2012) reported significantly increased mortality from cancers of the lip, oral cavity, or pharynx (SMR = 2.17, 95% CI 1.08–3.87) in a cohort of male and female chemical plant workers versus Hamburg's general population.

The existing evidence from all published studies conducted among Vietnam veterans or various occupational cohorts reporting on the incidence of or mortality from cancers of the nose, oral cavity, or pharynx is largely inconclusive. The majority of these studies have reported no association or non-significant modest excesses in risk, while not characterizing exposure as specifically as needed for the committee's decision making. In addition, the small numbers of oral, nasal, or pharyngeal cancer cases reported, in combination with a general lack of information on the smoking and drinking habits or HPV exposure status of the study participants, limit the interpretation of the data.

Studies evaluated previously and in the present report are summarized in Table 8-2.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

There have been no studies of US Vietnam veterans evaluating exposure to the COIs and oral, nasal, or pharyngeal cancers since *Update 2012*. However, two recent cohort studies of Vietnam War veterans (a majority of them males) from New Zealand and Korea reported on cancer incidence and mortality for cancers of the oral cavity, nasal cavity, and pharynx.

McBride and colleagues (2013) followed 2,783 male veterans from New Zealand who served in Vietnam from 1964 through 1972 for cancer incidence and mortality from 1988 through 2008 and compared them with the general population of New Zealand. With regard to incident head and neck cancers (n = 19), which by their definition excluded cancers of the larynx and esophagus, there was a modestly increased risk, albeit not a statistically significant one (standardized incidence ratio [SIR] = 1.34, 95% CI 0.81–2.09). A similar increase (SIR = 1.32, 95% CI 0.78–2.08) was observed when the analysis was restricted to cancers of the oral cavity, pharynx, and larynx (excluding cancers of lip, sinus cavities, or salivary glands) (n = 18). There were five incident cases and two deaths from laryngeal cancer in this cohort. Using the same groupings for cancer mortality, McBride et al. (2013) reported substantial and significant increased risks of death from head and neck cancers (SMR = 2.20, 95% CI 1.09–3.93) and from cancers of the oral cavity, pharynx, and larynx (SMR = 2.13, 95% CI 1.06–3.81) among the New Zealand Vietnam veterans based on 11 deaths in each grouping. McBride et al. (2013) did not report on nasal cancer separately.

Although the follow-up of the cohort of New Zealand Vietnam veterans was relatively long (20 years), the study did not have information on cancer incidence and mortality in the time period immediately after the service. In addition, information on potential confounding factors including smoking, drinking habits, and HPV status was not available, which limits the interpretation of the data, particularly regarding incident cancers. However, the greater than two-fold excess risks of mortality from head and neck cancers as well as from cancers of the oral cavity, pharynx, and larynx cannot be completely attributed to confounding by smoking, because excess risks were not found in this cohort for deaths from other smoking-related diseases such as lung cancer, chronic obstructive pulmonary disease (COPD), or coronary heart disease. Finally, because of the small sample size, the study did not report on tonsillar cancers specifically.

Several recent publications examined incidence (Yi, 2013; Yi and Ohrr, 2014) and mortality (Yi et al., 2014b) for cancers of the oral cavity, nasal cavity, and pharynx in the Korean Veterans Health Study, a large prospective cohort of

TABLE 8-2 Selected Epidemiologic Studies—Oral, Nasal, and Pharyngeal Cancers (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	Akhtar et al., 2004
Incidence			
Ranch Hand veterans (n = 1,189)	6	0.9 (0.4–1.9)	
With tours between 1966–1970	6	1.1 (0.5–2.3)	
SEA comparison veterans (n = 1,776)	5	0.6 (0.2–1.2)	
With tours between 1966–1970	4	0.6 (0.2–1.4)	
Mortality			
Through 1999—White subjects vs national rates			
Ranch Hand veterans (n = 1,189)	0	0.0 (nr)	
SEA comparison veterans (n = 1,776)	1	0.5 (nr)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality—Oral cavity and pharyngeal cancer			
Through 2005			Cypel and Kang, 2010
Deployed (2,872) vs non-deployed (2,737)	6 vs 2	1.7 (0.3–8.7)	
Army Chemical Corps vs US men			
Vietnam cohort	6	1.5 (0.6–3.3)	
Non-Vietnam cohort	2	0.8 (0.1–2.8)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000 (ICD-9 140–149)	6	nr	Boehmer et al., 2004
US CDC Selected Cancers Study—Case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953		**All COIs**	CDC, 1990a
89 nasopharyngeal carcinomas			
Vietnam service	3	0.5 (0.2–1.8)	
62 nasal carcinomas			
Vietnam service	2	0.7 (0.2–2.9)	
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed (lip, oral cavity, pharynx)	12	1.0 (0.5–1.8)	Visintainer et al., 1995

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000 (head and neck)	247	1.5 (1.3–1.6)	ADVA, 2005b
Navy	56	1.6 (1.1–2.0)	
Army	174	1.6 (1.3–1.8)	
Air Force	17	0.9 (0.5–1.5)	
Mortality			
All branches, return–2001			ADVA, 2005a
Head and neck	101	1.4 (1.2–1.7)	
Navy	22	1.5 (0.9–2.1)	
Army	69	1.5 (1.1–1.8)	
Air Force	9	1.1 (0.5–2.0)	
Nasal	3	0.8 (0.2–2.2)	
1980–1994			CDVA, 1997a
Lip (ICD-9 140)	0	nr	
Nasopharyngeal cancer (ICD-9 147)	2	0.5 (0.1–1.7)	
Nasal cavities (ICD-9 160)	2	1.2 (0.1–4.1)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000			ADVA, 2005c
Head and neck	44	2.0 (1.2–3.4)	
Mortality			
1966–2001			ADVA, 2005c
Head and neck	16	1.8 (0.8–4.3)	
Nasal	0	0.0 (0.0–48.2)	
1982–1994			CDVA, 1997b
Nasopharyngeal cancer (ICD-9 147)	1	1.3 (0.0– > 10)	
Nasal cavities (ICD-9 160)	0	0.0 (0.0– > 10)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)			
Head and neck	19	1.3 (0.8–2.1)	
Oral cavity, pharynx and larynx	18	1.3 (0.8–2.1)	

continued

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality (1988–2008)			
Head and neck	11	2.2 (1.1–3.9)	
Oral cavity, pharynx and larynx	11	2.1 (1.1–3.8)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)			Yi and Ohrr, 2014
Lip (C00)	1 vs 2	1.4 (0.1–26.2)	
Tongue (C01–C02)	17 vs 14	1.0 (0.5–2.2)	
Mouth (C03–C06)	23 vs 9	2.5 (1.1–5.7)	
Salivary gland (C07–C08)	13 vs 2	7.0 (1.5–32.3)	
Tonsil (C09)	10 vs 12	0.9 (0.4–2.2)	
Other oropharynx (C10)	6 vs 3	2.0 (0.5–8.2)	
Nasopharynx (C11)	21vs 29	0.7 (0.4–1.2)	
Hypopharynx (C12–C13)	18 vs 12	1.0 (0.5–2.2)	
Nose, sinuses, etc. (C30–C31)	11 vs 8	1.8 (0.7–4.7)	
Mortality (1992–2005)			Yi et al., 2014b
Oral cavity cancer (C00–C14)			
Categorized high vs low	45 vs 37	1.1 (0.7–1.7)	
HR per unit of log EOI (n = 180,639)	82	1.1 (0.9–1.2)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992			Kogevinas et al., 1997
Oral cavity, pharynx cancer (ICD-9 140–149)	26	1.1 (0.7–1.6)	
13,831 exposed to highly chlorinated PCDDs	22	1.3 (0.8–2.0)	
7,553 not exposed to highly chlorinated PCDDs	3	0.5 (0.1–1.3)	
Nasal, nasal sinus cancer (ICD-9 160)	3	1.6 (0.3–4.7)	
13,831 exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.5)	
7,553 not exposed to highly chlorinated PCDDs	3	3.8 (0.8–11.1)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Bucal cavity, pharynx (ICD-8 140–149)	11	1.2 (0.6–2.1)	
Nose, nasal cavities (ICD-8 160)	3	2.9 (0.6–8.5)	

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983			Coggon et al., 1986
Lip (ICD-9 140)	0	nr	
Tongue (ICD-9 141)	1	1.1 (0.0–6.2)	
Pharynx (ICD-9 146–149)	1	0.5 (0.0–3.0)	
Nose (ICD-9 160)	3	4.9 (1.0–14.4)	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991 (lip, oral cavity, pharynx)			Hooiveld et al., 1998
All working anytime in 1955–1985	1	2.3 (0.1–12.4)	
Cleaned up 1963 explosion	1	7.1 (0.2–39.6)	
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All for plants—Buccal cavity, pharynx (ICD-9 140–149)	9	3.0 (1.4–5.6)	Becher et al., 1996
Tongue	3	nr	
Floor of mouth	2	nr	
Tonsil	2	nr	
Pharynx	2	nr	
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4, 5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	6	8.2 (3.0–17.9)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (*not* part of IARC)		**Focus on TCDD**	

continued

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Through 1987		*90% CI*	Zober et al., 1990
Buccal cavity, pharynx	1	4.8 (0.3–22.9)	
Squamous-cell carcinoma of tonsil	1	nr	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 140–149)	11	2.2 (1.1–3.9)	Manuwald et al., 2012
Men	9	2.0 (0.9–3.8)	
Women	2	3.4 (0.4–12.5)	
Mortalilty 1952–1989	3	1.8 (0.4–5.2)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004 (buccal cavity and pharynx)			McBride et al., 2009a
Ever-exposed workers	3	2.6 (0.5–7.6)	
Never-exposed workers	0	0.0 (0.0–11.5)	
Production Workers— Mortality 1969–2000			
713 men and 100 women worked > 1 month in 1969–1984 (ICD-9)	2	2.8 (0.3–9.9)	't Mannetje et al., 2005
Lip (140)	0	nr	
Mouth (141–145)	2	5.4 (0.7–20.0)	
Oropharynx (146)	0	nr	
Nasopharynx (147)	0	0.0 (0.0–41.8)	
Hypopharynx, other (148–149)	0	nr	
Phenoxy herbicide sprayers (> 99% men)	1	1.0 (0.0–5.7)	't Mannetje et al., 2005
Lip (140)	0	nr	
Mouth (141–145)	0	0.0 (0.0–7.5)	
Oropharynx (146)	0	nr	
Nasopharynx (147)	1	8.3 (0.2–46.3)	
Hypopharynx, other (148–149)	0	nr	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All Dow PCP-Exposed Workers (All workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
1940–2005 (n = 2,122) (buccal, pharynx; ICD-9 140–149)	5	0.8 (0.3–1.8)	
PCP and TCP (n = 720)	1	0.5 (0.0–2.7)	
PCP (no TCP) (n = 1,402)	4	0.9 (0.2–2.3)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354 (Cohort 3)	7	1.1 (0.4–2.2)	Burns CJ et al., 2011
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM (oral cavity, pharynx)			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	33	0.9 (0.6–1.3)	
Ever	15	0.5 (0.3–0.9)	
Danish male, female paper workers			Rix et al., 1998
Buccal cavity (ICD-7 140–144)			
Men	24	1.0 (0.7–1.5)	
Women	4	1.5 (0.4–3.8)	
Pharynx (ICD-7 145–149)			
Men	15	2.0 (1.1–3.3)	
Women	2	2.1 (0.2–7.6)	
Tonsil cancers among pharyngeal cancers	11	nr	
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977		*90% CI*	Robinson et al., 1986
Buccal cavity, pharynx (ICD-7 140–148)	1	0.1 (0.0–0.7)	
Nasal (ICD-7 160)	0	nr	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Danish self-employed farmers			
Lip	182	1.8 ($p < 0.05$)	
Tongue	9	0.6 (nr)	

continued

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Salivary glands	13	0.9 (nr)	
Mouth	14	0.5 ($p < 0.05$)	
Pharynx	13	0.3 ($p < 0.05$)	
Nasal cavities, sinuses	11	0.6 (nr)	
Danish farming employees			
Lip	43	2.1 ($p < 0.05$)	
Tongue	2	0.6 (nr)	
Salivary glands	0	0.0 (nr)	
Mouth	0	0.0 ($p < 0.05$)	
Pharynx	9	1.1 (nr)	
Nasal cavities, sinuses	5	1.3 (nr)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (buccal cavity, pharynx, ICD-7 140–148)		**Herbicides**	Hansen et al., 2007
10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	6	1.1 (0.4–2.5)	
25-yr follow-up (1975–2001)			
Born before 1915 (high exposure)	3	0.7 (0.2–2.3)	
Born 1915–1934 (medium exposure)	6	0.7 (0.3–1.4)	
Born after 1934 (low exposure)	0	0.0 (0.0–1.0)	
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) *not* IARC		**Phenoxy herbicides**	Asp et al., 1994
Buccal, pharynx (ICD-8 140–149)			
Incidence	5	1.0 (0.3–2.3)	
Mortality 1972–1989	0	0.0 (0.0–3.0)	
"Other Respiratory" (ICD-8 160, 161, 163)—nose, larynx, pleura			
Incidence	4	1.1 (0.3–2.7)	
Mortality 1972–1989	1	0.5 (0.0–2.9)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (buccal cavity, pharynx)	18	0.3 (0.2–0.5)	Torchio et al., 1994
Italian Farmers—mortality odds ratios from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	13	0.9 (nr)	
Employee	4	0.5 (nr)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 649 incident buccal cavity cancer cases and 49 incident nasopharynx cancer cases vs 19,904 men with any incident cancer			Reif et al., 1989

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Forestry workers (n = 134)		**Herbicides**	
Buccal cavity	3	0.7 (0.2–2.2)	
Nasopharynx	2	5.6 (1.6–19.5)	
Aged 20–59	1	3.5 (0.6–22.6)	
Aged ≥ 60	1	13.4 (2.7–65.1)	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Nasopharynx	0	—	
NORWEGIAN farmers born 1925–1971—incidence, lip cancer		**Pesticides**	Nordby et al., 2004
Reported pesticide use	nr	0.7 (0.4–1.0)	
SWEDEN			
Swedish pesticide applicators—incidence			Wiklund et al., 1989a
Lip cancer	14	1.8 (1.0–2.9)	
Incident cancer cases 1961–1973 with agriculture as economic activity in 1960 census (male, female)		*99% CI*	Wiklund, 1983
Lip	508	1.8 (1.6–2.2)	
Tongue	32	0.4 (0.2–0.6)	
Salivary gland	68	1.0 (0.7–1.4)	
Mouth	70	0.6 (0.5–0.8)	
Throat	84	0.5 (0.4–0.7)	
Nose, nasal sinuses	64	0.8 (0.6–1.2)	
THE NETHERLANDS			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000			Swaen et al., 2004
Nose	0	—	
Pharynx	0	—	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	21	2.3 (1.4–3.5)	
Nonwhites (n = 11,446)	0	—	
Women			
Whites (n = 2,400)	1	12.2 (0.2–68.0)	
Nonwhites (n = 2,066)	0	0.0 (0.0–103.6)	

continued

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	93	0.6 (0.5–0.7)	
Commercial applicators	5	0.5 (0.2–1.3)	
Spouses	22	0.6 (0.4–1.0)	
Enrollment through 2002—buccal cavity			Alavanja et al., 2005
Private applicators (men and women)	66	0.7 (0.5–0.8)	
Lip	25	1.4 (0.9–2.1)	
Spouses of private applicators (> 99% women)	14	0.7 (0.4–1.2)	
Lip	2	1.4 (0.2–5.1)	
Commercial applicators	5	0.9 (0.3–2.2)	
Lip	3	2.7 (0.6–8.0)	
Mortality			
Enrollment through 2007, vs state rates (buccal cavity, pharynx)	16	0.3 (0.2–0.6)	Waggoner et al., 2011
Enrollment through 2000, vs state rates (buccal cavity, pharynx)			Blair et al., 2005a
Private applicators (men and women)	5	0.3 (0.1–0.7)	
Spouses of private applicators (> 99% women)	0	0.0 (0.0–25.4)	
White Male Residents of Iowa—Lip cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR	20	2.1 ($p < 0.01$)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Buccal cavity (140–149)			

TABLE 8-2 Oral, Nasal, and Pharyngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Zone B	6	1.7 (0.8–3.9)	
Zone R	28	1.2 (0.8–1.7)	
Nose, nasal cavities (160)			
Zone R	0	nr	
10-yr follow-up to 1991—women			Bertazzi et al., 1993
Buccal cavity (140–149)			
Zone B	0	nr	
Zone R	0	nr	
Nose, nasal cavities (160)			
Zone R	2	2.6 (0.5–13.3)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
US males born 1929–1953, all 70 nasal cancers (carcinomas, 11 lymphomas, 5 sarcomas) in CDC (1990a) study population		**Herbicides, pesticides**	Caplan et al., 2000
Selected landscaping, forestry occupation	26	1.8 (1.1–3.1)	
Living, working on farm	23	0.5 (0.3–0.8)	
Herbicides, pesticides	19	0.7 (0.4–1.3)	
Phenoxy herbicides	5	1.2 (0.4–3.3)	
International Case-Control Studies			
Residents of northern **Sweden** (44 nasal, 27 nasopharyngeal cancers)		**Phenoxy acids, chlorophenols**	Hardell et al., 1982
Phenoxy herbicide exposed	8	2.1 (0.9–4.7)	
Chlorophenol exposure	9	6.7 (2.8–16.2)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, 2,4-dichlorophenoxypropanoic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2 methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupational specialty; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxins (highly chlorinated, if four or more chlorines); PCP, pentachlorophenol; PCMR, proportionate cancer mortality ratios; PM, proportionate mortality; PMR, proportionate mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veteran Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

185,265 male Vietnam veterans who were alive in 1992 and were followed for cancer incidence through 2003 and for mortality through 2005. For the internal comparison analysis of high- versus low-exposure categories derived from the Exposure Opportunity Index (EOI) scores generated by the EOI model, Yi and Ohrr (2014) reported statistically significant increased hazard ratios (HRs) for cancers of the mouth [ICD-10 C03–C06] (HR = 2.54, 95% CI 1.13–5.70) and salivary glands [ICD-10 C07–C08] (relative risk [RR] = 6.98, 95% CI 1.50–32.3), and a non-significant increase in the risk of oropharyngeal cancer [ICD-10 C10] (HR = 1.98, 95% CI 0.48–8.17). Tonsil cancer [ICD-10 C09], which is rarely reported separately, has been the object of some focused attention in VAO updates, but no difference between the high- and low-exposure groups was found (HR = 0.88, 95% CI 0.35–2.20). Differences in incidence also were not observed for the other head and neck cancers analyzed separately: lip [ICD-10 C10], tongue [ICD-10 C01–C02], nasopharynx [ICD-10 C11], hypopharynx [ICD-10 C12–C13], and nose and sinuses [ICD-10 C30–C31]. In contrast to the incidence analyses of separate head and neck cancers, Yi et al. (2014b) reported only on these cancers as a group defined by ICD-10 codes C00–C14 and found no association when comparing the high- versus low-exposure categories (HR = 1.07, 95% CI 0.68–1.68, based on a total of 82 deaths, with 45 of them in high-exposure category) nor in the analysis based on the logarithms of the individual EOI scores (HR = 1.05, 95% CI 0.94–1.17).

Occupational, Environmental, and Case-Control Studies

There have been no occupational, environmental, or case-control studies of exposure to the COIs and oral, nasal, or pharyngeal cancers published since *Update 2012*.

Biologic Plausibility

As noted above, evidence exists linking HPV to cancers of the head and neck (Marur et al., 2010; Szentirmay et al., 2005), to tonsillar and base-of-tongue cancers (Ramqvist et al., 2015), and to oropharyngeal cancers in particular (Gillison and Shah, 2001; Gillison et al., 2012). There is considerable evidence from laboratory studies that TCDD may increase susceptibility to viral infection, but to date it is unknown whether exposure to the other COIs contributes to susceptibility to viral infection or action, however, this potential link warrants further exploration. Moreover, the sparseness of data on the specific tumor site and a general lack of information on smoking, drinking, and viral exposure status in the few available epidemiologic studies preclude exploration of this hypothesis in the current literature.

Long-term animal studies have examined the effects of exposure to the COIs on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). An NTP study (Yoshizawa et al., 2005a) reported

an increase in the incidence of gingival squamous-cell carcinoma in female rats treated orally (by gavage) with TCDD at 100 ng/kg 5 days/week for 104 weeks. The incidence of gingival squamous-cell hyperplasia was significantly increased in all groups treated at 3–46 ng/kg. In addition, squamous-cell carcinoma of the oral mucosa of the palate was increased. This NTP study did not, however, find any pathologic effect of TCDD on nasal tissues (Nyska et al., 2005). Increased neoplasms of the oral mucosa were previously observed and described as carcinomas of the hard palate and nasal turbinates (Kociba et al., 1978). Kociba et al. (1978) also reported a small increase in the incidence of tongue squamous-cell carcinoma.

Recently, DiNatale et al. (2012) utilized head and neck squamous-cell carcinoma cell lines to investigate mechanisms for tumor progression associated with AHR activation. This tumor type typically produces large amounts of cytokines, and its IL6 expression levels correlate with disease aggressiveness. In this model, AHR activation by TCDD enhances IL-6 production induced by another cytokine (IL 1β), so TCDD may promote head and neck squamous-cell carcinoma.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Tonsil cancers, or more generally squamous-cell carcinomas, remain of interest to Vietnam veterans and the committee, but very limited new information on them with respect to possible herbicide exposure became available in this update. The Korean Health Study did not find an association between herbicide exposure and the risk of tonsillar cancers. However, the Korean study reported a statistically significant 2.5-fold increased risk for oral cancer and a suggestive increase for oropharyngeal cancers, excluding tonsils, associated with the herbicide exposure group (Yi and Ohrr, 2014). There is some uncertainty about the reliability of exposure estimates derived from EOI scores used in studying the Korean Vietnam veterans. Moreover, a lack of information on potential confounding factors such as smoking, alcohol, and HPV exposure limits the interpretation of the results for the few positive associations. Among New Zealand veterans there was modest increased risk for incident head and neck cancers, but a significant 2.2-fold increased risk of death from head and neck cancers in comparison to general population.

In combination with the previously reviewed literature, the inconsistent results of these two new cohort studies do not support an association between the cancers of oral cavity, nose, or pharynx with the herbicides sprayed in Vietnam.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to

determine whether there is an association between exposure to the COIs and oral, nasal, or pharyngeal cancers.

CANCERS OF THE DIGESTIVE ORGANS

Until *Update 2006*, VAO committees had reviewed "gastrointestinal tract tumors" as a group consisting of stomach, colorectal, and pancreatic cancers; esophageal cancer has been formally included only since *Update 2004*. With more evidence from occupational studies available, VAO updates now address cancers of the digestive organs individually. The findings on cancers of the digestive organs as a group (ICD-9 150–159) are too broad for useful etiologic analysis and will no longer be considered.

Esophageal cancer (ICD-9 150), stomach cancer (ICD-9 151), colon cancer (ICD-9 153), rectal cancer (ICD-9 154), and pancreatic cancer (ICD-9 157) are among the most common cancers. ACS estimated that about 223,230 people would receive diagnoses of those cancers in the United States in 2015 and that 116,570 people would die from them (Siegel et al., 2015). Other digestive cancers (for example, small intestine, anal, and hepatobiliary cancers) added about 67,920 new diagnoses and 32,730 deaths to the 2015 estimates for the United States (Siegel et al., 2015). Collectively, tumors of the digestive organs were expected to account for 18 percent of new cancer diagnoses and 25 percent of cancer deaths in 2015. The average annual incidences of gastrointestinal cancers are presented in Table 8-3.

The incidences of stomach, colon, rectal, and pancreatic cancers increase with age. In general, the incidences are higher in men than in women and higher in blacks than in whites. Risk factors for the cancers vary but always include family history of the same form of cancer, some diseases of the affected organ, and diet. Tobacco use is a risk factor for pancreatic cancer and possibly stomach cancer (Maisonneuve and Lowenfels, 2015; Stewart et al., 2008). Infection with the bacterium *Helicobacter pylori* increases the risk of stomach and pancreatic cancers. Type 2 diabetes is associated with an increased risk of colorectal and pancreatic cancers (ACS, 2013a).

It is noteworthy that there has been one report of Vietnam veterans that included all gastrointestinal cancers collectively. Cypel and Kang (2010) published an update on disease-related mortality in ACC veterans who handled or sprayed herbicides in Vietnam in comparison with their non-Vietnam veteran peers or US men in general. The participant's vital status was determined through December 31, 2005. In the analyses, the site-specific rates of digestive cancers were not examined. No statistically significant excess mortality from all cancers of the digestive tract was found in ACC Vietnam veterans compared with non-Vietnam veterans (adjusted relative risk [RR] = 1.01, 95% CI 0.56–1.83).

Several studies identified for the present update did analyses that combined several digestive cancers, so the results are not particularly informative for any

TABLE 8-3 Average Annual Incidence (per 100,000) of Selected Gastrointestinal Cancers in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Stomach:									
Men	23.8	22.0	35.3	35.8	32.0	52.8	47.9	42.7	77.7
Women	10.4	8.9	16.8	15.3	12.9	22.0	23.2	19.1	39.5
Esophagus:									
Men	24.3	25.4	27.9	32.1	34.1	30.4	36.0	38.5	36.4
Women	4.0	4.0	6.7	6.0	5.8	9.8	8.7	8.4	13.3
Colon (excluding rectum):									
Men	75.5	71.3	112.5	113.6	109.3	164.5	158.4	155.4	223.5
Women	54.4	51.0	86.6	82.2	78.5	119.6	120.7	119.1	157.5
Rectum and Rectosigmoid Junction:									
Men	41.5	39.4	53.3	53.5	51.9	56.9	62.4	61.3	68.3
Women	23.0	22.1	28.6	30.3	29.0	35.3	35.1	34.7	34.2
Liver and Intrahepatic Bile Duct:									
Men	46.5	40.0	87.5	42.8	37.2	62.8	49.8	44.0	51.7
Women	11.3	9.8	17.3	15.0	13.0	16.9	19.8	17.1	17.7
Pancreas:									
Men	37.1	36.4	54.4	52.4	52.2	66.8	68.9	70.4	77.7
Women	25.1	24.5	35.0	38.2	37.1	55.3	54.0	53.1	68.3
Small Intestine:									
Men	7.0	6.9	10.6	9.4	9.1	16.1	11.7	11.5	20.6
Women	5.5	5.3	9.6	6.5	6.4	10.9	7.9	7.7	13.9
Anus, Anal Canal, and Anorectum:									
Men	3.5	3.7	3.9	4.4	4.9	3.7	4.8	5.0	5.1
Women	6.1	6.9	3.1	6.5	7.1	5.0	6.8	7.6	4.9
Other Digestive Organs:									
Men	1.6	1.4	3.1	2.0	1.8	2.7	3.1	3.2	4.7
Women	1.2	1.1	1.8	1.6	1.6	1.9	2.3	2.3	2.2
Gallbladder:									
Men	1.7	1.5	2.6	2.9	2.6	4.7	4.2	3.9	7.7
Women	3.3	3.0	5.1	5.2	4.9	7.3	6.9	6.9	8.0
Other Biliary:									
Men	5.2	5.1	4.0	7.8	7.5	5.9	11.4	10.8	10.9
Women	3.2	2.9	4.3	5.1	4.9	4.5	7.4	7.2	7.7

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

cancers in the group. Boers et al. (2012) reported on stomach and pancreatic cancers, leaving an additional 28 cases of other digestive cancers, which closely matched expectation. CJ Burns et al. (2011) reported on cancers of the stomach, colon, rectum, and pancreas individually, leaving eight deaths from "other GI and digestive cancers" (SIR = 0.73, 95% CI 0.32–1.44). After reporting on cancers of the esophagus, stomach, colon, rectum, and pancreas separately, 5 of 58 digestive

cancers remained unidentified in the update on mortality in the Hamburg cohort (Manuwald et al., 2012).

Esophageal Cancer

Epithelial tumors of the esophagus (squamous-cell carcinomas and adenocarcinomas) are responsible for more than 95 percent of all esophageal cancers (ICD-9 150); 16,980 newly diagnosed cases and 15,590 deaths were estimated for 2015 (Siegel et al., 2015). The considerable geographic variation in the incidence of esophageal tumors suggests a multifactorial etiology. The rates of esophageal cancer have been increasing in the past two decades, and nearly 50 percent of all cases occur in northwest Europe and North America. In the United States, adenocarcinoma of the esophagus has slowly replaced squamous-cell carcinoma as the most common type of esophageal malignancy; although squamous-cell carcinoma continues to be the most common form of esophageal cancer worldwide (Rubenstein and Shaheen, 2015). Squamous-cell esophageal carcinoma rates are higher in blacks than in whites and higher in men than in women. Smoking and alcohol ingestion are associated with the development of squamous-cell carcinoma; these risk factors have been less thoroughly studied for esophageal adenocarcinoma, but they appear to be associated. The rapid increase in obesity in the United States has been linked to increasing rates of gastroesophageal reflux disease (GERD), and the resulting rise in chronic inflammation has been hypothesized as explaining the link between GERD and esophageal adenocarcinoma (Rubenstein and Shaheen, 2015). The average annual incidence of esophageal cancers is shown in Table 8-3.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* explicitly excluded esophageal cancer from the group of gastrointestinal tract tumors, for which it was concluded that there was limited or suggestive evidence of *no* association with exposure to the herbicides used by the US military in Vietnam. Esophageal cancer was not separately evaluated and was not categorized with this group until *Update 2004*, so by default it fell into the category of inadequate or insufficient evidence of an association. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the COIs to sustain that negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence on each should be evaluated separately. Esophageal cancer was thus formally placed into the inadequate or insufficient category. No additional studies of esophageal cancer were reviewed in *Update 2008*.

Update 2010 considered a series of papers on mortality in TCP and PCP workers employed by Dow Chemical Company in Midland, Michigan, from

1937 to 1980. Collins et al. (2009b) followed 1,615 workers who worked at least 1 day in a department that had potential TCDD exposure, among whom five esophageal-cancer deaths were observed, for an SMR of 1.0 (95% CI = 0.3–2.2); none of the five had concurrent PCP exposure. Collins et al. (2009c) described mortality in 773 PCP workers who were exposed to chlorinated dioxins that did not include TCDD; there were two observed deaths from esophageal cancer (SMR = 0.8, 95% CI 0.1–2.9). McBride et al. (2009a) reported on a mortality follow-up of the workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. The SMR for esophageal-cancer deaths in exposed workers was 2.5 (95% CI 0.7–6.4) compared with an SMR of 2.1 (95% CI 0.1–12.2) in the never-exposed group. In following up on cancer incidence in the men and women exposed to dioxin in the Seveso accident, Pesatori et al. (2009) observed no esophageal cancers in the high-exposure zone and no exposure-related pattern in the occurrence of esophageal cancer in the medium- and low-exposure areas.

In *Update 2012*, the strongest evidence came from an occupational cohort of workers at a chemical plant in Hamburg, which reported a significant increased esophageal-cancer mortality relative to men in the general population of Hamburg (SMR = 2.56, 95% CI 1.27–4.57), whereas no deaths from esophageal cancer were observed among female workers, who made up a smaller portion of this cohort (Manuwald et al., 2012). By contrast, in the NIOSH cohort Ruder and Yiin (2011) reported no excess mortality of esophageal cancer in comparison with the US population (SMR = 0.99, 95% CI 0.43–1.96). In the AHS study, Koutros et al. (2010a), found a significant decrease in the incidence of esophageal cancer in the private applicators (52 cases, SIR = 0.64, 95% CI 0.48–0.85) in comparison with the general population, which could indicate a healthy worker effect.

Table 8-4 summarizes the results of the relevant studies concerning esophageal cancer.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies Several recent publications examined esophageal cancer incidence (Yi, 2013; Yi and Ohrr, 2014) and cancer-specific mortality (Yi et al., 2014b) in the Korean Veterans Health Study, a large prospective cohort of 185,265 male Vietnam veterans alive in 1992, who were followed for cancer incidence through 2003 and for mortality through 2005. Comparing the Vietnam veterans to the general Korean population, Yi (2013) reported a statistically significant decrease in the incidence of esophageal cancer (SIR = 0.70, 95% CI 0.64–0.85), which may be due to a "healthy soldier" effect. However, in the internal comparison of those with high versus low EOI scores, Yi and Ohrr (2014) reported a statistically significant 36 percent increased risk for esophageal cancer (HR = 1.36, 95% CI 1.00–1.85). This result was based on a large number of incident esophageal cancers (n = 184) observed during follow-up, of which 113 cases

TABLE 8-4 Selected Epidemiologic Studies—Esophageal Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	6	1.2 (0.4–4.0)	Boehmer et al., 2004
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	9	0.9 (0.4–1.6)	Vistainer et al., 1995
International Studies of Vietnam Veterans			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	70	1.2 (0.9–1.5)	ADVA, 2005b
Navy	19	1.6 (0.9–2.4)	
Army	40	1.1 (0.7–1.4)	
Air Force	11	1.5 (0.8–2.8)	
Mortality			
All branches, return–2001	67	1.1 (0.8–1.3)	ADVA, 2005a
Navy	13	1.0 (0.5–1.7)	
Army	42	1.0 (0.7–1.3)	
Air Force	12	1.5 (0.8–2.6)	
1980–1994	23	1.2 (0.7–1.7)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	9	1.9 (0.6–6.6)	ADVA, 2005c
Mortality			
1966–2001	10	1.3 (0.5–3.6)	ADVA, 2005c
1982–1994	1	1.3 (0.0– > 10)	CDVA, 1997b

TABLE 8-4 Esophageal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—esophagus (C15) categorized high (n = 113) vs low (n = 71)	113	1.4 (1.0–1.9)	Yi and Ohrr, 2014
Mortality (1992–2005)—esophagus categorized high (n = 98) vs low (n = 64)		1.3 (0.9–1.8)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	162	1.0 (0.9–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	28	1.0 (0.7–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	20	1.3 (0.8–1.9)	
7,553 not exposed to highly chlorinated PCDDs	6	0.5 (0.2–1.1)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	8	0.6 (0.3–1.2)	Saracci et al., 1991
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	8	0.9 (0.4–1.9)	Coggon et al., 1986
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 150)			Manuwald et al., 2012
Men	11	2.6 (1.3–4.6)	
Women	0	nr	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	

continued

TABLE 8-4 Esophageal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1969–2004			McBride
Ever-exposed workers	4	2.5 (0.7–6.4)	et al., 2009a
Never-exposed workers	1	2.1 (0.1–12.2)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	2	2.0 (0.2–7.0)	't Mannetje
Phenoxy herbicide sprayers (> 99% men)	1	0.7 (0.0–4.0)	et al., 2005
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)			Collins
Trichlorophenol workers	5	1.0 (0.3–2.2)	et al., 2009b
Pentachlorophenol workers	2	0.8 (0.1–2.9)	
All Dow PCP-Exposed Workers—all workers from two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	8	1.0 (0.4–2.0)	
PCP and TCP (n = 720)	2	0.8 (0.1–3.0)	
PCP (no TCP) (n = 1,402)	6	1.1 (0.4–2.3)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	27	0.7 (0.4–1.0)	
Ever	26	0.8 (0.5–1.2)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	32	0.4 ($p < 0.05$)	
Employee	13	0.9 (nr)	

TABLE 8-4 Esophageal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Women			
Self-employed	1	1.4 (nr)	
Employee	2	0.4 (nr)	
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC		**Phenoxy herbicides**	
Incidence	3	1.6 (0.3–4.6)	Asp et al., 1994
Mortality 1972–1989	2	1.3 (0.2–4.7)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 385 incident esophageal cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
	4	1.8 (0.7–4.8)	
Aged 20–59	1	1.6 (0.2–11.3)	
Aged ≥ 60	3	1.9 (0.6–5.8)	
Sawmill workers (n = 139)		**Herbicides, Chlorophenols**	
	2	0.7 (0.2–2.9)	
SWEDEN			
Incidence cancer cases 1961–1973 with agriculture as economic activity in 1960 census (male, female)	169	*99% CI* 0.6 (0.5–0.7)	Wiklund, 1983
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	52	0.6 (0.5–0.9)	
Commercial applicators	2	nr	
Spouses	2	nr	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	48	0.5 (0.4–0.7)	

continued

TABLE 8-4 Esophageal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Spouses (n = 676)	3	nr	
Enrollment through 2000, vs state rates			Blair et al.,
Private applicators (men and women)	16	0.5 (0.3–0.9)	2005a
Spouses of private applicators (> 99% women)	1	0.3 (0.1–1.9)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	0		Pesatori
Zone B	1	0.3 (0.0–1.9)	et al., 2009
Zone R	35	1.3 (0.9–1.9)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Nebraska—agricultural pesticide use and adenocarcinoma of the esophagus	137	**Phenoxy herbicides, 2.4-D**	Lee et al., 2004b
Insecticides		0.7 (0.4–1.1)	
Herbicides		0.7 (0.4–1.2)	
International Case-Control Studies			
UK men, 18–35 yrs of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.6 (0.7–3.6)	
Chlorophenols	nr	1.2 (0.7–2.2)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DCP, 2,4-dichlorophenol; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2 methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PM, proportionate mortality; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCP, pentachlorophenol; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

were among veterans in the high-exposure category. Yi et al. (2014b) reported a non-significant increase in mortality from esophageal cancer (HR = 1.26, 95% CI 0.91–1.75) when comparing those in the higher exposure category with those with lower estimated exposure; these results were based on 162 deaths due to esophageal cancer, of which 98 deaths occurred in the higher exposure category, Similarly, mortality from esophageal cancer was not found to be associated with the individual, log-transformed EOI scores (HR = 1.02, 95% CI 0.94–1.17) (Yi et al., 2014b). Information on smoking and alcohol consumption was not available, and thus some of the modest association could be due to confounding. Data from the self-reported questionnaires collected in a sub-cohort of Korean veterans who were alive in 2004 indicated that the prevalence of smoking was relatively high in this cohort (45 percent and 36 percent were former and current smokers, respectively), and 11 percent of veterans reported a high prevalence of drinking (> 5 drinks/week). However, the distributions of smoking and drinking habits were similar for veterans with high and low EOI scores (Yi et al., 2013b).

Occupational and Environmental Studies There have been no occupational or environmental studies of exposure to the COIs and esophageal cancers published since *Update 2012*.

Case-Control Studies There have been no case-control studies of exposure specifically to the COIs and esophageal cancers published since *Update 2012.*

However, a recently published hospital-based case-control study examined the risk of Barrett's esophagus and occupational exposures to asbestos, metal dust, organic solvents, and pesticides (Qureshi et al., 2013). Barrett's esophagus is a disorder characterized by intestinal metaplasia of the normally stratified squamous epithelium of the esophagus and is associated with an increased risk of adenocarcinoma of the esophagus. This study included 226 cases and 1,424 controls selected from among patients undergoing endoscopy at a VA medical center in Houston, Texas, from 2008 through 2010. They reported no association between self-reported use of pesticides and the risk of Barrett's esophagus (odds ratio [OR] = 0.97, 95% CI 0.50–1.90). The major limitations include the potential for selection/referral bias as well as recall bias because pesticide exposure information was collected via a self-reported questionnaire. The authors did not address TCDD or the specific herbicides of interest, and thus this study is not regarded as being informative for the committee's task.

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the COIs on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004), and no increase in the incidence of esophageal cancer has been reported in laboratory animals after exposure to them. A previous biomarker

study analyzed esophageal-cell samples from patients who had been exposed to indoor air pollution of different magnitudes and did or did not have high-grade squamous-cell dysplasia or a family history of upper gastrointestinal-tract (UGI) cancer (Roth et al., 2009). AHR expression was higher in patients that had a family history of UGI cancer, but it was not associated with indoor air pollution, esophageal squamous-cell dysplasia category, age, sex, or smoking. These results might be interpreted to suggest that enhanced expression of the AHR in patients who had a family history of UGI cancer may contribute to UGI-cancer risk associated with AHR ligands—such as polycyclic aromatic hydrocarbons, which are found in cigarette smoke—and with TCDD.

In a small series of studies, AHR expression was found to be higher in esophageal tumors than in corresponding normal mucosa and, somewhat surprisingly, played a role in the suppression of metastatic potential, in contrast to many other cancers (Safe et al., 2013). The significance of these observations and the mechanism underlying increased AHR expression was not determined (Zhang et al., 2012).

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

In this update, the only study that provided some evidence for a potential association between esophageal cancer and exposure to herbicides was the Korean Veterans Health Study, which reported a modestly increased risk for both incidence (RR = 1.36, 95% CI 1.00–1.85) and mortality from esophageal cancer (RR = 1.26, 95% CI 0.91–1.75) when comparing high- versus low-exposure categories. Despite several advantages, including the large sample size of this cohort and adequate numbers of cases both for incidence of and mortality from esophageal cancer, the difficulty in determining the validity and reliability of the herbicide exposure opportunity score developed by Stellman et al. (2003b) as well as a lack of information on smoking and alcohol consumption (two main risk factors for esophageal cancer) limit the interpretation of the results.

In combination with the studies reviewed previously, however, this single new finding did not provide adequate evidence to establish an association between exposure to the COIs and esophageal cancer. No toxicologic studies provide evidence of the biologic plausibility of an association between the COIs and tumors of the esophagus.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and esophageal cancer.

Stomach Cancer

The incidence of stomach cancer (ICD-9 151) increases with age. ACS estimated that 15,540 men and 9,050 women would receive diagnoses of stomach cancer in the United States in 2015 and that 6,500 men and 4,220 women would die from it (Siegel et al., 2015). In general, the incidence is higher in men than in women and in blacks than in whites. Other risk factors include a family history of this cancer, some diseases of the stomach, and diet. Infection with *Helicobacter pylori* increases the risk of stomach cancer. Tobacco or alcohol use and the consumption of nitrite- and salt-preserved food may also increase the risk (Ang and Fock, 2014; Brenner et al., 2009; Key et al., 2004). The average annual incidence of stomach cancer is shown in Table 8-3.

Conclusions from *VAO* and Previous Updates

Update 2006 considered stomach cancer independently for the first time. Prior updates had developed a table of results for stomach cancer but drew conclusions about the adequacy of the evidence of its association with herbicide exposure in the context of gastrointestinal tract cancers. The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the herbicides used by the US military in Vietnam and gastrointestinal tract tumors, including stomach cancer. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the COIs to sustain that negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence on each should be evaluated separately. Stomach cancer was thus reclassified into the default category of inadequate or insufficient evidence to determine whether there is an association. The conclusion that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and stomach cancer has been maintained by the committees responsible for subsequent updates.

Table 8-5 summarizes the results of the relevant studies concerning stomach cancer. Results new to this update are shaded.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies Since *Update 2012*, cohort studies of Vietnam veterans from New Zealand and Korea have reported on stomach cancer.

Mortality from (Yi et al., 2014b) and incidence of (Yi and Ohrr, 2014) stomach cancer were assessed among Korean veterans who had served in Vietnam between 1964 and 1973. In analyses of cancer incidence, Yi and Ohrr (2014) reported a modestly increased risk of stomach cancer (HR = 1.14, 95% CI 1.04–1.24) in the internal comparison of the high- and low-exposure groups based on

TABLE 8-5 Selected Epidemiologic Studies—Stomach Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g)	24	1.8 (0.8–3.9)	
Quartiles (pg/g):			
0.4–2.6	4	nr	
2.6–3.8	3	1.0 (0.2–4.8)	
3.8–5.2	7	2.0 (0.5–8.2)	
> 5.2	10	3.3 (0.9–12.5)	
Number of years served in SEA (per year of service)			
Quartiles (years in SEA):	24	1.2 (1.0–1.4)	
0.8–1.3	4	nr	
1.3–2.1	4	1.0 (0.2–3.8)	
2.1–3.7	5	1.1 (0.3–4.2)	
3.7–16.4	11	2.1 (0.6–7.3)	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	16	0.6 (0.4–1.0)	
With tours from 1966 through 1970	14	0.6 (0.4–1.1)	
SEA comparison veterans (n = 1,776)	31	0.9 (0.6–1.2)	
With tours from 1966 through 1970	24	0.9 (0.6–1.3)	
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	6	0.4 (0.2–0.9)	
SEA comparison veterans (n = 1,776)	14	0.7 (0.4–1.1)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	5	nr	Boehmer et al., 2004

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	88	1.1 (0.9–1.5)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	17	0.8 (0.4–1.6)	
State Studies of US Vietnam Veterans			
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	1	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	104	0.9 (0.7–1.1)	ADVA, 2005b
Navy	28	1.1 (0.7–1.6)	
Army	66	0.9 (0.7–1.1)	
Air Force	10	0.7 (0.3–1.3)	
Mortality			
All branches, return–2001	76	0.9 (0.7–1.2)	ADVA, 2005a
Navy	22	1.3 (0.8–1.8)	
Army	50	0.9 (0.7–1.2)	
Air Force	4	0.4 (0.1–1.0)	
1980–1994	32	1.1 (0.7–1.4)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	11	0.6 (0.2–1.2)	ADVA, 2005c
Mortality			
1966–2001	7	0.7 (0.2–2.0)	ADVA, 2005c
1982–1994	4	1.7 (0.3– > 10)	CDVA, 1997b

continued

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	9	0.8 (0.4–1.6)	
Mortality (1988–2008)	9	1.3 (0.6–2.4)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—Stomach (C16) categorized high (n = 1,154) vs low (n = 973)		1.1 (1.0–1.2)	Yi and Ohrr, 2014
Mortality (1992–2005)—Stomach (C16) categorized high (n = 613) vs low (n = 464)		1.2 (1.0–1.3)	Yi et al., 2014b
HR per unit of log EOI (n =180,639)	1,077	1.1 (1.0–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Phenoxy herbicides, chlorophenols**	
Mortality 1939–1992	72	0.9 (0.7–1.1)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	42	0.9 (0.7–1.2)	
7,553 not exposed to highly chlorinated PCDDs	30	0.9 (0.6–1.3)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Nested case-control study	40	0.9 (0.6–1.2)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	1	**TCDD** 1.4 (nr)	Kogevinas et al., 1993
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	26	0.9 (0.6–1.3)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982			Lynge, 1985
Men	12	1.3 (nr)	
Women	1	0.7 (nr)	

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1955–2006	14	1.1 (0.8–1.5)	Boers et al., 2012
TCDD plasma level (HRs, by tertile)			
Background (≤ 0.4)	8	—	
Low (0.4–1.9)	1	0.1 (0.0–1.0)	
Medium (1.9–9.9)	2	0.5 (0.1–2.6)	
High (≥ 9.9)	3	2.5 (0.7–9.2)	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	6	1.5 (1.1–2.2)	Boers et al., 2012
Mortality 1955–2006	5	2.2 (0.4–13.2)	Boers et al. 2010
Mortality 1955–1991	3	1.0 (0.2–2.9)	Hooiveld et al., 1998
Mortality 1955–1985	2	0.9 (0.1–3.4)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	4	1.2 (0.3–4.7)	Boers et al., 2010
Mortality 1965–1986	0	0.0 (0.0–6.5)	Bueno de Mesquita et al., 1993
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	nr	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	nr	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	

continued

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1956–1989	2	0.6 (0.1–2.3)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992	3	1.0 (0.2–2.9)	Ott and Zober, 1996a
TCDD < 0.1 µg/kg of body weight	0	0.0 (0.0–3.4)	
TCDD 0.1–0.99 µg/kg of body weight	1	1.3 (0.0–7.0)	
TCDD > 1.0 µg/kg of body weight	2	1.7 (0.2–6.2)	
Mortality			
Through 1987		*90% CI*	Zober et al., 1990
	3	3.0 (0.8–7.7)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 140–149)	17	1.0 (0.6–1.6)	Manuwald et al., 2012
Men	17	1.3 (0.7–2.0)	
Women	0	nr	
Mortalilty 1952–1989	12	1.3 (0.7–2.2)	Becher et al., 1996
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1996	12	1.2 (0.6–2.1)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	4	1.4 (0.4–3.6)	
Never-exposed workers	2	2.3 (0.3–8.4)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	2	1.1 (0.1–4.0)	’t Mannetje et al., 2005
Phenoxy herbicide sprayers (> 99% men)	3	1.4 (0.3–4.0)	

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	13	1.0 (0.6–1.8)	Steenland et al., 1999
Through 1987	10	1.0 (0.5–1.9)	Fingerhut et al., 1991
≥ 1-yr exposure, ≥ 20-yr latency	4	1.4 (0.4–3.5)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	0	0.0 (0.0–1.1)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	8	1.4 (0.6–2.7)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	1.5 (0.7–2.7)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	9	0.9 (0.4–1.7)	
PCP and TCP (n = 720)	3	1.0 (0.2–2.9)	
PCP (no TCP) (n = 1,402)	6	0.8 (0.3–1.8)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354 (Cohort 3)	3	0.8 (0.2–2.3)	Burns CJ et al., 2011
Through 1994 (n = 1,517) (digestive organs, peritoneum)	16	0.7 (0.4–1.2)	Burns et al., 2001
Through 1982 (n = 878)	0	nr (0.0–3.7)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	4	1.2 (0.3–3.1)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-yr latency	4	1.7 (0.5–4.3)	
15-yr latency	3	1.8 (0.4–5.2)	

continued

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)		**Dioxins, phenoxy herbicides**	
1,412 white male US flavor and fragrance chemical plant workers (1945–1965)	6	**Dioxin, 2,4,5-T** *Expected exposed cases* 4.2	Thomas, 1987
Automobile workers from Hubei province in China (worked 1 yr during 1980–1985)		**PCDD/F**	Wang et al., 2013
Mortality (1980–2005) (n = 3,529)	15	1.3 (0.6–2.7)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	146	0.9 (0.8–1.1)	
Ever	98	0.9 (0.7–1.1)	
14,362 **Danish paper workers** employed 1943–1990, followed through 1993			Rix et al., 1998
Men	48	1.1 (0.8–1.4)	
Women	7	1.0 (0.4–2.1)	
New Hampshire pulp and paper workers, 883 white men working ≥1 yr, mortality through July 1985	5	1.2 (0.4–2.8)	Henneberger et al., 1989
Pulp and paper cohorts independent of IARC cohort			
United Paperworkers International, 201 white men employed ≥ 10 yr and dying 1970–1984	1	0.5 (0.1–3.0)	Solet et al., 1989
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977	17	*90% CI* 1.2 (0.8–1.9)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from stomach cancer June 1971–Dec 1987			
Linkage of records for ~70,000 male Saskatchewan farmers (1971–1985)	246	0.9 (0.8–1.0)	Wigle et al., 1990

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
DENMARK			
Danish farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	286	0.9 (nr)	
Employee	71	1.2 (nr)	
Women			
Self-employed	5	1.0 (nr)	
Employee	5	1.7 (nr)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	126	0.7 (0.6–0.9)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	39	1.0 (0.7–1.3)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident stomach cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
	13	2.2 (1.3–3.9)	
Aged 20–59	3	0.7 (0.2–2.2)	
Aged ≥ 60	10	2.4 (1.2–4.5)	
Sawmill workers (n = 139)		**Herbicides, Chlorophenols**	
	7	1.0 (0.4–2.1)	
SWEDEN			
348 Swedish railroad workers (1957–October, 1978)—total exposure to herbicides	3	**Phenoxy acids** 2.2 (nr)	Axelson et al., 1980
Incident stomach cancer cases 1961–1973 with agriculture as economic activity in 1960 census	2,599	*99% CI* 1.1 (1.0–1.2)	Wiklund, 1983
THE NETHERLANDS			
Dutch licensed herbicide sprayers—1,341 certified before 1980			
Through 2000 (stomach, small intestine)	3	0.4 (0.1–1.3)	Swaen et al., 2004
Through 1987 (stomach, small intestine)	1	0.5 (0.0–2.7)	Swaen et al., 1992
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993

continued

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Men			
Whites (n = 119,648)	657	1.0 (1.0–1.1)	
Nonwhites (n = 11,446)	115	1.1 (0.9–1.3)	
Women			
Whites (n = 2,400)	12	1.2 (0.6–2.0)	
Nonwhites (n = 2,066)	23	1.9 (1.2–2.8)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	61	0.9 (0.7–1.1)	
Commercial applicators	2	nr	
Spouses	15	0.9 (0.5–1.5)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	462	0.8 (0.8–0.9)	
Spouses of private applicators (> 99% women)	161	0.9 (0.7–1.0)	
Commercial applicators	24	1.0 (0.6–1.4)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	26	0.5 (0.3–0.8)	
Spouses (n = 676)	5	0.4 (0.1–1.0)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	10	0.5 (0.2–1.0)	
Spouses of private applicators (> 99% women)	4	1.1 (0.3–2.8)	
California United Farm Workers of America		**2,4-D**	
Nested case-control study of agricultural exposure and gastric cancer in UFW cohort			Mills and Yang, 2007
Ever worked in area where 2,4-D used	42	1.9 (1.1–3.3)	
Quartile of lifetime exposure to 2,4-D (lb)			
0	58	1.0	
1–14	17	2.2 (1.0–4.6)	
15–85	14	1.6 (0.7–3.5)	
85–1,950	11	2.1 (0.9–5.1)	

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of stomach cancer		**Herbicides**	
Agricultural extension agents	10	0.7 (0.4–1.4)	Alavanja et al., 1988
Forest conservationists		p-trend < over yrs worked	Alavanja et al., 1989
	9	0.7 (0.3–1.3)	
Soil conservationists			
Florida pesticide applicators licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose–response by length of licensure)		*Expected exposed cases*	
	4	3.3	
White Male Residents of Iowa—stomach cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 yrs old when died 1964–1978—case-control	1,812	1.3 ($p < 0.05$)	Burmeister et al., 1983
H_0: only for "modern methods" → born after 1900			
Born before 1880	458	1.3 ($p < 0.05$)	
Born 1980–1900	639	1.3 ($p < 0.05$)	
Born after 1900	715	1.3 ($p < 0.05$)	
> 20 yrs old when died 1971–1978—PMR	338	1.1 ($p < 0.01$)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	3	0.9 (0.3–2.7)	Pesatori et al., 2009
Zone B	19	0.9 (0.6–1.4)	
Zone R	131	0.8 (0.7–1.0)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Zone B	7	1.0 (0.5–2.1)	
Zone R	45	0.9 (0.7–1.2)	
10-yr follow-up to 1991—women			Bertazzi et al., 1993
Zone B	2	0.6 (0.2–2.5)	
Zone R	25	1.0 (0.6–1.5)	

continued

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	3	0.7 (0.2–2.0)	et al., 2008
Zone B	24	0.8 (0.5–1.2)	
Zone R	212	1.0 (0.8–1.1)	
20-yr follow-up to 1996			Bertazzi
Zones A and B—men	16	0.9 (0.5–1.5)	et al., 2001
Zones A and B—women	11	1.0 (0.6–1.9)	
15-yr follow-up to 1991—men			Bertazzi
Zone B	10	0.8 (0.4–1.5)	et al., 1997, 1998
Zone R	76	0.9 (0.7–1.1)	
15-yr follow-up to 1991—women			Bertazzi
Zone A	1	0.9 (0.0–5.3)	et al., 1997, 1998
Zone B	7	1.0 (0.4–2.1)	
Zone R	58	1.0 (0.8–1.3)	
10-yr follow-up to 1986—men			Bertazzi
Zone A, B, R	40	0.8 (0.6–1.2)	et al., 1989a
10-yr follow-up to 1986—women			Bertazzi
Zone A, B, R	22	1.0 (0.6–1.5)	et al., 1989a
10-yr follow-up to 1986—men			Bertazzi
Zone B	7	1.2 (0.6–2.6)	et al., 1989b
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence—crude incidence rate in 1998 vs			
Men			
Regional (Samara)	nr	44.0 (nr)	
National (Russia)	nr	48.1 (nr)	
Women			
Regional (Samara)	nr	17.6 (nr)	
National (Russia)	nr	20.7 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Men	59	1.7 (1.3–2.2)	
Women	45	0.7 (0.5–0.9)	
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman	16	0.8 (0.5–1.3)	
Spouses	2	0.3 (0.0–1.1)	

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
JAPAN			
Residents of municipalities with and without waste incineration plants (cross-sectional)		**Dioxin emissions** age-adjusted mortality (per 100,000)	Fukuda et al., 2003
Men			
With		38.2 ± 7.8 vs	
Without		39.0 ± 8.8 (p = 0.29)	
Women			
With		20.7 ± 5.0 vs	
Without		20.7 ± 5.8 (p = 0.92)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	24	1.6 (1.0–2.4)	
West coast	71	0.9 (0.7–1.2)	
Mortality			
East coast	17	1.4 (0.8–2.2)	
West coast	63	0.9 (0.7–1.2)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Eastern **Nebraska**—population-based case-control, agricultural pesticide use and adenocarcinoma of stomach	170	**Herbicides, pesticides**	Lee et al., 2004b
Insecticides		0.9 (0.6–1.4)	
Herbicides		0.9 (0.5–1.4)	
International Case-Control Studies			
Swedish—population-based case-control study of residents (40–79 yrs of age) with gastric adenocarcinoma (February 1989–January 1995)		**Phenoxy herbicides**	Ekström et al., 1999
All occupational herbicide exposures	75	1.6 (1.1–2.2)	
Phenoxyacetic acid exposure	62	1.8 (1.3–2.6)	
Hormoslyr (2,4-D, 2,4,5-T)	48	1.7 (1.2–2.6)	
2,4-D only	3	nr (vs 0 controls)	
MCPA	11	1.8 (0.8–4.1)	
Duration of Exposure			
Unexposed to all herbicides	490	1.0	
< 1 mo	11	1.6 (0.7–3.5)	
1–6 mo	30	1.9 (1.1–3.2)	

continued

TABLE 8-5 Stomach Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
7–12 months	7	1.7 (0.6–4.7)	
> 1 yr	13	1.4 (0.6–3.0)	
Other herbicide exposure	13	1.0 (0.5–1.9)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofuran; PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; pg/g, picogram per gram; PMR, proportionate mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; UFW, United Farm Workers of America; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

the EOI scores. Similarly, for stomach cancer mortality, Yi et al. (2014b) reported a modestly increased risk for the high- versus low-exposure groups (HR = 1.17, 95% CI 1.03–1.33) and a positive association with the individual log-transformed EOI scores (HR = 1.05, 95% CI 1.02–1.08).

In a study of mortality and cancer incidence among 2,783 New Zealand Vietnam veterans who served in Vietnam between 1964 and 1975, McBride et al. (2013) reported that stomach cancer mortality was slightly elevated in the cohort (SMR = 1.27, 95% CI 0.58–2.42, based on nine deaths), while stomach cancer incidence was slightly less than expected (SIR = 0.82, 95% CI 0.38–1.56, based on nine cases).

Occupational Studies Wang et al. (2013) reported on mortality from 1980 to 2005 in a cohort of 3,529 workers, who had worked at least 1 year from 1980 through 1985 in an automobile foundry factory located in Hubei province in China with potential exposure to PCDD/Fs. When compared to the general population, the modest elevation in the risk of gastric cancers was not statistically significant (SMR = 1.28, 95% CI 0.60–2.74).

Environmental and Case-Control Studies No environmental or case-control studies of exposure to the COIs and stomach cancer have been published since *Update 2012*.

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the COIs (2,4-D and TCDD) on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). No increase in the incidence of gastrointestinal cancers has been reported in laboratory animals. However, studies of laboratory animals have observed dose-dependent increases in the incidence of squamous-cell hyperplasia of the forestomach or fundus of the stomach after administration of TCDD (Hebert et al., 1990; Walker et al., 2006). Similarly, in a long-term TCDD-treatment study in monkeys, hypertrophy, hyperplasia, and metaplasia were observed in the gastric epithelium (Allen et al., 1977). A transgenic mouse bearing a constitutively active form of the AHR has been shown to develop stomach tumors (Andersson et al., 2002); the tumors are neither dysplastic nor metaplastic but are indicative of both squamous-cell and intestinal-cell metaplasia (Andersson et al., 2005). The validity of the transgenic-animal model is indicated by the similarities in the phenotype of the transgenic animal (increased relative weight of the liver and heart, decreased weight of the thymus, and increased expression of AHR target gene CYP1A1) and animals treated with TCDD (Brunnberg et al., 2006). Recent cell culture work consistent with the in vivo studies showed that decreased AHR expression in two human gastric cancer cell lines was associated with decreased cell growth, migration, and invasion, all of which are hallmarks of malignant potential (Yin et al., 2013).

In a biomarker study of cancer patients, AHR expression and nuclear translocation were significantly higher in stomach-cancer tissue than in precancerous tissue (Peng et al., 2009a). The results suggest that the AHR plays an important role in stomach carcinogenesis. AHR activation in a stomach-cancer cell line (AGS) has also been shown to enhance stomach-cancer cell invasiveness potentially through a c-Jun-dependent induction of matrix metalloproteinase-9 (Peng et al., 2009b).

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Several case-control studies addressing agricultural exposures reported evidence of an association of stomach cancer: Both Ekström et al. (1999) and Mills and Yang (2007) found an association with herbicides and with phenoxy herbicides in particular; Cocco et al. (1999) found a relationship with herbicide exposure, but the results were not specific as to the type of herbicide. In contrast,

in occupational cohort studies there was little evidence of an exposure-related increase in stomach cancer. Updated mortality findings from Seveso concerning TCDD exposure (Consonni et al., 2008; Pesatori et al., 2009) found no evidence of an increase in stomach cancer. There was a modestly increased risk of stomach cancer in Korean veterans but inconsistent evidence in New Zealand Vietnam veterans, as has been the case in previously reviewed studies of Vietnam veterans.

There is some evidence of biologic plausibility in animal models, but overall the epidemiologic studies do not support an association between exposure to the COIs and stomach cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and stomach cancer.

Colorectal Cancers

Colorectal cancers include malignancies of the colon (ICD-9 153) and of the rectum and anus (ICD-9 154); less prevalent tumors of the small intestine (ICD-9 152) are often included. Findings on cancers of the retroperitoneum and other unspecified digestive organs (ICD-9 159) are considered in this category. Colorectal cancers account for about 55 percent of digestive tract tumors; ACS estimated that 132,700 people would receive diagnoses of colorectal cancer in the United States in 2015 and that 49,700 would die from it (Siegel et al., 2015). Excluding basal-cell and squamous-cell skin cancers, colorectal cancers are the third-most common form of cancer both in men and in women. The average annual incidence of colorectal cancers is shown in Table 8-3.

The incidence of colorectal cancers increases with age; it is higher in men than in women and in blacks than in whites. (Screening can affect the incidence, and screening is recommended for all persons over 50 years old). Other risk factors include a family history of this form of cancer, body weight, lack of physical exercise, and diet (Kamangar et al., 2006). Type 2 diabetes is associated with an increased risk of colorectal cancers (ACS, 2013a).

Conclusions from *VAO* and Previous Updates

Update 2006 considered colorectal cancers independently for the first time. Prior updates developed tables of results on colon and rectal cancers, but conclusions about the adequacy of the evidence of their association with herbicide exposure were reached only in the context of gastrointestinal tract cancers. The

committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the herbicides used by the US military in Vietnam and gastrointestinal tract tumors, including colorectal cancers. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the COIs to sustain that negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence on each should be evaluated separately. Colorectal cancers were thus reclassified into the default category of inadequate or insufficient evidence to determine whether there is an association. The additional information considered in subsequent updates did not provide evidence to suggest that colorectal cancers be moved out of the category of inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and colorectal cancers.

The results of the relevant studies concerning colon and rectal cancers are summarized in Table 8-6, in which results new to this update are shaded.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies McBride et al. (2013) reported on mortality among 2,783 male New Zealand veterans who had served in Vietnam between 1964 and 1975 and were alive in 1988 (when the electronic mortality database started). Follow-up was through 2008, with those who emigrated or were lost to follow-up excluded. Colorectal cancer mortality was slightly elevated in the cohort (SMR = 1.04, 95% CI 0.64–1.61, based on 20 deaths), while all-cause mortality was significantly in deficit in the cohort (all-cause SMR = 0.85, 95% CI 0.77–0.94). Colorectal cancer incidence was slightly lower than expected (SIR = 0.95, 95% CI 0.73–1.21, based on 63 cases).

In the internal comparison of high- versus low-exposure opportunity groups, Yi and Ohrr (2014) found a deficit of colon cancer [ICD-10 C18] among the higher exposed (HR = 0.87, 95% CI 0.72–1.08) and a small excess of rectal cancer [ICD-10 C19–C21] (HR = 1.14, 95% CI 0.95–1.38). With regard to mortality from colorectal cancers [ICD-10 C18–C21], Yi et al. (2014b) reported no evidence of an increase in mortality from these cancers combined for high- versus low-exposure opportunity groups (HR = 0.96, 95% CI 0.78–1.19) or in association with the individual log-transformed EOI scores (HR = 1.02, 95% CI 0.97–1.07). Results were presented separately for 30 incident cases of and 19 deaths from cancer of the small intestine [ICD-10 C17]. Comparing the high- versus low-exposure opportunity groups, Yi and Ohrr (2014) found a significant increase in the incidence of this rather uncommon cancer (HR = 2.30, 95% CI 1.03–5.15). For mortality from cancer of the small intestine, Yi et al. (2014b) found elevated risks for both the internal comparison (HR = 2.88, 95% CI 1.00–8.28) and for the analysis of the individual EOI scores (HR = 1.11, 95% CI 0.87–1.40).

TABLE 8-6 Selected Epidemiologic Studies—Colon and Rectal Cancers (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	9	1.0 (0.4–2.6)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982 (Colon, other gastrointestinal, ICD-8 152–154, 158, 159)			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	209	1.0 (0.7–1.3)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	33	1.3 (0.7–2.2)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004			Cypel and Kang, 2008
US Vietnam veterans	11	0.5 (0.2–1.0)	
Vietnam-veteran nurses—colon	9	0.6 (0.2–1.4)	
Through 1991			Dalager et al., 1995a
US Vietnam veterans	4	0.4 (0.1–1.2)	
Vietnam-veteran nurses—colon	4	0.5 (0.2–1.7)	
State Studies of US Vietnam Veterans			
923 white male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans			Anderson et al., 1986a,b
Colon	6	1.0 (0.4–2.2)	
Rectum	1	nr	
International Studies of Vietnam-Veterans			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
Colon—All branches, 1982–2000	376	1.1 (1.0–1.2)	ADVA, 2005b
Navy	91	1.3 (1.0–1.5)	
Army	239	1.1 (0.9–1.2)	
Air Force	47	1.1 (0.8–1.5)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Rectum—All branches, 1982–2000			ADVA, 2005a
Navy	54	1.1 (0.8–1.4)	
Army	152	1.0 (0.8–1.1)	
Air Force	28	1.0 (0.6–1.4)	
Validation Study		*Expected number of exposed cases*	
Men—colorectal cancer	188	221 (191–251)	AIHW, 1999
Men—self-reported colon cancer	405	117 (96–138)	CDVA, 1998a
Women—self-reported colon cancer	1	1 (0–5)	CDVA, 1998b
Mortality			
Colon—All branches, return–2001	176	1.0 (0.8–1.1)	ADVA, 2005a
Navy	49	1.3 (0.9–1.6)	
Army	107	0.9 (0.7–1.0)	
Air Force	21	0.9 (0.5–1.3)	
Rectum—All branches, return–2001			ADVA, 2005a
Navy	13	0.8 (0.4–1.4)	
Army	44	0.9 (0.6–1.1)	
Air Force	12	1.3 (0.6–2.2)	
1980–1994			CDVA, 1997a
Colon	78	1.2 (0.9–1.5)	
Rectum	16	0.6 (0.4–1.0)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000			ADVA, 2005c
Colon	54	0.9 (0.7–1.4)	
Rectum	46	1.4 (0.9–2.2)	
Mortality			
1966–2001			ADVA, 2005c
Colon	29	0.8 (0.5–1.3)	
Rectum	10	1.8 (0.6–5.6)	
1982–1994			CDVA, 1997b
Colon	6	0.6 (0.2–1.5)	

continued

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Rectum	3	0.7 (0.2–9.5)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008) (colorectal)	63	1.0 (0.7–1.2)	
Mortality (1988–2008) (colorectal)	20	1.0 (0.6–1.6)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)			Yi and Ohrr, 2014
Small intestine (C17) (19 vs 11)		2.3 (1.0–5.2)	
Colon cancer (C18) (210 vs 228)		0.9 (0.7–1.1)	
Rectal cancer (C19–C20) 265 vs 231)		1.1 (1.0–1.4)	
Anus (C21) (7 vs 2)		3.3 (0.6–17.1)	
Mortality (1992–2005)			Yi et al., 2014b
HR per unit of log EOI (n = 180,639)			
Small intestine (C17)	19	1.1 (0.9–1.4)	
Colorectal (C18–C21)	366	1.0 (1.0–1.1)	
High exposure vs low exposure			
Small intestine (C17) (14 vs 5)		2.9 (1.0–8.3)	
Colorectal (C18–C21) (187 vs 179)		1.0 (0.8–1.2)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Non-cancer mortality			Vena et al., 1998
Mortality 1939–1992			Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs			
Colon	86	1.1 (0.9–1.3)	
Rectum	44	1.1 (0.8–1.4)	
7,553 not exposed to highly chlorinated PCDDs			
Colon	52	1.0 (0.8–1.3)	
Rectum	29	1.3 (0.9–1.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Nested case-control study			
Colon (except rectum)	41	1.1 (0.8–1.5)	
Rectum	24	1.1 (0.7–1.6)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	Coggon et al., 1986
Mortality through 1983			
Colon	19	1.0 (0.6–1.6)	
Rectum	8	0.6 (0.3–1.2)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982			Lynge, 1985
Men			
Colon	10	1.0 (nr)	
Rectum	14	1.4 (nr)	
Women			
Colon	1	0.3 (nr)	
Rectum	2	1.0 (nr)	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991			Hooiveld
Colon	3	1.4 (0.3–4.0)	et al., 1998
Rectum	1	1.0 (0.0–5.6)	
Mortality 1955–1985			Bueno de
Large intestine, except colon	3	2.4 (0.5–7.0)	Mesquita
Rectum	0	0.0 (0.0–5.6)	et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–1986	3	1.8 (0.4–5.4)	Bueno de
Large intestine, except rectum	0	0.0 (0.0–9.5)	Mesquita
Rectum	0	0.0 (0.0–19.4)	et al., 1993
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992			Becher
Colon	0	nr	et al., 1996
Rectum	0	nr	

continued

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989			Becher
Colon	1	2.2 (0.1–2.2)	et al., 1996
Rectum	0	nr	
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989			Becher
Colon	0	nr	et al., 1996
Rectum	1	0.9 (0.0–4.9)	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992—colorectal	5	1.0 (0.3–2.3)	Ott and
TCDD < 0.1 µg/kg of body weight	2	1.1 (0.1–3.9)	Zober, 1996a
TCDD 0.1–0.99 µg/kg of body weight	2	1.4 (0.2–5.1)	
TCDD > 1.0 µg/kg of body weight	1	0.5 (0.0–3.0)	
Mortality			
Through 1987—colon, rectum		*90% CI*	Zober et al.,
	2	2.5 (0.4–7.8)	1990
Through 1970—(n = 74; 70 initially exposed, 4 involved with cleaning and testing procedures)	1	0.4 (nr)	Theiss et al., 1982
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997) (ICD-9)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (140–149)			Manuwald
Colon (153)	12	0.7 (0.4–1.3)	et al., 2012
Men	7	0.6 (0.3–1.3)	
Women	5	0.9 (0.3–2.1)	
Rectum, rectosigmoid junction, anus (154)	13	1.7 (0.9–2.9)	
Men	11	2.0 (0.98–3.5)	
Women	2	1.0 (0.1–3.7)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortalilty 1952–1989			Becher
Colon	2	0.4 (0.1–1.4)	et al., 1996
Rectum	6	1.9 (0.7–4.0)	
Mortality 1952–1989—stats on men only, 1,184 (tables for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966)			Manz et al., 1991
Colon	8	0.9 (0.4–1.8)	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride
Large intestine			et al., 2009a
Ever-exposed workers	3	0.6 (0.1–1.7)	
Never-exposed workers	0	0.0 (0.0–2.0)	
Rectum			
Ever-exposed workers	6	2.0 (0.7–4.4)	
Never-exposed workers	2	2.1 (0.3–7.7)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000			't Mannetje
Phenoxy herbicide producers (men and women)			et al., 2005
Colon	2	0.6 (0.0–2.3)	
Rectum, rectosigmoid junction, anus	5	2.5 (0.8–5.7)	
Phenoxy herbicide sprayers (> 99% men)			
Colon	8	1.9 (0.8–3.8)	
Rectum, rectosigmoid junction, anus	4	1.5 (0.4–3.8)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993			Steenland
Small intestine, colon	34	1.2 (0.8–1.6)	et al., 1999
Rectum	6	0.9 (0.3–1.9)	
Through 1987			Fingerhut
Entire NIOSH cohort			et al., 1991
Small intestine, colon	25	1.2 (0.8–1.8)	
Rectum	5	0.9 (0.3–2.1)	
≥ 1-yr exposure, ≥ 20-yr latency			
Small intestine, colon	13	1.8 (1.0–3.0)	
Rectum	2	1.2 (0.1–4.2)	

continued

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality, colon cancer—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	3	0.5 (0.1–1.3)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)			Collins
Large intestine	18	1.2 (0.7–1.8)	et al., 2009b
Rectum	2	0.6 (0.1–2.1)	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
Intestine (ICD-9 152–153)			
1940–2005 (n = 2,122)	26	1.1 (0.7–1.6)	
PCP and TCP (n = 720)	11	1.4 (0.7–2.6)	
PCP (no TCP) (n = 1,402)	15	0.9 (0.5–1.5)	
Rectum (ICD-9 154)			
1940–2005 (n = 2,122)	2	0.4 (0.0–1.3)	
PCP and TCP (n = 720)	1	0.5 (0.0–3.0)	
PCP (no TCP) (n = 1,402)	1	0.3 (0.0–1.5)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)			Burns CJ et al., 2011
Colon	16	1.0 (0.6–1.6)	
Rectum	6	0.8 (0.3–1.7)	
Through 1982 (n = 878)			Bond et al.,
Colon	4	2.1 (0.6–5.4)	1988
Rectum	1	1.7 (0.0–9.3)	
Dow PCP Production Workers (1937–1989 in Midland, MI) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)			Collins et al., 2009c
Large intestine	10	1.2 (0.6–2.3)	
Rectum	1	0.5 (0.0–2.9)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-yr latency			
Colon	4	0.8 (0.2–2.1)	
Rectum	0	nr	
15-yr latency			
Colon	4	1.0 (0.3–2.6)	
Rectum	0	nr	
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
1,412 white male US flavor and fragrance chemical plant workers (1945–1965)		**Dioxin, 2,4,5-T**	Thomas, 1987
Colon	4	0.6 (nr)	
Rectum	6	2.5 (nr)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Colon	62	0.7 (0.6–1.0)	
Rectum	60	0.9 (0.7–1.1)	
Danish paper workers			Rix et al., 1998
Men			
Colon	58	1.0 (0.7–1.2)	
Rectum	43	0.9 (0.6–1.2)	
Women			
Colon	23	1.1 (0.7–1.7)	
Rectum	15	1.5 (0.8–2.4)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 yr, mortality through July 1985			Henneberger et al., 1989
Colon	9	1.0 (0.5–2.0)	
Rectum	1	0.4 (0.0–2.1)	
Pulp and paper cohorts independent of IARC cohort			
United Paperworkers International, 201 white men employed ≥ 10 yr and dying 1970–1984			Solet et al., 1989
Colon	7	1.5 (0.6–3.0)	

continued

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977			Robinson et al., 1986
Intestines (ICD-7 152, 153)	7	0.4 (0.2–0.7)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed			
Colon	277	0.7 ($p < 0.05$)	
Rectum	309	0.8 ($p < 0.05$)	
Employee			
Colon	45	0.6 ($p < 0.05$)	
Rectum	55	0.8 (nr)	
Women			
Self-employed			
Colon	14	0.9 (nr)	
Rectum	5	0.6 (nr)	
Employee			
Colon	112	0.9 (nr)	
Rectum	55	0.8 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000			Swaen et al., 2004
Colon	7	1.0 (0.4–2.1)	
Rectum	5	2.1 (0.7–4.8)	
Through 1987			Swaen et al., 1992
Colon	4	2.6 (0.7–6.5)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)			Torchio et al., 1994
Colon	84	0.6 (0.5–0.7)	
Rectum	nr	nr	
Italian rice growers with documented phenoxy use (n = 1,487		**Phenoxy herbicides**	Gambini et al., 1997
Intestines	27	1.1 (0.7–1.6)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident cancer cases (colon, rectum, or small intestine) vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
Colon	7	0.5 (0.2–1.1)	
Rectum	10	1.2 (0.6–2.3)	
Small intestine	2	5.2 (1.4–18.9)	
Aged 20–59	2	11.2 (3.4–36.4)	
Aged ≥ 60	0	—	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Small intestine	0	—	
SWEDEN			
Incident cancer cases 1961–1973 with agriculture as economic activity in 1960 census			Wiklund, 1983
Colon	1.332		
Rectum		*99% CI*	
	1,083	0.8 (0.7–0.8)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Colon			
Men			
Whites (n = 119,648)	2,291	1.0 (0.9–1.0)	
Nonwhites (n = 11,446)	148	0.8 (0.7–0.9)	
Women			
Whites (n = 2,400)	59	1.0 (0.8–1.3)	
Nonwhites (n = 2,066)	40	1.0 (0.7–1.3)	
Rectum			
Men			
Whites (n = 119,648)	367	1.0 (0.9–1.1)	
Nonwhites (n = 11,446)	22	0.7 (0.5–1.1)	
Women			
Whites (n = 2,400)	4	0.5 (0.1–1.3)	
Nonwhites (n = 2,066)	5	1.1 (0.3–2.5)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	

continued

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Colon			
Private applicators	339	0.9 (0.8–1.0)	
Commercial applicators	17	1.0 (0.6–1.6)	
Spouses	144	0.8 (0.7–1.0)	
Rectum			
Private applicators	117	0.9 (0.7–1.1)	
Commercial applicators	8	1.2 (0.5–2.3)	
Spouses	30	0.7 (0.5–1.0)	
Enrollment through 2005—Interactions between dicamba and body mass index			Andreotti et al., 2010
Trend (with dicamba use reported)	96	1.1 (1.0–1.1)	
Trend (with no dicamba use reported)	102	1.0 (1.0–1.1)	
Enrollment through 2005—colorectal cancer			Lee WJ et al., 2007
2.4-D	204	0.7 (0.5–0.9)	
2,4,5-T	65	0.9 (0.7–1.2)	
2,4,5-TP	24	0.8 (0.5–1.2)	
Dicamba	110	0.9 (0.7–1.2)	
Enrollment through 2002—colon cancer			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	76	1.0	
1– < 20	9	0.4 (0.2–0.9)	
20– < 56	20	0.9 (0.5–1.5)	
56– < 116	13	0.8 (0.4–1.5)	
≥ 116	17	1.4 (0.8–2.9)	
		p-trend = 0.10	
Dicamba—intensity-weighted quartiles			
None	76	1.0	
Lowest	16	0.6 (0.4–1.1)	
Second	17	0.7 (0.4–1.2)	
Third	6	0.5 (0.2–1.2)	
Highest	20	1.8 (1.0–3.1)	
		p-trend = 0.02	
Enrollment through 2002			Alavanja et al., 2005
Colon			
Private applicators (men, women)	208	0.9 (0.8–1.0)	
Spouses of private applicators (> 99% women)	87	0.9 (0.7–1.1)	
Commercial applicators (men, women)	12	0.2 (0.6–2.1)	
Rectum			
Private applicators (men, women)	94	0.8 (0.7–1.0)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Spouses of private applicators (> 99% women)	23	0.6 (0.4–0.9)	
Commercial applicators (men, women)	7	1.3 (0.5–2.6)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Intestine			
Applicators (n = 1,641)	158	0.8 (0.6–0.9)	
Spouses (n = 676)	68	0.9 (0.7–1.1)	
Rectum			
Applicators (n = 1,641)	32	0.7 (0.5–1.0)	
Spouses (n = 676)	4	nr	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Colon			
Private applicators (men, women)	56	0.7 (0.6–1.0)	
Spouses of private applicators (> 99% women)	31	1.2 (0.8–1.6)	
Rectum			
Private applicators (men, women)	nr	nr	
Spouses of private applicators (> 99% women)	nr	nr	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of cancer		**Herbicides**	
Agricultural extension agents			Alavanja et al., 1988
Colon	41	1.0 (0.7–1.5)	
Rectum	5	nr	
Forest conservationists		p-trend < over yrs worked	Alavanja et al., 1989
Colon	44	1.5 (1.1–2.0)	
Rectum	9	1.0 (0.5–1.9)	
Soil conservationists			
Florida Licensed Pesticide Applicators [common phenoxy use assumed but not documented; had been listed by Blair et al., 1983]		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose–response by length of licensure)			
Colon	5	0.8 (nr)	
Rectum	2	nr	

continued

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
White Male Residents of Iowa—colon cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR			Burmeister,
Colon	1,064	0.9 (0.9–1.0)	1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A			Pesatori
Colon	2	0.7 (0.2–2.7)	et al., 2009
Rectum	0		
Zone B			
Colon	19	1.0 (0.7–1.6)	
Rectum	17	1.8 (1.1–2.9)	
Zone R			
Colon	137	1.0 (0.9–1.3)	
Rectum	71	1.1 (0.8–1.4)	
10-yr follow-up to 1991—men			Bertazzi
Zone B			et al., 1993
Colon	2	0.5 (0.1–2.0)	
Rectum	3	1.4 (0.4–4.4)	
Zone R			
Colon	32	1.1 (0.8–1.6)	
Rectum	17	1.1 (0.7–1.9)	
10-yr follow-up to 1991—women			Bertazzi
Zone B			et al., 1993
Colon	2	0.6 (0.1–2.3)	
Rectum	2	1.3 (0.3–5.4)	
Zone R			
Colon	23	0.8 (0.5–1.3)	
Rectum	7	0.6 (0.3–1.3)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A			et al., 2008
Colon	3	1.0 (0.3–3.0)	
Rectum	1	0.9 (0.1–6.4)	
Zone B			
Colon	12	0.6 (0.3–1.1)	
Rectum	11	1.5 (0.8–2.8)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Zone R			
Colon	137	0.9 (0.7–1.3)	
Rectum	50	0.9 (0.7–1.3)	
20-yr follow-up to 1996			Bertazzi et al., 2001
Zones A and B—men			
Colon	10	1.0 (0.5–1.9)	
Rectum	9	2.4 (1.2–4.6)	
Zones A and B—women			
Colon	5	0.6 (0.2–1.4)	
Rectum	3	1.1 (0.4–3.5)	
15-yr follow-up to 1991—men			Bertazzi et al., 1997
Zone B			
Colon	5	0.8 (0.3–2.0)	
Rectum	7	2.9 (1.2–5.9)	
Zone R			
Colon	34	0.8 (0.6–1.1)	
Rectum	19	1.1 (0.7–1.8)	
15-yr follow-up to 1991—women			Bertazzi et al., 1997
Zone A			
Colon	2	2.6 (0.3–9.4)	
Zone B			
Colon	3	0.6 (0.1–1.8)	
Rectum	2	1.3 (0.1–4.5)	
Zone R			
Colon	33	0.8 (0.6–1.1)	
Rectum	12	0.9 (0.5–1.6)	
10-yr follow-up to 1986—men			Bertazzi et al., 1989a,b
Zone A, B, R—colon	20	1.0 (0.6–1.5)	
Zone A, B, R—rectum	10	1.0 (0.5–2.7)	
Zone B—rectum	2	1.7 (0.4–7.0)	
10-yr follow-up to 1986—women			Bertazzi et al., 1989a
Zone A, B, R—colon	12	0.7 (0.4–1.2)	
Zone A, B, R—rectum	7	1.2 (0.5–2.7)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence— Crude incidence rate in 1998 vs			
Men			
Regional (Samara)			
Colon	nr	21.7 (nr)	
Rectum	nr	17.1 (nr)	
National (Russia)			
Colon	nr	17.9 (nr)	

continued

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Rectum	nr	16.6 (nr)	
Women			
Regional (Samara)			
Colon	nr	15.4 (nr)	
Rectum	nr	11.2 (nr)	
National (Russia)			
Colon	nr	14.1 (nr)	
Rectum	nr	10.3 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Men			
Colon	17	1.3 (0.8–2.2)	
Rectum	21	1.5 (1.0–2.4)	
Women			
Colon	24	1.0 (0.7–1.5)	
Rectum	24	0.9 (0.6–1.4)	
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)		**Chlorophenol**	Lampi et al., 1992
Colon—men, women	9	1.1 (0.7–1.8)	
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman		SMRs	
Colon	8	0.5 (0.2–1.0)	
Rectum	8	0.8 (0.4–1.6)	
Spouses			
Colon	10	1.3 (0.6–2.4)	
Rectum	8	2.1 (0.9–4.2)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast			
Colon	5	0.4 (0.1–0.9)	
Rectum	9	0.9 (0.4–1.6)	
West coast			
Colon	82	1.0 (0.8–1.2)	
Rectum	59	1.1 (0.8–1.4)	
Mortality			
East coast			
Colon	1	0.1 (0.0–0.7)	
Rectum	4	0.7 (0.2–1.9)	

TABLE 8-6 Colon and Rectal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
West coast			
Colon	58	1.0 (0.8–1.3)	
Rectum	31	1.0 (0.7–1.5)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
421 **Egyptian** colorectal cancer cases and 439 hospital controls	nr	**Herbicides** 5.5 (2.4–12.3)	Lo et al., 2010
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981
Colon			
Exposed to phenoxy herbicides	11	1.3 (0.6–2.8)	
Exposed to chlorophenols	6	1.8 (0.6–5.3)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; JEM, job–exposure matrix; MCPA, methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportionate mortality ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Environmental, Occupational, and Case-Control Studies No occupational, environmental, or case-control studies of exposure to the COIs and colorectal cancers have been published since *Update 2012*.

Biologic Plausibility

Long-term animal studies examining the effect of exposure to the COIs on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004) have reported no increase in the incidence of colorectal cancers. Recently, Xie et al. (2012) reported that AHR activation by TCDD induces robust proliferation in two human colon-cancer cell lines through Src-mediated epidermal growth factor receptor activation. That novel finding suggests

that TCDD and other AHR ligands may contribute to increased proliferation of colonic cells, but more studies are needed to understand the relation of increased proliferation of these cells to colorectal cancers, if any, and the potential role of AHR activation in colorectal and intestinal carcinogenesis.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Epidemiologic findings for colorectal cancers have not been particularly suggestive of an association with exposure to the COIs. The exceptionally large cohort of Korean Vietnam veterans generated results for cancer of the small intestine that presented a pattern of increased risk for both incidence and mortality, but no other epidemiologic findings for cancer of the small intestine have been encountered in these updates that could be used to appraise consistency.

There is no evidence of biologic plausibility of an association between exposure to any of the COIs and tumors of the colon or rectum or the small intestine. Overall, the available evidence does not support an association between the COIs and colorectal cancers.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and colorectal cancers.

Hepatobiliary Cancers

Hepatobiliary cancers include cancers of the liver (ICD-9 155.0, 155.2) and the intrahepatic bile duct (ICD-9 155.1). ACS estimated that 25,510 men and 10,150 women would receive diagnoses of liver cancer or intrahepatic bile duct cancer in the United States in 2015 and that 17,030 men and 7,520 women would die from these cancers (Siegel et al., 2015). Gallbladder cancer and extrahepatic bile duct cancer (ICD-9 156) are fairly uncommon and, when they are addressed, are often grouped with liver cancer.

In the United States, liver cancers account for about 2 percent of new cancer cases and 4 percent of cancer deaths. Misclassification of metastatic cancers as primary liver cancer can lead to an overestimation of the number of deaths attributable to liver cancer (Chuang et al., 2009). In developing countries, especially those in sub-Saharan Africa and Southeast Asia, liver cancers are common and are among the leading causes of death (Kamangar et al., 2006). Known risk factors for liver cancer include chronic infection with hepatitis B or hepatitis C virus

and exposure to the carcinogens aflatoxin and vinyl chloride. Alcohol cirrhosis and obesity-associated metabolic syndrome may also contribute to the risk of liver cancer (Chuang et al., 2009; Farazi et al., 2006). In the general population, the incidence of liver and intrahepatic bile duct cancers is higher in men than in women and higher in blacks than in whites (NCI, 2015). The average annual incidence of hepatobiliary cancers is shown in Table 8-3.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and hepatobiliary cancers. Additional information available to the committees responsible for subsequent updates did not change that conclusion.

Table 8-7 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies McBride et al. (2013) did not report results for this outcome.

Recent publications examined incidence of (Yi, 2013; Yi and Ohrr, 2014) and mortality from (Yi et al., 2014b) cancers among 185,265 Korean male Vietnam veterans in the Korean Veterans Health Study. When compared to the general Korean population, there was no evidence of excess liver cancer risk (SIR = 1.00, 95% CI 0.96–1.05) (Yi, 2013). In the internal comparison of the high- versus low-exposure opportunity group, Yi and Ohrr (2014) reported a marginal elevation in liver cancer for the higher group (RR = 1.09, 95% CI 0.99–1.20). Yi et al. (2014b) reported modestly increased risk of liver cancer mortality in the internal comparison (RR = 1.12, 95% CI 1.02–1.23) and from the analysis of the individual EOI scores (RR = 1.03, 95% CI 1.00–1.05).

Occupational Studies Among 3,529 employees of a Chinese automobile foundry, Wang et al. (2013) found a significantly elevated risk of liver cancer mortality (SMR = 1.71, 95% CI 1.21–2.42, based on 32 cancer deaths).

Environmental and Case-Control Studies No environmental or case-control studies of exposure to the COIs and liver cancer have been published since *Update 2012*.

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the COIs on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). Studies performed in laboratory animals have

TABLE 8-7 Selected Epidemiologic Studies—Hepatobiliary Cancers (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000—liver, intrahepatic bile ducts (ICD-9 155)	5	nr	Boehmer et al., 2004
US CDC Selected Cancers Study—case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953	8	**All COIs** 1.2 (0.5–2.7)	CDC, 1990a
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982—liver, bile duct			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	34	1.0 (0.8–1.4)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	6	1.2 (0.5–2.8)	
State Studies of US Vietnam Veterans			
923 white male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	0	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	27	0.7 (0.4–1.9)	ADVA, 2005b
Navy	8	1.0 (0.4–1.9)	
Army	18	0.7 (0.4–1.1)	
Air Force	1	0.2 (0.0–1.2)	
Mortality			
All branches, return–2001	48	0.9 (0.6–1.1)	ADVA, 2005a
Navy	11	1.0 (0.5–1.7)	
Army	33	0.9 (0.6–1.2)	
Air Force	4	0.6 (0.2–1.5)	
1980–1994			CDVA, 1997a

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Liver (ICD-9 155)	8	0.6 (0.2–1.1)	
Gallbladder (ICD-9 156)	5	1.3 (0.4–2.8)	
Australian Conscripted Army National Service 18,940 deployed vs 24,642 non-deployed		**All COIs**	
Incidence			
1982–2000	2	2.5 (0.1–147.2)	ADVA, 2005c
Mortality			
1966–2001 (liver, gallbladder)	4	2.5 (0.4–27.1)	ADVA, 2005c
1982–1994	1	nr	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual E4 exposure opportunity scores) (HRs)		**All COIs**	
Incidence (1992–2003)—categorized high (n = 85,809) vs low (n = 94,442)			Yi and Ohrr, 2014
Liver (C22)	1,023	1.1 (1.0–1.2)	
Gall bladder, etc. (C23–C24)	125	1.2 (0.9–1.6)	
Mortality (1992–2005)—categorized high (n = 85,809) vs low (n = 94,442)			Yi et al., 2014b
HR per unit of log EOI (n = 2,053)			
Liver (C22)	2,053	1.0 (1.0–1.1)	
Gallbladder (C23–C24)	215	1.1 (1.0–1.1)	
High exposure vs low exposure			
Liver (C22) (1,107 vs 946)		1.1 (1.0–1.2)	
Gallbladder (C23–C24) (120 vs 95)		1.2 (0.9–1.6)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	15	0.7 (0.4–1.2)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	12	0.9 (0.5–1.5)	
7,553 not exposed to highly chlorinated PCDDs	3	0.4 (0.1–1.2)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Liver, gallbladder, bile duct (ICD-8 155–156)	4	0.4 (0.1–1.1)	

continued

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982			Lynge, 1985
Men	3	1.0 (nr)	
Women	0	nr	
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	1	1.2 (0.0–6.9)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992—liver, gallbladder, bile duct	2	2.1 (0.3–7.5)	Ott and Zober, 1996a
TCDD < 0.1 µg/kg of body weight	1	2.8 (0.1–15.5)	
TCDD 0.1–0.99 µg/kg of body weight	0	0.0 (0.0–15.4)	
TCDD > 1.0 µg/kg of body weight	1	2.8 (0.1–15.5)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortalilty 1952–1989	0	—	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	1.4 (0.2–5.1)	
Never-exposed workers	0	0.0 (0.0–8.2)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000—ICD-9 155			't Mannetje et al., 2005
Phenoxy herbicide producers (men and women)	1	1.6 (0.0–8.8)	
Phenoxy herbicide sprayers (> 99% men)	0	0.0 (0.0–4.2)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993			Steenland et al., 1999
Liver, biliary tract (ICD-9 155–156)	7	0.9 (0.4–1.6)	
Through 1987 (liver, biliary tract)	6	1.2 (0.4–2.5)	Fingerhut et al., 1991
≥ 1-yr exposure, ≥ 20-yr latency	1	0.6 (0.0–3.3)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991); liver, biliary tract	2	1.4 (0.2–5.2)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	2	0.5 (0.1–1.6)	Collins et al., 2009b
March 1949–1978 (n = 121); 121 TCP workers with chloracne	0	nr	Zack and Suskind, 1980
Through 1982 (n = 878); liver, biliary tract (ICDA-8 155–156)	0	1.2 (nr)	Bond et al., 1988
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011

continued

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
1940–2005 (n = 2,122) (liver and biliary; ICD–9 155–156)	9	1.2 (0.6–2.3)	
PCP and TCP (n = 720)	0	– (0.0–1.6)	
PCP (no TCP) (n = 1,402)	9	1.8 (0.8–3.4)	
Dow PCP Production Workers (1937–1989 in Midland, MI) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	0	0.0 (0.0–1.7)	Collins et al., 2009c
Mortality 1940–1989 (n = 770); liver, primary (ICDA-8 155–156)			Ramlow et al., 1996
0-yr latency	0	nr	
15-yr latency	0	nr	
Other Studies of Industrial Workers (*not* related to IARC or NIOSH phenoxy cohort)			
Automobile workers from Hubei province in China (worked 1 yr during 1980–1985)		**PCDD/F**	Wang et al., 2013
Mortality (1980–2005) (n = 3,529)	32	1.7 (1.2–2.4)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	27	0.9 (0.6–1.3)	
Ever	16	0.7 (0.4–1.1)	
Danish paper workers			Rix et al., 1998
Men			
Liver	10	1.1 (0.5–2.0)	
Gallbladder	9	1.6 (0.7–3.0)	
Women			
Liver	1	0.6 (0.0–3.2)	
Gallbladder	4	1.4 (0.4–3.7)	
Pulp and paper cohorts independent of IARC cohort			
United Paperworkers International, 201 white men employed ≥ 10 yr and dying 1970–1984	2	2.0 (0.2–7.3)	Solet et al., 1989

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Liver			
Self-employed	23	0.4 ($p < 0.05$)	
Employee	9	0.8 (nr)	
Gallbladder			
Self-employed	35	0.8 (nr)	
Employee	7	0.8 (nr)	
Women			
Liver			
Family workers	5	0.5 (nr)	
Gallbladder			
Self-employed	7	2.7 ($p < 0.05$)	
Employee	1	0.7 (nr)	
Family workers	17	1.0 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	0	nr	Swaen et al., 2004
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC (liver, biliary tract)		**Phenoxy herbicides**	
Incidence	3	0.9 (0.2–2.6)	Asp et al., 1994
Mortality 1972–1989	2	0.6 (0.1–2.2)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	15	0.6 (0.3–0.9)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	7	1.3 (0.5–2.6)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident hepatobiliary cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
Liver	1	0.8 (0.1–5.8)	
Gallbladder	3	4.1 (1.4–12.0)	

continued

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Aged 20–59	1	6.3 (1.1–36.6)	
Aged ≥ 60	2	3.5 (0.9–13.3)	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Gallbladder	2	2.3 (0.6–9.1)	
SWEDEN			
Incident stomach cancer cases 1961–1973 with agriculture as economic activity in 1960 census		*99% CI*	Wiklund, 1983
Liver (primary)	103	0.3 (0.3–0.4)	
Biliary tract	169	0.6 (0.5–0.7)	
Liver (unspecified)	67	0.9 (0.7–1.3)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	326	1.0 (0.9–1.1)	
Nonwhites (n = 11,446)	24	0.7 (0.5–1.1)	
Women			
Whites (n = 2,400)	6	0.7 (0.3–1.6)	
Nonwhites (n = 2,066)	2	0.4 (0.0–1.3)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Liver			
Private applicators	32	0.7 (0.5–1.0)	
Commercial applicators	1	nr	
Spouses	6	0.8 (0.3–1.7)	
Gallbladder			
Private applicators	8	1.3 (0.6–2.6)	
Commercial applicators	0	nr	
Spouses	7	1.1 (0.4–2.3)	
Enrollment through 2002			Alavanja et al., 2005
Liver			
Private applicators (men, women)	35	1.0 (0.7–1.4)	

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Spouses of private applicators (> 99% women)	3	0.9 (0.2–2.5)	
Commercial applicators (men, women)	nr	0.0 (0.0–4.2)	
Gallbladder			
Private applicators (men, women)	8	2.3 (1.0–4.5)	
Spouses of private applicators (> 99% women)	3	0.9 (0.2–2.5)	
Commercial applicators (men, women)	nr	0.0 (0.0–35.8)	
Mortality			
Enrollment through 2007, vs state rates (liver and gallbladder)			Waggoner et al., 2011
Applicators (n = 1,641)	50	0.7 (0.5–0.9)	
Spouses (n = 676)	18	0.8 (0.5–1.3)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Liver			
Private applicators (men, women)	8	0.6 (0.2–1.1)	
Spouses of private applicators (> 99% women)	4	1.7 (0.4–4.3)	
Rectum			
Private applicators (men, women)	3	2.0 (0.4–5.7)	
Spouses of private applicators (> 99% women)	2	1.3 (0.1–4.6)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			Pesatori et al., 2009
Zone A			
Liver	0		
Biliary	0		
Zone B			
Liver	14	1.3 (0.8–2.2)	
Biliary	6	2.3 (1.0–5.2)	
Zone R			
Liver	56	0.7 (0.6–1.0)	
Biliary	16	0.8 (0.5–1.4)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Zone B			
Liver	4	2.1 (0.8–5.8)	
Gallbladder (ICD-9 156)	1	2.3 (0.3–17.6)	

continued

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Zone R			
Liver	3	0.2 (0.1–0.7)	
Gallbladder (ICD-9 156)	3	1.0 (0.3–3.4)	
10-yr follow-up to 1991—women			Bertazzi et al., 1993
Zone B			
Gallbladder (ICD-9 156)	4	4.9 (1.8–13.6)	
Zone R			
Liver	2	0.5 (0.1–2.1)	
Gallbladder (ICD-9 156)	7	1.0 (0.5–2.3)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
Zone A			
Liver	3	1.0 (0.3–3.2)	
Biliary	0	0.0 (nr)	
Zone B			
Liver	16	0.9 (0.5–1.4)	
Biliary	2	0.6 (0.1–2.3)	
Zone R			
Liver	107	0.8 (0.7–1.0)	
Biliary	31	1.2 (0.8–1.7)	
20-yr follow-up to 1996			Bertazzi et al., 2001
Zones A and B—men			
Liver, gallbladder	6	0.5 (0.2–1.0)	
Liver	6	0.5 (0.2–1.1)	
Zones A and B—women			
Liver, gallbladder	7	1.0 (0.5–2.2)	
Liver	6	1.3 (0.6–2.9)	
15-yr follow-up to 1991—men			Bertazzi et al., 1997
Zone B			
Liver, gallbladder	4	0.6 (0.2–1.4)	
Liver	4	0.6 (0.2–1.6)	
Zone R			
Liver, gallbladder	35	0.7 (0.5–1.0)	
Liver	31	0.7 (0.5–1.0)	
15-yr follow-up to 1991—women			Bertazzi et al., 1997
Zone B			
Liver, gallbladder	4	1.1 (0.3–2.9)	
Liver	3	1.3 (0.3–3.8)	
Zone R			
Liver, gallbladder	25	0.8 (0.5–1.3)	
Liver	12	0.6 (0.3–1.1)	
10-yr follow-up to 1986—men			Bertazzi et al., 1989b
Zone B—liver	3	1.2 (0.4–3.8)	
Zone R—liver	7	0.4 (0.2–0.8)	

TABLE 8-7 Hepatobiliary Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
10-yr follow-up to 1986—women			Bertazzi et al., 1989b
Zone A—gallbladder (ICD-9 156)	1	12.1 (1.6–88.7)	
Zone B—gallbladder (ICD-9 156)	2	3.9 (0.9–16.2)	
Zone R			
Liver	3	0.4 (0.1–1.4)	
Gallbladder (ICD-9 156)	5	1.2 (0.5–3.1)	
Quail Run Mobile Home Cohort		**TCDD**	Hoffman et al., 1986
154 exposed residents vs 155 unexposed area residents	0	nr	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	1	0.5 (0.0–2.7)	
West coast	9	0.9 (0.4–1.7)	
Mortality			
East coast	6	1.3 (0.5–2.9)	
West coast	24	1.0 (0.6–1.5)	
VIETNAM			
Risk factor for hepatocellular carcinoma in Hanoi		**Herbicides**	Cordier et al., 1993
Military service in South Vietnam for ≥ 10 yrs after 1960	11	8.8 (1.9–41.0)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Swedish patients (25–80 yrs of age) diagnosed with liver cancer (ICD-7 155, 156) between 1974–June 1981 vs national rates	102	**Phenoxy acids, chlorophenols** 1.8 (0.9–4.0)	Hardell et al., 1984

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interview; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; ICDA, *International Classification of Diseases*, Adapted for Use in the United States; JEM, job–exposure matrix; MCPA, methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratio; PCP, pentachlorophenol; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

consistently demonstrated that long-term exposure to TCDD results in the formation of liver adenomas and carcinomas (Knerr and Schrenk, 2006; Walker et al., 2006). Furthermore, TCDD increases the growth of hepatic tumors that are initiated by treatment with a complete carcinogen. Pathologic liver changes have been observed after exposure to TCDD, including nodular hyperplasia and massive inflammatory cell infiltration (Kociba et al., 1978; NTP, 2006; Walker et al., 2006; Yoshizawa et al., 2007); inflammation can be heavily involved in the development and progression of many cancers, including liver cancers (Mantovani et al., 2008). In monkeys treated with TCDD, hyperplasia and an increase in cells that stain positive for alpha-smooth muscle actin have been observed (Korenaga et al., 2007). Postive staining for alpha-smooth muscle actin is thought to be indicative of a process (the epithelial–mesenchymal transition) that is associated with the progression of malignant tumors (Weinberg, 2008). Zucchini-Pascal et al. (2012) showed that TCDD exposure induced an epithelial-to-mesenchymal transition in primary cultured human hepatocytes.

Bile duct hyperplasia (but not tumors) has been reported in rodents following chronic treatment with TCDD (Knerr and Schrenk, 2006; Walker et al., 2006; Yoshizawa et al., 2007). Similarly, monkeys treated with TCDD developed metaplasia, hyperplasia, and hypertrophy of the bile duct (Allen et al., 1977). Hollingshead et al. (2008) showed that TCDD-activated AHR in human breast and endocervical cell lines induces sustained high concentrations of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues, including cholangiocytes; thus, TCDD might promote carcinogenesis in biliary tissue.

TCDD may contribute to tumor progression by inhibiting p53 regulation (phosphorylation and acetylation) triggered by genotoxicants through the increased expression of the metastasis marker AGR2 (Ambolet-Camoit et al., 2010) and a functional interaction between the AHR and FHL2 (Kollara and Brown, 2009). The AHR was also shown to be a regulator of c-Raf and proposed cross-talk between the AHR and the mitogen-activated protein kinase signaling pathway in chemically induced hepatocarcinogenesis (Borlak and Jenke, 2008). TCDD inhibits ultraviolet-C radiation-induced apoptosis in primary rat hepatocytes and Huh-7 human hepatoma cells, which supports the hypothesis that TCDD acts as a tumor promoter by preventing initiated cells from undergoing apoptosis (Chopra et al., 2009). TCDD inhibited the proliferation of isolated mouse oval cells, which are liver precursor cells, via an AHR-dependent pathway, suggesting that these cells are not the precursor for TCDD-induced tumors in the mouse (Faust et al., 2013a).

Elyakim et al. (2010) found that human microRNA miR-191 was upregulated in hepatocellular carcinoma and that miR-191 was upregulated after TCDD treatment and may contribute to the mechanism of the carcinogenic activity of TCDD. Ovando et al. (2010) used toxicogenomics to identify genomic responses that may contribute to the development of hepatotoxicity in rats treated chronically with the AHR ligands, TCDD, or PCB 126. The researchers identified 24, 17, and 7

genes that were differentially expressed in the livers of rats exposed to those AHR ligands and in, respectively, human cholangiocarcinoma, human hepatocellular adenoma, and rat hepatocellular adenoma. These findings may help elucidate the mechanisms by which dioxin-like compounds induce their hepatotoxic and carcinogenic effects.

In rodents, TCDD may promote hepatocarcinogenesis through cytotoxicity, chronic inflammation, and liver regeneration and through hyperplastic and hypertrophic growth due to the sustained activation of the AHR (Köhle and Bock, 2007; Köhle et al., 2008). For example, dioxin (TCDD) exposure was reported to increase liver fibrosis in mice via an AHR-dependent pathway. A recent study by Kennedy et al. (2014) addressed two of these issues by using transgenic mouse strains to measure dioxin-induced liver cancers in a model in which TCDD was used as a tumor promoter. One set of experiments showed that the number of TCDD-induced liver tumors was significantly higher in mice that expressed AHR with high binding affinity to TCDD than in an isogenic strain that expressed a low-binding-affinity AHR. A second set of experiments showed that the genetic ablation of inflammatory cytokines reduced significantly TCDD-induced liver tumors. Likewise, genetic ablation of AHR reduced TCDD-induction of the inflammatory cytokines (Pierre et al., 2014). Species differences associated with AHR activation are demonstrated by the divergence in the transcriptomic responses to TCDD in mouse, rat, and human liver (Boutros et al., 2008, 2009; Carlson et al., 2009; Kim et al., 2009), but it should be noted that the in vitro human hepatocyte studies may not reflect the in vivo response of human liver to TCDD. In vitro studies with transformed cell lines and primary hepatocytes cannot replicate the complexity of a tissue response that is important in eliciting the toxic responses observed in vivo (Dere et al., 2006). Finally, a recent study showed that AHR expression is significantly elevated in human liver cancers, although the absolute level of increase is only about 30 to 40 percent, but the biological significance of this observation is not known (Liu et al., 2013).

In a study of gene-expression changes in adult female primary human and rat hepatocytes exposed to TCDD in vitro, Black et al. (2012) used whole-genome microarrays to show that TCDD produced different gene-expression profiles in rat and human hepatocytes both on an ortholog basis (conserved genes in different species) and on a pathway basis. For commonly affected orthologs or signaling pathways, the human hepatocytes were about one-fifteenth as sensitive as rat hepatocytes. Such findings are consistent with epidemiologic studies that show humans to be less sensitive to TCDD-induced hepatotoxicity. A more recent study of gene-expression changes in cultured rat liver cells (the WB-F344 cell line) showed that the AHR agonist PCB126 identified hundreds of dysregulated genes that increased in number as a function of time after exposure from 6 to 72 hours; these included the Wnt and TGF-b signaling pathways, which are involved in tumorogenesis (Faust et al., 2013b).

Chronic exposure of rats to TCDD was associated with fatty liver degeneration and necrosis (Chen X et al., 2012). Another group reported that the hepatotoxic effects of TCDD were exacerbated in mice that had glutathione deficiency (Chen YJ et al., 2012). The combined exposure to PCBs and TCDD induced significant hepatotoxicity in rats (Lu C et al., 2010). Studying the effects of environmental chemicals on nuclear hormone receptors, Shah et al. (2011) demonstrated that in vitro assays for stratifying environmental contaminants can serve as surrogates in combination with rodent toxicity evaluations.

Cacodylic acid (DMA^{III} and DMA^{V}) is carcinogenic and has been shown to induce renal cancer. In F344/DuCrj rats treated with a mixture of carcinogens for 4 weeks, subsequent exposure to DMA (not indicated whether this was DMA^{III} or ^{V}) via the drinking water for 24 weeks caused tumor promotion in the liver, kidney, urinary bladder, and thyroid gland but inhibited induction of tumors of the nasal passages (Yamamoto et al., 1995). Recent studies have also found that oral exposure of adult mice to 200 ppm DMA^{V} in addition to fetal arsenic exposure can act as a promoter of renal and hepatocellular carcinoma, markedly increasing tumor incidence beyond that produced by fetal arsenic exposure alone (Tokar et al., 2012).

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Since the previous report the additional literature provides modest evidence of excess liver cancer among Korean veterans and among Chinese foundry workers, although confounding remains a concern. The lack of evidence of association between exposure and this outcome in most occupational and environmental studies does not support this association. Despite the evidence of TCDD's activity as a hepatocarcinogen in animals, the evidence from epidemiologic studies remains inadequate to link the COIs with hepatobiliary cancers, which has a relatively low incidence in Western populations.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and hepatobiliary cancers.

Pancreatic Cancer

The incidence of pancreatic cancer (ICD-9 157) increases with age. ACS estimated that 24,840 men and 24,120 women would receive a diagnosis of

pancreatic cancer in the United States in 2015 and that 20,710 men and 19,850 women would die from it (Siegel et al., 2015). The incidence is higher in men than in women and in blacks than in whites. Other risk factors include family history, diet, and tobacco use. Chronic pancreatitis, obesity, and type 2 diabetes are also associated with an increased risk of pancreatic cancer (ACS, 2013a). The average annual incidence of pancreatic cancer is shown in Table 8-3.

Conclusions from *VAO* and Previous Updates

Update 2006 considered pancreatic cancer independently for the first time. Prior updates developed tables of results for pancreatic cancer but reached conclusions about the adequacy of the evidence of its association with herbicide exposure in the context of gastrointestinal tract cancers. The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the herbicides used by the US military in Vietnam and gastrointestinal tract tumors, including pancreatic cancer. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the COIs to sustain that negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence on each should be evaluated separately. Pancreatic cancer was thus reclassified into the default category of inadequate or insufficient evidence of an association.

In reviewing the existing evidence concerning an association between herbicide exposure and pancreatic cancer, the committee for *Update 2006* noted a report of increased rates of pancreatic cancer in US female Vietnam nurse veterans (Dalager et al., 1995a) but concluded that it alone did not constitute limited or suggestive evidence of an association. That increase persisted in the follow-up study of the American female veterans (Cypel and Kang, 2008), but committees for subsequent updates have concurred with the decision of the committee for *Update 2006*. Table 8-8 summarizes the results of the relevant studies concerning pancreatic cancer.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies Among 2,783 New Zealand veterans who served in Vietnam between 1964 and 1975, McBride et al. (2013) reported that pancreatic cancer mortality was in deficit in the cohort in comparison to the general population of New Zealand (SMR = 0.67, 95% CI 0.22–1.56, based on five deaths). Pancreatic cancer incidence was also lower than expected (SIR = 0.72, 95% CI 0.26–1.57, based on six cases). The wide confidence intervals resulting from the small number of observed cases make these results largely uninformative.

Kang et al. (2014) updated the vital status of 4,734 women who served in the US Army, Navy, Air Force, or Marines in Vietnam between July 4, 1965,

TABLE 8-8 Selected Epidemiologic Studies—Pancreatic Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	5	1.0 (0.3–3.5)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	82	0.9 (0.6–1.2)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	18	1.6 (0.5–5.8)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Mortality			
Through 2010—Vietnam-era veterans	50	1.7 (1.0–3.1)	Kang et al., 2014
Vietnam nurses only	35	2.1 (1.0–4.3)	
Through 2004—Vietnam-era veterans	17	2.1 (1.0–4.5)	Cypel and Kang, 2008
Vietnam-veteran nurses	14	2.5 (1.0–6.0)	
Through 1991—Vietnam-era veterans	7	2.8 (0.8–10.2)	Dalager et al., 1995a
Vietnam nurses only	7	5.7 (1.2–27.0)	
Through 1987—Vietnam-era veterans (Vietnam nurses not reported separately)	5	2.7 (0.9–6.2)	Thomas et al., 1991
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	14	1.0 (0.6–1.7)	Visintainer et al., 1995
Non-black	9	0.7 (0.3–1.3)	
Black	5	9.1 (2.9–21.2)	
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	4	nr	Anderson et al., 1986a,b

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	86	1.2 (0.9–1.4)	ADVA, 2005b
Navy	14	0.9 (0.5–1.5)	
Army	60	1.2 (0.9–1.5)	
Air Force	12	1.3 (0.7–2.3)	
Mortality			
All branches, return–2001	101	1.2 (1.0–1.5)	ADVA, 2005a
Navy	18	1.0 (0.6–1.6)	
Army	71	1.3 (1.0–1.6)	
Air Force	11	1.1 (0.5–1.8)	
1980–1994	38	1.4 (0.9–1.8)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	17	2.5 (1.0–6.3)	ADVA, 2005c
Mortality			
1966–2001	19	3.1 (1.3–8.3)	ADVA, 2005c
1982–1994	6	1.5 (nr)	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	6	0.7 (0.3–1.6)	
Mortality (1988–2008)	5	0.7 (0.2–1.6)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—pancreas (C25) categorized high (n = 100) vs low (n = 84)	100	1.1 (0.8–1.5)	Yi and Ohrr, 2014
Mortality (1992–2005)—pancreas (C25) categorized high (n = 141) vs low (n = 114)			Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	255	1.0 (1.0–1.1)	

continued

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	47	0.9 (0.7–1.3)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	30	1.0 (0.7–1.4)	
7,553 not exposed to highly chlorinated PCDDs	16	0.9 (0.5–1.4)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	26	1.1 (0.7–1.6)	Saracci et al., 1991
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	9	0.7 (0.3–1.4)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1982			Lynge, 1985
Men	3	0.6 (nr)	
Women	0	nr	
Mortality			
Mortality 1955–2006	7	1.2 (0.8–1.7)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	6	0.9 (0.5–1.6)	Boers et al., 2012
Mortality 1955–2006	4	0.9 (0.2–4.2)	Boers et al., 2010
Mortality 1955–1991	4	2.5 (0.7–6.3)	Hooiveld et al., 1998
Mortality 1955–1985	3	2.9 (0.6–8.4)	Bueno de Mesquita et al., 1993

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	1	nr	Boers et al., 2010
Mortality 1965–1986	0	0.0 (0.0–10.9)	Bueno de Mesquita et al., 1993
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	2	1.7 (0.2–6.1)	Becher et al., 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 157)	10	0.9 (0.4–1.7)	Manuwald et al., 2012
Men	7	0.9 (0.4–1.9)	
Women	3	1.0 (0.2–2.9)	
Mortality 1952–1989	2	0.6 (0.1–2.3)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	

continued

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1969–2004			McBride
Ever-exposed workers	3	1.3 (0.3–3.9)	et al., 2009a
Never-exposed workers	0	0.0 (0.0–4.9)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000			't Mannetje
Phenoxy herbicide producers (men, women)	3	2.1 (0.4–6.1)	et al., 2005
Phenoxy herbicide sprayers (> 99% men)	0	0.0 (0.0–2.1)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	16	1.0 (0.6–1.6)	Steenland et al., 1999
Through 1987	10	0.8 (0.4–1.6)	Fingerhut
≥ 1-yr exposure, ≥ 20-yr latency	4	1.0 (0.3–2.5)	et al., 1991
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	6	0.7 (0.2–1.4)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	18	1.3 (0.8–2.0)	
PCP and TCP (n = 720)	6	1.4 (0.5–3.0)	
PCP (no TCP) (n = 1,402)	12	1.3 (0.7–2.2)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	2	0.4 (0.1–1.5)	Burns CJ et al., 2011
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	5	1.1 (0.3–2.5)	Collins et al., 2009c

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1940–1989 (n = 770)			Ramlow
0-yr latency	2	0.7 (0.1–2.7)	et al., 1996
15-yr latency	2	0.9 (0.1–3.3)	
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
1,412 white male US flavor and fragrance chemical plant workers (1945–1965)	6	**Dioxin, 2,4,5-T** 1.4 (nr)	Thomas, 1987
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	67	0.8 (0.7–1.1)	
Ever	69	1.1 (0.9–1.4)	
Danish paper workers			Rix et al., 1998
Men	30	1.2 (0.8–1.7)	
Women	2	0.3 (0.0–1.1)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 yr, mortality through July 1985	9	1.9 (0.9–3.6)	Henneberger et al., 1989
United Paperworkers International, 201 white men employed ≥ 10 yr and dying 1970–1984	1	0.4 (0.0–2.1)	Solet et al., 1989
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977	4	*90% CI* 0.3 (0.1–0.8)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	137	0.6 ($p < 0.05$)	
Employee	23	0.6 ($p < 0.05$)	

continued

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Women			
Self-employed	7	1.2 (nr)	
Employee	4	1.3 (nr)	
Family workers	27	0.7 ($p < 0.05$)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	5	1.2 (0.4–2.7)	Swaen et al., 2004
Through 1987	3	2.2 (0.4–6.4)	Swaen et al., 1992
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	32	0.7 (0.5–1.0)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	7	0.9 (0.4–1.9)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident pantreatic cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	6	1.8 (0.8–4.1)	
Aged 20–59	0	—	
Aged ≥ 60	6	2.4 (1.1–5.4)	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
	2	0.5 (0.1–1.8)	
SWEDEN			
Incident pancreatic cancer cases 1961–1973 with agriculture as economic activity in 1960 census	777	*99% CI* 0.8 (0.8–0.9)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	1,133	1.1 (1.1–1.2)	
Nonwhites (n = 11,446)	125	1.2 (1.0–1.4)	
Women			
Whites (n = 2,400)	23	1.0 (0.6–1.5)	
Nonwhites (n = 2,066)	16	0.7 (0.4–1.2)	

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	80	0.7 (0.6–0.9)	
Commercial applicators	5	1.0 (0.3–2.3)	
Spouses	32	0.7 (0.5–1.0)	
Nested case-control (applicators, spouses combined)			Andreotti et al., 2009
2,4-D	48	0.9 (0.5–1.5)	
Dicamba	23	0.9 (0.6–1.6)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	46	0.7 (0.5–1.0)	
Spouses of private applicators (> 99% women)	20	0.9 (0.6–1.4)	
Commercial applicators	3	1.1 (0.2–3.2)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	171	0.8 (0.7–1.0)	
Spouses (n = 676)	1	nr	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	29	0.6 (0.4–0.9)	
Spouses of private applicators (> 99% women)	10	0.7 (0.3–1.2)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of pancreatic cancer		**Herbicides**	
Agricultural extension agents	21	1.3 (0.8–1.9)	Alavanja et al., 1988
Forest conservationists	22	1.5 (0.9–2.3)	Alavanja et al., 1989
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	

continued

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose–response by length of licensure)		*Expected exposed cases*	
	4	4.0	
White Male Residents of Iowa—pancreatic cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR	416	1.1 (nr)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	1	1.2 (0.2–8.2)	Pesatori
Zone B	3	0.6 (0.2–1.7)	et al., 2009
Zone R	38	1.0 (0.7–1.4)	
10-yr follow-up to 1991—men			Pesatori
Zone A, B	2	1.0 (0.3–4.2)	et al., 1992
10-yr follow-up to 1991—women			Pesatori
Zone A, B	1	1.6 (0.2–12.0)	et al., 1992
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	2	1.2 (0.3–4.7)	et al., 2008
Zone B	5	0.5 (0.2–1.1)	
Zone R	76	1.0 (0.7–1.7)	
20-yr follow-up to 1996			Bertazzi
Zones A and B—men	4	0.7 (0.3–1.9)	et al., 2001
Zones A and B—women	1	0.3 (0.0–2.0)	
15-yr follow-up to 1991—men			Bertazzi
Zone A	1	1.9 (0.0–10.5)	et al., 1997
Zone B	2	0.6 (0.1–2.0)	
Zone R	20	0.8 (0.5–1.2)	
15-yr follow-up to 1991—women			Bertazzi
Zone B	1	0.5 (0.0–3.1)	et al., 1997
Zone R	11	0.7 (0.4–1.3)	

TABLE 8-8 Pancreatic Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
10-yr follow-up to 1986—men			Bertazzi
Zone A, B, R	9	0.6 (0.3–1.2)	et al., 1989a,b
Zone B	2	1.1 (0.3–2.7)	
10-yr follow-up to 1986—women			Bertazzi
Zone A, B, R	4	1.0 (0.3–2.7)	et al., 1989a
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a,b
Incidence			
East coast	4	0.6 (0.2–1.6)	
West coast	37	1.0 (0.7–1.4)	
Mortality			
East coast	5	0.7 (0.2–1.6)	
West coast	33	0.8 (0.6–1.2)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
UK men, 18–35 yrs of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	0.7 (0.3–1.5)	
Chlorophenols	nr	0.8 (0.5–1.4)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; PMR, proportionate mortality ratio; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; UK, United Kingdom; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

and March 28, 1973. Using the cohort of Vietnam-era veterans who remained in the United States as the referent yielded an increased risk of pancreatic cancer mortality (RR = 1.74, 95% CI 0.97–3.14) for those deployed to Vietnam. Further analyses restricted to female nurses, again using the non-deployed cohort as the referent, yielded a slightly higher risk of mortality from pancreatic cancer (RR = 2.07, 95% CI 1.00–4.25) for those nurses deployed to Vietnam.

Among 185,265 Korean male Vietnam veterans, Yi (2013) found no evidence of excess pancreatic cancer [ICD-10 C25] risk in comparison to the general population (SIR = 0.92, 95% CI 0.80–1.06). In the internal comparison analysis of high- versus low-exposure opportunity groups, Yi and Ohrr (2014) reported a small excess of pancreatic cancer incidence (RR = 1.12, 95% CI 0.83–1.51). Yi et al. (2014b) reported little indication of increased risk of mortality from pancreatic cancers in association with herbicide exposure from either the internal comparison of the high- and low-exposure opportunity groups (RR = 1.15, 95% CI 0.89–1.48) or the analysis of the individual EOI scores (RR = 1.03, 95% CI 0.97–1.09).

Occupational, Environmental, and Case-Control Studies No occupational, environmental, or case-control studies of exposure to the COIs and pancreatic cancer have been published since *Update 2012*.

Biologic Plausibility

Long-term animal studies have examined the effect on tumor incidence of exposure to each of the COIs: 2,4-D and 2,4,5-T (Charles et al., 1996), TCDD (Walker et al., 2006), picloram (Stott et al., 1990), and DMA (Wanibuchi et al., 1996, 2004). No increase in the incidence of pancreatic cancer in laboratory animals after the administration of cacodylic acid, 2,4-D, or picloram has been reported. A 2-year study of female rats reported increased incidences of pancreatic adenomas and carcinomas after treatment at the highest dose of TCDD (100 ng/kg per day) (Nyska et al., 2004). Other studies have observed chronic active inflammation, acinar-cell vacuolation, and an increase in the proliferation of the acinar cells surrounding the vacuolated cells (Yoshizawa et al., 2005b). As previously discussed, chronic inflammation and hyperproliferation are closely linked to the formation and progression of cancers, including cancers of the pancreas (Hahn and Weinberg, 2002; Mantovani et al., 2008). Metaplastic changes in the pancreatic ducts were also observed in female monkeys treated with TCDD (Allen et al., 1977).

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The large excess of pancreatic cancers in female Vietnam veterans versus their non-deployed counterparts that was observed by Thomas et al. (1991) and

Dalager et al. (1995a) was replicated in a study by Cypel and Kang (2008), who found a significant increase in all female Vietnam veterans and in the nurse subset. The recent report by Kang et al. (2014) was also consistent with these findings. The committee responsible for *Update 2006* reported a higher incidence of and mortality from pancreatic cancer in deployed Australian National Service veterans than in non-deployed veterans (ADVA, 2005c). The current update notes no excess among New Zealand veterans (McBride et al., 2013). The Korean study of Vietnam veterans suggests a small and insignificant association between estimated herbicide exposure and pancreatic cancer (Yi et al., 2014b). A limitation of all the veteran studies considered has been the lack of control for the effect of smoking. In the 31 female and 62 male cases in the AHS case-control study considered in *Update 2010* (Andreotti et al., 2009), the risk of pancreatic cancer was not associated with 2,4-D exposure, so the relative increase in the AHS cohort overall (Waggoner et al., 2011) would most certainly not be attributable to 2,4-D exposure. No increase in risk has been reported in US male Vietnam veterans. The studies of production cohorts provide limited support for an association. Overall, however, the existing evidence does not support a conclusion that exposures to the COIs are associated with the occurrence of pancreatic cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and pancreatic cancer.

LARYNGEAL CANCER

ACS estimated that 10,720 men and 2,840 women would receive diagnoses of cancer of the larynx (ICD-9 161) in the United States in 2015 and that 2,890 men and 750 women would die from it (Siegel et al., 2015). Those numbers constitute a little more than 0.8 percent of new cancer diagnoses and 0.6 percent of cancer deaths. The incidence of cancer of the larynx increases with age, and it is more common in men than in women, with a sex ratio in the United States of about 4:1 in people 50 to 64 years old. The average annual incidence of laryngeal cancer is shown in Table 8-9.

Exposure to tobacco smoke, paint fumes, metalworking fluids, and asbestos have been associated with laryngeal cancer, as has alcohol and occupational exposures to wood dust and employment in the petroleum, plastics, and textile industries (ACS, 2012a; IOM, 2006a).

TABLE 8-9 Average Annual Cancer Incidence (per 100,000) of Laryngeal Cancer in the United States[a]

	60–64 Years Old			65–69 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	19.9	19.3	36.5	24.7	24.5	41.1	29.9	30.1	45.1
Women	3.7	3.7	5.5	4.7	4.8	7.6	5.2	5.5	7.4

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to at least one of the COIs and laryngeal cancer on the basis of the evidence discussed below in the section "Synthesis." Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion.

Table 8-10 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

There have been no studies of US Vietnam veterans that have evaluated exposure to the COIs and laryngeal cancer since *Update 2012*. However, two cohort studies of Vietnam War veterans (a majority of them male) from New Zealand and Korea have recently reported on cancer incidence and mortality for larynx cancer.

Among 2,783 New Zealand veterans who served in Vietnam between 1964 and 1975, McBride et al. (2013) reported a total of five incident cases and two deaths from larynx cancers, which were ascertained during the follow-up of this cohort from 1988 through 2008. The risk of mortality from cancer of the larynx (SMR = 2.00, 95% CI 0.23–7.39, based on two deaths) was increased compared to expectations based on national rates. Laryngeal cancer incidence was slightly greater than expected (SIR = 1.18, 95% CI 0.38–2.77, based on five cases). The CIs for both point estimates were wide and imprecise due to the few cases observed. The study lacked information on potential confounding factors, including smoking and alcohol. However, both the incidence of and mortality from lung cancer were not elevated in this cohort, and thus potential confounding by smoking is unlikely.

TABLE 8-10 Selected Epidemiologic Studies—Laryngeal Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	0	0.0 (nr)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988	50	1.3 (nr)	Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	50	1.4 ($p < 0.05$)	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	4	0.7 (nr)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	97	1.5 (1.2–1.8)	ADVA, 2005b
Navy	21	1.5 (0.9–2.1)	
Army	69	1.6 (1.2–1.9)	
Air Force	7	0.8 0.3–1.7)	
Mortality			
All branches, return–2001	28	1.1 (0.7–1.5)	ADVA, 2005a
Navy	6	1.1 (0.4–2.4)	
Army	19	1.1 (0.7–1.7)	
Air Force	3	0.9 (0.2–2.5)	
1980–1994	12	1.3 (0.7–2.2)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	8	0.7 (0.2–1.6)	ADVA, 2005c

continued

TABLE 8-10 Laryngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
1966–2001	2	0.4 (0.0–2.4)	ADVA, 2005c
1982–1994	0	0 (0– > 10)	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	5	1.2 (0.4–2.8)	
Mortality (1988–2008)	2	2.0 (0.2–7.4)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—larynx (C32) categorized high (n = 87) vs low (n = 67)	87	1.2 (0.9–1.7)	Yi and Ohrr, 2014
Mortality (1992–2005)—larynx (C32) categorized high (n = 50) vs low (n = 32)		1.3 (0.8–2.0)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	82	1.1 (1.0–1.3)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	21	1.6 (1.0–2.5)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	15	1.7 (1.0–2.8)	
7,553 not exposed to highly chlorinated PCDDs	5	1.2 (0.4–2.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	8	1.5 (0.6–2.9)	Saracci et al., 1991
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	4	1.7 (0.5–4.5)	Coggon et al., 1986

TABLE 8-10 Laryngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007	7	3.5 (1.4–7.2)	Manuwald et al., 2012
Men	6	3.8 (1.4–8.2)	
Women	1	2.5 (0.0–13.9)	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	2	2.0 (0.2–7.1)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	1	2.5 (0.1–14.0)	
Never-exposed workers	1	9.7 (0.2–54.3)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1987	7	2.1 (0.8–4.3)	Fingerhut et al., 1991
≥ 1-yr exposure, ≥ 20-yr latency	3	2.7 (0.6–7.8)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	3	1.3 (0.3–3.9)	Collins et al., 2009b

continued

TABLE 8-10 Laryngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	5	1.5 (0.5–3.4)	
PCP and TCP (n = 720)	1	0.9 (0.0–5.1)	
PCP (no TCP) (n = 1,402)	4	1.7 (0.5–4.3)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	4	1.1 (0.3–2.9)	Burns CJ et al., 2011
Through 1982 (n = 878)	1	3.0 (0.0–16.8)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	2	1.7 (0.2–6.2)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)	2	2.9 (0.3–10.3)	Ramlow
0-yr latency	2	2.9 (0.4–10.3)	et al., 1996
15-yr latency	1	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	18	0.9 (0.5–1.5)	
Ever	20	1.2 (0.8–1.9)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish gardeners (n = 3,124) exposed to pesticides	9	0.7 (0.3–1.4)	Kenborg et al., 2012
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			

TABLE 8-10 Laryngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1970–1986 (n = 23,401)	25	0.5 (0.3–0.7)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	7	0.9 (0.4–1.9)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 303 incident laryngeal cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	2	1.1 (0.3–4.7)	
SWEDEN			
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	0	nr	
THE NETHERLANDS			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	1	1.0 (0.0–5.1)	Swaen et al., 2004
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	162	0.7 (0.6–0.8)	
Nonwhites (n = 11,446)	32	1.1 (0.8–1.5)	
Women			
Whites (n = 2,400)	0	nr (0.0–3.3)	
Nonwhites (n = 2,066)	0	nr (0.0–4.8)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Mortality			
25-yr follow-up to 2001—men and women, all respiratory cancers (ICD-9 160–165) excluding lung cancers (ICD-9 162)			Consonni et al., 2008
Zone A	0	nr	
Zone B	≤ 8	nr	
Zone R	≤ 49	nr	

continued

TABLE 8-10 Laryngeal Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
20-yr follow-up to 1996—men and women, all respiratory cancers (ICD-9 160–165) excluding lung cancers (ICD-9 162)			Bertazzi et al., 2001
Zone A	0	nr	
Zone B	8	nr	
15-yr follow-up to 1991—men			Bertazzi et al., 1997, 1998
Zone B	6	nr	
Zone R	32	nr	
15-yr follow-up to 1991—women			Bertazzi et al., 1997, 1998
Zone B	0	nr	
Zone R	6	nr	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence— Crude incidence rate in 1998 vs			
Men			
Regional (Samara)		0	
National (Russia)		11.3	
Women			
Regional (Samara)		0	
National (Russia)		0.4	
Mortality—1995–1998 (SMR vs regional rates)			
Men	13	2.3 (1.2–3.8)	
Women	1	0.1 (0.0–0.6)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Several recent publications examined larynx cancer incidence (Yi, 2013; Yi and Ohrr, 2014) and cancer mortality (Yi et al., 2014b) in the Korean Veterans Health Study. A total of 157 incident cases of larynx cancer [ICD-10 C32] were identified in this cohort during follow-up. When compared to the general Korean population, the cohort showed no excess larynx cancer risk (SIR = 0.90, 95% CI 0.77–1.06) (Yi, 2013). Yi and Ohrr (2014) reported a modest increased risk of larynx cancer (RR = 1.21, 95% CI 0.87–1.69), albeit not statistically significant, despite the large number of cases (n = 87) in the high exposure category. The mortality experience of this cohort of Korean veterans of the Vietnam War was also studied. Deaths due to cancer of the larynx were positively associated with the log of EOI scores (HR = 1.13, 95% CI 1.0–1.28, based on 82 deaths), and a comparison of the high- to low-exposure groups yielded a modestly elevated risk (HR = 1.28, 95% CI 0.80–2.03, based on 50 deaths from larynx cancer in the high-exposure category). Adjustments were not made for smoking or drinking habits, but an analysis of the survey data from much of the cohort established that these behaviors did not differ systematically with opportunity for herbicide exposure (Yi et al., 2013b).

Occupational, Environmental, and Case-Control Studies

No occupational and environmental cohort studies, or case-control studies of exposure to the COIs and laryngeal cancer have been published since *Update 2012.*

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the COIs on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). No increase in the incidence of laryngeal cancer in laboratory animals after the administration of any of the COIs has been reported.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The original *VAO* committee reviewed five studies that presented data on laryngeal cancers separately (Bond et al., 1988; Coggon et al., 1986; Fingerhut et al., 1991; Manz et al., 1991; Saracci et al., 1991). It concluded that "although the numbers are too small to draw strong conclusions, the consistency of a mild increase in relative risk is suggestive of an association for laryngeal cancer." The weight of evidence with regard to laryngeal cancer has increased since the original VAO committee review. Notable among epidemiological studies

contributing to the evidence are studies of workers employed in manufacturing herbicides potentially contaminated with TCDD. An IARC study (Kogevinas et al., 1997) that included essentially all of the phenoxy herbicide production workers who previously had been studied found an elevated rate of laryngeal cancers in workers who were exposed to any phenoxyacetic acid herbicide or chlorophenol (SMR = 1.6, 95% CI 1.0–2.5, based on 21 deaths), especially workers who were exposed to TCDD or higher-chlorinated dioxins (SMR = 1.7, 95% CI 1.0–2.8, based on 15 deaths). Ongoing updates have continued to indicate an increase in larynx cancer in the occupational cohorts making up this IARC cohort.

An environmental study (Revich et al., 2001) of residents of Chapaevsk, Russia, which was heavily contaminated by many industrial pollutants, including dioxin, showed an association with laryngeal cancer in men (RR = 2.3, 95% CI 1.2–3.8). Analyses of Seveso have not reported findings for laryngeal cancer.

With regard to veteran studies, a positive association was found in the study of veterans in Australia that compared mortality from laryngeal cancer with that in the general population (ADVA, 2005a) but not in the study that compared Australian veterans of the Vietnam conflict with non-deployed soldiers (ADVA, 2005c). In contrast, Watanabe and Kang (1996) found a significant 40 percent excess of mortality from laryngeal cancer in Army personnel deployed to the Vietnam theater. The Ranch Hand study was not large enough to have sufficient power to detect an association if one existed. The Korean Vietnam Veterans Health Study reviewed in this update identified a large number of incident cases (n = 157) and deaths (n = 82) from larynx cancer during a 20-year follow-up (Yi, 2013; Yi and Ohrr, 2014b; Yi et al., 2014a,b). Despite the large sample size, the modestly increased risks of both incidence and mortality from larynx cancer were not statistically significant.

Overall, the majority of reports suggest an increased risk of laryngeal cancer although individual studies often are based on small numbers of cases and are not controlled for smoking. In addition, there is evidence of an excess risk of laryngeal cancer among those who experienced chloracne—a marker of high exposure. The literature provides a reasonable level of consistency with regard to evidence of a moderate increase in relative risk of laryngeal cancer. In larger occupational studies with good exposure characterizations that focus on the COIs, the associations are generally strong for laryngeal cancer, while studies of Vietnam veterans provide modest associations.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one COI and laryngeal cancer.

LUNG CANCER

Lung cancer (carcinoma of the lung or bronchus, ICD-9 162.2–162.9) is the second most common diagnosed non-skin cancer and the leading cause of cancer deaths in the United States. ACS estimated that 115,610 men and 105,590 women would receive diagnoses of lung cancer in the United States in 2015 and that about 86,380 men and 71,660 women would die from it (Siegel et al., 2015). Those numbers represent roughly 13 percent of new cancer diagnoses and 27 percent of cancer deaths in 2015. The principal types of lung neoplasms are identified collectively as bronchogenic carcinoma and carcinoma of the lung. Cancer of the trachea (ICD-9 162.0) is often grouped with cancers of the lung and bronchus under ICD-9 16.2, but it is a rare cancer. The lung is also a common site of metastatic tumors from other organ sites; in this chapter, however, we are only addressing primary lung cancer. The incidence of lung cancer increases with age and there is a racial/ethnic disparity of lung cancer risk; the incidence is consistently higher in black men than in white men or in women (either black or white) (NCI, 2015). The average annual incidence of lung cancer in the United States is shown in Table 8-11.

The Centers for Disease Control and Prevention's (CDC's) 2014 Surgeon General report estimates that 82 percent of lung cancer deaths are attributable to cigarette smoking (CDC, 2014). Smoking is a major risk factor for lung cancer and increases the risk of all histologic types of this disease, but the associations with squamous-cell and small-cell carcinomas are the strongest. Other risk factors include exposure to asbestos, uranium, vinyl chloride, nickel chromates, coal products, mustard gas, chloromethyl ethers, gasoline, diesel exhaust, and inorganic arsenic. The latter statement does not imply that cacodylic acid, which is a metabolite of inorganic arsenic, can be assumed to be a risk factor for lung cancer. Important environmental risk factors include exposure to secondary tobacco smoke and radon (ACS, 2013a).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to at least one COI and lung

TABLE 8-11 Average Annual Incidence (per 100,000) of Lung and Bronchial Cancers in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	167.6	163.7	261.6	288.0	289.7	390.4	401.4	409.7	494.9
Women	123.9	129.8	138.9	216.8	230.3	222.2	290.8	311.2	269.5

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998, Update 2000*, *Update 2002*, *Update 2004*, *Update 2006, Update 2008*, *Update 2010,* and *Update 2012* did not change that conclusion.

Table 8-12 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Kang et al. (2014) reported on lung cancer mortality in an update of vital status through 2010 of female Vietnam-era veterans who served in Vietnam (n = 4,734) or who remained in the United States (n = 5,313). A total of 95 and 100 deaths from respiratory cancers were ascertained in these two groups of female veterans, respectively, during follow-up. In comparison to the non-deployed women (internal comparison analysis), respiratory cancer mortality was not associated with service in Vietnam for all the women (RR = 1.12, 95% CI 0.84–1.50) or for just the nurses (RR = 0.94, 95% CI 0.66–1.32).

McBride et al. (2013) reported on 2,783 male veterans from New Zealand, who served in Vietnam between 1964 and 1972 and were followed for lung cancer incidence and mortality through 2008. A total of 58 incident cases and 50 deaths from lung cancers were identified in this cohort. When compared to the general male population of New Zealand, there were no excess risks for lung cancer incidence (SIR = 1.13, 95% CI 0.86–1.47) or lung cancer mortality (SMR = 1.15, 95% CI 0.85–1.51).

In the Korean Veterans Health Study, a total of 1,223 incident cases and 1,170 deaths from cancers of the lung and bronchus were identified during follow-up. Compared to the general Korean population, there was no excess lung cancer risk (SIR = 0.99, 95% CI 0.93–1.05) in the entire cohort (Yi, 2013). Comparing veterans with higher opportunity scores to those in the group with lower scores, Yi and Ohrr (2014) reported a modest elevation in lung cancer incidence (HR = 1.12, 95% CI 1.00–1.27, based on 649 incident cases in the higher exposure category). With regard to cancer mortality for lung and bronchus, Yi et al. (2014b) also reported modestly increased lung cancer mortality for the high- versus low-exposure opportunity groups (HR = 1.15, 95% CI 1.02–1.30, based on 673 lung cancer deaths in the higher herbicide exposure category). Information on smoking habits was not available for this cohort during follow-up through 2003, and thus the modest associations could be due to confounding by smoking. Yi et al. (2013b) collected information on cigarette smoking via self-reported questionnaires from 114,562 Korean Vietnam veterans who were alive in July 2004 and found that the prevalence of smoking was relatively high in this cohort (45 percent and 36 percent were former or current smokers, respectively). The distribution of smoking, however, was similar between veterans in the high- and low-exposure groups (Yi et al., 2013b).

TABLE 8-12 Selected Epidemiologic Studies—Lung, Bronchus, or Trachea Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US VietnamVeterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g)	36	1.7 (0.9–3.2)	
Quartiles (pg/g):			
0.4–2.6	6	1.0 (nr)	
2.6–3.8	8	1.1 (0.3–3.4)	
3.8–5.2	9	1.2 (0.4–3.5)	
> 5.2	13	1.9 (0.7–5.5)	
Number of years served in SEA (per year of service)			
Quartiles (years in SEA):	36	1.1 (0.9–1.2)	
0.8–1.3	8	1.0 (nr)	
1.3–2.1	4	0.5 (0.2–1.8)	
2.1–3.7	11	0.7 (0.3–2.0)	
3.7–16.4	13	0.7 (0.3–2.0)	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	33	1.1 (0.8–1.6)	
With tours between 1966–1970	26	1.1 (0.7–1.6)	
SEA comparison veterans (n = 1,776)	48	1.2 (0.9–1.6)	
With tours between 1966–1970	37	1.2 (0.9–1.6)	
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	21	0.9 (0.6–1.3)	
SEA comparison veterans (n = 1,776)	38	1.1 (0.8–1.5)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality—Respiratory system cancers			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)	60 vs 26	1.3 (0.8–2.1)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray	19	1.4 (0.5–3.4)	

continued

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Through 1991	11	1.4 (0.4–5.4)	Dalager and Kang, 1997
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed *Mortality*—trachea, bronchus, lung		**All COIs**	
1965–2000	41	1.0 (0.6–1.5)	Boehmer et al., 2004
Low grade pay at time of discharge	nr	1.6 (0.9–3.0)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988 (lung)			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	1,139	1.1 (nr) ($p < 0.05$)	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	215	1.2 (1.0–1.3)	
US VA Study of Marine Post-service Mortality—sample of Marines serving 1967–1969, deployed (n = 10,716) vs non-deployed (n = 9,346)		**All COIs**	
Mortality (lung), earlier of discharge or April 1973 through 1991	42	1.3 (0.8–2.1)	Watanabe and Kang, 1995
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only = 3,282) *Mortality*		**All COIs**	
Through 2004—lung	195	1.1 (0.8–1.5)	Kang et al., 2014
Vietnam nurses only	137	0.9 (0.7–1.3)	
Through 2004—lung	50	1.0 (0.7–1.4)	Cypel and Kang, 2008
Vietnam veteran nurses	35	0.8 (0.5–1.2)	
Through 1991—lung	15	0.9 (0.4–1.7)	Dalager et al., 1995a
Vietnam veteran nurses	9	0.5 (0.2–1.2)	
Through 1987—lung (Vietnam veteran nurses not reported separately)	8	0.6 (0.3–1.5)	Thomas et al., 1991
US VA using the Patient Treatment Files—329 Vietnam-era veterans and 269 non-cancer controls and 111 colon cancer controls (1983–1990)	134	**All COIs** 1.4 (1.0–1.9)	Mahan et al., 1997

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	80	0.9 (0.7–1.1)	Vistainer et al., 1995
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	576	1.2 (1.1–1.3)	ADVA, 2005b
Navy	141	1.4 (1.2–1.7)	
Army	372	1.2 (1.1–1.3)	
Air Force	63	1.0 (0.7–1.2)	
Histologic type—all service branches combined			
Adenocarcinoma	188	1.5 (1.2–1.7)	
Squamous	152	1.2 (1.0–1.4)	
Small-cell	87	1.2 (0.97–1.5)	
Large-cell	79	1.1 (0.8–1.3)	
Other	70	1.1 (0.8–1.3)	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	46	65 (49–81)	
Men–self report	120	65 (49–89)	CDVA, 1998a
Mortality			
All branches, return–2001	544	1.2 (1.1–1.3)	ADVA, 2005a
Navy	135	1.4 (1.2–1.6)	
Army	339	1.1 (1.0–1.3)	
Air Force	71	1.1 (0.9–1.4)	
1980–1994			CDVA, 1997a
Lung (ICD-9 162)	212	1.3 (1.1–1.4)	
Respiratory systems (ICD-9 163–165)	13	1.8 (1.0–3.0)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	78	1.2 (1.0–1.5)	ADVA, 2005c
Histologic type			
Adenocarcinoma	27	1.4 (0.8–1.9)	
Squamous	19	1.5 (0.9–2.3)	
Small-cell	14	1.4 (0.8–2.4)	
Large-cell	8	0.7 (0.3–1.3)	
Other	10	1.2 (0.6–2.2)	

continued

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
1966–2001	67	1.8 (1.2–2.7)	ADVA, 2005c
1982–1994	27	2.2 (1.1–4.3)	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	58	1.1 (0.9–1.5)	
Mortality (1988–2008)	50	1.2 (0.9–1.5)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—Lung cancer (C33–C34) categorized high (n = 649) vs low (n = 505)		1.1 (1.0–1.3)	Yi and Ohrr, 2014
Mortality (1992–2005)—Lung cancer (C33–C34) categorized high (n = 673) vs low (n = 497)		1.2 (1.0–1.3)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	1,170	1.0 (1.0–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates (ICD-9)			
Mortality 1939–1992			Kogevinas et al., 1997
Lung (162)	380	1.1 (1.0–1.2)	
Other respiratory organs (163–165)	12	2.3 (1.2–3.9)	
13,831 exposed to highly chlorinated PCDDs			
Lung (162)	225	1.1 (1.0–1.3)	
Other respiratory organs (163–165)	9	3.2 (1.5–6.1)	
7,553 not exposed to highly chlorinated PCDDs			
Lung (162)	148	1.0 (0.9–1.2)	
Other respiratory organs (163–165)	3	1.2 (0.3–3.6)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort (ICD-9)			Saracci et al., 1991
Trachea, bronchus, lung (162)	173	1.0 (0.9–1.2)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates (lung)	2	**TCDD** 1.4 (0.2–4.9)	Kogevinas et al, 1993

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort) (ICD-8)		**MCPA**	
Mortality through 1983 (lung, pleura, mediastinum) (162–164)	117	1.2 (1.0–1.4)	Coggon et al., 1986
Background exposure	39	1.0 (0.7–1.4)	
Low-grade exposure	35	1.1 (0.8–1.6)	
High-grade exposure	43	1.3 (1.0–1.8)	
British Production Workers at 4 plants (included in IARC cohort) (lung)		**Dioxins, but TCDD unlikely; MCPA**	Coggon et al., 1991
	19	1.3 (0.8–2.1)	
Workers with exposure above background	14	1.2 (0.7–2.1)	
Chinese Automobile Foundry Factory Workers (n = 3,529)		**PCDD/F**	Wang et al., 2013
Lung cancer mortality (1980–2005); comparison with Chinese general population	43	2.1 (1.6–2.9)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1987 (lung, men only)	13	1.6 (0.9–2.8)	Lynge, 1993
Incidence 1943–1982			Lynge, 1985
Men	38	1.2 (nr)	
Women	6	2.2 (nr)	
Dutch production workers in Plant A and Plant B, combined (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (Plant A, 1,020 workers; Plant B, 1,036 workers) (respiratory cancers)	54	1.0 (0.9–1.2)	Boers et al., 2012
TCDD plasma level (HRs, by tertile) (trachea, bronchus, lung)	52	1.0 (0.8–1.2)	
Background (≤ 0.4)	24	Referent	
Low (0.4–4.1)	11	0.5 (0.3–1.1)	
Medium (4.1–20.1)	12	1.2 (0.6–2.3)	
High (≥ 20.1)	5	1.2 (0.5–3.1)	
963 men exposed during production 1955–1985 vs 1,317 unexposed; mortality in 1986 (respiratory system cancers, ICD-8 160–163)	9 vs 3	1.7 (0.5–6.3)	Bueno de Mesquita et al., 1993

continued

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (hazard ratios for lagged TCDD plasma levels)			Boers et al., 2012
Respiratory cancer	30	1.1 (0.9–1.3)	
Trachea, bronchus, lung cancers	28	1.1 (0.9–1.3)	
Mortality 1955–2006			Boers et al., 2010
Respiratory cancer	21	1.1 (0.5–2.5)	
Trachea, bronchus, lung cancers	20	1.2 (0.5–2.8)	
Mortality 1955–1985			Bueno de Mesquita et al., 1993
Trachea, bronchus, lung cancers	9	1.0 (0.5–1.9)	
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006			Boers et al., 2010
Respiratory cancer	12	1.2 (0.6–2.7)	
Trachea, bronchus, lung cancers	12	1.2 (0.6–2.7)	
Mortality 1965–1986			Bueno de Mesquita et al., 1993
Trachea, bronchus, lung cancers	0	0.0 (0.0–1.3)	
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All for plants	47	1.4 (1.1–1.9)	Becher et al., 1996
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	2	0.7 (0.0–2.5)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	3	1.6 (0.3–4.6)	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	11	1.5 (0.7–2.6)	Becher et al., 1996

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
1953–1992			Ott and Zober, 1996a
Respiratory system	13	1.2 (0.6–2.0)	
TCDD 0.1–0.99 µg/kg of body weight	2	0.7 (0.1–2.5)	
TCDD ≥ 1 µg/kg of body weight	8	2.0 (0.9–3.9)	
Lung, bronchus	11	1.1 (0.6–2.0)	
TCDD 0.1–0.99 µg/kg of body weight	2	0.8 (0.1–2.8)	
TCDD ≥ 1.0 µg/kg of body weight	8	2.2 (1.0–4.3)	
Through 1987		*90% CI*	Zober et al., 1990
	4	2.0 (0.7–4.6)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg—1,144 men working > 1 mo in 1952–1984 (generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007	73	1.4 (1.1–1.8)	Manuwald et al., 2012
Men	68	1.5 (1.2–1.9)	
Women	5	0.8 (0.3–1.9)	
Mortalilty 1952–1989	31	1.5 (1.0–2.1)	Becher et al., 1996
Mortality (lung) 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	26	1.7 (1.1–2.4)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers			
Respiratory cancer	13	0.9 (0.5–1.6)	
Trachea, bronchus, lung	11	0.8 (0.4–1.5)	
Never-exposed workers			
Respiratory cancer	5	1.2 (0.4–2.7)	
Trachea, bronchus, lung	4	1.0 (0.3–2.5)	

continued

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984); mortality (1969–2000) (ICD-9)			
Trachea, bronchus, lung (162)	12	1.4 (0.7–2.4)	't Mannetje
Other respiratory system sites (163–165)	1	3.9 (0.1–21.5)	et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984); mortality 1973–2000 (ICD-9)			
Trachea, bronchus, lung (162)	5	0.5 (0.2–1.1)	't Mannetje
Other respiratory system sites (163–165)	1	2.5 (0.1–13.7)	et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	125	1.1 (0.9–1.3)	Steenland
Chloracne subcohort (n = 608)	30	1.5 (0.98–2.1)	et al., 1999
Through 1987 (Entire cohort) (ICD-9)			Fingerhut
Trachea, bronchus, lung (162)	89	1.1 (0.9–1.4)	et al., 1991
Respiratory system (160–165)	96	1.1 (0.9–1.4)	
≥ 1-yr exposure, ≥ 20-yr latency			
Trachea, bronchus, lung (162)	40	1.4 (1.0–1.9)	
Respiratory system (160–165)	43	1.4 (1.0–1.9)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615) (bronchus, trachea, lung)	46	0.7 (0.5–0.9)	Collins et al., 2009b
1940–1994 (n = 2,187 men) (lung)	54	0.8 (0.6–1.1)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
Respiratory cancer (ICD-9 160–165)			
1940–2005 (n = 2,122)	133	1.4 (1.2–1.6)[c]	
PCP and TCP (n = 720)	28	0.9 (0.6–1.3)	
PCP (no TCP) (n = 1,402)	105	1.6 (1.3–1.9)[c]	
Trachea, bronchus, lung (ICD-9 162)			
1940–2005 (n = 2,122)	126	1.4 (1.1–1.6)[c]	
PCP and TCP (n = 720)	27	0.9 (0.6–1.3)	
PCP (no TCP) (n = 1,402)	99	1.6 (1.3–1.9)[c]	

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354 (Cohort 3) (lung, bronchus)	36	0.9 (0.6–1.3)	Burns CJ et al., 2011
Through 1994 (n = 1,517) (respiratory system, ICD-8 160–163)	31	0.9 (0.6–1.3)	Burns et al., 2001
Through 1986 (n = 878) vs national vs 36,804 "unexposed" workers at same location			Bloemen et al., 1993
Respiratory system (ICD-8 162–163)	9	0.8 (0.4–1.5)	
Through 1982 (n = 878)			Bond
Lung (ICD-8 162–163)	8	1.0 (0.5–2.0)	et al., 1988
Respiratory (ICD-8 160–163) (exposure lagged 15 yrs)			
Low cumulative exposure	1	0.7 (nr)	
Medium cumulative exposure	2	1.0 (nr)	
High cumulative exposure	5	1.7 (nr)	
Dow PCP Production Workers (1937–1989 in Midland, MI) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP) (bronchus, trachea, lung)	30	1.0 (0.6–1.4)	Collins et al., 2009c
Mortality 1940–1989 (n = 770) (ICD-8)			Ramlow et al., 1996
0-yr latency			
Respiratory system (160–163)	18	1.0 (0.6–1.5)	
Lung (162)	16	0.9 (0.5–1.5)	
15-yr latency			
Respiratory system (160–163)	17	1.1 (0.6–1.8)	
Lung (162)	16	1.1 (0.6–1.8)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM (ICD-9)			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Lung (162)			
Never	356	1.0 (0.9–1.1)	
Ever	314	1.0 (0.9–1.2)	

continued

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Pleura (163)			
Never	17	2.8 (1.6–4.5)	
Ever	4	0.8 (0.2–2.0)	
Other respiratory (164–165)			
Never	8	2.1 (0.9–4.2)	
Ever	2	0.7 (0.1–2.4)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Ontario Forestry Workers—1,222 men working ≥ 6 mo 1950–1982		**Herbicides**	
80 deaths through 1982; 18 cancers (lung greatest with 5)	5	nr	Green, 1991
DENMARK			
Danish gardeners (n = 3,124) exposed to pesticides	139	1.0 (0.9–1.2)	Kenborg et al., 2012
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-yr follow-up (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	34	0.9 (0.6–1.3)	
Born 1915–1934 (medium exposure)	72	1.0 (0.8–1.2)	
Born after 1934 (low exposure)	8	0.8 (0.4–1.7)	
10-yr follow-up (1975–1984) of male gardeners	41	1.0 (0.7–1.3)	Hansen et al., 1992
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000 (trachea, lung)	27	0.7 (0.5–1.0)	Swaen et al., 2004
Through 1987 (trachea, lung)	12	1.1 (0.6–1.9)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC (ICD-8)		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
Trachea, bronchus, lung (162)	39	0.9 (0.7–1.3)	
Other respiratory (160, 161, 163)	4	1.1 (0.7–1.3)	
Mortality 1972–1989			
Trachea, bronchus, lung (162)	37	1.0 (0.7–1.4)	
Other respiratory (160, 161, 163)	1	0.5 (0.0–2.9)	

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (lung)	155	0.5 (0.4–0.5)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
Lung	45	0.8 (0.6–1.1)	
Pleura	2	2.2 (0.2–7.9)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 4,224 incident lung cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	30	1.3 (0.8–1.9)	
SWEDEN			
Swedish pesticide applicators—incidence			Wiklund et al., 1989a
Trachea, bronchus, lung	38	0.5 (0.4–0.7)	
348 Swedish railroad workers (1957–October, 1978)—total exposure to herbicides (lung)	3	**Phenoxy acids** 1.4 (nr)	Axelson et al., 1980
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	1	4.2 (0.0–23.2)	
Lumberjacks (n = 139)	0	—	
Unexposed lumberjacks (n = 241)	5	1.2 (0.4–2.7)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	6,473	0.9 (0.9–0.9)	
Nonwhites (n = 11,446)	664	1.0 (0.9–1.1)	
Women			
Whites (n = 2,400)	57	0.8 (0.6–1.1)	
Nonwhites (n = 2,066)	24	0.6 (0.4–0.9)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	

continued

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Incidence			
Enrollment through 2006—SIRs for participants (lung, bronchus)			Koutros et al.,
Private applicators	436	0.5 (0.4–0.5)	2010a
Commercial applicators	26	0.8 (0.5–1.1)	
Spouses	133	0.4 (0.4–0.5)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	95	1.0	
1– < 20	14	0.8 (0.5–1.5)	
20– < 56	11	0.6 (0.3–1.3)	
56– < 116	12	1.0 (0.5–1.9)	
≥ 116	15	1.5 (0.8–2.7 p-trend = 0.13	
Enrollment through 2002			Alavanja et al., 2005
Private applicators			
Lung	266	0.5 (0.4–0.5)	
Respiratory system	294	0.5 (0.4–0.5)	
Spouses of private applicators (> 99% women)			
Lung	68	0.4 (0.3–0.5)	
Respiratory system	71	0.4 (0.3–0.5)	
Commercial applicators			
Lung	12	0.6 (0.3–1.0)	
Respiratory system	14	0.6 (0.3–1.0)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Respiratory			
Applicators (n = 1,641)	422	0.4 (0.4–0.5)	
Spouses (n = 676)	110	0.4 (0.3–0.5)	
Trachea, bronchus, lung			
Applicators (n = 1,641)	417	0.4 (0.4–0.5)	
Spouses (n = 676)	108	0.4 (0.3–0.5)	
Other respiratory system			
Applicators (n = 1,641)	5	0.2 (0.1–0.3)	
Spouses (n = 676)	2	nr	
Enrollment through 2000, vs state rates			Blair et al.,
Private applicators (men and women)	129	0.4 (0.3–0.4)	2005a
Years handled pesticides			
≤ 10 yrs	25	0.4 (nr) ($p < 0.05$)	
≥ 10 yrs	80	0.3 (nr) ($p < 0.05$)	
Spouses of private applicators (> 99% women)	29	0.3 (0.2–0.5)	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented)		**Herbicides**	

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Pesticide applicators in **Florida** licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose–response by length of licensure)			
Only for lawn and ornamentals (lung, ICD-8 162–163)	7	0.9 (nr)	
Minnesota Highway Maintenance Workers (n = 4,849) who worked ≥ l day for the Department of Transportation and ≥ 1 day after January 1, 1945 (1984–1986) (ICD-9)		**Herbicides**	Bender et al., 1989
Trachea, bronchus, lung (162.0–162.8)	54	0.7 (0.5–0.9)	
All respiratory (160.0–165.9)	57	0.7 (0.5–0.9)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women (lung ICD-9 162)			Pesatori et al., 2009
Zone A	7	1.1 (0.5–2.4)	
Zone B	37	1.0 (0.7–1.3)	
Zone R	280	1.0 (0.9–1.2)	
10-yr follow-up to 1991—men			Bertazzi
Zone A	2	0.8 (0.2–3.4)	et al., 1993
Zone B	18	1.1 (0.7–1.8)	
Zone R	96	0.8 (0.7–1.0)	
10-yr follow-up to 1991—women			Bertazzi
Zone R	16	1.5 (0.8–2.5)	et al., 1993
Mortality			
25-yr follow-up to 2001—men and women (lung ICD-9 162)			Consonni et al., 2008
Zone A	11	1.1 (0.6–2.0)	
Zone B	62	1.1 (0.9–1.4)	
Zone R	383	1.0 (0.8–1.1)	
20-yr follow-up to 1996 (lung)			Bertazzi
Zones A, B—men	57	1.3 (1.0–1.7)	et al., 2001
Zones A, B—women	4	0.6 (0.2–1.7)	
15-yr follow-up to 1991—men (lung)			Bertazzi
Zone A	4	1.0 (0.4–2.6)	et al., 1998
Zone B	34	1.2 (0.9–1.7)	
Zone R	176	0.9 (0.8–1.1)	

continued

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
15-yr follow-up to 1991—women (lung)			Bertazzi et al., 1998
Zone A	0	nr	
Zone B	2	0.6 (0.1–2.3)	
Zone R	29	1.0 (0.7–1.6)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence—Crude incidence rate in 1998 vs			
Men			
Regional (Samara)	nr	102.4 (nr)	
National (Russia)	nr	89.4 (nr)	
Women			
Regional (Samara)	nr	11.1 (nr)	
National (Russia)	nr	9.8 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Men	168	3.1 (2.6–3.5)	
Women	40	0.4 (0.3–0.6)	
Other International Environmental Studies			
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics (larynx, trachea, lung, combined)		**Serum dioxin**	Turunen et al., 2008
Fisherman	72	0.8 (0.6–1.0)	
Spouses	8	0.7 (0.3–1.4)	
JAPAN			
Residents of municipalities with and without waste incineration plants (cross-sectional)		**Dioxin emissions** age-adjusted mortality (per 100,000)	Fukuda et al., 2003
Men			
With		39.0 ± 6.7 vs	
Without		41.6 ± 9.1 (p = 0.0001)	
Women			
With		13.7 ± 3.8 vs	
Without		14.3 ± 4.6 (p = 0.11)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast (lung)	24	1.2 (0.8–1.8)	
West coast (lung)	73	0.9 (0.7–1.1)	

TABLE 8-12 Lung, Bronchus, or Trachea Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
East coast	16	0.8 (0.5–1.3)	
West coast	77	0.9 (0.7–1.1)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Saskatchewan, Canada farmers (604 men, 223 women) diagnosed with lung cancer between November 1983 and July 1986		**Herbicides**	McDuffie et al., 1990
Interviews with lung cancer patients (273 men and 103 women) who sprayed herbicides	103	0.6 (nr)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupational specialty; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofuran; PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; pg/g, picogram per gram; PM, proportionate mortality; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]99% CI.

Occupational Studies

Wang et al. (2013) followed a cohort of 3,529 workers who had worked at least 1 year in 1980–1985 at an automobile foundry located in Hubei province in China. When compared to the general population, there was a 2.1-fold increased risk of lung cancer mortality in this cohort (SMR = 2.13, 95% CI 1.58–2.88; based on 43 deaths). Although there were several measurements of PCDD/Fs in samples collected from six sites of this factory, the authors did not link these exposure estimates with lung cancer mortality in order to do an exposure–response analysis.

Environmental and Case-Control Studies

No environmental studies or case-control studies of exposure to the COIs and cancers of the lung, bronchus, or trachea have been published since *Update 2012*.

Biologic Plausibility

Long-term animal studies have examined the effect on tumor incidence of exposure to each of the COIs: 2,4-D and 2,4,5-T (Charles et al., 1996), TCDD (Walker et al., 2006), picloram (Stott et al., 1990), and DMA (Wanibuchi et al., 1996, 2004). As noted in previous VAO reports, there is evidence of an increased incidence of squamous-cell carcinoma of the lung in male and female rats exposed to TCDD at high concentrations (Kociba et al., 1978; Van Miller et al., 1977). A significant increase in neoplastic and non-neoplastic lung lesions was found in female rats exposed to TCDD for 2 years (Kociba et al., 1978; NTP, 1982a,b, 2006; Walker et al., 2006, 2007). The most common non-neoplastic lesions were bronchiolar metaplasia and squamous metaplasia of the alveolar epithelium. Cystic keratinizing epithelioma was the most commonly observed neoplasm. The lung was also identified as a target organ in an NTP tumor-promotion study after 60 weeks of exposure to TCDD in ovariectomized female Sprague Dawley rats initiated with a single dose of diethyl-*N*-nitrosamine (Beebe et al., 1995; Tritscher et al., 2000). Those studies ended with increased incidences of alveolar epithelial hyperplasia and alveolar–bronchiolar metaplasia—results that were similar to what was observed in the earlier NTP studies (Tritscher et al., 2000). A recent study with female mice in the lung cancer sensitive A/J strain background showed that estrogen exposure increased lung tumor incidence significantly in ovariectomized mice treated with a chemical carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), known to induce these tumors. However, TCDD exposure did not increase lung tumor formation further in these ovariectomized and estrogen-treated mice (Chen et al., 2014a). TCDD by itself had little lung tumor–promoting activity in intact female A/J mice, but it exhibited a significant synergistic effect when combined with a low dose of NNK. Cell culture experiments suggested that the TCDD effect was via inhibition of apoptosis (Chen et al., 2014b). The AHR has been implicated in the chemical induction of lung tumors but not linked specifically at this time to TCDD or the other COIs (Tsay et al., 2013).

Cacodylic acid (DMA^{III} and DMA^{V}) is carcinogenic, but results from studies of DMA exposure and lung cancer in laboratory animals have not been consistent. In the mouse lung, cacodylic acid (DMA^{V}) was been shown to act as a tumor initiator (Yamanaka et al., 1996, 2009) and as a tumor promoter (Mizoi et al., 2005). DMA^{V} can also act as a complete carcinogen, inducing lung tumors in susceptible strains of mice, including those with deficient DNA-repair activity (Hayashi et al., 1998; Kinoshita et al., 2007). However, a 2-year study of F344 rats exposed to cacodylic acid at 0–100 ppm and B6C3F1 mice exposed at 0–500 ppm failed to detect lung neoplasms at any dose (Arnold et al., 2006). 2,4-D causes lung damage, and a recent report provided evidence that this effect occurs via disruption of the microtubule network (Ganguli et al., 2014).

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The recent evidence is consistent with and further strengthens the conclusion that there is limited but suggestive evidence of an association between exposure to at least one COI and the risk of developing or dying from lung cancer. In the past, the most compelling evidence has come from studies of heavily exposed occupational cohorts, including British 2-methyl-4-chlorophenoxyacetic acid (MCPA) production workers (Coggon et al., 1986), German production workers (Becher et al., 1996), a BASF cohort (Ott and Zober, 1996a), a NIOSH cohort (Fingerhut et al., 1991; Steenland et al., 1999), and Danish production workers (Lynge, 1993). The occupational study of Wang and colleagues reviewed in this update also reported a statistically significant two-fold increased risk of lung cancer mortality in this cohort in comparison to the general population (Wang et al., 2013). However, there was no exposure–response analysis conducted despite the fact that concentrations of PCDD/Fs were collected from six sites in the foundry factory. The methodologically sound AHS did not show any increased risk of lung cancer, but, although there was substantial 2,4-D exposure in this cohort (Blair et al., 2005b), dioxin exposure of the contemporary farmers was probably negligible.

In large part, the environmental studies have not been supportive of an association, although in the cancer-incidence update from Seveso (Pesatori et al., 2009), the highest risks of lung cancer occurred in the most exposed.

In veterans' studies, Cypel and Kang (2010) found a significantly increased lung-cancer risk in ACC veterans who used herbicides in Vietnam. The findings from the Ranch Hand study (Pavuk et al., 2005) suggested an increase in risk with serum TCDD concentration even in subjects who made up the comparison group, whose TCDD exposure was considerably lower than that of the Ranch Hand cohort (but not zero). The American and Australian cohort studies of Vietnam veterans (ADVA, 2005a,b,c; Dalager and Kang, 1997), which presumably cover a large proportion of exposed soldiers, showed higher than expected incidence of and mortality from lung cancer. The main limitations of those studies are that there was no assessment of exposure—as there was in, for example, the Ranch Hand study—and that some potential confounding variables, notably smoking, could not be accounted for. The committee believes that it is unlikely that the distribution of smoking differed greatly between the two cohorts of veterans, so confounding by smoking is probably minimal. The studies therefore lend support to the findings of the Ranch Hand study.

In this update, however, data from the US veteran women showed no excess lung cancer mortality in comparison to the US cohort of non-deployed women or those from the US general population. Similar results were observed also among male Vietnam veterans in New Zealand, although that cohort study was rather small and also lacked information on smoking. In contrast, the Korean Vietnam Veterans Health Study (Yi, 2013; Yi and Ohrr, 2014; Yi et al., 2014b) found

modestly elevated relative risks of both lung cancer incidence and mortality. The results were not adjusted for smoking, but earlier self-reported information from a large portion of the cohort indicated that smoking behavior did not appear related to the extent of a veteran's exposure to herbicides. Despite their limitations, these new studies of Vietnam veterans are largely suggestive of modest associations between herbicide exposure and lung cancer incidence and mortality.

Finally, the several lines of mechanistic activity discussed in the section on biologic plausibility provide further support for the conclusion that the evidence of an association is limited or suggestive.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between the exposure to at least one COI and carcinomas of the lung, bronchus, and trachea.

BONE AND JOINT CANCERS

ACS estimated that about 1,640 men and 1,330 women would receive diagnoses of bone or joint cancer (ICD-9 170) in the United States in 2015 and that 850 men and 640 women would die from these cancers (Siegel et al., 2015). Primary bone cancers are among the least common malignancies, but the bones are frequent sites of tumors secondary to cancers that have metastasized. Only primary bone cancer is considered here. The average annual incidence of bone and joint cancer is shown in Table 8-13.

Bone cancer is more common in teenagers than in adults. It is rare among people in the age groups of most Vietnam veterans (55–69 years). Among the risk factors for bone and joint cancer in adults are gender, ethnicity, genetic and familial factors, exposure to ionizing radiation in treatment for other cancers and a history of some non-cancer bone diseases, including Paget disease (Chung and Van Hul, 2012; Ottaviani and Jaffe, 2009).

TABLE 8-13 Average Annual Incidence (per 100,000) of Bone and Joint Cancers in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	1.3	1.4	0.9	1.6	1.7	0.9	2.2	2.3	1.5
Women	1.0	1.1	0.5	1.1	1.2	1.1	1.4	1.3	1.9

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and bone and joint cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion.

Table 8-14 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Since the *Update 2012*, two studies of Vietnam veterans from countries other than the United States have generated publications addressing exposure to the COIs and bone cancer (McBride et al., 2013; Yi and Ohrr, 2014; Yi et al., 2014b).

Mortality from (Yi et al., 2014b) and incidence of (Yi and Ohrr, 2014) bone cancer were assessed among Korean Veterans who had served in Vietnam between 1964 and 1973. In analyses of cancer incidence, Yi and Ohrr (2014) reported a decreased risk of bone cancer (HR = 0.70, 95% CI 0.27–1.82) in the internal comparison of the high- and low-exposure groups based on the EOI scores. Similarly for bone cancer mortality, Yi et al. (2014b) reported a decreased risk for the high- versus low-exposure groups (HR = 0.48, 95% CI 0.16–1.49) and a negative association with the individual log-transformed EOI scores (HR = 0.81, 95% CI 0.64–1.04).

Cancer incidence and mortality from 1998 to 2008 were determined for 2,783 male veterans from New Zealand who had survived service in Vietnam between 1964 and 1972 (McBride et al., 2013). Based upon only two deaths, a comparison with the general male population of New Zealand was largely uninformative for an association with bone and cartilage cancers (SIR = 2.78, 95% CI 0.31–10.0).

Occupational, Environmental, and Case-Control Studies

No occupational, environmental, or case-control studies with sufficiently specific characterization of exposure to the COIs and bone or joint cancers have been published since *Update 2012*.

Biologic Plausibility

No animal studies have reported an increased incidence of bone and joint cancer after exposure to the COIs. The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

TABLE 8-14 Selected Epidemiologic Studies—Bone and Joint Cancers (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1986, 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	27	0.8 (0.4–1.7)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	11	1.4 (0.1–21.5)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans aged 35–64 years in 1993—cases diagnosed 1988–1993 vs unexposed veterans with gastrointestinal cancers	4	0.9 (0.1–11.3)	Clapp, 1997
New York			
Deployed vs non-deployed veterans	8	1.0 (0.3–3.0)	Lawrence et al., 1985
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	1	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence–bone and cartilage (1988–2008)	2	2.8 (0.3–10.0)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—bone cancer (C40–C41) categorized high (n = 8) vs low (n = 11)	8	0.7 (0.3–1.8)	Yi and Ohrr, 2014
Mortality (1992–2005)—bone cancer (C40–C41) categorized high (n = 5) vs low (n = 11)		0.5 (0.2–1.5)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	16	0.8 (0.6–1.0)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			

TABLE 8-14 Bone and Joint Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1939–1992	5	1.2 (0.4–2.8)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	3	1.1 (0.2–3.1)	
7,553 not exposed to highly chlorinated PCDDs	2	1.4 (0.2–5.2)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	1	0.9 (0.0–5.0)	Coggon et al., 1986
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
Through 1987		*90% CI*	Zober et al., 1990
	0	0.0 (0.0–65.5)	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004	0	0.0 (0.0–21.8)	McBride et al., 2009a
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1987	2	2.3 (0.3–8.2)	Fingerhut et al., 1991
≥ 1-yr exposure, ≥ 20-yr latency	1	5.5 (0.1–29.0)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	2	5.0 (0.6–18.1)	Collins et al., 1993
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354 (Cohort 3) (bone, soft tissue)	1	0.8 (0.0–4.5)	Burns et al., 2011

continued

TABLE 8-14 Bone and Joint Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Through 1982 (n = 878)	0	nr (0.0–31.1)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–1989 (n = 770)	0	nr	Ramlow
0-yr latency	0	nr	et al., 1996
15-yr latency	0	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			
Danish paper workers			Rix et al., 1998
Men	1	0.5 (0.0–2.7)	
Women	0	nr	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	4	1.1 (0.4–2.4)	Hertzman
Mortality 1950–1989	5	1.3 (0.5–2.7)	et al., 1997
No exposed to highly chlorinated PCDDs	2	1.4 (0.2–5.2)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	9	0.9 (nr)	
Employee	0	nr	
Women			
Self-employed	0	0.0	
Employee	1	6.3 ($p < 0.05$)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	0	nr	Swaen et al., 2004

TABLE 8-14 Bone and Joint Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	10	0.8 (0.4–1.4)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	1	0.5 (0.0–2.6)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident bone cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	1	1.7 (0.2–13.3)	
SWEDEN			
Incident bone cancer cases 1961–1973 with agriculture as economic activity in 1960 census	44	*99% CI* 1.0 (0.6–1.4)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	49	1.3 (1.0–1.8)	
Nonwhites (n = 11,446)	4	1.0 (0.3–2.5)	
Women			
Whites (n = 2,400)	1	1.2 (0.0–6.6)	
Nonwhites (n = 2,066)	0	0.0 (0.0–6.3)	
White Male Residents of Iowa—bone cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR	56	1.1 (nr)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Mortality			
15-yr follow-up to 1991—men			Bertazzi
Zone R	2	0.5 (0.1–2.0)	et al., 1998
15-yr follow-up to 1991—women			Bertazzi
Zone B	1	2.6 (0.3–19.4)	et al., 1998
Zone R	7	2.4 (1.0–5.7)	

continued

TABLE 8-14 Bone and Joint Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Mortality—1995–1998 (SMR vs regional rates)			
Men	7	2.1 (0.9–4.4)	
Women	7	1.4 (0.6–3.0)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
European Multicentric study of association between occupational exposure and risk of bone sarcoma (96 cases, 35–69 yrs of age vs 2,632 hospital- and population-based controls	18	**Herbicides, pesticides** 2.6 (1.5–4.6)	Merletti et al., 2005

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportionate mortality ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Synthesis

The small amount of new data, in concert with the previous literature, summarized in Table 8-14 does not indicate an association between exposure to the COIs and bone cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and bone and joint cancer.

SOFT-TISSUE SARCOMAS

Soft-tissue sarcomas (STSs) (ICD-9 164.1, 171) arise in soft somatic tissues in and between organs. Three of the most common types of STS—liposarcomas,

fibrosarcomas, and rhabdomyosarcomas—occur in similar numbers in men and women. Because of the diverse characteristics of STS, accurate diagnosis and classification can be difficult. ACS estimated that about 6,110 men and 5,320 women would receive diagnoses of STS in the United States in 2015 and that about 4,870 men and 2,600 women would die from it (Siegel et al., 2015). The average annual incidence of STS is shown in Table 8-15.

Among the risk factors for STS are exposure to ionizing radiation during treatment for other cancers, some inherited genetic conditions (including Ewing's sarcoma and Li-Fraumeni syndrome), and several chemical exposures (Cormier and Pollock, 2004).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was sufficient epidemiologic data to support an association between exposure to the COIs and STS. Additional information available to the committees responsible for subsequent updates has not changed that finding.

As seen with Hodgkin lymphoma and non-Hodgkin lymphoma, the available epidemiologic evidence suggests that phenoxy herbicides rather than TCDD may be associated with developing STS. Some of the strongest evidence of an association between STS and exposure to phenoxy herbicides comes from a series of case-control studies conducted in Sweden (Eriksson et al., 1981, 1990; Hardell and Eriksson, 1988; Hardell and Sandstrom, 1979). The studies, involving a total of 506 cases, show an association between STS and exposure to phenoxy herbicides, chlorophenols, or both. The *VAO* committee concluded that although those studies have been criticized, there is insufficient justification to discount the consistent pattern of increased risks and the clearly described and sound methods used. In addition, a reanalysis of the data by Hardell (1981) to evaluate the potential influence of potential recall bias and interviewer bias confirmed the original results. Hansen et al. (2007) conducted a historical-cohort study of male gardeners who were members of the Danish Union; the cancer incidence was ascertained from 1975 to 2001. Birth date served as a surrogate for potential exposure to pesticides and herbicides, with older cohorts representing higher exposure potential. Men born before 1915 were

TABLE 8-15 Average Annual Incidence (per 100,000) of Soft-Tissue Sarcomas (Including Malignant Neoplasms of the Heart) in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	7.2	7.3	7.4	9.8	10.4	6.9	12.3	12.9	8.3
Women	5.2	4.9	7.1	6.3	6.4	6.3	7.8	8.0	7.2

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

much more likely to die from STS, although this finding was based on only three cases. Reif et al. (1989) performed a series of case-control analyses in a sample of specified occupations and found a significant association between STS and having recently been employed as a forestry worker.

Those findings are supported by a significantly increased risk in a NIOSH study of production workers most highly exposed to TCDD (Fingerhut et al., 1991); Steenland et al. (1999) published an update of the NIOSH cohort, but STS was not among the outcomes evaluated. A similar increased risk was seen in the IARC cohort in deaths that occurred 10 to 19 years after first exposure (Kogevinas et al., 1992; Saracci et al., 1991) according to a fairly crude exposure classification. An updated and expanded study of the IARC cohort by Kogevinas et al. (1997) found a non-significantly increased risk of STS when follow-up was extended to 1992. The NIOSH and IARC cohorts are among the largest and the most highly exposed occupational cohorts. Smaller studies of workers that are included in the multinational IARC cohort—Danish herbicide manufacturers (Lynge et al., 1985, 1993) and Dow production workers in Midland, Michigan, and New Zealand (Collins et al., 2009b; 't Mannetje et al., 2005)—showed an increased risk of STS, but the results were commonly non-significant, possibly because of the small samples (related to the relative rarity of STS in the population).

Several studies have reported on STS in relation to living near waste incinerators that release dioxin as a contaminant. Viel et al. (2000) reported on an investigation of apparent clusters of STS and non-Hodgkin lymphoma cases in the vicinity of a municipal solid waste incinerator in Doubs, France; Comba et al. (2003) and Costani et al. (2000) examined STS in the general population living near a chemical plant in the northern Italian city of Mantua; and Zambon et al. (2007) conducted a population-based case-control study in Venice, Italy, in an area that included 26 waste incinerators and other industrial plants. Each of those studies found a statistically significant excess of STS, but none showed any direct evidence of human exposure.

No cases of STS have been reported in Zones A and B in the Seveso cohort (Consonni et al., 2008); the incidence of STS was slightly increased in Zone R but not significantly (Pesatori et al., 2009). Veteran studies have not found a significant increase in STS. No increase was seen in Ranch Hand veterans (AFHS, 1996, 2000; Michalek et al., 1990) or in VA studies of US Vietnam veterans (Breslin et al., 1986, 1988; Bullman et al., 1990; Watanabe and Kang, 1995; Watanabe et al., 1991). A slight increase in the incidence of STS was seen in Australian Air Force veterans compared with the Australian population but not in Army or Navy personnel (ADVA, 2005a), and no increase in mortality was seen in Australian veterans who served in any of the military branches (ADVA, 2005b). A non-significant increase in mortality from STS was also seen in state studies of veterans in Massachusetts, Michigan, and New York.

Table 8-16 summarizes the relevant studies.

TABLE 8-16 Selected Epidemiologic Studies—Soft-Tissue Sarcomas (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Mortality			
Through 1987—Ranch Hand personnel (n = 1,261) vs SEA veterans (19,102)	1	nr	Michalek et al., 1990
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1984			
Army, deployed (n = 24,145) vs non-deployed (n = 27,917)	43	1.1	Watanabe et al., 1991
Served in I Corps (n = 6,668)	10	0.9 (0.4–1.6)	Bullman et al., 1990
Marine Corps, deployed (n = 5,501) vs non-deployed (n = 4,505)	11	0.7	Watanabe et al., 1991
1965–1982			Breslin
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	30	1.0 (0.8–1.2)	et al., 1986, 1988
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	8	0.7 (0.4–1.3)	
US VA Study of Marine Post-service Mortality—sample of Marines serving 1967–1969, deployed (n = 10,716) vs non-deployed (n = 9,346)		**All COIs**	
Mortality, earlier of discharge or April 1973 through 1991	0	nr	Watanabe and Kang, 1995
US VA Case-Control Study			
234 Vietnam veterans vs 13,496 Vietnam-era veterans	86	0.8 (0.6–1.1)	Kang et al., 1986
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era Veterans			
Veterans aged 35–65 years in 1993—cases diagnosed 1988–1993 vs gastrointestinal cancers	18	1.6 (0.5–5.4)	Clapp, 1997
Diagnosed 1972–1983	9	5.2 (2.4–11.1)	Kogan and Clapp, 1988
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	8	1.1 (0.5–2.2)	Vistainer et al., 1995

continued

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New York—deployed vs non-deployed	2	1.1 (0.2–6.7)	Lawrence et al., 1985
281 STS cases with service in Vietnam vs live matched controls	10	0.5 (0.2–1.3)	Greenwald et al., 1984
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	4	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/ 23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	35	1.0 (0.7–1.3)	ADVA, 2005b
Navy	6	0.8 (0.3–1.7)	
Army	29	1.2 (0.8–1.6)	
Air Force	0	0.0 (0.0–1.1)	
Validation Study	14	*Expected number of exposed cases* 27 (17–37)	AIHW, 1999
Men	398	27 (17–37)	CDVA, 1998a
Women	2	0 (0–4)	CDVA, 1998b
Mortality			
All branches, return–2001	12	0.8 (0.4–1.3)	ADVA, 2005a
Navy	3	0.9 (0.2–2.4)	
Army	9	0.8 (0.4–1.5)	
Air Force	0	0.0 (0.0–2.3)	
1980–1994	9	1.0 (0.4–1.8)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	10	1.0 (0.4–2.4)	ADVA, 2005c
Mortality			
1966–2001	3	0.5 (0.1–2.0)	ADVA, 2005c
1982–1994	2	0.7 (0.6–4.5)	CDVA, 1997b

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
1983–1985	1	1.3 (0.1–20.0)	Fett et al., 1987b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence–connective and soft-tissue (1988–2008)	3	1.0 (0.2–3.0)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—connective and soft tissue (C47, C49) categorized high (n = 13) vs low (n = 20)	13	0.6 (0.3–1.3)	Yi and Ohrr, 2014
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992			Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	6	2.0 (0.8–4.4)	
7,553 not exposed to highly chlorinated PCDDs	2	1.4 (0.2–4.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	4	2.0 (0.6–5.2)	Saracci et al., 1991
Nested case-control study			
IARC cohort (men and women)—incidence			Kogevinas et al., 1995
Exposed to 2,4,5-T	5	4.3 (0.7–26.3)	
Exposed to TCDD	5	5.2 (0.9–31.9)	
Mortality—IARC cohort (16,863 men and 1,527 women) 10–19 years since first exposure	4	6.1 (1.7–15.5)	Kogevinas et al., 1992
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	1	1.1 (0.0–5.9)	Coggon et al., 1986

continued

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1987 (men only)	5	2.0 (0.7–4.8)	Lynge, 1993
Incidence 1943–1982			Lynge, 1985
Men	5	2.7 (0.9–6.3)	
Women	0	nr	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991	0	nr	Hooiveld et al., 1998
Mortality 1955–1985	0	0.0 (0.0–18.4)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–1986	0	0.0 (0.0–73.8)	Bueno de Mesquita et al., 1993
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992			Ott and
TCDD < 0.1 µg/kg of body weight	0	nr	Zober, 1996a,b
TCDD 0.1–0.99 µg/kg of body weight	0	nr	
TCDD > 1.0 µg/kg of body weight	0	nr	
Mortality			
Through 1987		*90% CI*	Zober et al.,
	0	nr	1990

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	0	nr	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride
Ever-exposed workers	1	3.4 (0.1–19.5)	et al., 2009a
Never-exposed workers	0	0.0 (0.0–34.9)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	0	0.0 (0.0–19.3)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	4.3 (0.1–23.8)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	4	2.3 (0.6–5.9)	Steenland
Chloracne subcohort (n = 608)	3	11.3 (2.3–33.1)	et al., 1999
Through 1987	4	3.4 (0.9–8.7)	Fingerhut
≥ 1-yr exposure, ≥ 20-yr latency	3	9.2 (1.9–27.0)	et al., 1991
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	4	4.1 (1.1–10.5)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	2	2.4 (0.3–8.6)	Bodner et al., 2003

continued

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL) (connective tissue and soft tissue)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (connective tissue and soft tissue)	2	1.5 (0.2–5.5)	
PCP and TCP (n = 720)	1	2.3 (0.1–12.6)	
PCP (no TCP) (n = 1,402)	1	1.1 (0.0–6.4)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (bone, soft tissue)	1	0.8 (0.0–4.5)	Burns CJ et al., 2011
Through 1982 (n = 878)	0	nr	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	1	2.2 (0.0–12.1)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)	0	*Expected number of exposed cases* 0.2	Ramlow et al., 1996
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	8	1.2 (0.5–2.4)	
Ever	4	0.8 (0.2–2.0)	
Danish paper-mill workers			Rix et al., 1998
Men employed in sorting and packing	12	1.2 (0.6–2.0)	
Women employed in sorting and packing	8	4.0 (1.7–7.8)	

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	11	1.0 (0.6–1.7)	Hertzman et al., 1997
Mortality 1950–1989	6	1.2 (0.5–2.3)	
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-yr follow-up (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	3	5.9 (1.9–18.2)	
Born 1915–1934 (medium exposure)	0	0.0 (0.0–3.8)	
Born after 1934 (low exposure)	1	1.8 (0.3–12.9)	
10-yr follow-up (1975–1984) of male gardeners	3	5.3 (1.1–15.4)	Hansen et al., 1992
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	2	1.0 (0.1–3.5)	Torchio et al., 1994
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 142 incident STS cases vs remainder of 19,904 men with any incident cancer			
Forestry workers (n = 134)		**Herbicides**	Reif et al., 1989
Aged 20–59	4	3.2 (1.2–9.0)	
Aged ≥ 60	0	—	
SWEDEN			
Swedish pesticide applicators—incidence (n = 20,245)	7	*99% CI* 0.9 (0.8–1.1)	Wiklund et al., 1988b, 1989a
354,620 Swedish agricultural and forestry workers identified from 1960 census, followed 1961–1979; compared to reference population	331	0.9 (0.8–1.0)	Wiklund and Holmes, 1986
Incident STS cases 1961–1973 with agriculture as economic activity in 1960 census (connective tissue and muscle)	162	1.1 (0.9–1.3)	Wiklund, 1983

continued

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	98	0.9 (0.8–1.1)	
Nonwhites (n = 11,446)	10	1.5 (0.7–2.8)	
Women			
Whites (n = 2,400)	3	1.2 (0.2–3.5)	
Nonwhites (n = 2,066)	0	0.0 (0.0–1.9)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2002			Alavanja et al., 2005
Private applicators	10	0.7 (0.3–1.2)	
Spouses of private applicators (> 99% women)	3	0.5 (0.1–1.4)	
Commercial applicators	nr	0.0 (0.0–3.8)	
Mortality			
Enrollment through 2007, vs state rates (connective tissue)			Waggoner et al., 2011
Applicators (n = 1,641)	9	0.7 (0.3–1.5)	
Spouses (n = 676)	6	1.0 (0.4–2.2)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	4	0.7 (0.2–1.8)	
Spouses of private applicators (> 99% women)	3	1.4 (0.3–4.1)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of STS		**Herbicides**	
USDA forest and soil	2	1.0 (0.1–3.6)	Alavanja et al., 1989
Florida Pesticide Applicators licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose–response by length of licensure)	0	nr	

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	0	nr	Pesatori et al., 2009
Zone B	0	nr	
Zone R	9	1.3 (0.6–2.7)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993; Pesatori et al., 1992
Zone A	0	nr	
Zone B	0	nr	
Zone R	6	2.8 (1.0–7.3)	
10-yr follow-up to 1991—women			Bertazzi et al., 1993; Pesatori et al., 1992
Zone A	0	nr	
Zone B	0	nr	
Zone R	2	1.6 (0.3–7.4)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
Zone A	0	nr	
Zone B	0	nr	
Zone R	4	0.8 (0.3–2.1)	
20-yr follow-up to 1996			Bertazzi et al., 2001
Zone A—men and women	0	nr	
Zone B—men and women	0	nr	
Zones A and B—men	0	nr	
Zones A and B—women	0	nr	
15-yr follow-up to 1991—men			Bertazzi et al., 1997, 1998
Zone A	—	nr	
Zone B	0	nr	
Zone R	4	2.1 (0.7–6.5)	
15-yr follow-up to 1991—women			Bertazzi et al., 1997, 1998
Zone A	—	nr	
Zone B	0	nr	
Zone R	0	nr	

continued

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
10-yr follow-up to 1986—men			Bertazzi
Zone A, B, R	2	5.4 (0.8–38.6)	et al., 1989a
Zone R	2	6.3 (0.9–45.0)	Bertazzi et al., 1989b
10-yr follow-up to 1986—women			Bertazzi
Zone A, B, R	1	2.0 (0.2–1.9)	et al., 1989a
Zone B	1	17.0 (1.8–163.6)	Bertazzi et al., 1989b
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)	6	**Chlorophenol** 1.6 (0.7–3.5)	Lampi et al., 1992
FRANCE			
Residents near French solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2000
Spatial cluster	45	1.4 (p = 0.004)	
1994–1995	12	3.4 (p = 0.008)	
ITALY			
Italian rice growers		**Chlorophenoxy acids, chlorophenols**	Gambini et al., 1997
	1	4.0 (0.1–22.3)	
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand, near plant manufacturing 2,4,5-T in 1962–1987		2,4,5-T	Read et al., 2007
Incidence	56	1.0 (0.8–1.4)[c]	
1970–1974	7	1.0 (0.4–2.1)	
1975–1979	3	0.4 (0.1–2.1)	
1980–1984	10	1.3 (0.6–2.4)	
1985–1989	11	1.2 (0.6–2.2)	
1990–1994	9	0.9 (0.4–1.7)	
1995–1999	14	1.3 (0.7–2.2)	
2000–2001	2	0.8 (0.1–3.0)	
Mortality	27	1.2 (0.8–1.8)[c]	
1970–1974	5	1.8 (0.6–4.3)	
1975–1979	1	0.4 (0.0–2.0)	
1980–1984	4	1.1 (0.3–2.9)	
1985–1989	5	1.5 (0.5–3.6)	
1990–1994	5	1.3 (0.4–3.0)	
1995–1999	5	1.3 (0.4–3.0)	
2000–2001	2	0.9 (0.1–3.1)	

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	0	0.0 (0.0–2.6)	
West coast	3	0.5 (0.1–1.4)	
Mortality			
East coast	0	nr	
West coast	0	nr	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Kansas residents–duration and frequency of herbicide use—incidence		**Phenoxy herbicides, 2.4-D**	Hoar et al., 1986
All farmers	95	1.0 (0.7–1.6)	
Farm-use of herbicides	22	0.9 (0.5–1.6)	
Washington state residents—incidence (1983–1985)		**Phenoxy herbicides, chlorinated phenols**	Woods et al., 1987
High phenoxy exposure	nr	0.9 (0.4–1.9)	
Self-reported chloracne	nr	3.3 (0.8–14.0)	
International Case-Control Studies			
Australian residents in Victorian Cancer Registry (1982–1987)		**Phenoxy compounds**	Smith and Christophers, 1992
	30	1.0 (0.3–3.1)	
British agricultural workers		**Herbicides**	Balarajan and Acheson, 1984
Overall	42	1.7 (1.0–2.9)	
Under 75 yrs old	33	1.4 (0.8–2.6)	
Cross Canada Study of Pesticides and Health—Men (≥ 19 yrs of age) diagnosed Sept 1991–Dec 1994 (n = 357) vs matched population-based controls (n = 1,506); exposure to:			Pahwa et al., 2011
Phenoxy herbicides	80 vs 321	1.1 (0.8–1.5)	
2,4-D	69 vs 293	1.0 (0.7–1.4)	
Mecoprop	26 vs 81	1.3 (0.8–2.2)	
MCPA	13 vs 46	1.1 (0.6–2.2)	

continued

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Diclofop-methyl	8 vs 25	1.2 (0.4–2.9)	
Cross Canada Study of Pesticides and Health—Men (≥ 19 yrs of age) diagnosed Sept 1991–Dec 1994 (n = 357) vs matched population-based controls (n = 1,506); exposure to:		**Phenoxy herbicides**	Pahwa et al., 2006
Any phenoxyherbicide	80 vs 321	1.1 (0.7–1.5)	
2,4-D	69 vs 293	1.0 (0.6–1.5)	
Mecoprop	26 vs 81	1.0 (0.5–1.9)	
MCPA	13 vs 46	1.1 (0.5–2.2)	
Finnish STS patients vs controls within quintiles based on TEQ in subcutaneous fat—incidence	110	**Dioxin**	Tuomisto et al., 2004
Quintile 1 (median, ~12 ng/kg TEQ)	nr	1.0	
Quintile 2 (median, ~20 ng/kg TEQ)	nr	0.4 (0.2–1.1)	
Quintile 3 (median, ~28 ng/kg TEQ)	nr	0.6 (0.2–1.7)	
Quintile 4 (median, ~40 ng/kg TEQ)	nr	0.5 (0.2–1.3)	
Quintile 5 (median, ~62 ng/kg TEQ)	nr	0.7 (0.2–2.0)	
Italy			
Population-based Veneto Tumour Registry, Italy, average exposure based on duration and distance of residence from 33 industrial sources—incidence		**Dioxin**	Zambon et al., 2007
Sarcoma (ICD-9 158, 171, 173, visceral sites)			
Men			
< 4 TCDD (fg/m^3)	31	1.0	
4–6	39	1.1 (0.6–2.0)	
≥ 6	17	1.9 (0.9–4.0) p-trend = 0.15	
Women			
< 4 TCDD (fg/m^3)	24	1.0	
4–6	44	1.5 (0.8–2.7)	
≥ 6	17	2.4 (1.0–5.6) p-trend = 0.04	
Men, women combined			
Connective, other soft tissue (ICD-9 171)			
< 4 TCDD (fg/m^3)	25	1.0	
4–6	39	1.4 (0.7–2.5)	
≥ 6	17	3.3 (1.4–7.9)	

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
		p-trend = 0.01	
Skin (ICD-9 173)			
< 4 TCDD (fg/m^3)	5	1.0	
4–6	10	0.0 (0.3–4.7)[d]	
≥ 6	2	0.3 (0.0–3.4)	
		p-trend = 0.48	
Retroperitoneum, peritoneum (ICD-9 158)			
< 4 TCDD (fg/m^3)	6	1.0	
4–6	12	1.1 (0.3–3.4)	
≥ 6	3	0.8 (0.1–4.5)	
		p-trend = 0.86	
Visceral sites			
< 4 TCDD (fg/m^3)	19	1.0	
4–6	22	1.2 (0.6–2.6)	
≥ 6	12	2.5 (1.0–6.3)	
		p-trend = 0.08	
Residents near industrial-waste incinerator in Mantua, Italy—incidence		**Dioxin**	
Residence within 2 km of incinerator	5	31.4 (5.6–176.1)	Comba et al., 2003
Residents near chemical plant in Mantua, Italy—incidence	20	**TCDD emissions** 2.3 (1.3–3.5)	Costani et al., 2000
Italian rice weeders (1981–1983)		**Phenoxy herbicides**	Vineis et al., 1986
Among all living females (n = 31)	5	2.4 (0.4–16.1)	
New Zealand Pesticide Workers		**Phenoxy herbicides** *90% CI*	
Update of New Zealand workers (1976–1982)	133	1.1 (0.7–1.8)	Smith and Pearce, 1986
Reanalysis of New Zealand workers (1976–1980)	17	1.6 (0.7–3.8)	Smith et al., 1984
New Zealand workers exposed to herbicides (1976–1980)	17	1.6 (0.8–3.2)	Smith et al., 1983
Swedish agricultural and forestry workers (1974–1979)	25	**Phenoxy acids, chlorophenols** (2.5–10.4) 5:1 matched	Eriksson et al., 1979, 1981

continued

TABLE 8-16 Soft-Tissue Sarcomas, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981; Hardell and Sandström, 1979
Exposed to phenoxy herbicides	13	5.5 (2.2–13.8)	
Exposed to chlorophenols	6	5.4 (1.3–22.5)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; STS, soft-tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

[d]There appears to be an error in this entry because lower 95% CI (0.3) is not smaller than odds ratio (0.0)

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

In a study of mortality and cancer incidence among 2,783 New Zealand veterans who served in Vietnam between 1964 and 1975, McBride et al. (2013) reported that connective and soft tissue cancer incidence was slightly elevated in the cohort (SIR = 1.04, 95% CI 0.21–3.04, based on three cases).

Cancer incidence was also assessed among Korean veterans who had served in Vietnam between 1964 and 1973. Yi and Ohrr (2014) reported a decreased risk of connective and soft tissue cancers (ICD-10 C47 and C49) in the internal comparison of the high- (n = 13) and low-exposure (n = 20) groups based on the EOI scores (HR = 0.62, 95% CI 0.30–1.27).

Occupational, Environmental, and Case-Control Studies

No occupational, environmental, or case-control studies of exposure to the COIs and STS have been published since *Update 2012*.

Biologic Plausibility

In a 2-year study, dermal application of TCDD to Swiss-Webster mice led to an increase in fibrosarcomas in females but not in males (NTP, 1982b). There is some concern that the increase in fibrosarcomas may be associated with the treatment protocol rather than with TCDD. The NTP gavage study (NTP, 1982a) also found an increased incidence of fibrosarcomas in male and female rats and in female mice.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Previous committees have concluded that the occupational, environmental, and Vietnam-veteran studies showed sufficient evidence to link herbicide exposure to STS. Although the confidence intervals in the new cohort studies were broad because of the rarity of observed cases in small samples, that conclusion is consistent with the findings of Ruder and Yiin (2011). The rather extensive Canadian case-control study of pesticide exposure and STS (Pahwa et al., 2011), however, did not provide additional supportive evidence.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the COIs and STS.

SKIN CANCERS

Skin cancers are generally divided into two broad categories: neoplasms that develop from melanocytes (malignant melanoma, or simply melanoma) and neoplasms that do not. Non-melanoma skin cancers (primarily basal-cell and squamous-cell carcinomas) have a far higher incidence than melanoma but are considerably less aggressive and therefore more treatable. The average annual incidence of melanoma is shown in Table 8-17.

The committee responsible for *Update 1998* first chose to address melanoma studies separately from those of non-melanoma skin cancers. Some researchers report results by combining all types of skin cancers without specifying type.

TABLE 8-17 Average Annual Cancer Incidence (per 100,000) of Skin Cancers (Excluding Basal-Cell and Squamous-Cell Cancers) in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Melanomas of the Skin:									
Men	66.0	77.3	2.9	93.7	109.1	3.8	116.5	137.1	4.0
Women	35.0	41.4	2.4	42.1	49.8	2.6	45.1	53.0	4.2

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012. SEER incidence data not available for nonmelanocytic skin cancer (NCI, 2015).

The present committee believes that combined information is not interpretable (although there is a supposition that the mortality figures refer predominantly to melanoma and that the high-incidence figures refer to non-melanoma skin cancers); therefore, it is interpreting data only when the results specify melanoma or non-melanoma skin cancers.

ACS estimated that about 46,610 men and 33,490 women would receive diagnoses of cutaneous melanoma (ICD-9 172) in the United States in 2015 and that about 9,120 men and 4,220 women would die from it (Siegel et al., 2015). According to one report, more than 3 million cases of non-melanoma skin cancers (ICD-9 173), primarily basal-cell and squamous-cell carcinomas, are diagnosed in the United States each year (ACS, 2013b); it is not required to report them to registries, so the numbers of cases are not as precise as those of other cancers. ACS reports that although melanoma accounts for less than 5 percent of skin-cancer cases, it is responsible for about 75 percent of skin-cancer deaths (Siegel et al., 2015). It estimates that 3,400 people die each year from non-melanoma skin cancers (Siegel et al., 2015).

Melanoma occurs more frequently in fair-skinned people than in dark-skinned people; the risk in whites is roughly 20 times that in dark-skinned blacks. The incidence increases with age, more strikingly in males than in females. Other risk factors include the presence of particular kinds of moles on the skin, the suppression of the immune system, and excessive exposure to ultraviolet (UV) radiation, typically from the sun. A family history of the disease has been identified as a risk factor, but it is unclear whether that is attributable to genetic factors or to similarities in skin type and sun-exposure patterns (Rastrelli et al., 2014). In addition to the dermal forms of melanoma, these tumors occur much more infrequently in various tissues of the eye.

Excessive exposure to UV radiation is the most important risk factor for nonmelanoma skin cancers; radiation exposure, human papillomavirus, immune system problems, and family history of non-melanoma skin cancers have also been identified as potential risk factors (Bailey et al., 2010). Although exposure to inorganic arsenic is recognized as a risk factor for non-melanoma skin cancers

(Dubas and Ingraffea, 2013); this does not imply that exposure to cacodylic acid, which is a metabolite of inorganic arsenic, can be assumed to be a risk factor.

Melanoma

Conclusions from *VAO* and Previous Update

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and skin cancers. Additional information available to the committee responsible for *Update 1996* did not change that conclusion. The committee responsible for *Update 1998* considered the literature on melanoma separately from that of non-melanoma skin cancers and found that there was inadequate or insufficient information to determine whether there is an association between the COIs and melanoma. The committees responsible for *Update 2000*, *Update 2002*, and *Update 2004* concurred with the findings of *Update 1998*. The committee responsible for *Update 2006* was unable to reach a consensus as to whether there was limited or suggestive evidence of an association between exposure to the COIs and melanoma or inadequate or insufficient evidence to determine whether there is an association, so melanoma was left in the latter category. The committee for *Update 2008* determined that evidence of an association between exposure to the COIs and melanoma remained inadequate or insufficient to determine whether an association exists.

Cypel and Kang (2010) compared cause-specific mortality between deployed and non-deployed veterans in the Vietnam-era ACC cohort. In the comparison between the deployed and the non-deployed veterans, a moderate but not statistically significant increase in the risk of malignant skin cancer was observed in the deployed cohort. The updates of mortality in TCP workers in New Zealand (McBride et al., 2009a) and in the Dow cohort in Midland, Michigan (Collins et al., 2009b), did not find evidence of an association between the COIs and melanoma. In evaluating the use of specific pesticides and melanoma in the AHS, Dennis et al. (2010) found that only exposure to arsenic-based pesticides, among the COIs, showed any increase in risk, which was weak and far from statistically significant. Updates of cancer incidence in the Seveso cohort for the period 1977–1996 (Pesatori et al., 2009) continued to provide evidence that melanoma is associated with exposure to TCDD.

Table 8-18 summarizes the relevant melanoma studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies In a study of mortality and cancer incidence among 2,783 New Zealand veterans who served in Vietnam between 1964 and 1975, McBride et al. (2013) reported that melanoma mortality (SMR = 0.56, 95% CI

TABLE 8-18 Selected Epidemiologic Studies—Melanoma (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g)	25	2.7 (1.1–6.3)	
Quartiles (pg/g):			
0.4–2.6	3	1.0	
2.6–3.8	5	2.1 (0.4–11.0)	
3.8–5.2	8	3.2 (0.7–15.5)	
> 5.2	9	3.6 (0.7–17.2)	
Number of years served in SEA (per year of service)			
Quartiles (years in SEA):	25	1.1 (0.9–1.3)	
0.8–1.3	3	1.0	
1.3–2.1	4	1.9 (0.3–10.3)	
2.1–3.7	8	3.2 (0.7–15.3)	
3.7–16.4	10	4.1 (0.9–19.7)	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	17	2.3 (1.4–3.7)	
With tours between 1966–1970	16	2.6 (1.5–4.1)	
SEA comparison veterans (n = 1,776)	15	1.5 (0.9–2.4)	
With tours between 1966–1970	12	1.5 (0.8–2.6)	
White AFHS subjects			
Veterans who spent at most 2 yrs in SEA			
Per unit increase of –$\log_e$(TCDD) (pg/g)	14	2.2 (1.3–3.9)	
Comparison group	3	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	4	3.0 (0.5–16.8)	
Ranch Hand < 118.5 TCDD pg/g at end of service	4	7.4 (1.3–41.0)	
Ranch Hand > 118.5 TCDD pg/g at end of service	3	7.5 (1.1–50.2)	
Only Ranch Hands with 100% service in Vietnam, comparisons with no Vietnam service			

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Per unit increase of $-\log_e$(TCDD) (pg/g)	14	1.7 (1.0–2.8)	
Comparison group	2	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	5	3.9 (0.4–35.3)	
Ranch Hand < 118.5 TCDD pg/g at end of service	4	7.2 (0.9–58.8)	
Ranch Hand > 118.5 TCDD pg/g at end of service	3	5.5 (0.6–46.1)	
Ranch Hand veterans, comparisons through June 1997			Ketchum et al., 1999
Ranch Hand background exposure	4	1.1 (0.3–4.5)	
Ranch Hand low exposure	6	2.6 (0.7–9.1)	
Ranch Hand high exposure	2	0.9 (0.2–5.6)	
Comparisons	9	1.0	
Attended 1987 exam—Ranch Hand personnel (n = 995) vs SEA veterans (n = 1,299)	4	1.3 (0.3–5.2)	Wolfe et al., 1990
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Through 2005 (mortality)			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)	5 vs 4	1.5 (0.4–6.2)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray			
Vietnam cohort	5	1.3 (0.4–3.1)	
Non-Vietnam cohort	4	1.3 (0.4–3.4)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
1965–2000 (mortality)	6	1.4 (0.4–4.9)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1986, 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	145	1.0 (0.9–1.1)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	36	0.9 (0.6–1.5)	

continued

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans aged 35–65 years in 1993—melanoma cases diagnosed 1988–1993 vs gastrointestinal cancers	21	1.4 (0.7–2.9)	Clapp, 1997
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	756	1.3 (1.2–1.4)	ADVA, 2005b
Navy	173	1.4 (1.2–1.6)	
Army	510	1.2 (1.2–1.4)	
Air Force	73	1.4 (1.1–1.7)	
Validation Study		*Expected number of exposed cases*	
	483	380 (342–418)	
Men	2,689	380 (342–418)	CDVA, 1998a
Women	7	3 (1–8)	CDVA, 1998b
Mortality			
All branches, return–2001	111	1.1 (0.9–1.3)	ADVA, 2005a
Navy	35	1.6 (1.0–2.1)	
Army	66	1.0 (0.7–1.2)	
Air Force	10	1.0 (0.5–1.8)	
1980–1994	51	1.3 (0.9–1.7)	CDVA, 1997a
Sample of 1,000 Male Australian Vietnam Veterans—prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey	nr	4.7 (1.3–8.2)	O'Toole et al., 2009
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	204	1.1 (0.9–1.4)	ADVA, 2005c

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
1966–2001	14	0.6 (0.3–1.1)	ADVA, 2005c
1982–1994	16	0.5 (0.2–1.3)	CDVA, 1997b
International Vietnam-Veteran Studies			
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	33	0.7 (0.5–1.0)	
Mortality (1988–2008)	4	0.6 (0.2–1.4)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—categorized high (n = 9) vs low (n = 10)	9	0.9 (0.4–2.3)	Yi and Ohrr, 2014
Mortality (1992–2005)—categorized high (n = 6) vs low (n = 5)		1.5 (0.4–5.4)	Yi et al., 2014b
HR per unit of $\log_{10}$ EOI (n = 180,639)	11	1.3 (0.9–1.8)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	9	0.6 (0.3–1.2)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	5	0.5 (0.2–3.2)	
7,553 not exposed to highly chlorinated PCDDs	4	0.0 (0.3–2.4)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1987 (men only)	4	4.3 (1.2–10.9)	Lynge, 1993
Mortality			
Mortality 1955–2006	7	1.3 (0.9–1.8)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	

continued

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	5	1.3 (0.8–2.2)	Boers et al., 2012
Mortality 1955–1991	1	2.9 (0.1–15.9)	Hooiveld et al., 1998
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	1.0 (0.1–3.7)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	0	0.0 (0.0–3.0)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	0.6 (0.0–3.4)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	2	0.6 (0.1–2.3)	Collins et al., 2009b
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	8	1.2 (0.5–2.3)	Burns CJ et al., 2011
Dow PCP Production Workers (1937–1989 in Midland, MI) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	1	0.7 (0.0–4.0)	Collins et al., 2009c

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	20	0.8 (0.5–1.3)	
Ever	21	1.2 (0.7–1.8)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from melanoma June 1971–Dec 1987			
Deaths among Saskatchewan farmers ≥ 35 yrs of age, 1971–1985	24	1.1 (0.7–1.6)	Wigle et al., 1990
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	38	1.0 (0.7–1.3)	Hertzman et al., 1997
Mortality 1950–1989	17	1.4 (0.9–2.0)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	72	0.7 ($p < 0.05$)	
Employee	17	0.6 (nr)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners		**Herbicides**	Hansen et al., 2007
25-yr follow-up (1975–2001)	31	1.3 (0.9–1.8)	
Born before 1915 (high exposure)	28	0.9 (0.6–1.4)	
Born 1915–1934 (medium exposure)	36	0.6 (0.4–0.9)	
Born after 1934 (low exposure)	5	0.3 (0.1–0.7)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	5	3.6 (1.2–8.3)	Swaen et al., 2004
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	9	1.2 (0.6–2.3)	Torchio et al., 1994

continued

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Incident melanoma cases 1961–1973 with agriculture as economic activity in 1960 census	268	0.8 (0.7–1.0)	Wiklund, 1983
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)	0	nr	
Foremen (n = 15)	0	nr	
Lumberjacks (n = 139)	0	nr	
Unexposed lumberjacks (n = 241)	0	nr	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	244	1.0 (0.8–1.1)	
Nonwhites (n = 11,446)	5	1.2 (0.4–2.9)	
Women			
Whites (n = 2,400)	5	1.1 (0.4–2.7)	
Nonwhites (n = 2,066)	1	1.2 (0.0–6.6)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	173	0.9 (0.8–1.0)	
Commercial applicators	13	1.1 (0.6–1.9)	
Spouses	92	1.2 (0.9–1.4)	
Licensed, male pesticide applicators—150 cutaneous melanomas among 24,704 pesticide applicators			Dennis et al., 2010
Ever-exposed to arsenic-based pesticides vs never exposed	11	1.3 (0.7–2.4)	
Ever used lead arsenate insecticide	10	1.2 (0.6–2.3)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	32	1.0	
1– < 20	10	1.0 (0.5–2.1)	
20– < 56	18	1.6 (0.8–3.0)	

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
56– < 116	6	0.7 (0.3–1.8)	
≥ 116	6	0.8 (0.3–2.1)	
		p-trend = 0.51	
Enrollment through 2002			Alavanja
Private applicators	100	1.0 (0.8–1.2)	et al., 2005
Spouses of private applicators (> 99% women)	67	1.6 (1.3–2.1)	
Commercial applicators	7	1.1 (0.4–2.2)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner
Applicators (n = 1,641)	38	0.8 (0.5–1.1)	et al., 2011
Spouses (n = 676)	10	0.8 (0.4–1.4)	
Enrollment through 2000, vs state rates			Blair et al.,
Private applicators (men and women)	13	0.7 (0.4–1.3)	2005a
Spouses of private applicators (> 99% women)	2	0.4 (0.1–1.6)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			Pesatori
Zone A	1	1.6 (0.2–11.6)	et al., 2009
Zone B	2	0.5 (0.1–2.0)	
Zone R	19	0.7 (0.4–1.1)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	1	3.1 (0.4–22.0)	et al., 2008
Zone B	2	1.0 (0.2–3.9)	
Zone R	12	0.8 (0.4–1.5)	
20-yr follow-up to 1996			Bertazzi
Zones A and B—men	1	1.5 (0.2–12.5)	et al., 2001
Zones A and B—women	2	1.8 (0.4–7.3)	
15-yr follow-up to 1991—men			Bertazzi
Zone A	0	0.0 (0.0–60.2)	et al., 1997
Zone B	0	0.0 (0.0–9.1)	
Zone R	3	1.1 (0.2–3.2)	

continued

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
15-yr follow-up to 1991—women			Bertazzi et al., 1997
Zone A	1	9.4 (0.1–52.3)	
Zone B	0	0.0 (0.0–5.4)	
Zone R	3	0.6 (0.1–1.8)	
10-yr follow-up to 1986—men			Bertazzi et al., 1989a
Zone A, B, R	3	3.3 (0.8–13.9)	
10-yr follow-up to 1986—women			Bertazzi et al., 1989a,b
Zone A, B, R	1	0.3 (0.1–2.5)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	0	0.0 (0.0–0.7)	
West coast	20	0.8 (0.5–1.2)	
Mortality			
East coast	0	0.0 (0.0–1.7)	
West coast	6	0.7 (0.3–1.5)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
British Columbia—melanoma cases recruited for a study evaluating effects of ultraviolet exposure and gene variants using plasma specimens and sun-exposure data (80 cases vs 310 controls)		**PCBs**	Gallagher et al., 2011
Highest PCB-exposure quintile	29	6.0 (2.0–18.2)	
dl PCBs	25	2.8 (1.0–8.0)	
Non–dl PCBs	30	7.0 (2.3–21.4)	
European—uveal melanoma patients (n = 323), diagnosed 1994–1997, identified from hospital records (diagnosed 1994–1995) in nine countries and matched controls (n = 3,198)		**Herbicides**	Behrens et al., 2012
Personal application of herbicides	8	0.5 (0.2–1.3)	
Personal mixing of herbicides	6	0.5 (0.2–1.5)	

TABLE 8-18 Melanoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
UK men, 18–35 yrs of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.2 (0.4–4.0)	
Chlorophenols	nr	0.9 (0.4–2.3)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; ACC, Army Chemical Corps; AFHS, Air Force Health Study; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupational specialty; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; pg/g, picogram per gram; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Cohorts are male and outcome mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

0.15–1.42, based on four deaths) and incidence (SIR = 0.74, 95% CI 0.51–1.04, based on 33 cases) were less than expected.

Mortality (Yi et al., 2014b) and cancer incidence of (Yi and Ohrr, 2014) were assessed among Korean Veterans who had served in Vietnam between 1964 and 1973. In analyses of cancer incidence, Yi and Ohrr (2014) reported a decreased risk of melanoma (HR = 0.90, 95% CI 0.36–2.30) in the internal comparison of the high- and low-exposure groups based on the EOI scores. Similarly for melanoma mortality, Yi et al. (2014b) reported a modestly increased risk for the high- versus low-exposure groups (HR = 1.49, 95% CI 0.41–5.40) and the individual log-transformed EOI scores (HR = 1.26, 95% CI 0.89–1.77).

Occupational, Environmental, and Case-Control Studies Since *Update 2012*, no additional occupational, environmental, or case-control studies have been published on melanoma concerning relevant exposures to the COIs.

Other Studies Considered A recent study of cancer outcomes found an association with malignant melanoma and the total area of greenhouse agricultural fields in the Anatalya region of Turkey (Uysal et al., 2013). These results have limited bearing on the issue of herbicide exposure and melanoma because of the

absence of a precise measure of exposure (total area of greenhouse agricultural fields as a proxy for exposure) and the exposure of interest was pesticide usage rather than herbicide, which are not typically used in greenhouse operations.

Biologic Plausibility

TCDD and related herbicides have not been found to cause melanoma in animal models. In general, rodents, which are used in most toxicology studies, are not a good model for studying melanoma. TCDD does produce non-melanoma skin cancers in animal models (Wyde et al., 2004). As discussed elsewhere in this chapter, TCDD is a known tumor-promoter and could act as a promoter for skin cancer initiators, such as UV radiation. Ikuta et al. (2009) examined the physiologic role of the AHR in human skin and theorized that overactivation can lead to skin cancers, but they provided no evidence that melanoma incidence is increased after TCDD exposure. Recent work in this field has shown that the AHR mediates UVB-induced skin tanning in a murine model through an action on melanocytes; this is evidence that skin pigmentation and potentially the regulatory action of the target cell for melanoma may be affected by TCDD. Studies of human cells have also confirmed a role of the AHR in regulation of keratinocytes and melanocytes. Kalmes et al. (2011) showed that AHR signaling in immortalized HaCaT cells is associated with cell-cycle progression. In human melanocytes, Luecke et al. (2010) demonstrated that TCDD exposure induced tyrosinase and tyrosinase-related protein 2 gene expression—an indicatation that AHR signaling after TCDD exposure modulates melanogenesis. O'Donnell et al. (2012) further showed that the activity of the AHR was associated with the proliferation of melanoma cells. Finally, a study of a Han Chinese population (Wang XW et al., 2012) has shown that normal genetic variants of the AHR are associated with the occurrence of vitiligo; this strongly suggests that the AHR is associated with melanocyte distribution in humans.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

No compelling association between the COIs and melanoma was observed in any of the three new occupational studies.

The committee responsible for *Update 2006* was unable to reach a consensus as to whether there was limited or suggestive evidence of an association between exposure to the COIs and melanoma or inadequate or insufficient evidence to determine whether there is an association. That committee considered the findings from the Air Force Health Study (AFHS) on melanoma evaluated in terms of TCDD measurements (Akhtar et al., 2004; Pavuk et al., 2005) to be of prime interest. However, the data from the final AFHS examination cycle indicate that

many more melanoma cases were diagnosed in the comparison veterans than in the Ranch Hand subjects. Consequently, the committee responsible for *Update 2006* requested that a TCDD-based analysis be performed in a uniform manner on the most recent melanoma counts for all subjects in the AFHS in order to clarify whether the TCDD-based conclusions on updated information for only the comparison subjects (Pavuk et al., 2005) would strengthen or contradict the rather suggestive findings for the Operation Ranch Hand subjects using melanoma information current for an earlier examination cycle (Akhtar et al., 2004) and to permit definitive evaluation of the possible association between the COIs and melanoma. Such a comprehensive analysis of the most current melanoma data from the AFHS has not as yet been published.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and melanoma (dermal or ocular).

Basal-Cell and Squamous-Cell Cancers (Non-Melanoma Skin Cancers)

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and skin cancers, and additional information available to the committee responsible for *Update 1996* did not change that conclusion. The committee responsible for *Update 1998* considered the literature on non-melanoma skin cancers separately from that on melanoma and concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and basal-cell or squamous-cell cancers. The committees responsible for *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion.

Table 8-19 summarizes the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies The incidence of non-melanoma skin cancer was assessed among Korean veterans who had served in Vietnam between 1964 and 1973 (Yi and Ohrr, 2014). The researchers reported no increase in "other skin" cancers (HR = 0.99, 95% CI 0.63–1.57) in the internal comparison of the high- and low-exposure groups based on the EOI scores.

TABLE 8-19 Selected Epidemiologic Studies—Other Non-Melanoma (Basal-Cell and Squamous-Cell) Skin Cancers (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence—basal cell, squamous cell			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)	253	1.2 (0.9–1.4)	Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g)			
Quartiles (pg/g):			
0.4–2.6	50	nr	
2.6–3.8	59	1.2 (0.8–1.8)	
3.8–5.2	71	1.5 (1.1–2.3)	
> 5.2	73	1.4 (0.9–2.0)	
Number of years served in SEA (per year of service)	253	1.0 (0.9–1.1)	
Quartiles (years in SEA):			
0.8–1.3	55	nr	
1.3–2.1	50	0.9 (0.6–1.4)	
2.1–3.7	73	1.1 (0.8–1.6)	
3.7–16.4	75	1.2 (0.8–1.7)	
Attended 1987 exam—Ranch Hand personnel (n = 995) vs SEA veterans (n = 1,299)			Wolfe et al., 1990
Basal-cell carcinoma	78	1.5 (1.0–2.1)	
Squamous-cell carcinoma	6	1.6 (0.5–5.1)	
International Vietnam-Veteran Study			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters - 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
Validation Study (expected number of exposed cases)			
Men	6,936	nr	CDVA, 1998a
Women	37	nr	CDVA, 1998b

TABLE 8-19 Other Non-Melanoma Skin Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veteran Studies			
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—"other skin" (C44) categorized high (n = 40) vs low (n = 38)		1.0 (0.6–1.6)	Yi and Ohrr, 2014
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates	4	0.9 (0.3–2.4)	
Mortality 1939–1992			Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	4	1.3 (0.3–3.2)	
7,553 not exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.4)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	3	3.1 (0.6–9.0)	Coggon et al., 1986
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1994 (n = 1,517)	0	nr	Burns et al., 2001
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992

continued

TABLE 8-19 Other Non-Melanoma Skin Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Men			
Self-employed	493	0.7 ($p < 0.05$)	
Employee	98	0.7 ($p < 0.05$)	
Women			
Self-employed	5	0.3 ($p < 0.05$)	
Employee	10	0.9 (nr)	
Family worker	90	0.6 ($p < 0.05$)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (skin, ICD-7 190–191)	31	**Herbicides** 1.3 (0.9–1.8)	Hansen et al., 2007
25-yr follow-up (1975–2001)			
Born before 1915 (high exposure)	28	0.9 (0.6–1.4)	
Born 1915–1934 (medium exposure)	36	0.6 (0.4–0.9)	
Born after 1934 (low exposure)	5	0.3 (0.1–0.7)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000—melanoma, squamous-cell carcinoma, unknown skin cancer (mortality presumably attributable to melanoma)	5	3.6 (1.2–8.3)	Swaen et al., 2004
ICELANDIC pesticide users (n = 2,449, 1,860 men and 589 women), 2,4-D used most often, little 2,4,5-T			Zhong and Rafnsson, 1996
Men	5	2.8 (0.9–6.6)	
Men, women combined	5	2.6 (0.8–6.1)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	3	0.6 (0.1–1.8)	Torchio et al., 1994
SWEDEN			
Incident melanoma cases 1961–1973 with agriculture as economic activity in 1960 census	708	*99% CI* 1.1 (1.0–1.2)	Wiklund, 1983
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	1	16.7 (0.2–92.7)	
Lumberjacks (n = 139)	0	—	
Unexposed lumberjacks (n = 241)	3	2.0 (0.4–5.8)	

TABLE 8-19 Other Non-Melanoma Skin Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states (skin, including melanoma)		**Herbicides** *PCMRs*	Blair et al., 1993
Men			
Whites (n = 119,648)	425	1.1 (1.0–1.2)	
Nonwhites (n = 11,446)	13	1.0 (0.5–1.7)	
Women			
Whites (n = 2,400)	6	1.0 (0.4–2.1)	
Nonwhites (n = 2,066)	3	1.8 (0.4–5.4)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			Pesatori et al., 2009
Zone A	3	1.4 (0.5–4.3)	
Zone B	5	0.4 (0.2–0.9)	
Zone R	88	0.9 (0.8–1.2)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Zone A	1	2.4 (0.3–17.2)	
Zone B	2	0.7 (0.2–2.9)	
Zone R	20	1.0 (0.6–1.6)	
10-yr follow-up to 1991—women			Bertazzi et al., 1993
Zone A	1	3.9 (0.5–28.1)	
Zone B	2	1.3 (0.3–5.1)	
Zone R	13	1.0 (0.6–1.9)	
Other International Environmental Study			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995
Incidence			
East coast	22	2.3 (1.5–3.5)	
West coast	69	1.1 (0.9–1.4)	
Mortality			
East coast	0	0.0 (0.0–15.4)	
West coast	5	3.1 (1.0–7.1)	

continued

TABLE 8-19 Other Non-Melanoma Skin Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
International Case-Control Studies			
Alberta, **Canada** residents—squamous-cell carcinoma—incidence		**Herbicides**	Gallagher et al., 1996
All herbicide exposure	79	1.5 (1.0–2.3)	
Low herbicide exposure	33	1.9 (1.0–3.6)	
High herbicide exposure	46	3.9 (2.2–6.9)	
Alberta, **Canada** residents—basal-cell carcinoma		**Herbicides**	Gallagher et al., 1996
All herbicide exposure	70	1.1 (0.8–1.7)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Clemens et al. (2014) reviewed clinical characteristics of 100 consecutive male patients with Fitzpatrick skin types I though IV who enrolled in the Agent Orange registry at the Veterans Affairs Hospital of Washington, DC, between August 2009 and January 2010. Because by design all participants were selected on the basis of being presumably exposed to Agent Orange and being diagnosed with non-melanotic invasive skin cancers, the committee deemed this analysis of no value with respect to examining relationships between the COIs.

Occupational, Environmental, and Case-Control Studies Since *Update 2012*, no additional occupational, environmental, or case-control studies of non-melanoma skin cancers and exposure to the COIs have been published.

Biologic Plausibility

There are no new studies on animal models of skin cancers that are relevant to this update. TCDD has been shown to produce non-melanoma skin cancers in animal models (Wyde et al., 2004). As discussed elsewhere in this chapter, TCDD is a known tumor promoter and could act as a promoter for skin-cancer initiators,

such as UV radiation, but no experiments have been conducted specifically to support this potential mechanism.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

In accord with the results of reports previously assessed, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and basal-cell or squamous-cell cancers.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and basal-cell or squamous-cell cancers.

BREAST CANCER

Breast cancer (ICD-9 174 for females, ICD-9 175 for males) is the second most common type of cancer (after non-melanoma skin cancers) in women in the United States. ACS estimated that 231,840 women would receive diagnoses of breast cancer in the United States in 2015 and that 40,290 would die from it (Siegel et al., 2015). Overall, those numbers represent about 29 percent of the new cancers and 14 percent of cancer deaths in women. Incidence data on breast cancer are presented in Table 8-20. In men and women, breast cancer incidence generally increases with age. In the age groups of most Vietnam veterans, the incidence in men is higher in blacks than in whites; in women the incidence in whites is generally higher (NCI, 2015).

Established risk factors for women other than age include a personal or family history of breast cancer, alcohol consumption, and some characteristics

TABLE 8-20 Average Annual Incidence (per 100,000) of Breast Cancer in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	3.0	2.9	4.5	5.0	5.0	7.4	6.0	6.1	8.1
Women	343.6	353.6	341.6	422.6	437.9	397.8	440.6	460.1	422.8

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

of reproductive history—specifically, early menarche, late onset of menopause, and either no pregnancies or a first full-term pregnancy after the age of 30 years (Kamińska et al., 2015). In a meta-analysis of studies on alcohol consumption and female breast cancer, Corrao et al. (2004) reported that, in comparison to those who never drank, light drinkers (≤ 1 drink/day or 12.5 g/day) had an elevated pooled relative risk (RR = 1.25, 95% CI 1.20–1.29), whereas the risk was more markedly increased (RR = 1.55, 95% CI 1.44–1.67) for heavy drinkers (≥ 4 drinks/day or 50 g/day). Other lifestyle risk factors for breast cancer include high body mass index/obesity and physical inactivity. In addition, breast cancer risk is increased by the prolonged use of hormone-replacement therapy, particularly preparations that combine estrogen and progestins, whereas estrogen-only therapy (only applied in women without a uterus) slightly decreased the risk (Anderson et al., 2004; Chlebowski et al., 2003). The potential of other personal behavioral and environmental factors (including the use of exogenous hormones) to affect breast cancer incidence is being studied extensively.

The roughly 10,000 female Vietnam veterans who were potentially exposed to herbicides in Vietnam by now would have reached menopause. Given the high incidence of breast cancer in older and postmenopausal women in general, it is expected on the basis of demographics alone that the breast cancer burden in female Vietnam veterans will be increasing in the near future.

The vast majority of breast cancer epidemiologic studies involve women. Although there has been an increase in breast cancer incidence in men over the past 30 years (Kamińska et al., 2015), the disease occurs rarely in men, with 2,350 new cases expected in 2015 (Siegel et al., 2015). Instances of male breast cancer are noted below when reported, but the committee's conclusions are based on the studies in women.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and breast cancer. The additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. After consideration of a new study with positive findings on an association between 2,4-D exposure and breast cancer in female farm workers in California (Mills and Yang, 2005)—in conjunction with the earlier findings of Kang et al. (2000b), Kogevinas et al. (1997), Revich et al. (2001), and Warner et al. (2002)—the committee responsible for *Update 2006* was unable to reach consensus as to whether there might be limited or suggestive evidence of an association between the COIs and breast cancer. An increase in the incidence of breast cancer in the residents of Zone A in Seveso may be emerging with greater latency (Pesatori et al., 2009), but in light of the null findings on mortality from breast cancer in the important cohorts of

female Vietnam-era veterans (Cypel and Kang, 2008) and Seveso residents (Consonni et al., 2008), all members of the committees for *Update 2008* and *Update 2010* concurred that breast cancer should remain in the category of inadequate or insufficient evidence to determine whether there is an association.

Update 2012, examined several occupational and environmental cohort studies that had investigated breast cancer incidence or mortality The strongest evidence came from the Hamburg cohort of 398 women employed at an insecticide/herbicide plant in Hamburg (Manuwald et al., 2012), which reported an increased breast cancer mortality (SMR = 1.86, 95% CI 1.12–2.91) relative to the general population. Follow-ups of workers from Dow's Michigan cohort (Burns CJ et al., 2011) and from the NIOSH PCP cohort (Ruder and Yiin, 2011) found no increased rates of breast cancer; however, the number of women in these cohorts was relatively small. An update of the Seveso Women's Health Study through 2009 reported a non-statistically significant 46 percent increase in breast cancer incidence (95% CI 0.89–2.33) with increasing serum TCDD concentrations (Warner et al., 2011). With stratification by decade since the industrial accident in 1976, the breast cancer risk was highest in the interval 11–20 years after explosion (HR = 2.23, 95% CI 1.09–4.56) and then subsided in the latest period, 21–32 years after the explosion (HR = 1.06, 95% CI 0.58–1.93). After careful consideration of the new evidence and the results in previous updates, the committee for *Update 2012* did not change the previous category of association.

Table 8-21 summarizes the relevant research.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Since *Update 2012*, Kang et al. (2014) updated vital status through 2010 for three sets of female US Vietnam-era veterans: 4,734 deployed to Vietnam, 2,062 deployed to countries near Vietnam, and 5,313 non-deployed. From the end of the Vietnam War in 1973 through 2010, 81, 34, and 89 deaths from breast cancer were observed among those who, respectively, served in Vietnam, served near Vietnam, or were non-deployed. Compared to the general population of US women, there were slight, although not statistically significant, increases in the risk of breast cancer mortality in those who served in Vietnam (SMR = 1.11, 95% CI 0.88–1.38) or who were non-deployed (SMR = 1.12, 95% CI 0.90–1.37), but there was no excess for those serving near Vietnam (SMR = 1.03, 95% CI 0.71–1.44). Internal comparison to the non-deployed era veterans found that breast cancer mortality was not associated with service in Vietnam (RR = 1.05, 95% CI 0.77–1.43) or near Vietnam (RR = 0.93, 95% CI 0.62–1.39). Finally, when the analysis was restricted to nurses, who constitute the majority of female Vietnam-era veterans, those who served in Vietnam (RR = 0.88, 95% CI 0.61–1.27) or

TABLE 8-21 Selected Epidemiologic Studies—Breast Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	0	nr	Boehmer et al., 2004
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586); nurses only (n = 3,690); non-deployed (n = 5,325; nurses only (n = 3,282)		**All COIs**	
Incidence			
Breast cancer	170	1.2 (0.9–1.5)	Kang et al., 2000b
Mortality			
Through 2010	170	1.1 (0.8–1.4)	Kang et al., 2014
Vietnam nurses only	118	0.9 (0.6–1.3)	
Through 2004	57	1.0 (0.7–1.4)	Cypel and Kang, 2008
Vietnam nurses only	44	0.9 (0.6–1.4)	
Through 1991 (Vietnam nurses not reported separately)	26	1.0 (0.6–1.8)	Dalager et al., 1995a
Through 1987 (Vietnam nurses not reported separately)	17	1.2 (0.6–2.5)	Thomas et al., 1991
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	7	0.9 (0.4–1.9)	ADVA, 2005b
Navy	1	0.6 (0.0–3.3)	
Army	5	1.0 (0.3–2.2)	
Air Force	1	1.1 (0.0–6.3)	

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Validation Study		*Expected number of exposed cases*	
Women	17	5 (2–11)	CDVA, 1998b
Mortality			
All branches, return–2001	4	2.2 (0.6–5.4)	ADVA, 2005a
Navy	1	2.5 (0.0–13.5)	
Army	3	2.5 (0.5–7.2)	
Air Force	0	0.0 (0.0–14.6)	
1980–1994 (men)	3	5.5 (1.0– > 10.0)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	0	0.0 (0.0–2.4)	ADVA, 2005c
Mortality			
1966–2001	nr		ADVA, 2005c
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—breast cancer (C50) categorized high (n = 3) vs low (n = 5)		0.5 (0.1–2.3)	Yi and Ohrr, 2014
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992 (13,831 exposed to highly chlorinated PCDDs vs 7,553 unexposed)		**Phenoxy herbicides**	Kogevinas et al., 1997
Men	2	1.6 (0.2–2.1)	
Exposed to highly chlorinated PCDDs	2	2.6 (0.3–9.3)	
Not exposed to highly chlorinated PCDDs	0	nr	
Women	12	1.2 (0.6–2.1)	
Exposed to highly chlorinated PCDDs	9	2.2 (1.0–4.1)	
Not exposed to highly chlorinated PCDDs	3	0.5 (0.1–1.6)	

continued

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Men	2	3.5 (0.4–12.5)	
Women	1	0.3 (0.0–1.7)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	7	**TCDD** 0.9 (0.4–1.9)	Kogevinas et al., 1993
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982 (women)	13	0.9 (nr)	Lynge, 1985
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007			Manuwald et al., 2012
Women	19	1.9 (1.1–2.9)	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	9	2.2 (1.0–4.1)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	1.4 (0.2–5.0)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000			't Mannetje et al., 2005
Phenoxy herbicide producers			
Men	1	32 (0.8–175)	
Women	1	1.3 (0.0–7.2)	
Phenoxy herbicide sprayers (> 99% men)			
Men	0	0.0 (0.0–214)	
Women	0	0.0 (0.0–86.0)	

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	1	0.5 (0.0–2.9)	
PCP and TCP (n = 720)	0	nr	
PCP (no TCP) (n = 1,402)	1	0.6 (0.0–3.1)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	0	nr	Burns CJ et al., 2011
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	21	0.9 (0.6–1.4)	
Ever	32	0.9 (0.6–1.3)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	5	0.5 (nr)	
Employee	3	1.4 (nr)	
Women			
Self-employed	41	0.9 (nr)	
Employee	25	0.6 ($p < 0.05$)	
Family worker	429	0.8 ($p < 0.05$)	

continued

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Incident breast cancer cases 1961–1973 with agriculture as economic activity in 1960 census			Wiklund, 1983
Men, women		*99% CI*	
	444	0.8 (0.7–0.9)	
Men	nr	1.0 (nr)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	18	0.7 (0.4–1.2)	
Nonwhites (n = 11,446)	4	1.7 (0.5–4.4)	
Women			
Whites (n = 2,400)	71	1.0 (0.8–1.3)	
Nonwhites (n = 2,066)	30	0.7 (0.5–1.0)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/ farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	33	1.0 (0.7–1.3)	
Commercial applicators	0	nr	
Spouses	770	1.0 (0.9–1.1)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	27	1.1 (0.7–1.6)	
Spouses of private applicators (> 99% women)	474	1.0 (0.9–1.1)	
Commercial applicators	1	0.6 (0.1–3.5)	
Enrollment through 2001			Engel et al., 2005
Wives' own use of phenoxy herbicides	41	0.8 (0.6–1.1)	
2,4-D	41	0.8 (0.6–1.1)	
Husbands' own use of phenoxy herbicides	110	1.1 (0.7–1.8)	
2,4-D	107	0.9 (0.6–1.4)	
2,4,5-T	44	1.3 (0.9–1.9)	
2,4,5-TP	19	2.0 (1.2–3.2)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	11	0.9 (0.5–1.7)	
Spouses (n = 676)	136	0.8 (0.7–0.9)	

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Enrollment through 2000, vs state rates			Blair et al.,
Private applicators (men and women)	3	0.9 (0.2–2.7)	2005a
Spouses of private applicators (> 99% women)	54	0.9 (0.7–1.1)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	8	1.4 (0.7–2.9)	Pesatori
15+ yrs after accident	5	2.6 (1.1–6.2)	et al., 2009
10–14 yrs after accident	2	1.4 (0.4–5.7)	
5–9 yrs after accident	1	0.8 (0.1–5.7)	
Zone B	30	0.9 (0.6–1.2)	
Zone R	249	1.0 (0.9–1.2)	
10-yr follow-up to 1991—men			Bertazzi
Zone R	1	1.2 (0.1–10.2)	et al., 1993
10-yr follow-up to 1991—women			Bertazzi
Zone A	1	0.5 (0.1–3.3)	et al., 1993
Zone B	10	0.7 (0.4–1.4)	
Zone R	106	1.1 (0.9–1.3)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	2	0.6 (0.2–2.4)	et al., 2008
Zone B	13	0.6 (0.3–1.2)	
Zone R	133	0.9 (0.7–1.1)	
20-yr follow-up to 1996			Bertazzi
Zones A and B—women	14	0.7 (0.4–1.3)	et al., 2001
15-yr follow-up to 1991—women			Bertazzi
Zone A	1	0.6 (0.0–3.1)	et al., 1997
Zone B	9	0.8 (0.4–1.5)	
Zone R	67	0.8 (0.6–1.0)	
10-yr follow-up to 1986—women			Bertazzi
Zone A	1	1.1 (0.1–7.5)	et al., 1989a,b
Zone B	5	0.9 (0.4–2.1)	
Zone R	28	0.6 (0.4–0.9)	

continued

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Seveso (Italy) Women's Health Study—981 women who were infants to 40 yrs of age when exposed—incidence		**TCDD**	
HRs for 10-fold increase in TCDD [log10 lipid adjusted TCDD (ppt)]			Warner et al., 2011
1976–2009	33	1.4 (0.9–2.3)	
Years from accident to diagnosis			
0–10 yrs (1976–1986)	3	2.9 (0.9–9.4)	
11–20 yrs (1987–1996)	10	2.2 (1.1–4.6)	
21–32 yrs (1997–2009)	20	1.1 (0.6–1.9)	
1976–1997	15	2.1 (1.0–4.6)	Warner et al., 2002
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Women			
Regional (Samara)	nr	50.7 (nr)	
National (Russia)	nr	46.2 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Women	58	2.1 (1.6–2.7)	
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman's wives	18	0.8 (0.5–1.3)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
California—Women undergoing breast biopsies in San Francisco area hospitals—79 breast cancer cases vs 52 controls with benign breasts conditions—incidence		**PCDDs, PCDFs**	Reynolds et al., 2005
Total TEQs (pg/g) in adipose breast tissue			
≤ 14.0	24	1.0	
14.1–20.9	22	0.7 (0.3–1.9)	
≤ 21.0	33	0.3 (0.3–2.0) p-trend = 0.99	
California—Registry-based study of 128 Hispanic agricultural farm workers (women) diagnosed 1988–2001 and 640 cancer-free controls.		**Herbicides**	Mills and Yang, 2005
Cancer diagnosis 1987–1994			
Low 2,4-D use	12	0.6 (0.2–1.9)	
High 2,4-D use	8	0.6 (0.2–1.7)	

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Cancer diagnosis 1995–2001			
Low 2,4-D use	19	2.2 (1.0–4.9)	
High 2,4-D use	21	2.1 (1.1–4.3)	
California Teachers Study Cohort—residential proximity to use of "endocrine disruptors" (including 2,4-D, cacodylic acid)		**2,4-D, cacodylic acid**	Reynolds et al., 2004
Quartiles of use (lb/mi^2)			
< 1	1,027	1.0	
1–21	274	1.0 (0.8–1.1)	
22–323	114	0.9 (0.7–1.1)	
≥ 324	137	1.0 (0.9–1.3)	
California women (n = 146) receiving medical care in Woodland Hills (1995–1996), 73 breast cancer cases vs 73 controls undergoing mammoplasty	73	**Organochlorines** nr	Bagga et al., 2000
New York—Population-based study of lifetime residential pesticide use in Long Island; 1,508 newly diagnosed cases and 1,556 matched controls (1996–1997)		**Pesticides**	Teitelbaum et al., 2007
Used lawn and garden pesticides			
Never	240	1.0	
Ever	1,254	1.3 (1.1–1.6)	
Product for weeds	1,109	1.4 (1.2–1.8)	
North Carolina—862 female farm workers, residents diagnosed 1993–1996 and 790 controls		**Herbicides**	Duell et al., 2000
Used pesticides in garden	228	2.3 (0.7–3.1)	
Laundered clothes for pesticide user	119	4.1 (2.8–5.9)	
Connecticut patient at Yale–New Haven hospital with breast-related surgery; dl congener 156	nr	**dl PCBs** 0.9 (0.8–1.0)	Holford et al., 2000
International Case-Control Studies			
Canadian women in Quebec City—315 newly diagnosed breast cancer cases (and plasma concentrations) vs hospital- and population-based controls	314	**Organochlorines,** nr	Demers et al., 2000
Denmark females with breast cancer in Copenhagen City Heart Study (n = 195), 2 blood samples taken (1976–1978, 1981–1983)	195	**Organochlorines** *Overall survival RR* 2.8 (1.4–5.6)	Høyer et al., 2000
France—Besançon residents in zones of dioxin exposure around solid-waste incinerator (434 incident breast cancer cases; 2,170 randomly selected controls) (1996–2002)		**Dioxin**	Viel et al., 2008a
Women, 20–59 yrs of age			
Very low	41	1.0	

continued

TABLE 8-21 Breast Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Low	81	1.1 (0.7–1.6)	
Intermediate	64	1.3 (0.8–1.9)	
High	11	0.9 (0.4–1.8)	
Women, 20–59 yrs of age			
Very low	50	1.0	
Low	111	0.9 (0.6–1.3)	
Intermediate	72	1.0 (0.7–1.4)	
High	4	0.3 (0.1–0.9)	
Greenland Inuit women with breast cancer (n = 31) vs 115 matched controls, 2000–2003		**POPs, dl PCBs**	Bonefeld-Jorgensen and Long, 2011
dl PCBs in serum (mediam: cases vs controls)		56.8 vs 65.4 pg/g lipid p = 0.0009	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2 (2,4,5-trichlorophenoxy) propionic acid; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofurans; PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; pg/g, picogram per gram; POP, persistent organic pollutant; ppt, parts per trillion; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

near Vietnam (RR = 0.79, 95% CI 0.47–1.31) had lower breast cancer mortality than non-deployed US nurses, although the effect was not statistically significant (Kang et al., 2014).

Yi and Ohrr (2014) reported on male breast cancer in the Korean Veterans Health Study. Eight incident cases of male breast cancer (of which three were in the high-exposure category) were ascertained during follow-up of this cohort. Comparing veterans with higher EOI scores to those in the group with lower scores, there was an inverse association with male breast cancer risk (HR = 0.53, 95% CI 0.12–2.26), although the confidence interval was wide and included the null, possibly because of the low number of incident cases.

Occupational and Environmental Studies

No occupational or environmental studies of exposure to the COIs and breast cancer have been published since *Update 2012*.

Case-Control Studies

El-Zaemey et al. (2014) conducted a population-based case-control study of 1,205 breast cancer cases in Western Australia that were diagnosed and ascertained from 2009 through 2011 along with 1,789 controls. Information on household pesticide exposure was collected from self-report questionnaires, whereas occupational exposure to pesticides was constructed based on occupational history and potential exposure to pesticides using job-specific modules. Women's exposures to pesticides were not associated with an increased risk of breast cancer either for self-reported household use (OR = 1.10, 95% CI 0.86–1.37) or for occupational pesticide exposure (OR = 0.77, 95% CI 0.45–1.32). Although the sample size of the study was large, one limitation is that information on exposure was collected after the breast cancer diagnosis, and thus there was potential for recall bias. In addition, the results of this study were not specific to COI or herbicides, and thus are not considered relevant to the committee's task.

Biologic Plausibility

The experimental evidence indicates that 2,4-D, 2,4,5-T, and TCDD are weakly genotoxic at most. However, TCDD is a demonstrated carcinogen in animals and is recognized as having carcinogenic potential in humans because of the mechanisms discussed in Chapter 4.

There is no evidence from carcinogenicity bioassays that TCDD causes breast cancer in laboratory animals (Baan et al., 2009; IARC, 2012c). However, studies performed in laboratory animals indicate that TCDD may modify the carcinogenic process in the mammary gland and that the effect of TCDD may depend on the age of the animal. For example, a single oral exposure of 50-day-old Sprague Dawley rats to 10 µg/kg TCDD 3 days prior to a single administration of the chemical carcinogen dimethylbenzanthracene (DMBA) was found to inhibit mammary-tumor induction (Holcombe and Safe, 1994), but a single 2.5 µg/kg dose of TCDD to 18-day-old rats slightly increased tumor induction when followed by a single injection of the carcinogen methylnitrosourea (MNU) at 21 days of age (Desaulniers et al., 2001).

Fenton (2009) recently reviewed the literature on TCDD and breast cancer and suggested a mechanism that may be related to endocrine disruption, which might indicate a close association between the development of mammary cancers and mammary gland differentiation. Agents capable of disrupting the ability of the normal mammary epithelial cell to enter or maintain its appropriate status (a

proliferative, differentiated, apoptotic state), to maintain its appropriate architecture, or to conduct normal hormone (estrogen) signaling are likely to act as carcinogens, co-carcinogens, or tumor promoters for the breast (Fenton, 2006; McGee et al., 2006). In that light, it is interesting that postnatal exposure of pregnant rats to TCDD has been found to alter the proliferation and differentiation of cells in the mammary gland (Birnbaum and Fenton, 2003; Vorderstrasse et al., 2004). There is evidence that TCDD directly targets mammary epithelial cells and the surrounding stromal fat cells during pregnancy-induced mammary gland differentiation; this points to interference with stromal–epithelial cross-talk as one of several underlying pathways (Lew et al., 2011). Jenkins et al. (2007) used a rat carcinogen-induced mammary cancer model to show that prenatal exposure to TCDD alters mammary gland differentiation and increases susceptibility to mammary cancers by altering the expression of estrogen-receptor (ER) genes and of genes involved in oxidative-stress defense. Thus, the effect of TCDD may depend on the timing of the exposure and on the magnitude of gene expression at the time of exposure; TCDD may influence mammary-tumor development only if exposure to it occurs during a specific window during breast development (Rudel et al., 2011). Susceptibility to breast cancer appears to peak in utero and at puberty, which would not be relevant for female Vietnam veterans, who were potentially exposed as adults. The breast is the only human organ that does not fully differentiate until it becomes ready for use; nulliparous women have less-differentiated breast lobules, which are presumably more susceptible to carcinogenesis, because pregnancy is protective, particularly if carried to full term.

Activation of the AHR by dioxin or by the non-dioxin ligand indole-3-carbinol has also been shown to protect against experimental breast cancer by mechanisms that disrupt migration and metastasis (Bradlow, 2008; Hsu et al., 2007). Administration of TCDD to mice that harbored highly metastatic murine breast-cancer cells in the mammary fat pad reduced the rate of metastasis by 50 percent without suppressing primary tumor size—an indication that TCDD's protective effects are selective to the metastatic process (Wang T et al., 2011). In addition, AHR agonists inhibit the formation of lung metastases by ER-negative breast cancer cells (Zhang et al., 2012). However, Spink et al. (2013), using clones derived from the MCF-7 human breast cancer cell line that express different levels of AHR, showed that in nude mice AHR expression is not necessary for proliferation, migration, invasion, or tumor growth of ER-positive MCF-7 cells, and that the knock-down of AHR in wild-type MCF-7 cells did not affect the anti-proliferative effect of TCDD (Yoshioka et al., 2012). Also, the knock-down of the AHR in triple receptor-negative MDA-MB-231 cells inhibited their in-vivo growth and metastases (Goode et al., 2013). Collectively, these findings suggest that there may be species differences, ER-specific mechanisms, ER-independent mechanisms, or carcinogenic process-specific effects of the AHR in breast carcinogenesis. It is possible that some protective effects may be mediated through the known cross-talk between the AHR and ERα, which has

been studied extensively at the molecular level for potential therapeutic benefit. There is evidence to indicate that AHR controls ERα-regulated gene expression through its effects on DNA methylation (Marques et al., 2013) or through the recruitment of receptor-interacting protein 140 (RIP140), which can both activate and repress ER actions (Madak-Erdogan and Katzenellenbogen, 2012). In the presence of dioxin, the AHR can repress specific estrogen-dependent genes in MCF-7 breast cancer cells (Labrecque et al., 2012) and in triple receptor-negative MDA-MB-231 cells (Goode et al., 2014). TCDD can also activate AHR-mediated G_1cell-cycle arrest (Barhoover et al., 2010); however, in the presence of progesterone receptor, TCDD enriches the G2/M phase and stimulates the proliferation of MCF-7 cells (Chen YJ et al., 2012). Together, these results demonstrate a complicated interplay between the AHR and other nuclear transcription factors, including steroid hormone receptors, which can either stimulate or inhibit breast cancer growth in a manner that depends on cell context. The growth of MCF-7 cells as mammospheres appears to be negatively regulated by the AHR (Zhao et al., 2012), but in the context of an inflammatory microenvironment and HER2 overexpression, the opposite effect has been reported (Zhao et al., 2013).

TCDD may affect breast carcinogenesis by silencing the BRCA-1 tumor suppressor gene through promoter hypermethylation, thereby impairing DNA repair (Papoutsis et al., 2012). TCDD has also been shown to modulate the induction of DNA-chain breaks in human breast cancer cells by regulating the activity of the enzymes responsible for estradiol catabolism and generating more reactive intermediates, which might contribute to TCDD-induced carcinogenesis by altering the ratio of 4-OH-estradiol to 2-OH-estradiol, a marker of breast cancer risk (La Merrill et al., 2010; Lin et al., 2007, 2008). A similar imbalance in metabolite ratios has been observed in pregnant Taiwanese women, in whom the ratio of 4-OH-estradiol to 2-OH-estradiol decreased with increasing exposure to TCDD (Wang et al., 2006). The expression of CYP1B1, the cytochrome P450 enzyme responsible for 2-OH-estradiol formation, but not of CYP1A1, the one responsible for 4-OH-estradiol formation, was found to be highly increased in premalignant and malignant rat mammary tissues in which the AHR was constitutively active in the absence of ligand (Yang et al., 2008). On the basis of recent mechanistic data, it has been proposed that the AHR contributes to mammary-tumor cell growth by inhibiting apoptosis while promoting the transition to an invasive, metastatic phenotype (Marlowe et al., 2008; Schlezinger et al, 2006; Vogel et al., 2011). There is also evidence showing that AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues, including breast tissue, suggesting that TCDD might promote carcinogenesis in these tissues (DiNatale et al., 2010; Hollingshead et al., 2008). Similarly, TCDD induced IL-8 expression in an AHR-dependent manner and may contribute to inflammatory breast cancer (Vogel et al., 2011). Degner et al. (2009) have shown that AHR ligands

can upregulate the expression of COX-2, which may lead to a proinflammatory local environment that can support tumor development.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

In the early 1990s, it was suggested that exposure to some environmental chemicals, such as organochlorine compounds, might play a role in the etiology of breast cancer through estrogen-related pathways. The relationship between organochlorines and breast cancer risk has been studied extensively, especially in the past decade; TCDD and dioxin-like compounds have been among the organochlorines so investigated.

Because of the concerns raised by a combination of a new study that had good exposure assessment and positive findings (Mills and Yang, 2005) and several earlier studies (Kang et al., 2000b; Kogevinas et al., 1997; Revich et al., 2001; Warner et al., 2002), some members of the committee responsible for *Update 2006* believed that there was suggestive evidence of an association, but that committee was unable to reach a consensus. After reviewing new studies that had null findings on mortality from breast cancer in the important cohorts of female Vietnam-era veterans (Cypel and Kang, 2008) and Seveso residents (Consonni et al., 2008), the committee for *Update 2008* readily reached a consensus that breast cancer should remain in the category of inadequate or insufficient evidence of an association. The committees for *Update 2010* and *Update 2012* reviewed follow-up studies of cancer incidence in Seveso (Pesatori et al., 2009; Warner et al., 2011). Pesatori et al. (2009) reported a marginally significant increase in breast cancer incidence that peaked 15 or more years after the accident in the women in Zone A (RR = 2.57, 95% CI 1.07–6.20). The updated report of Warner et al. (2011), however, suggested the risk of breast cancer (HR = 1.46, 95% CI 0.89–2.33) had abated somewhat since 1998 when Warner et al. (2002) reported a risk of borderline statistical significance (HR = 2.1, 95% CI 1.0–4.6). A marginal increase was observed in the Hamburg cohort (Manuwald et al., 2012), while the study of the Dow 2,4-D production workers had null findings (Burns CJ et al., 2011).

In the present update, the follow-up on mortality through 2010 in the cohort of female US Vietnam-era veterans showed no evidence of increased breast cancer mortality associated with service in Vietnam (Kang et al., 2014). These results were similar to previous findings of no increased breast mortality on this study population through 2004 (Cypel and Kang, 2008) and to findings in reports by Thomas et al. (1991) and Dalager et al. (1995b). The data on male breast cancer from the Korean study are very sparse and imprecise mainly due to the very low incidence of breast cancer in men.

Biological mechanistic data also do not clearly indicate whether exposure to TCDD or the other COIs increases the risk of breast cancer. The age at which

TCDD exposure occurs as well as the exposure duration may be critical determinants of whether dioxin influences breast carcinogenesis, but there is no experimental evidence to support the hypothesis that TCDD by itself is a breast tissue carcinogen or enhances breast carcinogenesis.

Conclusion

Having considered the new evidence and the results of studies reviewed in previous updates, the present committee concludes that there is inadequate or insufficient evidence to determine whether there is an association (either positive or negative) between exposure to the COIs and breast cancer.

CANCERS OF THE FEMALE REPRODUCTIVE SYSTEM

This section addresses cancers of the cervix (ICD-9 180), endometrium (also referred to as the corpus uteri; ICD-9 182.0–182.1, 182.8), and ovary (ICD-9 183.0). Additional cancers of the female reproductive system that are infrequently reported separately are cancers of the uterus (ICD-9 179), placenta (ICD-9 181), fallopian tube and other uterine adnexa (ICD-9 183.2–183.9), and other female genital organs (ICD-9 184); findings on these cancers are included in this section. ACS estimates of the numbers of new female reproductive-system cancers in the United States in 2015 are presented in Table 8-22; they represent roughly 12 percent of new cancer cases and 11 percent of cancer deaths in women (Siegel et al., 2015).

Cervical cancer occurs more often in blacks than in whites, but endometrial and ovarian cancers occur more often in whites. The incidence of endometrial and ovarian cancers is higher in older women and in those who have family histories of these cancers. The use of unopposed (without progestogen) estrogen-hormone therapy and obesity, which increases endogenous concentrations of estrogen, both increase the risk of endometrial cancer. Human papilloma virus (HPV) infection, particularly infection with HPV types 16 and 18, is the most important risk factor for cervical cancer (McGraw and Ferrante, 2014).

TABLE 8-22 Estimates of New Cases of Deaths from Selected Cancers of the Female Reproductive System in the United States in 2015

Site	New Cases	Deaths
Cervix	12,900	4,100
Endometrium	54,870	10,170
Ovary	21,290	14,180
Vagina & other female genital	4,070	910

SOURCE: Adapted from Siegel et al., 2015.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and female reproductive cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* has not changed that conclusion.

Tables 8-23, 8-24, and 8-25 summarize the results of the relevant studies on, respectively, cancers of the cervix, uterus, and ovary.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Since *Update 2012*, Kang et al. (2014) updated mortality from 1992 through 2010 for three cohorts of US female veterans who served in Vietnam (n = 4,734), US female veterans who served in countries near Vietnam (n = 2,062), and non-deployed US military women (n = 5,313) for mortality through December 31, 2010, and reported on female reproductive cancers. The following sections summarize the results for mortality from cervical, uterine, and ovarian cancers, separately.

Cervical Cancer Very few deaths from cervical cancer were observed in this study of female US Vietnam-era veterans: five among those who served in Vietnam, one among those who served near Vietnam, and six among those who were non-deployed. Compared to the general population of US women, overall there were fewer than expected cervical cancer deaths in each cohort (SMRs between 0.27 and 0.65), with wide CIs largely due to the small number of cervical cancer deaths. In comparison to non-deployed female Vietnam-era veterans, those who served in Vietnam had no excess cervical cancer mortality (RR = 1.01, 95% CI 0.30–3.46). A further analysis restricted to female nurses, again using the non-deployed cohort as the referent, yielded virtually the same risk of mortality from cervical cancer (RR = 1.16, 95% CI 0.26–5.22).

Uterine Cancer There were also very few observed uterine cancer deaths of women who served in Vietnam, served near Vietnam, or were non-deployed, with 9, 4, and 12 deaths, respectively. Overall, there were no excess risks of uterine cancer mortality in any of the three cohorts (SMRs of 0.95, 0.91, and 1.13, respectively) when compared to the general population. In the internal comparison to non-deployed Vietnam-era veterans, uterine cancer mortality was not associated with service in Vietnam (RR = 0.90, 95% CI 0.37–2.20) or near Vietnam (RR = 0.83, 95% CI 0.26–2.60). Similar results were observed in analysis restricted to the nurses (RR = 0.94, 95% CI 0.35–2.52 and RR = 0.58, 95% CI 0.12–2.71, respectively).

TABLE 8-23 Selected Epidemiologic Studies—Cervical Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only 3,282)			
Incidence		**All COIs**	
Female Vietnam veterans	57	1.1 (0.7–1.7)	Kang et al., 2000b
Mortality		**All COIs**	
Through 2010	11	1.0 (0.3–3.5)	Kang et al., 2014
Vietnam nurses only	7	1.2 (0.3–5.2)	
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence		*Expected number of exposed cases*	CDVA, 1998b
Validation Study			
Self-reported cervical cancer	8	1 (0–5)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	3	1.1 (0.2–3.3)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.8)	
7,553 not exposed to highly chlorinated PCDDs	3	1.8 (0.4–5.2)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1987	7	3.2 (1.3–6.6)	Lynge, 1993

continued

TABLE 8-23 Cervical Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Cervix uteri (ICD-10 C53)	0	0.0 (0.0–14.6)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	7	0.5 ($p < 0.05$)	
Employees	12	0.8 (nr)	
Family workers	100	0.5 ($p < 0.05$)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Incident cervical cancer cases 1961–1973 with agriculture as economic activity in 1960 census	82	*99% CI* 0.6 (0.4–0.8)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Women			
Whites (n = 2,400)	6	0.9 (0.3–2.0)	
Nonwhites (n = 2,066)	21	2.0 (1.3–3.1)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	2	2.7 (0.7–10.8)	Pesatori et al., 2009
Zone B	7	1.5 (0.7–3.1)	
Zone R	28	0.8 (0.6–1.3)	

TABLE 8-23 Cervical Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence—Crude incidence rate in 1998 vs			
Regional (Samara)	nr	11.7 (nr)	
National (Russia)	nr	13.2 (nr)	
Mortality—1995–1998 (SMR vs regional rates)	13	1.8 (1.0–3.1)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Ovarian Cancer Totals of 27, 12, and 21 deaths from ovarian cancer were observed among the female Vietnam-era veterans who, respectively, served in Vietnam, served near Vietnam, or were non-deployed. There were no meaningful differences in the risk of ovarian cancer mortality among those who served in Vietnam (SMR = 1.13, 95% CI 0.75–1.65), who served near Vietnam (SMR = 1.12, 95% CI 0.58–1.95), or were non-deployed (SMR = 0.82, 95% CI 0.51–1.26) in comparison with the general population of US women. In the internal comparison to the non-deployed veterans, ovarian cancer mortality was slightly increased among Vietnam veterans (RR = 1.57, 95% CI 0.87–2.85) and among women who served near Vietnam (RR = 1.60, 95% CI 0.77–3.13). An analysis restricted to nurses revealed similar patterns of increased (albeit not statistically significant) ovarian cancer mortality both for veterans who served in Vietnam (RR = 1.35, 95% CI 0.69–2.62) and for veterans who served near Vietnam (RR = 0.37, 95% CI 0.60–3.14) when compared with non-deployed US nurses (Kang et al., 2014).

Occupational, Environmental, and Case-Control Studies

No occupational or environmental studies or case-control studies of exposure to the COIs and female reproductive cancers have been published since *Update 2012*.

TABLE 8-24 Selected Epidemiologic Studies—Uterine Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans		**All COIs**	
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only 3,282)			
Incidence			
Female Vietnam veterans	41	1.0 (0.6–1.6)	Kang et al., 2000b
Mortality			
Through 2010	21	0.9 (0.4–2.2)	Kang et al., 2014
Vietnam nurses only	17	0.9 (0.4–2.5)	
Through 2004—US non-Vietnam veterans	5	0.8 (0.2–2.8)	Cypel and Kang, 2008
vs non-Vietnam nurses	5	1.3 (0.3–5.0)	
Through 1991—US Vietnam veterans	4	2.1 (0.6–5.4)	Dalager et al., 1995a
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence		*Expected number of exposed cases*	
Validation Study			
Self-reported uterine cancer	4	1 (0–5)	CDVA, 1998b
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	3	3.4 (0.7–10.0)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	1	1.2 (0.0–6.5)	
7,553 not exposed to highly chlorinated PCDDs	4	2.3 (0.6–5.9)	

TABLE 8-24 Uterine Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Corpus uteri (ICD-10 C54–C55)	0	0.0 (0.0–30.6)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	8	0.6 (nr)	
Employees	9	0.9 (nr)	
Family workers	103	0.8 ($p < 0.05$)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Incident NHL cases 1961–1973 with agriculture as economic activity in 1960 census	135	*99% CI* 0.9 (0.7–1.1)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Women			
Whites (n = 2,400)	15	1.2 (0.7–2.1)	
Nonwhites (n = 2,066)	17	1.4 (0.8–2.2)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	4	nr	
Commercial applicators	1	nr	
Spouses	148	0.9 (0.8–1.1)	

continued

TABLE 8-24 Uterine Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-yr follow-up to 1996 (Uterus, ICD-9 179–182)			
Zone A	4	2.3 (0.9–6.3)	Pesatori et al., 2009
Zone B	10	0.9 (0.5–1.7)	
Zone R	61	0.8 (0.6–1.0)	
20-yr follow-up to 1996 (Endometrium, ICD-9 182)			
Zone A	1	1.2 (0.2–8.8)	
Zone B	3	0.6 (0.2–1.9)	
Zone R	27	0.7 (0.5–1.1)	
Mortality			
25-yr follow-up to 2001			
Zone A	0	0	Consonni et al., 2008
Zone B	2	0.5 (0.1–1.9)	
Zone R	41	1.3 (0.9–1.8)	
20-yr follow-up to 1996			
Zone A, B	2	0.5 (0.1–1.9)	Bertazzi et al., 2001
15-yr follow-up to 1991			
Zone B	1	0.3 (0.0–2.4)	Bertazzi et al., 1997, 1998
Zone R	27	1.1 (0.8–1.7)	
CASE-CONTROL STUDIES			
International Case-Control studies			
Swedish women—endometrial cancer and serum concentrations of chlorinated pesticides and PCB congeners	154	**Pesticides, PCB congeners** 1.0 (0.6–2.0)	Weiderpass et al., 2000

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; NHL, non-Hodgkin lymphoma; nr, not reported; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 8-25 Selected Epidemiologic Studies—Ovarian Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only 3,282)			
Incidence		**All COIs**	
Female Vietnam veterans	16	1.8 (0.7–4.6)	Kang et al., 2000b
Mortality			
Through 2010	48	1.6 (0.8–3.1)	Kang et al., 2014
Vietnam nurses only	38	1.4 (0.7–2.6)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence		*Expected number of exposed cases*	
Validation Study			
Self-reported uterine cancer	1	0 (0–4)	CDVA, 1998b
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	1	0.3 (0.0–1.5)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	0	0.0 (0.0–2.6)	
7,553 not exposed to highly chlorinated PCDDs	1	0.5 (0.0–2.5)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	1	**TCDD** 0.7 (nr)	Kogevinas et al., 1993
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ovarian cancer (ICD-10 C56)	0	0.0 (0.0–9.5)	

continued

TABLE 8-25 Ovarian Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	12	0.9 (nr)	
Employees	5	0.5 (nr)	
Family workers	104	0.8 ($p < 0.05$)	
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010			
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	9	2.5 (1.1–4.7)	
Commercial applicators	0	nr	
Spouses	58	0.7 (0.6–0.9)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators (men, women)	8	3.0 (1.3–5.9)	
Spouses of private applicators (> 99% women)	32	0.6 (0.4–0.8)	
Commercial applicators (men, women)	0	0.0 (0.0–16.0)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	5	1.6 (0.5–3.8)	
Spouses (n = 676)	45	0.7 (0.5–0.9)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men, women)	4	3.9 (1.1–10.1)	
Spouses of private applicators (> 99% women)	13	0.7 (0.4–1.2)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	

TABLE 8-25 Ovarian Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Incidence			
20-yr follow-up to 1996 (Uterus, ICD-9 179–182)			
Zone A	1	1.1 (0.2–7.9)	Pesatori et al., 2009
Zone B	1	0.2 (0.0–1.3)	
Zone R	45	1.1 (0.8–1.5)	
Mortality			
25-yr follow-up to 2001			
Zone A	1	1.2 (0.2–8.5)	Consonni et al., 2008
Zone B	2	0.4 (0.1–1.6)	
Zone R	37	1.0 (0.7–1.4)	
20-yr follow-up to 1996			
Zone A, B	3	0.7 (0.2–2.0)	Bertazzi et al., 2001
15-yr follow-up to 1991			
Zone B	1	2.3 (0.3–16.5)	Bertazzi et al., 1997, 1998
Zone R	21	1.0 (0.6–1.6)	
CASE-CONTROL STUDIES			
International Case-Control studies			
Italian women—hospital-based study of women with primary mesothelial ovarian tumors (n = 60) and 127 subjects with non-ovarian malignancies	18	**Herbicides** 4.4 (1.9–16.1)	Donna et al., 1984

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Biologic Plausibility

Yoshizawa et al. (2009) have shown that the chronic administration of TCDD and other AHR ligands to adult female Harlan Sprague Dawley rats results in chronic inflammation and increased incidences of reproductive-tissue preneoplasia and tumors, including cystic endometrial hyperplasia and uterine squamous-cell carcinoma. The mechanism of action might be related to endocrine disruption

and chronic inflammation. Qu et al. (2014) observed increased mRNA and protein expression of the AHR in human endometrial cancer tissue and human endometrial cancer cell lines (Ishikawa and ECC-1) compared with nonmalignant endometrium; increased AHR expression in human endometrial cancer tissue compared to nonmalignant tissue has also been reported by Li D et al. (2013). Qu et al. (2014) showed that a polycyclic hydrocarbon known to be an AHR ligand inhibited proliferation of Ishikawa and ECC-1 cells but that this was not mediated by the AHR. Wormke et al. (2000) reported that TCDD inhibited proliferation of Ishikawa endometrial cancer cells stimulated by estradiol and reduced estrogen receptor activity, but increased AHR-mediated gene expression in these cells, suggesting that the estrogen receptor, not the AHR, mediates the anti-proliferative effect of TCDD. Hollingshead et al. (2008) showed that TCDD activation of the AHR in human breast and endocervical cancer cell lines induces sustained high concentrations of the IL-6 cytokine. It is noteworthy that the effects of TCDD treatment differed between MCF-7 breast cancer cells and ECC-1 endometrial carcinoma cells with respect to the activation and repression of genes; this illustrates the role of cell context and organ specificity in responses to TCDD by cancer cells (Labrecque et al., 2012).

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The results on female reproductive cancers considered in this update came from a follow-up study on mortality among female US Vietnam-era veterans. For both cervical and uterine cancers there was no evidence of increased mortality risk; however, the small observed number of deaths for these outcomes in all three cohorts limited the statistical power to determine whether risk was increased or decreased. With regard to ovarian cancer, there was some evidence of slightly elevated mortality in veterans who served either in or near Vietnam, but for both risks the CIs were large and their point estimates imprecise. However, because ovarian cancer mortality was similar between veterans who served in Vietnam (with potential exposure to Agent Orange and the related COIs) and those who served near Vietnam (who presumably were not so exposed), this evidence is equivocal for the purpose of this review. The results of mechanistic studies provide more plausibility for a reduced risk of female reproductive cancers than for an increased risk.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and uterine, ovarian, or cervical cancers.

PROSTATE CANCER

ACS estimated that 220,800 new cases of prostate cancer (ICD-9 185; ICD-O-3 C61.9) would be diagnosed in the United States in 2015 and that 27,540 men would die from it (Siegel et al., 2015). That makes prostate cancer the second-most common cancer in men (after non-melanoma skin cancers); it is expected to account for about 6 percent of new cancer diagnoses and 9 percent of cancer deaths in men in 2015. The average annual incidence of prostate cancer is shown in Table 8-26.

The incidence of and mortality from prostate cancer varies widely with age and race. The incidence rate of prostate cancer more than doubles from the ages of 50–54 years to the ages of 55–59 years, and it nearly doubles again from the ages of 55–59 years to the ages of 60–64 years. As a group, African American men have the highest recorded incidence of prostate cancer in the world (Jemal et al., 2011); their risk is roughly twice that of whites in the United States, 5 times that in Alaska natives, and nearly 8.5 times that in Korean Americans. Little is known about the causes of prostate cancer. Other than race and age, the risk factors include a family history of the disease both in first- and second-degree relatives (Bruner et al., 2003; Zeegers et al., 2003). and probably some elements of the Western diet, including high consumption of red meat and saturated fats, but these have not been conclusively identified. Of note, selenium and vitamin E supplementation did not reduce, but rather slightly increased, prostate cancer incidence in a large clinical trial (Klein et al., 2011; Kristal et al., 2014; Lippman et al., 2009), and soy protein supplementation did not prevent the recurrence of prostate cancer after surgical treatment in a randomized study (Bosland et al., 2013). The 5α-reductase inhibiting drugs finasteride and dutasteride, which are widely used to treat benign enlargement of the prostate, were found to decrease the prevalence of prostate cancer by about 25 percent in two major randomized trials (Andriole et al., 2010; Thompson et al., 2003); however, in the finasteride trial the risk of high-grade prostate cancer was increased. Finasteride acts by decreasing the formation of the potent androgen metabolite 5α-dihydrotestosterone in the prostate.

TABLE 8-26 Average Annual Incidence (per 100,000) of Prostate Cancer in the United States[a]

60–64 Years Old			65–69 Years Old			70–74 Years Old		
All Races	White	Black	All Races	White	Black	All Races	White	Black
518.6	493.4	856.2	788.1	753.0	1,207.3	835.4	800.7	1,167.8

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

The study of the incidence of and mortality from prostate cancer is complicated by various approaches to screening for the disease in different countries and populations. The widespread adoption of serum prostate-specific antigen (PSA) screening in the 1990s led to very large increases in prostate cancer incidence in the United States, which have recently subsided as exposure to screening has become saturated. PSA screening has recently come under scrutiny and is no longer uniformly recommended or consistently applied in the United States following a D grade recommendation from the US Preventive Service Task Force in 2012 (Moyer et al., 2012). The long-term influence of PSA screening on incidence and mortality in any country or population is difficult to predict and will depend on the rapidity with which the PSA screening tool was adopted, its differential use in men of various ages, and the aggressiveness of tumors detected early with this test (Gann, 1997). Because exposure to PSA testing is such a strong determinant of prostate cancer incidence, epidemiologic studies must be careful to exclude differential PSA testing as a potential explanation of differences in risk observed between two groups.

Prostate cancer tends not to be fatal in many cases, particularly for screening-detected (i.e., localized stage/well-differentiated grade) prostate cancer, so mortality studies may miss an increase in incidence of the disease and thus potentially misclassify the outcome. In addition, findings that show an association between an exposure and prostate cancer mortality should be examined closely to determine whether the exposed group might have had poorer access to screening or treatment that would have decreased the likelihood of survival.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to the COIs and prostate cancer, based on positive associations observed in occupational and environmental studies. Additional information from various epidemiologic studies (available to the committees responsible for subsequent updates) has not changed that conclusion.

Table 8-27 summarizes results of the relevant studies, including both morbidity and mortality studies. The results from studies new to this update are shaded.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Since *Update 2012*, there have been two publications concerning prostate cancer among veterans at VA medical facilities and two international cohort studies of male Vietnam veterans from New Zealand and Korea have recently reported on cancer incidence and mortality for prostate cancer.

TABLE 8-27 Selected Epidemiologic Studies—Prostate Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
2,516 veterans (1,019 Ranch Hand, 1,497 SEA veterans) who participated in ≥ 1 physical examination and had recorded serum TCDD measurements			Pavuk et al., 2006
20-yr cumulative TCDD (ppt-yr)			
Comparison group	81	1.0	
Ranch Hand low (≤ 434 ppt-yr)	31	1.0 (0.7–1.6)	
Ranch Hand high (> 434 ppt-yr)	28	1.2 (0.8–1.9)	
		p-trend = 0.42	
Last tour in SEA before 1969 (heavy spraying)			
Yes			
Comparison group	17	1.0	
Ranch Hand low (≤ 434 ppt-yr)	9	1.0 (0.4–2.3)	
Ranch Hand high (> 434 ppt-yr)	15	2.3 (1.1–4.7)	
		p-trend = 0.04	
No			
Comparison group	64	1.0	
Ranch Hand low (≤ 434 ppt-yr)	22	1.1 (0.7–1.8)	
Ranch Hand high (> 434 ppt-yr)	13	0.9 (0.5–1.6)	
		p-trend = 0.75	
Less than 2 yrs served in SEA			
Yes			
Comparison group	16	1.0	
Ranch Hand low (≤ 434 ppt-yr)	20	1.9 (1.0–3.7)	
Ranch Hand high (> 434 ppt-yr)	14	2.2 (1.0–4.5)	
		p-trend = 0.03	
No			
Comparison group	65	1.0	
Ranch Hand low (≤ 434 ppt-yr)	11	0.8 (0.4–1.5)	
Ranch Hand high (> 434 ppt-yr)	14	1.1 (0.6–1.9)	
		p-trend = 0.89	

continued

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g)	83	1.1 (0.7–1.5)	
Quartiles (pg/g):			
0.4–2.6	13	1.0	
2.6–3.8	24	1.7 (0.8–3.3)	
3.8–5.2	24	1.5 (0.7–2.9)	
> 5.2	22	1.2 (0.6–2.4)	
Number of years served in SEA (per year of service)	83	1.1 (1.0–1.2)	
Quartiles (years in SEA):			
0.8–1.3	8	1.0	
1.3–2.1	11	1.3 (0.5–3.2)	
2.1–3.7	28	2.2 (1.0–4.9)	
3.7–16.4	36	2.4 (1.1–5.2)	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	36	1.5 (1.0–2.0)	
With tours between 1966–1970	34	1.7 (1.2–2.3)	
SEA comparison veterans (n = 1,776)	54	1.6 (1.2–2.1)	
With tours between 1966–1970	42	1.6 (1.2–2.2)	
White AFHS subjects who spent at most 2 yrs in SEA			
Per unit increase of –$\log_e$(TCDD)	28	1.5 (0.9–2.4)	
Comparison group	7	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	10	1.5 (0.5–4.4)	
Ranch Hand— < 118.5 TCDD pg/g at end of service	6	2.2 (0.7–6.9)	
Ranch Hand— > 118.5 TCDD pg/g at end of service	5	6.0 (0.4–24.6)	
Only Ranch Hands with 100% service in Vietnam and comparisons with no service in Vietnam			
Per unit increase of –$\log_e$(TCDD)	20	1.1 (0.6–1.8)	
Comparison group	3	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	9	2.5 (0.4–16.1)	
Ranch Hand— < 118.5 TCDD pg/g at end of service	4	2.4 (0.4–16.0)	
Ranch Hand— > 118.5 TCDD pg/g at end of service	4	4.7 (0.8–29.1)	

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	2	0.7 (0.1–2.3)	
SEA comparison veterans (n = 1,776)	3	0.8 (0.2–2.1)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality—Prostate cancers			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)	5 vs 2	1.0 (0.2–5.6)	
ACC veterans vs US men			
Vietnam cohort	5	1.1 (0.3–2.5)	
Non-Vietnam cohort	2	1.0 (0.1–3.4)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	1	0.4 (nr)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	58	0.9 (nr)	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	9	0.8 (nr)	
1965–1982			Breslin et al.,1986, 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	30	0.9 (0.6–1.2)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	5	1.3 (0.2–10.3)	
State Studies of US Vietnam Veterans			
US VA Hospital Medical Records—VVs who underwent radial prostatectomy between 2005 and 2009 (n = 93); dioxin levels (TEQs) measured in subcutaneous adipose tissue		**All COIs** (supposed AO exposure)	Li et al., 2013

continued

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Proportion of TEQ levels for AO-exposed (self-reported) vs unexposed Proportion of higher TEQ levels vs lower TEQs		27% vs 20% p = 0.68 28% vs 17% p = 0.23	
Veterans with radical prostatectomies examined in VA Healthcare facilities (California, Georgia, North Carolina)			Shah et al., 2009
AO-exposed veterans with biochemical progression	nr	1.5 (1.1–2.0)	
Northern California—prostate cancer (self-reported [before diagnosis] of AO exposed vs not)	239	**All COIs** 2.9 (2.3–3.6)	Chamie et al., 2008
Massachusetts veterans aged 35–65 years in 1993—prostate cases diagnosed 1988–1993 vs gastrointestinal cancers	15	**All COIs** 0.8 (0.4–1.6)	Clapp, 1997
Michigan Vietnam veterans using the VA Medical Center in Ann Arbor, MI (n = 47); 142 frequency-matched controls		**All COIs**	Giri et al., 2004
Cases reporting AO exposure	11	OR 2.1 (0.8–5.2)	
Cases in white veterans reporting AO exposure	nr	OR 2.7 (0.9–8.2)	
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed		**All COIs**	Vistainer et al., 1995
Male genital system	19	1.1 (0.6–1.7)	Clapp, 1997
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	0	**All COIs** nr	Anderson et al., 1986a,b
Oregon: A cohort of 2,720 veterans who underwent biopsy at Portland VA Medical Center (896 prostate cancers)		**All COIs** (supposed AO exposure)	Ansbaugh et al., 2013
All prostate cancer	74	1.5 (1.1–2.1)	
High grade prostate cancer (Gleason score > 7)	40	1.8 (1.1–2.7)	
Gleason score > 8 prostate cancer	nr	2.1 (1.2–3.6)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Incidence			
All branches, 1982–2000	692	1.3 (1.2–1.3)	ADVA, 2005b
Navy	137	1.2 (1.0–1.4)	
Army	451	1.3 (1.2–1.4)	
Air Force	104	1.3 (1.0–1.5)	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	212	147 (123–171)	
Men	428	147 (123–171)	CDVA, 1998a
Mortality			
All branches, return–2001	107	1.2 (1.0–1.5)	ADVA, 2005a
Navy	22	1.3 (0.8–1.8)	
Army	65	1.2 (0.9–1.5)	
Air Force	19	1.4 (0.8–2.1)	
Sample of 1,000 Male Australian Vietnam Veterans–prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey	nr	1.3 (0.3–6.7)	O'Toole et al., 2009
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	65	1.2 (0.9–1.5)	ADVA, 2005c
Mortality			
1966–2001	0	0.0 (0.0–0.7)	ADVA, 2005c
1982–1994	36	1.5 (1.0–2.0)	CDVA, 1997b
Other Australian Vietnam veterans		**All COIs**	
606 prostate cancer cases in Western Australia Vietnam service	25	2.1 (0.9–5.1)	Leavy et al., 2006
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	136	1.2 (1.0–1.4)	
Mortality (1988–2008)	13	1.0 (0.6–1.8)	
Korean Vietnam Veterans Health Study— entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—prostate cancer (C61) categorized high (n = 53) vs low (n = 71)	53	0.7 (0.5–1.0)	Yi and Ohrr, 2014
Mortality (1992–2005)—prostate cancer (C61) categorized high (n = 17) vs low (n = 21)		0.7 (0.4–1.3)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	38	0.9 (0.8–1.1)	

continued

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	68	1.1 (0.9–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	43	1.1 (0.8–1.5)	
7,553 not exposed to highly chlorinated PCDDs	25	1.1 (0.7–1.6)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	30	1.1 (0.8–1.6)	Saracci et al., 1991
British MCPA Plant—production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	18	1.3 (0.8–2.1)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Mortality 1955–2006	14	1.1 (0.8–1.5)	Boers et al., 2012
Incidence 1943–1982	9	0.8 (nr)	Lynge, 1985
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	8	1.3 (0.9–1.9)	Boers et al., 2012
Mortality 1955–2006	6 vs 2	2.9 (0.6–14.2)	Boers et al., 2010
Mortality 1955–1985	2	2.2 (0.3–7.8)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	4 vs 2	2.7 (0.5–14.9)	Boers et al., 2010

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1965–1986	1	4.8 (0.1–26.5)	Bueno de Mesquita et al., 1993
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	1	1.5 (0.0–8.5)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	1	0.7 (0.0–3.7)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992			Ott and Zober, 1996a
TCDD < 0.1 µg/kg of body weight	3	2.5 (0.5–7.4)	
TCDD 0.1–0.99 µg/kg of body weight	1	1.1 (0.0–5.9)	
TCDD > 1.0 µg/kg of body weight	0	0.0 (0.0–2.5)	
Mortality			
1953–1992			Ott and Zober, 1996a
TCDD < 0.1 µg/kg of body weight	0	0.0 (0.0–5.7)	
TCDD 0.1–0.99 µg/kg of body weight	0	0.0 (0.0–7.5)	
TCDD > 1.0 µg/kg of body weight	0	0.0 (0.0–4.6))	
Through 1987		*90% CI*	Zober et al., 1990
	0	0.0 (0.0–6.1)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working >1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	

continued

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1952–2007	19	1.4 (0.8–2.1)	Manuwald et al., 2012
Mortalilty 1952–1989	7	1.5 (0.6–3.0)	Becher et al., 1996
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	7	1.4 (0.6–2.9)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride
Ever-exposed workers	1	0.2 (0.0–1.2)	et al., 2009a
Never-exposed workers	2	1.9 (0.2–6.7)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	1	0.4 (0.0–2.1)	't Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	2	0.6 (0.1–2.2)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	28	1.2 (0.8–1.7)	Steenland et al., 1999
Through 1987	17	1.2 (0.7–2.0)	Fingerhut
≥ 1-yr exposure, ≥ 20-yr latency	9	1.5 (0.7–2.9)	et al., 1991
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	9	1.6 (0.7–3.0)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)			Collins et al.,
	21	1.4 (0.9–2.2)	2009b
1940–1994 (n = 2,187 men)			Bodner et al.,
	nr	1.7 (1.0–2.6)	2003

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	26	1.0 (0.7–1.5)	
PCP and TCP (n = 720)	8	1.1 (0.5–2.1)	
PCP (no TCP) (n = 1,402)	18	1.0 (0.6–1.6)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	51	0.8 (0.6–1.0)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	7	1.3 (0.5–2.8)	Burns et al., 2001
Through 1982 (n = 878)	1	1.0 (0.0–5.8)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	8	1.0 (0.4–1.9)	Collins et al., 2009c
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	117	0.9 (0.7–1.0)	
Ever	84	0.9 (0.7–1.2)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 yr, mortality through July 1985	9	1.0 (0.5–1.9)	Henneberger et al., 1989
United Paperworkers International, 201 white men employed ≥ 10 yr and dying 1970–1984	4	1.1 (0.3–2.9)	Solet et al., 1989

continued

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and CA, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977	17	*90% CI* 1.2 (0.7–1.7)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from prostate cancer June 1971–Dec 1987		**Herbicides**	Morrison et al., 1993
Herbicides sprayed on ≥ 250 acres vs 0 acres	20	2.2 (1.3–3.8)	
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	282	1.0 (0.9–1.1)	Hertzman et al., 1997
Mortality 1950–1989	116	1.2 (1.0–1.4)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	399	0.9 ($p < 0.05$)	
Employee	63	0.8 ($p < 0.05$)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-year follow-up (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	39	1.3 (1.0–1.8)	
Born 1915–1934 (medium exposure)	35	0.9 (0.6–1.2)	
Born after 1934 (low exposure)	3	0.4 (0.1–1.3)	
10-year follow-up (1975–1984) of male gardeners	20	1.2 (0.7–1.8)	Hansen et al., 1992
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	6	1.0 (0.4–2.2)	Swaen et al., 2004
Through 1987	1	1.3 (0.0–7.3)	Swaen et al., 1992

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC		**Phenoxy herbicides**	
Incidence	6	0.4 (0.1–0.8)	Asp et al., 1994
Mortality 1972–1989	5	0.8 (0.3–1.8)	
ICELAND			
Icelandic men (1,860), women (859) exposed to agricultural pesticides, primarily 2,4-D (other endocrine organs, ICD-9 194)—incidence	10	**2,4-D** 0.7 (0.3–1.3)	Zhong and Rafnsson, 1996
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	66	1.0 (0.7–1.2)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	19	**Phenoxy herbicides** 1.0 (0.6–1.5)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident prostate cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	12	0.7 (0.4–1.3)	
SWEDEN			
Swedish Cancer-Environment Registry— National cancer registry linked to census		**Herbicides**	Sharma-Wagner et al., 2000
36,269 incident prostate cancer cases 1961–1979 with 1960 census occupation of:			
Agriculture, stock raising	6,080	(1.0–1.1) ($p < 0.01$)	
Farmers, foresters, gardeners	5,219	(1.0–1.1) ($p < 0.01$)	
Paper-mill workers	304	0.9 (0.8–1.0)	
Pulp grinding	39	1.4 (1.0–1.9) ($p < 0.05$)	
Incident prostate cancer cases 1961–1973 with agriculture as economic activity in 1960 census	3,890	*99% CI* 1.0 (0.9–1.0)	Wiklund, 1983
Licensed Swedish Pesticide Sprayers—Incidence of prostate cancer	401	**Phenoxy herbicides** 1.1 (1.0–1.2)	Dich and Wiklund, 1998
Born 1935 or later	7	2.0 (0.8–4.2)	

continued

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Born before 1935	394	1.1 (1.0–1.2)	
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	2	4.7 (nr)	
Lumberjacks (n = 139)	3	0.9 (nr)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	3,765	1.2 (1.1–1.2)	
Nonwhites (n = 11,446)	564	1.1 (1.1–1.2)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	1,719	1.2 (1.1–1.3)	
Commercial applicators	73	1.3 (1.0–1.6)	
Spouses	7	1.1 (0.4–2.2)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	343	1.0	
1– < 20	106	1.0 (0.8–1.3)	
20– < 56	102	0.9 (0.7–1.2)	
56– < 116	76	1.0 (0.7–1.3)	
≥ 116	67	(0.8–1.5) p-trend 0.45	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	1.046	1.3 (1.2–1.3)	
Spouses of private applicators (> 99% women)	5	1.2 (0.4–2.8)	
Commercial applicators	41	1.4 (1.0–1.9)	
Enrollment through 1999 (n = 55,332)	566	1.1 (1.1–1.2)	Alavanja et al., 2003

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Enrollment through 2007, vs state rates			Waggoner
Applicators (n = 1,641)	171	0.8 (0.7–1.0)	et al., 2011
Enrollment through 2000, vs state rates			Blair et al.,
Private applicators (men and women)	48	0.7 (0.5–0.8)	2005a
Spouses of private applicators (> 99% women)	0	0.0 (0.0–1.6)	
US Agricultural Health Study—Nested CC study (776 cases vs 1,444 controls)		**Herbicides**	Karami et al., 2013
2,4 D (ever exposed)	617	0.8 (0.7–1.1)	(supplemental
2,4 D (high exposure)	295	0.8 (0.6–1.1)	Table S1)
2,4,5 T (ever exposed)	229	0.9 (0.7–1.1)	
2,4,5 T (high exposure)	56	0.7 (0.5–0.9)	
2,4,5 TP (ever exposed)	64	0.8 (0.6–1.1)	
2,4,5 TP (high exposure)	11	0.6 (0.3–1.1)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of prostate cancer		**Herbicides**	
Agricultural extension agents	nr	1.0 (0.7–1.5)	Alavanja et al., 1988
Forest conservationists		p-trend < over yrs worked	Alavanja et al., 1989
	nr	p < 0.05	
Soil conservationists	nr	p < 0.26	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
30,155 white men licensed 1975–1993			
Incidence 1975–1993	353	1.9 (1.7–2.1)	Fleming et al., 1999a
Mortality 1975–1993	64	2.4 (1.8–3.0)	Fleming et al., 1999b
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose–response by length of licensure)		*Expected number of exposed cases*	
	2	3.8 (nr)	

continued

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
> 30 yrs old when died 1964–1978—case-control	4,827	1.2 ($p < 0.05$)	Burmeister et al., 1983
H_0: only for "modern methods" → born after 1900			
Born before 1880	1,539	1.5 (nr)	
Born 1980–1900	2,081	1.3 (nr)	
Born after 1900	1,207	0.8 (nr)	
> 20 yrs old when died 1971–1978—PMR	1,138	1.1 ($p < 0.01$)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	0		Pesatori et al., 2009
Zone B	7	0.9 (0.5–2.0)	
Zone R	39	0.8 (0.5–1.1)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Zone R	16	0.9 (0.5–1.5)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
Zone A	1	0.9 (0.1–6.2)	
Zone B	8	0.9 (0.4–1.8)	
Zone R	65	1.1 (0.8–1.4)	
20-yr follow-up to 1996			Bertazzi et al., 2001
Zones A, B—men	8	1.1 (0.5–2.2)	
15-yr follow-up to 1991—men			Bertazzi et al., 1997
Zone B	6	1.2 (0.5–2.7)	
Zone R	39	1.2 (0.8–1.6)	
10-yr follow-up to 1986—men			Bertazzi et al., 1989b
Zone B	3	2.2 (0.7–6.9)	
Zone R	16	1.6 (0.9–2.7)	
Other International Environmental Studies			
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman	36	1.0 (0.7–1.4)	
Spouses	—	—	

TABLE 8-27 Prostate Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	38	1.1 (0.8–1.5)	
West coast	224	1.0 (0.9–1.1)	
Mortality			
East coast	12	1.0 (0.5–1.8)	
West coast	123	1.1 (0.9–1.3)	
CASE-CONTROL STUDIES			
CANADA—1,516 prostate cancer patients identified in the British Columbia Cancer Registry vs 4,994 matched controls; estimated lifetime exposure to:		**Pesticides**	Band et al., 2011
2,4-D	11	2.7 (1.1–6.6)	
2,4-DB	24	1.8 (1.0–3.0)	
MCPA	14	1.8 (1.0–3.2)	
Dicamba	22	2.0 (1.0–4.2)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DB, 4-(2,4-dichlorophenoxy)butyric acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; AFHS, Air Force Health Study; AO, Agent Orange; CATI, computer-assisted telephone interviewing; CC, case-control; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; pg/g, picogram per gram; PM, proportionate mortality; PMR, proportionate mortality ratio; ppt, parts per trillion; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs; VV, Vietnam veteran.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

A Vietnam-veteran cohort study conducted in Oregon State evaluated a possible relationship between herbicide exposure and the incidence of more aggressive cases of prostate cancer in a cohort of veterans undergoing prostate biopsies diagnosed with this cancer. Ansbaugh et al. (2013) conducted a retrospective cohort analysis among 2,720 veterans (94 percent Caucasian) who were referred

to the Portland VA Medical Center with an elevated serum PSA and underwent an initial prostate biopsy. A total of 896 incident prostate cancers were diagnosed in this cohort, of which 459 were intermediate- to high-grade tumors (Gleason scores ≥ 7). Herbicide exposure, as classified within the VA electronic medical records, was determined during the patients' enrollment into the VA hospital. In addition, all veterans completed a questionnaire that collected demographic and anthropometric factors, as well as a medical history and family history of prostate cancer. Of the 2,720 veterans, 203 (7.5 percent) were classified as having herbicide exposure. There was a statistically significant positive association between herbicde exposure and the overall risk of prostate cancer (OR = 1.52, 95% CI 1.07–2.13) after adjustment for age and receipt of PSA or digital rectal exam screening. Stratified analyses by tumor characteristics found a stronger association between herbicide exposure and intermediate- to high-grade prostate cancer (OR = 1.75, 95% CI 1.12–2.74) and an even stronger association with more aggressive (Gleason scores 8–10) prostate cancer (OR = 2.10; 95% CI 1.22–3.61). Although this study had a relatively large sample size and included a large number of incident prostate cancers, several limitations should be considered carefully when interpreting the results. First, potential selection/referral bias is a major issue because men who were referred for prostate biopsy probably had an elevated PSA and could possibly have had better access to health care in comparison to other veterans. In addition, the referring physician may have acted because he or she knew that the veteran could have had herbicide exposure. However, the authors argue, correctly, that the likelihood of this selection/referral bias was low and that the study physicians did not take such exposure into account at the time of the biopsy referral. The indication of herbicide exposure in the VA database is likely to have introduced exposure misclassification, because VA does not have accurate information on the extent to which individual Vietnam veterans were exposed to herbicides.

Q Li et al. (2013) recently published a small study conducted among 93 veterans who underwent radical prostatectomy between 2005 and 2009; the goal of the study was to determine the relationship between herbicide exposure and biochemical recurrence of prostate cancer during an average of 5.3 years of follow-up after the prostatectomy. Herbicide exposure was determined from the VA administrative databases, as had been done in the study by Ansbaugh et al. (2013). According to the study authors, herbicide exposure was determined by self-report and military records confirming that Vietnam veterans had served in an area in which herbicides had been sprayed. In this study, however, subcutaneous adipose tissue obtained during prostatectomy was assayed for dioxin. The measured TEQ levels of the 37 men with self-reported herbicide exposure were higher than those of the 56 purportedly unexposed men (medians 22.3 and 15.0 pg/g, respectively; $p < 0.001$). The proportions of men with biochemical recurrence were very modestly higher both for the veterans with self-reported herbicide exposure versus those said to be unexposed (27 percent and 20 percent, respectively; $p = 0.68$) and for those with higher TEQ levels compared with those with lower TEQ levels

(28 percent and 17 percent, respectively; p = 0.23); there were few recurrences in the groups categorized as exposed by the two criteria (8 and 13, respectively). Of note, in neither this study nor the previous publication of the same cohort (see Shah et al., 2009) was it clear how herbicide exposure was ascertained or defined.

McBride et al. (2013) followed 2,783 male veterans from New Zealand who had served in Vietnam between 1964 and 1972 and were still alive as of 1988. This cohort, which was followed for cancer incidence and mortality from 1988 through 2008, included 84 percent of all 3,322 New Zealand veterans who returned from service in Vietnam. Standardized incidence and mortality ratios were generated by comparing the observed incident cases and deaths in this cohort with the corresponding expected numbers of new cases and deaths from the general male population of New Zealand. A total of 136 incident cases and 13 deaths from prostate cancers were identified in this cohort. When compared to the general male population of New Zealand, there was a modest excess risk of prostate cancer incidence (SIR = 1.17, 95% CI 0.98–1.39), but no excess prostate cancer–specific mortality (SMR = 1.03, 95% CI 0.55–1.76). A limitation of this study was that information on prostate cancer incidence and mortality in the time period immediately following service in Vietnam (i.e., between 1973 and 1998) was not available. Moreover, there was no information on potential confounding factors, including a family history of prostate cancer; however, it is unlikely that family history would differ between men with and without herbicide exposure.

Several recent publications examined prostate cancer incidence (Yi, 2013; Yi and Ohrr, 2014) and cancer-specific mortality (Yi et al., 2014b) in the Korean Veterans Health Study. A total of 125 incident cases and 53 deaths from prostate cancer were identified in this cohort during follow-up. When compared to the general Korean population, there was a statistically significant excess prostate cancer risk (SIR = 1.22, 95% CI 1.02–1.46) in the entire cohort (Yi, 2013), which was mostly due to a significant 2.5-fold elevated prostate cancer incidence among officers (SIR = 2.49, 95% CI 1.93–3.21; based on 59 incident cases). By contrast, both enlisted soldiers and non-commissioned officers had lower incidence rates of prostate cancer (SIR = 0.85 and 0.81, respectively) relative to the general population, although the 95% confidence intervals for both risk estimates were large and the differences were not statistically significant. However, in the internal comparison analysis, Yi and Ohrr (2014) reported an inverse association between the EOI scores and prostate cancer incidence (RR = 0.70, 95% CI 0.49–1.00, when comparing high- versus low-exposure), which was based on 53 cases in the high-exposure category. It should be noted, however, that Yi and Ohrr (2014) did not stratify incident prostate cancer cases according to tumor characteristics (low- versus high-grade tumors) as is usually done in studies of prostate cancer incidence. With regard to exposure potential and prostate cancer–specific mortality, Yi et al. (2014b) reported a similar inverse association (RR = 0.68, 95% CI 0.36–1.31) when comparing high- versus low-exposure groups, which had 17 and 21 prostate cancer deaths, respectively.

Occupational Studies

Karami et al. (2013) recently evaluated the interactions between 41 pesticides and 152 single-nucleotide polymorphisms (SNPs) in nine vitamin D pathway genes among 776 prostate cancer cases and 1,444 male controls in a nested case-control study of Caucasian pesticide applicators within the AHS. In the main effect analysis of this study, the associations between pesticide use and prostate cancer risk were largely null. With regard to the COIs, the authors examined association between prostate cancer risk and ever-exposed or high exposures to 2,4-D, 2,4,5-T, and 2,4,5-TP. Most of the associations had ORs ranging from 0.6 to 0.8, with large CIs that included the null. However, for high exposure to 2,4,5-T there was a statistically significant inverse association with prostate cancer (OR = 0.67, 95% CI 0.48–0.93), based on 56 exposed cases. The AHS has been generating valuable information on the COIs for a number of years, but some of its results are not herbicide-specific and so cannot be regarded fully informative for the committee's task.

Environmental and Case-Control Studies

No environmental cohort studies or case-control studies of exposure to the COIs and prostate cancer have been published since *Update 2012.*

Biologic Plausibility

In prostate cells and prostate cancer cell lines TCDD can lead to the induction of various genes, including those involved in drug metabolism. Simanainen et al. (2004) used different rat lines (TCDD-resistant Hannover/Wistar and TCDD-sensitive Long Evans) and found that TCDD treatment resulted in a significant decrease in the weight of prostate lobes; the effect did not appear to be rat strain–specific. Different responses to TCDD in the human prostate cancer cell lines LNCaP and PC3 have been reported, including increased proliferation or no growth and stimulation or repression of AHR activity, which may be a function of coactivator–corepressor concentrations in the cells (Kollara and Brown, 2009, 2010). In addition AHR activation has been shown to interfere with androgen receptor binding to androgen response elements in LNCaP cells via the upregulation of AP-1, resulting in a reduced expression of PSA (Kizu et al., 2003). However, the number of CAG repeats in the androgen receptor gene, which affects androgen receptor activity, did not significantly affect the induction of CYP1A1 by TCDD in androgen receptor–negative prostate cells transfected with androgen receptor constructs with different CAG repeat lengths (Björk and Giwercman, 2013). In that study, TCDD altered androgen receptor activity in a CAG repeat length–dependent manner in PC-3 cells, but not in a non-tumorigenic, immortalized epithelial prostate cell line. The AHR is

upregulated in androgen receptor–negative, hormone-independent prostate cancer cells compared to androgen receptor–positive, hormone-dependent LNCaP cells, and treatment of these cells (PC3, PC3M, and DU145) with an AHR agonist suppressed their growth (Richmond et al., 2014). In contrast, even though the AHR is upregulated in castration-resistant C4-2 cells compared with the LNCaP cells from which they have been derived, silencing of the AHR caused a growth inhibition of these cells, perhaps because they retained androgen-receptor expression and are androgen-sensitive (Tran et al., 2013). TCDD suppressed expression of genes associated with cell-cycle progression in LNCaP cells but also suppressed DNA-repair genes and increased Wnt5a concentrations; these effects could lead to divergent responses with regard to prostate cancer progression (Hruba et al., 2011). AHR overexpression and activation reduced induction of the expression of vascular endothelial growth factor in PC3 cells, raising the possibility of interference with angiogenesis by AHR ligands (Wu PY et al., 2013). Transforming growth factor (TGF)-β suppressed AHR expression via SMAD4 and possibly also interfered with AHR signaling in a non-tumorigenic, but immortalized, epithelial prostate cell line (BPH-1) (Staršíchová et al., 2012); whether this also occurs in prostate cancer cells and has a bearing on prostate carcinogenesis is not known. In utero and lactational exposure to TCDD increases aging-associated cribiform hyperplasia in the murine prostate, which may be a pre-cancerous lesion (Fritz et al., 2005). In a follow-up, progeny of a genetic cross between AHR-null mice and the transgenic adenocarcinoma of the mouse-prostate (TRAMP) strain that models prostate cancer showed that the presence of the AHR inhibited the formation of prostate tumors that have a neuroendocrine phenotype (Fritz et al., 2008). As with breast cancer, these studies suggest that the timing of an exposure may be critical, with early-life exposures increasing prostate cancer susceptibility and adult AHR activation reducing it. Because male Vietnam veterans were exposed to herbicides after adolescence, toxicologic findings concerning early-life exposure are not particularly relevant to this population, although their exposure to herbicides could potentially influence risk of the prostate cancer later in life.

Taken together, there is some in vivo and in vitro laboratory evidence in support of a role of the AHR in prostate cancer and suggesting that dioxin exposure could affect processes involved in prostate carcinogenesis or prostate cancer growth and progression. However, there is no substantial understanding of the importance of these mechanisms and how they could affect prostate cancer risk. The general biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

This update describes several newly published studies involving prostate cancer in Vietnam veterans in the Korea, New Zealand, and United States; however, the results of these studies were inconsistent. The study of US veterans, all of

whom had been referred to the Portland VA Medical Center for prostate biopsies, reported a statistically significant positive association between herbicide exposure and the overall risk of prostate cancer and a two-fold increased risk for high-grade (Gleason score 8–10) prostate cancer. Although the study took into consideration the issues of screening and potential for referral/filter bias, the definition of herbicide exposure based on the VA database might have introduced potential exposure misclassification because VA does not have accurate information on Vietnam veterans who were exposed to herbicides. On the other hand, the two international studies of Vietnam veterans in New Zealand and Korea reported no association or else an inverse association between herbicide exposure and prostate cancer. The study of Vietnam veterans in New Zealand reported a modest, non-significant excess risk of prostate cancer incidence, but no excess prostate cancer–specific mortality relative to the general population. However, the number of prostate cancer cases in this cohort was small and the fact of deployment served as a proxy for herbicide exposure. The Korean study, which was very large, examined the risk of prostate cancer incidence and mortality with exposure estimates based on an EOI score developed by Stellman et al. (2003b). Internal comparison analyses found a marginally significant 30 percent reduction in the risk of prostate cancer, comparing groups with high and low EOI scores, as well as a 32 percent reduction in the risk of prostate cancer–specific mortality. Because the Stellman exposure opportunity model has not been validated or used in other epidemiologic studies, it is difficult to determine the reliability of this exposure metric.

Despite the above conflicting evidence from the new Vietnam veterans studies, the increased risks of prostate cancer reported from the earlier studies among US Air Force Ranch Hand troops and Australian Vietnam veterans, along with the positive associations reported from several occupational studies and the case-control study of specific agricultural exposures in British Columbia (Band et al., 2011) support the notion of an association between exposure to the herbicides used in Vietnam and prostate cancer.

The existing body of epidemiologic evidence supporting an association between exposure to the COIs and prostate cancer is robust enough and biologically plausible enough that this committee finds no justification for reversing the conclusion of prior VAO committees that there is limited or suggestive evidence of an association.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there remains limited or suggestive evidence of an association between exposure to at least one of the COIs and prostate cancer.

TESTICULAR CANCER

ACS estimated that 8,430 men would receive diagnoses of testicular cancer (ICD-9 186.0–186.9) in the United States in 2014 and that 380 men would die from it (Siegel et al., 2015). Other cancers of the male reproductive system that are infrequently reported separately are cancers of the penis and other male genital organs (ICD-9 187). The average annual incidence of testicular cancer is shown in Table 8-28.

Testicular cancer occurs most often in men between the ages of 25–29. On a lifetime basis, the risk in white men is about five times higher than in black men (Stevenson and Lowrance, 2015). Known risk factors for testicular cancer include cryptorchidism (undescended testes) and having a previous occurrence of testicular cancer. Several other hereditary, medical, and environmental risk factors have been suggested, but the results of research are inconsistent (Mikuz, 2015; Stevenson and Lowrance, 2015).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and testicular cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion.

Table 8-29 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran, Environmental, and Case-Control Studies

There have been no studies of US Vietnam veterans evaluating exposure to the COIs and testicular cancer since *Update 2012*. Furthermore, the study of Vietnam veterans from New Zealand (McBride et al., 2013) did not report results on testicular cancer.

TABLE 8-28 Average Annual Incidence (per 100,000) of Testicular Cancer in the United States[a]

60–64 Years Old			65–69 Years Old			70–74 Years Old		
All Races	White	Black	All Races	White	Black	All Races	White	Black
2.0	2.4	0.5	1.3	1.3	0.7	1.1	1.2	0.4

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

TABLE 8-29 Selected Epidemiologic Studies—Testicular Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)	2	—	
Through 1991	2	4.0 (0.5–14.5)	Dalager and Kang, 1997
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	114	1.1 (nr)	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	28	1.0 (nr)	
1965–1984			Watanabe et al., 1991
Army, deployed (n = 24,145) vs non-deployed (n = 27,917)	109	1.2 (ns)	
Served in I Corps (n = 6,668)	12	2.6 (1.1–6.2)	Bullman et al., 1990
Marine Corps, deployed (n = 5,501) vs non-deployed (n = 4,505)	28	0.8 (ns)	Watanabe et al., 1991
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	90	1.1 (0.8–1.5)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	26	1.3 (0.5–3.6)	
State Studies of US Vietnam Veterans			
District of Columbia patients (18–42 yrs of age) in 3 hospitals, diagnosed with testicular cancer (1976–June 30, 1981)	31	2.3 (1.0–5.5)	Tarone et al., 1991
Massachusetts Vietnam-era veterans			
Veterans aged 35–65 years in 1993—cases diagnosed 1988–1993 vs gastrointestinal cancers	30	1.2 (0.4–3.3)	Clapp, 1997

TABLE 8-29 Testicular Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	9	1.0 (0.5–1.9)	Anderson et al., 1986a,b
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	54	0.9 (0.6–1.1)	ADVA, 2005b
Navy	17	1.2 (0.7–1.8)	
Army	34	0.8 (0.5–1.0)	
Air Force	3	0.8 (0.2–2.3)	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	59	110 (89–139)	
Men	151	110 (89–131)	
Mortality			
All branches, return–2001	14	0.9 (0.4–1.4)	ADVA, 2005a
Navy	3	0.8 (0.2–2.4)	
Army	10	0.9 (0.4–1.7)	
Air Force	0	0.0 (0.0–3.3)	
1980–1994	4	ns	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	17	0.7 (0.4–1.2)	ADVA, 2005c
Mortality			
1966–2001	4	0.8 (0.2–2.0)	ADVA, 2005c
1982–1994	1	1.3 (nr)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)			Yi and Ohrr, 2014
Penis (C60) categorized high (n = 0) vs low (n = 1)		0.0 (NR)	

continued

TABLE 8-29 Testicular Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Testes (C62) categorized high (n = 2) vs low (n = 3)		0.5 (0.1–3.3)	
Other male genital organs (C63) categorized high (n = 1) vs low (n = 2)		1.0 (0.1–15.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	68	1.1 (0.9–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	43	1.1 (0.8–1.5)	
7,553 not exposed to highly chlorinated PCDDs	25	1.1 (0.3–1.6)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	7	2.3 (0.9–4.6)	Saracci et al., 1991
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	4	2.2 (0.6–5.7)	Coggon et al., 1986
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	0	0.0 (0.0–15.6)	
Never-exposed workers			
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003; testes and other male genital (n = 1,615)	1	1.6 (0.0–8.9)	Collins et al., 2009b
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1994 (n = 1,517)	1	2.2 (0.0–12.5)	Burns et al., 2001
Through 1982 (n = 878)	1	4.6 (0.0–25.7)	Bond et al., 1988

TABLE 8-29 Testicular Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP); testes and other male genital	0	0.0 (0.0–12.5)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)	0	nr	Ramlow et al., 1996
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	2	1.1 (0.1–4.1)	
Ever	5	3.6 (1.2–8.4)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	18	1.0 (0.6–1.4)	Hertzman et al., 1997
Mortality 1950–1989 (male genital cancers)	116	1.0 (0.8–1.1)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	74	0.9 (nr)	
Employee	23	0.6 ($p < 0.05$)	
ICELANDIC men (1,860), women (859) exposed to agricultural pesticides, primarily 2,4-D—incidence	2	**2,4-D** 1.2 (0.1–4.3)	Zhong and Rafnsson, 1996
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 339 incident testicular cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	6	1.0 (0.4–2.6)	

continued

TABLE 8-29 Testicular Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Incident testicular cancer cases 1961–1973 with agriculture as economic activity in 1960 census	101	*99% CI* 1.0 (0.7–1.2)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	32	0.8 (0.6–1.2)	
Nonwhites (n = 11,446)	6	1.3 (0.5–2.9)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/ farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	32	1.0 (0.7–1.4)	
Commercial applicators	6	1.2 (0.5–2.6)	
Spouses	0	nr	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	23	1.1 (0.7–1.6)	
Spouses of private applicators (> 99% women)	nr	0.0 (0.0–50.2)	
Commercial applicators	4	1.2 (0.3–3.2)	
Mortality			
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	0	nr	
Spouses of private applicators (> 99% women)	0	nr	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Mortality 1975–1993	23	2.5 (1.6–3.7)	Fleming et al., 1999b
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	

TABLE 8-29 Testicular Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	0		Pesatori
Zone B	2	0.8 (0.2–3.3)	et al., 2009
Zone R	22	1.4 (0.9–2.3)	
10-yr follow-up to 1991—men			Bertazzi
Zone B	1	1.0 (0.1–7.5)	et al., 1993
Zone R	9	1.4 (0.7–3.0)	
Mortality			
20-yr follow-up to 1996			Bertazzi
Zones A, B—men	17	1.0 (0.6–1.7)	et al., 2001
15-yr follow-up to 1991—men			Bertazzi
Zone B	10	1.0 (0.5–1.8)	et al., 1998
Zone R	73	1.0 (0.8–1.3)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Swedish Cancer Registry (1989–1992)—testicular cancer patients (20–75 yrs old) (n = 148)		**Herbicides**	Hardell et al., 1998
Exposed to herbicides	4	0.3 (0.1–1.0)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MOS, military occupation specialty; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not statistically significant; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

In a follow-up through 2003, the Korean Veterans Health Study identified only five incident cases of testicular cancers of which two cancers occurred among veterans with high exposure. Overall, no difference in the incidence of testicular cancer was seen in this cohort in comparison with the Korean general population (SIR = 1.05, 95% CI 0.42–2.63) (Yi, 2013). In the internal comparison analysis of high- versus low-exposure opportunity scores, Yi and Ohrr (2014) reported no association for testicular cancer (RR = 0.51, 95% CI 0.08–3.27);

however, this analysis was underpowered because it was based on only two cases in the higher herbicide category. Yi et al. (2014b) did not report results for testicular cancer mortality in the Korean Veterans Health Study.

Occupational, Environmental, and Case-Control Studies

No occupational, environmental, or case-control studies of exposure to the COIs and testicular cancer have been published since *Update 2012*.

Biologic Plausibility

No animal studies of the incidence of testicular cancer after exposure to any of the COIs have been published since *Update 2012*. That is undoubtedly due to the lack of a valid animal model of testicular cancer. SNPs of uncertain functional significance in the human AHR gene (11 SNPs) and the AHR repressor (AHRR) gene (18 SNPs) were studied in a case-control study of 278 Swedish men and 89 Danish men with testicular germ cell cancers (mean age 31 years) and 214 Swedish men without testicular cancer (mean age 18 years) (Brokken et al., 2013). There was no association between risk of testicular germ cell cancer and any of the SNPs analyzed, but four SNPs in the AHRR gene were significant associated with risk of metastatic cancer compared to localized cancer. The general biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The evidence from epidemiologic studies is inadequate to link herbicide exposure and testicular cancer. The relative rarity of this cancer makes it difficult to develop risk estimates with any precision. Most cases occur in men 25–35 years old, and men who have received such a diagnosis could have been excluded from military service; this could explain the slight reduction in risk observed in some veteran studies.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and testicular cancer.

BLADDER CANCER

Urinary bladder cancer (ICD-9 188) is the most common urinary tract cancer. Cancers of the urethra, and paraurethral glands and other or unspecified urinary

cancers (ICD-9 189.3–189.9) are infrequently reported separately; any findings on these cancers would be reported in this section. ACS estimated that 56,320 men and 17,680 women would receive a diagnosis of bladder cancer in the United States in 2015 and that 11,510 men and 4,490 women would die from it (Siegel et al., 2015). In males, in whom this cancer is about twice as common as it is in females, those numbers represent about 7 percent of new cancer diagnoses and 3 percent of cancer deaths. Overall, bladder cancer is fourth in incidence in men in the United States.

Bladder cancer risk rises rapidly with age. In men in the age groups that characterize most Vietnam veterans, bladder cancer incidence is about twice as high in whites as in blacks. The average annual incidence of urinary bladder cancer is shown in Table 8-30. The most important known risk factor for bladder cancer is tobacco smoke inhalation, which accounts for about one-half of the bladder cancers in men and one-third of them in women (Cumberbatch et al., 2015; Ferris et al., 2013a). Occupational exposure to hair dyes, aromatic amines (also called arylamines), polycyclic aromatic hydrocarbons, and some other organic chemicals used in the aluminum, rubber, leather, textile, paint-products, and printing industries is associated with higher incidence (Ferris et al., 2013a,b). In some parts of Africa and Asia, infection with the parasite *Schistosoma haematobium* contributes to the high incidence (Ferris et al., 2013a).

Exposure to inorganic arsenic is also a risk factor for bladder cancer. Although cacodylic acid is a metabolite of inorganic arsenic, as discussed in Chapter 4, the data are insufficient to conclude that studies of inorganic-arsenic exposure are directly relevant to exposure to cacodylic acid, so the literature on inorganic arsenic is not considered in this section. Cacodylic acid constituted about 30 percent of the approximately 4 million liters of Agent Blue mixtures sprayed in Vietnam (see Table 3-1), as compared with approximately 44 million liters of 100 percent phenoxy herbicide mixtures with various degrees of TCDD contamination. Moreover, other than studies of exposure in Vietnam, there have been no occupational or environmental epidemiologic studies investigating bladder cancer incidence or mortality involving direct exposure to cacodylic acid.

TABLE 8-30 Average Annual Incidence (per 100,000) of Bladder Cancer in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	70.5	77.0	47.0	123.1	134.9	75.2	182.9	200.7	112.4
Women	19.5	21.7	12.8	31.1	33.5	24.7	43.1	47.7	31.9

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2013- (NCI, 2015).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the COIs and urinary bladder cancer. The conclusion of no increased risk of bladder cancer was based largely on the null results (SMR = 0.8, 95% CI 0.4–1.4) from the overarching IARC cohort study of phenoxy herbicide production workers and sprayers (Saracci et al., 1991) and consistently inconclusive results from studies of additional occupationally exposed cohorts, environmentally exposed populations, and two small studies of Vietnam veterans. An almost statistically significant finding on bladder cancer mortality (SMR = 1.4, 95% CI 0.9–2.1) in the IARC cohort, augmented with 12 additional cohorts and updated through 1992 (Kogevinas et al., 1997) led the committee responsible for *Update 1998* to move bladder cancer to the default category of inadequate or insufficient information to determine whether there is an association. The committees responsible for subsequent updates did not change that conclusion.

Table 8-31 summarizes the results of the relevant studies; entries from primary epidemiologic publications new to this update are shaded.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

There have been no US Vietnam-veteran studies addressing bladder cancer since *Update 2012*, and neither bladder cancer incidence nor mortality was reported for the cohort of male veterans from New Zealand (McBride et al., 2013).

The prospective cohort of Korean veterans included 185,265 male veterans who had served in Vietnam from 1964 until 1973, were alive in 1992, and were followed for cancer incidence from 1992 through 2003 (Yi, 2013; Yi and Ohrr, 2014) and for mortality through 2005 (Yi et al., 2014b). A total of 264 incident cases and 61 deaths from bladder cancer were identified in this cohort during follow-up. The internal comparison analysis of the groups with high- versus low-exposure opportunity scores (Yi and Ohrr, 2014) revealed no difference in the risk of bladder cancer diagnosis (RR = 0.99, 95% CI 0.77–1.28), based on a large number of cases (122 in the low-exposure category and 133 in the high-exposure category). By contrast, Yi et al. (2014b) reported a statistically significant two-fold increase in bladder cancer–specific mortality (RR = 2.04, 95% CI 1.17–3.55) comparing the high- and low-exposure groups without adjustment for smoking; these results were based on 42 deaths from bladder cancer in the high category.

TABLE 8-31 Selected Epidemiologic Studies—Urinary Bladder Cancer (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	14	1.1 (0.6–1.7)	
With tours between 1966–1970	14	1.3 (0.7–2.1)	
SEA comparison veterans (n = 1,776)	8	0.4 (0.2–0.8)	
With tours between 1966–1970	4	0.3 (0.1–0.7)	
Mortality			
Through 1999—White subjects vs national rates			
Ranch Hand veterans	1	0.9 (nr)	
SEA comparison veterans	1	0.6 (nr)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	1	nr	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	9	0.6 (0.3–1.2)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	4	2.4 (0.1–66.4)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans served 1958–1973—cases diagnosed 1988–1993 (served in Vietnam) (updates Clapp et al., 1991)	80	0.6 (0.2–1.3)	Clapp, 1997
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (includes lymphosarcoma, reticulosarcoma)	1	nr	Anderson et al., 1986a,b

continued

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	164	1.0 (0.9–1.2)	ADVA, 2005b
Navy	34	1.0 (0.7–1.4)	
Army	104	1.0 (0.8–1.2)	
Air Force	26	1.3 (0.8–1.8)	
Mortality			
All branches, return–2001	22	0.7 (0.4–1.0)	ADVA, 2005a
Navy	4	0.6 (0.2–1.6)	
Army	13	0.7 (0.3–1.1)	
Air Force	5	1.1 (0.4–2.5)	
1980–1994	11	1.1 (0.6–1.9)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence—1982–2000	19	0.7 (0.4–1.1)	ADVA, 2005c
Mortality			
1966–2001	1	0.3 (0.0–1.7)	
1982–1994	1	0.6 (nr)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—bladder cancer (C67) categorized high (n = 133) vs low (n = 122)		1.0 (0.8–1.3)	Yi and Ohrr, 2014
Mortality (1992–2005)—bladder cancer (C67) categorized high (n = 85,809) vs low (n = 42)		2.0 (1.2–3.6)	Yi et al., 2014b
HR per unit of log EOI score (n = 19)	61	1.1 (1.0–1.3)	

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxins, phenoxy herbicides**	
Mortality 1939–1992	34	1.0 (0.7–1.5)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	24	1.4 (0.9–2.1)	
7,553 not exposed to highly chlorinated PCDDs	10	0.7 (0.3–1.2)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	13	0.8 (0.4–1.4)	Saracci et al., 1991
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	8	0.9 (0.4–1.7)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982 (men only)	11	0.8 (nr)	Lynge, 1985
Mortality 1955–2006	15	1.1 (0.8–1.4)	Boers et al., 2012
TCDD plasma level (HRs, by tertile)			
Background (≤ 0.4)	4	nr	
Low (0.4–4.1)	10	2.4 (0.8–8.3)	
Medium (4.1–20.1)	7	4.0 (1.1–14.3)	
High (≥ 20.1)	2	3.1 (0.6–17.0)	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	11	1.0 (0.7–1.5)	Boers et al., 2012
Mortality 1955–2006	9 vs 2	2.3 (0.5–10.3)	Boers et al., 2010
Mortality 1955–1991	4	3.7 (1.0–9.5)	Hooiveld et al., 1998
Accidentally exposed subcohort	1	2.8 (0.1–15.5)	
Mortality 1955–1985	1	1.5 (0.0–8.8)	Bueno de Mesquita et al., 1993

continued

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	2 vs 2	1.1 (0.2–7.2)	Boers et al., 2010
Mortality 1965–1986	0	0.0 (0.0–20.5)	Bueno de Mesquita et al., 1993
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992			Ott and Zober, 1996a
TCDD < 0.1 μg/kg of body weight	1	0.7 (0.0–4.0)	
TCDD 0.1–0.99 μg/kg of body weight	3	3.0 (0.6–8.9)	
TCDD > 1.0 μg/kg of body weight	1	0.8 (0.0–4.4)	
Mortality			
1960–1992			
TCDD < 0.1 μg/kg of body weight	0	0.0 (0.0–5.7)	
TCDD 0.1–0.99 μg/kg of body weight	2	4.1 (0.5–14.7)	
TCDD > 1.0 μg/kg of body weight	0	0.0 (0.0–5.4)	
Through 1987		*90% CI*	Zober et al., 1990
	0	nr (0.0–15.0)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007	13	1.8 (1.0–3.1)	Manuwald et al., 2012
Men	11	1.8 (0.9–3.3)	
Women	2	1.8 (0.2–6.6)	

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride
Ever-exposed workers	0	0.0 (0.0–2.9)	et al., 2009a
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	0	nr	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	16	2.0 (1.1–3.2)	Steenland
Chloracne subcohort (n = 608)	6	3.0 (1.4–8.5)	et al., 1999
Through 1987 (bladder, other)	9	1.6 (0.7–3.0)	Fingerhut
≥ 1-yr exposure, ≥ 20-yr latency	4	1.9 (0.5–4.8)	et al., 1991
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	16	6.8 (3.9–11.1)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	6	1.2 (0.5–2.7)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	0.7 (0.1–2.0)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (bladder and other urinary organs, ICD-9 188, 189.3, 189.9)	8	1.1 (0.5–2.1)	
PCP and TCP (n = 720)	1	0.4 (0.0–2.3)	
PCP (no TCP) (n = 1,402)	7	1.4 (0.6–2.9)	

continued

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	19	1.2 (0.7–1.9)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	1	0.5 (0.1–2.8)	Burns et al., 2001
Through 1982 (n = 878)	0	nr (0.0–7.2)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	2	0.7 (0.1–2.7)	Collins et al., 2009c
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	50	1.0 (0.7–1.3)	
Ever	43	1.1 (0.8–1.5)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 yr, mortality through July 1985	4	1.2 (0.3–3.2)	Henneberger et al., 1989
Pulp and Paper cohorts independent of IARC cohort			
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977	8	*90% CI* 1.2 (0.6–2.6)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	33	0.9 (0.7–1.2)	Hertzman et al., 1997
Mortality 1950–1989	94	1.0 (0.8–1.2)	

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Herbicide sprayers routinely exposed to herbicides for 6 mos or more (1950–1982)		**Phenoxy herbicides**	Green, 1991
Diseases of genitourinary system	1	1.0 (0.0–5.6)	
DENMARK			
Danish gardeners (n = 3,124) exposed to pesticides	59	0.8 (0.6–1.1)	Kenborg et al., 2012
Danish farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	300	0.6 ($p < 0.05$)	
Employee	70	0.7 ($p < 0.05$)	
Women			
Self-employed	1	0.2 (nr)	
Employee	2	0.6 (nr)	
Family worker	25	0.6 ($p < 0.05$)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (urinary system, ICD-7 180–181)			Hansen et al., 2007
25-yr follow-up (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	25	1.1 (0.7–1.6)	
Born 1915–1934 (medium exposure)	23	0.5 (0.4–0.8)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.1)	
10-yr follow-up (1975–1984) of male gardeners (lymphohematopoietic, ICD-7 200–2005)	18	0.9 (0.7–1.8)	Hansen et al., 1992
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	2	0.7 (0.1–2.4)	Swaen et al., 2004
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
No latency	12	1.6 (0.8–2.8)	
10-yr latency	11	1.7 (0.8–3.0)	
Mortality			
No latency	1	0.5 (0.0–2.6)	
10-yr latency	1	0.5 (0.0–3.0)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	31	0.5 (0.4–0.8)	Torchio et al., 1994

continued

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Italian rice growers with documented phenoxy use (n = 1,487)	12	**Phenoxy herbicides** 1.0 (0.5–1.8)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident stomach cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)	4	**Herbicides** 0.7 (0.3–1.8)	
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	191	0.6 (0.5–0.7)	
Commercial applicators	16	0.2 (0.7–1.9)	
Spouses	29	0.6 (0.4–0.9)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	43	1.0	
1– < 20	6	0.5 (0.2–1.3)	
20– < 56	9	0.7 (0.3–1.4)	
56– < 116	6	0.6 (0.3–1.5)	
≥ 116	8	0.8 (0.4–1.9)	
		p-trend = 0.66	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	184	0.7 (0.6–0.8)	
Spouses of private applicators (> 99% women)	17	0.7 (0.4–1.1)	
Commercial applicators	13	1.1 (0.6–1.8)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	35	0.6 (0.4–0.8)	
Spouses (n = 676)	9	0.8 (0.4–1.6)	

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Enrollment through 2000, vs state rates			Blair et al.,
Private applicators (men and women)	7	0.4 (0.1–0.7)	2005a
Spouses of private applicators (> 99% women)	2	0.8 (0.1–2.7)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents	8	0.7 (0.4–1.4)	Alavanja et al., 1988
Forest conservationists		p-trend < over years worked	Alavanja et al., 1989
	8	0.8 (0.3–1.6)	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose-response by length of licensure)		Expected exposed cases	
	3	1.6 (nr)	
White Male Residents of Iowa—NHL cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR	274	0.9 (nr)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	3	1.4 (0.5–4.5)	Pesatori
Zone B	17	1.3 (0.8–2.2)	et al., 2009
Zone R	84	0.9 (0.8–1.2)	
10-yr follow-up to 1991—men			Pesatori
Zone A, B	10	1.6 (0.9–3.1)	et al., 1992
Zone R	39	1.0 (0.7–1.4)	
10-yr follow-up to 1991—women			
Zone A, B	1	0.9 (0.1–6.8)	
Zone R	4	0.6 (0.2–1.5)	

continued

TABLE 8-31 Urinary Bladder Cancer, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	1	1.0 (0.2–7.4)	et al., 2008
Zone B	6	0.9 (0.4–2.0)	
Zone R	42	0.9 (0.6–1.2)	
20-yr follow-up to 1996			Bertazzi
Zones A and B—men	6	1.2 (0.5–2.7)	et al., 2001
15-yr follow-up to 1991—men			Bertazzi
Zone B	1	2.4 (0.3–16.8)	et al., 1998
Zone R	21	0.9 (0.6–1.5)	
15-yr follow-up to 1991—women			Bertazzi
Zone B	3	0.9 (0.3–3.0)	et al., 1998
Zone R	4	0.6 (0.2–1.8)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Mortality—1995–1998 (SMR vs regional rates)			
Men	31	2.6 (1.7–3.6)	
Women	17	0.8 (0.5–1.3)	
Other International Environmental Studies			
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)—incidence	14	**Chlorophenol** 1.0 (0.6–1.9)	Lampi et al., 1992
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	10	0.7 (0.4–1.3)	
West coast	55	0.9 (0.7–1.1)	
Mortality			
East coast	5	1.3 (0.4–3.1)	
West coast	20	1.0 (0..6–1.6)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CC, case-control; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCP, pentachlorophenol; PMR, proportional mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Occupational and Environmental Studies

No occupational or environmental studies of exposure to the COIs and bladder cancer have been published since *Update 2012*.

Case-Control Studies

Matic et al. (2014) conducted a hospital-based case-control study of bladder cancer in Serbia. A total of 143 cases and 114 matched controls were recruited in this study, and information on pesticide use was collected via self-reports. An increased risk of bladder cancer (OR = 3.5, 95% CI 0.9–12.9) was found to be associated with self-reported use of pesticides; however, the results were based on 15 exposed cases. Limitations include the potential for selection bias and recall bias because information on pesticide exposure was collected after bladder cancer diagnosis. In addition, exposure characterization was not specific to the COIs, so its results are not fully relevant to committee's task.

Biologic Plausibility

Cacodylic acid (DMA^{III} and DMA^{V}) is carcinogenic and has been shown to induce urinary bladder cancer in F344 rats (Arnold et al., 2006; Cohen et al., 2007b; Wang A et al., 2009; Wei et al., 2002; Yamamoto et al., 1995).

No studies have reported an increased incidence of urinary bladder cancer in TCDD- or 2,4-D-treated animals. Working with tissues from urothelial cancer patients, Ishida et al. (2010) found that activation of the AHR pathway by TCDD enhanced bladder cancer cell invasion by upregulated expression of matrix metalloproteinases 1 and 9 and that reduced expression of AHR resulted in the inhibition of invasive behavior of urothelial cancer cells. They also found that the level of nuclear AHR expression in human upper urinary tract urothelial cancers was positively associated with cancer grade and stage and that it predicted poor prognosis. In contrast, transgenic mice that have deletion of the AHR exhibit immune-cell infiltration in bladder submucosa and loss of e-cadherin in some epithelial cells in aged mice (Butler et al., 2012); although direct studies with TCDD were not undertaken, these findings suggest a protective effect of AHR signaling in bladder cancer.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Many of the available analyses of an association between exposure to the COIs and bladder cancer risk are characterized by low precision because of the small numbers of exposed cases, low exposure specificity, and a lack of ability

to control for confounding, particularly cigarette smoking, which is a major risk factor for bladder cancer. However, there are some studies with considerable numbers of bladder cancer cases.

Because of the large sample size of the Korean Vietnam Veterans Health Study and a correspondingly ample number of incident cases, the observed absence of an association between herbicide exposure and incident bladder cancer cannot be considered a meaningful finding. In contrast, there was a statistically significant two-fold increase in mortality from bladder cancer among veterans in the high-exposure-opportunity group relative to those in the low-exposure group. Because information on smoking was not available in the cancer incidence and mortality publications (Yi and Ohrr, 2014; Yi et al., 2014b), it might be hypothesized that the results for bladder cancer mortality could be explained in part by uncontrolled confounding. However, self-reported information on smoking among surviving Korean veterans (Yi et al., 2013b) revealed that the distribution of smoking habits was similar, regardless of exposure opportunity score, indicating that the results for bladder cancer mortality are unlikely to have been majorly confounded by smoking.

The evidence for bladder cancer mortality found in the Korean Vietnam Veterans Health Study is consistent with some previous mortality studies in occupationally exposed cohorts that had reasonable numbers of cases and exposure assessments. When augmented with 12 additional subcohorts and updated through 1992, the IARC cohort had an almost statistically significant finding for deaths from bladder cancer (SMR = 1.4, 95% CI 0.9–2.1) among those workers exposed to highly chlorinated PCDDs (Kogevinas et al., 1997). Subsequently, follow-up reports on mortality after 1992 in several of the IARC subcohorts found elevations in bladder cancer mortality. For the NIOSH subcohort, Steenland et al. (1999) reported significant increases in mortality through 1993 due to bladder cancer in the entire cohort (SMR = 2.0, 95% CI 1.1–3.2) and a stronger result in the subgroup with chloracne (SMR = 3.0, 95% CI 1.4–8.5). Manuwald et al. (2012) reported a marginally significant increase in bladder cancer mortality through 2007 (SMR = 1.8, 95% CI 1.0–3.1) in the Hamburg cohort, and Boers et al. (2010) also reported increased mortality through 2006 (HR = 2.3, 95% CI 0.5–10.3, n = 9 versus 2) in Plant A of the Dutch subcohort. However, updates of Plant B of the Dutch subcohort (Boers et al., 2010), the Dow PCP cohort through 2005 (Ruder and Yiin, 2011), and the Dow 2,4-D cohort through 2007 (Burns CJ et al., 2011) found minimal increases in bladder cancer mortality, and the update of mortality in the New Zealand subcohort through 2004 still found no deaths from bladder cancer (McBride et al., 2009a). In addition, Revich et al. (2001) also reported an increase in bladder cancer mortality (SMR = 2.6, 95% CI 1.7–3.6, based on 31 deaths) during 1995–1998 among male residents of Chapaevsk, Russia, in comparison with the general population, possibly because of dioxin exposure from a local chemical plant.

Mortality data for bladder cancer are considered to be of more importance than incidence data because the majority of bladder cancers are detected early or

incidentally, when they are non-invasive and therefore can be treated curatively (ACS, 2015). Investigations of bladder cancer incidence evaluated in VAO updates have not stratified cases based on tumor invasiveness, and thus any positive association there might have been with invasive tumors could have been masked.

The toxicologic information on cacodylic acid is consistent with findings of an increase in bladder cancer among Vietnam veterans exposed to herbicides, but there are no occupational or environmental epidemiologic studies investigating bladder cancer incidence or mortality in relation to cacodylic acid exposure. The evidence from mortality studies in populations occupationally exposed to TCDD or the phenoxy herbicides, however, do suggest the possibility of increased risk of death from bladder cancer. The new data on bladder cancer mortality in the Korean Vietnam veterans reviewed in this update add to the existing epidemiologic evidence suggesting a possible increased risk of bladder cancer mortality associated with herbicide exposure based on a large number of bladder cancer deaths in the high-exposure category. An increase may have become evident only recently because of the long latency of most fatal bladder cancers. Although the results of this study lack adjustment for smoking and other potential confounders, as do other occupational studies, it is unlikely that smoking prevalence differed by exposure category.

After careful consideration and discussion, the VAO committee determined that the available data and scientific literature, taken as a whole, are sufficiently consistent to conclude that there is limited or suggestive evidence for an association of bladder cancer with exposure to the COIs.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the COIs and bladder cancer.

RENAL CANCERS

Cancers of the kidney other than the renal pelvis (ICD-9 189.0) and cancer of the renal pelvis (ICD-9 189.1) are often grouped in epidemiologic studies; cancer of the ureter (ICD-9 189.2) is sometimes also included. Although diseases of these organs have different characteristics and could have different risk factors, there is some logic to grouping them: the structures are all exposed to filterable chemicals, such as polycyclic aromatic hydrocarbons, that appear in urine. ACS estimated that 38,270 men and 23,290 women would receive diagnoses of renal cancer (ICD-9 189.0, 189.1) in the United States in 2015 and that 9,070 men and 5,010 women would die from it (Siegel et al., 2015).Those figures represent 2 to 4 percent of all new cancer diagnoses and cancer deaths. The average annual incidence of renal cancers is shown in Table 8-32.

TABLE 8-32 Average Annual Incidence (per 100,000) of Kidney and Renal Pelvis Cancers in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	61.1	61.6	79.0	83.3	84.7	108.0	94.5	98.2	107.5
Women	28.7	29.4	35.7	39.6	40.3	52.7	46.8	48.0	59.2

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

Renal cancers are twice as common in men as in women. In the age groups that include most Vietnam veterans, black men have a higher incidence than white men. With the exception of Wilms tumor, which is more likely to occur in children, renal cancers are more common in people over 50 years old.

Tobacco use is a well-established risk factor for renal cancers (Qayyum et al., 2013). Obesity is also another risk factor for renal cell carcinoma, and a recently published meta-analysis of 21 cohort studies reported an elevated risk for renal cancers (RR = 1.77, 95% CI 1.68–1.87) when comparing obese to normal weight participants (Wang and Xu, 2014). Some rare syndromes—notably, von Hippel–Lindau syndrome and tuberous sclerosis—are associated with an elevated risk of renal cancer. Other potential risk factors include acetaminophen or non-aspirin non-steroidal anti-inflammatory drug use, organic solvents, or a history of kidney stones in men (Cheungpasitporn et al., 2015; Choueiri et al., 2014; Qayyum et al., 2013). Firefighters, who are routinely exposed to numerous pyrolysis products, have a significantly increased mortality risk after 20 or more years of employment (Youakim, 2006).

Conclusions from *VAO* and Previous Updates

The committee responsible for *Update 1998 VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and renal cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion.

Table 8-33 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran, Environmental, and Case-Control Studies

There have been no studies of US Vietnam veterans that addressed renal cancers since *Update 2012*. In addition, the study of male veterans from New Zealand (McBride et al., 2013) did not report on renal cancer incidence or mortality.

TABLE 8-33 Selected Epidemiologic Studies—Renal Cancers (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veteran			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	1	nr	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	55	0.9 (0.5–1.5)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	13	0.9 (0.5–1.5)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam veterans diagnosed 1972–1983	9	1.8 (1.0–3.5)	Kogan and Clapp, 1988
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed 923 White male Vietnam veterans	21	1.4 (0.9–2.2)	Visintainer et al., 1995
Wisconsin death certificate (1968–1978) vs proportions for Vietnam-era veterans (includes lymphosarcoma, reticulosarcoma)	2	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	125	1.0 (0.8–1.2)	ADVA, 2005b
Navy	34	1.3 (0.9–1.7)	
Army	77	0.9 (0.7–1.1)	
Air Force	14	1.1 (0.6–1.8)	
Mortality			
All branches, return–2001	50	1.0 (0.7–1.2)	ADVA, 2005a
Navy	12	1.1 (0.6–1.9)	
Army	33	0.9 (0.6–1.3)	
Air Force	5	0.8 (0.3–1.8)	
1980–1994	22	1.2 (0.7–1.8)	

continued

TABLE 8-33 Renal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence—1982–2000	19	0.7 (0.4–1.0)	ADVA, 2005c
Mortality			
1966–2001	4	0.4 (0.1–1.1)	
1982–1994	3	3.9 (nr)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—categorized high (n = 85,809) vs low (n = 94,442)			Yi and Ohrr, 2014
Kidney cancer (C64) categorized high (n = 79) vs low (n = 102)		0.7 (0.6–1.0)	
Renal pelvis cancer (C65) categorized high (n = 11) vs low (n = 12)		1.1 (0.4–2.5)	
Ureter cancer (C66) categorized high (n = 11) vs low (n = 8)		1.3 (0.5–3.2)	
Mortality (1992–2005)—renal cancer (C64–C66) categorized high (n = 30) vs low (n = 33)		0.9 (0.5–1.5)	Yi et al., 2014b
HR per unit of EOI scores (n = 180,639)	63	1.0 (0.9–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	29	1.1 (0.7–1.6)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	26	1.6 (1.1–2.4)	
7,553 not exposed to highly chlorinated PCDDs	3	0.3 (0.1–0.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	11	1.0 (0.5–1.7)	Saracci et al., 1991
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	5	1.0 (0.3–2.3)	Coggon et al., 1986

TABLE 8-33 Renal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982 (men only)	3	0.6 (nr)	Lynge, 1985
Mortality 1955–2006	8	1.2 (0.8–1.6)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	8	0.8 (0.5–1.5)	Boers et al., 2012
Mortality 1955–2006	8	*HR = "infinitively large"*	Boers et al., 2010
Mortality 1955–1991	4	3.7 (1.0–9.5)	Hooiveld et al., 1998
Total cohort—kidney cancer	4	4.1 (1.1–10.4)	
Total cohort—"urinary organs"	8	3.9 (0.7–7.6)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,4,5-TCP; 2,5-DCP**	
Mortality 1952–2007 (kidney and other and unspecified urinary organs)	9	2.1 (0.9–3.9)	Manuwald et al., 2012
Men	7	2.0 (0.8–4.1)	
Women	2	2.3 (0.3–8.1)	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	3	1.6 (0.3–4.6)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	3	2.3 (0.5–6.7)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	1	1.2 (0.0–6.6)	't Mannetje et al., 2005

continued

TABLE 8-33 Renal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	3	2.7 (0.6–8.0)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	13	1.6 (0.8–2.7)	Steenland et al., 1999
Through 1987 (bladder, other)	8	1.4 (0.6–2.8)	Fingerhut
≥ 1-yr exposure, ≥ 20-yr latency	2	1.1 (0.1–3.8)	et al., 1991
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	2	0.4 (0.1–1.5)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (kidney, ICD-9 189.0–189.2)	8	1.2 (0.5–2.4)	
PCP and TCP (n = 720)	4	1.8 (0.5–4.6)	
PCP (no TCP) (n = 1,402)	4	0.9 (0.3–2.3)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (kidney, renal pelvis)	5	0.8 (0.3–1.8)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	2	0.9 (0.1–3.3)	Burns et al., 2001
Through 1982 (n = 878)	0	nr (0.0–6.2)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	4	1.7 (0.5–4.4)	Collins et al., 2009c

TABLE 8-33 Renal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	41	0.9 (0.7–1.3)	
Ever	18	0.5 (0.3–0.8)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 yr, mortality through July 1985	3	1.5 (0.3–4.4)	Henneberger et al., 1989
Pulp and Paper cohorts independent of IARC cohort			
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977	6	*90% CI* 1.2 (0.5–3.0)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	141	0.6 ($p < 0.05$)	
Employee	18	0.4 ($p < 0.05$)	
Women			
Self-employed	4	0.9 (nr)	
Employee	3	1.0 (nr)	
Family Worker	30	0.8 (nr)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (urinary system, ICD-7 180–181)			Hansen et al., 2007
25-yr follow-up (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	25	1.1 (0.7–1.6)	
Born 1915–1934 (medium exposure)	23	0.5 (0.4–0.8)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.1)	
10-yr follow-up (1975–1984) of male gardeners (lymphohematopoietic, ICD-7 200–2005)	18	0.9 (0.7–1.8)	Hansen et al., 1992

continued

TABLE 8-33 Renal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	4	1.3 (0.4–3.4)	Swaen et al., 2004
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	16	0.6 (0.4–1.0)	Torchio et al., 1994
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident stomach cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)	2	**Herbicides** 0.6 (0.2–2.3)	
SWEDEN			
Incident cancer cases 1961–1973 with agriculture as economic activity in 1960 census (male, female)	775	*99% CI* 0.8 (0.7–0.9)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	522	1.1 (1.0–1.2)	
Nonwhites (n = 11,446)	30	0.8 (0.5–1.1)	
Women			
Whites (n = 2,400)	6	0.8 (0.3–1.7)	
Nonwhites (n = 2,066)	6	1.4 (0.5–3.1)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	148	0.8 (0.7–1.0)	
Commercial applicators	2	nr	
Spouses	39	0.7 (0.5–1.0)	

TABLE 8-33 Renal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Enrollment through 2007, vs state rates			Waggoner
Applicators (n = 1,641)	71	0.9 (0.7–1.1)	et al., 2011
Spouses (n = 676)	12	0.6 (0.3–1.1)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents	nr	1.7 (0.9–3.3)	Alavanja et al., 1988
Forest conservationists		p-trend < over years worked	Alavanja et al., 1989
	2.3	0.1	
Soil conservationists	2.1	0.6	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976	1	0.5 (nr)	Blair et al., 1983
White Male Residents of Iowa—NHL cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR	178	1.1 (ns)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			Pesatori
Zone B	6	0.9 (0.4–2.0)	et al., 2009
Zone R	43	0.9 (0.7–1.2)	
10-yr follow-up to 1991 (kidney, other urinary organs)			Bertazzi et al., 1993
Zone R—men	10	0.9 (0.4–1.7)	
Zone R—women	7	1.2 (0.5–2.7)	
10-yr follow-up to 1991—men			Pesatori
Zone A, B	0	nr	et al., 1992
Zone R	11	0.9 (0.5–1.7)	
10-yr follow-up to 1991—women			
Zone A, B	1	1.1 (0.2–8.1)	
Zone R	7	1.2 (0.5–2.6)	

continued

TABLE 8-33 Renal Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	0	nr	et al., 2008
Zone B	3	0.6 (0.2–2.0)	
Zone R	39	1.2 (0.8–1.6)	
20-yr follow-up to 1996			Bertazzi
Zones A and B—men	3	0.8 (0.3–2.6)	et al., 2001
Zones A and B—women	3	1.8 (0.6–5.8)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Danish Cancer Registry patients (n = 365) and 396 referents, occupational herbicide exposure		**Herbicides**	Mellemgaard et al., 1994
Men	13	1.7 (0.7–4.3)	
Women	3	5.7 (0.6–58.0)	
UK men, 18–35 yrs of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.3 (0.6–3.1)	
Chlorophenols	nr	0.9 (0.4–1.9)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; PMR, proportional mortality ratio; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

The Korean Veterans Health Study, a prospective study of a of more than 180,000 Korean male veterans, examined renal cancer incidence from 1992 through 2003 (Yi, 2013; Yi and Ohrr, 2014) and mortality through 2005 (Yi et al., 2014). Results were reported separately for kidney cancer (ICD-10 C64) and renal pelvis cancer (ICD-10 C65). During the follow-up period, 186 incident cases of kidney cancers and 23 cases of renal pelvis cancers were identified. Compared

to the general Korean population, there was no excess cancer risk for the kidney (SIR = 1.09, 95% CI 0.94–1.27) or renal pelvis (SIR = 1.24, 95% CI 0.81–1.89) in the entire cohort (Yi, 2013). From internal comparisons of high- versus low-exposure opportunity scores, Yi and Ohrr (2014) reported an inverse association for renal cancer risk (HR = 0.74, 95% CI 0.55–1.00) based on 79 cases in the high exposure category, but no association for cancer of the renal pelvis (HR = 1.05, 95% CI 0.44–2.50), based on 11 cases in the high exposure category. A non-significant increased risk of ureter cancer (ICD-10 C66) was also reported (HR = 1.26, 95% CI 0.50–3.18).

For cancer-specific mortality, Yi et al. (2014) reported results combined for kidney cancer (ICD-10 C64), renal pelvis cancer (ICD-10 C65), and ureter cancer (ICD-10 C66), giving a total of 63 deaths. A comparison of the high- and low-exposure groups revealed no excess cancer mortality for the three types of renal cancers combined (HR = 0.88, 95% CI 0.53–1.47), based on 30 deaths in the high-exposure group. Comparability of the incidence and mortality risks for renal cancers is obscured by the different groupings used for reporting the results. Moreover, information on smoking or other lifestyle habits was not available for this cohort during follow-up through 2003, and thus the modest associations could be due to confounding by smoking or obesity.

Occupational, Environmental, and Case-Control Studies

No occupational studies, environmental studies, or case-control studies of exposure to the COIs and renal cancers have been published since *Update 2010*.

Biologic Plausibility

Cacodylic acid (DMA^{III} and DMA^{V}) is carcinogenic and has been shown to induce renal cancer. In F344/DuCrj rats treated with a mixture of carcinogens for 4 weeks, subsequent exposure to DMA (not indicated whether this was DMA^{III} or ^{V}) via the drinking water for 24 weeks caused tumor promotion in the kidney, liver, urinary bladder, and thyroid gland but inhibited induction of tumors of the nasal passages (Yamamoto et al., 1995). Recent studies have also found that oral exposure of adult mice to 200 ppm DMA^{V} in addition to fetal arsenic exposure can act as a promoter of renal and hepatocellular carcinoma, markedly increasing tumor incidence beyond that produced by fetal arsenic exposure alone (Tokar et al., 2012).

No animal studies with exposure to the other COIs have reported an increased incidence of renal cancers.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The available analyses of an association between exposure to the COIs and renal cancer risk are limited by the small number of cases and a lack of exposure specificity. The Korean Vietnam veterans study reviewed in this update had a relatively large number of incident renal cases; however no association was observed for either renal cancer incidence or mortality with herbicide exposure index. One challenge was the comparability of results for renal cancer incidence and mortality because data on cancer incidence was reported separately for cancers of the kidney and renal pelvis, whereas results were combined for mortality. The renal cell carcinoma and renal pelvis cancers are histologically different, and thus herbicide exposure could potentially affect them differently. The new data reviewed in this update were not sufficient to alter the committee's conclusion that the evidence is inadequate or insufficient to determine whether there is an association between the COIs and renal cancers.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and renal cancers.

BRAIN CANCER

Nervous-system cancers (ICD-9 191–192) involve the central nervous system (CNS) and include tumors of the brain and spinal cord, the cranial nerves, and the meninges (the outer coverings of the brain and spinal cord). Any of the cell types in the CNS can develop into cancer. Tumors of the peripheral nervous system and autonomic nervous system are considered soft-tissue tumors (ICD-9 171). Most cancers that are found in the CNS are not primary tumors arising from nervous system tissues, but instead originated from tissues in other parts of the body, such as the lung or breast, and metastasized to the brain or spinal cord. This section focuses on cancers that originate in the CNS.

Cancer of the eye (ICD-9 190) was considered in *Update 2006*, but the present committee decided that findings concerning cancer of the eye would be tracked with the results on brain cancer because when cancer of the eye is reported, it is often grouped with brain cancer.

The average annual incidence of primary CNS cancers is shown in Table 8-34. About 95 percent of cases originate in the brain, cranial nerves, and cranial meninges. In people over 45 years old, about 90 percent of tumors that originate in the brain are gliomas—astrocytoma, ependymoma, oligodendroglioma, or glioblastoma multiforme. Glioblastoma multiforme is the most common brain tumor and has the worst prognosis (Muth et al., 2015). Meningiomas make up 20 to 40

TABLE 8-34 Average Annual Incidence (per 100,000) of Brain and Other Nervous System Cancers in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	15.9	17.8	9.0	19.5	21.4	13.0	23.4	25.9	13.0
Women	11.1	12.6	6.4	13.3	14.9	8.2	15.1	16.8	8.6

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

percent of CNS cancers; they tend to occur in middle age and are more common in women than in men. Most meningiomas are benign and can be removed surgically.

ACS estimated that about 12,900 men and 9,950 women would receive diagnoses of brain and other nervous-system cancers in the United States in 2015 and that 8,940 men and 6,380 women would die from them (Siegel et al., 2015). Those numbers represent about 1 percent of new cancer diagnoses and 3 percent of cancer deaths. ACS estimated that 1,360 men and 1,220 women would receive diagnoses of cancers of the eye and orbit in the United States in 2015 and that 140 men and 130 women would die from them (Siegel et al., 2015).

In reviewing the descriptive epidemiology of these cancers, it is important to recognize the variation with which specific cancers are included in published reports, many of which distinguish between benign and malignant tumors. Another variation is whether cancers derived from related tissues (such as the pituitary or the eye) are included with CNS cancers. Various types of cancer are usually grouped; although this may bias results in unpredictable ways, the most likely consequence is a dilution of risk estimates toward the null.

The only well-established environmental risk factor for brain tumors is exposure to high doses of ionizing radiation (ACS, 2012b; Wrensch et al., 2002). Other environmental exposures—such as to petroleum products, electromagnetic fields, and cell-phone use—are unproved as risk factors (Gomes et al., 2011; Ostrom et al., 2015). The causes of most cancers of the brain and other portions of the nervous system are not known.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the COIs and brain cancer. The committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion.

The committee responsible for *Update 2006* changed the classification for brain cancer (formally expanding it to include cancers of the eye and orbit) to inadequate or insufficient evidence to determine whether there is an association

between exposure to the COIs and brain cancer. That committee considered one study that suggested a relationship between phenoxy acid herbicides and adult gliomas (Lee et al., 2005), studies that reported slightly but not statistically significantly higher risks of brain cancer in deployed versus non-deployed Australian Vietnam-era veterans (ADVA, 2005a,b) and in pesticide applicators in the AHS (Alavanja et al., 2005), and several studies that had essentially neutral findings (Carreon et al., 2005; Magnani et al., 1987; McLean et al., 2006; Ruder et al., 2004; Torchio et al., 1994). Overall, the studies discussed in *Update 2006* suggested that a conclusion of *no* association between exposure to the COIs and brain cancer had been too definitive.

The committee for *Update 2008* agreed, after review of two new studies, that brain cancer should remain in the inadequate or insufficient category. The relevance of the largely null findings on the association with occupational exposure to herbicides from a case-control study of gliomas and meningiomas (Samanic et al., 2008) was limited in that no specific compounds were addressed. In evaluating mortality through 2001 in the Seveso cohort, Consonni et al. (2008) found no increase in mortality from brain cancer in any of the three exposure zones with increasing exposure and no indication of a dose–response relationship.

Update 2010 considered several new studies. A study of Vietnam War–era ACC veterans found no difference in brain cancer rates between deployed and non-deployed veterans (Cypel and Kang, 2010), and studies of TCP and 2,4,5-T production workers in two settings also found no difference in brain cancer incidence (Collins et al., 2009b) or mortality (Collins et al., 2009c; McBride et al., 2009a) compared with general population rates. A 20-year follow-up of brain cancer after the Seveso exposure incident found a statistically non-significantly increased rate of brain cancer in those in the closest zone (RR = 2.43, 95% CI 0.60–9.79), but not in Zones B and R (Pesatori et al., 2009). *Update 2012* reviewed several studies relevant to the possibility of an association between the COIs and brain cancer, including cohort and case-control studies. Most of the recent studies did not identify a relationship between exposure to the COIs and the development of brain cancers. A few studies were somewhat suggestive of an association, but they had limited exposure specificity or limited precision because of small sample sizes. The committee concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and brain cancer or other nervous system cancers.

Table 8-35 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran and Environmental Studies

Since *Update 2012*, Kang et al. (2014) performed a retrospective study of three cohorts of US military women—4,734 who served in Vietnam, 2,062 who

TABLE 8-35 Selected Epidemiologic Studies—Brain Tumors (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates (brain and nervous system)			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	5	1.8 (0.7–4.1)	
With tours between 1966–1970	5	2.2 (0.8–4.8)	
SEA comparison veterans (n = 1,776)	2	0.5 (0.1–1.8)	
With tours between 1966–1970	2	0.7 (0.1–2.3)	
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	3	1.3 (0.3–3.6)	
SEA comparison veterans (n = 1,776)	1	0.3 (nr)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (7/1/1965–3/28/1973)		**All COIs**	
Mortality—brain tumors			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)	4 vs 2	1.7 (0.3–10.2)	
ACC veterans vs US men			
Vietnam cohort	4	0.9 (0.2–2.2)	
Non-Vietnam cohort	2	0.5 (0.1–2.0)	
Through 1991	2	1.9 (nr)	Dalager and Kang, 1997
894 ACC members assigned to Vietnam in 1966–1971 through 1987	2	nr	Thomas and Kang, 1990
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000 (meninges, brain, other CNS)	9	1.2 (0.4–3.2)	Boehmer et al., 2004
Post-service–1983	3	nr	Boyle et al., 1987

continued

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	116	1.0 (0.3–3.2)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	25	1.1 (0.2–7.1)	
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only 3,282)		**All COIs**	
Mortality—brain or other nervous system			
Through 2010	22	2.3 (0.9–5.7)	Kang et al., 2014
Vietnam nurses only	16	4.6 (1.3–16.8)	
Through 2004 (all female Vietnam veterans)	8	2.0 (0.7–5.9)	Cypel and Kang, 2008
Vietnam veteran nurses only	8	3.6 (0.9–14.5)	
Through 1991	4	1.4 (0.4–3.7)	Dalager et al., 1995a
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	36	1.1 (0.8–1.5)	Vistainer et al., 1995
New York —deployed vs non-deployed (brain, CNS)	4	0.5 (0.2–1.5)	Lawrence et al., 1985
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	8	0.8 (0.3–1.5)	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/ 23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000 (brain)	97	1.1 (0.9–1.2)	ADVA, 2005b
Navy	24	1.2 (0.7–1.7)	
Army	63	1.0 (0.8–1.3)	
Air Force	10	1.1 (0.6–2.1)	

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
All branches, return–2001 (brain, CNS)	99	1.0 (0.8–1.1)	ADVA, 2005a
Navy	23	1.0 (0.6–1.4)	
Army	66	0.9 (0.7–1.2)	
Air Force	9	0.9 (0.4–1.6)	
1980–1994	39	1.1 (0.7–1.4)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence (brain, CNS)			
1982–2000	23	1.4 (0.7–2.6)	ADVA, 2005c
Mortality (brain, CNS)			
1966–2001	27	1.6 (0.9–3.1)	ADVA, 2005c
1982–1994	13	1.4 (nr)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—brain cancer (C70–C72) categorized high (n = 32) vs low (n = 30)		1.0 (0.6–1.7)	Yi and Ohrr, 2014
Mortality (1992–2005)—CNS cancer (C70–C72) categorized high (n = 36) vs low (n = 37)		0.9 (0.6–1.4)	Yi et al., 2014b
HR per unit of log EOI score (n = 180,639)	73	1.0 (0.9–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	22	0.7 (0.4–1.0)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	12	0.6 (0.3–1.1)	
7,553 not exposed to highly chlorinated PCDDs	10	0.8 (0.4–1.5)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	6	0.4 (0.1–0.8)	Saracci et al., 1991

continued

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983 (brain, CNS)	11	1.2 (0.6–2.2)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982	4	0.7 (nr)	Lynge, 1985
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	0	—	Becher et al., 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortalilty 1952–1989	3	2.3 (0.5–6.8)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	4	2.0 (0.6–5.2)	
Never-exposed workers	0	0.0 (0.0–5.5)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	1	0.8 (0.0–4.6)	't Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	1	0.6 (0.0–3.4)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993 (brain, CNS)	8	0.8 (0.4–1.6)	Steenland et al., 1999
Through 1987 (brain, CNS)			Fingerhut et al., 1991
≥ 1-yr exposure, ≥ 20-yr latency	2	1.1 (0.1–3.8)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	3	0.6 (0.1–1.7)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	0.6 (0.1–1.8)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (brain, other nervous system)	6	0.9 (0.3–1.9)	
PCP and TCP (n = 720)	1	0.4 (0.0–2.4)	
PCP (no TCP) (n = 1,402)	5	1.1 (0.4–2.6)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (brain, other CNS)	3	1.1 (0.2–3.2)	Burns CJ et al., 2011

continued

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Through 1994 (n = 1,517)	3	1.1 (0.1–3.2)	Burns et al., 2001
Through 1982 (n = 878) (brain, other system tissues)	0	nr (0.0–4.1)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	1	0.4 (0.0–2.3)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow
0-yr latency	1	nr	et al., 1996
15-yr latency	1	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	44	1.0 (0.7–1.4)	
Ever	28	0.8 (0.5–1.2)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 yr, mortality through July 1985	2	1.2 (0.1–4.2)	Henneberger et al., 1989
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 yr 1945–1955, mortality through March 1977	4	0.6 (0.2–2.1)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from brain cancer June 1971–Dec 1987			
210 histologically confirmed deaths attributed to brain cancer in farmers ≥ 35 yrs of age			Morrison et al., 1992
Herbicides sprayed on ≥ 250 acres vs 0 acres	24	0.8 (0.5–1.2)	
70,000 male Saskatchewan farmers identified in 1971 census data linked to mortality records (brain)	96	1.0 (0.8–1.3)	Wigle et al., 1990

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	194	1.1 (nr)	
Employee	39	0.9 (nr)	
Women			
Self-employed	5	1.0 (nr)	
Employee	2	0.5 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	4	1.6 (0.4–4.1)	Swaen et al., 2004
Through 1987	3	3.2 (0.6–9.3)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC (eye, brain)		**Phenoxy Herbicides**	
Incidence	3	0.7 (0.1–2.0)	Asp et al., 1994
Mortality 1972–1989	3	1.2 (0.3–3.6)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)			Torchio
Brain, nervous system	15	0.5 (0.3–0.9)	et al., 1994
Eye	4	2.4 (0.7–6.1)	
Italian rice growers with documented phenoxy use (n = 1,487) (brain, CNS)		**Phenoxy herbicides**	Gambini et al., 1997
	4	0.9 (0.2–2.3)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident brain cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134) (brain, CNS)	4	1.2 (0.4–3.3)	
SWEDEN			
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)	0	—	
Foremen (n = 15)	0	—	
Lumberjacks (n = 139)	0	—	
Unexposed lumberjacks (n = 241)	1	0.9 (0.0–5.1)	

continued

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)			
Brain	447	1.2 (1.1–1.3)	
Eye	17	1.6 (0.9–2.5)	
Nonwhites (n = 11,446) (brain)	16	1.0 (0.6–1.6)	
Women			
Whites (n = 2,400) (brain)	9	1.1 (0.5–2.1)	
Nonwhites (n = 2,066) (brain)	1	0.4 (0.0–2.1)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	51	0.8 (0.6–1.0)	
Commercial applicators	5	1.2 (0.4–2.8)	
Spouses	26	0.9 (0.6–1.4)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	33	0.8 (0.6–0.8)	
Spouses of private applicators (> 99% women)	15	0.9 (0.5–1.4)	
Commercial applicators	5	1.9 (0.6–4.3)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641) (brain, other nervous system)	59	0.8 (0.6–1.0)	
Spouses (n = 676)	25	0.8 (0.5–1.2)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	19	0.7 (0.4–1.1)	
Years handled pesticides			
≤ 10 yrs	5	0.9 (ns)	
> 10 yrs	12	0.6 (ns)	
Spouses of private applicators (> 99% women)	11	1.1 (0.5–1.8)	

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of brain cancer		**Herbicides**	
Agricultural extension agents	nr	1.0 (0.4–2.4)	Alavanja et al., 1988
Forest conservationists	6	1.7 (0.6–3.7)	Alavanja et al., 1989
Soil conservationists			
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976	5	**Herbicides** 2.0 (nr)	Blair et al., 1983
White Male Residents of Iowa—brain cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR	111	1.1 (ns)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	2	2.4 (0.6–9.8)	Pesatori et al., 2009
Zone B	4	0.8 (0.3–2.1)	
Zone R	37	1.0 (0.7–1.5)	
10-yr follow-up to 1991—men			Bertazzi
Zone R	6	0.6 (0.3–1.4)	et al., 1993
10-yr follow-up to 1991—women			Bertazzi
Zone R	6	1.4 (0.6–3.4)	et al., 1993
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	0	nr	et al., 2008
Zone B	3	0.7 (0.2–2.1)	
Zone R	34	1.1 (0.8–1.6)	
20-yr follow-up to 1996			Bertazzi
Zones A, B—men	1	0.4 (0.1–3.0)	et al., 2001
Zones A, B—women	3	1.9 (0.6–6.0)	
15-yr follow-up to 1991—men			Bertazzi
Zone B	1	0.8 (0.1–5.5)	et al., 1998
Zone R	12	1.3 (0.7–2.5)	

continued

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
15-yr follow-up to 1991—women			Bertazzi
Zone B	3	3.2 (1.0–10.3)	et al., 1998
Zone R	8	1.1 (0.5–2.4)	
10-yr follow-up to 1986—men			Bertazzi
Zone A, B, R	5	1.2 (0.4–3.1)	et al., 1989a
10-yr follow-up to 1986—women			Bertazzi
Zone A, B, R	5	2.1 (0.8–5.9)	et al., 1989a
Other International Environmental Studies			
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995
Incidence			
East coast	3	0.5 (0.1–1.5)	
West coast	24	0.9 (0.6–1.4)	
Mortality			
East coast	2	0.6 (0.1–2.1)	
West coast	15	1.1 (0.6–1.7)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
NIOSH UMHS—farm pesticide exposure and glioma risk in adults (18–80 yrs of age) living in Iowa, Michigan, Minnesota, Wisconsin (glioma cases diagnosed 1995–January 1997		**Arsenicals, phenoxy herbicides, 2.4-D**	
798 glioma cases vs 1,175 population-based controls (excluding proxy, 438 vs 1,141)			Yiin et al., 2012
Herbicide use—including proxy (160 vs 265)		0.8 (0.6–1.0)	
Herbicide use—excluding proxy (90 vs 260)		0.8 (0.6–1.1)	
341 female glioma cases vs 528 population-based controls			Carreon et al., 2005
Arsenicals	13	1.0 (0.5–1.9)	
Phenoxy herbicides	25	0.9 (0.5–1.5)	
2,4-D	24	0.9 (0.5–1.6)	
457 male glioma cases vs 648 population-based controls			Ruder et al., 2004
Arsenicals	15	0.7 (0.4–1.4)	
Phenoxy herbicides	67	0.9 (0.6–1.2)	
2,4-D	nr	nr	

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US hospital-based study of 462 glioma and 195 meningioma patients vs 765 patient controls; cumulative lifetime occupational exposure to herbicides vs unexposed		**Herbicides**	Samanic et al., 2008
Gliomas			
Men	65	0.9 (0.6–1.3)	
Low quartile	20	1.0 (0.5–1.9)	
Second quartile	16	1.0 (0.5–2.1)	
Third quartile	12	0.6 (0.3–1.3)	
Fourth quartile	17	0.8 (0.4–1.6)	
		p-trend = 0.50	
Women	35	1.3 (0.8–2.0)	
Below median	23	1.5 (0.8–2.7)	
Above median	12	1.0 (0.5–2.1)	
		p-trend = 0.91	
Meningiomas (women only)	33	2.4 (1.4–4.3)	
Below median	16	2.1 (1.0–4.4)	
Above median	17	2.9 (1.3–6.2)	
		p-trend = 0.01	
Nebraska men and women diagnosed with gliomas between 1988 and 1993; association between farming and pesticide use (251 cases vs 498 controls)			Lee et al., 2005
Phenoxy herbicides—combined reports (identical with results for 2,4-D specifically)	32	1.8 (1.0–3.3)	
By self	7	0.6 (0.2–1.6)	
By proxy	25	3.3 (1.5–7.2)	
2,4,5-T—combined reports	7	1.3 (0.5–3.6)	
By self	2	0.4 (0.1–2.3)	
By proxy	5	2.7 (0.7–9.8)	
International Case-Control Studies			
Irish farmers and farm workers		**Herbicides**	Dean, 1994
Men	195	nr	
Women	72	nr	
Italian hospital-based study of 240 brain glioma patients vs 742 controls		**Herbicides**	Musicco et al., 1988
Male, female farmers	61	1.6 (1.1–2.4)	
French hospital-based study of 125 brain glioma patients vs 238 controls		**Herbicides**	Cordier et al., 1988
Woodworkers		OR = 1.6 ($p > 0.05$)	

continued

TABLE 8-35 Brain Tumors, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
UK men, 18–35 yrs of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.2 (0.7–2.1)	
Chlorophenols	nr	1.1 (0.7–1.8)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DCP, 2,4-dichlorophenol; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; ACC, Army Chemical Corps; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; CNS, central nervous system; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not statistically significant; OR, odds ratio; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; PMR, proportional mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; UMHS, Upper Midwest Health Study; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

served in countries near Vietnam, and 5,313 who served primarily in the United States—and evaluated mortality outcomes. Overall, there was no association between cohort and brain or nervous system cancers. The adjusted RR for the Vietnam cohort versus the US cohort was 2.27, with a 95% CI of 0.91–5.65. The near-Vietnam cohort versus the US cohort was 1.67, with a 95% CI of 0.57–4.89. In a sub-analysis, nurses who served in Vietnam had an almost five-fold higher risk of brain cancer death than nurses who served in the United States (adjusted RR = 4.61, 95% CI = 1.27–16.83). In that sub-analysis, nurses who served near Vietnam did not have an elevated risk (adjusted RR = 2.12, 95% CI = 0.42–10.83). The study is problematic because of the issue of multiple comparisons and the possibility of Type I statistical error (i.e., false positives).

In the Korean Veterans Health Study, the National Cancer Incidence Database and death records from the National Statistical Office were screened to determine cancer incidence in 1992–2003 (Yi and Ohrr, 2014) and mortality in 1992–2005 (Yi et al., 2014b). The herbicide exposure index was based on the proximity of the veteran's unit to herbicide-sprayed areas. For CNS cancers (C70–C72), a comparison of the low- and high-exposure groups showed no difference for either incidence (HR = 1.01, 95% CI = 0.60–1.68) or mortality (HR = 0.88, 95% CI = 0.55–1.40).

Occupational, Environmental, and Case-Control Studies

No occupational, environmental, or case-control studies of exposure to the COIs and brain cancer have been published since *Update 2012*.

Biologic Plausibility

No animal studies have reported an association between exposure to the COIs and brain cancer. The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Since *Update 2012*, two studies relevant to the possibility of an association between the COIs and brain cancer were published. One of these reported no association. The second provides somewhat suggestive evidence of an association; however, this was not in the main analysis but only in a sub-analysis. With such a large cohort and scores of comparisons, the study is prone to false positive associations, further weakening the conclusions that may be drawn from a particular positive finding.

Conclusion

On the basis of the epidemiologic evidence from new and previously reported studies of populations that had potential exposure to the COIs, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and brain cancer or other nervous system cancers.

ENDOCRINE CANCERS

Cancers of the endocrine system as grouped by the Surveillance, Epidemiology, and End Results program (see Table C-2 in Appendix C) have a disparate group of ICD codes: thyroid cancer (ICD-9 193) and other endocrine cancers (ICD-9 194).

ACS estimated that 15,220 men and 47,230 women would receive diagnoses of thyroid cancer in the United States in 2015 and that 870 men and 1,080 women would die from it, and it estimated that 1,300 men and 1,110 women would receive diagnoses of other endocrine cancers in 2015 and that 480 men and 460 women would die from them (Siegel et al., 2015). Incidence data on cancers of the endocrine system are presented in Table 8-36.

Thyroid cancer is the most prevalent endocrine cancer. Several types of tumors can develop in the thyroid, most of them benign. The thyroid contains two main

TABLE 8-36 Average Annual Incidence (per 100,000) of Endocrine System Cancers in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	17.1	18.2	9.4	19.6	20.2	14.0	20.3	21.0	18.5
Women	33.9	34.4	29.0	36.7	37.2	28.5	33.6	34.0	25.6

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

types of cells: follicular cells, which make and store thyroid hormones and make thyroglobulin, and C cells, which make the hormone calcitonin, which helps to regulate calcium metabolism. Different cancers of varied severity can develop from each kind of cell, and the classification of thyroid cancer is still evolving (Liu et al., 2006; Nikiforov, 2011). Papillary carcinoma is the most common type and usually affects women of childbearing age; the most common variant of papillary carcinoma is the follicular sub-type (also known as mixed papillary–follicular variant), which metastasizes slowly and is the least malignant type of thyroid cancer. Follicular carcinoma (or follicular adenocarcinoma), which is associated with inadequate dietary iodine intake, accounts for about 10 percent of all cases and has greater rates of recurrence and metastasis. Medullary carcinoma, cancer of parafollicular cells in the thyroid, is less common (4 percent of all cases) and tends to occur in families. Anaplastic carcinoma (also called giant-cell cancer and spindle-cell cancer) is rare but is the most aggressive form of thyroid cancer; it does not respond to radioiodine therapy and metastasizes quickly, invading such nearby structures as the trachea and causing compression and breathing difficulties.

Thyroid cancer can occur in all age groups. As radiation exposure is recognized as a risk factor for thyroid cancer, increased incidence is being observed in people who received radiation therapy directed at the neck (a common treatment in the 1950s for enlarged thymus, adenoids, and tonsils and for skin disorders) or who were exposed to iodine-125, for example, from the Chernobyl nuclear power-plant accident. If the radiation exposure occurred in childhood, then the risk of thyroid cancer is further increased. Other risk factors are a family history of thyroid cancer and chronic goiter.

Small thyroid tumors are common incidental findings, as are tumors of the pituitary and adrenal glands, which are far less common tumor types than malignant thyroid tumors and are rarely malignant. Malignant thymus tumors are exceedingly rare.

Conclusions from *VAO* and Previous Updates

The committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not consider endocrine cancers

separately and therefore reached no conclusion as to whether there was an association between exposure to the COIs and endocrine cancers. The committees responsible for *Update 2006*, *Update 2008*, *Update 2010,* and *Update 2012* did consider endocrine cancers separately and concluded that there was inadequate or insufficient evidence to determine whether there is an association between the COIs and endocrine cancers.

Table 8-37 summarizes the pertinent results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Several recent publications of Vietnam-veteran studies of exposure to the COIs and thyroid have been published since *Update 2012* regarding incidence (Yi, 2013; Yi and Ohrr, 2014) and cancer-specific mortality (Yi et al., 2014b) in the Korean Veterans Health Study. A total of 84 incident cases and 11 deaths from thyroid cancer were identified in this cohort during follow-up. When compared to the general Korean population, there was no statistically significant excess thyroid cancer risk (SIR = 1.05, 95% CI 0.84–1.31) in the entire cohort (Yi, 2013). In an internal comparison of the high- versus low-exposure groups, Yi and Ohrr (2014), did not find an association between exposure and thyroid cancer incidence (RR = 1.05, 95% CI 0.67–1.65), based on 41 cases in the high-exposure category. In contrast, Yi et al. (2014b) reported a statistically significant association between exposure and thyroid cancer–specific mortality both when analyzed in terms of log increments in the exposure opportunity scores (HR = 2.88, 95% CI 1.12–7.39) and when comparing high- versus low-exposure groups (HR = 11.31, 95% CI 1.33–96.55). However, the number of thyroid cancer deaths was low (n = 10) in the highest exposure category and very low (n = 1) in the low-exposure category, which reduces the reliability of these results from Yi et al. (2014b).

Occupational, Environmental, and Case-Control Studies

No occupational, environmental studies, or case-control studies of exposure to the COIs and thyroid or other endocrine cancers have been published since *Update 2012.*

Biologic Plausibility

The NTP conducted carcinogenesis bioassays in Osborne-Mendel rats and B6C3F1 mice that were exposed to TCDD by gavage (NTP, 1982a). The incidence of follicular-cell adenoma, but not of carcinoma, increased with increasing TCDD dose in male and female rats; the increase was significant in male but not in female rats. There was a significant increase in follicular-cell adenoma in

TABLE 8-37 Selected Epidemiologic Studies—Endocrine Cancers (Thyroid, Thymus, and Other) (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982 (thyroid and other endocrine, ICD-9 193–194)			Breslin et al., 1986, 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	15	0.6 (0.3–1.2)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	4	0.6 (0.1–3.4)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans aged 35–65 years in 1993—cases diagnosed 1988–1993 vs thyroid cancer	4	1.2 (0.3–4.5)	Clapp, 1997
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence—thyroid			
All branches, 1982–2000	17	0.6 (0.3–0.9)	ADVA, 2005b
Navy	3	0.5 (0.1–1.3)	
Army	11	0.5 (0.3–1.0)	
Air Force	3	1.2 (0.2–3.5)	
Mortality—thyroid			
All branches, return–2001	2	0.5 (0.0–1.8)	ADVA, 2005a
Navy	1	1.2 (0.0–6.5)	
Army	1	0.4 (0.0–2.0)	
Air Force	0	0.0 (0.0–7.8)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence—thyroid			
1982–2000	4	0.6 (0.1–2.2)	ADVA, 2005c
Mortality—thyroid			
1966–2001	1	1.2 (0.0–91.7)	ADVA, 2005c

TABLE 8-37 Endocrine Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—thyroid cancer (C73) categorized high (n = 41) vs low (n = 43)		1.1 (0.7–1.7)	Yi and Ohrr, 2014
Mortality (1992–2005)—thyroid cancer (C73) categorized high (n = 10) vs low (n = 1)		11.3 (1.3–96.6)	Yi et al., 2014b
HR per unit of log EOI scores (n = 180,639)	11	2.9 (1.1–7.4)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992			Kogevinas et al., 1997
Thyroid (ICD-9 193)	4	1.7 (0.5–4.3)	
13,831 exposed to highly chlorinated PCDDs	2	1.4 (0.2–4.9)	
7,553 not exposed to highly chlorinated PCDDs	2	2.2 (0.3–7.9)	
Other endocrine organs (ICD-9 194)	5	3.6 (1.2–8.4)	
13,831 exposed to highly chlorinated PCDDs	2	2.3 (0.3–8.1)	
7,553 not exposed to highly chlorinated PCDDs	3	6.4 (1.3–18.7)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983 (thyroid)	1	1.8 (0.4–9.8)	Coggon et al., 1986
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004 (thyroid, other endocrine)			McBride et al., 2009a
Ever-exposed workers	0	0.0 (0.0–19.8)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	0	nr	’t Mannetje et al., 2005

continued

TABLE 8-37 Endocrine Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1982 (n = 878)	0	nr	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–1989 (n = 770)	0	nr	Ramlow et al., 1996
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Herbicide sprayers routinely exposed to herbicides for 6 mos or more (1950–1982)	1	**Phenoxy herbicides** nr	Green, 1991
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	13	0.7 (nr)	
Employee	5	1.1 (nr)	
Women			
Self-employed	1	1.3 (nr)	
Employee	1	1.4 (nr)	
Family worker	15	1.7 ($p < 0.05$)	
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks), not IARC		**Phenoxy herbicides**	
Incidence (thyroid, other endocrine)			Asp et al., 1994
No latency	2	1.9 (0.3–7.0)	
10-yr latency	2	2.4 (0.3–8.6)	
15-yr latency	2	3.4 (0.4–12.2)	

TABLE 8-37 Endocrine Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality (thyroid)			
No latency	1	3.8 (0.1–21.3)	
10-yr latency	1	4.7 (0.1–26.4)	
15-yr latency	1	6.5 (0.2–36.2)	
ICELANDIC men (1,860), women (859) exposed to agricultural pesticides, primarily 2,4-D (other endocrine organs, ICD-9 194)—incidence	2	**2,4-D** 1.3 (0.1–4.7)	Zhong and Rafnsson, 1996
SWEDEN			
Swedish pesticide applicators—incidence	6	1.1 (0.4–2.4)	Wiklund et al., 1989a
Incident NHL cases 1961–1973 with agriculture as economic activity in 1960 census		*99% CI*	Wiklund, 1983
Thyroid	126	0.9 (0.7–1.1)	
Other endocrine gland	117	0.7 (0.5–0.9)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	39	1.3 (1.0–1.8)	
Nonwhites (n = 11,446)	1	0.6 (0.0–3.0)	
Women			
Whites (n = 2,400)	1	0.8 (0.0–4.4)	
Nonwhites (n = 2,066)	1	1.1 (0.0–6.4)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/ farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	39	1.0 (0.7–1.3)	
Commercial applicators	5	1.4 (0.5–3.3)	
Spouses	49	0.9 (0.7–1.2)	
Enrollment through 2002 (thyroid, other endocrine)			Alavanja et al., 2005
Private applicators	29	1.3 (0.8–1.8)	
Spouses of private applicators (> 99% women)	24	0.9 (0.5–1.4)	
Commercial applicators	3	1.6 (0.3–5.0)	

continued

TABLE 8-37 Endocrine Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Enrollment through 2007, vs state rates			Waggoner
Applicators (n = 1,641)	8	1.5 (0.7–3.0)	et al., 2011
Spouses (n = 676)	1	nr	
Enrollment through 2000, vs state rates (thyroid)			Blair et al., 2005a
Private applicators (men and women)	3	1.8 (0.4–5.3)	
Spouses of private applicators (> 99% women)	0	0.0 (0.0–2.2)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	1	2.6 (0.4–18.9)	Pesatori
Zone B	4	1.6 (0.6–4.4)	et al., 2009
Zone R	19	1.2 (0.7–1.9)	
Seveso population (1976–1996); incidence cases identified by hospital discharge records			
Zone A (prolactinoma)	1	6.2 (0.9–45.5)	Pesatori
Zone B (nonfunctioning pituitary tumors)	2	1.9 (0.5–7.7)	et al., 2008
Zone R (2 nonfunctioning pituitary adenomas and 3 prolactinomas)	5	0.7 (0.3–1.8)	
Mortality			
15-yr follow-up to 1991—men			Bertazzi
Zone B	1	4.9 (0.6–39.0)	et al.,
Zone R	0	nr	1997, 1998
15-yr follow-up to 1991—women			Bertazzi
Zone B	1	3.2 (0.4–24.5)	et al.,
Zone R	2	0.8 (0.2–3.6)	1997, 1998
CASE-CONTROL STUDIES			
International Case-Control Studies			
Sweden—male, female thyroid cancers from Swedish Cancer Registry, 1980–1989		**Phenoxy herbicides, chlorophenols**	Hallquist et al., 1993

TABLE 8-37 Endocrine Cancers, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Phenoxy herbicide exposure	3	0.5 (0.0–2.0)	
Chlorophenols	4	2.8 (0.5–18.0)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

female but not in male mice. More recently, the NTP carried out a similar study in female Sprague Dawley rats (NTP, 2006), and Walker et al. (2006) compared the data from that study and the results of the Dow Chemical assessment of TCDD carcinogenicity (Kociba et al., 1978). In the NTP and Dow studies, the incidence of C-cell adenoma and carcinoma decreased with increasing dose of TCDD. However, an increased incidence of slight thyroid follicular-cell hypertrophy was noted in rats that were given TCDD at 22 ng/kg of body weight or more. A more recent 2-year NTP study (Yoshizawa et al., 2010) treated female Sprague Dawley rats with TCDD, 2,3,4,7,8-pentachlorodibenzofuran, dioxin-like PCB congeners (PCB 126 or 118), a non–dioxin-like PCB (PCB 153), or mixtures of these chemicals; it did not find any increases in either thyroid adenoma or carcinoma. Thus, although human and animal studies showed that dioxin and dioxin-like compounds alter thyroid hormones (Chapter 13 on other health effects) and increase follicular-cell hyperplasia, there is little evidence of an increase in thyroid cancer.

There are some reports of therapeutic treatment with arsenic trioxide and later development of thyroid cancer (Au et al., 2014; Firkin, 2014), raising the possibility of an association between arsenic and a risk of this malignancy. DMA treatment via the drinking water for 24 weeks caused increases in the incidence of thyroid hyperplasia and adenoma, but not adenocarcinoma, in male F344/DuCrj rats that were first exposed for 4 weeks to a mixture of five carcinogens to induce tumor initiation in a wide range of tissues (Yamamoto et al., 1995). These increases were statistically significant at DMA doses of 200 and 400 ppm, but not at 50 or 100 ppm. Animals treated with 200 and 400 ppm DMA but not

given the carcinogens did not develop thyroid lesions, which is consistent with the absence of elevated incidences of endocrine organ tumors in other bioassays with DMA (see Chapter 4).

As indicated in Chapter 4, 2,4-D and 2,4,5-T are at most weakly mutagenic or carcinogenic, and no studies that addressed a possible association between exposure to those herbicides and thyroid cancer in animal models have been identified.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The studies reviewed previously did not provide sufficient evidence to determine whether there is an association between exposure to the COIs and cancers of the endocrine organs. The results from the Korean Vietnam Veterans Study reviewed in this update did not alter this conclusion. Consequently, the present committee retained the categorization for endocrine cancers assigned by previous VAO committees.

Conclusion

On the basis of the epidemiologic evidence reviewed here, the committee concludes that there is insufficient evidence to determine whether there is an association between exposure to the COIs and thyroid or other endocrine cancers.

LYMPHOHEMATOPOIETIC CANCERS

Lymphohematopoietic cancers (LHCs) constitute a heterogeneous group of clonal hematopoietic and lymphoid-cell disorders, including leukemias, lymphomas, and multiple myeloma. They are among the most common types of cancer induced by environmental and therapeutic agents. As in the case of other cancers that are subject to evolving and complex grouping in reports of the results of epidemiologic studies (notably, head and neck cancers and gastrointestinal cancers), the conclusions that the VAO committees have drawn about associations between herbicide exposure to the COIs and specific LHCs have been complicated and curtailed by the lack of specificity and by inconsistencies in groupings in the available evidence. For LHCs, that has been a function not only of epidemiologists' seeking to combine related cancers to produce categories that have enough cases to permit statistical analysis but also of continuous alterations in the prevailing system used by the medical community to classify these malignancies. The categorization of cancers of the lymphatic and hematopoietic systems has changed over time, guided by growing information about gene expression and

the lineage of the clonal cancer cells that characterize each of a broad spectrum of neoplasms arising in these tissues (Jaffe, 2009). The World Health Organization (WHO) categorization presented in the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue* (WHO, 2008) bases its primary partition on whether the cancer cells are of myeloid or lymphoid origin (see Figure 8-1). This classification is to be updated in 2015.

Stem cells arising in the bone marrow generate two major lineages of leukocytes: myeloid and lymphoid. Myeloid cells include monocytes and three types of granulocytes (neutrophils, eosinophils, and basophils). Lymphoid cells include T and B lymphocytes and a smaller set of cells called natural killer (NK) cells. All those cells circulate in the blood and are collectively referred to as white blood cells or leukocytes. Monocytes move out of the bloodstream into inflamed tissues, where they differentiate into macrophages or dendritic cells. Stem cells that are destined to become T lymphocytes migrate from the bone marrow to the thymus, where they acquire antigen-specific receptors. Antigen stimulation induces the T cells to differentiate into the several types involved in cell-mediated immunity. Progenitor or pre-B cells mature in the bone marrow into antigen-specific B cells. On encountering their cognate antigens, B cells differentiate into antibody-secreting plasma cells involved in humoral immunity; these result in multiple myeloma when they undergo malignant transformation.

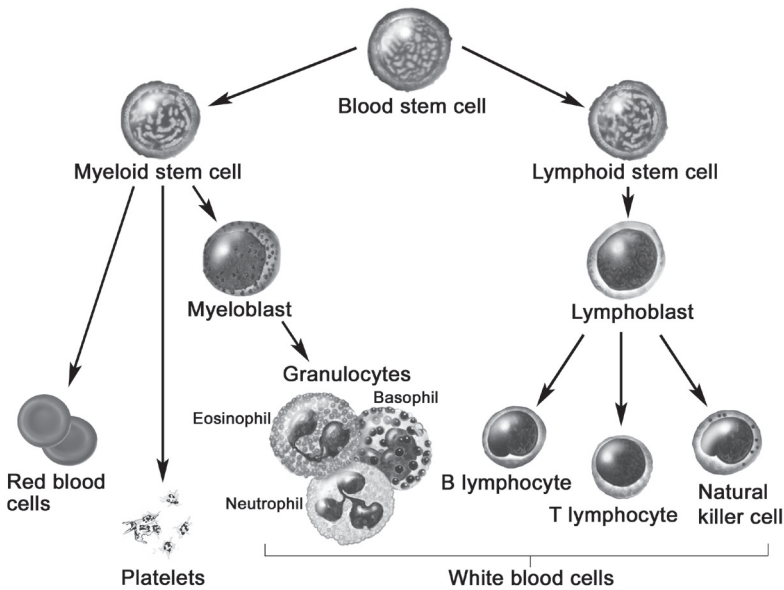


FIGURE 8-1 Hematopoiesis of stem cell differentiation.
SOURCE: © Winslow, 2007, US government has certain rights.

LHCs originate in specific pluripotent or lineage-restricted cells at different stages in hematopoiesis and immune-cell development. The normal cells are transformed into a malignant tumor through multistep processes that involve genetic and epigenetic alterations. Traditionally, LHCs have been divided into leukemias, lymphomas, myelomas, and so on, according to their cell type and site of origin (see Figure 8-1). That information and morphologic, cytochemical, and immunophenotypic data are used to characterize LHCs further by their distinct subtypes.

Leukemias occur when a cell residing in the bone marrow becomes cancerous and its daughter cells crowd normal cells in the bone marrow or are released from the bone marrow and circulate in the blood. Leukemias have generally been classified as myeloid or lymphoid, depending on the lineage of the original mutated cell. If the original mutated cell of a cancer of the blood arises in a lymphocytic cell line, then the cancer is called lymphocytic leukemia; lymphocytic leukemias have been further partitioned into acute lymphocytic leukemia (ALL) forms, which are derived from precursor B or T lymphoid cells, and indolent lymphoproliferative disorders (ILDs), which are derived from more mature lymphoid cells, which tend to replicate less rapidly. Although "chronic lymphocytic leukemia" is commonly used to refer generally to this group of ILDs, chronic lymphocytic leukemia (CLL) is actually a specific form of ILD. Similarly, myeloid leukemias arise from a myeloid cell line and are classified into acute (AML) and chronic (CML) forms.

Lymphoma is a general term for cancers that arise from lymphocytes (B, T, or NK cells). Lymphomas generally present as solid tumors at lymphoid proliferative sites, such as lymph nodes and spleen. As stem cells mature into B or T cells, they pass through several developmental stages, each with unique functions. The developmental stage at which a cell becomes malignant defines the kind of lymphoma. About 85 percent of lymphomas are of B-cell origin, and 15 percent are of NK-cell or T-cell origin, referred to as NKTCL by WHO (Jaffe et al., 2001) and Liao et al. (2012). There are two major types of B-cell lymphomas: Hodgkin lymphoma (HL), previously referred to as Hodgkin disease, and non-Hodgkin lymphoma (NHL). B cells give rise to a number of types of neoplasms, which are given names based on the stage at which B-cell development was arrested when the cells became cancerous. Follicular, large-cell, and immunoblastic lymphomas result when a malignancy develops *after* a B cell has been exposed to antigens (such as bacteria and viruses). CLL is now believed to be a tumor of antigen-experienced (memory) B cells, not naive B cells (Chiorazzi et al., 2005); small lymphocytic lymphoma (SLL), which presents primarily in lymph nodes rather than in the bone marrow and blood, is now considered to be the same disease as CLL at a different stage (Jaffe et al., 2008).

Myeloma is another type of lymphohematopoietic malignancy derived from antibody-secreting plasma cells, which also have a B-cell lineage, that accumulate in the marrow of various bones. In most cases (90 percent), tumors are formed at multiple sites, and the disease is called *multiple myeloma*. The related

premalignant condition AL amyloidosis also arises from B cell–derived plasma cells. It occurs in 5 to 15 percent of patients who have multiple myeloma and causes an abnormal deposition of antibody fragments. Monoclonal gammopathy of undetermined significance (MGUS) is also recognized as a clonal condition that may progress to multiple myeloma.

ICD partitions these malignancies into leukemias and lymphomas primarily on the basis of whether the cancer cells circulated in the blood (disseminated) or appeared in the lymphatic system (solid tissue), respectively, before subdividing according to cell type. The emerging WHO classification of lymphohematopoietic malignancies (Campo et al., 2011; Jaffe, 2009) stratifies cancers of the blood and lymph nodes into disease categories according to their cell lineages—lymphoid or myeloid—as shown in Figure 8-1. It represents a substantial advance in understanding the biologic paths by which these cancers develop. The present committee decided, however, that it would not be productive to reformulate this entire section to correspond to the WHO categories. In practice, LHCs have routinely been reported in a variety of groupings, so it is a continuing challenge to parse out results, noting when results for broader groupings are presented in the results tables for several more specific diagnoses, while recognizing that the specific results will be muted by being "misclassified" with other entities. Most epidemiologic studies already in the evidentiary database that did specify diseases precisely used ICD-9 or earlier versions, but some recent studies have applied ICD-10. Furthermore, the existing records that will serve as the basis of many current and even future studies will use earlier and evolving classifications, so this is likely to remain the case even in new literature for a considerable period. The nomenclature has become more uniform in recent studies, but the possibility of ambiguity remains if earlier researchers did not use a unique code in accordance with some established system.

Because it has been the objective of VAO committees to address disease entities in as great specificity as possible with the available data, the overall results on the coarser grouping of LHCs are of little consequence for the conclusions of association that have been drawn for the more specific entities. The committee for *Update 2010* noted, however, that the common biologic origin of LHCs that have been judged to have a substantial amount of evidence supporting association with the COIs (HL, NHL, CLL, hairy-cell leukemia [HCL], multiple myeloma, and AL amyloidosis) means that the WHO approach is supportive of and consistent with these decisions on the part of VAO committees. For this update, the committee decided to familiarize itself with the classification systems that have been used for lymphoid malignancies, taking particular care to investigate the recent efforts made by the International Lymphoma Epidemiology Consortium (InterLymph) to propose a classification of these cancers into subtypes that are particularly appropriate for epidemiologic research (Morton et al., 2007). The WHO classification system and its history were reviewed with presentations to the committee in a public forum. The committee was impressed by the implications of the now successful

efforts of the InterLymph to harmonize data, with standardized definitions of disease entities and rigorous quality control of these subtype assessments, and attempts to understand the implications of etiologic heterogeneity (Morton et al., 2014a,b). At the same time, as has been recognized by others (Saberi Hosnijeh et al., 2012c), given the type and quality of the historical data that constitute the vast majority of the material available to the committee for review and judgement, little of this impressive effort can be applied to our assessment of association.

VA asked previous VAO committees to address CLL, AML, and HCL individually. A scrutiny of the entire body of epidemiologic results on leukemias for findings on particular types (as had been the most common manner of grouping) revealed several studies that showed increased risks specifically of CLL (or ILDs more generally) but that did not provide support for an association of AML with exposure to the COIs. The committee for *Update 2002* advised VA that CLL is recognized as a form of NHL, which is already recognized as a service-related condition, whereas the committee for *Update 2006* did not recognize an association between the COIs and AML. Later, the committee responsible for *Update 2008* advised VA that HCL should be grouped as an ILD. In light of the history and in accord with the current WHO classification, the present committee has incorporated data specifically on CLL and HCL into the section on NHL. After a brief synopsis of biologic plausibility of the LHCs overall, the more common cancers of the lymphatic system are described in the sections below on HL, NHL, and multiple myeloma (with a section on the related condition, AL amyloidosis), and then evidence on leukemias in general is discussed with a focus on information regarding those of myeloid origin.

Biologic Plausibility

Recent data indicate that the AHR pathway plays an integral role in B-cell maturation and that TCDD and dioxin-like chemical (DLC) exposure may alter the function of these cells and lead to critical changes in the immune response. Suppression of the immune response by TCDD and similar chemicals in rodents and primates has been known for more than 30 years, but the effect on human cells is less clear. Some recent reports indicate that TCDD and DLCs elicit similar effects in humans. The activation of nontransformed human B cells results in an increase in the expression of the AHR, and additional data indicate that this pathway has a role in normal B-cell function (Allan and Sherr, 2010; Sherr and Monti, 2013). Furthermore, treatment of these cells with benzo[a]pyrene suppresses B-cell differentiation. H Lu et al. (2010) demonstrated that, although human B cells appeared less responsive to TCDD in terms of increasing expression of AHR battery genes, the ability of TCDD to decrease immunoglobulin M production is similar in both mouse and human B cells. More recent work modeled the mode by which TCDD suppresses the terminal differentiation of B cells, offering distinct pathways whose action can be altered by exposure (Zhang

et al., 2013). Data on human hematopoietic stem cells (HSCs) and from the use of knockout AHR mouse models show that the AHR is critical in HSC maturation and differentiation (Ahrenhoerster et al., 2014; Fracchiolla et al., 2011; Singh et al., 2011, 2014; Smith et al., 2013). TCDD not only alters HSC maturation but alters proliferation and migration in vivo and in vitro (Casado et al., 2011). Finally, emblematic of the potential pleotropic effects of TCDD, Hughes et al. (2014) recently demonstrated that the AHR plays a critical role in promoting lymphocyte differentiation into mature NK cells. Several recent reviews have highlighted the complex and varied nature of the interaction of TCDD with the immune system (Gasiewicz et al., 2014; Lindsey and Papoutsakis, 2012).

Saberi Hosnijeh et al. (2012b, 2013a) recently assessed both the immune profile and levels of soluble immune signaling proteins in TCDD-exposed workers. Consistent with data published from the ACC, in 47 highly TCDD-exposed and 38 low TCDD-exposed workers, they found no effect of TCDD on major leukocyte subsets or on white blood cell counts. They did note a non-significant decrease in most lymphocyte subsets, which was most prominent for B cells. In these same workers, a study of soluble CD27 and soluble CD30 in sera found no clear dose–response relationship of TCDD with the level of these signaling proteins. However, there was a significant negative association of serum IL1RA (interleukin 1 receptor agonist) level with TCDD serum level among workers without chronic disease. Taken together, these data indicate that exposure to TCDD (and alteration of normal AHR function) may have multiple effects on immune cell differentiation and function.

On occasion, the observed number of cases is so small that researchers cannot perform useful analyses for each type of LHC and will provide summary statistics for the entire group of them. In updating mortality in the Hamburg cohort in 1952–2007, Manuwald et al. (2012) found non-significant increases in mortality from LHC in both men (SMR = 1.53, 95% CI 0.89–2.45) and women (SMR = 1.84, 95% CI 0.74–3.80), which combined to give a significant association between TCDD and all LHC deaths in the whole cohort (SMR = 1.61, 95% CI 1.03–2.40). In a Dutch cohort of workers in two phenoxy-herbicide plants, Boers et al. (2012) assessed plasma TCDD concentrations at the time of the assumed last exposure and reported a modest but nearly significant increase in the HR for LHC in the total cohort (HR = 1.12, 95% CI 0.94–1.35) but no increase in plant A, where workers were occupationally exposed to TCDD (HR = 0.96, 95% CI 0.71–1.30).

Hodgkin Lymphoma

HL (ICD-9 201), also known as Hodgkin disease, is distinguished from NHL primarily on the basis of its neoplastic cells, mononucleated Hodgkin cells, and multinucleated Reed–Sternberg cells originating in germinal-center B cells (Küppers et al., 2002). ACS estimated that 5,100 men and 3,950 women would

receive diagnoses of HL in the United States in 2015 and that 660 men and 490 women would die from it (Siegel et al., 2015). The average annual incidence is shown in Table 8-38.

The possibility that HL has an infectious etiology has been a topic of discussion since its earliest description. A higher incidence in people who have a history of infectious mononucleosis has been observed in some studies, and a link with Epstein–Barr virus has been proposed (Balfour et al., 2015; Murray and Bell, 2015). In addition to the occupational associations discussed below, higher rates of the disease have been observed in people who have suppressed or compromised immune systems.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* determined that there were sufficient epidemiologic data to support an association between exposure to the COIs and HL. Additional studies available to the committees responsible for later updates have not changed that conclusion.

Of the 32 studies reviewed by the committee responsible for *VAO*, two well-conducted Swedish studies with good exposure characterization provide the most comprehensive information on the association between exposure to phenoxy herbicides (2,4-D and 2,4,5-T), picloram, or chlorophenols and HL. Hardell et al. (1981) considered NHL and HL together, and Hardell and Bengtsson (1983) considered HL separately; they found statistically significant associations with exposure to phenoxy acids (after excluding people who were exposed to chlorophenols) and with exposure to chlorophenols. In a study of 54 HL cases, Persson et al. (1989) found a large but not statistically significant risk associated with exposure to phenoxy acids. Several of the other case-control and occupational-cohort studies reviewed in *VAO* showed an increased risk of HL, but only a few of the results were statistically significant. As with NHL, even the largest studies of production workers who were exposed to TCDD did not indicate an increased risk. The few studies of HL in Vietnam veterans tended to show increased risks, but only one (Holmes et al., 1986) was statistically significant.

TABLE 8-38 Average Annual Incidence (per 100,000) of Hodgkin Lymphoma in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	3.1	3.3	2.9	4.1	4.3	3.5	5.0	5.4	3.4
Women	2.5	2.5	3.9	2.6	2.9	2.7	3.5	3.8	2.5

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

Update 1996 reviewed studies that showed no excess of HL in the IARC phenoxy-herbicide cohort (Kogevinas et al., 1993) or in US farmers in 23 states (Blair et al., 1993). A smaller study of Finnish herbicide appliers (Asp et al., 1994) showed a non-significant increase, whereas Persson et al. (1993) reported a significant increase in Swedish farmers who were exposed to phenoxy acid herbicides. Studies of the Seveso cohort (Bertazzi et al., 1993) and of Vietnam-era veterans in Michigan (Visintainer et al., 1995) did not provide data that strengthened the association.

In *Update 1998*, a proportionate mortality ratio analysis that compared the experience of 33,833 US Army and Marine Corps Vietnam veterans who died during 1965–1988 with that of 36,797 deceased non-Vietnam veterans found a significant increase in Marine Corps veterans, but not Army veterans, who had served in Vietnam (Watanabe and Kang, 1996). Two studies of manufacturing workers found no association between TCDD and HL (Becher et al., 1996) or between PCP and HL (Ramlow et al., 1996). An update of the large IARC phenoxy-herbicide cohort (Kogevinas et al., 1997) showed no association between phenoxy herbicides or chlorophenols and HL but did show a non-significant increase in HL in workers who were exposed to TCDD or higher chlorinated hydrocarbons. Waterhouse et al. (1996) demonstrated a significant increase in the combined incidence of lymphopoietic neoplasms in a prospective study of a Michigan farming community. A 15-year follow-up study of the Seveso cohort (Bertazzi et al., 1997) found no deaths from HL in Zone A and a non-significant increase in deaths from HL in men and women in Zone B.

The committee responsible for *Update 2000* reviewed the 15-year update of the Ranch Hand study (AFHS, 2000), but the findings on HL were non-significant. In a retrospective cohort study of Dutch production and contract workers who were exposed to phenoxy herbicides, chlorophenols, and contaminants during 1950–1976, Hooiveld et al. (1998) reported a non-significant increase in HL. Rix et al. (1998) compared mortality in a cohort of Danish paper-mill workers with that in the general Danish population and found a statistically significant increase in men but not women. In an update and expansion of cohorts involved in the NIOSH study, Steenland et al. (1999) found that the three deaths attributed to HL were consistent with the number expected. The 20-year mortality update after the Seveso accident reported no additional HL deaths in Zone A or B (Bertazzi et al., 2001).

The only new study reviewed in *Update 2002* followed mortality to 1994 in a cohort of Dow workers (Burns et al., 2001); the single death attributed to HL resulted in a slight but non-significant increase in mortality.

Update 2004 reviewed a study by Akhtar et al. (2004) that had found no excess of lymphopoietic cancers when comparing incidence and mortality between Ranch Hand veterans and veterans who had not served in Southeast Asia. Swaen et al. (2004) extended the follow-up of mortality by 13 years in a cohort of Dutch herbicide appliers; with no additional deaths observed, the earlier increase in HL remained non-significant (Swaen et al., 1992).

Update 2006 reviewed reports on the cancer experience of Australian Vietnam veterans. In comparison with the general population, the incidence of HL was significantly higher when veterans from the different armed forces were combined (ADVA, 2005a); there was a significant association between HL and service in the Army, but Navy and Air Force veterans showed non-significant increases. Mortality from HL was non-significantly increased in the Army veterans but not in all veterans combined or in the other branches (ADVA, 2005b). A comparison of deployed and non-deployed Vietnam-era Australian conscripted Army National Service veterans (ADVA, 2005c) found no association between deployment and the incidence of or mortality from HL. In a multinational IARC cohort of 60,468 pulp-and-paper-industry workers, McLean et al. (2006) found that death from HL was significantly higher in those who had ever been exposed to nonvolatile organochlorine compounds (which would include TCDD) but not in those who had never been exposed. Two reports from the US AHS (Alavanja et al., 2005; Blair et al., 2005a) found no excess risk of HL in pesticide applicators, commercial applicators, or their spouses. In the Cross Canada Study of Pesticides and Health, Pahwa et al. (2006) found no association of any exposure to phenoxy herbicides, 2,4-D, Mecoprop, or MCPA and HL.

The committee responsible for *Update 2008* reviewed a study by Cypel and Kang (2008) that compared mortality from lymphopoietic cancers in female Vietnam veterans with that of female era-veterans and the US population; deaths from lymphopoietic cancers were not higher in those who served in Vietnam. Consonni et al. (2008) reported no statistically significant increase in deaths from HL in the Seveso cohort 25 years after the accident.

The committee for *Update 2010* reviewed several occupational cohorts, a case-control study, and an update of cancer incidence in the Seveso cohort. No deaths from HL were identified in Dow PCP workers in Midland, Michigan (Collins et al., 2009c), but the TCP workers (Collins et al., 2009b) had an increased SMR of HL with a wide confidence interval. McBride et al. (2009a) examined mortality in TCP manufacturing workers in the Dow AgroSciences plant in New Plymouth, New Zealand, but a single observed HL death yielded inconclusive results. A French hospital-based case-control study of lymphoid neoplasms (Orsi et al., 2009) found a modest increase in the risk of HL after occupational exposure to herbicides in general and a greater increase after occupational exposure to phenoxy herbicides in particular, but neither was statistically significant; no association was observed with the domestic use of herbicides. In the 20-year follow-up of cancer incidence in the Seveso cohort (Pesatori et al., 2009), there were still no cases of HL in Zone A, whereas a modest non-significant increase in HL risk was found in Zone R and a less clear increase in Zone B.

The *Update 2012* included no additional studies of Vietnam veterans, although there were several follow-up studies of occupational exposure to the COIs. Several of these noted very small numbers of additional cases of HL, which did not produce substantive changes in prior findings. Burns et al. (2011) reported

an additional case among Dow 2,4-D production workers. Ruder and Yin (2011) likewise reported one additional HL death in the NIOSH cohort of PCP workers. Updates of cancer incidence (Koutros et al., 2010a) and mortality (Waggoner et al., 2011) among participants in the AHS did not find increases in private applicators or their spouses, but the analyses were not herbicide specific. In case-control studies of Canadian pesticide and herbicide exposure, Karunanayake et al. (2012) and Pahwa et al. (2003) found no significant associations of exposure to COIs with HL, although many point estimates for association were greater than unity.

Table 8-39 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies After following up on a cohort of male Vietnam veterans from New Zealand, McBride et al. (2013) reported one death from HL compared with 0.4 expected (SMR = 2.30, 95% CI 0.03–12.8) and 3 incident cases of HL with 1.4 expected (SIR = 2.08, 95% CI 0.42–6.09).

Mortality (Yi et al., 2014b) and cancer incidence of (Yi and Ohrr, 2014) were assessed among Korean veterans who had served in Vietnam between 1964 and 1973. In analyses of cancer incidence, Yi and Ohrr (2014) reported a modestly increased risk of Hodgkin lymphoma (HR = 1.27, 95% CI 0.41–3.93) in the internal comparison of the high- and low-exposure groups based on the EOI scores. Yi et al. (2014b) did not provide mortality information for HL.

Occupational and Environmental Studies No occupational or environmental studies of exposure to the COIs and HL specifically have been published since the *Update 2012*.

Case-Control Studies The Cross Canada Study of Pesticides and Health was a population-based incident case-control study in six Canadian provinces conducted between 1991 and 1994. In a study using these data (Navaranjan et al., 2013), men 19 years and older who had a first diagnosis of soft tissue sarcoma, NHL, multiple myeloma, or HL during these years were included and followed in mailed and telephone interviews. Adjusting for age and province of residence, no risk of HL was observed for overall exposure to any one phenoxy herbicide (OR = 0.94, 95% CI 0.63–1.41), two phenoxy herbicides (OR = 1.01, 95% CI 0.57–1.78), or three or more phenoxy herbicides (OR = 1.01, 95% CI 0.48–2.11). Exposure specificity remains a major issue for this study.

Biologic Plausibility

HL arises from the malignant transformation of a germinal-center B cell and is characterized by malignant cells that have a distinctive structure and

TABLE 8-39 Selected Epidemiologic Studies—Hodgkin Lymphoma (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—white subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
Attended 1987 exam—Ranch Hand personnel (n = 995) vs SEA veterans (n = 1,299)	0	nr	Wolfe et al., 1990
Mortality			
Through 1987—Ranch Hand personnel (n = 1,261) vs SEA veterans (n = 19,102)	0	nr	Michalek et al., 1990
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			
1965–2000	2	0.9 (nr)	Boehmer et al., 2004
Post-service–1983	0	nr	Boyle et al., 1987
US CDC Selected Cancers Study—case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953 (CDC, 1990a)		**All COIs**	CDC, 1990a
Vietnam veterans	28	1.2 (0.7–2.4)	
Army	12	1.0 (0.5–2.0)	
Marine Corps	4	1.7 (0.5–5.9)	
Air Force	5	1.7 (0.6–4.9)	
Navy	7	1.1 (0.4–2.6)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	125	1.0 (nr)	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	25	1.9 (1.2–2.7)	

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
1965–1984			Watanabe et al., 1991
Army, deployed (n = 24,145) vs non-deployed (n = 27,917)			
Vs Army non-Vietnam veterans	116	1.0 (nr)	
Vs all non-Vietnam veterans	116	1.1 (nr)	
Marine Corps, deployed (n = 5,501) vs non-deployed (n = 4,505)			
Vs Marine non-Vietnam veterans	25	1.9 (nr)	
Vs all non-Vietnam veterans	25	1.0 (nr)	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	92	1.2 (0.7–1.9)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	22	1.3 (0.7–2.6)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004 (lymphopoietic cancers[c])	18	0.7 (0.4–1.3)	Cypel and Kang, 2008
Vietnam-veteran nurses	14	0.7 (0.3–1.3)	
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	20	1.1 (0.7–1.8)	Vistainer et al., 1995
New York—deployed vs non-deployed		*99% CI*	Lawrence
(lymphoma, HD)	10	1.0 (0.4–2.2)	et al., 1985
West Virginia—deployed vs non-deployed	5	8.3 (2.7–19.5)	Holmes et al., 1986
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	4	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	51	2.1 (1.5–2.6)	ADVA, 2005b
Navy	7	1.3 (0.5–2.6)	
Army	40	2.3 (1.6–3.0)	
Air Force	4	2.1 (0.6–5.3)	
Mortality			
All branches, return–2001	13	0.9 (0.5–1.5)	ADVA, 2005a
Navy	2	0.6 (0.1–2.1)	
Army	11	1.1 (0.5–1.9)	
Air Force	0	0.0 (0.0–2.9)	

continued

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	12	0.9 (0.4–2.0)	ADVA, 2005c
Mortality			
1982–2000	12	0.9 (0.4–2.0)	ADVA, 2005c
1966–2001	4	1.7 (0.3–11.8)	ADVA, 2005c
1983–1985	0	nr	Fett et al., 1987b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	3	2.1 (0.4–6.1)	
Mortality (1988–2008)	1	2.3 (0.0–12.8)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—HL (C81) categorized high (n = 7) vs low (n = 6)		1.3 (0.4–3.9)	Yi and Ohrr, 2014
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	10	1.0 (0.5–1.8)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	8	1.3 (0.6–2.5)	
7,553 not exposed to highly chlorinated PCDDs	1	0.3 (0.0–1.5)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	2	0.4 (0.1–1.4)	Saracci et al., 1991
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	1	**TCDD** nr	Kogevinas et al., 1993
Mortality—IARC cohort (16,863 men and 1,527 women) 10–19 years since first exposure	3	0.6 (0.1–1.7)	Kogevinas et al., 1992

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort) **Dutch production workers in Plant A** (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP** **Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991	1	3.2 (0.1–17.6)	Hooiveld et al., 1998
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	nr	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1965–1989	0	nr	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1956–1989	0	nr	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
Through 1987 [Table 2]	0	nr	Zober et al., 1990
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–1989	0	nr	Becher et al., 1996

continued

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; 2,4,5-TCP; MCPA; MCPB; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	1	4.2 (0.1–23.3)	
Never-exposed workers	0	0.0 (0.0–47.1)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	1	5.6 (0.1–31.0)	't Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	0	0.0 (0.0–16.1)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	3	1.1 (0.2–3.2)	Steenland et al., 1999
Chloracne subcohort (n = 608) (lymphatic, hematopoietic; ICD-9 200–208)	6	1.1 (0.4–2.5)	
Through 1987	3	1.2 (0.3–3.5)	Fingerhut et al., 1991
≥ 1-yr exposure, ≥ 20-yr latency	1	2.8 (0.1–15.3)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	0	0.0 (0.0–6.4)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	1	0.6 (0.0–3.6)	
PCP and TCP (n = 720)	0	nr (0.0–6.9)	
PCP (no TCP) (n = 1,402)	1	1.0 (0.0–5.4)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	1	1.3 (0.0–7.2)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	1	1.5 (0.0–8.6)	Burns et al., 2001
Through 1982 (n = 878)	1	2.7 (0.0–14.7)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	2	1.8 (0.2–6.4)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-yr latency	0	nr	
15-yr latency	0	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	7	0.6 (0.2–1.2)	
Ever	17	1.8 (1.0–2.8)	
Danish paper workers			Rix et al., 1998
Men	18	2.0 (1.2–3.2)	
Women	2	1.1 (0.1–3.8)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Ontario Forestry Workers—1,222 men working ≥ 6 mo 1950–1982			
80 deaths through 1982; 18 cancers (lung greatest with 5)	0	nr	Green, 1991
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992

continued

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Men			
Self-employed	27	0.6 ($p < 0.05$)	
Employee	13	1.0 (nr)	
Women			
Self-employed	1	1.1 (nr)	
Employee	1	1.2 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	0	nr	Swaen et al., 2004
Through 1987	1	3.3 (0.0–18.6)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC		**Phenoxy herbicides**	
Incidence	2	1.7 (0.2–6.0)	Asp et al., 1994
Mortality 1972–1989	0	0.0 (0.0–5.0)	
Except for lung cancer, numbers too small for reporting mortality 1972–1980	0	nr	Riihimaki et al., 1982
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	11	1.0 (0.5–1.7)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	1	**Phenoxy herbicides** 0.7 (0.0–3.6)	Gambini et al., 1997
SWEDEN			
Swedish Cancer-Environment Registry— National Cancer Registry linked to census		**Herbicides**	
Incidence data from Swedish Cancer Environment Register (1971–1984) linked to 1970 census			Eriksson et al., 1992a
Male sawmill workers	10	2.1 (1.0–4.0)	
Male farmers	97	1.2 (nr)	
Male forestry workers	35	1.2 (nr)	
Male horticulture workers	11	1.2 (nr)	
20,245 Swedish pesticide applicators with license issued between 1965 and 1976	15	1.5 (0.8–2.4)	Wiklund et al., 1989a
354,620 Swedish agriculture, forestry workers			Wiklund
Workers in land or in animal husbandry	242	1.0 (0.9–1.2)	et al., 1988a
Workers in silviculture	15	2.3 (1.3–3.7)	
Incident HD cases 1961–1973 with agriculture as economic activity in 1960 census	226	*99% CI* 1.0 (0.9–1.2)	Wiklund, 1983

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	56	1.0 (0.8–1.3)	
Nonwhites (n = 11,446)	2	0.7 (0.1–2.6)	
Women			
Whites (n = 2,400)	0	0.0 (0.0–3.4)	
Nonwhites (n = 2,066)	0	0.0 (0.0–7.2)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	18	1.0 (0.6–1.5)	
Commercial applicators	1	nr	
Spouses	7	0.9 (0.3–1.7)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	11	0.9 (0.4–1.6)	
Spouses of private applicators (> 99% women)	4	0.7 (0.2–1.9)	
Commercial applicators	1	0.8 (0.1–4.2)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	5	1.0 (0.3–2.4)	
Spouses (n = 676)			
Enrollment through 2000, vs state rates	3	1.1 (0.2–3.3)	Blair et al., 2005a
Private applicators (men and women)	3	1.7 (0.3–4.8)	
Spouses of private applicators (> 99% women)	0	0.0 (0.0–2.5)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of HD		**Herbicides**	
Agricultural extension agents			Alavanja et al., 1988
PM analysis	6	2.7 (1.2–6.3)	
Case-control analysis	6	1.1 (0.3–3.5)	

continued

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
USDA forest, soil conservationists	4	2.2 (0.6–5.6)	Alavanja et al., 1989
White Male Residents of Iowa—HD on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 yrs old when died 1971–1978—PMR	47	1.2 (ns)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	0	nr	Pesatori et al., 2009
Zone B	3	1.2 (0.4–3.8)	
Zone R	23	1.5 (0.9–2.3)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Zone B	1	1.7 (0.2–12.8)	
Zone R	4	1.1 (0.4–3.1)	
10-yr follow-up to 1991—women			Bertazzi et al., 1993
Zone B	1	2.1 (0.3–15.7)	
Zone R	3	1.0 (0.3–3.2)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
Zone A	0	nr	
Zone B	3	2.2 (0.7–6.9)	
Zone R	9	0.9 (0.5–1.9)	
20-yr follow-up to 1996			Bertazzi et al., 2001
Zones A, B—men	2	2.6 (0.6–10.9)	
Zones A, B—women	2	3.7 (0.9–16.0)	
15-yr follow-up to 1991—men			Bertazzi et al., 1997
Zone B	2	3.3 (0.4–11.9)	
15-yr follow-up to 1991—women			Bertazzi et al., 1997
Zone B	2	6.5 (0.7–23.5)	
Zone R	4	1.9 (0.5–4.9)	
Other International Environmental Studies			
FRANCE			
Residents near French solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2000
1980–1995	9	1.5 (nr) (p = 0.89)	

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		2,4,5-T	Read et al., 2007
Incidence	49	1.1 (0.8–1.5)[d]	
1970–1974	9	1.2 (0.6–2.3)	
1975–1979	9	1.1 (0.5–2.2)	
1980–1984	8	1.1 (0.5–2.1)	
1985–1989	9	1.3 (0.6–2.5)	
1990–1994	7	1.3 (0.5–2.7)	
1995–1999	4	0.7 (0.2–1.7)	
2000–2001	3	1.0 (0.2–3.1)	
Mortality	22	1.3 (0.8–2.0)[d]	
1970–1974	7	1.6 (0.7–3.3)	
1975–1979	4	1.2 (0.3–3.0)	
1980–1984	6	2.1 (0.8–4.5)	
1985–1989	3	1.2 (0.2–3.5)	
1990–1994	1	0.6 (0.0–3.5)	
1995–1999	1	0.6 (0.0–3.6)	
2000–2001	0	nr	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Kansas residents–duration and frequency of herbicide use—incidence		**Phenoxy herbicides, 2.4-D**	Hoar et al., 1986
All farmers	71	0.8 (0.5–1.2)	
Farm-use of herbicides (phenoxy acids, others)	28	0.9 (0.5–1.5)	
Farmers using herbicides > 20 days/yr	3	1.0 (0.2–4.1)	
Farmers using herbicides > 15 days/yr	10	1.2 (0.5–2.6)	
Tecumseh, Michigan residents participating in longitudinal study (1959–1987)	13	**Herbicides** 2.0 (1.1–3.4)	Waterhouse et al., 1996
Hancock County, **Ohio**, residents—farmers	3	2.7 (nr)	Dubrow et al., 1988
International Case-Control Studies			
Cross Canada Study of Pesticides and Health—men in 1 of 6 Canadian provinces (≥ 19 yrs of age) diagnosed September 1991–December 1994 (n = 316) vs matched population-based controls (n = 1,506)		**Phenoxy herbicides**	

continued

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Effect of multiple pesticide exposure on HL risk		**Phenoxy herbicides**	Navaranjan et al., 2013
Any 1 phenoxy herbicide	36	0.9 (0.6–1.4)	
Any 2 phenoxy herbicides	18	1.0 (0.6–1.8)	
3 or more phenoxy herbicides	10	1.0 (0.5–2.1)	
Association with specific herbicides and HL			Karunanayake et al., 2012; Pahwa et al., 2006
Any phenoxy herbicides	65	0.9 (0.7–1.3)	
2,4-D	57	0.9 (0.6–1.3)	
Mecoprop	20	1.4 (0.8–2.4)	
MCPA	11	1.0 (0.4–2.2)	
Diclofopmethyl	10	1.8 (0.7–4.5)	
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	7	1.5 (0.6–4.1)	
Phenoxy herbicides	6	2.5 (0.8–7.7)	
Domestic use of herbicides	19	0.8 (0.4–1.6)	
Italian incident cases of malignancies of hematolymphopoietic system (HD = 258) in men and women (20–74 yrs of age) from agricultural and mixed use areas		**Herbicides**	Miligi et al., 2006
Men	5	0.4 (0.1–1.3)	
Women	1	0.5 (0.1–4.0)	
Italy—Residents of Milan area (men and women)—incidence		**Herbicides**	LaVecchia et al., 1989
Agricultural occupations	nr	2.1 (1.0–3.8)	
Chemical-industry occupations	nr	4.3 (1.4–10.2)	
New Zealand National Cancer Registry (1977–1981) (≥ 20 yrs of age) with agricultural occupations—incidence (ICD-9 200, 202)	107	**Herbicides** 1.1 (0.6–2.0)	Pearce et al., 1985
Swedish Regional Cancer Registry—HD patients		**Phenoxy herbicides**	Persson et al., 1993
Exposed to phenoxy herbicides	5	*90% CI* 7.4 (1.4–40.0)	
Örebro (**Sweden**) Hospital (men and women)—incidence		**Phenoxy herbicides, chlorophenols**	Persson et al., 1989
		90% CI	
Farming	6	1.2 (0.4–3.5)	
Exposed to phenoxy acids	4	3.8 (0.7–21.0)	
Sweden—Umea Hospital patients (men and women, 25–85 yrs of age) (1974–1978)		**Phenoxys, chlorophenols**	Hardell and Bengtsson, 1983
Exposed to phenoxy acids	14	5.0 (2.4–10.2)	

TABLE 8-39 Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Exposed to high-grade chlorophenols	6	6.5 (2.2–19.0)	
Exposed to low-grade chlorophenols	5	2.4 (0.9–6.5)	
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981
Exposed to phenoxy herbicides	41	4.8 (2.9–8.1)	
Exposed to chlorophenols	50	4.3 (2.7–6.9)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HD, Hodgkin disease; HL, Hodgkin lymphoma; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy) butanoic acid; MCPP, methylchlorophenoxypropionic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; PMR, proportional mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all of forms of lymphoma (including Hodgkin disease and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

[d]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

phenotype; these binucleate cells are known as Reed–Sternberg cells (Jaffe et al., 2008). No animal studies have shown an increase in HL after exposure to the COIs. Reed–Sternberg cells have not been demonstrated in mice or rats, so there is no good animal model of HL. Thus, there are no specific animal data to support the biologic plausibility of an association between the COIs and HL.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The relative rarity of HL complicates the evaluation of epidemiologic studies because their statistical power is generally low. Earlier studies (Eriksson et al., 1992; Hardell et al., 1981; Holmes et al., 1986; LaVecchia et al., 1989; Persson

et al., 1993; Rix et al., 1998; Waterhouse et al., 1996; Wiklund et al., 1988a) were generally well conducted and included excellent characterizations of exposure, and they formed the basis of previous VAO committees' conclusions. Later findings have not contradicted those conclusions, especially given that most studies have had low statistical power. Although it has not been demonstrated as clearly as for NHL, a positive association between the COIs and the development of HL is biologically plausible because of the common lymphoreticular origin of HL and NHL and their common risk factors.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the COIs and HL.

Non-Hodgkin Lymphoma

NHL (ICD-9 200.0–200.8, 202.0–202.2, 202.8–202.9) is a general name for cancers of the lymphatic system other than HL or multiple myeloma. NHL consists of a large group of lymphomas that can be partitioned into acute and aggressive (fast-growing) or chronic and indolent (slow-growing) types of either B-cell or T-cell origin. B-cell NHL includes Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, large-cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle-cell lymphoma. T-cell NHL includes mycosis fungoides and anaplastic large-cell lymphoma. Precursor T-lymphoblastic lymphoma is not considered a type of NHL and is considered part of T-lymphoblastic lymphoma/leukemia, a precursor lymphoid neoplasm included with the broad group of "acute lymphoid leukemias," which can be of either T-cell or B-cell origin.

As noted in earlier VAO updates, in response to requests from VA, CLL and HCL have been recognized as sharing many traits with NHL (including B-cell origin and immunohistochemical properties). The proposed WHO classification of NHL notes that CLL (ICD-9 204.1) and its lymphomatous form, SLL, are both derived from mature B cells (Chiorazzi et al., 2005; IARC, 2001). The committee for *Update 2012* determined that it is more appropriate to consider those lymphatic malignancies with other forms of NHL. Therefore, the discussion of CLL and HCL has been moved into the NHL grouping.

ACS estimated that 39,850 men and 32,000 women would receive diagnoses of NHL in the United States in 2015 and that 11,480 men and 8,310 women would die from it (Siegel et al., 2015). The incidence of NHL is uniformly higher in men than in women and typically higher in whites than in blacks. In the groups that characterize most Vietnam veterans, incidence increases with age. In addition, ACS estimated that about 8,140 men and 6,480 women would receive diagnoses of CLL in the United States in 2015 and that 2,830 men and

1,820 women would die from it (Siegel et al., 2015). Nearly all cases occur after the age of 50 years. Average annual incidences of NHL are shown in Table 8-40 with the additional incidences of CLL.

The causes of NHL are poorly understood. People who have suppressed or compromised immune systems are known to be at higher risk, and some studies show an increased incidence in people who have HIV, human T-cell leukemia virus type I, Epstein–Barr virus, or gastric *Helicobacter pylori* infections. The human retrovirus HTLV-1 causes adult T-cell lymphoma, but early reports that HTLV-2 might play a role in the etiology of HCL have not been substantiated. A broad spectrum of behavioral, occupational, and environmental risk factors have been proposed as contributors to the occurrence of NHL, but given the diversity of malignancies included under this name and the evolving classification of the subtypes (to date, minimal exploration of etiologic heterogeneity has been done), it is not too surprising that—aside from infectious agents, immune problems, and particular chemotherapies—specific risk factors have not been definitively established (Morton et al., 2008, 2014a,b; Wang and Nieters, 2010).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was sufficient evidence to support an association between exposure to at least one of the COIs and NHL. Additional information available to the committees responsible for later updates has not changed that conclusion.

As with HL, the epidemiologic data reviewed by previous VAO committees suggest that the phenoxy herbicides (including 2,4-D) rather than TCDD may be associated with NHL. The original VAO committee concluded that a positive association existed between exposure to herbicides and the development of NHL, and studies reviewed by later committees have continued to support that finding. A large, well-conducted case-control study in Sweden by Hardell (1981) examined NHL and HL together and found a significantly increased risk associated with exposure to phenoxy acids or chlorophenols on the basis of 105 cases. Those results were replicated in further investigations of the validity of the exposure

TABLE 8-40 Average Annual Incidence (per 100,000) of Non-Hodgkin Lymphoma in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	51.9	54.0	41.2	75.2	78.7	52.3	99.3	106.2	57.3
Women	37.2	39.1	28.8	54.4	57.9	40.8	69.2	74.4	42.3

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

assessment and potential biases (Hardell, 1981). Another Swedish case-control study by Hardell et al. (1994) found a statistically significant risk in a comparison of the occupational histories of 105 people who were exposed to phenoxy herbicides and chlorophenols and received diagnoses of NHL in 1974–1978 with 335 control subjects. Similar data by Persson et al. (1989) showed an increased risk of NHL in those exposed to phenoxy acids on the basis of a logistic regression analysis of 106 cases.

Studies of production workers have shown some association between TCDD exposure and NHL. A larger study of 21,863 workers in the IARC phenoxy-herbicide cohort by Kogevinas et al. (1997) found a non-significant increase in NHL risk. Subjects in that expanded multinational study were followed from 1939 to 1992. Other studies of Danish and Dutch phenoxy-herbicide workers who were part of the IARC cohort have shown a non-significant increased risk of NHL (Boers et al., 2010; Bueno de Mesquita et al., 1993; Hooiveld et al., 1998; Lynge, 1993). A cohort of 2,479 workers in four plants in Germany with exposure to phenoxy herbicide and contaminants (dioxins and furans) had significantly increased risk of NHL on the basis of five cases (Becher et al., 1996). A variety of herbicides were produced in the plants, including those known to have been contaminated with TCDD. Increased but non-significant increases in risk have also been found in the NIOSH mortality study (Steenland et al., 1999). Risks were not significantly increased in the Dow Chemical Company Midland, Michigan, or Plymouth, New Zealand, chemical production workers, phenoxy-herbicide sprayers, or 2,4-D production workers (Bloemen et al., 1993; Bodner et al., 2003; Burns et al., 2001; Collins et al., 2009b,c; McBride et al., 2009a,b; Ramlow et al., 1996; 't Mannetje et al., 2005). A multinational IARC cohort study of paper-and-pulp workers found a statistically significant increase in workers who were exposed to chlorophenols (McLean et al., 2006).

Studies of farmers and agricultural workers have been generally positive for an association between herbicides or TCDD and NHL; however, only a few were statistically significant. A meta-analysis of several studies of the association between employment as a farmer in the central United States and NHL showed a statistically significant risk (Keller-Bryne et al., 1997). All the studies of US agricultural workers reviewed showed increased RRs, and two NCI studies of farmers in Kansas and Nebraska (Hoar et al., 1986; Zahm et al., 1990) showed patterns of increased risk linked to use of 2,4-D. A study of a subcohort of Hispanic workers in a larger cohort of 139,000 California members of the United Farm Workers of America (Mills et al., 2005) and a population-based case-control study in Italy of NHL and CLL cases (combined) identified during 1991–1993 (Miligi et al., 2006) both showed statistically significant associations with 2,4-D.

A large, well-conducted, population-based, cross-Canada case-control study reported on pesticide use and NHL incidence in men identified from cancer registries of six Canadian provinces from 1991 through 1994. Statistically significant associations were found between exposure to phenoxy herbicides, 2,4-D,

or Mecocrop and NHL. A reanalysis of the data from that study confirmed the findings on phenoxy herbicides but found that the association with 2,4-D, although still increased, was no longer significantly so (McDuffie et al., 2001). A population-based case-control study in 2000–2001 in men and women 20–74 years old living in New South Wales, Australia, found an increased risk of NHL associated with "substantial" exposure to phenoxy herbicides (Fritschi et al., 2005). Spinelli et al. (2007) reported on a population-based case-control study in Vancouver and Victoria, British Columbia, which found strong monotonic increases in serum concentrations of two dioxin-like PCBs (PCB 118 and 156). Chiu et al. (2004) and Lee et al. (2004a) conducted a pooled (combined) analysis of two case-control studies that were carried out in three midwestern US states—Iowa and Minnesota (Cantor et al., 1992) and Nebraska (Zahm et al., 1990)—and found that risks were increased in farmers by use of herbicides, including 2,4-D and 2,4,5-T. In a study of NHL incidence in people who lived in the vicinity of 13 French municipal waste incinerators, Viel et al. (2008b) found a small but statistically significant increase in the risk of NHL and evidence of a dose–response relationship with increased exposure to dioxin. A case-control study of NHL rates in people who lived near a municipal solid-waste incinerator in Bensaçon, France, found that the incidence of NHL was significantly increased in the area determined to have the highest dioxin contamination, but no increases were found in the low and intermediate categories (Floret et al., 2003). A French hospital-based case-control study of lymphoid neoplasms (Orsi et al., 2009) did not find the occurrence of NHL to be associated with occupational or domestic use of pesticides or phenoxy herbicides in particular.

Evidence of an association between the COIs and NHL in Vietnam veterans, the primary population of interest in the VAO updates, has been lacking. The CDC Selected Cancers Study (CDC, 1990e) showed a significantly increased risk of NHL in all Vietnam veterans; however, in an analysis that took into account the branch of service, Army and Air Force personnel were found not to be at increased risk. Marine Corps veterans had higher mortality in the CDC Selected Cancers Study and significantly increased risks in several other studies (Breslin et al., 1988; Burt et al., 1987; Watanabe and Kang, 1996; Watanabe et al., 1991), but the implications of these findings are unclear. No increased risk has been seen in Ranch Hand veterans (AFHS, 2000; Akhtar et al., 2004; Michalek et al., 1990; Wolfe et al., 1990) or in members of the ACC (Boehmer et al., 2004).

With 25 years of follow-up of the Seveso population and a relatively small number of observed cases, evidence of an increased incidence of NHL is emerging in the subgroup who lived in the most highly exposed zones (Bertazzi et al., 1989b, 1993, 1997, 2001; Consonni et al., 2008; Pesatori et al., 1992, 2009).

The findings of several PCB-focused studies (Bertrand et al., 2010; Engel et al., 2007; Laden et al., 2010) are consistent with the associations with NHL repeatedly observed in connection with the COIs in the VAO series, but the extent

of intercorrelation of these persistent organic pollutants greatly curtails the degree to which any effect can be specifically attributed to dioxin-like activity.

Table 8-41 summarizes the results of the relevant studies of all forms of NHL.

Update 2002 was the first to discuss CLL separately from other leukemias. The epidemiologic studies indicated that farming, especially with exposure to 2,4-D and 2,4,5-T, is associated with significant mortality from CLL. Many more studies support the hypothesis that herbicide exposure can contribute to NHL risk. Most cases of CLL and NHL reflect the malignant transformation of germinal-center B cells, so these diseases could have a common etiology.

Studies concerning CLL reviewed in *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* are summarized in Table 8-42.

Update of the Epidemiologic Literature

Vietnam-Veteran and Environmental Studies Based on deaths rates from the general male population of New Zealand, McBride et al. (2013) calculated that seven were expected (SMR = 0.43, 95% CI 0.09–1.25). In assessing incidence, based upon 14 cases, the incidence of NHL was not elevated (SIR = 0.85, 95% CI 0.46–1.42). The researchers also reported on lymphoid leukemia, showing an SMR of 0.57 (95% CI 0.01–3.16) based upon one observed death. Similarly, there were 14 observed cases of lymphoid leukemia (which would include any cases of CLL, a specific NHL), which did constitute a significant increase (SIR = 1.91, 95% CI 1.04–3.20).

Mortality (Yi et al., 2014b) and cancer incidence (Yi and Ohrr, 2014) were assessed among Korean Veterans who had served in Vietnam from 1964 through 1973. In analyses of cancer incidence, Yi and Ohrr (2014) reported a small excess risk of NHL (HR = 1.09, 95% CI 0.81–1.47) in the internal comparison of the high- and-low exposure groups based on the EOI scores. Similarly for NHL mortality, Yi et al. (2014b) reported a modestly increased risk for the high- versus low-exposure groups (HR = 1.18, 95% CI 0.79–1.77) and a small increased risk with the individual log-transformed EOI scores (HR = 1.04, 95% CI 0.95–1.15). Lymphoid leukemia had an aHR of 0.45 (95% CI 0.15–1.37) based upon nine low-exposure and five high-exposure deaths.

Occupational Studies Since *Update 2012*, two new NHL occupational studies have been published (Cocco et al., 2012; Pronk et al., 2013). Using the EPILYMPH multicenter study (conducted in the Czech Republic, France, German, Ireland, Italy, and Spain from 1998 to 2004), Cocco et al. (2012) assessed occupational exposure in 2,348 lymphoma cases and 2,462 controls, seeking to understand the relationship of pesticide use with lymphomas. In assessing exposure, a "crop-exposure" matrix was assembled and the exposure was estimated by a group of trained occupational experts. There were numerous analyses of multiple

TABLE 8-41 Selected Epidemiologic Studies—Non-Hodgkin Lymphoma (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates (lymphopoietic cancer[c])			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
Attended 1987 exam—Ranch Hand personnel (n = 995) vs SEA veterans (n = 1,299)	1	nr	Wolfe et al., 1990
Mortality			
Through 1987—Ranch Hand personnel (n = 1,261) vs SEA veterans (n = 19,102)	0	nr	Michalek et al., 1990
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Army enlisted Vietnam veterans (all lymphomas) (1965–1983)	7	1.8 (nr)	O'Brien et al., 1991
Mortality			
1965–2000	6	0.9 (0.3–2.9)	Boehmer et al., 2004
US CDC Selected Cancers Study—case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953 (CDC, 1990a)	99	**All COIs** 1.5 (1.1–2.0)	CDC, 1990b
Army Vietnam veterans	45	1.2 (0.8–1.8)	
Marine Vietnam veterans	10	1.8 (0.8–4.3)	
Air Force Vietnam veterans	12	1.0 (0.5–2.2)	
Navy Vietnam veterans	32	1.9 (1.1–3.2)	
Blue Water Navy Vietnam veterans	28	2.2 (1.2–3.9)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	171	—	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	46	1.7 (1.2–2.2)	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
1965–1984—Army, deployed (n = 24,145) vs non-deployed (n = 27,917) (ICD-8 200, 202)	140	1.7 (1.2–2.2)	Watanabe et al., 1991
Army Vietnam veterans vs combined Army and Marine Vietnam-era veterans	140	0.9 (nr)	
Marine Vietnam veterans vs non-Vietnam veterans	42	1.8 (1.3–2.4)	
Marine Vietnam veterans vs combined Army and Marine Vietnam-era veterans	42	1.2 (nr)	
1965–1982 (ICDA-8 200, 202)			Breslin et al.,1986, 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	108	0.8 (0.6–1.0)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	35	2.1 (1.2–3.8)	
Nested case-control study of NHL	39	1.1 (0.7–1.5)	Burt et al., 1987
Army combat Vietnam veterans	17	3.2 (1.4–7.4)	
Marine combat Vietnam veterans	64	0.9 (0.7–1.3)	
Army Vietnam veterans (service 1967–1969)	17	2.5 (1.1–5.8)	
Marine Vietnam veterans (service 1967–1969)	4	1.8 (0.4–8.0)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004 (lymphopoietic cancers[c])	18	0.7 (0.4–1.3)	Cypel and
Vietnam–veteran nurses	14	0.7 (0.3–1.3)	Kang, 2008
Through 1987 (ICD-8 200, 200–203, 208)	3	1.3 (0.3–1.8)	Thomas et al., 1991
US Navy Enlisted Personnel (1974–1983)			
Active duty	68	0.7 (0.5–0.9)	Garland et al., 1988
VA Case-Control Studies			
US Vietnam veterans—incidence	100	1.0 (0.7–1.5)	Dalager et al., 1991b
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans who served 1958–1973—cases diagnosed 1982–1988 (served in Vietnam)	—	1.2 (0.6–2.4)	Clapp et al., 1991
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	32	1.5 (1.0–2.1)	Vistainer et al., 1995
New York—deployed vs non-deployed	10	1.0 (0.4–2.2)	Lawrence et al., 1985
West Virginia—deployed vs non-deployed	2	1.1 (nr)	Holmes et al., 1986

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (includes lymphosarcoma, reticulosarcoma)	4	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	126	0.7 (0.6–0.8)	ADVA, 2005b
Navy	31	0.8 (0.5–1.0)	
Army	86	0.7 (0.5–0.8)	
Air Force	9	0.5 (0.2–0.9)	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	62	48 (34–62)	
Men	137	48 (34–62)	CDVA, 1998a
Women	2	0 (0–4)	CDVA, 1998b
Mortality			
All branches, return–2001	70	0.8 (0.6–1.0)	ADVA, 2005a
Navy	10	0.5 (0.3–0.9)	
Army	52	0.9 (0.6–1.1)	
Air Force	8	0.9 (0.4–1.6)	
1980–1994	33	0.9 (0.6–1.2)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	35	1.1 (0.7–1.9)	ADVA, 2005c
Mortality			
1966–2001	21	1.4 (0.7–2.8)	ADVA, 2005c
1983–1985 (ICD-8 200, 202)	4	1.8 (0.4–8.0)	Fett et al., 1987b

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	14	0.9 (0.5–1.4)	
Mortality (1988–2008)	3	0.4 (0.1–1.3)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—NHL (C82–C85) categorized high (n = 96) vs low (n = 89)		1.1 (0.8–1.5)	Yi and Ohrr, 2014
Mortality (1992–2005)—categorized high (n = 56) vs low (n = 47)		1.2 (0.8–1.8)	Yi et al., 2014b
HR per unit of log EOI scores (n = 180,639)	103	1.0 (1.0–1.2)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	34	1.3 (0.9–1.8)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	24	1.4 (0.9–2.1)	
7,553 not exposed to highly chlorinated PCDDs	9	1.0 (0.5–1.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Nested case-control study			
IARC cohort (men and women)—incidence			Kogevinas et al., 1995
Exposed to 2,4,5-T	10	1.9 (0.7–4.8)	
Exposed to TCDD	11	1.9 (0.7–5.1)	
Mortality—IARC cohort (16,863 men and 1,527 women) 10–19 yrs since first exposure	11	1.0 (0.5–1.7)	Kogevinas et al., 1992
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Mortality 1955–2006	7	1.4 (1.1–1.7)	Boers et al., 2012
TCDD plasma level (HRs, by tertile)			
Background (≤ 0.4)	1	nr	
Low (0.4–4.1)	3	3.8 (0.4–34.3)	

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Medium (4.1–20.1)	2	7.8 (0.7–89.3)	
High (≥ 20.1)	1	8.1 (0.4–149.1)	
Incidence 1943–1987 (men only)	10	1.7 (0.5–4.5)	Lynge, 1993
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	6	1.3 (1.0–1.7)	Boers et al., 2012
Mortality 1955–2006	4 vs 3	0.9 (0.2–4.5)	Boers et al. 2010
Mortality 1955–1991	3	3.8 (0.8–11.0)	Hooiveld et al., 1998
Mortality 1955–1985	1	2.0 (0.1–11.4)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	1 vs 0	nr	Boers et al., 2010
Mortality 1965–1986	1	5.6 (0.1–31.0)	Bueno de Mesquita et al., 1993
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All 4 plants	6	3.3 (1.2–7.1)	Becher et al., 1996
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	2	12.0 (1.5–43.5)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1965–1989	0	—	Becher et al., 1996

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1956–1989	0	—	Becher et al., 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,5-DCP; 2,4,5-T; 2,4,5-TCP**	
Mortality 1952–2007	7	1.6 (0.6–3.3)	Manuwald et al., 2012
Men	5	1.6 (0.5–3.7)	
Women	2	1.7 (0.2–6.0)	
Mortalilty 1952–1989	4	3.8 (1.0–9.6)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	3	1.6 (0.3–4.7)	
Never-exposed workers	1	1.6 (0.0–8.7)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	1	0.9 (0.0–4.9)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	0.7 (0.0–3.8)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	12	1.1 (0.6–1.9)	Steenland et al., 1999
Chloracne subcohort (n = 608) (Lymphatic and hematopoietic, ICD-9 200–208)	6	1.1 (0.4–2.5)	

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	9	1.3 (0.6–2.5)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	1.4 (0.6–2.7)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (ICD-9 200, 202, 273.3)	17	1.8 (1.0–2.8)	
PCP and TCP (n = 720)	8	2.5 (1.1–4.9)	
PCP (no TCP) (n = 1,402)	9	1.4 (0.6–2.7)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	14	1.7 (0.9–2.9)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	3	1.0 (0.2–2.9)	Burns et al., 2001
Through 1986 (n = 878) vs national vs 36,804 "unexposed" workers at same location	2	2.0 (0.2–7.1)	Bloemen et al., 1993
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	8	2.4 (1.0–4.7)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
All lymphopoietic cancer (ICDA-8 200–209)			
0-yr latency	7	1.4 (0.6–2.9)	
15-yr latency	5	1.3 (0.4–3.1)	
Other, unspecified lymphopoietic cancer (ICDA-8 200, 202–203, 209)			
0-yr latency	5	2.0 (0.7–4.7)	
15-yr latency	4	2.0 (0.5–5.1)	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	35	0.9 (0.7–1.3)	
Ever	25	0.9 (0.6–1.3)	
Exposure to chlorophenols	50	4.3 (2.7–6.9)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from NHL June 1971–December 1987			
Farm operators ≥ 35 yrs of age (June 1971–December 1987)			Morrison et al., 1994
All farm operators	nr	0.8 (0.7–0.9)	
Highest quartile of herbicides sprayed	19	2.1 (1.1–3.9)	
Highest quartile of herbicide sprayed relative to no spraying	6	3.0 (1.1–8.1)	
Farm operators ≥ 35 yrs of age during study period (June 1971–December 1985)			Wigle et al., 1990
All farmers	103	0.9 (0.8–1.1)	
Spraying herbicides on 250+ acres	10	2.2 (1.0–4.6)	
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-yr follow-up (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	16	1.4 (0.9–2.3)	
Born 1915–1934 (medium exposure)	25	1.2 (0.8–1.8)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.0)	
10-yr follow-up (1975–1984) of male gardeners (ICD-7) (lymphohematopoietic, 200–2005)	15	1.4 (0.8–2.4)	Hansen et al., 1992
NHL (200, 202, 205)	6	1.7 (0.6–3.8)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 1987	0	nr	Swaen et al., 1992

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
No latency	1	0.4 (0.0–2.0)	
10-yr latency	1	0.4 (0.0–2.4)	
Except for lung cancer, numbers too small for reporting mortality 1972–1980	0	nr	Riihimaki et al., 1982, 1983
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (ICD-8 202.0–202.9)	15	0.9 (0.5–1.5)	Torchio et al., 1994
Incidence 1976–1983 (n = 25,945)			Corrao et al.,
Licensed pesticide users and nonusers	45	1.4 (1.0–1.9)	1989
Farmers in arable land areas	31	1.8 (1.2–2.5)	
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	4	1.3 (0.3–3.3)	
SWEDEN			
20,245 Swedish pesticide applicators with license issued from 1965 through 1976	27	1.1 (0.7–1.6)	Wiklund et al., 1989b
354,620 Swedish agriculture, forestry workers			Wiklund
Workers in land, animal husbandry	670	1.0 (0.9–1.1)	et al., 1988a
Timber cutters	111	0.9 (0.7–1.1)	
Incident NHL cases 1961–1973 with agriculture as economic activity in 1960 census	476	*99% CI* 1.1 (0.9–1.2)	Wiklund, 1983
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	0	—	
Lumberjacks (n = 139)	1	1.9 (0.0–10.7)	
Unexposed lumberjacks (n = 241)	1	0.8 (0.0–4.5)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	843	1.2 (1.1–1.3)	
Nonwhites (n = 11,446)	24	0.7 (0.5–1.1)	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Women			
Whites (n = 2,400)	18	1.1 (0.6–1.7)	
Nonwhites (n = 2,066)	6	1.1 (0.4–2.3)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
NHL			
Private applicators	195	1.0 (0.9–1.1)	
Commercial applicators	9	0.8 (0.4–1.6)	
Spouses	86	1.0 (0.8–1.2)	
B-cell			
Private applicators	167	1.0 (0.9–1.2)	
Commercial applicators	8	0.9 (0.4–1.7)	
Spouses	78	1.1 (0.8–1.3)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	39	1.0	
1– < 20	18	1.8 (1.0–3.2)	
20– < 56	14	1.3 (0.7–2.5)	
56– < 116	7	0.9 (0.4–2.2)	
≥ 116	7	1.2 (0.5–2.9)	
		p-trend = 0.92	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	114	1.0 (0.8–1.2)	
Spouses of private applicators (> 99% women)	42	0.9 (0.6–1.2)	
Commercial applicators	6	1.0 (0.4–2.1)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	90	0.8 (0.7–1.0)	
Spouses (n = 676)	42	1.1 (0.8–1.5)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	33	0.9 (0.6–1.2)	
Spouses of private applicators (> 99% women)	16	1.2 (0.7–2.0)	

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
California United Farm Workers of America			
Nested case-control analysis of Hispanic workers in cohort of 139,000 CA United Farm Workers			Mills et al., 2005
Ever used 2,4-D	nr	3.8 (1.9–7.8)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents (from Table 3)	nr	1.2 (0.7–2.3)	Alavanja et al., 1988
White Male Residents of Iowa—NHL cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 yrs old when died 1964–1978—case-control	1,101	1.3 (nr)	Burmeister et al., 1983
H_0: only for "modern methods" → born after 1900			
Born before 1880	154	2.9 (nr)	
Born 1980–1900	336	1.6 (nr)	
Born after 1900	611	0.9 (nr)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			Pesatori et al., 2009
Zone A	1	0.8 (0.1–5.7)	
Zone B	12	1.5 (0.9–2.7)	
Zone R	49	0.9 (0.7–1.2)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Zone A	0	nr	
Zone B	3	2.3 (0.7–7.4)	
Zone R	12	1.3 (0.7–2.5)	
10-yr follow-up to 1991—women			Bertazzi et al., 1993
Zone A	0	nr	
Zone B	1	0.9 (0.1–6.4)	
Zone R	10	1.2 (0.6–2.3)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
Zone A	3	3.4 (1.1–10.5)	
Zone B	7	1.2 (0.6–2.6)	
Zone R	40	1.0 (0.7–1.4)	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
20-yr follow-up to 1996			Bertazzi et al., 2001
Zone A—men and women	2	3.3 (0.8–13.1)	
Zone B—men and women	5	1.2 (0.5–3.0)	
Zones A and B—men	3	1.2 (0.4–3.9)	
Zones A and B—women	4	1.8 (0.7–4.9)	
15-yr follow-up to 1991—men			Bertazzi et al., 1997, 1998
Zone A	0	0.0 (0.0–18.1)	
Zone B	2	1.5 (0.2–5.3)	
Zone R	10	1.1 (0.5–2.0)	
15-yr follow-up to 1991—women			Bertazzi et al., 1997, 1998
Zone A	0	0.0 (0.0–19.6)	
Zone B	0	0.0 (0.0–3.0)	
Zone R	8	0.9 (0.4–1.7)	
10-yr follow-up to 1986—men			Bertazzi et al., 1989a,b
Zone B	nr	nr	
Zone R	3	1.0 (0.3–3.4)	
10-yr follow-up to 1986—women			
Zone B	2	1.0 (0.3–4.2)	
Zone R	4	1.6 (0.5–4.7)	
Other International Environmental Studies			
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)—incidence	16	**Chlorophenol** 2.8 (1.4–5.6)	Lampi et al., 1992
FRANCE			
Residents near French solid-waste incinerator in Besancon. NHL cases diagnosed 2003–2005—incidence		**Dioxin, furans, PCBs**	Viel et al., 2011
pg WHO_{1998} TEQ/g lipid:			
Σ PCDD	13.4	1.1 (1.0–1.3) (p-trend < 0.01)	
Σ PCDF	9.4	1.2 (1.0–1.4) (p-trend = 0.01)	
Σ dl PCBs	33.1	1.0 (1.0–1.1) (p-trend = 0.01)	
Residents near French solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2008a
Highly exposed census group vs slightly exposed	nr	1.1 (1.0–1.3)	

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Residents near municipal solid-waste incinerator—incidence		**Dioxin**	Floret et al., 2003
High exposure category	31	2.3 (1.4–3.8)	
Residents near municipal solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2000
Spatial cluster	286	1.3 (p = 0.00003)	
1994–1995	109	1.8 (p = 0.00003)	
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		2,4,5-T	Read et al., 2007
Incidence	223	1.0 (0.9–1.1)[d]	
1970–1974	33	1.8 (1.2–2.5)	
1975–1979	29	1.3 (0.9–1.9)	
1980–1984	22	0.8 (0.5–1.3)	
1985–1989	24	0.7 (0.5–1.1)	
1990–1994	35	0.8 (0.6–1.1)	
1995–1999	61	1.1 (0.8–1.4)	
2000–2001	19	0.8 (0.5–1.3)	
Mortality	138	1.1 (0.9–1.3)[d]	
1970–1974	19	1.6 (0.9–2.4)	
1975–1979	24	1.6 (1.0–2.4)	
1980–1984	14	1.0 (0.5–1.6)	
1985–1989	25	1.3 (0.9–2.0)	
1990–1994	23	0.9 (0.6–1.4)	
1995–1999	21	0.7 (0.4–1.1)	
2000–2001	12	1.0 (0.5–1.8)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Central US—meta-analysis of NHL and farmers	nr	**Pesticides** 1.3 (1.2–1.6)	Keller-Byrne et al., 1997
Pooled incidence data on herbicide use from 3 case-control studies in **Iowa/Minnesota**, **Kansas**, and **Nebraska** (n = 973)		**Herbicides**	Chiu et al., 2004
Farmers (no herbicide use)	294	1.2 (1.0–1.5)	
Farmers (herbicide use)	273	1.0 (0.8–1.2)	
Pooled data from case-control studies in **Iowa**, **Minnesota**, and **Nebraska—**effect of asthma on NHL and pesticide use (n = 872)		**Pesticides**	Lee et al., 2004a
Asthmatics—incidence			
Herbicide exposure—phenoxy acid	17	1.3 (0.7–2.4)	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Exposure among farmers			
2,4-D	17	1.3 (0.7–2.5)	
2,4,5-T	7	2.2 (0.8–6.1)	
Non-asthmatics—incidence			
Herbicide exposure—phenoxy acid	176	1.0 (0.8–1.3)	
Exposure among farmers			
2,4-D	172	1.0 (0.8–1.3)	
2,4,5-T	36	1.1 (0.7–1.8)	
Kansas residents–duration and frequency of herbicide use—incidence		**Phenoxy herbicides, 2.4-D**	Hoar et al., 1986
All farmers	133	1.4 (0.9–2.1)	
Farm-use of herbicides	7	6.0 (1.9–19.5)	
NCI SEER study (Iowa, Los Angeles County, Detroit, Seattle), 1998–2000; 1,321 NHL patients and 1,057 controls—residential exposures		**2,4-D**	Hartge et al., 2005
2,4-D exposure in carpet dust (ng/g)			
Under detection limit	147	1.0	
< 500	257	1.1 (0.8–1.6)	
500–999	86	0.9 (0.6–1.5)	
1,000–9,999	165	0.7 (0.5–1.0)	
> 10,000	24	0.8 (0.4–1.7)	
Nebraska residents (men and women), NHL reclassified according to specific chromosomal translocation (t[14;18][q32;q21])—incidence		**Herbicides**	Chiu et al., 2006
Translocation present in cases			
Herbicides	25	2.9 (1.1–7.9)	
Translocation present in cases			
Herbicides	22	0.7 (0.3–1.2)	
Females on Eastern **Nebraska** farms		**Herbicides**	Zahm et al., 1993
	119	1.0 (0.7–1.4)	
Eastern **Nebraska** residents—incidence		**2,4-D**	Zahm et al., 1990
Ever done farm work	147	0.9 (0.6–1.4)	
Ever mixed or applied 2,4-D	43	1.5 (0.9–2.5)	
Upstate New York—population-based study, women (20–79 yrs old), 1995–1998 (376 cases vs 463 controls)		**Herbicides, pesticides**	Kato et al., 2004
Home use only of herbicides, pesticides (times)			
0	231	1.0	
1–4	33	0.9 (0.5–1.5)	
5–17	30	0.7 (0.4–1.3)	
18–39	27	1.0 (0.6–1.7)	
≥ 40	40	0.9 (0.5–1.5)	

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Hancock County, **Ohio**, residents—farmers	15	1.6 (0.8–3.4)	Dubrow et al., 1988
Washington state residents—incidence (1983–1985)		**Phenoxy herbicides, chlorinated phenols**	Woods et al., 1987
Phenoxy herbicide use	nr	1.1 (0.8–1.4)	
Chlorophenol use	nr	1.0 (0.8–1.2)	
Farming occupations	nr	1.3 (1.0–1.7)	
Forestry herbicide appliers	nr	4.8 (1.2–19.4)	
Self-reported chloracne	nr	2.1 (0.6–7.0)	
Wisconsin residents—farmers (ICD-8 200.0, 200.1, 202.2)	175	**Herbicides** 1.2 (1.0–1.5)	Cantor, 1982
International Case-Control Studies			
Asian patients (≥ 20 yrs old) from China, Korea, and Japan diagnosed with NKTCL between March 2000 and March 2005–occupational exposures		**Herbicides, pesticides**	Xu et al., 2006
Pesticide use	23	4.0 (2.0–8.1)	
Herbicide	13	3.2 (1.4–7.4)	
Insecticide	20	3.5 (1.7–7.1)	
Fungicide	10	6.1 (2.0–18.5)	
Australian population-based study in New Wales (2000–2001)		**Phenoxy compounds**	Fritschi et al., 2005
Phenoxy herbicides			
Nonsubstantial exposures	10	0.7 0.3–1.7)	
Australian residents in Victorian Cancer Registry (1982–1987)		**Phenoxy compounds**	Smith and Christophers, 1992
Exposure > 1 day	15	1.5 (0.6–3.7)	
Exposure > 30 days	7	2.7 (0.7–9.6)	
Canadian population-based study (March 2000–February 2004), men and women subjects and matched controls (20–79 yrs of age)—organochlorines and NHL		**dl PCBs**	Spinelli et al., 2007
Total dl PCBs			
Lowest quartile	82	1.0	
Second quartile	96	1.4 (0.9–2.2)	
Third quartile	82	1.6 (1.0–2.5)	
Highest quartile	143	2.4 (1.5–3.7) p-trend < 0.001	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Cross Canada Study of Pesticides and Health—men in 1 of 6 Canadian provinces (≥ 19 yrs of age) diagnosed (09/1991–12/1994) (n = 517) vs matched population-based controls (n = 1,506)		**Phenoxy herbicides, 2,4-D**	
Pesticide use, immunologic conditions, and NHL risk			Pahwa et al., 2012b
Phenoxy herbicides	44	1.5 (1.0–2.3)	
MCPA	7	2.7 (0.9–7.9)	
Mecoprop	16	1.7 (0.9–3.4)	
2,4-D	39	1.4 (0.9–2.2)	
Exposure to multiple pesticides			Hohenadel et al., 2011
0	369	1.0 (nr)	
1	45	1.2 (0.9–1.8)	
2–4	73	1.6 (1.2–2.2)	
5+	26	1.6 (1.0–2.6)	
Exposure to phenoxy herbicides			
0	384	1.0 (nr)	
1	66	1.3 (1.0–1.8)	
2+	63	1.8 (1.3–2.5)	
Exposure to Mecoprop	23	2.1 (1.2–5.4)	
Exposure to 2,4-D	49	0.9 (0.7–1.3)	
Pesticide exposure of ≥ 10 h/yr	131	1.4 (1.1–1.8)	McDuffie et al., 2001
2,4-D	111	1.3 (1.0–1.7)	
Mecoprop	53	2.3 (1.6–3.4)	
Danish residents (Copenhagen and Aarhus) in the Diet, Cancer and Health prospective study diagnosed with NHL from enrollment (1994–5/1977) through 2008		**Organochlorines**	Bräuner et al., 2012
Organochlorines in adipose tissue (ug/kg lipids)			
dl PCB 118			
10–25	53	1.0 (nr)	
25–34	63	0.9 (0.5–1.6)	
34–48	58	1.0 (0.6–1.7)	
48–62	34	0.7 (0.3–1.3)	
62–150	25	0.7 (0.4–1.4)	
dl PCB 156			
13–28	62	1.0 (nr)	
28–34	51	0.6 (0.3–1.0)	
34–41	54	0.7 (0.4–1.2)	
41–50	45	0.9 (0.5–1.8)	
50–88	23	0.7 (0.3–1.4)	

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Denmark—Danish farm workers—incidence		**Phenoxy herbicides**	Ronco et al., 1992
	147	1.0 (nr)	
Italian farm workers—mortality	14	1.3 (nr)	
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	25	1.3 (0.7–2.2)	
Phenoxy herbicides	11	0.9 (0.4–1.9)	
Domestic use of herbicides	86	1.0 (0.7–1.5)	
German population-based study (1986–1998), men and women, 15–75 yrs of age—occupational factors associated with NHL		**TCDD, Herbicides**	Richardson et al., 2008
Chlorophenols			
NHL—high-grade malignancy	61	2.0 (1.3–2.9)	
NHL—low-grade malignancy	77	1.3 (1.0–1.8)	
CLL	44	0.9 (0.6–1.3)	
Herbicides			
NHL—high-grade malignancy	56	2.2 (1.4–3.3)	
NHL—low-grade malignancy	79	1.4 (1.0–1.9)	
CLL	43	1.2 (0.8–1.7)	
Irish farmers and farm workers		**Herbicides**	Dean, 1994
Other malignant neoplasms of lymphoid and histiocytic tissue (including some types of NHL) (ICD-9 202)	164	1.8 (1.2–2.6)	
Italian incident cases of malignancies of the hematolymphopoietic system in men and women (20–74 yrs of age) from agricultural and mixed use areas (HD cases = 258)		**Herbicides**	Miligi et al., 2006
Men, women	73	1.0 (0.7–1.4)	
Men	49	0.8 (0.5–1.3)	
Women	24	1.3 (0.7–2.5)	
NHL (men, women)			
Phenoxy herbicides—ever	32	1.1 (0.6–1.8)	
Probability of use more than "low," lack of protective equipment	13	2.4 (0.9–7.6)	
2,4-D—ever	17	0.9 (0.5–1.8)	
Probability of use more than "low," lack of protective equipment	9	4.4 (1.1–29.1)	
MCPA—ever	18	0.9 (0.4–1.8)	
Probability of use more than "low," lack of protective equipment	7	3.4 (0.8–23.2)	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Italian residents of 11 areas (NHL other than lymphosarcoma and reticulosarcoma)—incidence		**Herbicides**	Miligi et al., 2003
Phenoxy acid herbicides exposure			
Men	18	1.0 (0.5–2.0)	
Women	11	1.3 (0.5–3.7)	
2,4-D exposure			
Men	6	0.7 (0.3–1.9)	
Women	7	1.5 (0.4–5.7)	
Italian farming and animal-breeding workers (men and women) (NHL other than lymphosarcoma and reticulosarcoma)—incidence		**Herbicides**	Nanni et al., 1996
Exposure to herbicides	3	1.4 (0.4–5.7)	
Italian farming, animal-breeding workers (men and women)—incidence		**Herbicides**	Amadori et al., 1995
NHL, CLL combined	164	1.8 (1.2–2.6)	
Residents of selected **Italian** provinces		**Herbicides**	Vineis et al., 1991
Male residents of contaminated areas	nr	2.2 (1.4–3.5)	
Residents of Milan, **Italy**, area (men and women)—incidence		**Herbicides**	LaVecchia et al., 1989
Agricultural occupations	nr	2.1 (1.3–3.4)	
New Zealand National Cancer Registry (1980–1984)—case-control study of 652 incident NHL cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)			
Aged 20–59	4	2.0 (0.7–5.6)	
Aged ≥ 60	3	1.7 (0.5–5.4)	
Sawmill workers (n = 139)		**Herbicides, Chlorophenols**	
	4	1.2 (0.4–3.2)	
New Zealand National Cancer Registry (1977–1981) (< 70 yrs of age)—incidence (1977–1981) (ICD-9 200, 202)		**Herbicides**	Pearce et al., 1987
Farming occupations	33	1.0 (0.7–1.5)	
Fencing work	68	1.4 (1.0–2.0)	
New Zealand National Cancer Registry (1977–1981) (< 70 yrs of age)—incidence (1977–1981) (ICD-9 202 only)		**Phenoxy herbicides**	Pearce et al., 1986b
Agricultural sprayers	19	1.5 (0.7–3.3)	

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
New Zealand National Cancer Registry (1977–1981) (≥ 20 yrs of age) with agricultural occupations—incidence (ICD-9 200 and 202)	nr	**Herbicides** 1.4 (0.9–2.0)	Pearce et al., 1985
Sweden—male, female subjects (18–74 yrs of age) with NHL living in Sweden between Dec 1, 1999, and April 30, 2002 vs controls from national population registry		**Pesticides, herbicides**	Eriksson et al., 2008
Herbicides, total	74	1.7 (1.2–2.5)	
≤ 20 days	36	1.6 (1.0–2.7)	
> 20 days	38	1.9 (1.1–3.2)	
Phenoxyacetic acids	47	2.0 (1.2–3.4)	
≤ 45 days	32	2.8 (1.5–5.5)	
> 45 days	15	1.3 (0.6–2.7)	
MCPA	21	2.8 (1.3–6.2)	
≤ 32 days	15	3.8 (1.4–10.5)	
> 32 days	6	1.7 (0.5–6.0)	
2,4,5-T, 2,4-D	33	1.6 (0.9–3.0)	
≤ 29 days	21	2.1 (1.0–4.4)	
> 29 days	12	1.3 (0.6–3.1)	
Sweden—male and female patients (18–74 yrs of age) diagnosed Dec 1999–April 2002		**Pesticides, herbicides**	Hardell et al., 2002
Chlorophenols			
NHL—high grade malignancy	61	2.0 (1.3–2.9)	
Sweden—pooled analysis of case-control NHL, hairy-cell leukemia studies		**Herbicides**	Hardell et al., 2002
Herbicide exposure	77	1.8 (1.3–2.4)	
Phenoxyacetic acids	64	1.7 (1.2–2.3)	
MCPA	21	2.6 (1.4–4.9)	
2,4-D, 2,4,5-T	48	1.5 (1.0–2.2)	
Other	15	2.9 (1.3–6.4)	
Substantial exposure	5	1.8 (0.4–7.4)	
Sweden—adipose tissue from 33 NHL patients and 39 surgical controls from Örebro-Uppsala medical region (1994–1997)		**Dioxin, dibenzofurans**	Hardell et al., 2001
TEQ > 27.8, EA > 80	8	2.8 (0.5–18.0)	
Umea (**Sweden**) Hospital patients—incidence		**Phenoxy herbicides, chlorophenols**	Hardell et al., 1994
Exposed to phenoxy herbicides	25	5.5 (2.7–11.0)	
Exposed to chlorophenols	35	4.8 (2.7–8.8)	

continued

TABLE 8-41 Non-Hodgkin Lymphoma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Swedish Regional Cancer Registry—NHL patients		**Phenoxy herbicides**	Persson et al., 1993
Exposed to phenoxy herbicides	10	2.3 (0.7–7.2)	
Exposed to chlorophenols	9	6.0 (1.1–31.0)	
Örebro (**Sweden**) Hospital (men and women)—incidence		**Phenoxy herbicides, chlorophenols**	Persson et al., 1989
Exposed to phenoxy acids	6	4.9 (1.0–27.0)	
Lund (**Sweden**) Hospital patients—incidence		**Herbicides**	Olsson and Brandt, 1988
Exposed to herbicides	nr	1.3 (0.8–2.1)	
Exposed to chlorophenols	nr	1.2 (0.7–2.0)	
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981
Exposed to phenoxy herbicides	41	4.8 (2.9–8.1)	
Exposed to chlorophenols	50	4.3 (2.7–6.9)	
CASE-CONTROL STUDIES			
Participants in the EPILYMPH study in six European countries (1998–2003)		**Pesticides**	Cocco et al., 2012
Exposure to phenoxy herbicides and CLL	2	0.9 (0.2–4.1)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; CA, California; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CLL, chronic lymphocytic leukemia; COI, chemical of interest; dl, dioxin-like; EA, early antigen; EOI, Exposure Opportunity Index; HD, Hodgkin disease; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; ICDA, *International Classification of Diseases*, Adapted for Use in the United States; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; NKTCL, NK/T-cell lymphoma; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofuran; PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; USDA, United States Department of Agriculture; VA, US Department of Veterans Affairs; WHO, World Health Organization.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all of forms of lymphoma (including Hodgkin disease and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

[d]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

TABLE 8-42 Selected Epidemiologic Studies—Chronic Lymphocytic Leukemia (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
International Vietnam-Veteran Study			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	58	1.2 (0.7–1.7)	ADVA, 2005b
Navy	12	1.5 (0.8–2.6)	
Army	42	1.7 (1.2–2.2)	
Air Force	4	0.9 (0.2–2.2)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence—all leukemias (1969–1989)	47	1.2 (0.9–1.5)	Hertzman et al., 1997
ALL	2	1.0 (0.2–3.1)	
CLL	24	1.7 (1.2–2.4)	
AML	5	0.8 (0.3–1.7)	
CML	7	1.1 (0.5–2.0)	
Other, unspecified	5	0.5 (0.2–1.0)	
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners		**Herbicides**	Hansen et al., 1992, 2007
10-year follow-up (1975–1984) of Danish gardeners			
All gardeners	6	2.5 (0.9–5.5)	
Male gardeners	6	2.8 (1.0–6.0)	
UNITED STATES			
White Male Residents of Iowa—chronic lymphocytic leukemia on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 yrs old when died 1964–1978—case-control (1,675 leukemia deaths, 1968–1978)			Burmeister et al., 1982
Farmer usual occupation on death certificate		1.2 ($p < 0.05$))	

continued

TABLE 8-42 Chronic Lymphocytic Leukemia, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
CLL	132	1.7 (1.2–2.4)	
Lived in counties with highest herbicide use	nr	1.9 (1.2–3.1)	
White Male Residents of Iowa and Minnesota— > 30 yrs old diagnosed 1981–1983 in Iowa or 1980–1982 in Minnesota—case-control		**Herbicides**	
> 30 yrs old diagnosed 1981–1983 in Iowa or 1980–1982 in Minnesota—case-control (ever farmer)			Brown et al., 1990
Ever farmed	156	1.4 (1.1–1.9)	
Any herbicide used	74	1.4 (1.0–2.0)	
Ever used 2,4,5-T	10	1.6 (0.7–3.4)	
Use at least 20 yrs before interview	7	3.3 (1.2–8.7)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women (lymphatic leukemia, ICD-9 204)			
Zone A	1	2.8 (0.4–19.9)	Pesatori et al., 2009
Zone B	0	nr	
Zone R	13	0.8 (0.5–1.5)	
Mortality			
25-yr follow-up to 2001—men and women (lymphatic leukemia, ICD-9 204)			Consonni et al., 2008
Zone A	0	nr	
Zone B	3	1.3 (0.4–4.1)	
Zone R	23	1.4 (0.9–2.2)	
20-yr follow-up to 1996 (lymphatic leukemia)			Bertazzi et al., 2001
Zones A, B—men	2	1.6 (0.4–6.8)	
Zones A, B—women	0	nr	
Other International Environmental Studies			
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		2,4,5-T	Read et al., 2007
Incidence	104	1.3 (1.1–1.6)[c]	
1970–1974	16	2.5 (1.4–4.1)	
1975–1979	7	0.9 (0.4–1.8)	

TABLE 8-42 Chronic Lymphocytic Leukemia, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
1980–1984	21	2.6 (1.6–3.9)	
1985–1989	16	1.4 (0.8–2.3)	
1990–1994	13	0.9 (0.5–1.6)	
1995–1999	19	0.9 (0.5–1.4)	
2000–2001	12	1.1 (0.6–1.9)	
Mortality	40	1.3 (0.9–1.8)[c]	
1970–1974	7	1.7 (0.7–3.5)	
1975–1979	7	1.8 (0.7–3.6)	
1980–1984	6	1.4 (0.5–3.0)	
1985–1989	4	0.8 (0.2–2.2)	
1990–1994	6	1.1 (0.4–2.5)	
1995–1999	8	1.3 (0.6–2.6)	
2000–2001	2	0.8 (0.1–2.8)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Tecumseh, Michigan residents participating in longitudinal study (1959–1987)	10	**Herbicides** 1.8 (0.8–3.2)	Waterhouse et al., 1996
Nebraska—1,084 leukemia deaths in 1957–1974; farmers–usual occupation on death certificate	nr	**Herbicides, pesticides** 1.3 ($p < 0.05$)	Blair and White, 1985
248 CLL cases	nr	1.7 ($p < 0.05$)	
International Case-Control Studies			
Europe—Participants in the EPILYMPH study in six European countries (1998–2003)		**Pesticides**	Cocco et al., 2012
Exposure to phenoxy herbicides and CLL	2	0.9 (0.2–4.1)	
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	5	0.5 (0.2–1.3)	
Phenoxy herbicides	3	0.4 (0.1–1.7)	
German population-based study (1986–1998), men and women, 15–75 yrs of age—occupational factors associated with CLL		**TCDD, Herbicides**	Richardson et al., 2008
Chlorophenols	44	0.9 (0.6–1.3)	
Lowest tertile cumulative exposure	12	0.9 (0.4–1.8)	
Middle tertile	15	0.9 (0.5–1.8)	
Highest tertile	17	0.9 (0.5–1.6) p-trend = 0.770	
Herbicides	43	1.2 (0.8–1.7)	
Lowest tertile cumulative exposure	13	1.3 (0.7–2.7)	
Middle tertile	15	1.3 (0.7–2.5)	
Highest tertile	15	1.0 (0.5–1.9) p-trend = 0.755	

continued

TABLE 8-42 Chronic Lymphocytic Leukemia, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Italian farming, animal-breeding workers (men and women)—incidence	15	**Herbicides** 2.3 (0.9–5.8)	Amadori et al., 1995
Farming workers only	5	1.6 (0.5–5.2)	
Breeding workers only	10	3.1 (1.1–8.3)	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; nr, not reported; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]The total SMR/SIR were computed by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

pesticide exposures, and no significant association was observed between any kind of pesticide or herbicide use and lymphomas or its subtypes, including between exposure to phenoxy acid and CLL (OR = 0.9, 95% CI 0.2–4.1).

Pronk et al. (2013) conducted a population-based case-control study of NHL in four NCI SEER Centers (Detroit, Iowa, Los Angeles, and Seattle) from 1998 to 2000. They used residential history from 15 years prior to diagnoses to link residence to EPA databases of dioxin-emitting facilites, studying 969 cases and 749 controls. Proximity to any dioxin-emitting facility was not associted with NHL (3km OR = 1.0, 95% CI 0.8–1.3). However despite the fact that these are relatively well-conducted studies, the lack of exposure specificity makes both of limited utility for the committee.

Environmental and Case-Control Studies The Cross Canada Study of Pesticides and Health is a population-based incident case-control study in six Canadian provinces conducted between 1991 to 1994. Men 19 years and older who had a first diagnosis of STS, NHL, multiple myeloma, or HL during these years were included and followed in mailed and telephone interviews. Pahwa et al. (2012b) used these data to examine the joint effects of asthma, allergies, or asthma and allergies and hay fever combined with pesticide exposure in the genesis of NHL. Incident NHL cases (n = 513) diagnosed between 1991 and 1994 were compared with the experience of 1,506 controls, and a stratified analysis was employed to calculate adjusted ORs in estimating effect modification. Subjects with asthma, allergies, or hay fever had non-significantly elevated risks associated with the use of phenoxy herbicides (OR = 1.49, 95% CI 0.95–2.33), MCPA

(4-chloro-2-methylphenoxy) acetic (OR = 2.67, 95% CI 0.90–7.93), or 2,4-D (OR = 1.36, 95% CI 0.86–2.16). The results overall were not supportive of any major effect modification by these immune conditions.

Boccolini et al. (2013) sought to examine the possible correlation between sales of pesticides and NHL mortality rates in Brazil. This ecological study included a lagged design (exposure from sales in 1985 with deaths from NHL in 1996–2005) with examinations of sales in microregions (proxies for exposure levels) of the country. The authors reported a moderate correlation of per capita pesticide sales and the SMR for NHL (r = 0.597). There was a suggestion of an increase in the correlation of sales and NHL occurrence by quartile of pesticide consumption, as well. However, the exposure is essentially unknowable, making this work of minimal use to the committee.

Finally, Salem et al. (2014) conducted a relatively small case-control study in Egypt, assessing self-reported pesticide exposure and lymphoproliferative disorders in a hospital-based retrospective study of 130 cases and 130 controls conducted in 2011–2012. In this study, exposure to pesticides was a significant risk factor (OR = 2.24, 95% CI 1.22–4.11). While this is supportive of much of the large body of evidence reviewed here, again there is no exposure specificity and the study is quite underpowered, again offering the committee little new information.

Biologic Plausibility

The diagnosis of NHL encompasses a wide variety of lymphoma subtypes. In humans, about 85 percent are of B-cell origin and 15 percent of T-cell origin. In commonly used laboratory mice, the lifetime incidence of spontaneous B-cell lymphomas is about 30 percent in females and about 10 percent in males. Although researchers seldom note the subtypes of B-cell lymphomas observed, lymphoblastic, lymphocytic, follicular, and plasma-cell lymphomas are seen in mice and are similar to the types of NHL seen in humans. Laboratory rats, however, are less prone to develop lymphomas, although Fisher 344 rats do have an increased incidence of spontaneous mononuclear-cell leukemia of non-specific origin. The lifetime incidence of leukemia is about 50 percent in male rats and about 20 percent in female rats. Neither mice nor rats develop T-cell lymphomas spontaneously at a predictable incidence, but T cell–derived tumors can be induced by exposure to some carcinogens.

Several long-term feeding studies of various strains of mice and rats have been conducted over the past 30 years to determine the effects of TCDD on cancer incidence. Few of them have shown effects of TCDD on lymphoma or leukemia incidence. The NTP (1982a) reported no increase in the overall incidence of lymphoma in female B6C3F1 mice exposed to TCDD at 0.04, 0.2, or 2.0 μg/kg per week for 104 weeks but found that histiocytic lymphomas (now considered to be equivalent to large B-cell lymphomas) were more common in

the high-dose group. No effects on lymphoma incidence were seen in Osborne–Mendel rats treated with TCDD at 0.01, 0.05, or 0.5 µg/kg per week. Sprague Dawley rats treated with TCDD at 0.003, 0.010, 0.022, 0.046, or 0.100 µg/kg per day showed no change in incidence of malignant lymphomas. Long-term exposure to phenoxy herbicides or cacodylic acid also has not resulted in an increased incidence of lymphomas in laboratory animals. Thus, few laboratory animal data support the biologic plausibility of promotion of NHL by TCDD or the other COIs, but it should be noted that the standard rodent models are not particularly sensitive for the detection of chemicals that cause lymphohematopoietic cancers.

In contrast, more recent studies at the cellular level indicate that activation of the AHR by TCDD inhibits apoptosis, a mechanism of cell death that controls the growth of cancer cells. Vogel et al. (2007) studied human cancer cells in tissue culture and showed that the addition of TCDD inhibited apoptosis in histiocytic-lymphoma cells, Burkitt-lymphoma cells, and NHL cell lines. The reduction in apoptosis was associated with an increase in the expression of *Cox-2*, *C/EBP* β, and *Bcl-xL* mRNA in the cells. Those genes code for proteins that protect cells from apoptosis. The effects of TCDD on apoptosis were blocked when an AHR antagonist or a Cox-2 inhibitor was added to the culture; this demonstrated the underlying AHR-dependent mechanism of the effects. More important, when C57Bl/10J mice were given multiple doses of TCDD over a period of 140 days, premalignant lymphoproliferation of B cells was induced before the appearance of any spontaneous lymphomas in the control mice. When the B cells were examined, they were found to manifest changes in gene expression similar to those induced by TCDD in the human cell lines, which provided support for this mechanism of lymphoma promotion by TCDD.

It is well established that AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the interleukin-6 (IL-6) cytokine, which has tumor-promoting effects in numerous tissues (Hollingshead et al., 2008). IL-6 plays a roll in B-cell maturation and induces a transcriptional inflammatory response. It is known to be increased in B-cell neoplasms, including multiple myeloma and various lymphomas, especially diffuse large B-cell lymphomas (Hussein et al., 2002; Kato et al., 1998; Kovacs, 2006).

An alternative link that could help to explain the association between TCDD and NHL has been explored in human studies. Chromosomal rearrangements, with the consequent dysregulation of expression of various genes, are prevalent in B-cell lymphomas, and the t(14;18) reciprocal translocation, which juxtaposes the BCL2 with the locus of the immunoglobin heavy chain, is found in tumor cells in most cases of follicular lymphoma. Roulland et al. (2004) investigated the prevalence of the t(14;18) translocation that is characteristic of most cases of follicular lymphoma in 53 never-smoking and pesticide-using men in a cohort of French farmers whose pesticide exposures and confounding information had previously been well characterized; blood samples had been gathered from 21 of them during periods of high pesticide use and samples from the other 32 during

a period of low pesticide use. The authors found a higher prevalence of cells carrying the translocation in the farmers whose blood had been drawn during a period of high pesticide use than in those whose blood had been drawn during a low-use period. Baccarelli et al. (2006) reported an increase in t(14;18) chromosomal translocation in lymphocytes from humans who were exposed to TCDD in the Seveso accident. In most cases of follicular lymphoma, tumor cells carry the t(14;18) chromosomal translocation, and there is evidence that an increased frequency of lymphocytes from the peripheral blood carrying this tumor marker may be a necessary but not sufficient step toward development of follicular lymphoma (Roulland et al., 2006).

More recently, Saberi Hosnijeh et al. (2011, 2012a,b, 2013a,b) have published a series of papers examining factors associated with immune regulations and possibly related to B-cell neoplasms and serum TCDD levels in Dutch production workers from a subcohort of the IARC study sample. The mortality status of the entire subcohort was updated and blood samples were gathered in 2007–2008 from a small number of survivors (Boers et al., 2010)—45 who had TCDD exposure in factory A, 39 whose jobs in factory A did not expose them to TCDD, and 69 in factory B that produced phenoxy herbicides not subject to TCDD contamination. Boers et al. (2012) modeled the resulting contemporary TCDD serum levels to back extrapolated TCDD concentrations at the end of employment for each worker. When examining immunoglobulin (IgG, IgA, IgM, IgD, and IgE) and complement (C3 and C4) concentrations measures of humoral immunity, Saberi Hosnijeh et al. (2011) found a consistent pattern only for C4, which was negatively associated with both measured current and estimated maximum TCDD serum concentrations. Limiting the analyses to workers from Factory A and examining *serum concentrations of 16 cytokines, 10 chemokines, and 6 growth factors*, Saberi Hosnijeh et al. (2012a) found most analytes were *negatively* associated with current and estimated past maximum TCDD levels. Saberi Hosnijeh et al. (2012b) found that for both cell counts and lymphocytes, results were similar between high- and low-exposed workers from Factory A, except for a non-dose-dependent increase in the CD4/CD8 ratio among the high-exposed workers. Most lymphocyte subsets, in particular the B-cell compartment, showed decreases with higher levels of both current and estimated maximum levels of TCDD. Saberi Hosnijeh et al. (2013a) addressed plasma levels of *CD27*, *CD30*, and IL1RA, which are proteins that regulate immune function and thought to be involved in lymphopoeitic neoplasms, and found a tendency toward decreased levels with increasing TCDD concentrations, which would be consistent with immune suppression. Similarly, Saberi Hosnijeh et al. (2013b) investigated the possibility of a relationship between TCDD levels and serum metabolites, but found no notable patterns. Overall, this set of findings in a group of workers with an elevated incidence of NHL at its most recent mortality update provides some insight into the biological processes, particularly immunological ones, that TCDD might stimulate on the path to this malignancy.

Synthesis

The first VAO committee found the evidence to be sufficient to support an association between exposure to at least one of the COIs and NHL. The evidence was drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components. As has generally been the case in previous updates, the new studies of NHL incidence and mortality that were reviewed in this update (McBride et al., 2013; Pahwa et al., 2012; Yi and Ohrr, 2014; Yi et al., 2014b) were largely concordant with the conclusion that there is an association with the COIs, as were the new analyses of various biomarkers of immune function and TCDD serum levels in workers from the Dutch IARC subcohort (Saberi Hosnijeh et al., 2012b, 2013a,b).

Individual findings on CLL are fairly few compared with the considerable number of studies supporting an association between exposure to the COIs and NHL. Results of some high-quality studies show that exposure to 2,4-D and 2,4,5-T appears to be associated with CLL, including the incidence study of Australian veterans (ADVA, 2005a), the case-control study by Hertzman et al. (1997) of British Columbia sawmill workers who were exposed to chlorophenates, the Danish-gardener study (Hansen et al., 1992), and the population-based case-control study in two US states by Brown et al. (1990) that showed increased risks associated with any herbicide use and specifically the use of 2,4,5-T for at least 20 years before the interview. Other studies that showed positive associations but do not contribute greatly to the overall conclusion include the population-based case-control study by Amadori et al. (1995) that used occupational titles but did not include specific assessments of exposure to the chemicals; the cancer-incidence study in Tecumseh County, Michigan, in which no exposure assessments were available (Waterhouse et al., 1996); and proportionate-mortality studies by Blair and White (1985) and Burmeister et al. (1982).

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the COIs and NHL.

Multiple Myeloma

Multiple myeloma (ICD-9 203.0) is characterized by a proliferation of bone-marrow stem cells that results in an excess of neoplastic plasma cells and in the production of excess abnormal proteins, usually fragments of immunoglobulins. Multiple myeloma is sometimes grouped with other immunoproliferative neoplasms (ICD-9 203.8). ACS estimated that 14,090 men and 12,760 women would receive diagnoses of multiple myeloma in the United States in 2015 and that

6,240 men and 5,000 women would die from it (Siegel et al., 2015). The average annual incidence of multiple myeloma is shown in Table 8-43.

The incidence of multiple myeloma is highly age-dependent and is relatively low in people under 40 years old. The incidence is slightly higher in men than in women, and the difference becomes more pronounced with age.

An increased incidence of multiple myeloma has been observed in several occupational groups, including farmers and other agricultural workers and those with workplace exposure to paint strippers, petroleum, and certain metals, minerals, and chemical substances (Sergentanis et al., 2015). People who have high exposure to ionizing radiation and those who suffer from other plasma-cell diseases, such as monoclonal gammopathy of unknown significance or solitary plasmacytoma, are also at greater risk (Sergentanis et al., 2015).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to the COIs and multiple myeloma. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion.

Table 8-44 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran and Environmental Studies McBride and colleagues (2013) followed 2,783 male veterans from New Zealand, who served in Vietnam between 1964 and 1972, for cancer incidence and mortality. Standardized incidence and mortality ratios were generated by comparing the observed incident cases and deaths in this cohort with the corresponding expected numbers of new cases and deaths rates from the general male population of New Zealand. The researchers reported a non-significant excess of deaths from multiple myeloma (SMR = 1.58, 95% CI 0.51–3.69), based upon five deaths. Consistent with this, they also report

TABLE 8-43 Average Annual Incidence (per 100,000) of Multiple Myeloma in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	19.5	18.1	39.4	29.2	26.9	60.9	41.7	39.1	79.8
Women	13.1	10.9	32.7	19.6	17.6	41.7	24.9	22.1	53.1

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

TABLE 8-44 Selected Epidemiologic Studies—Multiple Myeloma (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Mortality			Boehmer et al., 2004
1965–2000	1	0.4 (nr)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	36	0.9 (nr)	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	4	0.6 (nr)	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs non-deployed (n = 22,904)	18	0.8 (0.2–2.5)	
Marine Corps, deployed (n = 4,527) vs non-deployed (n = 3,781)	2	0.5 (0.0–17.1)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality, through 2004	18	0.7 (0.4–1.3)	Cypel and Kang, 2008
Vietnam-veteran nurses only	14	0.7 (0.3–1.3)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	31	0.7 (0.4–0.9)	ADVA, 2005b

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Navy	4	0.4 (0.1–1.0)	
Army	21	0.7 (0.4–1.0)	
Air Force	6	1.1 (0.4–2.4)	
Mortality			
All branches, return–2001	24	0.9 (0.5–1.2)	ADVA, 2005a
Navy	3	0.5 (0.1–1.5)	
Army	15	0.8 (0.4–1.3)	
Air Force	6	1.7 (0.6–3.6)	
1980–1994	6	0.6 (0.2–1.3)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence			
1982–2000	8	2.1 (0.7–6.0)	ADVA, 2005c
Mortality			
1966–2001	5	0.9 (0.2–3.4)	ADVA, 2005c
1982–1994	0	nr	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	9	1.5 (0.7–2.9)	
Mortality (1988–2008)	5	1.6 (0.5–3.7)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)—MM (90) categorized high (n = 28) vs low (n = 23)	28	1.1 (0.7–2.0)	Yi and Ohrr, 2014
Mortality (1992–2005)—MM (90) categorized high (n = 19) vs low (n = 20)		0.8 (0.4–1.5)	Yi et al., 2014b
HR per unit of log EOI scores (n = 180,639)	39	1.0 (0.9–1.1)	
OCCUPATIONAL—Industrial			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			

continued

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1939–1992	17	1.3 (0.8–2.1)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	9	1.2 (0.6–2.3)	
7,553 not exposed to highly chlorinated PCDDs	8	1.6 (0.7–3.1)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	4	0.7 (0.2–1.8)	Saracci et al., 1991
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1987 (men only)	0	nr	Lynge, 1993
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991	0	0.0 (nr)	Hooiveld et al., 1998
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	nr	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1965–1989	0	nr	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1956–1989	0	nr	Becher et al., 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,5-DCP; 2,4,5-T; 2,4,5-TCP**	

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality 1952–1989	3	5.4 (1.1–15.9)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	2.2 (0.2–8.1)	
Never-exposed workers	0	0.0 (0.0–12.2)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			't Mannetje et al., 2005
Mortality 1969–2000	3	5.5 (1.1–16.1)	
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	0	0.0 (0.0–5.3)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	10	2.1 (1.0–3.8)	Steenland et al., 1999
Through 1987	5	1.6 (0.5–3.9)	Fingerhut
≥ 1-yr exposure, ≥ 20-yr latency	3	2.6 (0.5–7.7)	et al., 1991
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	7	1.5 (0.6–3.1)	
PCP and TCP (n = 720)	1	0.7 (0.0–4.0)	
PCP (no TCP) (n = 1,402)	6	1.8 (0.7–4.0)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	2	0.8 (0.1–2.9)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	1	0.8 (0.0–4.5)	Burns et al., 2001

continued

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—Paper And Pulp Workers		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	21	0.8 (0.5–1.3)	
Ever	20	1.1 (0.7–1.7)	
OCCUPATIONAL—Herbicide-Using Workers (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from MM June 1971–Dec 1987			
Farmers from Canadian prairie provinces	160	0.8 (0.7–1.0)	Semenciw et al., 1994
DENMARK			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	3	2.1 (0.4–6.1)	Swaen et al., 2004
Through 1987	3	8.2 (1.6–23.8)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC		**Phenoxy herbicides**	
Incidence	2	1.5 (0.2–5.2)	Asp et al., 1994
Mortality 1972–1989	3	2.6 (0.5–7.7)	
Except for lung cancer, #s too small for reporting mortality 1972–1980		*Expected number of exposed cases*	Riihimaki et al., 1982
	1	0.2 (nr)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	5	0.4 (0.1–1.0)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	0	nr	

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident multiple myeloma cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	1	0.5 (0.1–3.7)	
SWEDISH lumberjacks—Used phenoxys 1954–1967, incidence (1958–1992)			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	0		
Lumberjacks (n = 139)	0		
Unexposed lumberjacks (n = 241)	1	1.5 (0.0–8.6)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	413	1.2 (1.0–1.3)	
Nonwhites (n = 11,446)	51	0.9 (0.7–1.2)	
Women			
Whites (n = 2,400)	14	1.8 (0.97–3.0)	
Nonwhites (n = 2,066)	11	1.1 (0.6–2.0)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	71	1.2 (0.9–1.5)	
Commercial applicators	1	nr	
Spouses	21	0.9 (0.6–1.4)	
Nested case-control study of MGUS among male private and commercial applicators			Landgren et al., 2009
2,4-D	33	1.8 (0.7–4.8)	
Dicamba	17	0.9 (0.5–1.8)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	43	1.3 (1.0–1.8)	

continued

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Spouses of private applicators (> 99% women)	13	1.1 (0.6–1.9)	
Commercial applicators	0	0.0 (0.0–2.7)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner
Applicators (n = 1,641)	52	1.0 (0.8–1.3)	et al., 2011
Spouses (n = 676)	10	0.6 (0.3–1.0)	
Enrollment through 2000, vs state rates			Blair et al.,
Private applicators (men and women)	11	0.6 (0.3–1.2)	2005a
Spouses of private applicators (> 99% women)	5	0.9 (0.3–2.1)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of MM		**Herbicides**	
Forest conservationists	1.3	nr (p-trend = 0.35)	Alavanja et al., 1989
Soil conservationists	1.3	nr (p-trend = 0.32)	
White Male Residents of Iowa—MM on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 yrs old diagnosed 1981–1984—case-control (ever farmer)	111	1.2 (0.8–1.7)	Brown et al., 1993
> 30 yrs old when died 1964–1978—case-control			Burmeister et al., 1983
H_0: only for "modern methods" → born after 1900			
Born 1980–1900	nr	2.7 ($p < 0.05$)	
Born after 1900	nr	2.4 ($p < 0.05$)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence			
20-yr follow-up to 1996—men and women			
Zone A	1	2.9 (0.4–20.7)	Pesatori
Zone B	6	2.8 (1.2–6.3)	et al., 2009
Zone R	18	1.2 (0.7–1.9)	

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
10-yr follow-up to 1991—men			Bertazzi
Zone B	2	3.2 (0.8–13.3)	et al., 1993
Zone R	1	0.2 (0.0–1.6)	
10-yr follow-up to 1991—women			Bertazzi
Zone B	2	5.3 (1.2–22.6)	et al., 1993
Zone R	2	0.6 (0.2–2.8)	
Mortality			
25-yr follow-up to 2001—men and women			Consonni
Zone A	2	4.3 (1.1–17.5)	et al., 2008
Zone B	5	1.7 (0.7–4.1)	
Zone R	24	1.1 (0.7–1.7)	
20-yr follow-up to 1996			Bertazzi
Zones A, B—men	1	0.6 (0.1–4.3)	et al., 2001
Zones A, B—women	4	3.2 (1.2–8.8)	
15-yr follow-up to 1991—men			Bertazzi
Zone B	1	1.1 (0.0–6.2)	et al., 1997
Zone R	5	0.8 (0.3–1.9)	
15-yr follow-up to 1991—women			Bertazzi
Zone B	4	6.6 (1.8–16.8)	et al., 1997
Zone R	5	1.0 (0.3–2.3)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
ACS Prevention Study II subjects, MM on death certificate (128 MM cases vs 154 controls)		**Herbicides, pesticides**	Boffetta et al., 1989
	12	2.1 (1.0–4.2)	
Farmers using herbicides, pesticides	8	4.3 (1.7–10.9)	
Residents of four SEER program areas, 698 cases (< 80 yrs of age) vs 1,683 controls (July 1977–June 1981)	nr	**Pesticides** 2.9 (1.5–5.5)	Morris et al., 1986
Nebraska herbicide and pesticide use by Nebraska residents		**Herbicides**	Zahm et al., 1992
Eastern Nebraska users of herbicides			
Men	8	0.6 (0.2–1.7)	
Women	10	2.3 (0.8–7.0)	
Eastern Nebraska users of insecticides			
Men	11	0.6 (0.2–1.4)	
Women	21	2.8 (1.1–7.3)	
Wisconsin mortality listings (1968–1976)—farmers (30–39 yrs of age) in counties with highest herbicide use	nr	**Herbicides** 1.4 (0.8–2.3)	Cantor and Blair, 1984

continued

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
International Case-Control Studies			
Cross Canada Study of Pesticides and Health—men in 1 of 6 Canadian provinces (> 19 yrs of age) diagnosed 09/1991–12/1994 (n = 342) vs population-based matched controls (n = 1,506)		**Phenoxy herbicides**	Kachuri et al., 2013; Pahwa et al., 2006, 2012a,b
Expose to any phenoxy herbicide	87	1.3 (1.0–1.8)	
2,4-D	80	1.3 (1.0–1.8)	
Mecoprop	27	1.9 (1.2–3.2)	
MCPA	8	0.7 (0.3–1.5)	
Days/year of mixing or applying phenoxy herbicides			
> 0 and ≤ 2	35	1.5 (1.0–2.3)	
> 2 and ≤ 5	23	1.3 (0.8–2.8)	
> 5	26	1.1 (0.7–1.9)	
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	12	2.9 (1.3–6.5)	
Phenoxy herbicides	7	2.6 (0.9–7.0)	
Domestic use of herbicides	22	1.0 (0.6–2.0)	
Irish farmers and farm workers		**Herbicides**	Dean, 1994
Other malignant neoplasms of lymphoid and histiocytic tissue (including some types of NHL) (ICD-9 202)	171	1.0 (nr)	
Italian residents of 11 areas (NHL other than lymphosarcoma and reticulosarcoma)—incidence		**Herbicides**	Miligi et al., 2003
Herbicide exposure	11	1.6 (0.8–3.5)	
Men	8	1.4 (0.6–3.5)	
Women	3	3.2 (0.7–14.7)	
Residents of Milan, **Italy**, area (men and women)—incidence		**Herbicides**	LaVecchia et al., 1989
Agricultural occupations	nr	2.0 (1.1–3.5)	
New Zealand National Cancer Registry (1977–1981)—agricultural workers (< 70 yrs of age) (76 MM cases vs 315 controls)—incidence		**Phenoxy herbicides, chlorophenols**	Pearce et al., 1986a
Use of agricultural spray	16	1.3 (0.7–2.5)	
Likely sprayed 2,4,5-T	14	1.6 (0.8–3.1)	

TABLE 8-44 Multiple Myeloma, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Swedish residents from 4 counties diagnosed with MM (n = 275) vs 275 controls from population registry (July 1982–June 1986)		**Phenoxy herbicides** 90% CI	Eriksson and Karlsson, 1992
Exposed to phenoxy herbicides	20	2.2 (1.2–4.7)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACS, American Cancer Society; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SEA, Southeast Asia; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

a non-significant excess incidence (SIR = 1.51, 95% CI 0.69–2.86) based upon nine cases.

Mortality (Yi et al., 2014b) and cancer incidence (Yi and Ohrr, 2014) were assessed among Korean veterans who had served in Vietnam between 1964 and 1973. In analyses of cancer incidence, Yi and Ohrr (2014) reported a non-significant increased risk of multiple myeloma (HR = 1.14, 95% CI 0.65–2.01) in the internal comparison of the high- and low-exposure groups based on the EOI scores. Similarly for multiple myeloma mortality, Yi et al. (2014b) reported a decreased risk for the high- versus low-exposure groups (HR = 0.81, 95% CI 0.43–1.54) and with the individual log-transformed EOI scores (HR = 1.0, 95% CI 0.85–1.14).

Occupational and Environmental Studies Since *Update 2012* there have been no new publications on occupational or environmental studies of association between multiple myeloma and exposure to the COIs.

Case-Control Studies The Cross Canada Study of Pesticides and Health is a population-based incident case-control study in six Canadian provinces conducted between 1991 and1994. Men 19 years and older who had a first diagnosis

of STS, NHL, multiple myeloma, or HL during these years were included and followed in mailed and telephone interviews. Kachuri et al. (2013) assessed the association of pesticide exposures in these agricultural workers, asking if lifetime use of multiple pesticides was associated with multiple myeloma risk. Studying 342 cases (58 percent of those contacted) and 1,357 controls (48 percent of those contacted), they grouped pesticides by type, chemical class, and their carcinogenic potential and estimated risk, adjusted for age, residence, medical history and smoking. An increased risk of multiple myeloma was seen with exposure to Mecoprop (OR = 1.94, 95% CI 1.19–3.19) but not with exposure to 2,4-D (OR = 1.3, 95% CI 0.95–1.78). An evaluation of days per year of mixing or applying phenoxy herbicides were non-significantly elevated for less than or equal to 2 days per year (OR = 1.47, 95% CI 0.95–2.28), between 2 and 5 days (OR = 1.33, 95% CI 0.80–2.23), and more than 5 days (OR = 1.23, 95% CI 0.75–2.02). Although more precise in its exposure characterization than many similar studies, this work was limited in its usefulness by the lack of exposure specificity.

Biologic Plausibility

No animal studies have reported an association between exposure to the COIs and multiple myeloma. Thus, there are no specific animal data to support the biologic plausibility of such an association between the COIs and multiple myeloma.

The AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues (Hollingshead et al., 2008). IL-6 plays a role in B-cell maturation and induces a transcriptional inflammatory response. It is known to be increased in B-cell neoplasms, including multiple myeloma and various lymphomas (Hussein et al., 2002; Kovacs, 2006).

In comparing the frequency of specific variants of several metabolic genes between multiple myeloma cases and controls, Gold et al. (2009) found some indication of differences, particularly in *CYP1B1* and *AHR* alleles, that might reflect increased susceptibility to multiple myeloma after exposure to particular chemicals. A biochemical link to the COIs, however, is far from being established.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

Previous VAO reports found limited or suggestive evidence of an association between exposure to at least one of the COIs and multiple myeloma. Multiple myeloma is a type of lymphohematopoietic malignancy that is derived from antibody-secreting plasma cells from the B-cell lineage. The evidence of an association between the COIs and lymphomas (NHL, HL, and CLL/HCL) has

been classified as sufficient. Most of these cancers also arise from B cells, so the committee hypothesized that it would be etiologically plausible for the association with multiple myeloma to belong with the lymphomas in the sufficient category. Although many studies of exposure to pesticides in general and multiple myeloma found strong or at least positive associations, a review of studies that addressed an association between the specific COIs and multiple myeloma found that the results were considerably weaker than those for the other B-cell neoplasms and did not justify advancing multiple myeloma out of the limited or suggestive category.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one of the COIs and multiple myeloma.

AL Amyloidosis

The committee responsible for *Update 2006* moved the discussion of AL amyloidosis from the chapter on miscellaneous non-neoplastic health conditions to the cancer chapter to put it closer to related neoplastic conditions, such as multiple myeloma and some types of B-cell lymphomas. The conditions share several biologic features, notably the clonal hyperproliferation of B cell–derived plasma cells and the production of abnormal amounts of immunoglobulins.

The primary feature of amyloidosis (ICD-9 277.3; ICD-10 E85) is the accumulation and deposition in various tissues of insoluble proteins that were historically denoted by the generic term *amyloid*. Amyloid protein accumulates in the extracellular spaces of various tissues. The pattern of organ involvement depends on the nature of the protein; some amyloid proteins are more fibrillogenic than others. Amyloidosis is classified according to the biochemical properties of the fibril-forming protein. Excessive amyloid protein can have modest clinical consequences or can produce severe, rapidly progressive multiple-organ-system dysfunction. The annual incidence is estimated at 1/100,000; there are about 2,000 new cases each year in the United States.[3] Amyloidosis occurs mainly in people 50 to 70 years old and occurs more often in males than in females.

AL amyloidosis is the most common form of systemic amyloidosis; the *A* stands for *amyloid*, and the *L* indicates that the amyloid protein is derived from immunoglobin *light* chains. That links AL amyloidosis with other B-cell disorders that involve the overproduction of immunoglobin, such as multiple myeloma and some types of B-cell lymphomas. AL amyloidosis results from the overproduction of immunoglobulin light-chain protein from a monoclonal

[3]See http://www.cancer.net/cancer-types/amyloidosis/statistics, accessed June 13, 2013.

population of plasma cells. Clinical findings can include excessive AL protein or immunoglobulin fragments in the urine or serum, renal failure with nephrotic syndrome, liver failure with hepatomegaly, heart failure with cardiomegaly, marcroglossia, carpal tunnel syndrome, and peripheral neuropathy. Bone marrow biopsies commonly show an increased density of plasma cells, which suggests a premalignant state. Historically, that test emphasized routine histochemical analysis, but modern immunocytochemistry and flow cytometry now commonly identify monoclonal populations of plasma cells with molecular techniques. AL amyloidosis can progress rapidly and is often far advanced by the time it is diagnosed (Buxbaum, 2004).

Conclusions from *VAO* and Previous Updates

VA identified AL amyloidoisis as of concern after the publication of *Update 1998*. The committees responsible for *Update 2000*, *Update 2002*, and *Update 2004* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and AL amyloidosis. Although there are few epidemiologic data specifically on AL amyloidosis, the committee responsible for *Update 2006* changed the categorization to limited or suggestive evidence of an association on the basis of commonalities in its cellular lineage with multiple myeloma and B-cell lymphomas. Later committees have not changed that categorization.

Update of the Epidemiologic Literature

Epidemiologic results for amyloidosis (E85) were reported for the first time in Vietnam veterans in the publication from the Korean Veterans Health Study (Yi et al., 2014a) on the prevalence of diseases as confirmed by insurance records, but no information on mortality from this condition was presented in Yi et al. (2014b). From the internal comparison of veterans in the category with high EOI scores (nine cases) to those in the low-potential-exposure group (six cases) with adjustment for age, rank, smoking, drinking, physical activity, domestic herbicide use, education, income, and body mass index, Yi et al. (2014a) reported a significantly elevated risk of amyloidosis (OR = 3.02, 95% CI 1.02–8.93). When regression with the same adjustments was performed on the logarithms of the individual EOI scores for the entire set of veterans, a significant relationship was again found (OR = 1.32, 95% CI 1.02–1.71).

Biologic Plausibility

A 1979 study reported the dose-dependent development of a "generalized lethal amyloidosis" in Swiss mice that were treated with TCDD for 1 year (Toth et al., 1979). That finding has not been validated in 2-year carcinogenicity studies

of TCDD in mice or rats, but the use of differing strains may explain the discrepancies. Thus, few animal data support an association between TCDD exposure and AL amyloidosis in humans, and no animal data support an association between the other COIs and AL amyloidosis.

It is known, however, that AL amyloidosis is associated with B-cell diseases, and 15 to 20 percent of cases of AL amyloidosis occur with multiple myeloma. Other diagnoses associated with AL amyloidosis include B-cell lymphomas (Cohen et al., 2004), monoclonal gammopathy, and agammaglobulinemia (Rajkumar et al., 2006).

Synthesis

AL amyloidosis is very rare, and previous VAO committees have noted that it was unlikely that population-based epidemiology will ever provide substantial direct evidence regarding its causation. Assignment of this condition to the "limited or suggestive" category of association has been based on the biologic and pathophysiologic features linking AL amyloidosis, multiple myeloma, and some types of B-cell lymphomas—especially the clonal hyperproliferation of plasma cells and abnormal immunoglobulin production—thus indicating that AL amyloidosis is pathophysiologically related to these conditions. Although the positive findings in the cohort of Korean Vietnam veterans was based on a small number of cases and validation of the EOI scores has not been possible, the committee was very interested to see the confirmatory information of an elevation in this condition among Korean veterans who served in Vietnam.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the COIs and AL amyloidosis.

Leukemias

Leukemias (ICD-9 202.4, 203.1, 204.0–204.9, 205.0–205.9, 206.0–206.9, 207.0–207.2, 207.8, 208.0–208.9) have traditionally been divided into four primary types: acute and chronic lymphocytic leukemias and acute and chronic myeloid leukemias. There are numerous subtypes of AML (ICD-9 205), which is also called acute myelogenous leukemia, granulocytic leukemia, or acute nonlymphocytic leukemia.

ACS estimated that 30,900 men and 23,370 women would receive diagnoses of some form of leukemia in the United States in 2015 and that 14,210 men and 10,240 women would die from it (Siegel et al., 2015). Collectively, leukemias were expected to account for 3 percent of all new diagnoses of cancer and 4

percent of deaths from cancer in 2015. Different forms of leukemias have different patterns of incidence and in some cases different risk factors. The incidences of the various forms of leukemias are presented in Table 8-45.

Myeloid Leukemias

In adults, acute leukemia is nearly always in the form of AML (ICD-9 205.0, 207.0, 207.2). ACS estimated that about 12,730 men and 8,100 women would receive new diagnoses of AML in the United States in 2015 and that 6,110 men and 4,350 women would die from it (Siegel et al., 2015). Overall, AML is slightly more common in men than in women. Risk factors associated with AML include high doses of ionizing radiation, occupational exposure to benzene, and exposure to some medications used in cancer chemotherapy (such as melphalan). Fanconi anemia and Down syndrome are associated with an increased risk of AML, and tobacco use is thought to account for about 20 percent of AML cases.

Vietnam veterans have expressed concern about whether myelodysplastic syndromes, most often precursors to AML, are associated with Agent Orange

TABLE 8-45 Average Annual Incidence (per 100,000) of Leukemias in the United States[a]

	60–64 Years Old			65–69 Years Old			70–74 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
All Leukemias:									
Men	32.0	33.9	22.4	49.7	52.4	40.2	67.0	70.4	53.6
Women	18.5	19.2	17.7	27.2	28.6	24.0	36.9	38.8	32.2
Acute Lymphocytic Leukemia:									
Men	1.3	1.4	1.1	1.7	1.9	0.9	1.6	1.6	0.6
Women	1.3	1.3	1.1	1.3	1.2	1.6	1.3	1.4	0.8
Acute Myeloid Leukemia:									
Men	8.8	9.1	7.4	13.9	15.0	10.2	20.2	21.4	15.1
Women	6.3	6.4	6.1	9.0	9.5	7.4	12.5	12.5	14.0
Chronic Lymphocytic Leukemia:									
Men	14.2	15.3	8.2	23.5	24.8	18.6	31.1	32.9	23.6
Women	7.4	7.8	5.8	11.4	12.2	8.5	15.6	16.8	11.4
Chronic Myeloid Leukemia:									
Men	4.0	4.1	3.4	5.9	6.0	5.6	7.8	8.1	7.0
Women	2.3	2.3	3.1	3.4	3.5	4.1	4.3	4.6	3.2
All Other Leukemia[b]									
Men	1.1	1.2	1.1	1.5	1.4	2.4	2.4	2.4	3.8
Women	0.5	0.5	0.6	1.0	1.0	1.1	1.4	1.5	1.7

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2008–2012 (NCI, 2015).

[b]Includes leukemic reticuloendotheliosis (hairy cell leukemia), plasma-cell leukemia, monocytic leukemia, and acute and chronic erythremia and erythroleukemia.

exposure. However, no results on those conditions in conjunction with the COIs have been found in VAO literature searches. Epidemiologic research on those hematologic disorders has been undertaken fairly recently; for instance, the LATIN case-control study (Maluf et al., 2009) has undertaken investigation of aplastic anemia in South America, but the reported exposures have been only as specific as "herbicides" and "agricultural pesticides."

The incidence of CML increases steadily with age in people older than 30 years. Its lifetime incidence is roughly equal in whites and blacks and is slightly higher in men than in women. CML accounts for about one-fifth of cases of leukemias in people in the age groups that include most Vietnam veterans. It is associated with an acquired chromosomal abnormality known as the Philadelphia chromosome, for which exposure to high doses of ionizing radiation is a known risk factor.

Lymphoid Leukemias

ALL is a disease of young children (peak incidence at the age of 2–5 years) and of people over 70 years old. It is relatively uncommon in the age groups that include most Vietnam veterans. The lifetime incidence of ALL is slightly higher in whites than in blacks and higher in men than in women. Exposure to high doses of ionizing radiation is a known risk factor for ALL, but there is little consistent evidence on other factors.

CLL shares many traits with lymphomas (such as immunohistochemistry, B-cell origin, and progression to an acute, aggressive form of NHL), so the committee now considers it in the section above on NHL, as classified in the WHO system.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and all types of leukemias. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, and *Update 2010* did not change that conclusion.

The committee responsible for *Update 2002*, however, considered CLL separately and judged that there was sufficient evidence of an association with the herbicides used in Vietnam and CLL alone, and *Update 2008* noted that HCL is closely related to CLL.

The committee responsible for *Update 2006* considered AML individually but did not find evidence to suggest that its occurrence is associated with exposure to the COIs, and there is still not sufficient evidence to support such

an association, so AML has been retained with other non-CLL leukemias in the category of inadequate and insufficient evidence.

Table 8-46 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies After following up on cancer for incidence and mortality in 2,783 male Vietnam veterans from New Zealand, McBride et al. (2013) reported four leukemia deaths, for an SMR overall of 0.71 (95% CI 0.19–1.83). This included three non-lymphoid and one lymphoid leukemia (SMR = 0.78, 95% CI 0.16–2.28 and 0.57, 95% CI 0.01–3.16, respectively). They also reported the incidence of 21 leukemias overall, for a significantly elevated SIR of 1.64 (95% CI 1.02–2.51). There were 7 incident non-lymphoid and 14 incident lymphoid leukemias (SIR = 1.29, 95% CI 0.52–2.66 and 1.91, 95% CI 1.04–3.20, respectively), as noted above in the NHL section.

From the Korean Health Study, Yi et al. (2014b) reported 107 leukemia deaths, with 49 low-exposure deaths (HR = 1.04, 95% CI 0.95–1.14) and a high-exposure HR of 1.18 (95% CI 0.80–1.76). This included 5 ALL (low-exposure HR 0.86, 95% CI 0.57–1.28; high-exposure HR 0.66, 95% CI 0.11–4.10), 46 AML (low-exposure HR 1.02, 95% CI 0.89–1.18; high-exposure HR 1.17, 95% CI 0.64–2.15), and 15 CML deaths (low-exposure HR 1.55, 95% CI 1.06–2.27; high-exposure HR 7.91, 95% CI 1.67–37.52). There were 2 low-exposure deaths from CML and 13 high-exposure deaths, making these risk estimates quite unstable. When examined including the Stellman exposure modeling (Stellman et al., 2003; Yi and Ohrr, 2014) the adjusted HR for myeloid leukemia in the high-exposure group was 1.13 (95% CI 0.73–1.77), including 25 and 20 AML cases in the low- and high-exposure groups, respectively (HR for AML = 0.84, 95% CI 0.46–1.56). There were 6 low- and 17 high-exposure CML cases for an HR = 2.37 (95% CI 0.91–6.18).

Occupational, Environmental, and Case-Control Studies No occupational, environmental, or case-control studies of exposure to the COIs and leukemias have been published since *Update 2012*.

Biologic Plausibility

Leukemias are a relatively rare spontaneous neoplasm in mice, but it is less rare in some strains of rats. A small study reported that 5 of 10 male rats fed TCDD at 1 ng/kg per week for 78 weeks showed an increased incidence of various cancers, one of which was lymphocytic leukemia (Van Miller et al., 1977). Later studies of TCDD's carcinogenicity have not shown an increased incidence of lymphocytic leukemia in mice or rats.

TABLE 8-46 Selected Epidemiologic Studies—Leukemias (Shaded entries are new information for this update)

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates (lymphopoietic cancer[c])			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
Mortality			
Through 1999—White subjects vs national rates (lymphopoietic cancer[c])			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	6	1.0 (0.4–2.0)	
SEA comparison veterans (n = 1,776)	5	0.6 (0.2–1.2)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (7/1/1965–3/28/1973)		**All COIs**	
Mortality—Through 2005			Cypel and Kang, 2010
All lymphopoietic			
Deployed vs non-deployed	6 vs 6	1.1 (0.4–2.5)	
ACC veterans vs US men			
Vietnam cohort	6	0.5 (0.2–1.0)	
Non-Vietnam cohort	6	0.6 (0.2–1.4)	
Leukemia			
Deployed vs non-deployed	2 vs 4	0.6 (0.1–3.2)	
ACC veterans vs US men			
Vietnam cohort	2	0.4 (0.1–1.5)	
Non-Vietnam cohort	4	1.2 (0.3–3.0)	
Mortality—Through 2001		1.0 (0.1–3.8)	Dalager and Kang, 1997
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	

continued

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
1965–2000	8	1.0 (0.4–2.5)	Boehmer et al., 2004
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004 (lymphopoietic cancers[c])	18	0.7 (0.4–1.3)	Cypel and Kang, 2008
Vietnam–veteran nurses	14	0.7 (0.3–1.3)	
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs non-deployed	30	1.0 (0.7–1.5)	Vistainer et al., 1995
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	130	1.1 (1.0–1.4)	ADVA, 2005b
Lymphocytic leukemia	72	1.4 (1.1–1.7)	
Myeloid leukemia	54	1.0 (0.8–1.3)	
Navy	35	1.5 (1.0–2.0)	
Lymphocytic leukemia	14	1.3 (0.7–2.1)	
Myeloid leukemia	19	1.7 (1.0–2.6)	
Army	80	1.1 (0.8–1.3)	
Lymphocytic leukemia	50	1.4 (1.0–1.8)	
Myeloid leukemia	28	0.8 (0.5–1.1)	
Air Force	15	1.2 (0.7–2.0)	
Lymphocytic leukemia	8	1.4 (0.6–2.7)	
Myeloid leukemia	7	1.3 (0.5–2.6)	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	27	26 (16–36)	
Men	64	26 (16–36	CDVA, 1998a
Women	1	0 (0–4)	CDVA, 1998b
Mortality			
All branches, return–2001	84	1.0 (0.8–1.3)	ADVA, 2005c
Lymphocytic leukemia	24	1.2 (0.7–1.7)	
Myeloid leukemia	55	1.1 (0.8–1.3)	
Army	48	0.1 (0.7–1.2)	
Lymphocytic leukemia	17	1.3 (0.7–2.0)	
Myeloid leukemia	30	0.8 (0.5–1.1)	

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Air Force	14	1.6 (0.8–2.6)	
Lymphocytic leukemia	6	2.7 (1.0–5.8)	
Myeloid leukemia	8	1.3 (0.5–2.5)	
1980–1994	33	1.3 (0.8–1.7)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Incidence—1982–2000	16	0.6 (0.3–1.1)	ADVA, 2005c
Lymphocytic leukemia	9	0.8 (0.3–2.0)	
Myeloid leukemia	7	0.5 (0.2–1.3)	
Mortality—1966–2001	11	0.6 (0.3–1.3)	ADVA, 2005c
Lymphocytic leukemia	2	0.4 (0.0–2.4)	
Myeloid leukemia	8	0.7 (0.3–1.7)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)			
All leukemia	21	1.6 (1.0–2.5)	
Non-lymphoid leukemia	7	1.3 (0.5–2.7)	
Lymphoid leukemia	14	1.9 (1.0–3.2)	
Mortality (1988–2008)			
All leukemia	4	0.7 (0.2–1.8)	
Non-lymphoid leukemia	3	0.8 (0.2–2.3)	
Lymphoid leukemia	1	0.6 (0.0–3.2)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Incidence (1992–2003)			Yi and Ohrr, 2014
Lymphoid leukemia (C91)	5 vs 9	0.5 (0.2–1.4)	
ALL (C91)	3 vs 5	0.5 (0.1–2.2)	
Myeloid leukemia (C92–C94)	45 vs 38	1.1 (0.7–1.8)	
AML (C92)	20 vs 25	0.8 (0.5–1.6)	
CML (C92.1)	17 vs 6	2.4 (0.9–6.2)	
Mortality (1992–2005)			Yi et al., 2014b
HR per unit of log EOI (n = 180,639)			
Leukemia (C91–C95)	107	1.0 (1.0–1.1)	
ALL (C91)	5	0.9 (0.6–1.3)	
AML (C92)	46	1.0 (0.9–1.2)	
CML (C92.1)	15	1.6 (1.1–2.3)	

continued

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
High exposure vs low exposure			
Leukemia (C91–C95)	58 vs 49	1.2 (0.8–1.8)	
ALL (C91)	2 vs 3	0.7 (0.1–4.1)	
AML (C92)	24 vs 22	1.2 (0.6–2.2)	
CML (C92.1)	13 vs 2	7.9 (1.7–37.5)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	34	1.0 (0.7–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	16	0.7 (0.4–1.2)	
7,553 not exposed to highly chlorinated PCDDs	17	1.4 (0.8–2.3)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	18	1.2 (0.7–1.9)	Saracci et al., 1991
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates (myeloid leukemia)	1	**TCDD** 2.0 (0.2–7.1)	Kogevinas et al., 1993
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Mortality 1955–2006	9	0.9 (0.6–1.4)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	5	0.7 (0.4–1.4)	Boers et al., 2012
Mortality 1955–2006			Boers et al., 2010
LHC	11 vs 7	0.9 (0.3–2.6)	
Leukemia	2 vs 3	0.3 (0.0–2.6)	
Mortality 1955–1991	1	1.0 (0.0–5.7)	Hooiveld et al., 1998
Mortality 1955–1985			Bueno de Mesquita et al., 1993
Leukemia, aleukemia (ICD-8 204–207)	1	1.5 (0.0–8.2)	
Myeloid leukemia (205)	1	2.9 (0.0–15.9)	

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006			Boers
LHC	3 vs 3	1.5 (0.3–7.5)	et al., 2010
Leukemia	2 vs 2	1.5 (0.2–10.8)	
Mortality 1965–1986			Bueno de
Leukemia, aleukemia (ICD-9 204–207)	1	4.4 (0.1–24.2)	Mesquita
Myeloid leukemia (ICD-8 205)	1	7.7 (0.2–42.9)	et al., 1993
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
Through 1987		*90% CI*	Zober
All cohorts (n = 247)	1	1.7 (nr)	et al., 1990
Cohort 3	1	5.2 (0.4–63.1)	
German Production Workers at Bayer Plant in Uerdingen (135 men working >1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	0	—	Becher et al., 1996

continued

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortalilty 1952–1989	4	1.8 (0.5–4.7)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004 (leukemia, aleukemia)			McBride et al., 2009a
Ever-exposed workers	1	0.6 (0.0–3.1)	
Never-exposed workers	0	0.0 (0.0–6.0)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	0	0.0 (0.0–5.3)	’t Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	1.2 (0.0–6.4)	’t Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	10	0.8 (0.4–1.5)	Steenland et al., 1999
Through 1987	6	0.7 (0.2–1.5)	Fingerhut et al., 1991
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615) (leukemia, aleukemia)	13	1.9 (1.0–3.2)	Collins et al., 2009b
Excluding subset with PCP exposure	2	1.9 (1.0–3.4)	
1942–2003 (n = 1,615) (other lymphopoietic)	2	0.6 (0.1–2.3)	
Excluding subset with PCP exposure	2	0.7 (0.1–2.6)	

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	9	0.9 (0.4–1.7)	
PCP and TCP (n = 720)	2	0.6 (0.1–2.2)	
PCP (no TCP) (n = 1,402)	7	1.0 (0.4–2.1)	
Dow PCP Production Workers (1937–1989 in Midland, MI) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)			Collins et al., 2009c
1942–2003 (n = 773) (leukemia, aleukemia)	2	0.6 (0.1–2.0)	
Excluding subset with TCP exposure	1	0.4 (0.0–2.0)	
1942–2003 (n = 773) (other lymphopoietic)	2	1.3 (0.2–4.6)	
Excluding subset with TCP exposure	2	1.7 (0.2–6.0)	
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-yr latency	2	1.0 (0.1–3.6)	
15-yr latency	1	nr	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	5	0.9 (0.3–2.0)	Burns CJ et al., 2011
Through 1994 (n = 1,517)—lymphopoietic mortality in workers with high 2,4-D exposure	4	1.3 (0.4–3.3)	Burns et al., 2001
Through 1982 (n = 878)	2	3.6 (0.4–13.2)	Bond et al., 1988
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	49	1.0 (0.7–1.3)	
Ever	35	0.9 (0.6–1.2)	
Danish paper workers			Rix et al., 1998
Men	20	0.8 (0.5–1.2)	
Women	7	1.3 (0.5–2.7)	

continued

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—Herbicide-Using Workers (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from leukemia June 1971–Dec 1987		**Herbicides**	
Farm operators ≥ 35 yrs of age (June 1971–Dec 1987)	357	0.9 (0.8–1.0)	Semenciw et al., 1994
Lymphatic	132	0.9 (0.8–1.1)	
Myeloid	127	0.8 (0.7–0.9)	
Farm operators ≥ 35 yrs of age during study period (June 1971–Dec 1985)	138	0.9 (0.7–1.0)	Wigle et al., 1990
Sawmill workers in British Columbia—23,829 workers for ≥ 1 yr at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	Hertzman et al., 1997
All leukemias—incidence	47	1.2 (0.9–1.5)	
ALL	2	1.0 (0.2–3.1)	
CLL	24	1.7 (1.2–2.4)	
AML	5	0.8 (0.3–1.7)	
CML	7	1.1 (0.5–2.0)	
Other, unspecified	5	0.5 (0.2–1.0)	
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners (ICD-7)		**Herbicides**	Hansen et al., 2007
25-yr follow-up (1975–2001)	42	1.1 (0.8–1.4)	
Leukemia (204)	22	1.4 (0.9–2.1)	
Born before 1915 (high exposure)	16	1.4 (0.9–2.3)	
Leukemia (204)	12	2.3 (1.3–4.1)	
Born 1915–1934 (medium exposure)	25	1.2 (0.8–1.8)	
Leukemia (204)	9	1.0 (0.5–2.0)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.0)	
Leukemia (204)	1	0.5 (0.0–3.4)	
10-yr follow-up (1975–1984) reported in Hansen et al. (1992) (ICD-7)	15	1.4 (0.8–2.4)	
NHL (200, 202, 205)	6	1.7 (0.6–3.8)	
HD (201)	0	nr	
Multiple myeloma (203)	0	nr	
CLL (204.0)	6	2.8 (1.0–6.0)	
Other leukemia (204.1–204.4)	3	1.4 (0.3–4.2)	

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
10-yr follow-up (1975–1984) of male gardeners			Hansen et al., 1992
All gardeners—CLL	6	2.5 (0.9–5.5)	
Men	6	2.8 (1.0–6.0)	
All gardeners—all other types of leukemia	3	1.2 (0.3–3.6)	
Men	3	1.4 (0.3–4.2)	
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	145	0.9 (nr)	
Employee	33	1.0 (nr)	
Women			
Self-employed	8	2.2 ($p < 0.05$)	
Employee	3	1.3 (nr)	
Family worker	27	0.9 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	3	1.3 (0.3–3.7)	Swaen et al., 2004
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 wks) not IARC		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
Lymphatic	3	1.0 (0.2–3.0)	
Mortality	2	nr	
Lymphatic	1	0.9 (0.0–5.1)	
Myeloid	1	0.7 (0.0–3.7)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (ICD-8 202.0–202.9)	27	0.8 (0.5–1.1)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
	4	0.6 (0.2–1.6)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 571 incident pancreatic cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134) (leukemia)	4	1.0 (0.4–2.6)	
Aged 20–59 (AML)	2	2.8 (0.7–11.0)	
Aged ≥ 60 (AML)	1	1.6 (0.2–11.5)	

continued

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Leukemia (ICD-7 204–248)	2	0.5 (0.1–2.1)	
AML (ICD-7 205.0)	1	0.9 (0.1–6.4)	
SWEDEN			
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992	0	nr	Thörn et al., 2000
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	1,072	1.3 (1.2–1.4)	
Nonwhites (n = 11,446)	55	0.9 (0.7–1.3)	
Women			
Whites (n = 2,400)	24	1.5 (0.9–2.2)	
Nonwhites (n = 2,066)	8	0.9 (0.4–1.9)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/ farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	133	1.0 (0.8–1.1)	
Commercial applicators	7	0.9 (0.4–1.9)	
Spouses	37	0.8 (0.6–1.1)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	70	0.9 (0.7–1.2)	
Spouses of private applicators (> 99% women)	17	0.7 (0.4–1.2)	
Commercial applicators	4	0.9 (0.3–2.4)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	91	0.9 (0.7–1.0)	
Spouses (n = 676)	33	1.1 (0.8–1.5)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	27	0.8 (0.5–1.1)	
Spouses of private applicators (> 99% women)	14	1.4 (0.8–2.4)	

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
California United Farm Workers of America			
Nested case-control analysis of Hispanic workers in cohort of 139,000 CA United Farm Workers			Mills et al., 2005
Ever used 2,4-D—total leukemia	nr	1.0 (0.4–2.6)	
Lymphocytic leukemia	nr	1.5 (0.3–6.6)	
Granulocytic (myeloid) leukemia	nr	1.3 (0.3–5.4)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents	23	1.9 (1.0–3.5)	Alavanja et al., 1988
Lymphatic	nr	2.1 (0.7–6.4)	
Trend over years worked		($p < 0.01$)	
Myeloid	nr	2.8 (1.1–7.2)	
Trend over years worked		($p < 0.01$)	
White Male Residents of Iowa—leukemia cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 yrs old when died 1964–1978—case-control		1.2 ($p < 0.05$)	Burmeister et al., 1983
ALL	28	0.7 (0.4–1.2)	
CLL	132	1.7 (1.2–2.4)	
Lived in one of 33 counties with highest herbicide use	nr	1.9 (1.2–3.1)	
Unspecified lymphatic	64	1.7 (1.0–2.7)	
AML	86	1.0 (0.8–1.5)	
CML	46	1.0 (0.7–1.7)	
Unspecified myeloid	36	0.8 (0.5–1.4)	
Acute monocytic	10	1.1 (0.4–2.6)	
Unspecified leukemia	31	1.1 (0.6–2.0)	
White Male Residents of Iowa and Minnesota— > 30 yrs old diagnosed 1981–1983 in Iowa or 1980–1982 in Minnesota (ever farmer, used herbicides)	578	**Herbicides**	Brown et al., 1990
Ever farmed	335	1.2 (1.0–1.5)	
AML	81	1.2 (0.8–1.8)	
CML	27	1.1 (0.6–2.0)	
CLL	156	1.4 (1.1–1.9)	
ALL	7	0.9 (0.3–2.5)	
Myelodysplasias	32	0.8 (0.5–1.4)	
Any herbicide use	157	1.2 (0.9–1.6)	
AML	39	1.3 (0.8–2.0)	
CML	16	1.3 (0.7–2.6)	

continued

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
CLL	74	1.4 (1.0–2.0)	
ALL	2	0.5 (0.1–2.2)	
Myelodysplasias	10	0.7 (0.3–1.5)	
Phenoxy acid use	120	1.2 (0.9–1.6)	
2,4-D use	98	1.2 (0.9–1.6)	
2,4,5-T use	22	1.3 (0.7–2.2)	
First use > 20 yrs before	11	1.8 (0.8–4.0)	
MCPA	11	1.9 (0.8–4.3)	
First use > 20 yrs before	5	2.4 (0.7–8.2)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9)		**TCDD**	
Incidence—20-yr follow-up to 1996—men and women			
Leukemia (204–208)			Pesatori et al., 2009
Zone A	2	2.2 (0.5–8.8)	
Zone B	8	1.4 (0.7–2.7)	
Zone R	31	0.8 (0.5–2.1)	
Lymphatic leukemia (204)			
Zone A	1	2.8 (0.4–19.9)	
Zone B	0	nr	
Zone R	13	0.8 (0.5–1.5)	
Myeloid leukemia (205)			
Zone A	1	2.2 (0.3–16.0)	
Zone B	7	2.4 (1.1–5.2)	
Zone R	15	0.8 (0.4–1.3)	
Leukemia, unspecified (208)			
Zone A	0	nr	
Zone B	1	2.2 (0.3–16.1)	
Zone R	2	0.6 (0.1–2.6)	
10-yr follow-up to 1991—men			Bertazzi et al., 1993
Zone B	2	1.6 (0.4–6.5)	
Myeloid leukemia (205)	1	2.0 (0.3–14.6)	
Zone R	8	0.9 (0.4–1.9)	
Myeloid leukemia (205)	5	1.4 (0.5–3.8)	
10-yr follow-up to 1991—women			Bertazzi et al., 1993
Zone B	2	1.8 (0.4–7.3)	
Myeloid leukemia (205)	2	3.7 (0.9–15.7)	
Zone R	3	0.4 (0.1–1.2)	
Myeloid leukemia (205)	2	0.5 (0.1–2.1)	

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Mortality—25-yr follow-up to 2001 (men and women)			
Leukemia (204–208)			Consonni
Zone A	1	0.9 (0.1–6.3)	et al., 2008
Zone B	13	1.7 (1.0–3.0)	
Zone R	51	1.0 (0.7–1.3)	
Lymphatic leukemia (204)			
Zone A	0	nr	
Zone B	3	1.3 (0.4–4.1)	
Zone R	23	1.4 (0.9–2.2)	
Myeloid leukemia (205)			
Zone A	1	2.1 (0.3–15.2)	
Zone B	6	2.0 (0.9–4.5)	
Zone R	16	0.7 (0.4–1.2)	
Monocytic leukemia (206)	0	nr	
Leukemia, unspecified (208)			
Zone A	0	nr	
Zone B	4	2.4 (0.9–6.5)	
Zone R	10	0.8 (0.4–1.6)	
20-yr follow-up to 1996			Bertazzi
Zones A, B—men	9	2.1 (1.1–4.1)	et al., 2001
Zones A, B—women	3	1.0 (0.3–3.0)	
15-yr follow-up to 1991—men			Bertazzi
Zone B	7	3.1 (1.4–6.7)	et al., 1998
Zone R	12	0.8 (0.4–1.5)	
15-yr follow-up to 1991—women			Bertazzi
Zone B	1	0.6 (0.1–4.0)	et al., 1998
Zone R	12	0.9 (0.5–1.6)	
Chapaevsk, Russia Residential Cohort		**Dioxin**	Revich
Incidence—Crude incidence rate in 1998 vs			et al., 2001
Men			
Regional (Samara)	nr	14.6 (nr)	
National (Russia)	nr	15.2 (nr)	
Women			
Regional (Samara)	nr	13.9 (nr)	
National (Russia)	nr	10.7 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Men	11	1.5 (0.8–2.7)	
Women	15	1.5 (0.8–2.4)	

continued

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Other International Environmental Studies			
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
Lymphocytic			
East coast (higher serum TEQs)	4	1.2 (0.3–3.3)	
West coast (lower serum TEQs)	16	1.3 (0.8–2.2)	
Myeloid			
East coast (higher serum TEQs)	2	0.9 (0.1–3.1)	
West coast (lower serum TEQs)	6	0.5 (0.2–1.1)	
Mortality—all leukemias			
East coast (higher serum TEQs)	5	1.4 (0.5–3.2)	
West coast (lower serum TEQs)	24	1.0 (0.6–1.5)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
1,084 leukemia deaths in Nebraska in 1957–1974; farmers–usual occupation on death certificate		**Herbicides, pesticides**	Blair and White, 1985
		1.3 ($p < 0.05$)	
99 ALL cases	nr	1.3 (nr)	
248 CLL cases	nr	1.7 ($p < 0.05$)	
105 unspecified lymphatic cases	nr	0.9 (nr)	
235 AML cases	nr	1.2 (nr)	
96 CML cases	nr	1.1 (nr)	
39 unspecified myeloid cases	nr	1.0 (nr)	
39 acute monocytic cases	nr	1.9 (nr)	
52 acute unspecified leukemia cases	nr	2.4 (nr)	
65 unspecified leukemia cases	nr	1.2 (nr)	
Tecumseh, Michigan residents participating in longitudinal study (1959–1987)		**Herbicides**	Waterhouse et al., 1996
All leukemias			
Men	42	1.4 (1.0–1.9)	
Women	32	1.2 (0.9–1.8)	
CLL	10	1.4 (1.0–1.9)	
International Case-Control Studies			
Italian residents of 11 areas (incidence of leukemia excluding CLL)		**Herbicides**	Miligi et al., 2003
Exposure to phenoxy herbicides	6	2.1 (0.7–6.2)	

TABLE 8-46 Leukemias, continued

Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Italian farming, animal-breeding workers (men and women)—incidence (CLL)	15	**Herbicides** 2.3 (0.9–5.8)	Amadori et al., 1995
Farmers	5	1.6 (0.5–5.2)	
Breeders	10	3.1 (1.1–8.3)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; COI, chemical of interest; EOI, Exposure Opportunity Index; HD, Hodgkin disease; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; LHC, lymphohematopoietic cancers; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all forms of lymphoma (including HL and NHL) and leukemia (ALL, AML, CLL, CML).

Two studies that used cells in tissue culture suggested that TCDD exposure does not promote leukemia. The proliferation of cultured human bone marrow stem cells (the source of leukemic cells) was not influenced by the addition of TCDD to the culture medium (van Grevenynghe et al., 2005). Likewise, Mulero-Navarro et al. (2006) reported that the AHR promoter is silenced in ALL—an effect that could lead to a reduced expression of the receptor, which binds TCDD and mediates its toxicity. No reports of animal studies have noted an increased incidence of leukemia after exposure to the phenoxy herbicides or other COIs. The AHR plays a role in hematopoetic stem cell expansion as well as in erythroid and megakaryocytic differentiation (Smith et al., 2013). In this context, information in a letter to the editor of the *American Journal of Hematology* from Nguyen-Khac et al. (2014) is interesting. The researchers described a chromosomal translocation found in a human acute leukemia that recombines the *TEL* gene with the *ARNT* (AhR-Aryl Receptor Nuclear Translocator) gene producing a fusion gene product. This recent functional work strongly suggests that

the translocation impairs the normal functions of ARNT, potentially contributing to leukemogenesis.

The biologic plausibility of the carcinogenicity of the COIs is discussed in general at the beginning of this chapter.

Synthesis

The new epidemiologic data, which is largely null, is not coherent, and the committee continues to have concerns about the misclassification of leukemia types and finds the correspondence between the intensity of exposure and the magnitude of risk for leukemias (other than CLL) to be erratic.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and leukemias in general. An exception is the specific leukemia subtypes of chronic B-cell hematoproliferative diseases, including CLL and HCL, which are more appropriately grouped with lymphomas.

Non-Malignant Myeloid Diseases

The myelodysplastic syndromes (MDSs) are a collection of proliferative diseases (ICD-9 238.7, ICD-10 D46) that involve myeloid dysplasia. Patients often develop anemia and cytopenia caused by progressive bone marrow failure. MDSs are neither malignancies, nor necessarily fatal, but aggressive cases of MDS frequently progress to AML. On the basis of SEER program data collected from 2001 to 2003, the age-adjusted incidence of MDS in the United States was estimated to be 3.4 per 100,000 people per year, which means about 10,000 new cases per year (Sekeres, 2011). Various factors determine prognosis, and several scoring systems are used. Most involve the number of cytopenias, dependence on transfusion, cytogenetic abnormalities, and the number of blasts in the marrow. For low-risk disease, the median survival is about 7 years; for high risk, it is less than 1 year. MDS does not always progress to AML, and the incidence of progression varies with the risk category. Of cases with high-risk MDS, around 25 to 35 percent progress to AML. More people die from complications of infection or bleeding than through transformation to AML. Myeloproliferative neoplasms (ICD-9 205.1, 238.4, 289.89, 289.9; ICD-10 D47.1) are generally less serious clonal diseases of the myeloid lineage, but they may progress into MDS or AML.

Aplastic anemia (AA) (ICD-9 284, ICD-10 D60-D61) is another disease of the bone marrow in which stem cells are damaged in such a way that there are simultaneous decreases in red blood cells (anemia), white blood cells (leukopenia),

and platelets (thrombocytopenia)—pancytopenia. Exposures to radiation, a number of drugs, and some industrial chemicals (such as benzene) are recognized as risk factors for this condition, but it may also arise from an autoimmune disease.

Update of the Epidemiologic Literature

Vietnam Veteran Studies Cancer incidence (Yi and Ohrr, 2014) was assessed among Korean veterans who had served in Vietnam between 1964 and 1973. Researchers reported a non-significant increased risk of MDS (HR = 1.46, 95% CI 0.24–8.86) in the internal comparison of the high- and low-exposure groups, based on the EOI scores.

Occupational, Environmental, and Case-Control Studies There were no case-control, environmental, or occupational studies with adequate exposure specificity to contribute to the committee's work since *Update 2012*.

Biologic Plausibility

Singh et al. (2014) have explored the relationship of the absence of the AHR locus and changes in hematopoetic stem cells (HSCs) associated with aging. They followed AHR-null mice, showing that they have diminished survival, splenomegaly, leukocytosis, and anemia. The HSCs showed diminished self-renewal capacity with somatic changes in the HSCs compatible with a profile of accelerated aging and HSC exhaustion.

Synthesis

There are minimal data with which to assess the role that specific COIs may play in the occurrence of the various nonmalignant bone marrow–derived diseases.

Conclusion

On the basis of the available tangential information, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and nonmalignant myeloid diseases.

9

Effects on Veterans' Fertility and Reproductive Success

Chapter Overview

Based on new evidence and a review of prior studies, the committee for Update 2014 *did not find any new significant associations between the relevant exposures and fertility or gestational outcomes.The current evidence supports the findings of earlier studies that*

- *None of the fertility or gestational outcomes had sufficient evidence of an association with the chemicals of interest.*
- *None of the fertility or gestational outcomes had limited or suggestive evidence of an association between the chemicals of interest.*
- *There is inadequate or insufficient evidence to determine whether there is an association between the chemicals of interest and endometriosis; decreased sperm counts or sperm quality, subfertility, or infertility; spontaneous abortion, stillbirth, neonatal death, or infant death; and low birth weight or preterm delivery.*
- *There is limited or suggestive evidence of* no *association between paternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and spontaneous abortion.*

This chapter summarizes the scientific literature published since *Veterans and Agent Orange: Update 2012*,[1] hereafter referred to as *Update 2012* (IOM,

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

2014), on the association between exposure to herbicides and adverse effects on fertility and during gestation. (The analogous shortened names are used to refer to the updates for 1996, 1998, 2000, 2002, 2004, 2006, 2008, and 2010 [IOM, 1996, 1999, 2001, 2003, 2005, 2007, 2009, 2011] of the original report *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* [*VAO*; IOM, 1994].) The literature considered in this chapter includes studies of a broad spectrum of reproductive effects in Vietnam veterans and in other populations exposed occupationally or environmentally to the herbicides sprayed in Vietnam or to TCDD. Because some polychlorinated biphenyls (PCBs), some polychlorinated dibenzofurans (PCDFs), and some polychlorinated dibenzodioxins (PCDDs) other than TCDD have dioxin-like biologic activity, studies of populations exposed to PCBs or PCDFs were reviewed if their results were presented in terms of TCDD toxic equivalents (TEQs). Although all studies reporting TEQs based on PCBs were reviewed, those studies that reported TEQs based only on mono-ortho PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given very limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the World Health Organization's (WHO's) revised toxicity equivalency factors (TEFs) of 2005 (La Rocca et al., 2008; van den Berg et al., 2006).

The adverse outcomes evaluated in this chapter include impaired fertility (in which declines in sperm quality may be involved), endometriosis, increased fetal loss (spontaneous abortion and stillbirth), neonatal and infant mortality, and the adverse gestational outcomes of low birth weight and preterm delivery. In this update, consideration of the possibility of adverse health outcomes at any time during the lives of all progeny of Vietnam veterans has been moved to a separate chapter: Chapter 10, "Effects on Veterans Descendants."

Because the vast majority of Vietnam veterans are men, the primary focus of the VAO series has been on potential adverse effects of herbicide exposure on men, and the etiologic importance of the exposed party's sex does not play the same dominant role in nonreproductive outcomes that it does in reproductive outcomes. However, about 8,000 women served in Vietnam (H. Kang, US Department of Veterans Affairs, personal communication, December 14, 2000), so findings relevant to female reproductive health, such as those concerning endometriosis, are also included in the present chapter. Whenever the information was available, an attempt has been made to evaluate the effects of exposure on adult men and women separately.

The categories of association and the approach to categorizing the health outcomes are discussed in Chapters 1 and 2. To reduce repetition throughout the report, Chapter 6 characterizes study populations and presents design information related to new publications that report findings on multiple health outcomes or that revisit study populations considered in earlier updates.

BIOLOGIC PLAUSIBILITY OF EFFECTS ON FERTILITY AND REPRODUCTION

This chapter opens with a general discussion of the plausibility of the various suggested adverse reproductive effects of TCDD and the four herbicides used in Vietnam. There have been few reproductive studies of the four herbicides in question, particularly picloram and cacodylic acid, and those studies generally have shown toxicity only at very high doses, so the preponderance of the following discussion concerns TCDD, which other than in controlled experimental circumstances, usually occurs in a mixture of dioxins (dioxin congeners in addition to TCDD).

TCDD is stored in fat tissue and has a long biologic half-life, so internal exposure at generally constant concentrations may continue after an episodic, high-level exposure to an external sources ceases. If a person had a high exposure, then high amounts of dioxins may still be stored in fat tissue and be mobilized, particularly at times of weight loss. That would not be expected to be the case for nonlipophilic chemicals, such as cacodylic acid.

Dioxin exposure has the potential to disrupt male reproductive function by altering gene expression that is pertinent to spermatogenesis and by altering steroidogenesis (Wong and Cheng, 2011) and to disrupt female reproductive function by altering gene expression relevant to ovarian follicle growth and maturation, uterine function, placental development, and fetal morphogenesis and growth.

A father's direct contribution to a pregnancy is limited to the contents of the sperm that fertilizes an egg; those contents had long been thought to consist of greatly condensed, transcriptionally inert deoxyribonucleic acid (DNA) constituting half the paternal genome (a haploid set of chromosomes). Consequently, it was believed that paternally derived damage to the embryo or offspring could only result from changes in sperm DNA, and dioxins have not been shown to mutate DNA sequence. However, as discussed in Chapter 4, TCDD can have epigenetic effects that modify expression of a cell's genetic material that persist in the daughter cells following cell division, whether the division involves an individual's own somatic tissues or production of his (or her) gametes. This provides an alternative pathway to creating permanent (heritable) changes in gene expression without altering the DNA sequence. Epigenetic changes include chemical modifications made to DNA (usually involving methylation) or to other cellular components such as histones and RNAs (Jirtle and Skinner, 2007). As a sperm matures, most of its histones are replaced by protamines, which renders it transcriptionally quiescent and permits extensive DNA compaction. The core histones that are retained in human sperm carry epigenetic modifications to maintain open nucleosomes, which permits transcription of genes that are important during embryo development (Casas and Vavouri, 2014). Sperm also carry a considerable collection of ribonucleic acid (RNA) fragments (Kramer and Krawetz, 1997; Krawetz et al., 2011) including ribosomal RNAs (rRNAs), messenger

RNAs (mRNAs), and small noncoding RNAs (miRNAs and piRNAs) (Casas and Vavouri, 2014; Lane et al., 2014). Small RNAs have been found to play critical roles in fertilization (Amanai et al., 2006), early embryonic development (Hamatani, 2012; Suh and Blelloch, 2011), and epigenetic modifications (Gapp et al., 2014; Kawano et al., 2012). Therefore, male infertility or fetal loss associated with exposure to the chemicals of interest (COIs) might be mediated by epigenetic modifications to components of sperm other than their DNA (Krawetz, 2005).

A mother's contribution to a pregnancy is obviously more extensive, and damage to an embryo or offspring can result from epigenetic changes in the egg DNA or from the direct effects of exposure on placenta formation and the fetus during gestation. The mobilization of dioxin during pregnancy may be increased because the body is drawing on fat stores to supply nutrients to the developing fetus. TCDD has been measured in human circulating maternal blood, cord blood, and placenta. Thus, dioxin in the mother's bloodstream could cross the placenta and expose the developing embryo and fetus. Data indicate that dioxin can accumulate in placental tissue, but the amount of TCDD that can transfer to the fetus appears to be very limited—TCDD's transfer index was the lowest of 13 environmental toxicants evaluated in perfusion studies of human placentas (Mose et al., 2012).

On the basis of laboratory animal studies, it is known that TCDD can affect reproduction, so a connection between TCDD exposure and human reproductive and gestational effects is biologically plausible. However, making definitive conclusions based on animal studies about the potential for TCDD to cause reproductive and gestational toxicity in humans is complicated by differences in sensitivity and susceptibility among different species including strain-specific differences; by the lack of strong evidence of organ-specific effects across species; by differences in the route, dose, duration, and timing of exposure in experimental protocols and real-world exposure; and by substantial differences between laboratory animals and humans in the toxicokinetics of TCDD. Experiments with 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) indicate that these chemicals have subcellular effects that could constitute a biologically plausible mechanism for reproductive and gestational effects. However, the preponderance of evidence from animal studies indicates that these chemicals do not have reproductive effects. There is insufficient information on picloram and cacodylic acid to assess the biologic plausibility of their potential reproductive or gestational effects.

The sections on the biologic plausibility of the specific outcomes considered in this chapter present more detailed toxicologic findings that are of particular relevance to the outcomes discussed.

ENDOMETRIOSIS

Endometriosis (*International Classification of Diseases, 9th revision* [ICD-9], code 617) affects 5.5 million women in the United States and Canada at any

given time (NICHD, 2007). The endometrium, the tissue that lines the inside of the uterus, is built up and shed each month during menstruation. In endometriosis, endometrial cells are found outside the uterus—usually in other parts of the reproductive system, in the abdomen, or on surfaces near the reproductive organs. The ectopic tissue develops into growths or lesions that continue to respond to hormonal changes in the body and break down and bleed each month in concert with the menstrual cycle. Unlike blood released during normal shedding of the endometrium, blood released from endometrial lesions has no way to leave the body and results in inflammation and internal bleeding. The degeneration of blood and tissue can cause scarring, pain, infertility, adhesions, and intestinal problems.

There are several theories of the etiology of endometriosis, including one that posits a genetic contribution, but the cause remains unknown. Estrogen dependence and immune modulation are established features of endometriosis but do not adequately explain its cause. It has been proposed that endometrium is distributed through the body via blood or the lymphatic system; that menstrual tissue backs up into the fallopian tubes, implants in the abdomen, and grows; and that all women experience some form of tissue backup during menstruation but only those who have immune-system or hormonal problems experience the tissue growth associated with endometriosis. Despite numerous symptoms that can indicate endometriosis, diagnosis is possible only through laparoscopy or a more invasive surgical technique. Several treatments for endometriosis are available, but there is no cure.

Conclusions from *VAO* and Previous Updates

Endometriosis was first reviewed in this series of reports in *Update 2002*, which identified two relevant environmental studies. Additional studies considered in later updates have not changed the conclusion that the evidence is inadequate or insufficient to support an association with herbicide exposure. Table 9-1 provides a summary of relevant studies that have been reviewed.

Update of the Epidemiologic Literature

No Vietnam-veteran, occupational, or case-control studies of exposure to the COIs and endometriosis have been published since *Update 2012*.

Environmental Studies

Upson et al. (2013) measured persistent organic pollutants in a subset of women enrolled in the Women's Risk of Endometriosis Study. An increased risk of endometriosis was observed for exposure to β-hexachlorocylohexane (HCH), which is a component of the insecticide lindane, and mirex, but the authors did not measure the COIs.

TABLE 9-1 Selected Epidemiologic Studies—Endometriosis

Study Population	Study Results	Reference
ENVIRONMENTAL		
Studies Conducted in the United States		
Case-control study of women in Atlanta, GA, with endometriosis; 60 cases and 64 controls	Results for cases vs controls: Total TEQ (determined by GC/MS): OR = 01.0 (95% CI 0.9–1.1)	Niskar et al., 2009
Studies Conducted in Belgium		
88 matched triads (264 total); patients with deep endometriotic nodules, pelvic endometriosis, controls matched for age, gynecologic practice in Belgium; routes of exposure to DLCs examined	Results for pelvic endometriosis vs controls: Dietary fat: OR = 1.0 (95% CI 1.0–1.0) BMI: OR = 1.0 (95% CI 0.9–1.0) Occupation: OR = 0.5 (95% CI 0.2–1.1) Traffic: OR = 1.0 (95% CI 0.3–2.8) Incinerator: OR = 1.0 (95% CI 1.0–1.1)	Heilier et al., 2007
Serum DLC and aromatase activity in endometriotic tissue from 47 patients in Belgium	No association between TEQs (determined by GC/MS) of DLCs in serum and aromatase activity by regression analyses p-values = 0.37–0.90 for different endometriosis subgroups	Heilier et al., 2006
Endometriosis in Belgian women with overnight fasting serum levels of PCDD, PCDF, PCB	50 exposed cases, risk of increase of 10 pg/g lipid of TEQ compounds (determined by GC/MS); OR = 2.6 (95% CI 1.3–5.3)	Heilier et al., 2005
Belgian women with environmental exposure to PCDDs, PCDFs; compared analyte concentrations in cases vs controls	Mean concentration of TEQ (determined by GC/MS) Cases (n = 10), 26.2 (95% CI 18.2–37.7) Controls (n = 132), 25.6 (95% CI 24.3–28.9) No significant difference	Fierens et al., 2003a
Patients undergoing infertility treatment in Belgium; compared number of women with, without endometriosis who had serum dioxin levels up to 100 pg TEQ/g of serum lipid (determined by CALUX bioassay)	Six exposed cases: OR = 4.6 (95% CI 0.5–43.6)	Pauwels et al., 2001

TABLE 9-1 Endometriosis, continued

Study Population	Study Results	Reference
Studies Conducted in Italy		
Case-control study of Italian women with endometriosis; 80 cases and 78 controls (TEQs determined by CALUX bioassay)	Results for endometriosis vs controls: dl PCB118 compared to ≤ 13.2 ng/g: 13.3–24.2 ng/g; OR = 3.17 (95% CI 1.36–7.37) ≥ 24.3 ng/g; OR = 3.79 (95% CI 1.61–8.91) Total TEQ compared to ≤ 15.6 pgC-TEQ/g fat: 15.7–29.5 pgC-TEQs/g fat; OR = 0.52 (95% CI 0.18–1.48) ≥ 29.6 pgC-TEQ/g fat; OR = 0.73 (95% CI 0.26–2.01)	Porpora et al., 2009
Case-control study of Italian women with endometriosis, measured serum PCBs	Mean total PCBs (ng/g) Cases, 410 ng/g Control, 250 ng/g All PCB congeners: OR = 4.0 (95% CI 1.3–13)	Porpora et al., 2006
Pilot study of Italian, Belgian women of reproductive age; compared concentrations of TCDD, total TEQ (determined by GC/MS) in pooled blood samples from women who had diagnosis endometriosis with controls	Mean concentration of TCDD (ppt of lipid): Italy: Controls (10 pooled samples), 1.6 Cases (two sets of 6 pooled samples), 2.1, 1.3 Belgium: Controls (7 pooled samples), 2.5 Cases (Set I, 5 pooled samples; Set II, 6 pooled samples), 2.3, 2.3 Mean concentration of TEQ (ppt of lipid): Italy: Controls (10 pooled samples), 8.9 ± 1.3 (99% CI 7.2–11.0) Cases (two sets of 6 pooled samples), 10.7 ± 1.6; 10.1 ± 1.5 Belgium: Controls (7 pooled samples), 24.7 ± 3.7 (99% CI 20–29) Cases (Set I, 5 pooled samples; Set II, 6 pooled samples), 18.1 ± 2.7; 27.1 ± 4.0	De Felip et al., 2004
Residents of Seveso Zones A and B up to 30 yrs old in 1976; population-based historical cohort comparing incidence of endometriosis across serum TCDD concentrations	Serum TCDD (ppt): ≤ 20 (n = 2 cases), RR = 1.0 (reference) 20.1–100, (n = 8), RR = 1.2 (90% CI 0.3–4.5) > 100, (n = 9), RR = 2.1 (90% CI 0.5–8.0)	Eskenazi et al., 2002b

continued

TABLE 9-1 Endometriosis, continued

Study Population	Study Results	Reference
Studies Conducted in Israel		
Residents of Jerusalem being evaluated for infertility; compared number of women with high TCDD who had (n = 44), did not have (n = 35) diagnosis of endometriosis	8 exposed cases: OR = 7.6 (95% CI 0.9–169.7)	Mayani et al., 1997
Studies Conducted in Japan		
17 women undergoing diagnostic laparoscopy for infertility, 10 were found to have endometriosis and 7 did not	TEQ calculated for each person based on PCDDs, PCDFs, and 12 dl-PCBs. No difference in lipid-adjusted exposure levels between those with and without endometriosis. Association was seen with endometriosis and women with high PCDD and PCDF (OR = 2.5, 95% CI 1.2–5.3)	Cai et al., 2011
138 infertility patients in Japan; laparoscopically confirmed case-control status, serum dioxin, PCB TEQ (determined by GC/MS); P450 genetic polymorphism	Results for advanced endometriosis: Total TEQ: OR = 0.5 (95% CI 0.2–1.7) Genotype-specific: ORs = 0.3–0.6 No significant interaction between genotype, dioxin TEQ	Tsuchiya et al., 2007

NOTE: BMI, body mass index; CALUX, chemical activated luciferase gene expression; CI, confidence interval; dl, dioxin-like; DLC, dioxin-like compound; GA, Georgia; GC/MS, gas chromatography/mass spectrometry; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; RR, relative risk or risk ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent.

Biologic Plausibility

Laboratory studies that used animal models and examined gene-expression changes associated with human endometriosis provide evidence of the biologic plausibility of a link between TCDD exposure and endometriosis. Genetic polymorphisms in the aryl hydrocarbon receptor (AHR) signaling complex have recently been associated with a susceptibility to advanced endometriosis in humans (Li Y et al., 2013; Wu et al., 2012), although another recently published study found no association in Japanese women (Matsuzaka et al., 2012). The first suggestion that TCDD exposure may be linked to endometriosis came as a secondary finding of a study that exposed female rhesus monkeys (*Macaca mulatta*) chronically to low concentrations of dietary TCDD for 4 years (Bowman et al., 1989). Ten and 13 years after the exposure ended, the investigators documented an increased incidence of endometriosis in the monkeys that correlated with the TCDD exposure concentration (Rier et al., 1993, 2001). The sample was too small to

yield a definitive conclusion that TCDD was a causal agent of endometriosis, but this study led to additional studies of the ability of TCDD to promote the growth of pre-existing endometriotic lesions (Bruner-Tran et al., 1999; Johnson et al. 1997; Yang et al., 2000).

There are a number of mechanisms by which TCDD may promote endometrial lesions, which provide additional support of the biologic plausibility of a link between TCDD and endometriosis. Human endometrial tissue and cultured human endometrial epithelial cells both express the AHR; its dimerization partner, the aryl hydrocarbon nuclear translocator (Khorram et al., 2002); and three AHR target genes—CYP1A1, 1A2, and 1B1 (Bulun et al., 2000; Willing et al., 2011). These findings suggest that endometrial tissue is responsive to TCDD. MN Singh et al. (2008) showed that CYP1A1 expression is greater in ectopic endometrial tissue than in eutopic uterine tissue in the absence of TCDD exposure, which suggests that CYP1A1 may play a role in the etiology of the disease or that AHR and its signaling pathway have been activated by an endogenous ligand other than TCDD, such as bilirubin (Seubert et al., 2002). Other mechanisms by which TCDD may promote endometriosis include altering the ratio of progesterone receptor A to progesterone receptor B and blocking the ability of progesterone to suppress matrix metalloproteinase expression—actions that promote endometrial-tissue invasion and that are observed in women who have endometriosis (Igarashi et al., 2005).

TCDD also induces changes in gene expression that mirror those observed in endometrial lesions. In addition to the induction of CYP1A1 noted above, TCDD can induce expression of histamine-releasing factor, which is increased in endometrial lesions and accelerates their growth (Oikawa et al., 2002, 2003). TCDD disrupts cannabinoid signaling in endometrial stromal cells by inhibiting progesterone-induced expression of cannabinoid receptor type 1 (CB1-R), which is also observed in women with endometriosis (Resuehr et al., 2012). TCDD also stimulates the expression of RANTES (*r*egulated on *a*ctivation, *n*ormal *T*-cell–*e*xpressed, and *s*ecreted protein) in endometrial stromal cells, and RANTES concentration and bioactivity are increased in women who have endometriosis (Zhao et al., 2002). The two CC-motif chemokines (chemotactic cytokines), RANTES and macrophage-inflammatory protein 1α (MIP-1α), have been identified as potential contributors to the pathogenesis and progression of endometriosis. Previous studies have shown that the combination of 17β-estradiol and TCDD increases the secretion of RANTES and MIP-1α in endometrial stromal cells (Yu et al., 2008), and a more recent study showed that the same combination suppresses the expression of tetraspanin CD82, a tumor-metastasis suppressor, and thus promotes the invasion of endometrial stromal cells (Li MQ, 2011). Those results support the idea that TCDD in combination with estradiol may contribute to the development of endometriosis by increasing the invasiveness of endometrial cells. Despite that evidence, chronic exposure of rats to TCDD, PCB 153, dioxin-like PCB 118 or PCB 126, or 2,3,4,7,8-PeCDF (the furan congener

with the highest TEF), either individually or in various combinations, fails to alter endometrial histology in a consistent manner (Yoshizawa et al., 2009). The differences between rodent and human endometrium could account for the lack of observed effects in rats.

In summary, experimental studies, particularly ones that used human eutopic and ectopic endometrial tissue, provide evidence of the biologic plausibility of a link between TCDD exposure and endometriosis.

Synthesis

The studies linking dioxin exposure with endometriosis are few and inconsistent. Although animal studies support the biologic plausibility of an association, contemporary human exposures may be too low to show an association consistently.

Conclusion

On the basis of the evidence reviewed here, in *VAO*, and in the previous VAO updates, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and human endometriosis.

FERTILITY

Male reproductive function is under the control of a variety of components whose proper coordination is important for normal fertility. Several of these components and some health outcomes related to male fertility, including reproductive hormones and sperm characteristics, can be studied as indicators of fertility. The reproductive neuroendocrine axis involves the central nervous system, the anterior pituitary gland, and the testis. The hypothalamus integrates neural inputs from the central and peripheral nervous systems and regulates the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Both are secreted into the circulation in episodic bursts by the anterior pituitary gland and are necessary for normal spermatogenesis. In the testis, LH interacts with receptors on Leydig cells, where it stimulates increased testosterone synthesis. FSH and the testosterone from the Leydig cells interact with Sertoli cells in the seminiferous tubule epithelium to regulate spermatogenesis. A more detailed review of the male reproductive hormones can be found elsewhere (Strauss and Barbieri, 2013). Several agents, such as lead and dibromochloropropane, affect the neuroendocrine system and spermatogenesis (for reviews, see Schrader and Marlow, 2014; Sengupta, 2013). Reviews on the effects of various environmental toxicants, including TCDD, on testicular steroidogenesis and spermatogenesis provide insights into potential underlying mechanisms, including reducing

testosterone production in Leydig cells and inhibiting the formation of cAMP (Mathur and D'Cruz, 2011; Svechnikov et al., 2010).

Studies of the relationship between chemicals and fertility are less common in women than in men. Some chemicals may disrupt the female hormonal balance necessary for proper functioning. Normal menstrual-cycle functioning is also important in the risk of hormonally related diseases, such as osteopenia, breast cancer, and cardiovascular disease. Chemicals can have multiple effects on the female system, including modulation of hormone concentrations that result in menstrual-cycle or ovarian-cycle irregularities, changes in menarche and menopause, and impairment of fertility (Bretveld et al., 2006a,b).

Conclusions from *VAO* and Previous Updates

The committee responsible for the original *VAO* report (IOM, 1994) concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and alterations in sperm characteristics or infertility. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change the conclusion that exposure to the COIs had not been found to be associated with impaired fertility in either men or women. Reviews of the relevant studies are presented in the earlier reports. Tables 9-2 and 9-3 summarize the studies related to male and female fertility, respectively.

Update of the Epidemiologic Literature

Male Fertility

Ferguson et al. (2012) reported on a number of male fertility markers in a study of 358 men seeking infertility treatment with their partners. Of the four PCB congeners reported on individually, only the common, mono-ortho PCB 118 has dioxin-like activity, but results were reported for a group of PCBs (95/66, 74, **77**/110, 105/141, **118**, **156**, **167**, 128, 138, 170) characterized by Wolff et al. (1997) as having antiestrogenic and dioxin-like activity (although only the four congeners bolded in the preceding list are recognized by WHO as having dioxin-like activity). After adjusting for age, BMI, and serum lipids, inverse relationships were observed for PCB 118 with steroid hormone binding globulin (SHBG) ($\beta = -0.13$, $p < 0.01$) and with total testosterone ($\beta = -22.1$, $p = 0.08$). A similar, but weaker pattern was seen for the group including dioxin-like PCBs with SHBG ($\beta = -0.08$, $p = 0.08$) and with total testosterone ($\beta = -25.9$, $p = 0.09$); it is not clear what impact on fertility might arise from these at-best marginally significant changes in a PCB grouping of questionable relevance with respect to dioxin-like activity.

TABLE 9-2 Selected Epidemiologic Studies—Male Fertility (Altered Hormone Concentrations, Decreased Sperm Counts or Quality, Subfertility, or Infertility) (Shaded entry is new to this update)

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
AFHS (964 Ranch Hands, 1,259 comparisons)		Coefficient (p-value) for ln(Testosterone) vs ln(TCDD) in 1987	Gupta et al., 2006b
Comparison TCDD quartile I (mean, 2.14 ppt)	nr	0 (referent)	
Comparison TCDD quartile II (mean, 3.54 ppt)	nr	–0.063 (0.004)	
Ranch Hand TCDD quartile I (mean, 4.14 ppt)	nr	0.002 (0.94)	
Comparison TCDD quartile III (mean, 4.74 ppt)	nr	–0.048 (0.03)	
Comparison TCDD quartile IV (mean, 7.87 ppt)	nr	–0.079 (< 0.001)	
Ranch Hand TCDD quartile II (mean, 8.95 ppt)	nr	–0.052 (0.03)	
Ranch Hand TCDD quartile III (mean, 18.40 ppt)	nr	–0.029 (0.22)	
Ranch Hand TCDD quartile IV (mean, 76.16 ppt)	nr	–0.056 (0.02)	
Effects on specific hormone concentrations or sperm count in Ranch Hands			Henriksen et al., 1996
Low testosterone			
High dioxin (1992)	18	1.6 (0.9–2.7)	
High dioxin (1987)	3	0.7 (0.2–2.3)	
Low dioxin (1992)	10	0.9 (0.5–1.8)	
Low dioxin (1987)	10	2.3 (1.1–4..9)	
Background (1992)	9	0.5 (0.3–1.1)	
High FSH			
High dioxin (1992)	8	1.0 (0.5–2.1)	
Low dioxin (1992)	12	1.6 (0.8–3.0)	
Background (1992)	16	1.3 (0.7–2.4)	
High LH			
High dioxin (1992)	5	0.8 (0.3–1.9)	
Low dioxin (1992)	5	0.8 (0.5–3.3)	
Background (1992)	8	0.8 (0.4–1.8)	
Low sperm count			
High dioxin	49	0.9 (0.7–1.2)	
Low dioxin	43	0.8 (0.6–1.0)	
Background	66	0.9 (0.7–1.2)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	

TABLE 9-2 Male Fertility, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Detailed description of cohort			CDC, 1989c
Lower sperm concentration	42	2.3 (1.2–4.3)	
Proportion of abnormal sperm	51	1.6 (0.9–2.8)	
Reduced sperm motility	83	1.2 (0.8–1.8)	
US American Legion Cohort		**All COIs**	
American Legionnaires who served in SEA			Stellman SD et al., 1988b
Difficulty in having children	349	1.3 ($p < 0.01$)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
NIOSH Cross-sectional Medical Study—248 Chemical workers employed at plants in Newark, NJ (1951–1969) and Verona, MI (1968–1972) vs 231 unexposed neighborhood referents, measured in 1987		**Dioxins, phenoxy herbicides**	
Testosterone (< 10.4 nmol/L)			Egeland et al., 1994
Referents (TCDD < 20 ppt)	11	1.0	
Workers	25	2.1 (1.0–4.6)	
Quartile I (TCDD < 20 ppt)	2	0.9 (0.2–4.5)	
Quartile II (TCDD 20–75 ppt)	7	3.9 (1.3–11.3)	
Quartile III (TCDD 76–240 ppt)	6	2.7 (0.9–8.2)	
Quartile IV (TCDD 241–3,400 ppt)	10	2.1 (0.8–5.8)	
FSH (> 31 IU/L)	20	1.5 (0.7–3.3)	
LH (> 28 IU/L)	23	1.6 (0.8–3.3)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
Canada—Sawmill Workers in British Columbia: 26,487 workers for ≥ 1 yr at 14 mills using chlorophenates 1950–1985		**Chlorophenates, not TCDD**	
Workers having a live-birth within 1 yr after the initiation of employment			Heacock et al., 1998
Standard fertility ratio	18,016 (births)	0.7 (0.7–0.8)[b]	
Mantel-Haenszel rate-ratio estimator	18,016 (births)	0.9 (0.8–0.9)[b]	
Cumulative exposure (hours)			
120–1,999	7,139	0.8 (0.8–0.9)[b]	
2,000–3,999	4,582	0.9 (0.8–1.0)[b]	

continued

TABLE 9-2 Male Fertility, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
4,000–9,999	4,145	1.0 (0.9–1.1)[b]	
≥ 10,000	1,300	1.1 (1.0–1.2)[b] ($p < 0.01$ overall)	
Denmark—Danish farmers (n = 1,146), 18–50 yrs of age, who used any potentially spermatotoxic pesticides, including 2,4-D		**Herbicides**	Larsen et al., 1998
Farmers using pesticides vs organic farmers	523	1.0 (0.8–1.4)[c]	
Used three or more pesticides	nr	0.9 (0.7–1.2)[c]	
Used manual sprayer for pesticides	nr	0.8 (0.6–1.1)[c]	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Men exposed in Seveso, Zone A vs age-matched men residing outside the contamination zone, measured semen characteristics, estradiol, FSH, testosterone, LH, inhibin B		*Author's evaluation*	Mocarelli et al., 2008
Age at 1976 exposure:		(data not shown)	
Infant/prepuberty (1–9 yrs), n = 71 vs 176		Sensitive	
Puberty (10–17 yrs), n = 44 vs 136		Intermediate response	
Adult (18–26 yrs), n = 20 vs 60		No associations	
Other International Environmental Studies			
Belgian men in general population		**PCBs, dioxin**	Dhooge et al., 2006
Association with 2-fold increase in CALUX-TEQ		Change (p-value)	
Sperm concentration		25.2% (p = 0.07)	
Semen volume		–16.0% (p = 0.03)	
Total testosterone		–7.1% (p = 0.04)	
Free testosterone		–6.8% (p = 0.04)	
Belgium—Adolescent girls (17 yrs of age) in communities close to industrial sources of heavy metals, PCBs, VOCs, and PAHs—delays in sexual maturity	200	PCBs, DLCs	Staessen et al., 2001
In Hoboken, Belgium	8	4.0 (nr)	
In Wilrik, Belgium	15	1.7 (nr)	
Poland, Greenland, Ukraine, Sweden men in general population; AHR binding measured with CALUX assay		**dl activity**	Toft et al., 2007
Measurement of semen quality (concentration, motility, percentage normal)		No consistent associations	

TABLE 9-2 Male Fertility, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
United States—Male partners (aged 18–51) in subfertile couples seeking infertility evaluations and treatment in Massachusetts General Hospital (01/2000–05/2003)		Dl-PCBs	Ferguson et al., 2012
PCB 118 with steroid hormone binding globulin		(β = –0.13, p < 0.01)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Missouri—men with or without low sperm quality (21–40 yrs of age)		**2,4-D**	Swan et al., 2003
Increased urinary metabolite markers for 2,4-D	5	0.8 (0.2–3.0)	
International Case-Control Studies			
Argentinean farmers exposed to 2,4-D (n = 32) vs 25 unexposed controls, March–July 1989		**2,4-D**	Lerda and Rizzi, 1991
Sperm count (millions/mL)	exposed: 49.0 vs control: 101.6		
Motility (%)	exposed: 24.8 vs control: 70.4		
Sperm death (%)	exposed: 82.9 vs control: 37.1[d]		
Anomalies (%)	exposed: 72.9 vs control: 33.4		
Canada—study of erectile dysfunction in urology patients in Ontario		**PCBs/**Highest vs lowest PCB groups	Polsky et al., 2007
PCB 118 (TEF = 0.0001)		1.0 (0.5–2.1)	
PCB 118 (TEF = 0.0001)		0.9 (0.5–1.6)	
PCB 170		0.6 (0.3–1.2)	
PCB 180		0.7 (0.4–1.4)	
Greenland Inuit men (n = 53) and European men (n = 247), DNA sperm integrity among Inuit men		**POPs**	Krüger et al., 2008
Median % DNA fragmentation index			
Inuits		6.8	
Europeans		12	
Median % DNA stainability			
Inuits		11	
Europeans		8.9	

continued

TABLE 9-2 Male Fertility, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Korean male waste incinerator workers (n = 6) vs controls (n = 8), dioxin measured by air monitoring		**Phenoxy herbicides**	Oh et al., 2005
Reduced number of sperm (10^6/ml)		(p = 0.050)	
Workers		42.9 ± 18.0	
Controls		56.1 ± 44.5	
DNA damaged sperm (%)		(p = 0.001)	
Workers		1.40 ± 0.08	
Controls		1.26 ± 0.03	
Turkey (Ankara)—Adipose-tissue samples from fertile and infertile men (21–46 yrs of age) assayed for PCB 118, April 2002–June 2007	21 fertile	**DLCs** 68.8 ng/g lipid	Cok et al., 2010
	25 infertile	21.7 ng/g lipid (p = 0.003)	
Turkey (Ankara)—Adipose-tissue samples from fertile and infertile men (21–45 yrs of age) assayed for dioxin, furans, dl PCBs, June 2003–September 2005	22 fertile	**DLCs** 9.4 TEQ pg/g lipid (p = 0.003)	Cok et al., 2008
	23 infertile	12.5 TEQ pg/g lipid (p = 0.065)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; AHR, aryl hydrocarbon receptor; CALUX, assay for determination of dioxin-like activity; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemicals of interest; dl, dioxin-like; DLC, dioxin-like chemical; DNA, deoxyribonucleic acid; FSH, follicle-stimulating hormone; ICD, *International Classification of Diseases*; IU, international unit; LH, luteinizing hormone; ln, natural logarithm; nr, not reported; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; POP, persistent organic pollutants; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, toxicity equivalency factor; TEQ, (total) toxic equivalent; VOC, volatile organic compound.

[a]Given when available; results other than estimated risk explained individually.

[b]For this study, relative risk has been replaced with standardized fertility ratio, for which value less than 1.0 indicates adverse effect.

[c]For this study, relative risk has been replaced with fecundability ratio, for which value less than 1.0 indicates adverse effect.

[d]Table 1 in reference reverses these figures—control, 82.9%; exposed, 37.1%—but text ("The percentages of asthenospermia, mobility, necrosperma and teratospermia were greater in the exposed group than in controls. . .") suggests that this is a typographical error.

TABLE 9-3 Selected Epidemiologic Studies—Female Fertility (Altered Hormone Concentrations, Subfertility, or Infertility)

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
8,038 premenopausal women aged 30–55 at enrollment			Farr et al., 2006
Pesticide exposure	5,013	0.9 (0.8–1.0)	
Herbicide exposure	3,725	0.9 (0.7–1.1)	
Phenoxy herbicide exposure	1,379	0.9 (0.7–1.1)	
Menstrual-cycle characteristics of 3,103 premenopausal women aged 21–40			Farr et al., 2004
Reported at enrollment had used herbicides	1,291		
Short menstrual cycle		0.6 (0.4–1.0)	
Long menstrual cycle		1.0 (0.5–2.0)	
Irregular		0.6 (0.3–0.9)	
Missed period		1.4 (1.0–2.0)	
Intermenstrual bleeding		1.1 (0.8–1.7)	
ENVIRONMENTAL			
Seveso (Italy) Women's Health Study—Industrial accident July 10, 1976 ; 981 women between infancy and 40 yrs of age at the time of the accident, who resided in Zones A and B		**TCDD**	
Time to pregnancy and infertility in women from Zones A and B who attempted pregnancy after 1976			Eskenazi et al., 2010
20-yr follow-up to 1996—men and women			
Time to pregnancy (adjusted fecundability OR)			
Log_{10} TCDD	278	0.8 (0.6–1.0)	
Categorical TCDD (ppt)			
≤ 20	52	1.0 (reference)	
20.1–44.4	76	0.8 (0.5–1.3)	
44.5–100	75	0.7 (0.5–1.1)	
> 100	75	0.6 (0.4–1.0)	
Infertility (adjusted OR)			
Log_{10} TCDD	49	1.9 (1.1–3.2)	

continued

TABLE 9-3 Female Fertility, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Categorical TCDD (ppt)			
≤ 20	6	1.0 (reference)	
20.1–44.4	9	1.1 (0.4–3.6)	
44.5–100	16	2.5 (0.8–7.3)	
> 100	18	2.8 (1.0–8.1)	
Fibroids among women from Zones A and B who were newborn to age 40 in 1976			Eskenazi et al., 2007
Uterine fibroids (age-adjusted HR)			
Log_{10} TCDD (ppt)	251	0.8 (0.7–1.1)	
Categorical TCDD (ppt)			
≤ 20	62	1.0 (reference)	
20.1–75.0	110	0.6 (0.4–0.8)	
> 75	79	0.6 (0.4–0.9)	
Ovarian function in women from Zones A and B who were newborn to age 40 in 1976; results are for a 10-fold increase in serum TCDD			Warner at al., 2007
Ovarian follicles (age-adjusted OR):			
in follicular phase	65	1.0 (0.4–2.2)	
Ovulation (age-adjusted OR):			
in luteal phase	87	1.0 (0.5–1.9)	
in midluteal phase	55	1.0 (0.4–2.7)	
Estradiol (age-adjusted ß):		slopes for log TCDD	
in luteal phase	87	−1.8 (−10.4–6.8)	
in midluteal phase	55	−3.1 (−14.1–7.8)	
Progesterone (age-adjusted ß):			
in luteal phase	87	−0.7 (−2.4–1.0)	
in midluteal phase	55	−0.8 (−3.7–2.0)	
Age at menopause in women from Zones A and B who were newborn to age 40 in 1976			Eskenazi et al., 2005
Onset of natural menopause (unadjusted HR)			
Log_{10} TCDD	169	1.0 (0.8–1.3)	
Menopause Category		Serum TCDD median (IQR)	
Premenopause	260	43.6 (0.2–0.9)	
Natural menopause	169	45.8 (0.3–1.0)	
Surgical menopause	83	43.4 (0.3–1.0)	
Impending menopause	13	43.8 (0.2–1.1)	
Perimenopause	33	36.5 (0.2–0.9)	
Other	58	39.6 (0.2–0.9)	
Age at menarche in women from Zones A and B who were premenarcheal in 1976	282	1.0 (0.8–1.1)	Warner et al., 2004
All premenarcheal women in 1976 (unadjusted HR)			

TABLE 9-3 Female Fertility, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Log_{10} TCDD	282	1.0 (0.8–1.1)	
Women < 8 years in 1976 (unadjusted HR)			
Log_{10} TCDD	158	1.1 (0.9–1.3)	
Menstrual-cycle characteristics in women from Zones A and B who were premenopausal, less than age 44, and not recently pregnant, breastfeeding, or using hormonal medications			Eskenazi et al., 2002a
Menstrual-cycle length (adjusted ß)			
Log_{10} TCDD	277	0.4 (–0.1–0.9)	
Premenarcheal at explosion		0.9 (0.0–1.9)	
Postmenarcheal at explosion		0.0 (–0.6–0.5)	
Days of menstrual flow (adjusted ß)			
Log_{10} TCDD	301	0.2 (–0.1–0.4)	
Premenarcheal at explosion		0.2 (–0.2–0.5)	
Postmenarcheal at explosion		0.2 (–0.2–0.5)	
Heaviness of flow (scanty vs moderate/heavy; adjusted OR)			
Log_{10} TCDD	30	0.8 (0.4–1.6)	
Premenarcheal at explosion		0.3 (0.1–1.1)	
Postmenarcheal at explosion		1.4 (0.7–2.6)	
Irregular cycle (vs regular; adjusted OR)			
Log_{10} TCDD	24	0.5 (0.2–1.0)	
Premenarcheal at explosion		0.5 (0.2–1.4)	
Postmenarcheal at explosion		0.4 (0.2–1.2)	
Other International Environmental Studies			
Taiwanese pregnant women (18–40 yrs of age); placental TEQ concentrations of TCDDs, TCDFs, PCBs		**Dioxin/** Regression adjusted for maternal age, BMI, parity	Chao et al., 2007
Older of "regular menstrual cycle"			
Dioxin TEQ		p = 0.032	
PCB TEQ		p = 0.077	
Longer "longest menstrual cycle"			
Dioxin TEQ		p = 0.269	
PCB TEQ		p = 0.006	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Women in Wisconsin with or without infertility (maternal exposure)—incidence		**Phenoxy herbicides**	Greenlee et al., 2003

continued

TABLE 9-3 Female Fertility, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Mixed or applied herbicides	21	2.3 (0.9–6.1)	
Used 2,4,5-T	9	9 cases (2.7%) 11 controls (3.4%)	
Used 2,4-D	4	4 cases (1.2%) 4 controls (1.2%)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; BMI, body mass index; CATI, computer-assisted telephone interviewing; CI, confidence interval; HR, hazard ratio; IARC, International Agency for Research on Cancer; IQR, inter-quartile range; OR, odds ratio; PCB, polychlorinated biphenyl; ppt, parts per trillion; TCDD, 2,3,7,8–tetrachlorodibenzo-*p*-dioxin; TCDF, tetrachlorodibenzofuran; TEQ, (total) toxic equivalent.

[a]Given when available; results other than estimated risk explained individually.

Female Fertility

No Vietnam-veteran, occupational, environmental, or case-control studies of exposure to the COIs and female fertility have been published since *Update 2012*.

Biologic Plausibility

Although a recent study reported that doses of 2,4-D greater than 50 mg/kg/day produce acute testicular toxicity in male rats (Joshi et al., 2012), there is little evidence that lower doses of either 2,4-D or 2,4,5-T (when free of TCDD contamination) given chronically have substantial effects on reproductive organs or fertility (Charles et al., 2001; Munro et al., 1992). The no-observed-adverse-effect level [NOAEL] for 2,4-D is recognized as 15 mg/kg/day (Gervais et al., 2008). In contrast, many diverse laboratory studies have provided evidence that TCDD can affect reproductive-organ function and reduce fertility in both males and females.

The administration of TCDD to male animals elicits reproductive toxicity by affecting testicular, epididymal, prostate, and seminal vesicle weight and function and by decreasing the rate of sperm production (Foster et al., 2010; Rider et al., 2010; Schneider et al., 2014). The mechanisms underlying those effects are not known, but the primary hypotheses are that they are mediated through the dysregulation of testicular steroidogenesis, altered Sertoli cell function, and increased oxidative stress. The exposure of cultured testicular Leydig cells to 25 nM TCDD markedly alters gene expression (Naville et al., 2011), and the exposure of cultured Sertoli cells to 5 nM TCDD decreases viability and increases markers

of oxidative stress (Aly and Khafagy, 2011). The exposure of adult rats or mice to TCDD (2–7 µg/kg/week for 45–60 days) reduces testicular and reproductive function, and these effects can be attenuated by co-treatment with various antioxidants (Beytur et al., 2012; Ciftci et al., 2012; Sönmez et al., 2011; Yin et al., 2012). The results of those studies are supported by the transgenic mouse model that harbors a constitutively active AHR in which testicular and ventral prostate weights and sperm number are reduced (Brunnberg et al., 2011).

Many studies have examined the effects of TCDD on the female reproductive system. Two primary mechanisms that probably contribute to abnormal follicle development and decreased numbers of ova after TCDD exposure are the "cross-talk" of the AHR with the estrogen receptor and the dysregulation of the hypothalamic–pituitary–gonadal axis (Pocar et al., 2005; Safe and Wormke, 2003). Oocytes are directly responsive to TCDD, so TCDD's effects on hormone concentrations, hormone-receptor signaling, and ovarian responsiveness to hormones all probably contribute to TCDD-induced female reproductive toxicity. The data of Jung et al. (2010) in rats show that a single gavage treatment of 32 µg/kg TCDD reduces the proliferation of granulosa cells and thus attenuates cell-cycle progression and potentially contributes to the reduction in ovulation rates observed in other studies. In contrast, Karman et al. (2012) found that 1 nM TCDD exposure in vitro did not reduce the rates of growth of murine antral follicles, but did reduce the secretion of progesterone and estradiol by the follicles. The concentrations of those hormones could be restored by the addition of the precursor pregnenolone, which suggests that TCDD acts upstream of pregnenolone formation. This would be consistent with previous observations in zebrafish that 10, 40, and 100 ppb TCDD in food depressed estradiol biosynthesis (Heiden et al., 2008).

The effects on early embryo development and the effects on placenta formation attributable to dioxin are well documented (Chen et al., 2010; Ishimura et al., 2009; Tsang et al., 2012). Petroff et al. (2011) used a rat in vitro fertilization model to demonstrate that 100 nM TCDD perturbs chromatin and cytoskeletal remodeling at the earliest stages of embryo development, but these changes failed to result in any apparent morphologic changes at later stages of development. The long-term potential effects of these early changes on pregnancy outcome are unknown. It has previously been shown that TCDD may have direct effects on human trophoblast formation at 0.2–2.0 nM in vitro and thus may have the capacity to influence the developing fetus (Chen et al., 2010). That idea is supported by a study showing the ability of 5 nM TCDD to activate the AHR signaling pathway in both rat and human placental trophoblasts (Stejskalova et al., 2011). Finally, a study has demonstrated that TCDD at 0.1, 1.0, and 10.0 nM reduces in a dose-dependent fashion the ability of trophoblastic spheroids (which constitute an embryo surrogate) to attach to endometrial epithelial cells (Tsang et al., 2012). The more recent literature continues to support the biologic plausibility of TCDD having effects on male and female reproduction.

Sex Ratio

Although it would not constitute an adverse health outcome in an individual veteran, perturbations in the sex ratio of children born to an exposed population would suggest that the exposure had an impact on the reproductive process. As shown in Table 9-4, studies of the sex ratios observed among children born to people exposed during the 1976 Seveso accident (Mocarelli et al., 1996, 2000) suggested that paternal exposure to dioxin results in a lower sex ratio (i.e., a smaller-than-expected proportion of male infants at birth), particularly when the father was exposed early in his life (sex ratio [SR] = 0.382). However, a consideration of all 481 singleton births in 1994–2005 to women who resided in Zones A and B and were less than 28 years old at the time of the Seveso accident (ages 18–46 years at the beginning of period when births were identified) generated crude sex ratios showing that male births slightly exceeded female births in Zones A and B (SR = 0.516) and that the increase (SR = 0.571) was more pronounced for the 56 births in Zone A (Baccarelli et al., 2008).

A similar depression in the sex ratio concentrated in fathers who were under 20 years old at the time of the Yucheng poisoning with oil contaminated with PCBs, PCDFs, and PCDDs was reported by del Rio Gomez et al. (2002). On the other hand, Yoshimura et al. (2001) found a nonsignificant increase in the sex ratio (SR = 0.574) of children born in the 4 years following the similar 1967 Yusho poisoning by rice oil contaminated with PCBs and PCDFs (but not TCDD) when at least one parent was exposed. Following up on the Yusho cohort, however, Tsukimori et al. (2012b) noted modest nonsignificant decreases in the sex ratio when either the mother (SR = 0.450) or the father (SR = 0.465) was less than 20 years old at the time of the poisoning. In considering the second generation of Yusho offspring, Tsukimori et al. (2012b) found no effect on the sex ratio in the grandchildren of the exposed men, but the daughters of exposed women showed a tendency toward decreased sex ratios, especially if the grandmother had been young when exposed (results not tabled).

Chao et al. (2007) mentioned that they did not find an association between the sex ratio of offspring and the TEQ concentrations of dioxins, furans, or PCBs in the placentas from 119 Taiwanese women. Hertz-Picciotto et al. (2008) found evidence of an effect on sex ratio in an analysis of the serum concentrations of nine PCB congeners (of which the two dioxin-like congeners were the mono-ortho PCBs 105 and 118) in blood gathered during the 1960s from 399 pregnant women in the San Francisco Bay area. The adjusted odds of male birth were significantly decreased when the 90th percentile of the total concentration of all nine PCBs was compared with the 10th percentile (OR = 0.45, 95% CI 0.26–0.80, p = 0.007). The proportion of male births was significantly reduced for only two of the PCBs when analyzed separately: Dioxin-like, mono-ortho PCB 105 and non–dioxin-like PCB 170 (p = 0.02 for each).

TABLE 9-4 Selected Epidemiologic Studies—Sex Ratio[a]

Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)			
Births from service through 1993 in AFHS			Michalek et al., 1998a
Comparison group	0.504	Not formally analyzed	
Dioxin level in Ranch Hand personnel			
Background	0.502		
Low	0.487		
High	0.535		
OCCUPATIONAL—INDUSTRIAL			
NIOSH Cross-Sectional Study			
Workers producing trichlorophenol and derivatives, including 2,4,5-T		No difference on basis of age at first exposure	Schnorr et al., 2001
Serum TCDD in fathers			
Neighborhood controls (< 20 ppt)	0.544	Referent	
Working fathers			
< 20 ppt	0.507	None significantly decreased (or increased)	
20–255 ppt	0.567		
255– < 1,120 ppt	0.568		
≥ 1,120 ppt	0.550		
Other Studies of Industrial Workers (not related to NIOSH phenoxy cohort)			
Austrian chloracne cohort—157 men, 2 women; exposed to TCDD during 2,4,5-T production			Moshammer and Neuberger, 2000
Children born after starting TCDD exposure in 1971	0.464 (26 boys: 30 girls)	Fewer sons, especially if father was under 20 years old when exposed: SR = 0.20 (1 boy: 4 girls)	
Children born before 1971	0.613 (19 boys: 12 girls)		
Russian workers manufacturing 2,4,5,-trichlorophenol (1961–1988) or 2,4,5-T (1964–1967)			Ryan et al., 2002
Either parent exposed	0.401 (91 boys: 136 girls)	$p < 0.001$	

continued

TABLE 9-4 Sex Ratio, continued

Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments	Reference
Only father exposed	0.378 (71 boys: 117 girls)	$p < 0.001$	
Only mother exposed	0.513 (20 boys: 19 girls)	ns	
OCCUPATIONAL—PAPER AND PULP WORKERS			
Canada—British Columbian sawmill workers (n = 26,487)			Heacock et al., 1998
Chlorophenate-exposed workers	0.515		
Unexposed workers	0.519		
Province overall	0.512		
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
Canadian OFFHS fathers' exposure during 3 mo before conception:			Savitz et al., 1997
No chemical activity	0.503	Referent	
Crop herbicides (some phenoxy herbicides)	0.500	ns	
Protective equipment used/not used	0.510	ns	
No protective equipment	0.450	ns	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)			
Births 1994–2005 in women 0–28 yrs old at time of Seveso accident			Baccarelli et al., 2008
Zone A	0.571		
Zone B	0.508		
Zone R	0.495		
Births 1977–1996 in people from Zones A, B, R, 3–45 yrs old at time of 1976 Seveso accident	0.514	Referent	Mocarelli et al., 2000
Neither parent exposed	0.608	ns	
Father exposed (whether or not mother exposed)	0.440	$p = 0.03$	
Father under 19 yrs old in 1976	0.382	$p = 0.002$	
Father at least 19 yrs old in 1976	0.469	ns	
Only mother exposed	0.545	ns	
Parent (either sex) from Seveso Zone A			Mocarelli et al., 1996
Births 1977–1984	0.351 (26 boys: 48 girls)	$p < 0.001$, related to parental TCDD serum	

TABLE 9-4 Sex Ratio, continued

Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments	Reference
Births 1985–1994	0.484 (60 boys: 64 girls)	ns	
Ecological Study of Residents of Chapaevsk, Russia			
Residents near chemical plant in operation 1967–1987 in Chapaevsk, Russia			Revich et al., 2001
1983–1997	0.507	No clear pattern	
Minimum in 1989	0.401		
Maximum in 1987	0.564		
Maximum in 1995	0.559		
Other International Environmental Studies			
JAPAN—Yusho incident			
Parents (one or both) exposed to PCBs, PCDFs (not TCDD) in 1968			Yoshimura et al., 2001
All Japan in 1967	0.513	Referent	
Births 1967 (before poisoning incident)	0.516	ns	
Births 1968–1971 (after incident)	0.574	ns	
Births 1968–2009			Tsukimori et al., 2012b
Father exposed (whether or not mother exposed)	0.505	p = 0.74	
Father under 20 yrs old in 1967	0.465	p = 0.15	
Mother exposed (whether or not father exposed)	0.501	p = 0.62	
Mother under 20 yrs old in 1967	0.450	p = 0.06	
TAIWAN			
Taiwanese pregnant women (18–40 yrs old); placental TEQ concentrations of TCDDs, TCDFs, PCBs	nr	No association	Chao et al., 2007
Births in individuals exposed to PCBs, PCDFs, PCDDs in 1979 **Yucheng incident**		vs unexposed with same demographics	del Rio Gomez et al., 2002
Father exposed (whether or not mother exposed)	0.490	p = 0.037	
Father under 20 yrs old in 1979	0.458	p = 0.020	
Father at least 20 yrs old in 1979	0.541	p = 0.60	
Mother exposed (whether or not father exposed)	0.504	p = 0.45	
Mother under 20 yrs old in 1979	0.501	p = 0.16	
Mother at least 20 yrs old in 1979	0.500	p = 0.40	

continued

TABLE 9-4 Sex Ratio, continued

Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments	Reference
UNITED STATES			
San Francisco Bay area—serum concentrations in pregnant women during 1960s	OR for male birth (not SR)		Hertz-Picciotto et al., 2008
90th percentile vs 10th percentile		SRs all < 0.5	
Total PCBs	0.4 (0.3–0.8)	p = 0.007	
dl PCBs			
PCB 105	0.6 (0.4–0.9)	p = 0.02	
PCB 118	0.7 (0.5–1.2)	p = 0.17	
PCB 170	0.6 (0.4–0.9)	p = 0.02	
PCB 180	0.8 (0.5–1.2)	p = 0.32	
Births after 1963 to Michigan fish-eaters with serum PCBs in both parents			Karmaus et al., 2002
Paternal PCBs > 8.1 µg/L	0.571	p < 0.05 (but for *more* sons)	
Maternal PCBs > 8.1 µg/L	0.494	ns	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; dl, dioxin-like; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; ns, not significant; nr, not reported; OFFHS, Ontario Farm Family Health Study; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofurans; ppt, parts per trillion; SEA, Southeast Asia; SR, sex ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDF, tetrachlorodibenzofuran; TEQ, (total) toxic equivalent.

[a]*VAO* reports before *Update 1998* did not address association between perturbations in sex ratio of offspring and exposure to chemicals of interest.

[b]Given when available.

Reductions in the expected number of male offspring have also been reported in cohorts of men who were occupationally exposed to dioxin (Moshammer and Neuberger, 2000; Ryan et al., 2002), but other such cohorts did not manifest this relationship (Heacock et al., 1998; Savitz et al., 1997; Schnorr et al., 2001). In the single report relevant to this outcome in Vietnam veterans, however, the sex ratio was increased in the Ranch Hand group that had the highest serum dioxin concentrations (Michalek et al., 1998a), but no formal analysis of this outcome was reported.

A population-level finding of a paternally mediated effect would be a strong indicator that dioxin exposure can interfere with the male reproductive process. James (2006) has interpreted the perturbation of sex ratios by dioxins and other agents as being an indicator of parental endocrine disruption. If James's hypothesis were demonstrated to be true, then it would be concordant with a reduction

in testosterone in exposed men. Another pathway to an altered sex ratio might involve male embryos' experiencing more lethality from induction of mutations due to their unmatched X chromosome. A genotoxic mechanism has not been expected to apply to TCDD, but sex-specific adverse consequences of the modified imprinting of gametes might be a possible mechanism leading to the observation of altered sex ratios at birth. To date, however, results regarding the proportion of sons among the children of fathers exposed to dioxin-like chemicals do not present a clear pattern of reduction.

No experimental animal studies have specifically examined the effects of TCDD on the sex ratios of offspring, nor have any alterations in sex ratio been reported in animal studies that examined the developmental effects of TCDD on offspring.

Synthesis

Reproduction is a sensitive toxic endpoint of TCDD and dioxin-like compounds (DLCs) in rodents, and the fetal rodent is more sensitive than the adult rodent to the adverse effects of TCDD. The sensitivity of these endpoints in humans is less apparent. There is little evidence that exposure to dioxin is associated with a reduction in sperm quality or a reduction in fertility. However, the committee for *Update 2008* noted that the evidence that TCDD exposure reduces serum testosterone in men is consistent across several epidemiologic studies with an appropriate consideration of confounders, including one of Vietnam veterans that found a dose–response relationship. The biologic plausibility of such a relationship is supported by concomitant increases observed in gonadotropins and the results of animal studies. Human populations showing evidence of reduced testosterone with exposure to DLCs include a general population sample (Dhooge et al., 2006), occupationally exposed people (Egeland et al., 1994), and Vietnam veterans in the Air Force Health Study (AFHS) (Gupta et al., 2006b). The evidence that DLCs may modify the sex ratio lends credence to the hypothesis that these chemicals have an effect on male reproductive functioning.

Despite the relative consistency of the finding of a reduction in testosterone, the testosterone concentrations observed even in the highest-exposure groups studied are well within the normal range. The small reduction in testosterone is not expected to have adverse clinical consequences. There is evidence of compensatory physiologic mechanisms. The occupational study by Egeland et al. (1994) found increased gonadotropins in addition to reduced testosterone. Gonadotropins stimulate the production of testosterone in men.

Eskenazi et al. (2010) published the only study to date that has examined dioxin exposure in women with respect to time-to-pregnancy (number of contraceptive-free months before pregnancy) and infertility (more than 12 contraceptive-free months to pregnancy). Dose–response relationships between TCDD serum levels in women who were less than 40 years of age at the time of

the Seveso accident and both time to pregnancy and infertility were observed, which is consistent with published observations in the rat model. Epidemiologic studies have not provided sufficient data to interpret the effects of dioxin specifically on menstrual-cycle function in humans.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the present committee concludes that there is inadequate or insufficient evidence of an association between exposure to the COIs and decreased sperm counts or sperm quality, subfertility, or infertility.

SPONTANEOUS ABORTION, STILLBIRTH, NEONATAL DEATH, AND INFANT DEATH

Spontaneous abortion is the expulsion of a nonviable fetus, generally before 20 weeks of gestation, that is not induced by physical or pharmacologic means. The background risk of recognized spontaneous abortion is generally 11 to 22 percent (Avalos et al., 2012, but it is established that many more pregnancies terminate before women become aware of them (Wilcox, 2010). Such terminations are known as subclinical pregnancy losses and generally are not included in studies of spontaneous abortion. Estimates of the risk of recognized spontaneous abortion vary with the design and method of analysis. Studies have included cohorts of women asked retrospectively about pregnancy history, cohorts of pregnant women (usually those receiving prenatal care), and cohorts of women who are monitored for future pregnancies. The value of retrospective reports can be limited by differential recall of details (e.g., exposure history) specific to pregnancies that occurred long before the interview. Studies that enroll women who appear for prenatal care require the use of life tables and specialized statistical techniques to account for differences in the times at which women seek medical care during pregnancy. The enrollment of women before pregnancy provides the theoretically most valid estimate of risk, but it can attract nonrepresentative study groups because the study protocols are demanding for the women.

Countries and US states have different legal definitions of the age of fetal viability and apply these terms differently, but typically “stillbirth” or “late fetal death” refers to the delivery at or after 20 weeks of gestation of a fetus that shows no signs of life, including a fetus that weighs more than 400 g regardless of gestational age (Lamont et al., 2015); “neonatal death” refers to the death of a liveborn infant within 28 days of birth (Whitworth et al., 2015); and “postnatal death” refers to a death that occurs before the first birthday (Andrews et al., 2008).

The causes of stillbirth and early neonatal death overlap considerably, so they are commonly analyzed together in a category referred to as "perinatal mortality" (Andrews et al., 2008). Stillbirths make up less than 1 percent of all births (CDC, 2000). The most common causes of mortality during the neonatal period are low birth weight (< 2.5 kg at birth), preterm delivery, congenital malformations, pregnancy or delivery complications, and placenta or cord conditions. The most common causes of postnatal death of infants is SIDs (sudden infant death syndrome) (Andrews et al., 2008).

Conclusions from *VAO* and Previous Updates

The committee responsible for the original *VAO* report concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and spontaneous abortion or perinatal death. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, and *Update 2000* did not change that conclusion.

The committee responsible for *Update 2002*, however, found that there was enough evidence available concerning paternal exposure specifically to TCDD to conclude that there was "limited or suggestive evidence" of *no* association between that paternal exposure to TCDD and the risk of spontaneous abortion. That conclusion was based primarily on the National Institute for Occupational Safety and Health study (Schnorr et al., 2001), which investigated a large number of pregnancies fathered by workers whose serum TCDD concentrations were extrapolated back to the time of conception; no association was observed up to the highest exposure group (1,120 ppt or higher). Indications of a positive association were seen in studies of Vietnam veterans (CDC, 1989c; Field and Kerr, 1988; Stellman SD et al., 1988b), but the committee for *Update 2002* asserted that they might be due to an exposure to phenoxy herbicides rather than to TCDD and concluded that there was insufficient information to determine whether there is an association between maternal exposure to TCDD and the risk of spontaneous abortion or between maternal or paternal exposure to 2,4-D, 2,4,5-T, picloram, or cacodylic acid and the risk of spontaneous abortion.

The additional information (none of which concerned paternal exposure) reviewed by the committees responsible for *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change these conclusions.

The relevant studies concerning perinatal death are reviewed in the earlier reports, and Table 9-5 summarizes the findings of studies concerning spontaneous abortion.

TABLE 9-5 Selected Epidemiologic Studies—Spontaneous Abortion[a] (Shaded entry is new to this update)

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Air Force Ranch Hand veterans	157		Wolfe et al., 1995
Background	57	1.1 (0.8–1.5)	
Low exposure	56	1.3 (1.0–1.7)	
High exposure	44	1.0 (0.7–1.3)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Overall	1,566	1.3 (1.2–1.4)	CDC, 1989c
Self-reported low exposure	489	1.2 (1.0–1.4)	
Self-reported medium exposure	406	1.4 (1.2–1.6)	
Self-reported high exposure	113	1.7 (1.3–2.1)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Female Vietnam-era veterans (maternal exposure)		1.0 (0.82–1.21)	Kang et al., 2000a
Vietnam veterans (1,665 pregnancies)	278	nr	
Vietnam-era veterans who did not serve in Vietnam (1,912 pregnancies)	317	nr	
US National Vietnam Veterans		**All COIs**	
Female Vietnam veterans (maternal exposure)			Schwartz, 1998
Women who served in Vietnam	113	nr	
Women who did not serve in the war zone	124	nr	
Civilian women	86	nr	
US American Legion Cohort		**All COIs**	
American Legionnaires with service 1961–1975			Stellman SD et al., 1988b
Vietnam veterans vs Vietnam-era veterans			
All Vietnam veterans	231	1.4 (1.1–1.6)	
Low exposure	72	1.3 (1.0–1.7)	
Medium exposure	53	1.5 (1.1–2.1)	
High exposure	58	1.7 (1.2–2.4)	
Vietnam-era veterans vs herbicide handlers	9	1.6 (0.7–3.3)	
Vietnam veterans			
Low exposure	72	1.0	
Medium exposure	53	1.2 (0.8–1.7)	
High exposure	58	1.4 (0.9–1.9)	

TABLE 9-5 Spontaneous Abortion, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
State Studies of US Vietnam Veterans			
Massachusetts—Wives of Vietnam veterans presenting at Boston Hospital for Women			Aschengrau and Monson, 1989
27 weeks of gestation	10	0.9 (0.4–1.9)	
13 weeks of gestation	nr	1.2 (0.6–2.8)	
International Vietnam Veterans Studies			
Tasmanian Veterans with Service in Vietnam		**All COIs**	
Follow-up of Australian Vietnam veterans	199	1.6 (1.3–2.0)	Field and Kerr, 1988
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxins, phenoxy herbicides**	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Wives and partners of men in NIOSH cohort			Schnorr et al., 2001
Estimated paternal TCDD serum at time of conception			
< 20 ppt	29	0.8 (0.5–1.2)	
20 to < 255 ppt	11	0.8 (0.4–1.6)	
255 to < 1120	11	0.7 (0.3–1.6)	
≥ 1120 ppt	8	1.0 (0.4–2.2)	
Dow Workers with Potential TCDD Exposure and reproductive outcomes studied in offspring of 930 men working with chlorophenol, 1939–1975		**Dioxins, phenoxy herbicides**	Townsend et al., 1982
Wives of men employed involved in chlorophenol processing at Dow Chemical Co.	85	1.0 (0.8–1.4)	
Monsanto workers in Nitro, WV occupationally exposed and potentially exposed after 1949 explosion (1948–1969)		**Dioxins, phenoxy herbicides**	
Follow-up of current and retired 2,4,5-T production workers (n = 235; 117 with chloracne exposure), 1948–1969	14	0.9 (0.4–1.8)	Moses et al., 1984

continued

TABLE 9-5 Spontaneous Abortion, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Follow-up of 2,4,5-T production workers (204 exposed, 163 unexposed), 1948–1969	69	0.9 (0.6–1.2)	Suskind and Hertzberg, 1984
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
New Zealand—Follow-up of 2,4,5-T sprayers vs nonsprayers (n = 989)	43	**Herbicides** *90% CI* 0.9 (0.6–1.3)	Smith et al., 1982
US Forest Service		**Herbicides**	
Women employed by US Forest Service—miscarriages (maternal exposure)	141	2.0 (1.1–3.5)	Driscoll et al., 1998
ENVIRONMENTAL			
Seveso (Italy) Women's Health Study—Industrial accident July 10, 1976; 981 women between infancy and 40 yrs of age at the time of the accident, who resided in Zones A, B		**TCDD**	
SWHS—30-yr updated analysis of pregnancy outcomes			Wesselink et al., 2014
10-fold increase in TCDD level at time of accident	160	0.8 (0.6–1.0)	
Effects on first birth after explosion	75	0.8 (0.6–1.2)	
SWHS participants living in zones A, B in 1976 (maternal exposure)			Eskenazi et al., 2003a
Pregnancies 1976–1998	97	0.8 (0.6–1.2)	
Pregnancies 1976–1984	44	1.0 (0.6–1.6)	
Ecological Study of Residents of Chapaevsk, Russia		**TCDD**	
Residents of Samara Region, Russia (maternal and paternal exposure)			Revich et al., 2001
Chapaevsk	nr	24.4% (20.0–29.5%)[c]	
Samara	nr	15.2% (14.3–16.1%)[c]	
Toliatti	nr	10.6% (9.8–11.5%)[c]	
Syzran	nr	15.6% (13.4–18.1%)[c]	
Novokuibyshevsk	nr	16.9% (14.0–20.3%)[c]	

TABLE 9-5 Spontaneous Abortion, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Other small towns	nr	11.3% (9.4–13.8%)[c]	
Ontario Farm Family Health Study		**Phenoxy herbicides**	
Ontario farm families (maternal, paternal exposures)			Arbuckle et al., 2001
Phenoxyacetic acid herbicide exposure in preconception period, spontaneous-abortion risk	48	1.5 (1.1–2.1)	
Other International Environmental Studies			
Japan—Spontaneous abortions among pregnancies (excluding induced abortions) of women in 1968 Yusho incident (maternal exposure)		**PCBs, PCDFs**	Tsukimori et al., 2008
10 yrs after vs 10 yrs before 10-fold increase in maternal blood concentration (drawn 2001–2005) of:	nr	2.1 (0.8–5.2)	
PeCDF	nr	1.6 (1.1–2.3)	
PCB 126 (TEF = 0.1)	nr	2.5 (0.9–6.9)	
PCB 169 (TEF = 0.01)	nr	2.3 (1.1–4.8)	
Taiwanese pregnant women (18–40 yrs old; placental TEQ concentrations of PCDDs, PCDFs, PCBs		**PCDD, PCBs** nr, but reported ns	Chao et al., 2007
Vietnamese women who were or whose husbands were exposed to herbicides sprayed during Vietnam War	nr	**COIs**/nr, anecdotal reports of miscarriage in pilot study	Tuyet and Johansson, 2001
CASE-CONTROL STUDIES			
US Case-Control Studies			
Washington, Oregon—wives of men occupationally exposed to 2,4-D; all reported work exposure to herbicides (high and medium)	63	**2,4-D** *90% CI* 0.8 (0.6–1.1)	Carmelli et al., 1981
Farm exposure	32	0.7 (0.4–1.5)	
Forest and commercial exposure	31	0.9 (0.6–1.4)	
Exposure during conception period			
Farm exposure	15	1.0 (0.5–1.8)	
Forest and commercial exposure	16	1.6 (0.9–1.8)	
Fathers 18–25 yrs old			
Farm exposure	1	0.7 (nr)	
Forest and commercial exposure	3	4.3 (nr)	
Fathers 26–30 yrs old			
Farm exposure	4	0.4 (nr)	
Forest and commercial exposure	8	1.6 (nr)	

continued

TABLE 9-5 Spontaneous Abortion, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Fathers 31–35 yrs old			
Farm exposure	10	2.9 (nr)	
Forest and commercial exposure	5	1.0 (nr)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant (usually refers to $p < 0.05$); PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; ppt, parts per trillion; SEA, Southeast Asia; SWHS, Seveso Women's Health Study; TCDD, 2,3,7,8–tetrachlorodibenzo-*p*-dioxin; TEF, toxic equivalency factor; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]Unless otherwise indicated, results are for paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Spontaneous abortion rate per 100 full-term pregnancies for 1991–1997.

Update of the Epidemiologic Literature

No Vietnam-veteran, occupational, or case-control studies of exposure to the COIs and spontaneous abortion or perinatal death have been published since *Update 2012*.

Environmental Studies

Wesselink et al. (2014) reported the results of a 30-year updated analysis of pregnancy outcomes in the Seveso Women's Health Study (described in Chapter 6). Overall, the lack of association between TCDD and spontaneous abortion, fetal growth, and gestational length observed in the 20-year follow-up (Eskenazi et al., 2003a) was confirmed in this updated analysis. No effect of note was observed between a 10-fold increase in TCDD levels at the time of the accident and the risk of spontaneous abortion (OR = 0.78, 95% CI 0.59–1.02, n = 160) or when only the first births after the explosion were considered (OR = 0.81, 95% CI 0.55–1.18, n = 75).

Biologic Plausibility

Laboratory animal studies have demonstrated that TCDD exposure during pregnancy can alter the concentrations of circulating steroid hormones and disrupt placental development and function and thus contribute to a reduction in the

survival of implanted embryos and to fetal death (Huang et al., 2011; Ishimura et al., 2009; Wang J et al., 2011; Wu Y et al., 2013, 2014). There is no evidence of a relationship between paternal or maternal exposure to TCDD and spontaneous abortion. Exposure to 2,4-D or 2,4,5-T causes fetal toxicity and death after maternal exposure in experimental animals. However, that effect occurs only at high doses and in the presence of maternal toxicity. No fetal toxicity or death has been reported to occur after paternal exposure to 2,4-D.

Laboratory studies of maternal TCDD exposure during pregnancy have demonstrated the induction of fetal death; neonatal death, however, is only rarely observed and is usually the result of cleft palate, which leads to an inability to nurse. Studies addressing the potential for perinatal death as a result of paternal exposure to TCDD or herbicides are inadequate to support conclusions.

Synthesis

A single study concerning the COIs and spontaneous abortion, stillbirth, neonatal death, or infant death has been published since *Update 201*2, but it did not provide supporting evidence of an association with the COIs and these outcomes. Furthermore, toxicologic studies do not provide clear evidence for the biologic plausibility of an association.

Conclusions

On the basis of the evidence reviewed to date, the committee concludes that there is limited or suggestive evidence that paternal exposure to TCDD is *not* associated with risk of spontaneous abortion and that insufficient information is available to determine whether there is an association between maternal exposure to TCDD or either maternal or paternal exposure to 2,4-D, 2,4,5-T, picloram, or cacodylic acid and the risk of spontaneous abortion. The committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and stillbirth, neonatal death, or infant death.

BIRTH WEIGHT AND PRETERM DELIVERY

Birth weight and the length of the gestation period can have important effects on neonatal morbidity and mortality and on health over the life span. Typically, low birth weight (LBW) is defined as a birth weight under 2,500 g (UNICEF, 2004). In the absence of congenital malformations or chromosomal anomalies, LBW is the consequence of either preterm delivery (PTD) or intrauterine growth-restriction (IUGR). PTSD is delivery at less than 259 days or 37 weeks gestation from the date of the first day of the last menstrual period (Jones and Lopez, 2013), and IUGR is birth weight that is lower than average according to local or national fetal-growth graphs (Romo et al., 2009). LBW occurs in about

7 percent of live births. When no distinction is made between IUGR and PTD, the factors most strongly associated with LBW are maternal tobacco use during pregnancy, multiple births, and race or ethnicity. Other potential risk factors are low socioeconomic status, malnutrition, maternal weight, birth order, maternal complications during pregnancy (such as severe pre-eclampsia or intrauterine infection) and obstetric history, job stress, and cocaine or caffeine use during pregnancy (Alexander and Slay, 2002; Alexander et al., 2003; Ergaz et al., 2005; Jones and Lopez, 2013; Peltier, 2003). Established risk factors for PTD include race (black), extremes of maternal age, low socioeconomic status, previous LBW or PTD, multiple gestations, tobacco use, and low maternal prepregnancy weight or poor pregnancy weight gain (Rubens et al., 2014).

The importance and interpretation of associations with birth weight are often unclear and a subject of controversy among researchers (Barker et al., 2012; Wilcox, 2010). Across populations, the frequency distribution of birth weight is Gaussian, with an extended lower tail, or "residual distribution," that includes preterm and LBW infants. The predominant, normal distribution corresponds largely to term births. In general, shifts in the predominant distribution do not tend to correspond to notable shifts in infant mortality (Wilcox, 2001). A number of factors may result in shifts in the predominant distribution; altitude, race or ethnicity, and maternal smoking are among the better studied, producing a larger (or smaller) percentage of LBW babies. However, populations that have a larger percentage of LBW infants do not always have higher infant mortality (Wilcox, 2001, 2010). While birth weight is tracked internationally as a public health indicator to identify opportunities for intervention and to understand country-specific infant mortality (UNICEF, 2004), strategies to increase birth weight have not been effective in reducing mortality.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and LBW or PTD.

Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* did not change that conclusion. Reviews of the relevant studies are presented in the earlier reports. The most relevant findings on birth weight after paternal and maternal exposure to the COIs are summarized in Tables 9-6 and 9-7, respectively.

Update of the Epidemiologic Literature

No Vietnam-veteran, occupational, or case-control studies of exposure to the COIs and LBW or PTD have been published since *Update 2012*.

TABLE 9-6 Selected Epidemiologic Studies—Birth Weight Following Paternal Exposure

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
VIETNAM VETERANS				
US Air Force Health Study—Ranch Hand veterans vs SEA veterans; births from service through 1993 in AFHS				
Ranch Hands	2,082 births	No association with IUGR	Adjusted by stratification for father's race, mother smoking during pregnancy, mother's alcohol use, mother's age, father's age, father's military occupation	Michalek et al., 1998d
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed				
Military service in VA	1,771 Vietnam; 1,561 non-Vietnam	LBW/RR 1.1 (0.8–1.4)	Maternal age and gravidity. Also model with smoking history, alcohol use, educational attainment, marital status, illicit drug use in military	CDC, 1989b,c
US American Legion Cohort—American Legionnaires with service 1961–1975				
US men deployed to SEA during Vietnam War, and other deployed men during same time period	2,858 in SEA 3,933 deployed elsewhere (n = 6,081)	"no difference between the birth weight of boys born to servicemen stationed in SEA compared to those born to controls, nor did girls' birth weight differs between two groups"	Sex, age of father at time of child's birth, age of mother, mother smoking during pregnancy, military service in SEA and exposure to combat and AO—these were not multivariate adjusted models, so strong smoking effect might have had an influence. These appear to have all been independent models.	Stellman SD et al., 1988b
Tasmanian Veterans with Service in Vietnam— Follow-up of Australian Vietnam veterans				
Military service in Vietnam	~550	LBW/RR 1.6 (1.0–2.5)	RR calculated by committee member	Field and Kerr, 1988

continued

TABLE 9-6 Birth Weight Following Paternal Exposure, continued

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
OCCUPATIONAL—INDUSTRIAL				
Wives of chemical workers highly exposed to TCDD-contaminated chemicals	~500 exposed 600 referents	No association with birth weight overall	Adjusted for sex, education, parity, smoking, length of gestation, no stratification by sex	Lawson et al., 2004
OCCUPATIONAL—HERBICIDE-USING WORKERS				
Chlorophenate, wood preservative in sawmill industry	19,675 births	No association (ORs for SGA ~1)	Sex, maternal and paternal age, birth yr, matching	Dimich-Ward et al., 1996

NOTE: AFHS, Air Force Health Study; AO, Agent Orange; CDC, Centers for Disease Control and Prevention; IUGR, intrauterine growth restriction; LBW, low birth weight; OR, odds ratio; RR, relative risk; SEA, Southeast Asia; SGA, small for gestational age; TCDD, 2,3,7,8-trichlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

Environmental Studies

Since *Update 2012*, several studies have examined potential relationships between the COIs and birth weight. Papadopoulou et al. (2013a) analyzed infant weight, length, and head circumference at birth using estimated maternal dietary intake of dioxins during pregnancy. They considered the entire Norwegian Mother and Child (MoBa) cohort enrolled from 2002 to 2008, of which the births occurring in 2007–2008 form a subcohort of the NewGeneris cohort discussed below. The estimated dietary intakes of dioxin-like activity for the 50,651 eligible mothers were partitioned into quartiles inversely associated with birth weight (−62.1 g, 95% CI −73.8 to −50.5). A similar association was observed when the sexes were looked at separately; boys (−68.9 g, 95% CI −85.2 to −52.2) and girls (−55.2 g, 95% CI −71.7 to −38.6). Two other measures of infant growth (length and head circumference at birth) showed similar patterns.

Papadopoulou et al. (2014) used the CALUX assay to measure dioxin-like activity in maternal blood samples collected at delivery from the 604 mothers in the NewGeneris cohort. Maternal dietary intake of dioxins was estimated using data from food frequency questionnaires and was correlated with the TEQ concentration measured in maternal blood. For mothers in the highest category of dietary intake of dioxin-like compounds, an inverse relationship with birth weight (−121 g, 95% CI −232 to −10) was observed after adjustment for maternal education, energy intake, age, prepregnancy BMI, parity, smoking, and country of

TABLE 9-7 Selected Epidemiologic Studies—Birth Weight Following Maternal Exposure (Shaded entries are new information for this update)

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
VIETNAM VETERANS				
US VA Cohort of Female Vietnam Veterans				
Military Service	2,689	BW girls = + 0.5 oz BW boys = −0.8 oz (Difference in boys comes to −22.7 g)	Unadjusted differences and major uncontrolled confounders (smoking, parity, race)	H. Kang, personal correspondence, February 27, 2013
Military Service	4,140	LBW (OR = 1.06, 95% CI 0.8–1.5)	Maternal age, education, race, marital status, military characteristics, smoking, drinking, average number of hours worked during pregnancy, complications during pregnancy	Kang et al., 2000a
ENVIRONMENTAL				
International Studies				
Mother-child pairs from four European cohorts	967	BW decreased with increased dioxin measured in cord blood	Country, gestational age, gestational age squared, parity, maternal prepregnancy BMI, gender	Vafeiadi et al., 2014a
Japan				
Yusho, Japan—population exposed to PCDDs, PCDFs, and PCBs in contaminated cooking oil	190	~ −200g BW reduction with PCDD TEQ (p = 0.003) in males, also overall effect but driven by effect in boys	Gestational age, maternal age, parity, smoking, duration breastfeeding, seafood consumption	Tsukimori et al., 2012a; Kuratsune et al., 1972
Sapporo, Japan; contemporary cohort	514	BW (−220.5 g per 10-fold increase in TEQ, 95% CI −399.2 to −41.9); effect driven by males	Gestational age, maternal age, maternal height, maternal weight before pregnancy, parity, smoking, inshore fish intake, blood sampling period, infant sex	Konishi et al., 2009

continued

TABLE 9-7 Birth Weight Following Maternal Exposure, continued

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
Coastal Japan; contemporary cohort	75	Some weak negative correlations	Unadjusted; Spearman correlations	Tawara et al., 2009
Breast milk dioxin levels	42	Negative correlation for TEQ-PCDD and TEQ, PCDF, but not "significant"	Spearman correlations	Nishijo et al., 2008
Finland				
Random sampling of mother/infant pairs from urban/rural Finland	167	BW decreased with increasing concentrations of I-TEQ, especially among boys	Unadjusted; effect goes away when restricted to primiparas	Vartiainin et al., 1998
Italy				
Seveso Women's Health Study—30-yr updated analysis	807	Small inverse relationship with LBW	Gestational age, maternal height, pre-explosion history of LBW, yr of pregnancy, parity, maternal age	Wesselink et al., 2014; Eskenazi et al., 2003a
Seveso Residential Cohort	51	No association with LBW	None	Baccarelli et al., 2008
Netherlands				
Dutch children—PCB 118 exposure (only total)	207	BW = −119 (53.7); p = 0.03	Smoking, alcohol, gestational age, target height, parity	Patandin et al., 1998
Norway				
NewGeneris cohort—Maternal dietary intake of dioxins and PCBs	604	BW decreased with increased dl-compounds in diet; only significant in boys	Maternal educational level, energy, maternal age, pre-pregnancy BMI, parity, smoking during pregnancy country	Papadopoulou et al., 2014
Norwegian Mother and Child Cohort Study—Maternal dietary intake of dioxins and PCBs	50,651	BW decreased with increased dl-compounds in diet	Maternal age, energy intake, maternal education, pre-pregnancy BMI, parity, weight gain and smoking during pregnancy, gestational age, child's gender	Papadopoulou et al., 2013a

TABLE 9-7 Birth Weight Following Maternal Exposure, continued

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
United States				
California Child Health and Human Development Study	600	No association with BW	Race, age, smoking status, BMI, sex, length of gestation, lipids	Kezios et al., 2012
Cord blood in Massachusetts infants (1993–1998)—PCB 118	722	Negative BW effects with increasing exposure quartile, non-significant—0, −18.0, −72.0, −69.5	Gestational age, infant size, birth year, maternal age, race parity, height, prepregnancy BMI, smoking, local fish consumption	Sagiv et al., 2007
Times Beach and Quail Run cohorts—TCDD soil contamination in Missouri	Matched sets, ~400 (2:1)	LBW: 1.5 (95% CI 0.2–2.3)	Sex, maternal education, parity, marital status, prepregnancy weight, smoking, history of previous SAB and fetal deaths	Stockbauer et al., 1988
Vietnamese Studies				
Vietnam—people living around contaminated airbase	210	At birth no effect, but BW discrepancy grows with months from delivery. Significant at 4 months. Effect only seen in boys	Parity, maternal age, weight, educational period, alcohol use, family income, family smoking, gestational weeks, infant age on the day of examination	Nishijo et al., 2012

NOTE: BMI, body mass index; BW, birth weight; CI, confidence interval; I-TEQ, International (total) toxic equivalent; LBW, low birth weight; OR, odds ratio; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofurans; SAB, spontaneous abortion; TCDD, 2,3,7,8-trichlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

cohort, plus infant's gestational age and gender. When the sexes were examined separately, the inverse relationship was maintained, but it only achieved statistical significance for boys (−170 g, 95% CI −332 to −8). Similarly, when the highest dietary intake group was compared with the lowest, a small, inverse relationship with gestational age was observed (−1.4 days, 95% CI −3.8–1.0 days). The estimate of gestational exposure employed in these two studies (Papadopoulou et al., 2013a; 2014) is a more indirect and presumably less precise metric than the CALUX results used in the next article.

Vafeiadi et al. (2014) examined dioxin-like activity measured by CALUX in maternal and cord blood samples and birth outcomes in 967 mother–child pairs enrolled in four European cohorts. When the highest tertile of TEQs values measured in cord blood was compared with the lowest exposure category, inverse associations were observed for birth weight (−82 g, 95% CI −216–53; p-trend = 0.225) and gestational age (−0.4 weeks, 95% CI −0.8 to −0.1; p-trend = 0.029). In analyses performed on the two sexes independently, nonsignificant inverse relationships with dioxin-like activity in cord blood and birth weight were observed in both boys (−124 g, 95% CI −391–144) and girls (−57 g, 95% CI −300–185). No indication of association was observed for dioxin-like activity measured in maternal plasma and birth outcomes.

Wesselink et al. (2014) reported the results of an updated analysis of pregnancy outcomes in the Seveso Women's Health Study (described in Chapter 6). Overall, the lack of association between TCDD and spontaneous abortion, fetal growth, and gestational length observed in the first 20-year follow-up (Eskenazi et al., 2003a) was confirmed in this updated analysis. A small inverse association (−22.8 g, 95% CI −80.1–34.6) between a 10-fold increase in serum TCDD levels estimated at pregnancy and birth weight was observed, with the strongest reduction observed for the first births after the explosion (−47.7g, 95% CI −107.3–11.9).

Biologic Plausibility

The available evidence from experimental animal studies indicates that TCDD exposure during pregnancy can reduce body weight at birth, but only at high doses. A recent study in human placental explants suggests that TCDD exposure may enhance placental inflammation and may influence pre-term births associated with infection (Peltier et al., 2013). Laboratory studies of the potential male-mediated developmental toxicity of TCDD and herbicides as a result of exposure of adult male animals are inadequate to support conclusions. TCDD and herbicides are known to cross the placenta, which leads to the direct exposure of the fetus. Data from studies of experimental animals also suggest that the preimplantation embryo and developing fetus are sensitive to the toxic effects of 2,4-D and TCDD after maternal exposure.

Synthesis

Two analyses from European birth cohorts observed a small decrease in birth weight in relation to maternal dietary intake of DLCs (Papadopoulou et al., 2013, 2014). A small decrement in gestational age (1.4 days) was also observed when comparing the highest to lowest dietary intake categories. A similar reduction in birth weight was observed in an analysis of mother–infant pairs enrolled in four European birth cohorts, with an inverse association with birth weight observed

when comparing cord blood measurements of the highest to lowest categories. In all three analyses, the reduction in birth weight was less than 200 grams and not likely to be of clinical relevance. In a final study, an update of the Seveso cohort observed no association between TCDD and fetal growth, confirming an earlier analysis of this cohort.

There are a number of challenges in conducting these types of epidemiologic studies in a rigorous way. First, the prenatal and immediate postpartum period is not a stable pharmacokinetic state, because it involves substantial changes in body volume and fat mobilization. Biomarker measures during pregnancy may be substantially affected by weight change during pregnancy. Moreover, the extrapolation of a more recent biomarker measure back many years to a more relevant period is complicated by intervening pregnancy and breastfeeding events, which result in a substantial uncertainty in the index exposure level. Overall, although the committee notes that the animal literature does support an effect of TCDD exposure at high doses on birth weight, the epidemiologic literature is insufficiently robust to allow a final determination.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and low birth weight or preterm delivery.

10

Effects on Veterans' Descendants

Chapter Overview

Based on new evidence and a review of prior studies, the committee for Update 2014 *did not find any new significant associations between the relevant exposures and adverse outcomes in future generations. Furthermore, the committee has changed the previous categorization of exposure to the chemicals of interest (COIs) and spina bifida from limited suggestive to inadequate or insufficient, consistent with all other birth defects and parental exposures to the COIs. Current evidence supports the findings of earlier studies that*

- *No adverse outcomes in future generations had sufficient evidence of an association with the COIs.*
- *There is inadequate or insufficient evidence to determine whether there is an association between parental exposure to the COIs and birth defects, childhood cancers, or disease in their children as they mature or in later generations.*

The original report in this series, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*[1] (*VAO*; IOM, 1994) contained a single chapter devoted to reproductive outcomes, as was the case through the publication of

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

Veterans and Agent Orange: Update 2000, hereafter referred to as *Update 2000* (IOM, 2001). (Analogous shortened names are used to refer to the updates for 1996, 1998, 2002, 2004, 2006, 2008, 2010, and 2012 [IOM, 1996, 1999, 2003, 2005, 2007, 2009, 2011, 2014].) In *Update 2002*, the chapter's concerns were extended to include the consideration of developmental effects. In *Update 2008*, the chapter also addressed the possibility that adverse effects of exposure to the chemicals in the herbicides used by the military in Vietnam might extend beyond the children of exposed people and affect future generations.

The committee for *Update 2012* decided to divide the material into two separate chapters. Chapter 9 contains information on reproductive outcomes affecting the parental generation and the course of gestation. This chapter focuses on the potential adverse health outcomes in the first generation and on issues related to the possibility of adverse effects occurring in even later generations. Adverse health outcomes due to parental exposure that demonstrate their ongoing heritability by being transmitted to grandchildren and beyond are termed transgenerational effects. Since its inception, the VAO series has considered birth defects (primarily limited to problems detectable at birth or within the first year of life) and childhood cancers (usually restricted to particular cancers that characteristically appear in infants and children and are diagnosed before the age of 18 years). Because of concerns increasingly expressed by veterans and a corresponding interest in the Department of Veterans Affairs, in *Update 2010* the attention of the VAO committees was extended to include all types of medical issues occurring in the veterans' children regardless of age and to include such problems in successive generations. The research community has made considerable progress in understanding the processes that may result in such delayed outcomes, often referred to as the Developmental Origins of Health and Disease (DOHaD). It is hoped that by devoting a separate chapter to the potential problems for the progeny of Vietnam veterans—and perhaps their descendants—we can more clearly present the evidence for maternally and paternally mediated effects separately, because the underlying biology is quite distinct in the two cases.

This chapter summarizes the scientific literature published since *Update 2012* that investigated associations between parental exposure to herbicides and adverse effects on offspring, including future generations, throughout their lifespans. The epidemiologic literature considered in this chapter includes studies of a broad spectrum of effects in the children of Vietnam veterans or other populations occupationally or environmentally exposed to the herbicides sprayed in Vietnam or to the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Because some polychlorinated biphenyls (PCBs), some polychlorinated dibenzofurans (PCDFs), and some polychlorinated dibenzodioxins (PCDDs) other than TCDD have dioxin-like biologic activity, studies of populations exposed to PCBs or PCDFs were reviewed if their results were presented in terms of TCDD toxic equivalents (TEQs). Although all studies reporting TEQs based on PCBs were reviewed, those studies that reported TEQs based only on mono-ortho

PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given very limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the World Health Organization (WHO) revised toxicity equivalency factor (TEF) of 2005 (La Rocca et al., 2008; van den Berg et al., 2006). Although some multigenerational studies have been conducted on laboratory animals, to date there have not been human studies of descendants beyond the first generation for the chemicals of interest (COIs).

Because most Vietnam veterans are men, the primary focus of the VAO series has been on the potential adverse effects of herbicide exposure on men. For nonreproductive outcomes, the etiologic importance of an exposed person's sex does not play a dominant role; but for consideration of the biological mechanisms for the possible transmission of adverse effects to future generations, the gender of the exposed individual is critically important, as discussed below. About 8,000 women served in Vietnam (H. Kang, US Department of Veterans Affairs, personal communication, December 14, 2000), so adverse outcomes in the offspring of female Vietnam veterans are a concern. Exposure scenarios in human populations and experimental animals studied differ in their applicability to our population of concern according to whether the exposed parent was male or female, and it is necessary to evaluate the effects of maternal and paternal exposure separately. As will be noted repeatedly, however, almost all Vietnam veterans were men, but the amount of research providing reliable information on the consequences of paternal exposure is extremely sparse for the COIs in the VAO report series and also for the full array of environmental agents that may pose threats to the health of future generations.

In addition, for published epidemiologic or experimental results to be fully relevant to evaluation of the plausibility of reproductive effects in Vietnam veterans, whether female or male, the veterans' exposure needs to have occurred before the conception of the children. With the exception of female veterans who became pregnant while serving in Vietnam, pregnancies that might have been affected occurred after deployment, when primary exposure had ceased. In the case of pregnancies of women who have previously been substantially exposed to the lipophilic dioxins, the direct exposure of the fetus throughout gestation is possible through the mobilization of toxicants from the mother's adipose tissue. In contrast, adverse effects on offspring mediated by male veterans would be via alterations in the sperm genome and associated ribonucleic acids (RNAs) or semen that would have been transmitted after exposure and deployment.

The categories of association and the approach to categorizing the health outcomes are discussed in Chapters 1 and 2. To reduce repetition throughout the report, Chapter 6 characterizes the study population and presents design information on new publications that report findings on multiple health outcomes or that revisit study populations considered in earlier updates.

BIOLOGIC PLAUSIBILITY OF EFFECTS IN VETERANS' DESCENDANTS

Few offspring studies of the four herbicides in question have been conducted, particularly for picloram and cacodylic acid, and those studies generally have shown toxicity only at very high doses. Thus, the preponderance of the following discussion concerns TCDD exposures, which outside controlled experimental circumstances usually occurred in a mixture of dioxins (dioxin congeners in addition to TCDD).

Because TCDD is stored in fat tissue and has a long biologic half-life, internal exposure at generally constant concentrations may continue after episodic, high-level exposure to external sources has ceased. If a person had a high exposure, then large amounts of dioxins may be stored in fat tissue, which could be mobilized subsequently, as during weight loss. This would not be expected to be the case for non-lipophilic chemicals, such as cacodylic acid.

The mechanisms of possible effects on offspring differ greatly for men and women exposed to the COIs during their service in Vietnam. A father's (paternal) contribution to adverse effects in his offspring is limited mainly to the contents of the fertilizing sperm and perhaps the seminal fluid (Lane et al., 2014). The sperm epigenome had long been believed to consist almost exclusively of a greatly condensed, transcriptionally inert haploid genome. As a result, it was thought that any paternally derived damage to the embryo or offspring would have to arise from changes in sequence (i.e., mutations) or arrangement of the sperm's DNA. However, because dioxins are not genotoxic skepticism persisted concerning whether adverse outcomes in offspring could arise from paternal exposure to the COIs. Recent investigation of DOHaD and epigenetics in particular, however, have raised the possibility that epigenetic mechanisms might constitute a plausible mechanism by which parental exposures to the COIs might contribute to adverse outcomes in offspring.

Epigenetic effects are effects that elicit changes in gene expression without a change in DNA sequence but instead via covalent modifications to the DNA (usually involving methylation) or to other cellular components such as histones and miRNAs that interact with DNA to regulate gene expression and that persist through cell division (Jirtle and Skinner, 2007). Alterations in DNA expression arising from the epigenetic modification of an individual's somatic cells may not be manifested for long periods of time. By definition, epigenetic transgenerational inheritance involves an alteration in the germ line that must be maintained for at least three generations following in utero exposures and for at least two generations after adult exposures (Jirtle and Skinner, 2007). The presumption is that this process requires exposure precisely at the time in germ line development when epigenetic programming is being established, although the mechanisms involved and whether they change from one generation to the next are not known (Skinner et al., 2010). (It should be noted that an adverse effect in the offspring of male or female Vietnam veterans need not be demonstrated to be transgenerational in

this strict sense in either humans or animals, but there must at least be coherent evidence of increased occurrence of the particular effect reported from epidemiologic studies of parents of the sex in question who were exposed to the COIs. Demonstration of epigenetic activity in animal experiments for the COIs would be regarded as supportive evidence of biologic plausibility.)

Paternally derived adverse outcomes in offspring associated with exposure to the COIs could be mediated by alterations of the DNA sequence, but, as noted in Chapter 4, genotoxic effects have not been shown for most of these chemicals. Thus, epigenetic modifications to the developing sperm epigenome, including altered RNAs, are a presumed mechanism (Krawetz, 2005). If the body burden were sufficiently high, then it is also possible that TCDD exposure might occur via absorption of seminal plasma through the vaginal wall, which could affect gestating offspring in an otherwise unexposed mother, although, as noted below, this scenario is unlikely.

A mother's (maternal) contribution to a pregnancy and to her offspring is more extensive than the father's contribution, and any damage to the resulting offspring or later generations can result from epigenetic changes in the egg or from direct effects of exposure on the fetus during gestation and on the neonate during lactation. Gestational exposures and resulting epigenetic change during development are consistent with the Barker hypothesis (also known as the developmental origins of disease), which proposes that some health outcomes occurring throughout the lifespan are established in part during fetal development. The Barker hypothesis also predicts a role for placental morphology and function in offspring health outcomes via epigenetic programming of the developing fetus (Barker and Thornburg, 2013), and TCDD has been reported to affect vascular remodeling of the placenta via an aryl hydrocarbon receptor (AHR)-dependent pathway (Wu et al., 2014). Herein, we review biologic plausibility and relevant data on female veterans and male veterans separately because the underlying pathways for adverse effects in offspring are so different.

Paternal Preconception and Postconception Exposure

There is particular interest in the possibility of paternally mediated effects on offspring and later generations because the vast majority of Vietnam veterans are male. Paternal exposures to TCDD or the other COIs could lead to developmental and later-life effects in offspring and potentially future generations by three feasible pathways. One involves direct alterations in the paternal fertilizing sperm cells that transmit adverse effects to resulting offspring through genetic or epigenetic mechanisms as delineated in Chapter 4. These effects would occur before conception. A second involves transmission of the contaminants to a female partner through seminal fluid during an established pregnancy, that is, after conception. A third is that TCDD contamination of the seminal fluid affects newly discovered functions.

Preconception Exposure

There is no evidence that dioxins can mutate DNA sequences; thus, genetic changes in sperm genes—as has been shown in connection with irradiation or the anticancer drug cyclophosphamide (Codrington et al., 2004)—due to preconception exposures to TCDD are not likely. On the other hand, the potential exists for TCDD to alter the sperm cells of adults before fertilization through epigenetic pathways. The sperm epigenome is distinctive from that of the egg (oocyte) or somatic cells (all other non-gamete cells in the body). The mature sperm cell has less global methylation than somatic cells, particularly at gene promoters, and unique DNA methylation marks (particularly on paternally imprinted genes) that put the sperm genomes in a pluripotent-like state before fertilization (Hales et al., 2011). However, rapid demethylation of most of the remainder of the paternal genome occurs shortly after fertilization (Dean, 2014), suggesting that additional changes are required for the nascent embryo to become truly pluripotent. Chemical alterations of DNA methylation foci of adult sperm have the potential to contribute to permanent effects in offspring, as suggested for male transmittance in fetal alcohol syndrome (Jenkins and Carrell, 2012a). During spermatogenesis in the adult, most sperm histones are replaced by protamines, which render the sperm transcriptionally quiescent and permit extensive DNA compaction. However, some core histones are retained in human sperm with appropriate epigenetic modifications to maintain open nucleosomes at sites that are important during embryo development (Casas and Vavouri, 2014), so their perturbation by exogenous chemicals remains a possibility. This is particularly important because although genome-wide DNA demethylation occurs in paternal DNA after fertilization (Dean, 2014) and should erase most sites that have been reprogrammed by chemicals, histone modification patterns are retained and thus may transmit chemical-induced alterations across generations (Puri et al., 2010).

Despite the exclusion of almost all cytoplasm, mature sperm have been found to carry a diverse spectrum of RNAs, including messenger RNAs (mRNAs), ribosomal RNAs (rRNAs), and small noncoding RNAs (miRNAs and piRNAs), which may affect the developing embryo (Casas and Vavouri, 2014; Hamatani, 2012; Kawano et al., 2012; Krawetz, 2005; Krawetz et al., 2011; Lane et al., 2014; Suh and Blelloch, 2011). For example, small RNAs of paternal origin may direct epigenetic modifications during embryo development and lead to changes in phenotype later in life (Hales et al., 2011). When newborn male mice were stressed by unpredictable separation from their mothers, miRNAs in their sperm have recently been shown to transmit the effects of this early trauma for two generations (Gapp et al., 2014). Heavy metals interact with sperm's nuclear proteins, and this mechanism is suspected to be a basis of paternally mediated lead toxicity (Quintanilla-Vega et al., 2000). Disturbances in the establishment of the epigenetic marks in mature sperm may change cell fate in the early embryo and have effects throughout development and postnatal life (Jenkins and

Carrell, 2012b). Direct evidence of dioxin-mediated changes in the epigenome of mature sperm is not available. However, dioxins have been shown to modify DNA methylation in somatic cells (Hou et al., 2012), so an epigenetic pathway is biologically plausible. A related observation is a recent demonstration that the AHR plays an important role in normal sperm development (Hansen et al., 2014). To date, the only transgenerational effect shown in humans has been from a comparison of food supplies in Sweden during the 1800s and health outcomes in the children and grandchildren of men who were prepubescent when food supplies were relatively high or low. These studies found an association between high food supply levels in grandfathers with decreased longevity and increased risk of cardiovascular disease and diabetes in grandsons that was paternally transmitted, although no mechanistic information was obtained (Kaati et al., 2002, 2007). Whether transgenerational effects can occur in humans from chemical exposures is unknown at this time.

Postconception Exposure

Contaminants such as TCDD that are present in the tissues and blood of exposed males can be transported as parent compounds or metabolites into seminal fluid, the noncellular component of the ejaculate. Typically, concentrations of contaminants in seminal fluid are lower than those in serum, but direct assessments of the ratios of serum to seminal fluid in TCDD have not been reported. Seminal-fluid contaminants can be transmitted to a female during sexual intercourse and be absorbed through the vaginal wall; if the concentrations are high, then they could potentially affect a current pregnancy (Chapin et al., 2004; Klemmt and Scialli, 2005). TCDD and other persistent organic pollutants have been identified and quantified in the seminal plasma of exposed men, including Vietnam veterans (Schecter et al., 1996; Schlebusch et al., 1989; Stachel et al., 1989); thus, this transmission route is theoretically possible. In the Schecter study, serum TCDD was measured in 50 Vietnam veterans from Michigan who had a confirmed or self-reported potential for herbicide exposure and had blood drawn an average of 26 years after the possible exposure. Of those, six had TCDD greater than 20 parts per trillion (ppt) on a lipid-adjusted basis, which supports the idea that some veterans had high initial exposures. A subgroup of 17 men contributed semen at the time of blood draw, and dioxin congeners were analyzed in three randomly pooled samples—a process necessary to provide sufficient volume for chemical analysis. Although the measured concentrations were very low, the results documented the existence of dioxins and dibenzofurans in the seminal plasma of the veterans long after the possible herbicide exposure to TCDD-contaminated herbicides. Because results on serum and semen concentrations could not be linked to individual veterans and because it is unknown whether any of the ones who had high serum dioxin concentrations after 26 years contributed semen for the seminal-fluid measurements, the value of this information is slight.

Seminal-fluid concentrations of TCDD and related chemicals closer to the period of exposure in Vietnam have not been determined, so it is not possible to assess the clinical consequences of this exposure route for female partners and gestating offspring. Banked Ranch Hand specimens, however, might provide a valuable resource for comparing TCDD concentrations in serum and seminal fluid. A recent Institute of Medicine report describes available data and biospecimens from the Ranch Hand study and the potential for future analyses (IOM, 2015).

Despite the potential for a seminal fluid route of exposure, the critical question of dose sufficiency remains unanswered. That is, could absorbed TCDD concentrations be high enough to transmit adverse effects in the fetus? To answer that question, one must take into account several factors. First, the volume of seminal plasma is relatively low (1–5 mL) and because of leakage, only a fraction of seminal constituents is absorbed across the vaginal wall. Moreover, the dilution of absorbed chemicals in the female blood stream (i.e., in a high volume) before transmission across the placenta is estimated at 3 orders of magnitude or more (Klemmt and Scialli, 2005), which reduces a serum concentration of 20 ppt to a scale of parts per quadrillion (10^{-15}). Although studies to address the issue directly have not been undertaken, the dilution factor makes adverse fetal and offspring outcomes as a consequence of seminal plasma exposures to TCDD during pregnancy extremely unlikely. One caveat to this conclusion, however, is that seminal fluid is now known to play an important role in the metabolic phenotype of offspring because it stimulates embryotrophic factors (Bromfield, 2014; Bromfield et al., 2014). Whether TCDD contamination of the seminal fluid can affect this function is not known and should be tested.

Empirical Epidemiologic Evidence on Paternal Transmission

The idea that the exposure of either parent to a toxicant before conception could result in an adverse outcome in offspring is not new and remains a topic of much interest (Schmidt, 2013). Epidemiologic studies have reported occasional findings of paternally transmitted adverse outcomes associated with paternal exposures to certain agents, but none has been replicated convincingly. Even in instances in which an agent is recognized as mutagenic or potentially carcinogenic for exposed men, adverse consequences have not been demonstrated in their children. For example, the hypothesis was extensively investigated in the early 1990s in relation to fathers' exposure to ionizing radiation before conception and an increase in leukemias in their offspring. The initial study (Gardner et al., 1990) was conducted in men who worked at the Sellafield nuclear facility in West Cumbria, United Kingdom. It was presumed that the men were exposed to radiation as a result of working at Sellafield. An association was found between radiation exposures to fathers before conception and an increase in leukemias among their children. However, later studies failed to confirm that finding (Draper et al., 1997; Kinlen, 1993; Kinlen et al., 1993; Parker et al., 1993; Urquhart et al.,

1991). Similarly, a rigorous follow-up of children of atomic-bomb survivors has not demonstrated increased risks of cancer or birth defects (Fujiwara et al., 2008; Izumi et al., 2003; Schull, 2003), and other studies of effects (birth defects and cancers) in the children of male cancer survivors after chemotherapy or radiation treatment have found little support for paternal transmission (Chow et al., 2009; Dohle, 2010; Howell and Shalet, 2005; Madanat-Harjuoja et al., 2010), although sperm and fertility clearly are adversely effected (Green et al., 2010).

An additional problem when trying to determine whether adult male exposure of any type (including to the COIs) can lead to pathological effects in descendants is that almost all experimental exposure studies to identify male transmission have been limited to developmental exposures in rodents (Guerrero-Bosagna and Skinner, 2014; Paoloni-Giacobino, 2014). An early experiment examining male mice treated with simulated Agent Orange mixtures prior to breeding with unexposed females failed to find an increase in a variety of different birth defects in progeny compared with the progeny of untreated males (Lamb et al., 1981). Epigenetic effects have been shown for male gametes in adult mice exposed to a relevant pesticide (methoxyclor) and fungicide (vinclozin) (Paoloni-Giacobino, 2014). However, the chemically induced DNA methylation changes in sperm DNA were not transmitted from one mouse generation to the next for imprinted genes; they were, presumably lost during the period of active demethylation that occurs shortly after fertilization. This observation suggests that transgenerational effects on imprinted genes in mice that might be paternally transmitted may not necessarily involve DNA methylation (Iqbal et al., 2015). Nonetheless, a recent study showed that odor fear conditioning in the father could be paternally transmitted to the F1 and F2 generations and implicated reduced DNA methylation in the responsible odor receptor gene (Dias and Ressler, 2013). Thus, more research is required to understand better how transgenerational effects can be transmitted paternally when they are demonstrated (Dias and Ressler, 2014).

The committee was unable to find a single instance of epidemiologic evidence that convincingly demonstrated paternal exposure to any particular chemical before conception resulting in cancers or birth defects in offspring. However, few data exist to address the hypothesis of paternal exposure and adverse effects in human offspring in which the exposure occurred before conception only to the father and was measured with an objective dosimeter. Thus, it is difficult to assert conclusively that the available epidemiologic evidence either supports or does not support paternal transmission; considerable uncertainty remains on many fronts and would presumably vary by agent and mode of exposure. Several systematic reviews of the topic have been conducted (Chia and Shi, 2002; Weselak et al., 2007, 2008; Wigle et al., 2007, 2008) and have not established firm relationships between specific agents and particular effects in offspring. Paternal occupation (by job title or job–exposure matrices) has been linked to an increased risk of selected birth defects (Desrosiers et al., 2012; Fear et al., 2007; Shaw et al., 2002) and neuroblastoma (De Roos et al., 2001a,b). Moreover, increased risks of

childhood brain cancer have been reported in relation to paternal exposure to selected pesticides, particularly herbicides and fungicides (van Wijngaarden et al., 2003), although the authors noted considerable uncertainty in the robustness of the findings. Therefore, the hypothesis that paternal preconception exposure to toxic agents may result in harm to their children remains unresolved in significant part because of the sparseness of epidemiologic research on the subject.

Maternal Exposure

A mother's exposures can affect a pregnancy and the resulting offspring far more extensively than can paternal exposures. Because of the long half-life of TCDD and its bioaccumulation in adipose tissues, women exposed to herbicides in Vietnam would have the potential to expose their offspring to TCDD directly during later pregnancies. Thus, damage to the resulting offspring or future generations could result from epigenetic changes in an egg before conception or from the direct effects of exposure on the fetus during gestation and on the neonate during lactation. Dioxin in the mother's bloodstream can cross the placenta and expose the developing embryo and fetus. Furthermore, the mobilization of dioxin during pregnancy or lactation may be increased because the body is drawing on fat stores to supply nutrients to the developing fetus or nursing infant. TCDD has been measured in circulating human maternal blood, cord blood, placenta, and breast milk (Suzuki et al., 2005), and it is estimated that an infant breastfed for 1 year accumulates a dose of TCDD that is six times as high as an infant not breastfed (Lorber and Phillips, 2002). Offspring effects of maternal exposures may not be manifested immediately and could be a result of dioxin-mediated reprogramming of developing organs and lead to a disease onset later in life. As noted above, placental structure and function are believed to play a major role in fetal programming, and TCDD has been shown to alter placental vascular remodeling (Wu et al., 2013, 2014).

As mentioned above in conjunction with the role of the placenta in fetal development, the developmental basis of adult disease (Barker et al., 2012) is being actively researched by investigating maternal nutritional exposures, stress, and alcohol exposure, and more recent studies have examined exposures to TCDD and other environmental toxicants. The molecular basis of the later-life effects is believed to be primarily epigenetic. Maladies that may be manifested later in life include neurologic and reproductive disorders, thyroid changes, diabetes, obesity, and adult-onset cancers. Furthermore, germ cells (eggs and spermatogonia) in offspring pass through critical developmental stages during fetal life (Hansen et al., 2014), and emerging evidence demonstrates that fetal exposures are capable of altering the germ cells epigenetically, resulting in a transmission of adverse effects to future generations (i.e., transgenerational inheritance) (Hansen et al., 2014).

Laboratory animal studies have established that TCDD can affect development, so a connection between TCDD exposure and effects on offspring,

including developmental disruption and disease onset in later life, is biologically plausible. It has been established in several animal studies that TCDD at high doses is a potent teratogen. Recent studies with rodent models have demonstrated male, female, and sex-independent effects in the immediate offspring of females exposed during pregnancy. These include epigenetic modification of imprinted genes (Somm et al., 2013), increased DNA methylation of the *BRCA1* tumor suppressor gene in mammary tissue (Papoutsis et al., 2013), altered uterine response to estradiol (Burns et al., 2013), dysregulation of lipid metabolism in the presence of a high-caloric diet (Sugai et al., 2014), aberrant emotional behaviors (Nguyen et al., 2013), reduced capacity for lymphocyte differentiation (Ahrenhoerster et al., 2014), testicular inflammation (Bruner-Tran et al., 2014), and a variety of adult diseases including kidney, prostate, ovarian primordial follicle loss, and polycystic ovarian disease (Manikkam et al., 2012a). Transgenerational inheritance to the F3 generation was shown for the last two studies. However, definitive conclusions based on animal studies about the potential for TCDD to cause later-life toxicity in human offspring are complicated by differences in sensitivity and susceptibility among individual animals, strains, and species; by differences in route, dose, duration, and timing of exposure in experimental protocols and real-world exposure; and by differences in the toxicokinetics of TCDD between laboratory animals and humans. Experiments with 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) indicate that they have subcellular effects that could constitute a biologically plausible mechanism for developmental effects, but only at very high doses. There is insufficient information on picloram and cacodylic acid to assess the biologic plausibility of their developmental or delayed effects in offspring.

Chapter 4 presents more detailed toxicologic findings that are relevant to the biologic plausibility of the outcomes discussed here.

BIRTH DEFECTS

A birth defect is an abnormality of structure, function, or metabolism, whether genetically determined or resulting from an environmental influence during embryonic or fetal life (Christianson et al., 2006). Other terms, often used interchangeably, are "congenital anomaly" and "congenital malformation." Major birth defects, which occur in 2 to 3 percent of live births, are abnormalities present at birth that are severe enough to interfere with viability or physical well-being. Birth defects are detected in another 5 percent of babies through the first year of life. Genetic factors, exposure to some medications, exposure to environmental contaminants, occupational exposures, and lifestyle factors have been implicated in the etiology of birth defects (Christianson et al., 2006), although causes of the vast majority of birth defects are unknown. Most etiologic research has focused on the effects of maternal and fetal exposures, but as discussed in the beginning of this chapter, it is theoretically possible that epigenetic alterations of

the paternal gamete caused by preconception exposures could result in paternally mediated effects. It should be noted that a substantial amount of epidemiologic research on suspect toxic agents has been conducted, but none of it has not definitively established *paternal* preconception exposures as a contributing factor to the occurrence of birth defects (Chow et al., 2009; Desrosiers et al., 2012; Dohle, 2010; Schull, 2003).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to 2,4-D, 2,4,5-T or its contaminant TCDD, picloram, or cacodylic acid and birth defects in offspring. Additional information from the Air Force Health Study (AFHS) available to the committee responsible for *Update 1996* led it to conclude that there was limited or suggestive evidence of an association between at least one of the COIs and spina bifida in the children of veterans; there was no change in the conclusions regarding other birth defects. The committee for *Update 2002*, which reviewed the study of female Vietnam veterans that reported significant increases in birth defects in their offspring (Kang et al., 2000a), did not find those results adequate to modify prior conclusions. Nonetheless, Congress did mandate that a number of birth defects in the children of female Vietnam veterans be assigned service-related status. Later VAO committees have not encountered enough additional data to merit changing the conclusion that the evidence is inadequate to support an association between exposure to the COIs and birth defects (aside from spina bifida) in the offspring of either male or female veterans. Summaries of the results of studies of birth defects and specifically of neural-tube defects that were reviewed in the current report and in earlier VAO reports are in Tables 10-1 and 10-2, respectively.

Update of the Epidemiologic Literature

No Vietnam-veteran, occupational, or environmental studies of exposure to the COIs and LBW or PTD have been published since *Update 2012*.

Case-Control Studies

Since *Update 2012*, two studies have examined residential proximity to applications of commercial pesticides in California and birth defects. Using data from the California Pesticide and Birth Defects Monitoring programs, Carmichael et al. (2013) examined pesticide applications within 500 meters of a residence and hypospadias in 690 cases and 2,195 controls. Among the cases classified as the least severe, applications of 2,4-D within 500 meters of the home occurred during the first 14 weeks of pregnancy (the critical window of exposure for birth

TABLE 10-1 Selected Epidemiologic Studies—Birth Defects in Offspring of Subjects[a] (Shaded entries are new information for this update)

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Verified birth defects in children born to AFHS veterans			Michalek et al., 1998a
Before service in SEA	nr	0.7 (nr)	
After service in SEA	nr	1.5 (nr)	
High-exposure Ranch Hands relative to comparisons			Wolfe et al.,1995
All anomalies	57	1.0 (0.8–1.3)	
Nervous system	3	nr	
Eye	3	1.6 (0.4–6.0)	
Ear, face, neck	5	1.7 (0.6–4.7)	
Circulatory system, heart	4	0.9 (0.3–2.7)	
Respiratory system	2	nr	
Digestive system	5	0.8 (0.3–2.0)	
Genital system	6	1.2 (0.5–3.0)	
Urinary system	7	2.1 (0.8–5.4)	
Musculoskeletal	31	0.9 (0.6–1.2)	
Skin	3	0.5 (0.2–1.7)	
Chromosomal anomalies	1	nr	
CDC Birth Defects Study—Hospital records reviewed for offspring of 7,924 Vietnam veterans and 7,364 non-Vietnam veterans		**All COIs**	
General Birth Defects Study—hospital records	130	1.0 (0.8–1.3)	CDC, 1989a
Major birth defects	51	1.2 (0.8–1.9)	
Digestive system defects	18	2.0 (0.9–4.6)	
Birth defects—black Vietnam veterans only	21	3.4 (1.5–7.6)	
Vietnam veterans identified through CDC Metropolitan Atlanta Congenital Defects Program			Erikson et al., 1984a,b
Any major birth defects	428	1.0 (0.8–1.1)	
Multiple birth defects with reported exposure	25	1.1 (0.7–1.7)	
EOI-5: spina bifida	1	2.7 (1.2–6.2)	
EOI-5: cleft lip with or without cleft palate	5	2.2 (1.0–4.9)	

continued

TABLE 10-1 Birth Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
US CDC Vietnam Experience Study— Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Reproductive outcomes—interview data			CDC, 1989b
Total anomalies	826	1.3 (1.2–1.4)	
Nervous system defects	33	2.3 (1.2–4.5)	
Ear, face, neck defects	37	1.6 (0.9–2.8)	
Integument	41	2.2 (1.2–4.0)	
Musculoskeletal defects	426	1.2 (1.1–1.5)	
Hydrocephalus	11	5.1 (1.1–23.1)	
Spina bifida	9	1.7 (0.6–5.0)	
Hypospadias	10	3.1 (0.9–11.3)	
Multiple defects	71	1.6 (1.1–2.5)	
Children of veterans reporting high exposure	46	1.7 (1.2–2.4)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Female Vietnam-era veterans—deployed vs non-deployed (maternal exposure)			Kang et al., 2000a
"Likely" birth defects	nr	1.7 (1.2–2.2)	
"Moderate-to-severe" birth defects	nr	1.5 (1.1–2.0)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans		**All COIs**	
Vietnam veterans whose children were born at Boston Hospital for Women			Aschengrau and Monson, 1990
All congenital anomalies (crude OR)			
vs men without known military service	55	1.3 (0.9–1.9)	
vs non-Vietnam veterans	55	1.2 (0.8–1.9)	
One or more major malformations (crude OR)			
vs men without known military service	18	1.8 (1.0–3.1)	
vs non-Vietnam veterans	18	1.3 (0.7–2.4)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
Down syndrome	67	92 expected (73–111)	

TABLE 10-1 Birth Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Tracheo-esophageal fistula	10	23 expected (14–32)	
Anencephaly	13	16 expected (8–24)	
Cleft lip or palate	94	64 expected (48–80)	
Absent external body part	22	34 expected (23–45)	
Extra body part	74	74 expected (nr)	
Vietnam veterans vs all other men	127	1.0 (0.8–1.3)	Donovan et al., 1984
National Service veterans—Vietnam service vs no Vietnam service	69	1.3 (0.9–2.0)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort— Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Wives of workers with measured serum TCDD in NIOSH cohort	14	nr	Lawson et al., 2004
Dow Workers with Potential TCDD Exposure and reproductive outcomes in offspring of 930 men working with chlorophenol 1939–1975	30	0.9 (0.5–1.4)	Townsend et al., 1982
Monsanto workers in Nitro, WV occupationally exposed and potentially exposed after 1949 explosion (1948–1969)		**Dioxins, phenoxy herbicides**	
Follow-up of current and retired 2,4,5-T production workers (n = 235; 117 with chloracne exposure), 1948–1969	11	1.3 (0.5–3.4)	Moses et al., 1984
Follow-up of 2,4,5-T production workers (204 exposed, 163 unexposed), 1948–1969	18	1.1 (0.5–2.2)	Suskind and Hertzberg, 1984
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
Canada—Pregnancies with one or more birth defects in OFFHS	108	**Herbicides**	Weselak et al., 2008
Use on farm, during 3 mo before conception, of:			

continued

TABLE 10-1 Birth Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Herbicides	24	0.7 (0.4–1.1)	
Male offspring	19	0.9 (0.5–1.6)	
Direct paternal use	19	0.5 (0.3–1.0)	
Phenoxy herbicides	12	0.6 (0.3–1.1)	
Male offspring	9	0.8 (0.4–1.7)	
Direct paternal use	8	0.4 (0.2–0.9)	
2,4-D	10	1.1 (0.6–2.1)	
Male offspring	7	1.3 (0.6–2.8)	
Direct paternal use	6	0.6 (0.3–1.5)	
Dicamba	8	1.7 (0.8–3.5)	
Male offspring	7	2.4 (1.1–5.5)	
Use on farm, during 3 mo after conception, of:			
Herbicides	7	0.5 (0.2–1.2)	
Phenoxy herbicides	9	0.8 (0.4–1.5)	
2,4-D	7	1.0 (0.4–2.3)	
Canadian sawmill workers with exposure in upper three quartiles for any job held up to 3 mo before conception			Dimich-Ward et al., 1996
Cataracts	11	5.7 (1.4–22.6)	
Genital organs	105	1.3 (0.9–1.5)	
New Zealand—Follow-up of 2,4,5-T sprayers vs nonsprayers (n = 989)	13	**Herbicides** *90% CI* 1.2 (0.6–2.5)	Smith et al., 1982
Norway—farmers (maternal, paternal exposure)	4,189	1.0 (1.0–1.1)	Kristensen et al., 1997
United States—Minnesota private pesticide appliers		**Pesticides**	Garry et al., 1996
All births with anomalies	125	1.4 (1.2–1.7)	
Circulatory, respiratory	17	1.7 (1.0–2.8)	
Gastrointestinal	6	1.7 (0.8–3.8)	
Urogenital	20	1.7 (1.1–2.6)	
Musculoskeletal, integumental	30		
Maternal age under 30 yrs	11	0.9 (0.5–1.7)	
Maternal age over 30 yrs	19	2.5 (1.6–4.0)	
Chromosomal	8	1.1 (0.5–2.1)	
Other	48		
Maternal age under 35 yrs	36	1.1 (0.8–1.6)	
Maternal age over 35 yrs	12	3.0 (1.6–5.3)	

TABLE 10-1 Birth Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Maternal, paternal, in utero exposure		*90% CI*	Mastroiacovo et al., 1988
Zones A, B, R—total defects	137	1.0 (0.8–1.1)	
Zones A and B—total defects	27	1.2 (0.9–1.6)	
Zones A and B—mild defects	14	1.4 (0.9–2.2)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Congenital malformations	nr	nr, but ns	
Times Beach/Quail Run Cohorts		**Dioxin**	
Persons in Missouri with documented TCDD soil contamination near residence (maternal, paternal, in utero exposure)		**TCDD**	Stockbauer et al., 1988
Total birth defects	17	0.8 (0.4–1.5)	
Major defects	15	0.8 (0.4–1.7)	
Midline defects	4	0.7 (0.2–2.3)	
Other International Environmental Studies			
France—Case-control study (2001–2003 births) of urinary tract defects (n = 304) vs regional controls (n = 226) (Same population as Cordier et al., 2004)		**Dioxin**	Cordier et al., 2010
Maternal exposure to:			
Atmospheric dioxin	63	2.0 (1.2–3.4)	
Above median	33	2.8 (1.3–6.1)	
Below median	30	1.4 (0.7–2.9)	
Dioxin deposits	75	1.8 (1.1–3.0)	
Above median	41	3.0 (1.5–5.9)	
Below median	34	1.2 (0.6–2.2)	
France—Births (1988–1997): maternal residence in municipality with solid-waste incinerator vs not		**Dioxin**	Cordier et al., 2004
Minor anomalies	518	0.9 (0.8–1.1)	
Chromosomal anomalies	204	1.0 (0.9–1.2)	
Monogenic anomalies	83	1.1 (0.8–1.4)	
Unknown or multifactoral etiology	964	1.1 (1.0–1.2)	
Specific major anomalies with significant increases reported (of 23 categories reported)			
Facial clefts	152	1.3 (1.1–1.6)	
Renal dysplasia	60	1.6 (1.1–2.2)	

continued

TABLE 10-1 Birth Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Turkey—Cross-sectional study of MIH in Turkey; n = 109 from industrialized community with high levels of PCDDs and n = 44 from low industrialized community		**PCDDs** Prevalence of MIH 4/44 and 10/109, no difference	Kuscu et al., 2009
United States—Rural or farm residents of Minnesota, Montana, North Dakota, South Dakota (maternal, paternal exposure)		2,4-D, MCPA	Schreinemachers, 2003
Any birth anomaly	213	1.1 (0.9–1.3)	
Central nervous system anomalies	12	0.8 (0.5–1.4)	
Circulatory, respiratory anomalies	39	1.7 (1.1–2.6)	
Digestive system anomalies	24	0.9 (0.6–1.5)	
Urogenital anomalies	44	1.0 (0.7–1.5)	
Musculoskeletal, integumental anomalies	70	1.5 (1.1–2.1)	
Chromosomal anomalies	17	0.9 (0.6–1.6)	
United States—Persons exposed to an electric-transformer fire in Binghamton, NY—total birth defects (maternal, paternal exposure)	1	**Chlorophenols** 2.1 (0.1–11.9)	Fitzgerald et al., 1989
CASE-CONTROL STUDIES			
US Case-Control Studies			
Arkansas—hypospadias as function of mother's residence within 500 m of agricultural pesticide use during gestation weeks 6–16		Dicamba	Meyer et al., 2006
Dicamba (lb)			
0	nr	1.0	
> 0– < 0.04	nr	0.5 (0.3–1.0)	
≥ 0.04	nr	0.9 (0.4–2.1)	
California—US National Birth Defects Prevention Study (8 counties in San Joaquin Valley), residential proximity to agricultural pesticide applications during early pregnancy (785 controls)		**2,4-D**	
Atrial septal defect (n = 132 cases)	14	2.3 (1.2–4.5)	Carmichael et al., 2014
Pulmonary valve stenosis (n = 53 cases)	6	2.9 (1.0–7.9)	
Anencephaly (n = 73 cases)	7	2.0 (0.8–5.1)	Yang et al., 2014
Cleft palate (n = 117 cases)	4	nr	
Cleft lip and palate (n = 277 cases)	16	1.1 (0.6–2.1)	
Spina bifida (n = 123 cases)	4	nr	
Gastroschisis (n = 156 cases)	11	1.6 (0.8–3.2)	Shaw et al., 2014

TABLE 10-1 Birth Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Hypospadias and maternal occupational herbicide exposure; JEM to determine exposure from conception through first trimester of pregnancy (647 cases vs 1,496 controls)		**Herbicides**	Rocheleau et al., 2011b
Second- or third-degree hypospadias	178	1.0 (0.5–2.1)	
California—Hypospadias and residential proximity to commercial pesticide applications (690 cases, 2,195 controls)	5	**2,4-D** 2.1 (0.8–5.6)	Carmichael et al., 2013
Maryland—Baltimore mothers in the BWIS exposed to herbicides during first trimester (maternal exposure)	8	**Herbicides** 2.8 (1.2–6.9)	Loffredo et al., 2001
International Case-Control Studies			
Denmark/Finland—Relationship between congenital cryptorchidism and PCBs and dioxins in breast milk (130 samples)		**Dioxin, PCBs** ns	Krysiak-Baltyn et al., 2012
Denmark/Finland—Relationship between congenital cryptorchidism and PCBs and dioxins in placentas; 112 Finnish subjects (56 cases, 56 controls) and 168 Danish subjects (39 cases, 129 controls)		**Dioxin, PCBs** ns	Virtanen et al., 2012
Finland—Follow-up of participants from previous case-control study of cleft lip and palate, n = 167 placenta tissue analyzed for PCDD/Fs and children assessed for MIH		**PCDDs, PCDFs** 24/167 with MIH TEQ of PCDDs not association with MIH; duration of breast feeding not association with MIH	Laisi et al., 2008
Japan—Investigated multiple pregnancy outcomes in Japan-infant deaths from congenital defects	42	**Dioxin** nr, but ns	Tango et al., 2004
New Zealand—Residents of areas subject to aerial 2,4,5-T spraying		**2,4,5-T** *90% CI*	Hanify et al., 1981
All birth malformations excluding dislocated or dislocatable hip	164	1.7 (1.4–2.1)	
All heart malformations	20	3.9 (2.1–7.4)	
Hypospadias, epispadias	18	5.6 (2.7–11.7)	
Talipes	52	1.7 (1.2–2.3)	
Cleft lip	6	0.6 (0.3–1.3)	
Isolated cleft palate	7	1.4 (0.6–3.2)	

continued

TABLE 10-1 Birth Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Spain—Residents of agricultural areas—at least median score on chlorophenoxy-herbicide exposure duration (months) index	14	**Herbicides** 3.1 (0.6–16.9)	García et al., 1998
The Netherlands—Infants born in Zeeburg, Amsterdam, clinics 1963–1965 with orofacial cleft (maternal exposure)		**Dioxin**	ten Tusscher et al., 2000
Births in 1963	5	nr, but said to be significant	
Births in 1964	7	nr, but said to be significant	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; BWIS, Baltimore–Washington Infant Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; JEM, job–exposure matrix; IARC, International Agency for Research on Cancer; MCPA, 4-chloro-2-methylphenoxyacetic acid; MIH, molar incisor hypomineralization; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; OFFHS, Ontario Farm Family Health Study; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; SEA, Southeast Asia; TEQ, (total) toxic equivalent; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

defects) for five cases. After adjusting for confounders, the observed risk was elevated (odds ratio [OR] = 2.11, 95% confidence interval [CI] 0.80–5.56) but statistically imprecise due to the small number of exposed cases. No increased risk was observed for cases classified as more severe and applications of 2,4-D.

Using a similar strategy for the California cases and controls enrolled in the US National Birth Defects Prevention Study (NBDPS), a population-based case-control study of congenital malformations, Carmichael et al. (2014), Yang et al. (2014) and Shaw et al. (2014) examined a number of birth defects that were verified by clinical geneticists. Cases and controls were considered exposed when applications of 2,4-D occurred within 500 meters of the maternal residence during the critical period of pregnancy. After an adjustment for confounders, elevated risks of pulmonary valve stenosis (OR = 2.9, 95% CI 1.0–7.9), atrial septal defect (OR = 2.3, 95% CI 1.2–4.5), and anencephaly (OR = 2.0, 95% CI 0.8–5.1) were observed. No association was observed for cleft lip with or without cleft palate, and there were insufficient numbers of exposed cleft palate (n = 4) and spina bifida (n = 4) cases to calculate adjusted risks. Finally, applications of 2,4-D were associated with an increased risk of gastroschisis (OR = 1.6, 95% CI 0.8–3.2).

TABLE 10-2 Selected Epidemiologic Studies—Neural-Tube Defects in Offspring of Subjects[a] (Shaded entries are new information for this update)

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Air Force Operation Ranch Hand personnel—neural-tube defects	4[c]	nr	Wolfe et al., 1995
CDC Birth Defects Study—Hospital records reviewed for offspring of 7,924 Vietnam veterans and 7,364 non-Vietnam veterans		**All COIs**	
Vietnam veterans identified through CDC Metropolitan Atlanta Congenital Defects Program			Erickson et al., 1984a,b
Service in Vietnam			
Spina bifida	19	1.1 (0.6–1.7)	
Anencephaly	12	0.9 (0.5–1.7)	
Military records indicate opportunity for exposure			
Spina bifida	20	2.7 (1.2–6.2)	
Anencephaly	7	0.7 (0.2–2.8)	
US CDC Vietnam Experience Study— Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
VES cohort—reproductive outcomes			CDC, 1989a
Spina bifida			
Vietnam veterans' children	9	1.7 (0.6–5.0)	
Non-Vietnam veterans' children	5	1.0	
Anencephaly			
Vietnam veterans' children	3	nr	
Non-Vietnam veterans' children	0	1.0	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
Spina bifida—maximums	50	33 (22–44)	
Anencephaly	13	16 (8–24)	

continued

TABLE 10-2 Neural-Tube Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
		All COIs	
Australian Vietnam veterans—neural-tube defects	16	0.9 (nr)	ADVA, 1983
OCCUPATIONAL—HERBICIDE-USING WORKERS			
Norwegian farmers—spina bifida (maternal, paternal exposures)		**Herbicides**	Kristensen et al., 1997
Tractor spraying equipment	28	1.6 (0.9–2.7)	
Tractor spraying equipment, orchards, greenhouses[d]	5	2.8 (1.1–7.1)	
United States—birth defects in children born to licensed pesticide appliers in Minnesota linked to state birth registries		**Herbicides, pesticides**	Garry et al., 1996
Central nervous system defects	6	1.1 (0.5–2.4)	
ENVIRONMENTAL			
Times Beach/Quail Run Cohorts		**Dioxin**	
Persons in Missouri with documented TCDD soil contamination near residence (maternal, paternal, in utero exposure)		**TCDD**	Stockbauer et al., 1988
Central nervous system defects	3	3.0 (0.3–35.9)	
Other International Environmental Studies			
France—Population-based birth defects registry in Rhône-Alpes region (1988–1997): maternal residence in municipality with solid-waste incinerator vs not	49	**Dioxin** 0.9 (0.6–1.2)	Cordier et al., 2004
CASE-CONTROL STUDIES			
Canada—British Columbian sawmill workers with exposure in upper three quartiles for any job held up to 3 mo before conception		**Herbicides**	Dimich-Ward et al., 1996
Spina bifida, anencephaly	22	2.4 (1.1–5.3)	
Spina bifida only	18	1.8 (0.8–4.1)	
New Zealand—Residents of areas subject to aerial 2,4,5-T spraying		**2,4,5-T** *90% CI*	Hanify et al., 1981
Anencephaly	10	1.4 (0.7–2.9)	
Spina bifida	13	1.1 (0.6–2.1)	
The Netherlands—Children of Dutch farmers who were born with spina bifida (1980–1992), 470 cases vs 456 healthy controls		**Herbicides, pesticides**	Blatter et al., 1997

TABLE 10-2 Neural-Tube Defects, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Spina bifida—moderate, heavy exposure			
Pesticide use	8	1.7 (0.7–4.0)	
Herbicide use	7	1.6 (0.6–4.0)[e]	
US National Birth Defects Prevention Study—California (8 counties in San Joaquin Valley), residential proximity to agricultural pesticide applications during early pregnancy (785 controls)		**2,4-D**	Yang et al., 2014
Anencephaly (n = 73 cases)	7	2.0 (0.8–5.1)	
Spina bifida (n = 123 cases)	4	nr	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; nr, not reported; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Of four neural-tube defects reported in Ranch Hand offspring, two were spina bifida (high dioxin exposure), one spina bifida (low dioxin), one anencephaly (low dioxin); no neural-tube defects reported in comparison cohort; 454 postservice births studied in Ranch Hand veterans; 570 in comparison cohort.

[d]Greenhouse workers would not have been exposed to the COIs.

[e]Calculated from data presented in the paper.

An additional study examined musculoskeletal defects and maternal occupational exposure to pesticides in the NBDPS, but exposure classification was limited to herbicides and did not meet the exposure classification criteria for the COI (Kielb et al., 2014).

Biologic Plausibility

2,4-D has been previously shown to be a teratogen, although at exposures that exceed maternal renal clearance and thus are not relevant to herbicide exposure in Vietnam. A recent study has shown for the first time that late in utero and early postnatal 2,4-D exposure can result in nephrotoxicity in offspring, although at one-sixth of the LD_{50} (Troudi et al., 2011). Other herbicides of interest can induce fetal malformations but typically only at high doses that are toxic to pregnant women. TCDD is a potent teratogen in all laboratory species that have been studied, although the patterns of birth defects that are produced are often species specific. However, specific mechanisms that link TCDD exposure to specific birth defects have not been fully elucidated.

A variety of animal model studies, including in utero exposures, work with cultured cells, and zebrafish embryos, have investigated the mechanisms underlying various TCDD-induced birth defects including hydronephrosis, cleft palate, reproductive organ anomalies, neurogenesis, and perturbed heart, kidney, and lung development (Dong et al., 2010; Falahatpisheh et al., 2011; Jacobs et al., 2011; Lanham et al., 2012; Latchney et al., 2011; Neri et al., 2011; Tait et al., 2011; Yamada et al., 2014; Yoshioka et al., 2012; Yuan et al., 2012). Interestingly, the AHR is required for TCDD-induced birth defects. In contrast, the induction of cytochrome P4501A1 is not required (Dragin et al., 2006; Jang et al., 2007; Mimura et al., 1997). When pregnant AHR-null mice are exposed to TCDD, the fetuses do not exhibit any of the typical developmental malformations associated with TCDD exposure, but fetuses of TCDD-exposed pregnant CYP1A1-null mice do. In addition, an AHR antagonist can attenuate TCDD-induced birth defects in mice. Thus, the activation of the AHR by TCDD during development appears to be a key first step in mediating TCDD's developmental toxicity, but this step does not depend on CYP1A1 activity. Although structural differences in the AHR have been identified among species, it functions similarly in animals and humans. Therefore, a common mechanism mediated by the AHR in which tissue growth and differentiation processes are affected probably underlies the developmental toxicity of TCDD in humans and animals.

Antioxidant treatment provides protection against some TCDD-induced teratogenicity, which suggests that reactive oxygen species might be involved in the pathways that lead to these structural changes (Jang et al., 2008). A few studies indicate the stem cells and organ-specific progenitor cells may be direct targets and that maternal TCDD exposures interfere with proliferation and cell differentiation through the AHR and result in defects in organ morphogenesis (Latchney et al., 2011; Neri et al., 2011). Few laboratory studies of potential male-mediated developmental toxicity (and specifically birth defects) attributable to exposure to TCDD and herbicides have been conducted. As noted, the feeding of simulated Agent Orange mixtures to male mice produced no adverse effects in offspring (Lamb et al., 1981).

In sum, studies with maternal exposure in animal models suggest that a role for TCDD and related chemicals in causing birth defects is plausible and also that the AHR plays a causal role. However, translating these results to human populations has been difficult.

Synthesis

Embryonic and fetal development in rodents is sensitive to the toxic effects of exposure to TCDD and dioxin-like chemicals. It is clear that the fetal rodent is more sensitive to the adverse effects of TCDD than the adult rodent. Human data are generally lacking, however, and the sensitivity to developmental disruption in humans is less apparent, in part because contemporary studies of environmental

dioxin exposure and birth defects have involved extremely low exposures. As noted, recent human population-based studies have provided mixed results in attempts to link TCDD or the other COI exposures to birth defects. Two studies in California found no or very limited evidence for associations between population exposures and neural tube defects, orofacial clefts, gastroschisis, and congenital heart defects (Carmichael et al., 2014; Shaw et al., 2014; Yang et al., 2014). Congenital heart defects are the most common congenital malformations and persistent organic pollutants (POPs) are suspected of playing a contributing role, but firm statistical links are still lacking (Gorini et al., 2014). An additional California study looked for a link between pesticide exposures and hypospadias, but also failed to make a strong association (Carmichael et al., 2013). The studies since *Update 2012* that have assessed exposure to relevant chemicals and congenital malformations examined only maternal or residential exposure, which is of little relevance to the majority of Vietnam veterans. Furthermore, those case-control studies were conducted in populations exposed to contemporary concentrations, which may be too low for adverse fetal effects to be observed. The studies were well designed and adjusted for important confounders, but they do not provide evidence of an association at these exposure levels.

Given the long-standing concern of the Vietnam veterans about the potential of the COIs to adversely affect the health of their children, birth defects and childhood cancers have been among the outcomes considered by VAO committees since the first comprehensive review published in 1994.

As indicated in the section above summarizing the findings of prior VAO committees, the committee for the second VAO report (*Update 1996*) concluded that there was "limited or suggestive" evidence of an association between herbicide exposure and a single type of birth defect (the neural-tube defect spina bifida). That committee extracted an item of evidence concerning spina bifida from a new publication regarding the AFHS (Wolfe et al., 1995).The authors of the paper noted that the category of nervous system birth defects involved too few case to permit analysis (three from the comparison group; in the categories for serum dioxin levels measured in the fathers who served in Operation Ranch Hand [ORH], zero with background levels, two with low levels, and three with high levels). The committee for *Update 1996* calculated a marginally significant exact p-value of 0.04 for the three cases of spina bifida and one case of anencephaly among the children of the ORH subjects in comparison to zero cases for the fathers in the comparison group (the nature of the remaining nervous system defects—three in the controls and one in the high serum TCDD group of ORH veterans—is not evident in the original paper). This result was added to a fairly extensive body of evidence regarding birth defects overall that the preceding committee for *VAO* had judged to be imprecise and inconsistent and to contain little evidence of an association with paternal occupational exposure to herbicides or dioxin. As shown in Table 10-2, that dataset contained two studies (CDC, 1989a; Erickson et al., 1984a,b) with results on neural-tube defects consistent with an

association with paternal exposure to the COIs. Because the Agent Orange Act did not have provisions for compensation of the veterans' offspring, Congress passed legislation to permit this.

Although a number of studies published since *Update 1996* have examined exposures to pesticides and spina bifida, the four that examined paternal exposure and spina bifida (Blatter et al., 1997; Dimich-Ward et al., 1996; Garry et al., 1996; Kristensen et al., 1997) used paternal occupation (e.g., farmer, pesticide applier) as the basis for exposure classification and were not able to examine the COIs specifically. The remaining studies published since the 1996 report examined residential proximity to pesticide applications. As previously discussed, this form of exposure classification assumes the potential for both maternal and paternal exposure prior to and during pregnancy but cannot verify that such an exposure occurred.

Only a very small portion of Vietnam veterans are women, but a VA study (Kang et al., 2000a) of their health and reproductive history in comparison to their non-deployed Vietnam-era counterparts found a significant increase in birth defects overall. The committee for *Update 2002* reviewed this study but had reservations about exposure being defined simply as deployment and also about the fact that verification with medical records of the problems these women reported in their children was less complete than planned. Congress did, however, legislate eligibility for compensation for children of female Vietnam veterans with a broad range of birth defects not attributable to familial conditions.

It is extremely difficult to conduct epidemiology studies assessing risks to children arising from their parents' exposure, particularly when a distinction between maternal and paternal contributions is sought. As with studies of paternal exposure, additional confirmatory epidemiologic evidence has not become available to support an association of spina bifida with maternal exposure to the components of the herbicides sprayed in Vietnam. In fact, an increase in birth defects following adult exposure of only the male parent has not (as yet) been definitively demonstrated for any toxic agent.

With the continued increase in the number of women serving during deployments, concern about adverse consequences in the offspring of veterans merits increased attention. For Vietnam veterans, however, the existing evidence supporting an increase in spina bifida specifically in the children of men or women who were deployed is very sparse.

Conclusions

The committee concludes that the new evidence concerning the occurrence of birth defects in association with exposure to the COIs, in combination with existing evidence, remains inadequate and insufficient to support an association for birth defects overall in the children of Vietnam veterans. In light of the fact that evidence anticipated by the committee for *Update 1996* that would support an association between spina bifida and paternal exposure to the COIs has not

materialized from the AFHS or from any other population with relevant exposures, the committee concludes that spina bifida should be demoted from the category of limited or suggestive evidence of an association to the default category of inadequate or insufficient evidence of an association. Increased scrutiny of mechanisms by which paternal exposure might contribute to adverse effects in offspring has not as yet definitively established the biologic plausibility of this phenomenon, whereas understanding of how maternal exposures may disrupt fetal development has grown substantially. There are, however, no epidemiologic results supporting an association between maternal exposure to the COIs and spina bifida specifically, so spina bifida in association with exposure of either parent has been moved to the inadequate and insufficient category of association.

CANCERS IN OFFSPRING

The American Cancer Society (ACS) estimated that 11,630 children under 15 years old will receive a diagnosis of cancer in the United States in 2013 (ACS, 2013a). The treatment and supportive care of children who have cancer have continued to improve. The 5-year survival rate for children who receive a cancer diagnosis has increased from less than 60 percent in the 1970s to more than 80 percent in 2013. Despite those advances, cancers remain the leading cause of death from disease in children under 15 years old, and 1,310 deaths were projected for 2013 (ACS, 2013a).

Leukemias are the most common cancer in children, accounting for about one-third of all childhood cancer cases. In 2015, ACS forecast that about 3,314 children would receive a leukemia diagnosis (ACS, 2015). Of those, nearly 2,500 would have acute lymphocytic leukemia (ALL), and most of the rest would have acute myeloid leukemia (AML). AML (*International Classification of Diseases, Revision, 9th Revision* [ICD-9] 205) is also referred to as acute myelogenous leukemia or acute nonlymphocytic leukemia. For consistency, this report uses "acute myeloid leukemia," or AML, regardless of the usage in the source materials. ALL is most common in early childhood, peaking at the ages of 2–3 years, and AML is most common during the first 2 years of life. ALL incidence is consistently higher in boys than in girls; AML incidence is similar in boys and girls (NCI, 2001). Through early adulthood, ALL rates are about twice as high in whites as in blacks; AML exhibits no consistent pattern in this respect. Chapter 8 contains additional information on leukemias as part of the discussion of adult cancers.

The second-most common group of cancers in children consists of cancers of the central nervous system—the brain and the spinal cord. Other cancers in children include lymphomas, bone cancers, soft-tissue sarcomas, renal cancers, eye cancers, and adrenal cancers. In contrast with adult cancers, relatively little is known about the etiology of most childhood cancers, especially about potential environmental risk factors and the effects of parental exposures.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and childhood cancers. The additional information available to the committees responsible for *Update 1996* and *Update 1998* did not change that conclusion. The committee responsible for *Update 2000* reviewed the material in earlier VAO reports and in newly available published literature and concluded that there was limited or suggestive evidence of an association between exposure to at least one of the COIs and AML. After the release of *Update 2000*, investigators involved in one study discovered an error in their published data. The *Update 2000* committee reconvened to evaluate the previously reviewed and new literature regarding AML, and it produced *Acute Myelogenous Leukemia* (IOM, 2002). It reclassified AML from "limited/suggestive evidence of an association" to "inadequate evidence to determine whether an association exists."

Table 10-3 summarizes the results of the relevant studies. The committees responsible for *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* reviewed the material in earlier VAO reports and in newly available published literature and agreed that there remained inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and childhood cancers.

Update of Epidemiologic Literature

No Vietnam-veteran, occupational, or environmental studies of exposure to the COIs and childhood cancers have been published since *Update 2012*.

Case-Control Studies

Glass et al. (2012) examined ALL and parental occupational exposure to pesticides around the time of conception in a case-control study. Job–exposure modules were used to collect parental occupational history, and an expert rater classified pesticide exposure. A strength of this study was the ability to examine both maternal and paternal exposures. After adjustment for confounders among the 327 cases with paternal exposure information, 8 reported exposure to phenoxy herbicides. Only 2 of the 378 cases with maternal information reported exposure to phenoxy herbicides. No associations were observed with ALL and occupational exposure to phenoxy herbicides.

Metayer et al. (2013) examined 252 ALL cases and 308 controls in the Northern California Childhood Leukemia Study, a population-based case-control study. Pesticides, including 2,4-D, were detected in the majority of house dust samples collected in this study as a proxy for exposure during pregnancy. However, no

TABLE 10-3 Selected Epidemiologic Studies—Childhood Cancer[a] (Shaded entries are new information for this update)

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
CDC Birth Defects Study—Hospital records reviewed for offspring of 7,924 Vietnam veterans and 7,364 non-Vietnam veterans		**All COIs**	
Vietnam veterans identified through CDC Metropolitan Atlanta Congenital Defects Program			Erickson et al., 1984b
"Other" neoplasms	87	1.8 (1.0–3.3)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
VES cohort—reproductive outcomes			CDC, 1988a
Cancer	25	1.5 (0.7–2.8)	
Leukemia	12	1.6 (0.6–4.0)	
US veterans—case-control study of children's leukemia			Wen et al., 2000
AML, ALL			
Father ever served in Vietnam, Cambodia	117	1.2 (0.9–1.6)	
< 1 yr in Vietnam or Cambodia	61	1.4 (0.9–2.0)	
> 1 yr in Vietnam or Cambodia	49	1.2 (0.8–1.7)	
AML only			
Father ever served in Vietnam, Cambodia	40	1.7 (1.0–2.9)	
< 1 yr in Vietnam or Cambodia	13	2.4 (1.1–5.4)	
> 1 yr in Vietnam or Cambodia	16	1.5 (0.7–3.2)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans' children—revised validation study		**All COIs**	
AML	12[c]	1.3 (0.8–4.0)	ADVA, 2005b
Australian Vietnam veterans' children—validation study—AML			*AIHW, 2000*
This study, which incorrectly calculated expected number of AML cases, is updated by AIHW, 2001 above			
Tasmanian Veterans with Service in Vietnam		**All COIs**	
Cancer in children of Australian Vietnam veterans	4	nr	Field and Kerr, 1988

continued

TABLE 10-3 Childhood Cancer, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS			
Canada—Sawmill Workers in British Columbia; 26,487 workers for ≥ 1 yr at 14 mills using chlorophenates 1950–1985		**Chlorophenates, not TCDD**	
Workers having a live-birth within 1 yr after the initiation of employment			Heacock et al., 1998
Leukemia			
All workers' offspring—incidence	11	1.0 (0.5–1.8)	
Chlorophenate exposure: high- vs low-exposure subjects	5	0.8 (0.2–3.6)	
Brain cancer			
All workers' offspring—incidence	9	1.3 (0.6–2.5)	
Chlorophenate exposure: high- vs low-exposure subjects	5	1.5 (0.4–6.9)	
United States—US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Offspring of male pesticide applicators in Iowa from AHS			Flower et al., 2004
Maternal exposure to chlorophenoxy herbicides	7	0.7 (0.3–1.5)	
Paternal exposure to chlorophenoxy herbicides	28	1.3 (0.6–2.6)	
Maternal exposure to 2,4-D	7	0.7 (0.3–1.6)	
Paternal exposure to 2,4-D	26	1.3 (0.7–2.4)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Seveso residents 0–19 yrs old—10-yr follow-up, morbidity, all exposure zones			Pesatori et al., 1993
All cancers	17	1.2 (0.7–2.1)	
Ovary, uterine adnexa	2	nr (0 cases expected)	
Brain	3	1.1 (0.3–4.1)	

TABLE 10-3 Childhood Cancer, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Thyroid	2	4.6 (0.6–32.7)	
HL	3	2.0 (0.5–7.6)	
Lymphatic leukemia	2	1.3 (0.3–6.2)	
Myeloid leukemia	3	2.7 (0.7–11.4)	
Seveso residents 0–19 yrs old—10-yr follow-up, mortality, all exposure zones			Bertazzi et al., 1992
All cancers	10	7.9 (3.8–13.6)	
Leukemias	5	3.9 (1.2–1.8)	
Lymphatic leukemia	2	1.6 (0.1–4.5)	
Myeloid leukemia	1	0.8 (0.0–3.1)	
Leukemia, others	2	1.6 (0.1–4.6)	
Central nervous system tumors	2	1.6 (0.1–4.6)	
Other International Environmental Studies			
Canada—ALL in children (0–9 yrs old) in households using herbicides (1980–1993)		**Herbicides**	Infante-Rivard et al., 1999
Exposure during pregnancy	118	1.8 (1.3–2.6)	
Exposure during childhood	178	1.4 (1.1–1.9)	
England—Renal cancer in subjects (1–15 yrs of age) with paternal occupation in agriculture		**Herbicides, pesticides**	Pearce and Parker, 2000
	21	0.9 (0.2–3.8)	
Norway—Cancer in children of agricultural workers (n = 1,275) identified in cancer registries (1965–1991)		**Pesticides**	Kristensen et al., 1996
Children with AML whose parents purchased pesticides	12	1.4 (0.6–2.9)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Children's Oncology Group—Studies association between infant leukemia and maternal herbicide exposure (443 cases vs 324 population controls)		**Herbicides** ns	Slater et al., 2011
Children's Oncology Group—Childhood GCTs residential exposure to herbicides 6 mos before conception, during gestation, through breastfeeding period		**Pesticides**	Chen Z et al., 2006
Maternal exposure	47	1.3 (0.9–1.7)	
Daughters	36	1.4 (1.0–2.0)	
Sons	11	1.0 (0.5–1.8)	
Paternal exposure	90	1.0 (0.7–1.3)	
Daughters	32	1.2 (0.7–2.0)	
Sons	58	1.0 (0.7–1.4)	
Children's Oncology Group—Parental occupational exposure to pesticide and GCTs, 1993–2001 (253 cases vs 394 controls)		**Pesticides**	Chen et al., 2005

continued

TABLE 10-3 Childhood Cancer, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Maternal	32	1.1 (0.7–1.6)	
Paternal	39	0.9 (0.6–1.3)	
Children's Cancer Group—exposure to pesticides, weed killers—AML		**Pesticides**	Buckley et al., 1989
Any paternal exposure	27	2.3 (p = 0.5)	
Paternal exposure over 1,000 days	17	2.7 (1.0–7.0)	
Maternal exposure over 1,000 days	7	undefined	
California (Northern California Childhood Leukemia Study)—exposure to "outdoor herbicides" and ALL (and variants in metabolic genes)		**Herbicides**	
Exposure to 2,4-D measured in house dust (252 cases, 306 controls)	236	1.0 (0.9–1.1)	Metayer et al., 2013
Outdoor herbicide use before birth (377 cases, 448 controls)		1.5 (1.0–2.0)	Chokkalingam at al., 2012
California—Maternal exposure to agricultural pesticide in class of "probable human carcinogens" (including cacodylic acid) during 9 mos before delivery		**Pesticides**	Reynolds et al., 2005
All sites	223	1.0 (0.9–1.2)	
Leukemias	179	1.2 (0.9–1.5)	
Central nervous system tumors	31	0.9 (0.5–1.4)	
New York State—Neuroblastoma risk in children, age ≤ 14 yrs of age (1976–1987)		**Pesticides**	Kerr et al., 2000
Maternal occupational exposure to insecticides	40	2.3 (1.4–3.7)	
Paternal exposure to dioxin	7	6.9 (1.3–68.4)	
International Case-Control Studies			
Australia—ALL in offspring and parental occupational exposure to pesticides			Glass et al., 2012
Paternal exposure to phenoxy herbicides (327 cases, 751 controls)	8	0.9 (0.4–2.2)	
Maternal exposure to phenoxy herbicides (378 cases, 854 controls)	2	1.9 (0.3–11.8)	
Canada and United States—Study of Wilm's tumor		**Herbicides**	Cooney et al., 2007
Maternal report of household use of herbicides from month before conception through child's diagnosis	112	1.0 (0.7–1.4)	

TABLE 10-3 Childhood Cancer, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
Canada and United States—Neuroblastoma risk in children (538 cases, 504 controls) from 139 hospitals in US and Canada (exposures as reported by both parents)		**Herbicides, pesticides**	Daniels et al., 2001
Pesticides in home (used ever)	nr	1.6 (1.0–2.3)	
Herbicides in garden	nr	1.9 (1.1–3.2)	
Pesticides in garden	nr	2.2 (1.3–3.6)	
Costa Rica—parental occupational exposure to pesticide, childhood leukemia		**Herbicides**	Monge et al., 2007
Parental exposures in yr before conception to:			
Herbicides	53	1.2 (0.8–1.7)	
Phenoxyacetic acids	28	1.0 (0.6–1.6)	
Picloram (all ALL)	11	1.6 (0.7–3.4)	
High vs low	8	6.3 (1.0–38.6)	
Maternal exposures to:			
Herbicides			
In yr before conception	9	2.0 (0.8–5.0)	
In 1st trimester	8	5.3 (1.4–20.0)	
In 2nd trimester	8	5.3 (1.4–20.0)	
In 3rd trimester	7	2.3 (0.8–6.8)	
Phenoxyacetic acids in year before conception	4	1.3 (0.4–4.8)	
West Germany—population-based study of childhood cancer (1993–1997) (2,358 cases vs 2,588 controls)		**Pesticides**	Meinert et al., 2000
Leukemia			
Paternal exposure yr before pregnancy	62	1.5 (1.1–2.2)	
Paternal exposure during pregnancy	57	1.6 (1.1–2.3)	
Maternal exposure yr before pregnancy	19	2.1 (1.1–4.2)	
Maternal exposure during pregnancy	15	3.6 (1.5–8.8)	
Lymphomas			
Paternal exposure yr before pregnancy	11	1.5 (0.7–3.1)	
Paternal exposure during pregnancy	10	1.6 (0.7–3.6)	
Maternal exposure yr before pregnancy	3	2.9 (0.7–13.0)	
Maternal exposure during pregnancy	4	11.8 (2.2–64.0)	
France—Hematopoietic malignancies in children < 15 yrs of age (2003–2004)		**Herbicides**	Rudant et al., 2007
Maternal household herbicide use during pregnancy			
Acute leukemia	53	1.5 (1.0–2.2)	
Without paternal exposure	4	5.0 (1.3–19.0)	

continued

TABLE 10-3 Childhood Cancer, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[b]	Reference
All ALL	nr	1.7 (1.2–2.5)	
Common B-cell ALL	nr	1.9 (1.3–2.9)	
Mature B-cell ALL	nr	1.5 (0.3–6.4)	
T-cell ALL	nr	0.5 (0.1–2.0)	
AML	nr	1.2 (0.5–2.8)	
HL	9	1.1 (0.5–2.4)	
Without paternal exposure	0	nr	
Nodular sclerosis	nr	1.3 (0.5–3.1)	
Mixed cell	nr	0.8 (0.1–6.6)	
NHL	14	1.5 (0.8–2.7)	
Without paternal exposure	0	nr	
Burkitt's lymphoma	nr	1.7 (0.7–4.0)	
B-cell lymphoblastic	nr	0.7 (0.2–3.0)	
T-cell lymphoblastic	nr	2.6 (0.7–9.0)	
Anaplastic large cell	nr	1.4 (0.3–2.8)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; AHS, Agricultural Health Study; AIHW, Australian Institute for Health and Welfare; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; GCT, germ-cell tumor; HL, Hodgkin lymphoma; ICD, *International Classification of Diseases*; NHL, non-Hodgkin lymphoma; nr, not reported; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Of the 12, nine were observed, three additional cases estimated to have occurred in portion of cohort whose data were not validated.

difference in ALL risk was observed between cases and controls (OR = 0.96, 95% CI 0.85–1.08).

Biologic Plausibility

Paternal or maternal exposure to xenobiotics potentially could increase the susceptibility of offspring to cancer through multiple mechanisms. Susceptibility could be increased by causing a tumor-promoting mutation in germ cells that would be present in all of the somatic cells of the child. This de novo mutation could then be passed on to subsequent generations via Mendelian inheritance, assuming that the child survived to reproduce. However, as discussed earlier in this chapter and in earlier chapters, TCDD and other COIs are not genotoxic (i.e., they do not cause mutations), which makes the mutation-induction and inheritance

scenario unlikely. Alternatively, a maternally mediated increase in susceptibility to childhood cancers could result from direct exposure of a fetus in utero or the newborn via lactation to a xenobiotic that induces epigenetic alterations that increase cancer susceptibility.

The biological plausibility overview for this chapter presented several pre- and post-conception scenarios for how toxicant exposures could cause disease in first-generation offspring and perhaps in later generations based on epigenetic mechanisms (Vaiserman, 2014). Perhaps the most straightforward scenario is in utero exposure affecting the developing epigenome, which predisposes the child to cancer. The best example of this happening is when otherwise very rare vaginal cancers arose in the daughters of women who took the estrogenic agent diethylstilbestrol (DES) to prevent miscarriage (Herbst et al., 1971). Thus this scenario is quite plausible for humans. Although TCDD is an antiestrogen, as noted, its toxicity via the AHR likely involves transcriptional changes that could induce epigenetic mechanisms. With regard to cancers, if the affected gene or genes are involved in cancer pathways and epigenetic modifications stabilize the gene-expression changes, then the susceptibility to cancer could increase.

Prenatal TCDD exposure of rats is associated with altered mammary gland differentiation and an increase in the number of mammary adenocarcinomas (Brown et al., 1998). Perhaps related, prenatal TCDD exposure led to increased DNA methylation at the *BRCA1* (breast cancer) gene promoter in the female offspring of exposed pregnant rats (Papoutsis et al., 2013). The demonstration that early postnatal TCDD exposure does not increase mammary-cancer risk (Desaulniers et al., 2004) does not contradict the finding that TCDD-induced changes in utero mediate the increase in cancer susceptibility (Fenton et al., 2000, 2002), and is consistent with ultimate carcinogenic effect being greatest when epigenomic changes are most dynamic. Thus, developmental epigenetic alterations may be involved in the prenatal effects. TCDD has been shown to suppress the expression of two tumor-suppressor genes, $p16^{Ink4a}$ and *p53*, via an epigenetic mechanism that appears to involve DNA methylation (Ray and Swanson, 2004). Similarly, it was reported that prenatal TCDD exposure increases methylation of two growth-related imprinted genes, *H19* and *Igf2*, in the developing fetus (Wu et al., 2004).

No direct evidence from animal models shows that TCDD increases the risk of childhood cancers, such as acute leukemia and germ-cell tumors, although a recent study showed a reduced capacity of hematopoietic stem cells to undergo differentiation in offspring (Ahrenhoerster et al., 2014). Emerging research suggests that prenatal TCDD exposure can disrupt epigenetic imprinting patterns and alter organ differentiation and thus could contribute to an increased susceptibility to cancer later in life. Smith et al. (2005) showed that chromosomal rearrangements associated with childhood ALL are evident in the neonatal blood spots, which suggests that childhood leukemias begin before birth, perhaps due to maternal exposures to carcinogenic xenobiotics.

Synthesis

No associations were observed in the two case-control studies that considered childhood ALL and exposure to phenoxy herbicides and to 2,4-D in particular. Furthermore, evidence is sparse that exposure to the COIs increases the risk for childhood cancers.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and childhood cancers.

EFFECTS OCCURRING LATER IN OFFSPRING'S LIFE OR IN LATER GENERATIONS

In response to a special request from the Department of Veterans Affairs, continuing inquiries from veterans and their families, and increasing attention in research efforts, the committee for *Update 2010* addressed whether it was feasible to assess associations between exposure to the herbicides sprayed in Vietnam and health effects that occur later in the lives of children of Vietnam veterans and even in their grandchildren; such associations had not been formally reviewed in prior VAO updates. The previously considered outcomes of birth defects observable within the first year of life and childhood cancers (diagnosis before the age of 18 years) were augmented to include all cancers and physical and neurobehavioral problems that might be manifested at any age, thereby broadening the scope of DOHaD research relevant to the VAO mission.

In addition, for the first time, the committee for *Update 2010* explored the possibility of transgenerational effects resulting from exposure-related epigenetic changes in the parents or exposed fetuses that would lead to adverse health effects in later generations, such as grandchildren. As noted above, effects in persons exposed in utero are not considered transgenerational because the fetus was likely exposed directly. This exception includes the children of women exposed in Vietnam even if they are conceived after their tour of duty was over because TCDD remains in the body for a long time and is mobilized during pregnancy. Likewise, the children of men exposed to TCDD in Vietnam and born after the soldiers' tour of duty was over could possibly have health outcomes due in part to TCDD's effect on the sperm epigenome. In contrast, any adverse health effects in grandchildren associated with exposure would be considered to be transgenerational.

Conclusions from *VAO* and Previous Updates

The potential effect that herbicide exposure in male and female Vietnam veterans would have on the development of diseases other than cancers in the veterans' children after the first year of life or in later generations had not been considered in updates before *Update 2010*.

For *Update 2010*, epidemiologic studies that evaluated the potential for effects of maternal or paternal exposure to the COIs in offspring were identified. Rather than identifying specific diseases in offspring, much of the research involved the measurement of physiologic biomarkers that might indicate a potential for disease development later in life. The committee for *Update 2010* therefore cautioned strongly that the *clinical consequences* of any observed changes are highly uncertain. The committee maintained its standard requirement for exposure specific to components of the herbicides sprayed in Vietnam.

Although, as noted above, it may be physiologically possible for paternal exposure to cause changes in offspring that are manifested later in life, none of the published epidemiologic studies assessed such potential. Thus, the observation of any changes reported in studies discussed in this section should be applicable only to children born to female Vietnam veterans during or after their deployment in Vietnam. Thus, no transgenerational studies have been reported to date.

Changes Detected in Children After Parental Exposure

Growth and Development

Since *Update 2012*, three studies have examined exposure to environmental contaminants, including PCBs, and the subsequent growth and development of children. Delvaux et al. (2014) measured the height and weight of 114 children included in the Flemish Environment and Health Study when they were between the age of 7 and 9 years old. Dioxin-like activity was measured in the cord blood collected at birth with the CALUX assay. No association between prenatal exposure to dioxin-like chemicals and height or weight was observed 7 to 9 years after birth.

In another cohort, Wohlfahrt-Veje et al. (2014) measured dioxin levels and PCBs in maternal breast milk and markers of growth and development at a number of time points from birth through 36 months of age in 418 mother–child pairs. For the 368 pairs with non-smoking mothers, in the first month after birth total TEQs were associated with a depression in adjusted measures of weight (–0.38, 95% CI –0.76–0.00), length (–0.34, 95% CI –0.70–0.01), and fat percentage (–0.52, 95% CI 1.08 to –0.03). However, the changes observed between 0 and 18 months in weight (0.69, 95% CI 0.18–1.21) and height (0.79, 95% CI 0.33–1.26)

indicated accelerated growth. With adjustment for maternal smoking during pregnancy, similar findings were observed for all 418 pairs.

Sioen et al. (2013) enrolled 270 mothers and newborns in a prospective cohort study of behavior and markers of behavior and neurodevelopment. Dioxin-like activity was measured in cord blood using the CALUX assay. Prenatal exposure to dioxin like compounds was not associated with assessed behavior in the children at age 7–8.

Cognitive or Motor Development

In a study from Vietnam, Tai et al. (2013) enrolled 216 infant–mother pairs and assessed markers of neurodevelopment through 4 months of age. Dioxin levels were measured in breast milk, and infant neurodevelopment was measured using the Bayley Scales of Infant and Toddler Development. After adjustment for confounders (gender, parity, gestational week, age, birth weight, education, age, socioeconomic status, alcohol consumption, smoking status, environmental tobacco smoke, and maternal residence), PCDDs/Fs ≥ 17.6 pgTEQ/g lipid were significantly correlated with lower cognitive function and fine motor skills when compared to PCDDs/Fs ≤ 7.4 pq TEQ/g lipid ($p = 0.009$ and 0.030, respectively). Similarly, infants with daily dioxin intake (≥ 118.2 pg TEQ/kg/day) from breast milk had lower mean measures of cognitive function and fine motor skills compared to infants with ≤ 49.8 pg TEQ/kg/day ($p = 0.006$ and 0.017, respectively).

In 2014 ten Tusscher et al. published a study that compared dioxin levels in breast milk with subsequent neurodevelopment between 7 and 12 years of age for 41 children and for 33 of those same children between 14 and 18 years of age. Psychologists, parents, and teachers completed standardized scales designed to measure neurodevelopmental outcomes and behaviors in the children (the Weschler Intelligence Scale for Children [WISC], the Child Behavior Checklist and the Teacher Report Form, respectively). Increased social problems ($\beta = 0.03$, $p = 0.001$), aggressive behavior ($p = 0.001$), and problems thinking ($p = 0.005$) as measured by the Teacher Report Form were associated with increasing postnatal dioxin levels. In addition, prenatal exposure was associated with a number of behavioral indicators measured on the Child Behavior Checklist, including social problems ($p = 0.001$), anxiety ($p = 0.002$), and internalized behavior ($p = 0.007$). In contrast, behavior assessed by a psychologist using the WISC-R showed no associations with prenatal or postnatal exposure to dioxin.

Winneke et al. (2014) examined hormonal influences on behavioral development in 232 mother–child pairs using the Preschool Activities Inventory to measure markers of behavior that may indicate potential sexual dimorphism. Dioxin was measured in both maternal blood collected in the period 28–42 weeks after conception and breast-milk samples. While most comparisons were not statistically significant, a doubling of maternal blood levels of PCDD/F and PCDD/F+PCB

combined was associated with a difference in the score for markers of sexual dimorphism in boys (β = 2.60, 95% CI 0.39–4.80), but not in girls (β = 2.62, 95% CI 0.52–4.71). Similarly PCDD/F and PCDD/F+PCBs measured in breast milk were associated with the same markers in boys (β = 4.02, 95% CI 1.77–6.28; β = 3.90, 95% CI 1.74–6.06, respectively). Prenatal measures of dioxin were not associated with behavioral markers in girls. However, PCDD/F+PCBs as measured in breast milk was associated with markers of dimorphism in girls (β = −4.22, 95% CI −7.24 to −1.19).

Immune-Cell Populations and Prevalence of Allergies or Asthma in Children

Hansen et al. (2014) measured prenatal exposures to POPs and the development of asthma in 965 children enrolled in the Danish Fetal Origins cohort study. Six PCB congeners were measured from maternal serum collected during pregnancy and grouped by dioxin-like activity. However TEQs were not calculated. The confirmation of prescriptions for asthma medication data, as obtained from the medication registry, was used to classify asthma cases for children ranging in age from 6 to 20 years. Asthma risk was increased (RR = 1.90, 95% CI 1.12–3.23) for children whose mothers had the highest tertile of PCB 118 exposure during pregnancy (−20.0–0.61 ng/ml). Similarly, risk was increased (RR = 1.75, 95% CI 1.02–2.98) for children whose mothers were classified in the highest tertile of exposure for dioxin-like PCBs (> 0.96 pmol/ml–4.10 pmol/ml).

Offspring Reproductive Function

In addition to evaluating the overall health and survival of the children of Vietnam-era veterans, The Australian Vietnam Veterans Family Study (ADVA, 2014b) assessed a number of self-reported outcomes related to the reproductive success of the children of these veterans. In comparing self-reports from children of deployed veterans to those of children of non-deployed veterans, no significant differences were found with respect to difficulty in conceiving or in the incidence of miscarriages, stillbirths, or the specific birth defects spina bifida and cleft lip or palate.

Two studies on subcohorts of the collaborative European NewGeneris study of mother–child pairs examined anogenital distance and maternal exposure to dioxin and dioxin-like compounds. Anogenital distance has historically been used as a marker of androgen function in toxicology studies involving animals. Recently, this marker has been used in epidemiology studies to examine the effects of exposures that may affect hormonally related outcomes. Using the Greek and Spanish subcohorts, Papadopoulou et al. (2013b) examined anogenital distance in light of self-reported information on maternal diet during pregnancy. A high-fat diet was correlated with dioxin-like activity as measured in 121 maternal blood

samples in this cohort. High fat-in-diet scores for the mothers were associated with a decrease in anoscrotal distance in their infant sons ($\beta = -4.2$, 95% CI –6.6 to −1.8). Dietary fat intake was not associated with anoforchetal distance in the newborn females or anogenital distance in boys or girls at 1–2 years of age.

Vafeiadi et al. (2013) used dioxin-like activity measured in maternal blood samples collected at the time of delivery to study the same outcome. Included in the analyses were 237 newborns (119 boys and 118 girls) and 462 children aged 1–31 months (239 boys and 223 girls) from the same two subcohorts of the New-Generis study. No associations between dioxin-like activity and three measures of anogenital distance were observed in either female newborns or girls. In male newborns, dioxin-like activity was significantly associated with shortened anogenital distance ($\beta = 0.44$ mm, 95% CI –0.80 to –0.08) per a 10 pg CALUX-toxic equivalent/g lipid. A similar association, although not statistically significant, was observed in boys. These two sets of findings about anogenital distance are consistent, but this use of the actual measures of dioxin-like activity would be considered more reliable than the indirect measure of gestational exposure based on maternal diet used by Papadopoulou et al. (2013b).

Biologic Plausibility

Results of studies in rodent models provide support for the idea that prenatal exposure to TCDD can result in adverse effects in offspring later in life, including immune disorders, behavioral disturbances, reproductive impairment, kidney disease, and cancers (Foster et al., 2010; Prescott, 2011; Puga, 2011; Takeda et al., 2012). Using two mouse models, investigators showed that prenatal TCDD (2.5–5.0 mg/kg) modified multiple immune signatures in adult offspring that were indicative of adult-onset autoimmunity (Holladay et al., 2011). Adult-onset inflammatory disease and lupus-like autoimmunity were also observed in mice at 36 weeks of age after high-dose prenatal TCDD exposures (Mustafa et al., 2011). A single prenatal exposure of rats to TCDD (0.7 μg/kg of body weight) reduced brain developmental myelination and compromised remyelination potential in adults (Fernández et al., 2010), and in utero TCDD in mice altered neural progenitor differentiation (Mitsuhashi et al., 2010). However, another study suggested that, unlike murine neurospheres (which represent neural progenitor cells), human neurospheres were nonresponsive to TCDD because of lack of the AHR—an indication of species specificity in response (Gassmann et al., 2010). Perinatal TCDD (0.2–0.4 μg/kg of body weight) in rats perturbed neuroendocrine function as measured by thyrotropin and growth hormone concentrations in exposed offspring through peripubertal postnatal day 30, which supports the idea of continued later-life thyroid hormone disturbances (Ahmed, 2011). These include the epigenetic modification of imprinted genes (Somm et al., 2013), increased DNA methylation of the *BRCA1* tumor suppressor gene in mammary tissue (Papoutsis et al., 2013), altered uterine response to estradiol (Burns et al., 2013),

dysregulation of lipid metabolism in the presence of a high-caloric diet (Sugai et al., 2014), aberrant emotional behaviors (Nguyen et al., 2013), a reduced capacity for lymphocyte differentiation (Ahrenhoerster et al., 2014), testicular inflammation (Bruner-Tran et al., 2014), and a variety of adult diseases including kidney disease, prostate disease, ovarian primordial follicle loss, and polycystic ovarian disease (Manikkam et al., 2012a). As discussed below, a few animal studies have provided evidence of transmission of adverse effects to later generations.

Mechanisms that could underlie later-life effects in offspring and effects in later generations (transgenerational inheritance) could involve epigenetic processes as described at the beginning of this chapter. Research into dioxin's potential as an epigenetic agent is in its early stages, but a few studies have suggested that dioxin has such properties that are, in significant part, linked to the AHR. Direct evidence, however, is limited to maternal exposures of the developing embryo or fetus during in utero growth, and no reports exist showing paternal TCDD exposure and later-life effects in offspring or paternally mediated transgenerational effects. Wu et al. (2004) demonstrated that TCDD exposure of mouse embryos before implantation in unexposed females resulted in epigenetic changes, including increased methylation and reduced expression of imprinted genes, which implied that early embryonic exposure alone was sufficient to alter gene expression in the resulting offspring. Transmission of effects to later generations would involve epigenetic alterations in the developing germ cells of a fetus that was directly exposed to maternal TCDD in utero, and, as noted earlier in this chapter, a recent study suggests that environmental epigenetic effects are erased during the post-fertilization DNA demethylation period (Iqbal et al., 2015). In addition, odor fear conditioning in the father could be paternally transmitted to F1 and F2 generations, and reduced DNA methylation in the responsible odor receptor gene was implicated (Dias and Ressler, 2013). Clearly, the development of more and better research models will be required to improve understanding of how transgenerational effects can be transmitted paternally (Dias and Ressler, 2014).

Results of a few recent studies support a transgenerational inheritance due to in utero exposure to TCDD. Exposing pregnant mice to TCDD (at 10 μg/kg) reduced fertility and increased premature birth in three later generations (Bruner-Tran and Osteen, 2011); effects were transmitted through both male and female offspring (Ding et al., 2011; McConaha et al., 2011). Exposing gestating female rats (F0) to dioxin (TCDD) at 100 ng/kg was recently shown to result in earlier puberty in the offspring (F1) and two later generations (F2 and F3) and to reduce ovarian follicle numbers in the females of the F3 generation; this implies transgenerational inheritance (Manikkam et al., 2012a). The F3 effects appear to be transmitted through the sperm that were initially exposed to maternal dioxin in utero. In a second paper by the same research team, additional diseases appeared later in life in the first generation (directly exposed offspring), including prostate disease in males and ovarian follicle loss and polycystic ovarian disease

in females (Manikkam et al., 2012b). Further third-generation effects were noted, including kidney disease in males and polycystic ovarian disease in females, which imply transgenerational inheritance. The latter appear to be transmitted through the sperm originally exposed to maternal dioxin in utero inasmuch as sperm DNA methylation changes were observed at 50 chromosomal sites in generations F1–F3. Testicular inflammation from TCDD exposure has also been reported to manifest in multiple generations (Bruner-Tran et al., 2014).

The zebrafish has been used as a model to examine the transgenerational effects from dioxin exposure, although different groups have reported different aspects of these effects since *Update 2012*. One group reported that exposing zebrafish at 3 and 7 weeks old (during sexual development) to TCDD in water for 1 hour at 50 pg/ml increased female-to-male ratios and skeletal abnormalities and reduced fertility in the F1 and F2 descendants (equivalent to F2 and F3 in mammals) (Baker et al., 2014a,b). Another group studying DNA methylation changes in the offspring of mothers fed 20 µg/kg TCDD in their food reported no changes in global methylation in offspring when looking at the total levels of DNA methylation in the genome. However, gene-specific increases or decreases in promoter DNA methylation were observed with a tiling array assay for a limited number of genes in the F1 generation. CYP1A1 transcription, a marker of TCDD exposure, was elevated in F1 offspring. Unfortunately, no F2 fish were generated from TCDD exposure because the F1 fish died 1 to 2 weeks post hatching (Olsvik et al., 2014). Further work with this model will be helpful for providing targets for mammalian biologists as they continue to probe for transgenerational effects from TCDD and the other COIs.

Another mode of epigenetic change is the modification of the spatial arrangement of chromosomes, which can influence gene expression and cell differentiation. Oikawa et al. (2008) found that TCDD, through the AHR, modifies the positions of chromosomes in the interphase nuclei of human preadipocytes.

The studies discussed above suggest that TCDD has the potential to influence the epigenome and therefore could promote changes in offspring that lead to disease later in life, although research addressing this issue in model systems is still at an early stage.

Synthesis

The epidemiologic studies designed to examine the effects of the COIs in more mature offspring have evaluated a variety of biomarkers pertaining to the neurologic, immunologic, and endocrine systems. More studies are required before conclusions can be reached as to whether such outcomes in the offspring of exposed parents are replicable. In particular, it would be of interest to obtain information on neuropsychiatric conditions, such as attention-deficit hyperactivity disorder and other clinically defined neurodevelopmental outcomes, in children who were exposed in utero. The animal literature contains evidence that

environmental agents mediated by maternal exposure affect later generations through fetal and germline modifications, but in the case of adult male exposures before conception of the next generation, there is insufficient evidence of transgenerational affects.

Conclusions

There is inadequate or insufficient evidence to determine whether there is an association between the exposure of men and women to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid before conception or during pregnancy and disease in their children as they mature or in later generations. Although the results of laboratory research support the plausibility of transgenerational clinical conditions, human data are currently lacking to support an association between the COIs and such disease states in human offspring.

11

Neurologic Disorders

Chapter Overview

The Department of Veterans Affairs (VA) gave the committee for Update 2014 *the special task to address whether various diagnoses with Parkinsonian symptoms should be included in the presumptive service related category for Parkinson disease (PD). Because diagnostic specificity is improbable in both the studies upon which the conclusion of limited or suggestive association with exposure to military herbicides were based and in the documentation for the claims submitted to VA by Vietnam veterans, the committee clarifies that the finding for PD should be interpreted by VA to include all diseases with Parkinson-like symptoms unless those symptoms can be definitively attributed to be secondary to an external agent other than the herbicides sprayed in Vietnam.*

Based on new evidence and a review of prior studies, the committee for Update 2014 *did not find any new significant associations between the relevant exposures and neurological disorders. Current evidence supports the findings of earlier studies that:*

- *There is limited or suggestive evidence of an association between the chemicals of interest and PD and diseases that present with Parkinson-like symptoms.*
- *There is inadequate or insufficient evidence to determine whether there is* an *association between the chemicals of interest and any of the other adverse neurologic outcomes.*

The immediate effects of toxicants may involve all regions of the nervous system, whereas delayed effects are likely related to focal deficits. Diffuse damage to the central nervous system (CNS) may cause alterations in thinking, consciousness, or attention, sometimes in combination with abnormalities of movement, while focal dysfunction can cause myriad syndromes, depending on which area of the brain is involved and the extent and severity of damage. For the purposes of this review, neurologic deficits associated with Vietnam service are distinguished from psychiatric/psychologic conditions—such as posttraumatic stress disorder (PTSD), depression, and anxiety—and from chronic fatigue syndrome. While the increased risks of these conditions among veterans of all US conflicts are of scientific and public health concern, this committee, like previous Veterans and Agent Orange (VAO) committees, believes that two major underlying principles justify their exclusion from systematic review and evaluation:

- First, military service alone, including deployment and service in Vietnam, confers a range of potentially traumatic psychological exposures that may be expected to increase the risk of developing PTSD and related psychological comorbidities. To illustrate this point, compelling evidence has established that the prevalence of PTSD is more than twice as high for operational infantry units exposed to direct combat than in the general population (Kok et al., 2012). Given the known relationship between combat exposure and an increased risk of mental health conditions, a synthesis of the literature would not provide the opportunity to disentangle any potential adverse effects from exposure to the chemicals of interest (COIs) on mental health outcomes that may occur independently of effects (psychological) accrued through military service.
- Second, a review of the vast toxicology literature that relates to the COIs reveals that there is a dearth of reports that address the potential associations and mechanistic explanations relating to how exposure to the COIs experienced during military service in Vietnam may influence the risk of developing mental health conditions. This applies specifically to an overall absence of published evidence as to how dioxin/2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure could be etiologically implicated in the development of PTSD and related psychological comorbidities.

This chapter will consider possible diffuse CNS effects of toxic exposure to the COIs and specific clinical conditions associated with focal dysfunctions. Examples of diseases that result from the degeneration of specific brain areas are PD, Alzheimer disease (AD), spinocerebellar degeneration, and amyotrophic lateral sclerosis (ALS). These diseases may occur in the absence of any toxicant exposure, but all may be triggered by environmental factors, including toxicant exposure (Bronstein et al., 2009; Chin-Chan et al., 2015; de la Monte and Ming, 2014; Kang H et al., 2014; Tanner et al., 2014; Wang et al., 2014).

Disorders of the peripheral nervous system (PNS) are generally referred to as neuropathies. Neuropathies can be purely motor, presenting as deficits in strength, but most often present with involvement of both motor and sensory fibers. Neuropathies are often symmetric and start with symptoms related to dysfunction of fibers that travel the greatest distance to their target organ. For that reason, the symptoms of neuropathy often start in the digits and travel toward the torso. Many neuropathies also affect autonomic fibers and thus can result in changes in blood pressure and heart rate and in symptoms related to the control of digestion. Toxicant exposure can induce immediate (i.e., acute) damage to peripheral nerves, and previous updates found limited or suggestive evidence that dioxin exposure can cause such short-term effects. Evidence related to the rapid onset of these conditions is summarized in Appendix B. However, the overall focus of this chapter is on *delayed* adverse effects on both the PNS and the CNS.

Timing is important in assessing the effects of chemical exposure on neurologic function and must be considered in the design and critique of epidemiologic studies. In the original *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*[1] report, hereafter referred to as *VAO* (IOM, 1994), attention was focused on persistent neurobehavioral disorders. That focus was maintained in *Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), and *Update 2002* (IOM, 2003). A slight change in emphasis toward chronic neurodegenerative disorders was reflected in the name change of this chapter to "Neurologic Disorders" in *Update 2004* (IOM, 2005), which was carried forward in *Update 2006* (IOM, 2007), *Update 2008* (IOM, 2009), *Update 2010* (IOM, 2012), and *Update 2012* (IOM, 2014). The present chapter reviews data pertinent to persistent neurologic disorders of all types.

Case identification in neurologic disorders is often difficult because there are few disorders for which there are specific diagnostic tests. Many disorders result only in molecular or biochemical effects, so even the most advanced imaging techniques can miss abnormalities. Because the nervous system is not readily accessible for biopsy, pathologic confirmation is usually not feasible. However, identifiable neurologic disorders always result in objective abnormalities that are reflected in anatomic or functional tests or discovered via clinical examination.

Many studies have addressed the possible contribution of various chemical exposures to neurologic disorders, but the COIs that constitute the committee's focus are a particular set of chemicals: four herbicides—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram (4-amino-3,5,6-trichloropicolinic acid), and cacodylic acid (dimethyl arsenic acid)—and TCDD, a contaminant of 2,4,5-T. The committee also considered

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like chemicals to be informative if their results were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of specific congeners. While all studies reporting TEQs based on PCBs were reviewed, those studies that reported TEQs based only on mono-ortho PCBs (PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the World Health Organization (WHO) revised toxicity equivalent factors (TEFs) of 2005 (La Rocca et al., 2008; van den Berg et al., 2006). The specificity of exposure assessment is an important consideration in weighing evidence relevant to the committee's charge.

This chapter reviews the association between exposure to the COIs and neurobehavioral disorders, neurodegenerative disorders, and chronic peripheral system disorders. The scientific evidence supporting biologic plausibility is also reviewed here. More complete discussions of the categories of association and of this committee's approach to categorizing health outcomes are presented in Chapters 1 and 2. For citations new to this update that revisit previously studied populations, relevant details on experimental design can be found in Chapter 6.

BIOLOGIC PLAUSIBILITY

Experimental data regarding the biologic plausibility of a connection between exposure to the COIs and various neurologic disorders continue to accrue. This section summarizes in a general way some of the information reviewed in the current update and, for completeness, includes pertinent information from prior updates.

Several studies have dealt with mechanisms of neurotoxicity that might be ascribed to the COIs, notably 2,4-D and TCDD. Molecular effects of the COIs are described in detail in Chapter 4. Some aspects of the biochemical activity of the COIs suggest pathways by which there could be effects on the neural systems. A number of studies suggest that the COIs, primarily 2,4-D, have neurologic effects, both neurochemical and behavioral, in animal models if exposure occurs during development or in cultured nerve cells (Konjuh et al., 2008; Rosso et al., 2000a,b; Stürtz et al., 2008); older references described the behavioral effects of a developmental exposure of rodents to a 2,4-D–2,4,5-T mixture (Mohammad and St. Omer, 1986; St. Omer and Mohammad, 1987). Perinatal exposures to TCDD and to coplanar, dioxin-like PCBs have reportedly caused deficits in learning behavior in rats (Curran et al., 2011; Haijima et al., 2010; Hojo et al., 2008). However, caution in interpreting the significance of those studies is warranted because the developing nervous system is different from the mature nervous system and may not be an appropriate model for the possible consequences of exposure to the COIs by adults, as was the case for Vietnam veterans.

Some studies further support suggestions that the concentration of reactive oxygen species (ROS) could alter the functions of specific signaling cascades and

be involved in neurodegeneration (Drechsel and Patel, 2008). Such studies do not specifically concern the COIs but are potentially relevant to these chemicals inasmuch as TCDD and herbicides have been reported to elicit oxidative stress (Byers et al., 2006; Celik et al., 2006; Kumar et al., 2014c; Shen et al., 2005; Wan et al., 2014). TCDD has been shown to affect phosphokinase C biochemistry in nerve cells and so could affect the integrity and physiology of nerve cells (Kim et al., 2007; Lee HG et al., 2007). TCDD has also been shown to affect signaling pathways that regulate nitric oxide synthesis in neural and glial cells, leading to neurotoxicity and cell death (Jiang et al., 2014; Li Y et al., 2013). Cytochrome P450 1A1, the aryl hydrocarbon receptor (AHR), and the AHR nuclear transporter occur in the brain, so TCDD may exert effects in the brain (Huang et al., 2000). In addition, earlier studies in hepatocytes indicated that 2,4-D affects aspects of mitochondrial energetics and mitochondrial calcium flux (Palmeira et al., 1994a,b, 1995a,b); such that, if these effects occur in mitochondria of nervous-system cells, the energy balance and pathways of cells in the nervous system could be affected to later disrupt nervous-system function.

Basic scientific studies have emphasized the importance of alterations in neurotransmitter systems as potential mechanisms underlying TCDD-induced neurobehavioral disorders (Jiang et al., 2014; Xie et al., 2013). Neuronal cultures treated with 2,4-D exhibited decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis (Rosso et al., 2000a,b). Those mechanisms are important for maintaining the connections between nerve cells, which are necessary for neuronal function and are involved in axon regeneration and recovery from peripheral neuropathy. Early animal experiments have demonstrated that TCDD treatments affect the fundamental molecular events that underlie neurotransmission initiated by calcium uptake (Hong et al., 1998). Mechanistic studies have demonstrated that 2,4,5-T can alter cellular metabolism and the cholinergic transmission necessary for neuromuscular transmission (Sastry et al., 1997).

TCDD treatment of rats at doses that do not cause general systemic illness or wasting produces electric changes in peripheral nerves associated with altered functions and pathologic findings that are characteristic of toxicant-induced axonal peripheral neuropathy (Grahmann et al., 1993; Grehl et al., 1993).

As discussed in Chapter 4, extrapolating observations of cells in culture or animal models to humans is complicated by differences in sensitivity and susceptibility among animals, strains, and species; by the lack of strong evidence of organ-specific effects occurring consistently across species; and by differences in route, dose, duration, and timing of chemical exposures. Thus, although the toxicologic observations themselves cannot establish a conclusion that the COIs produced neurotoxic effects in humans, they establish biologic plausibility and point to potential mechanisms that might have come into play.

NEUROBEHAVIORAL (COGNITIVE OR NEUROPSYCHIATRIC) DISORDERS

This section summarizes the findings of *VAO* and previous updates on neurobehavioral disorders and incorporates information published in the past 2 years into the evidence database.

Conclusions from *VAO* and Previous Updates

On the basis of the data available at the time, the committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, *Update 2010*, and *Update 2012* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and neurobehavioral disorders. The data that informed that conclusion were mostly from the Air Force Health Study (AFHS, 1991a,b, 1995, 2000; Barrett et al., 2001, 2003). Urban et al. (2007) confirmed that acute neurologic symptoms experienced shortly after an acute exposure to TCDD could be sustained more than 30 years after the exposure, but this study did not address delayed effects. In other studies (Kamel et al., 2007a; Solomon et al., 2007), no relationship was found with diverse neurologic outcomes and exposure to unspecified herbicides. Many of the studies reviewed were found to be methodologically flawed (Dahlgren et al., 2003a; Pazderova-Vejlupkova et al., 1981; Pelclová et al., 2001, 2002) or uninformative (ADVA, 2005c; Decoufle et al., 1992; Park et al., 2005; Visintainer et al., 1995).

Update of the Epidemiologic Literature

Vietnam-Veteran and Case-Control Studies

Since *Update 2012*, no new Vietnam-veteran, occupational, or case-control studies have been published concerning cognitive or neuropsychiatric disorders and exposure to the COIs.

Environmental Studies

Since the previous update, Bouchard et al. (2014) examined the cross-sectional association between serum PCB concentrations and cognitive function in 708 adults ranging in age from 60 to 84 who participated in the 1999–2000 or 2001–2002 iterations of the National Health and Nutrition Examination Survey (NHANES). Analyses were limited to the 12 of the 23 PCB congeners measured that were detected in at least 75 percent of the subjects; among these, the dioxin-like compounds (DLCs) were two of the mono-ortho PCBs 118 and 156 and the relatively less potent non-ortho PCBs 126 and 169. Cognitive function was

assessed, in a limited fashion, with the Digit-Symbol Coding Test (Wechsler, 1997). Neither dioxin-like nor non–dioxin-like PCB concentrations were associated with cognitive scores of concern ($p = 0.4$ and 0.7, respectively). The authors observed a significant interaction between age and serum concentrations of dioxin-like PCB congeners in the older group (70–84 years of age), for whom a 100 ng/g increase in serum concentration of dioxin-like PCBs was associated with a 2.65 point lower cognitive score ($p = 0.04$).

Krieg (2013) performed a limited assessment of cognition in 700 adults, aged 20–59 years, participating in NHANES III. Twelve pesticide metabolites were measured in the urine, including two chemicals found in the urine after 2,4-D exposure: unmetabolized 2,4-D and 2,4-dichlorophenol (2,4-DCP) (Sauerhoff et al., 1977). A limited battery of three neurobehavioral tests was administered (simple reaction time, symbol–digit substitution, and serial digit learning). The authors found that urine levels of 2,4-D itself, which is the main form of elimination, were not associated with detrimental effects in any of the neurobehavioral tests. In contrast, increased urine levels of the trace metabolite 2,4-DCP were associated with an improved performance on the serial digit learning test ($p = 0.0002$).

Other Recent Literature

Sapbamrer and Nata (2014) studied neurobehavioral symptoms (headache, dizziness, epilepsy, balance problem, fatigue) in 182 rice farmers and 122 non-farmers in northern Thailand. None of the endpoints measured differed in frequency between the two groups. Of the rice farmers, 63.2 percent reported exposure to herbicides, but exposure specificity for the comparisons was insufficient for the results to be regarded as fully informative for VAO purposes.

Biologic Plausibility

Some toxicologic studies have suggested a possible involvement of the COIs in the occurrence of neurobehavioral effects. Akahoshi et al. (2009) produced a mouse neuroblastoma cell line that overexpressed the AHR, a TCDD-induced protein hypothesized to be important in the synthesis of dopamine, whose perturbation has been implicated in a number of neurobehavioral syndromes. Elevated expression of AHR in these cells was associated with increased production of neurotransmitters and augmented dopamine expression, but the implication of that finding is not clear. In vitro exposure of human CD34+ cells to TCDD has been associated with modulation of gene expression of the GABAergic pathway, which may be associated with altered synaptic transmission, visual perception, and other neurologic conditions (Fracchiolla et al., 2011). Lensu et al. (2006) gavaged rats with 50 µg/kg TCDD or with leptin, whose effect on food consumption is recognized. When the hypothalamuses of the two groups were compared

24 hours later, the results were not consistent with a primary role for the hypothalamus in TCDD-induced wasting syndrome.

Other studies have focused on neurobehavioral outcomes following perinatal exposure, which as discussed in Chapter 10, is of relevance in understanding possible consequences in the offspring of Vietnam veterans, particularly women. Haijima et al. (2010) found that gavage treatment of pregnant mice with 3 µ/kg TCDD on gestation day 12.5 (resulting in in utero and lactational exposure of the offspring) impaired memory in male offspring. Mitsui et al. (2006) reported that hippocampus-dependent learning could be impaired in male rats exposed to TCDD in utero and that the impairment could affect fear conditioning. Curran et al. (2011) assessed the effect of CYP1A2 and AHR genotype on altered learning and memory in mice exposed to an environmentally relevant mixture of dioxin-like (coplanar) and non–dioxin-like PCBs in utero and during lactation. They observed the most significant deficits in response to PCB treatment in *Ahrb1_Cyp1a2*(–/–) mice, including impaired novel-object recognition and increased failure rate in the Morris water maze. Studies in week-old rodents have also detected molecular effects of TCDD in cerebellar granule cells and neuroblasts, which may be relevant to motor function and cognitive processes (Kim and Yang, 2005; Williamson et al., 2005). Stürtz et al. (2008) found alterations in how female rats fed on postpartum days 1–7 with diets containing 15, 25, or 50 mg/kg 2,4-D interacted with their pups. The specific relevance of the scientific evidence to neurobehavioral effects in humans exposed as adults is unclear.

A general summary of the biologic plausibility of neurologic effects arising from exposure to the COIs is presented at the beginning of this chapter.

Synthesis

There is not consistent epidemiologic evidence of an association between exposure to the COIs and neurobehavioral (cognitive or neuropsychiatric) disorders. More research on the COIs and these endpoints, particularly in the offspring of exposed parents, is warranted given findings in studies that address biologic plausibility.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and neurobehavioral (cognitive or neuropsychiatric) disorders.

NEURODEGENERATIVE DISEASES

This section summarizes the findings on neurodegenerative diseases—specifically PD, ALS, and AD—discussed in previous VAO reports.

Previous VAO reports have not identified epidemiologic results for multiple sclerosis (MS) in relation to exposure to the COIs, so this committee notes that two studies new to this update reported on MS without providing enough substance to justify developing a section for this health outcome. MS is already eligible for service-connected consideration for all veterans who experienced symptoms while in the military or within 7 years of honorable discharge. In addition to reporting on the deaths from PD and ALS in the female Vietnam-era veterans, Kang HK et al. (2014) found an elevated risk of death from MS, although its confidence interval (CI) was wide due to a small number of cases, but no suggestion of increased risk of death from "other nervous system diseases." In addition to reporting on the prevalence of PD, ALS, and AD, Yi et al. (2014a) found no association with herbicide exposure for the prevalence of MS, but the substantial power of this very large study did identify associations for a number of neurological conditions (paroxysmal disorders, nerve/plexus disorders, and paralytic syndromes), which are considerably more specific than the outcomes evaluated in previous VAO updates.

Parkinson Disease and Parkinsonism

PD is a progressive neurodegenerative disorder that affects millions of people worldwide. Its primary clinical manifestations are bradykinesia, resting tremor, cogwheel rigidity, and gait instability. These signs were first described as a single entity in 1817 by James Parkinson. In recent years, many nonmotor manifestations of PD have been described, and they can be the presenting symptoms of the disease. These include cognitive dysfunction that often progresses to frank dementia, sleep disturbances, hallucinations, psychosis, mood disorders, fatigue, and autonomic dysfunction (Langston, 2006).

In the nearly two centuries since its initial description, much has been learned about the genetic predisposition and pathophysiology of PD, but its etiology in most patients and specific environmental risk factors remain largely unknown. The diagnosis of PD is based primarily on clinical examination, although in recent years, magnetic resonance imaging and functional brain imaging have become increasingly useful. PD is difficult to distinguish from a variety of Parkinsonian syndromes, including drug-induced Parkinsonism, and neurodegenerative diseases, such as atrophy of multiple systems, that present with Parkinsonian features combined with other abnormalities. Ultimately, a diagnosis of PD can be confirmed with postmortem pathology examination of brain tissue for the characteristic loss of neurons from the substantia nigra and telltale Lewy body intracellular inclusions. Pathology findings in other forms of Parkinsonism show different patterns of brain injury.

The incidence of PD is estimated to range from 2 to 22 per 100,000 person-years, while its prevalence ranges from 18 to 182 per 100,000 persons. It affects

about 1 percent of all persons over 60 years old and up to 5 million people worldwide. PD is the second-most common neurodegenerative disease (after AD).

Research on the genetic, epigenetic, and environmental causes of PD suggests that it has multiple risk factors, including aging, environmental exposure, and genetic predisposition (Gao and Hong, 2011; Kwok, 2010). The peak incidence and prevalence of PD are consistently found in people 60–80 years old. A consensus statement from a 2007 meeting of PD experts (Bronstein et al., 2009) concluded that, in addition to firm evidence that the toxicant 1-methyl-4-phenyl-1,2,4,6-tetrahydropyridine (MPTP) can induce PD, there is substantial evidence that men are at greater risk and that smoking and coffee consumption are associated with reduced risk. Further evidence of environmental exposures playing a role in the development of PD has continued to accrue (Chin-Chan et al., 2015; Tanner et al., 2014).

Heredity has long been suspected of being an important risk factor for PD; as many as 25 percent of all PD patients have at least one first-degree relative who has PD. At least 13 gene mutations have been identified in autosomal dominant PD, including mutations in parkin and α-synuclein (Klein and Lohmann-Hedrich, 2007). Mutations associated with an autosomal recessive inheritance pattern have also been described. Complex genetics may be found to account for an increasing number of PD cases in coming years, but environmental risk factors clearly are also important.

Conclusions from *VAO* and Previous Updates

The committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, and *Update 2006* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and PD. Five case-control studies reviewed by those committees had investigated association between PD and "herbicide" exposure without providing further specificity. Two of these did not find associations with herbicide exposure (Stern et al., 1991; Taylor et al., 1999), but they were limited because their subjects had experienced little actual herbicide exposure. Three found significant associations with herbicide exposure (Butterfield et al., 1993; Gorell et al., 1998; Semchuk et al., 1992).

Two new studies reviewed by the committee responsible for *Update 2008* examined association specifically with chlorophenoxy acid and the esters and found increased odds ratios (ORs) (Brighina et al., 2008; Hancock et al., 2008). The doubling in risk observed by Hancock et al. (2008) did not achieve statistical significance (OR = 2.07, 95% CI 0.69–6.23), while increases for the chemical class of chlorophenoxy acids or esters noted by Brighina et al. (2008) reached statistical significance only in the quartile of cases who were youngest at diagnosis (OR = 1.52, 95% CI 1.04–2.22). In the prospective Agricultural Health Study (AHS), incident PD was related in a dose–response manner to increasing

days of pesticide use (Kamel et al., 2007b). On the basis of the evidence summarized above, *Update 2008* concluded that there was limited/suggestive evidence associating exposure to the COIs with PD. Additional studies considered by the committees responsible for *Update 2010* and *Update 2012* led them to affirm this conclusion.

The findings of the literature reviewed are summarized in Table 11-1.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies Since the previous update, Kang HK et al. (2014) performed a retrospective study of mortality through 2010 in three cohorts of Vietnam-era military women—4,734 deployed to the theater of the war, 2,062 who served in countries near Vietnam, and 5,313 who were not deployed and served primarily in the United States. PD mortality, adjusted for age, race, duration of military service, officer status, and nursing status was not elevated in those deployed to Vietnam versus the non-deployed cohort (relative risk [RR] = 1.25, 95% CI = 0.34–4.59), and there was no suggestion of an increase when this comparison was made for the subsets of only nurses (RR = 0.78, 95% CI 0.17–3.50).

In the Korean Veterans Health Study (Yi et al., 2014b), 180,639 Korean veterans were followed up for vital statistics and cause of death. An Exposure Opportunity Index (EOI) score was assigned to each veteran based on the proximity of his unit to herbicide-sprayed areas. No association was found between PD *(International Classification of Diseases, Revision 10* [ICD-10] G20-G21) mortality and the individual EOI scores (HR = 1.01, 95% CI 0.83–1.22) or when the high-exposure group was compared to the low-exposure group (HR = 0.88, 95% CI 0.40–1.95).

When Yi et al. (2014a) compared the high- and low-exposure groups with respect to the prevalence data for primary PD (ICD-10 G20) and secondary Parkinsonism (ICD-10 G21), the results for both adjusted for age, rank, smoking, drinking, physical activity, domestic use of herbicides, education, income, and body mass index (BMI) were less suggestive of an association with herbicide exposure (OR = 1.18, 95% CI 0.99–1.42 and OR = 1.26, 95% CI 0.93–1.69, respectively) than were the unadjusted results (p = 0.002 and p = 0.014, respectively).

Occupational Studies No occupational studies addressing exposure to the COIs and PD have been published since *Update 2012*.

Environmental Studies Blood samples were drawn from 40,221 individuals between 1968 and 1972 in the course of the Finnish Mobile Clinic Health Examination Survey. From among those who were 20 to 79 years of age and had not been diagnosed with PD or psychosis at the time of sampling, Weisskopf et al. (2012) identified 196 individuals certified before 1994 to receive medication for PD from the national reimbursement program; hospital records were obtained

TABLE 11-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease and Parkinson-Like Conditions (Shaded entries are new information for this update)

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Kang et al., 2014	10 PD deaths (2,260 in Vietnam cohort and 1,781 in near-Vietnam cohort)	5,313 non-deployed US female VV	Vietnam veterans—information obtained from death certificates, VA records, Social Security Death Master File, NCHS National Death Index	All COIs	10 PD cases (8 PD cases in nurses)	Vietnam cohort: 1.3 (0.3–4.6) Nurses only: 0.8 (0.2–3.5)	Diagnosis from death records
van der Mark et al., 2014	444 cases	876 matched controls	JEM and an algorithm derived from the AHS were used to derive cumulative exposure to herbicides; a crop-based method was used to estimate exposure to particular pesticides	JEM group (medium) JEM group (high) AHS-algorithm group (medium) AHS-algorithm group (high) 2,4-D (low) 2,4-D (high)		1.3 (0.7–2.4) 0.3 0.6–2.5) 1.2 (0.6–2.3) 1.5 (0.8–3.0) 1.1 (0.5–2.4) 1.7 0.8–3.5)	Neurologist review of medical records
Weisskopf et al., 2012	101 PD cases	349 (186 matched controls)	PCBs analyzed in serum	Mono-ortho dioxin-like PCBs (PCBs 105, 118, 156, 157, 167, 189)		PCB 118: 0.4 (0.4–1.0) Dioxin-like PCBs; 0.3 (0.1–0.9)	Neurologist review of medical records
Yi et al., 2014a	474 PD cases	VV with low exposure (69,305) vs VV with high exposure (42,421)	Korean Vietnam veterans—prevalence data obtained from Korea National Health Insurance claims (01/2000–09/2005)	AO (based on self-report and proximity of veteran's military unit to AO-sprayed area)	213 cases with high exposure; 261 cases with low exposure	PD and high vs low exposure: HR = 1.2 (1.0–1.4) Log EOI scores: HR = 1.0 (1.0–1.1) Secondary PD and high vs low exposure: HR = 1.3 (0.9–1.7) Log EOI scores: HR = 1.0 (0.9–1.1)	Insurance claim data

Yi et al., 2014b	25 PD deaths; total population 17,529	VV with low exposure (7,973) vs VV with high exposure (9,556)	VV (Korean Veterans Health Study)—cause of death ascertained from National Statistical Office (1992–2005)	AO (based on self-report and proximity of veteran's military unit to AO-sprayed area)	13 high-exposure deaths; 12 low-exposure deaths	PD and high vs low exposure: HR = 0.9 (0.4–2.0) Log EOI scores: HR = 1.0 (0.8–1.2)	Diagnosis from death records
Kenborg et al., 2012; Denmark	28 PD cases from male members of Danish Union of Gardeners (n = 3,124)	Incidence of PD in general population of Denmark	Hospital diagnosis of PD between 1977–2008	Pesticides (including phenoxy herbicides)	28 11 16 1	Hospitalization: 1.1 (0.8–1.7) Born before 1915: 1.6 (0.8–2.8) Born 1915–1934: 1.2 (0.7–1.9) Born 1935 or later: 0.3 (0.0–1.6) 1.8 (0.97–3.4) 1.8 (0.95–3.3)	Not specified
Rugbjerg at al., 2011; Canada	403 PD cases from pharmacy database	405 matched controls	Initial screening phone-interview followed by an in-person physical assessment employing a checklist and record of symptoms, reviewed by a neurologist specializing in movement disorders	Herbicides Neurotoxic pesticides (including 2,4-D, 2,4,5-T)	33 35	1.8 (0.97–3.4) 1.8 (0.95–3.3)	Parkinsonian tremor, rigidity, bradykinesia, masked facies, micrographia, or postural imbalance
Firestone et al., 2010 (updates and expands Firestone et al., 2005); Washington, US	Enrolled cases increased from 250 (in original study) to 404	526 unrelated controls	Structured face-to-face interviews; demographic information collected, job descriptions (if held for more than 6 mos), and workplace exposures to various industrial toxicants identified from a checklist were recorded	2,4-D	8	0.8 (0.3–2.0)	≥ 2 of 4 cardinal signs; must have bradykinesia or resting tremor, may have cogwheel rigidity, or postural reflex impairment

continued

TABLE 11-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease and Parkinson-Like Conditions, continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Elbaz et al., 2009; France	224 PD cases	557 controls	Initial self-assessment, plus individual interview with occupational specialist	Phenoxy herbicides Age of onset > 65 yrs	na na	1.8 (0.9–3.3) 2.9 (1.1–7.3)	≥ 2 cardinal signs (rest tremor, bradykinesia, rigidity, impaired postural reflexes)
Tanner et al., 2009; US	519 cases; consecutively eligible subjects between July 1, 2004, and May 31, 2007	521 controls frequency matched to cases by age, sex, and location	Telephone interviewers collected information about exposures before the reference age; employment history—industry, location, processes, materials, and job tasks Toxicant exposure collected for some jobs	2,4-D	16	2.6 (1.0–6.5)	Enrolling investigator determined diagnosis and type of Parkinsonism, Unified Parkinson Disease Rating Scale score, and clinical features
Brighina et al., 2008; US (Mayo Clinic)	833 PD sequential cases from clinic; median age = 67.7 yrs, 208 cases 59.8 yrs	472 unaffected siblings and 361 unrelated controls	Self-report down to specific herbicides; 2,4-D said to be most prevalent in cases, but published analysis not that detailed	For youngest quartile at diagnosis: Pesticides (ever): Herbicides (ever): Phenoxy herbicides: Insecticides (ever): Fungicides (ever):	 87	 1.8 (1.1–2.9) 2.5 (1.3–4.5) 1.5 (1.0–2.2) 1.0 (0.6–1.7) 1.0 (0.3–3.2)	PD diagnosed by movement disorder specialist
Dhillon et al., 2008; US (University of Texas)	100 PD cases recruited from a medical center's neurological	84 controls without PD recruited from the same medical center	Professionally administered questionnaire used to determine military history (including spraying herbicides/pesticides), personal use/mixing	Ever personally used/mixed or applied: Herbicide use-home or agricultural 2,4-D 2,4,5-T Silvex or other 2,4,5-TP	 34 17 4 1	 0.8 (0.4–1.4) 1.2 (0.6–2.8) 0.5 (0.1–1.6) 0.3 (0.0–2.7)	PD diagnosed by neurologist specializing in movement disorders using standard clinical/lab diagnostic criteria

	institute in East Texas		and average duration of exposure to herbicides and specific pesticides, among other exposures	products		
Hancock et al., 2008; US (Duke)	319 cases	296 unaffected relatives and others	All comparisons referent to those who never applied any pesticide	Pesticide application:	200	1.6 (1.1–2.3)
				Insecticides:		1.8 (1.2–2.8)
				Botanical:	7	5.9 (0.6–56)
				Organophosphate:	53	1.9 (1.1–3.6)
				Herbicides:		1.6 (1.0–2.5)
				Chlorophenoxy:	15	2.1 (0.7–6.2)
				Phosophonoglycine:	57	1.5 (0.9–2.5)
				Triazine:	5	1.1 (0.3–3.6)
Kamel et al., 2007b; US (Agricultural Health Study) [Updates Kamel et al., 2005]	83 prevalent cases at enrollment; 78 incident cases during follow-up among private applicators and spouses	79,557 without PD at enrollment; 55,931 without PD followed up	Self-report of individual herbicides (2,4-D; 2,4,5-T; 2,4,5-TP) on detailed self-administered questionnaires at enrollment or telephone interview for follow-up	For incident cases:		
				2,4-D:	49	1.0 (0.5–2.1)
				2,4,5-T:	24	1.8 (1.0–3.3)
				2,4,5-TP:	7	0.9 (0.4–1.8)
				Dicamba:	32	1.5 (0.8–2.8)
				Paraquat:	11	1.0 (0.5–1.9)
				Trifuralin:	32	1.7 (1.0–3.2)
				Cyanazine	26	1.0 (0.5–1.8)
				For prevalent cases:		
				2,4-D:	47	0.9 (0.5–1.8)
				2,4,5-T:	16	0.9 (0.5–1.7)
				2,4,5-TP:	4	0.8 (0.3–1.9)
				Dicamba:	26	0.9 (0.5–1.6)
				Paraquat:	14	1.8 (1.0–3.4)
				Trifuralin:	31	0.9 (0.5–1.6)
				Cyanazine	30	2.6 (1.4–4.9)

continued

TABLE 11-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease and Parkinson-Like Conditions, continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Firestone et al., 2005; Washington, US (Updated by Firestone et al., 2010)	250 (156 men) newly diagnosed 1992–2002 at Group Health Cooperative	388 (241 men)	Interview determining occupational and home-based pesticide exposure characterized by chemical name or brand, duration, and frequency	Occupational, men only			Controlled for age, sex, smoking
				Pesticides:	19	1.0 (0.5–1.9)	
				Insecticides:	15	0.9 (0.4–1.8)	
				Fungicides:	2	0.4 (0.1–3.9)	
				Herbicides:	9	1.4 (0.5–3.9)	
				Paraquat:	2	1.7 (0.2–12.8)	
				Home use, all subjects			
				Pesticides:	178	1.0 (0.7–1.4)	
				Insecticides:	141	0.8 (0.6–1.1)	
				Fungicides:	14	0.6 (0.3–1.1)	
				Herbicides:	116	1.1 (0.8–1.5)	
Behari et al., 2001; India	377 (301 men, 76 women)	377 matched for age (± 3 yrs), but not sex	Structured interview	McNemar chi-square:			
				Herbicides:		p = 0.010	
				(protective effect—not confirmed by multivariate analysis)			
				Insecticide:		p = 0.169	
				Rodenticide:		p = 0.662	
Engel et al., 2001; US (cross-sectional, but otherwise fairly high-quality design)	238	72	Self-administered questionnaire for occupational exposure	[prevalence ratios]			
				Any pesticide:		0.8 (0.5–1.2)	Neurologic exam by trained nurse
				Herbicides:		0.9 (0.6–1.3)	
				Insecticides:		0.9 (0.6–1.5)	
				Fungicides:		0.8 (0.6–1.3)	

Kuopio et al., 1999; Finland	123 (onset of PD before 1984; 63 men, 60 women)	246 matched on sex, age (± 2 yrs), and urban/rural	Interview—pesticides or herbicides regularly or occasionally used	Pesticide use: Occasional use: Regular use: Herbicide use: Occasional use: Regular use:	39 26 13 33 20 13	1.0 (0.6–1.7) 1.2 (0.7–2.0) 0.7 (0.3–1.3) 1.4 (0.8–2.5) 1.7 (0.9–3.2) 0.8 (0.4–1.7)	Neurologic exam
Taylor et al., 1999; Boston Medical Center	140	147 controls referred by cases	Interview—exposure recorded as total days for lifetime	Logistic analysis adjusted for age, sex, family history, education, smoking, water source, head injury, depression Pesticides: Herbicides:		 1.0 (0.9–1.2) 1.1 (0.7–1.7)	Neurologic exam
Gorell et al., 1998; US	144 (age > 50 yrs)	464	Interview—herbicide and insecticide use while working on a farm or gardening	All occupations contributing exposure to: Herbicides: Insecticides: Fungicides:		 4.1 (1.4–12.2) 3.6 (1.8–7.2) 1.6 (0.5–5.5)	Standard criteria of PD by history
Liou et al., 1997; Taiwan	120	240 hospital controls matched for age (± 2 yrs) and sex	Interview—occupational exposures to herbicides or pesticides	Pesticides vs no pesticides: But no paraquat use: Paraquat use: Paraquat use vs no paraquat:		2.9 (2.3–3.7) 2.2 (0.9–5.6) 4.7 (2.0–12)) 3.2 (2.4–4.3)	Neurologic exam
Seidler et al., 1996; Germany	380 (age < 66 yrs with PD after 1987)	755 (379 neighborhood, 376 regional; neighborhood controls may be over-matched)	Interview—dose-years = years of application weighted by use	Pesticides: Herbicides—high dose: Dose trend vs neighbor controls vs regional controls Insecticides—high dose: Dose trend vs neighbor controls vs regional controls		2.1 (1.6–2.6) 2.4 (1.0–6.0) p = 0.06 p < 0.001 2.1 (0.9–4.8) p = 0.12 p < 0.001	Neurologic exam

continued

TABLE 11-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease and Parkinson-Like Conditions, continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Hertzman et al., 1994; Canada	127 (71 men and 56 women)	245 (121 with cardiac disease; 124 voters)	Interview—occupation with probable pesticide exposure	Cases vs voters—among men			Neurologic exam
				Pesticides:			
				Herbicides:		2.3 (1.1–4.9)	
				Chlorophenoxys:		1.2 (0.6–2.5)	
				Paraquat:		1.2 (0.6–2.4)	
				Insecticides:		1.3 (0.3–4.6)	
				Fungicides:		0.3 (0.1–0.9)	
Butterfield et al., 1993; US	63 young onset cases (age < 50 yrs)	68	Questionnaire—pesticide or insecticide use 10 times in any year	Herbicides:		3.2 ($p = 0.033$)	Standard criteria of PD by history
				Insecticides:		5.8 ($p < 0.001$)	
				Dwelling fumigated:		5.3 ($p = 0.45$)	
Semchuk et al., 1992; Calgary, Alberta, Canada	130 living cases from register of Calgary residents (population-based)	260 community controls matched for age (± 2.5 yrs) and sex, identified by RDD	Interview—self-report of exposure for each job held > 1 mo	Pesticides:	32	2.3 (1.3–4.0)	Neurologic exam confirming idiopathic PD without dementia (average 7.8 yrs from diagnosis)
				Herbicides:	17	3.1 (1.3–7.0)	
				Exposed during age interval:			
				16–25 yrs		1.4 (0.5–4.3)	
				26–35 yrs		4.8 (1.5–15.0)	
				36–45 yrs		3.8 (1.2–13.0)	
				46–55 yrs		4.9 (1.3–19.0)	
				Insecticides:	17	2.1 (1.0–4.1)	
				Fungicides:	16	1.6 (0.8–3.3)	

Stern et al., 1991; NJ and PA, US	69—all young onset cases identified (age < 40 yrs); 80—random selection of old onset cases (age > 59 yrs)	149 nominated by each case or picked from hospital; matched by age (± 6 yrs), sex, and race	Interview—self-report of insecticide and pesticide use by self or others in home or garden	Insecticides: Onset < 40 yrs: Onset > 59 yrs: Herbicides: Onset < 40 yrs: Onset > 59 yrs: Adjusted for smoking, head injury, rural residence: Insecticides: Herbicides:		0.7 (0.3–1.4) 0.6 (0.2–1.7) 0.8 (0.3–2.1) 1.1 (0.7–1.7) 0.9 (0.5–1.7) 1.3 (0.7–2.4) 0.5 (0.2–1.1) 0.9 (0.6–1.5)	Review of medical records, responsive to PD medication (under treatment average of 8.2 yrs), without major cognitive impairment
Hertzman et al., 1990; British Columbia, Canada	57 prevalent PD patients (age < 79 yrs) (50–54 had confirmed PD, not clear exactly how many)	122 aged 50–79 yrs who responded from electoral rolls	Questionnaire—ever worked in an orchard	Work in orchards: Paraquat:	 4/57	3.7 (1.3–10.3) (p = 0.01)	Neurologic exam confirmed diagnostic criteria in 55 of 69 cases identified by asking physicians in area

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid or Silvex; AHS, Agricultural Health Study; AO, Agent Orange; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; JEM, job–exposure matrix; HR, hazard ratio; na, not applicable; NCHS, National Center for Health Statistics; OR, odds ratio; PCB, polychlorinated biphenyl; PD, Parkinson disease; RDD, random-digit dialing; VA, US Department of Veterans Affairs; VV, Vietnam veteran.

[a]For the objective of the VAO review series, only associations with herbicides are of possible relevance; only the phenoxy herbicides, cacodylic acid, and picloram are of specific interest.

for 126 of these cases, and from this information neurologists confirmed the PD diagnosis for all but 25. The 101 established PD cases were matched to controls without PD by age, sex, municipality, and vital status. The serum samples were analyzed in 2005–2007 for 55 PCB congeners, including the dioxin-like PCBs 105, 118, 156, 157, 167, 189. This set of dioxin-like PCBs consists only of mono-ortho congeners, which have considerably lower TEFs than the four non-ortho dioxin-like congeners, which were not covered in the serum analyses. In addition to analyses on total PCBs and three common non–dioxin-like congeners, results were reported individually for the common PCB 118 and for the measured set of dioxin-like PCBs. Concentrations (ng/g serum) for each congener group were partitioned into quintiles. With adjustments for smoking, occupation, BMI, triglycerides, cholesterol, and serum dieldrin concentration, the number of PD cases in the highest quintile was compared to the number in the lowest quintile, and a trend test was performed. Reduced ORs for PD in the highest quintile and the suggestion of an inverse relationship with increasing concentration were reported for both PCB 118 (OR = 0.37, 95% CI 0.37–0.95; p = 0.10) and for total dioxin-like PCBs (OR = 0.34, 95% CI 0.13–0.90; p = 0.05). These findings are not supportive of an association between dioxin-like activity and PD, but the committee does not attribute much weight to evidence based only on these mono-ortho PCBs whose dioxin-like activity is weak. Furthermore, the association that has been noted for the COIs is based primarily on exposure to the phenoxy herbicides themselves, rather than the dioxin-like activity of the contaminated mixtures sprayed in Vietnam.

Case-Control Studies van der Mark et al. (2014) identified PD cases newly diagnosed in 2006–2011 at five hospitals in the Netherlands. For each case, two controls matched on age and sex were identified from among patients without neurodegenerative symptoms who had been seen in the respective neurology department in that period. Of the 1,001 PD cases identified, 993 were alive and had current addresses. Of those, 45 percent completed computer-assisted telephone interviews addressing occupational histories with especially detailed information gathered on farming and gardening jobs. Of the matched controls, 35 percent completed the interview, giving a final sample for analysis of 444 cases and 876 controls. The responses were processed by a job–exposure matrix (JEM) and by an algorithm from the AHS to derive cumulative exposure to herbicides (as well as to insecticides or to fungicides); the exposure estimates were partitioned into three groups for comparison to those with no reported exposure. A crop-based method was used to estimate exposures to particular pesticides, with 2,4-D being one of the four herbicides assessed in this fashion; these estimates were partitioned into high and low groups for comparison to the never-exposed group. The analyses were adjusted for smoking, coffee consumption, occupational skill, and estimated endotoxin exposure (the other risk factor investigated in this study). For the overall herbicide exposure estimates, the medium and high groups

consistently showed non-significantly elevated risks: medium (OR = 1.30, 95% CI 0.70–2.39) and high (OR = 1.25, 95% CI 0.62–2.53) JEM groups; medium (OR = 1.21, 95% CI 0.62–2.33) and high (OR = 1.52, 95% CI 0.78–2.97) AHS-algorithm groups. However, only the product-specific results of the crop-based exposure estimation model provided findings fully informative for the VAO task; the two exposure groups for 2,4-D versus the never-exposed group had findings similar to those for herbicides overall: low (OR = 1.13, 95% CI 0.49–2.364) and high (OR = 1.68, 95% CI 0.81–3.49) groups. The only statistically significant finding was for the group with high exposure to the fungicide benomyl.

Biologic Plausibility

McDowell and Chesselet (2012) recently reviewed the literature on the ability of both toxicant-induced (6-hydroxydopamine, MPTP, rotenone, cycad) and genetically based animal models to reproduce the nonmotor symptoms of PD. The very clear PD-like toxicity resulting from human exposure to MPTP has indicated that select chemicals can result in the same type of damage to dopaminergic neurons as occurs in classical PD, and MPTP has become an important toxicant in studies that use animal and in vitro models. It is notable that MPTP's bioactive metabolite, MPP+, is similar in chemical structure to Paraquat (a commonly used herbicide, but not one that was used in Vietnam), but structurally unrelated to any of this report's COIs. Pesticides shown to produce PD-like toxicity in animal models include Paraquat, rotenone, maneb, and dieldrin. Substantial research has gone into understanding the molecular mechanisms responsible for the toxicity, especially in connection with Paraquat and rotenone (Blandini and Armentero, 2012; Di Monte et al., 2002; Drechsel and Patel, 2008; Duty and Jenner, 2011; Hatcher et al., 2008; Moretto and Colosio, 2013; Nunomura et al., 2007; Sherer et al., 2002; Yadav et al., 2012). The damage done to dopaminergic neurons in PD is probably caused by oxidative stress and inflammation and may well also involve damage to mitochondria in the target cells (Anderson and Maes, 2014: Janda et al., 2012; Liang et al., 2007; Littleljohn et al., 2011; Sarnico et al., 2008).

The COIs to this committee are known to be distributed to the CNS. Bongiovanni et al. (2007) found that rat cerebellar granule cells in culture (an in vitro model using cells not involved in PD pathology) produce increased concentrations of ROSs when exposed to 2,4-D. The COIs have not been investigated, however, in experimental systems such as those that have shown that compounds, such as Paraquat, cause inflammation and oxidative stress, so it is not known whether any of the COIs could produce these responses.

Research on the neurotoxicity of 2,4-D has been going on for a number of years, but most of it has focused on its effects on the developing rodent nervous system. The studies have often used high doses of 2,4-D that have resulted in adverse changes in the developing nervous system—both neurochemical (such as

changes in D2 receptors, tyrosine hydroxylase, and dopamine beta-hydroxylase) and behavioral (for example, Bortolozzi et al., 1999, 2002, 2003, 2004; Duffard et al., 1996; Evangelista de Duffard et al., 1990, 1995; Garcia et al., 2004, 2006; Rosso et al., 2000a,b). The injection of 2,4-D directly into the rat brain yields toxicity in the basal ganglia (Bortolozzi et al., 2001), but this route of administration is highly artificial. Postpartum dietary exposure of females to 2,4-D results in adverse alterations in maternal behavior and neurochemical changes, including increases in dopamine and its metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid (Stürtz et al., 2008). Such an increase in dopamine is the reverse of what is seen in PD, in which a degradation of the dopaminergic system occurs. In addition, a study of mice and 2,4-D yielded no evidence of neurochemical damage to the dopaminergic system (Thiffault et al., 2001). One study indicated that 2,4-D, among a variety of pesticides and metals, causes fibrillation of α-synuclein in vitro, but the study used purified protein and reported only a generalized result rather than data on 2,4-D (Uversky et al., 2002), so little confidence can be placed in it. Because most of the studies were on the developing nervous system, not the mature nervous system, and some studies yielded evidence of a lack of a role of 2,4-D in the development of PD, the existing studies do not support a role for the COIs in the etiology of PD.

A general summary of the biologic plausibility of neurologic effects arising from exposure to the COIs is presented at the beginning of this chapter.

Synthesis

The committee responsible for *Update 2014* reviewed two new epidemiologic studies that examined herbicide exposure and PD mortality in Vietnam veterans that did not find an association (Kang HK et al., 2014; Yi et al., 2014b). When investigating the prevalence of PD among the Korean Vietnam veterans, however, Yi et al. (2014a) found indications of an elevation. While the Finnish study of environmental exposures was not particularly informative for the committee, its findings on exposure to herbicides, and 2,4-D in particular, are consistent with the conclusion that exposure to the phenoxy herbicides sprayed in Vietnam may be associated with the development of PD. A biologic mechanism by which the COIs may cause PD has not been demonstrated. Nevertheless, the overall epidemiologic evidence continues to support an association between herbicide exposure and PD and to be consistent with an association with exposure to the phenoxy herbicides specifically.

For this update, VA added a special task to the committee's charge to evaluate the evidence of any association between neurodegenerative diseases with Parkinson-like symptoms and herbicide exposure. Strictly speaking, "genuine" or primary PD is a diagnosis of exclusion, and a patient with Parkinson-like symptoms would be diagnosed as having "Secondary Parkinsonism" if his condition were known to have been caused by exposure to herbicides, as indicated by the

TABLE 11-2 Correspondence of ICD-9 and ICD-10 Codes for Parkinson Disease and Other Extrapyramidal Disease and Abnormal Movement Disorders

ICD-9 Code	Description of Condition	ICD-10 Code	Description of Condition
332	Parkinson Disease	**G20**	Parkinson disease
332.0	Paralysis agitans		Paralysis agitans
			Hemiparkinsonism
	Idiopathic Parkinsonism or PD		Idiopathic Parkinsonism or PD
	Parkinsonism or PD NOS		Parkinsonism or PD NOS
	Primary Parkinsonism or PD		Primary Parkinsonism or PD
332.1	Secondary Parkinsonism	**G21**	Secondary Parkinsonism
	Parkinsonism attributable to a drug or identified toxicant	**G21.0**	Malignant neuroleptic syndrome
		G21.1	Other drug-induced secondary Parkinsonism
		G21.11	Neuroleptic induced Parkinsonism
		G21.19	Other drug induced secondary Parkinsonism
		G21.2	Secondary Parkinsonism due to other external agents
		G21.3	Postencephalitic Parkinsonism
		G21.4	Vascular Parkinsonism
		G21.8	Other Secondary Parkinsonism
		G21.9	Secondary Parkinsonism, unspecified
333	Other extrapyramidal disease and abnormal movement disorders		
333.0	Other degenerative diseases of the basal ganglia	**G23**	Other degenerative diseases of basal ganglia
	Atrophy or degeneration:	**G23.0**	Hallervorden-Spatz disease
	olivopontocerebellar (Déjérine-Thomas syndrome)	**G23.1**	Progressive supranuclear ophthalmoplegia
	pigmentary pallidal (Hallervorden-Spatz disease)	**G23.2**	Striatonigral degeneration
	striatonigral	**G23.8**	Other specified degenerative diseases of basal ganglia
	Parkinsonian syndrome associated with:	**G23.9**	Degenerative disease of basal ganglia, unspecified
	idiopathic orthostatic hypotension		
	symptomatic orthostatic hypotension		
	Progressive supranuclear ophthalmoplegia		
	Shy-Drager syndrome		

continued

TABLE 11-2 Continued

ICD-9 Code	Description of Condition	ICD-10 Code	Description of Condition
333.1	Essential and other specified forms of tremor		
333.2	Monoclonus		
333.3	Tics of organic origin		
333.4	Huntington chorea		
333.5	Other choreas		
333.6	Idiopathic torsion dystonia		
333.7	Symptomatic torsion dystonia		
333.8	Fragments of torsion dystonia		
333.9	Other and unspecified Restess legs Stiffman syndrome		
		G90.3	Multi-system degeneration of the autonomic nervous system

NOTE: ICD, *International Classification of Diseases*; NOS, not otherwise specified; PD, Parkinson disease.
SOURCE: Excerpted from CDC's ICD-10-CM (http://www.cdc.gov/nchs/icd/icd9cm.htm; http://www.cdc.gov/nchs/icd/icd10cm.htm#icd2016, accessed November 11, 2015).

description of ICD-9 332.1 in Table 11-2. For some patients with Parkinson-like symptoms, the details of their medical records may establish that their condition is definitively attributable to a specific genetic syndrome or to some identified external agent (other than possible exposure to herbicides in Vietnam). Contemporary sophisticated techniques and a thorough knowledge of a patient's history may permit making distinctions among conditions having characteristics of PD with some degree of confidence, but in practice clinicians would not be expected to uniformly settle on the same diagnostic code for a given patient. Such variations in diagnostic specificity are factors that extend to the epidemiology studies supporting the conclusion of prior VAO committees that there is limited or suggestive evidence of association between PD and exposure to the herbicides sprayed in Vietnam.

In the ICD coding system, several codes are allocated to conditions with constellations of symptoms that are Parkinson-like, but their assignments differ somewhat between the ICD-9 and the ICD-10 classifications, as shown in Table 11-2. The revised coding system has progressed by providing individual codes for specific types of secondary Parkinsonism, which should facilitate VA's processing of claims submitted since the ICD-10 codes became effective on October 1, 2015. Because the veteran is to be given the benefit of the doubt in the claims process, the current committee does not judge it reasonable to exclude from coverage for this presumptively service-related condition any Vietnam veterans with Parkinsonian symptoms unless VA can definitively establish, on a

case-by-case basis, that those symptoms are secondary to an external agent other than the herbicides sprayed in Vietnam or to a specific genetic condition.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the COIs and PD, including Parkinson-like conditions such as Parkinsonism, in the setting of dementia, multiple system atrophy, and progressive supranuclear palsy.

Amyotrophic Lateral Sclerosis

ALS is a progressive, adult-onset, motor neuron disease that presents with muscle atrophy, weakness, and fasciculations and with signs that indicate the involvement of motor neuron pathways in the CNS. The incidence of sporadic ALS is 1–2 per 100,000 person-years, and the incidence of ALS peaks at the ages of 55–75 years (Brooks, 1996). The diagnosis of ALS is made through clinical examination and electrodiagnostic testing and has a high degree of accuracy when performed by experienced neurologists (Rowland, 1998; Rowland and Shneider, 2001).

The cause of most cases of ALS is unknown, but about 5–10 percent of cases are recognized as resulting from inheritance of autosomal dominant or recessive genes (Wood, 2014). One-fifth of familial-ALS patients have mutations in the gene that encodes superoxide dismutase-1 (Rosen et al., 1993). Many other possible etiologic factors have been investigated (Breland and Currier, 1967; Gallagher and Sander, 1987; Hanisch et al., 1976; Kang H et al., 2014; Kurtzke and Beebe, 1980; Mitchell and Borasio, 2007; Roelofs-Iverson et al., 1984; Sutedja et al., 2009a,b; Wang et al., 2014), including military service (Weisskopf et al., 2005), but they have not found conclusive evidence of association with any of the environmental exposures addressed.

Summary of Previous Updates

ALS was first evaluated as a disease that might be associated with the COIs by the committee for *Update 2002*.

Pesticide or herbicide exposure has been associated with an increased risk of ALS, including a doubling of the risk after long-term occupational exposure to pesticides (Deapen and Henderson, 1986) and a tripling after exposure to agricultural chemical products (Savettieri et al., 1991) and herbicides (McGuire et al., 1997), but none of the risk estimates was statistically significant. A population-based case-control study demonstrated associations between exposure to agricultural chemical products and ALS in men, with an OR of 2.4 and a trend with duration of exposure that were both statistically significant (McGuire

TABLE 11-3 Epidemiologic Studies of Pesticide[a] Exposure and Amyotrophic Lateral Sclerosis (Shaded entries are new information for this update)

Reference; Country	Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides[a]	Exposure of Interest/ Estimated Risk (95% CI)	Neurologic Dysfunction
Yi et al., 2014a	290	111,436	Korean Vietnam veterans—self-report and proximity of veteran's military unit to AO-sprayed area	+	Low (158) vs high (132) exposure: HR = 1.3 (1.0–1.6) Log EOI score: HR = 1.1 (1.0–1.1)	Spinal muscular atrophy (G12)
Yi et al., 2014b	17	17,529	Korean Vietnam veterans—vital status and cause of death and proximity of veteran's military unit to AO-sprayed area		Low (9) vs high (8) exposure: HR = 0.8 (0.3–2.2) Log EOI score: HR = 0.9 (0.7–1.2)	Spinal muscular atrophy (G12)
Kamel et al., 2012; US (AHS)	41	84,698	Self-administered questionnaire		Herbicides: 1.6 (0.7–3.7) 2,4-D: 1.0 (0.5–2.1) 2,4,5-T: 1.3 (0.5–3.2)	ALS cases identified via linkage with National Death Index
Pamphlett, 2012; Australia (follow-up to Morahan and Pamphlett, 2006)	614	778	Questionnaire	+	Herbicide/pesticide exposure: Men: 1.8 (1.3–2.4) Women: 1.4 (1.0–2.0)	Self-reported and fulfilled probable or definite revised El Escorial criteria
Morahan and Pamphlett, 2006; Australia	179	179	Questionnaire—exposure to environmental toxicants	+	Herbicide, pesticide exposure: 1.6 (1.0–2.4); industrial exposure: 5.6 (2.1–15.1)	Self-reported
ADVA, 2005c; Australia	nr	nr	Deployment to Vietnam	+	4.7 (1.0–22.8)	

Weisskopf et al., 2005	nr	nr	Self-administered questionnaire	+	1.5 (1.1–2.1); p = 0.007	Self-reported military services, death certificates
Burns et al., 2001; US	1,567	40,600	Industrial hygienist ranked jobs for exposure to 2,4-D to derive years of exposure and cumulative exposure	+	3.45 (1.1–11.1)	Death certificates
McGuire et al., 1997; US	174	348	Self-reported lifetime job history, workplace exposures reviewed by panel of four industrial hygienists	+	Herbicide exposure: 2.4 (1.2–4.8); significant trend analysis for dose–effect relationship with agricultural chemicals: p = 0.03	New diagnosis of ALS 1990–1994 in western Washington state
Chancellor et al., 1993; Scotland	103	103	Required regular occupational exposure to pesticides for 12 months or more		1.4 (0.6–3.1)	Scottish Motor Neuron Register
Savettieri et al., 1991; Italy	46	92	Continual exposure to agricultural chemicals		3.0 (0.4–20.3)	Cases reviewed by neurologists
Deapen and Henderson, 1986; US	518	518	Ever worked in presence of pesticides		2.0 (0.8–5.4)	ALS Society of America

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AHS, Agricultural Health Study; ALS, amyotrophic lateral sclerosis; AO, Agent Orange; CI, confidence interval; EOI, Exposure Opportunity Index; HR, hazard ratio; nr, not reported.

[a]For the objective of the VAO review series, only associations with herbicides are of possible relevance; only phenoxy herbicides, cacodylic acid, and picloram are of specific interest.

et al., 1997). A mortality study of Dow Chemical Company employees exposed to 2,4-D found three deaths from ALS with a significant positive association (RR = 3.45, 95% CI 1.10–11.11) (Burns et al., 2001). Morahan and Pamphlett (2006) published an Australian case-control study in which the cases were self-reported and the controls chosen in non-random fashion. The authors found an increased risk of ALS after exposure to pesticides or herbicides, but the lack of appropriate case and control ascertainment and the fact that specific COIs were not identified make the results of this study difficult to interpret. Weisskopf et al. (2005) followed the vital status of status of subjects in the American Cancer Society's cohort for the Cancer Prevention Study II and demonstrated an increased risk of ALS in those who served in any of the armed services during times of conflict. They adjusted for a variety of confounding variables in their model, including exposure to herbicides, and found that none of them significantly altered their conclusions; thus, this large study indirectly suggests the lack of a strong effect of herbicide exposure on ALS risk. Finally, a case-control study of Australian Vietnam veterans reported an association between deployment in Vietnam and ALS (ADVA, 2005c) but did not specifically study exposure to pesticides or herbicides. Weisskopf et al. (2009) found no association between self-reported pesticide or herbicide exposure in the American Cancer Society's Cancer Prevention Study II, but the lack of exposure specificity and the possibility of exposure estimation error limit the weight of this evidence.

Table 11-3 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies Too few cases of ALS mortality were observed by Kang HK et al. (2014) in the study of female Vietnam-era veterans for a calculation of the relative risks comparing the deployed and non-deployed women.

In the Korean Veterans Health study, Yi et al. (2014b) determined the vital status and cause of death through 2005 for 180,639 Korean veterans who were alive in 1992. Individual EOI scores were derived based on the proximity of the veteran's unit to given areas when herbicides were sprayed, which were partitioned into high- and low-exposure groups. No association was found between spinal muscular atrophy [ICD-10 G12] and the EOI scores (HR = 0.94, 95% CI 0.74–1.18) and when the high-exposure group was contrasted with the low-exposure group (HR = 0.80, 95% CI 0.29–2.15).

In the study of disease prevalence among the Korean Vietnam veterans, after adjusting for age, rank, smoking, drinking, physical activity, domestic use of herbicides, education, income, and BMI, Yi et al. (2014a) found the risk for spinal muscular atrophy showed signs of slight elevation in both the analysis of the scores as a continuous variable (OR = 1.06, 95% CI 1.00–1.12) and for the two-group comparison (OR = 1.27, 95% CI 1.00–1.61). The more specific diagnosis of motor neuron disease [ICD-10 G12.2], which includes ALS, had nearly

the same risk estimate, but because these cases represented only about one-third of those in the entire G12 grouping, the CIs were wider for the scores (OR = 1.04, 95% CI 0.94–1.14) and for the comparison of the high- and low-exposure groups (OR = 1.24, 95% CI 0.83–1.85).

Occupational Studies Since the last update, Malek et al. (2014) compared 66 ALS patients to 66 controls, administering a questionnaire on occupational, vocational, and avocational exposures. Self-reported pesticide exposure was associated with ALS (OR = 3.17, 95% CI 1.27–7.93). This association was more robust after controlling for smoking and education in a multivariate model (OR = 6.50, 95% CI 1.78–23.77). Additional analyses conducted on occupational exposure to insecticides, to herbicides, or to fungicides and fumigants, individually, found no associations with ALS, but the sample sizes were very small. None of the results is based on sufficiently specific exposure metrics to be fully informative for VAO purposes.

Environmental or Case-Control Studies Since *Update 2012*, no new environmental or case-control studies have been published concerning ALS and exposure to the COIs.

Biologic Plausibility

Several studies have addressed mechanisms of neurotoxicity that might be ascribed to COIs, notably 2,4-D and TCDD. The molecular effects of the COIs are described in Chapter 4. Some of those effects suggest possible pathways by which the COIs could disrupt neuronal systems. A number of the studies suggest that the COIs have had neurologic effects in animal models when exposure occurred during development. There also are studies that suggest ROS could alter specific signaling cascades and be involved in neurodegeneration. Although they do not specifically concern the COIs, such studies are potentially relevant inasmuch as TCDD and herbicides have been reported to elicit oxidative stress (Celik et al., 2006; Shen et al., 2005). The mechanistic studies suggest avenues that might be pursued to determine linkages between the COIs and neurologic outcomes that could result in adult humans. No toxicology studies concerning exposure to the COIs and ALS have been published since *Update 2006*.

A general summary of the biologic plausibility of neurologic effects of exposure to the COIs is presented at the beginning of this chapter.

Synthesis

Although there is overall limited evidence of an association between pesticides and ALS in broad terms, the published studies to date have had low power to detect associations, which has resulted in numerous studies with wide CIs and

non-significant ORs for exposure to the COIs. Four studies have been published since *Update 2012*, but these do not indicate a consistent association between herbicides as a class, or specifically 2,4-D or 2,4,5-T, and ALS.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that the evidence of an association between exposure to the COIs and ALS remains inadequate or insufficient.

Alzheimer Disease

Alzheimer disease is a progressive, neurodegenerative form of dementia that is characterized by memory loss, confusion, mood changes, social withdrawal, and deteriorating judgment. The course of the disease is divided into four stages—pre-dementia, early, moderate, and advanced—depending on the level of cognitive and functional impairment. Diagnosis typically occurs in people over 60 years old as symptoms develop, although pre-dementia and early AD are occasionally seen in people as young as 30 years old. AD is the sixth-leading cause of death in the United States and the fifth-leading cause of death in people over 65 years old (Singh et al., 2012). In 2012, an estimated 5.4 million Americans were living with the diagnosis. Mean life expectancy is 7 years after an AD diagnosis; about 3 percent of people who receive the diagnosis live 14 years or more (Alzheimer's Association, 2012). Although the etiology of the disease remains elusive, suspected risk factors for AD include diet, exposure to aluminum or solvents, and genetics (Chin-Chan et al., 2015; de la Monte and Ming, 2014; Tanner et al., 2014).

Summary of Previous Updates

Update 2012 was the first VAO update to address AD directly. Until that time literature searches had not identified epidemiologic studies that assessed the possible association of AD with exposure to the specific COIs. However, an association with exposure to the broad classification of "pesticides" had been investigated. Because AD is a condition of considerable interest to aging Vietnam veterans, for that update the committee members thought it appropriate to present the small amount of peripherally related available information. In doing so, they revisited two publications that include inadequately specific exposure characterizations that were mentioned briefly in *Update 2002* (Gauthier et al., 2001) and *Update 2004* (Baldi et al., 2003). Gauthier et al. (2001) found that long-term exposure to herbicides and insecticides was not significantly related to the development of AD. In a study by Baldi et al. (2003), pesticide exposure (including herbicides, insecticides, and fungicides together) was defined on the

basis of job histories. A significant association between pesticide exposure and AD was found in men (RR = 2.39, 95% CI 1.02–5.63), but not in women (RR = 0.89, 95% CI 0.49–1.62). On the basis of the evidence reviewed in *Update* 2012, the committee concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and AD.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies Since the last update, the Korean Veterans Health Study (Yi et al., 2014b) was published. In this study, 180,639 Korean veterans were followed for vital status and cause of death. The EOI scores were based on the temporal proximity of the veteran's unit to herbicide-sprayed areas. There was no association between AD [ICD-10 G30] and the EOI scores analyzed as a continuous variable (HR = 0.87, 95% CI 0.60–1.25) or between the high- and low-exposure groups (HR = 0.86, 95% CI 0.17–4.31).

In the study of disease prevalence among the Korean Vietnam veterans, after adjustiing for age, rank, smoking, drinking, physical activity, domestic use of herbicides, education, income, and BMI, Yi et al. (2014a) found the risk for AD to be elevated in both the analysis of the scores as a continuous variable (OR = 1.12, 95% CI 1.02–1.23) and the two-group comparison (OR = 1.64, 95% CI 1.12–2.41).

Environmental Studies The Canadian Study of Health and Aging has been monitoring more than 10,000 Canadian men and women who were at least 65 years old when this random sample was assembled in 1991. Clinical examinations were conducted on a portion of the full sample in 1991–1992 (n = 2,914), 1996–1997 (n = 2,914), and 2001–2002 (n = 2,914), with blood samples being drawn from a subset of these groups (422, 1,312, and 385, respectively). The study population addressed by Medehouenou et al. (2014) consisted of the 2,023 subjects for whom blood was available and who had a firm diagnosis of having dementia (n = 574, of which 399 were specifically diagnosed with AD) or not (n = 1,449). Among the 10 PCB congeners measured in the serum analyses were the mono-ortho PCBs 105, 118, and 156, which exhibit dioxin-like activity only to a modest extent. Two models were applied to the data; the first adjusted for time of age, sex, education, blood draw, total plasma lipids, and ApoE4, and the second additionally adjusted for BMI, alcohol and tobacco use, rural or urban residence, and a vascular score. Of the 10 PCBs analyzed, only PCBs 105 and 118 showed an inverse association with dementia overall in the first model (OR = 0.87, 95% CI 0.77–0.99; OR = 0.86, 95% CI 0.74–0.99, respectively), but adjustment for additional confounders in the second model eliminated the effect (OR = 0.90, 95% CI 0.79–1.02; OR = 0.88, 95% CI 0.76–1.02, respectively). Thus, no relationship with AD specifically was seen for any of the PCBs using either model.

Occupational and Case-Control Studies No occupational or case-control studies addressing exposure to the COIs and AD have been published since *Update 2012*.

Biologic Plausibility

There has been little toxicologic investigation of adult exposure to the COIs and endpoints relevant to AD.

A general summary of the biologic plausibility of neurologic effects of exposure to the COIs is presented at the beginning of this chapter.

Synthesis

The findings in the Korean Vietnam Veterans Study (Yi et al., 2014a,b) are the first in which the risk of AD has been investigated in association with a fully relevant exposure, but its findings for prevalence and mortality are not entirely consistent. The only relevant findings in Medehouenou et al. (2014) are for the mono-ortho PCBs 105, 118, and 156, which have only weak dioxin-like activity. The preliminary results of a "protective" effect against dementia in general for PCBs 105 and 118 vanished with an adjustment for additional possible confounders, so this study contributes little to deciding whether AD is associated with the COIs.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and AD.

CHRONIC PERIPHERAL SYSTEM DISORDERS

The peripheral neuropathies are an array of disorders caused by damage to nerve fibers (axonal neuropathies) or to the myelin sheath that surrounds many fibers (demyelinating neuropathies). Manifestations of neuropathy can include a combination of sensory changes, weakness, and autonomic instability. Clinically, various forms of peripheral neuropathy can be characterized by the distribution of nerve abnormalities and their patterns of progression.

Peripheral neuropathy resulting from toxic exposure usually affects nerve fibers in a symmetric pattern, beginning distally in the longest fibers (in the toes) and moving proximally (toward the spine). This kind of neuropathy is called symmetric axonal sensorimotor polyneuropathy. Sensory deficits begin at the toes, progress above the ankles, and only later affect the hands. Motor symptoms show the same general pattern. Physiologically, various forms of peripheral neuropathy

can be characterized by results of electrodiagnostic testing to indicate which neural structures are affected. Most toxicant-induced neuropathies involve injury to the nerve-cell bodies or the axons, giving rise to changes in the amplitude of a nerve's response to an electric stimulus.

The clinical mainfestations of most symmetric axonal neuropathies are similar except for variation in the rates of progression and in whether pain is prominent. No specific signature distinguishes a toxicant-related neuropathy from one induced by other causes. As many as 30 percent of neuropathies are "idiopathic," that is, no etiology is determined despite exhaustive clinical evaluation.

The most common toxicant-induced neuropathy occurs as a result of chronic alcohol exposure. Peripheral neuropathy also occurs commonly as a complication of diabetes; its reported prevalence in people who have chronic diabetes is up to 50 percent. Thus, it is important to include an assessment of alcohol use and diabetes as covariates in epidemiologic studies because the neuropathies that are related to these conditions are clinically and physiologically indistinguishable from other toxicant-induced neuropathies.

Toxicant exposure can result in early-onset (immediate) peripheral neuropathy or delayed-onset peripheral neuropathy, which occurs years after the external exposure has ended. For classification purposed, the committee considers a neuropathy early onset if abnormalities appear within 1 year after external exposure ends and delayed-onset if abnormalities appear more than 1 year after external exposure ends. A review of the data supporting the association of exposure with early-onset peripheral neuropathy is presented in Appendix B and will not be repeated here. Because the exposures of interest for Vietnam veterans are long past, the immediate effects of the COIs are no longer pertinent for this cohort. The focus of this section will be on data related to delayed-onset peripheral neuropathy.

Summary from *VAO* and Previous Updates

The committee for *Update 2010* decided to move health outcomes that are manifested shortly after exposure to the COIs (TCDD in particular) to an appendix because they are no longer of interest for Vietnam veterans whose exposure occurred decades ago. Early-onset peripheral neuropathy was in this group with chloracne and porphyria cutanea tarda (PCT). That committee, however, noted that early-onset peripheral neuropathy is not necessarily a transient condition, as had been the previous judgment. This means that early-onset peripheral neuropathy may become a chronic condition that should be distinguished from delayed-onset peripheral neuropathy.

Henceforth, this section will address only studies of delayed-onset peripheral neuropathy.

A study by the Centers for Disease Control (now the Centers for Disease Control and Prevention [CDC]); (CDC, 1988b) reported a slight excess in the signs or symptoms of peripheral neuropathy among deployed versus non-deployed

Vietnam-era veterans. Decoufle et al. (1992) reported no association between self-reported exposure to herbicides in Vietnam and peripheral neuropathy.

There was no indication of an increased incidence of peripheral neuropathy in the first examination, which established the baseline for Ranch Hand veterans (AFHS, 1984a). A peer-reviewed article described the peripheral-neuropathy data on the AFHS cohort (Michalek et al., 2001c). In a primary analysis, the investigators had included diabetes as a potential confounder in the statistical model. In a secondary analysis, the subjects who had conditions that were known to be associated with neuropathy were excluded, and the subjects who had diabetes were enumerated. In both analyses, there were strong and significant associations between dioxin concentrations and possible and probable neuropathy, and significant trends were found with increasing concentrations of dioxin. However, there were too few nondiabetic subjects to produce useful estimates of risk in the absence of the contribution of diabetes. Thus, questions remained about the specific association between exposure to the COIs and peripheral neuropathy in the absence of any effect of diabetes. The large veteran studies are limited by the confounding nature of concurrent diabetes and alcohol exposure, both of which are also related to neuropathy.

Lee et al. (2008) evaluated the association of exposure to a variety of toxicants to the presence of neuropathy in subjects who had either frank diabetes or impaired glucose tolerance. Concentrations of dioxin-like PCBs were ranked, and those subjects who had hemoglobin A1C levels of greater or less than 7 were compared separately. In neither group was there evidence of an increased incidence of neuropathy or of a dose–response relationship that suggested a concentration-dependent risk of neuropathy. Given the underlying risk of neuropathy inherent in patients who have diabetes, the lack of information regarding the duration of diabetes and the small numbers of subjects render this study difficult to evaluate.

Update of the Scientific Literature

Vietnam-Veteran Studies

In the study of disease prevalence among the Korean Vietnam veterans, after adjusting for age, rank, smoking, drinking, physical activity, domestic use of herbicides, education, income, and BMI, Yi et al. (2014a) found that the risk for polyneuropathies of the PNS [ICD-10 G60–G64] to be slightly elevated in both the analysis of the scores as a continuous variable (OR = 1.02, 95% CI = 1.01–1.03) and the two-group comparison (OR = 1.09, 95% CI = 1.04–1.13).

Occupational, Environmental, and Case-Control Studies

No occupational, environmental, or case-control studies addressing exposure to the COIs and chronic peripheral neuropathy have been published since *Update 2012*.

Biologic Plausibility

No new toxicity studies directly pertinent to the COIs and peripheral neuropathy were identified in the present update. However, it is worth reiterating findings from earlier updates. Neuronal cell cultures treated with 2,4-D showed decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis (Rosso et al., 2000a,b). The normal activity of those target processes is important for maintaining synaptic connections between nerve cells and supporting the mechanisms involved in axon regeneration during recovery from peripheral neuropathy. Grahmann et al. (1993) and Grehl et al. (1993) reported observation of, respectively, electrophysiologic and pathologic abnormalities in the peripheral nerves of rats treated with TCDD. When the animals were sacrificed 8 months after exposure, there was pathologic evidence of persistent axonal nerve damage and histologic findings typical of toxicant-induced injury. These results constitute evidence of biologic plausibility for an association between exposure to the COIs and peripheral neuropathy.

A general summary of the biologic plausibility of neurologic effects arising from exposure to the COIs is presented at the beginning of this chapter.

Synthesis

The committee concludes that the evidence reviewed here does not support an association between exposure to COIs and the development of delayed-onset chronic neuropathy. The findings of the large study of Korean Vietnam veterans were small and non-compelling.

Conclusions

The committee for *Update 2010* concluded that, in addition to evidence supporting an association for transient early-onset peripheral neuropathy, there is limited or suggestive evidence of an association between exposure to the COIs and early-onset peripheral neuropathy that may be persistent.

On the basis of the evidence reviewed to date, however, the present committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and delayed-onset chronic neuropathy.

HEARING LOSS

Hearing loss increases markedly with age, and about one-fourth of people over 70 years old are affected (NCHS, 2010). Its prevalence is somewhat higher in men than in women (NCHS, 1994). The most common forms of hearing impairment in adults are presbycusis and tinnitus. Heritable factors may influence the susceptibility to hearing loss, but external agents can also contribute. Aspirin at high doses can cause reversible tinnitus, and permanent hearing loss may be induced by pharmaceuticals (particularly antibiotics and antineoplastic drugs) and by some environmental and industrial chemicals (primarily solvents and metals). In occupational medicine, hearing loss is most often regarded as noise-induced. Cochlear development may be impaired by the hypothyroidism associated with exposures to endocrine disruptors (Howdeshell, 2002), but such a gestational effect would not pertain to Vietnam veterans exposed to herbicides as adults.

Summary from *VAO* and Previous Updates

Epidemiologic results on hearing loss in relation to service in Vietnam or to herbicide exposure more generally were first discussed in *Update 2010*. The literature searches for that report found two citations that addressed this health outcome. O'Toole et al. (2009) re-examined the health status of a cohort of Australian Vietnam veterans; as for almost every health endpoint surveyed in that group, the incidences of self-reported complete or partial deafness and of tinnitus showed statistically significant increases compared to the general population. The committee for *Update 2010* had serious concerns that the results reported in O'Toole et al. (2009) were compromised by recall bias and other methodologic problems. Excesses in self-reported hearing loss were also found among licensed pesticide applicators in the AHS at the time of the 5-year follow-up interview (Crawford et al., 2008), but this effect was associated with insecticide exposure, not with herbicide use.

Update of the Epidemiologic Literature

No epidemiologic studies addressing herbicide exposure and hearing loss have been published since *Update 2012*.

Biologic Plausibility

Although no studies of hearing loss in adult animals directly exposed to the COIs were found, Crofton and Rice (1999) reported that perinatal maternal PCB 126 exposure resulted in low-frequency hearing deficits in the offspring of exposed maternal rats. Increased auditory thresholds occurred in the group treated at 1.0 µg/kg/day for 0.5- and 1-kHz tones, but higher frequencies were

not significantly affected. The frequency-specific deficit was hypothesized to be secondary to postnatal hypothyroxinemia that occurred during a sensitive period for development of the low-frequency regions of the cochlea. This conclusion was consistent with that hypothesis that pups from the study were found to have decreased serum T4 concentrations on postnatal day 21. It is important to note that PCB 126 is a potent dioxin-like compound, having one-tenth the toxic potency of TCDD (see Chapter 4).

A general summary of the biologic plausibility of neurologic effects arising from exposure to the COIs is presented at the beginning of this chapter.

Synthesis

Two prior studies observed increased prevalence of hearing loss in Vietnam veterans and pesticide applicators, but neither was able to examine exposure specifically to the COIs or to confirm hearing loss clinically. Furthermore, the report from the AHS (Crawford et al., 2008) observed an association only in insecticide applicators, not in herbicide applicators. The O'Toole study evaluated Vietnam veterans, but it used the general population as a comparison group, not veterans from the same era who were not deployed to Vietnam, so it could not distinguish between hearing loss that may be associated with noise-related to military service and hearing loss potentially associated with exposures to toxic chemicals. In the absence of new studies, the synthesis remains unchanged since *Update 2010*.

Conclusion

On the basis of the evidence reviewed here, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and hearing loss.

12

Cardiovascular and Metabolic Outcomes

Chapter Overview

Based on new evidence and a review of prior studies, the committee for Update 2014 *found no new associations between the relevant exposures and adverse cardiovascular or metabolic outcomes. The current committee concurs that the current evidence supports the findings of the committees for earlier updates concerning cardiovascular and metabolic outcomes:*

- *No adverse cardiovascular or metabolic outcome has sufficient evidence of an association with the chemicals of interest.*
- *There is limited or suggestive evidence of an association between the chemicals of interest and type 2 diabetes, hypertension, ischemic heart disease, and stroke.*
- *There is inadequate or insufficient evidence to determine whether there is* a*n association between the chemicals of interest and any other adverse cardiovascular or metabolic outcome.*

This chapter summarizes and presents conclusions about the strength of the evidence from epidemiologic studies regarding an association between exposure to the chemicals of interest (COIs)—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid—and type 2 diabetes and circulatory disorders. The committee also considers studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like chemicals (DLCs) to be informative if their results were reported in terms of TCDD toxic equivalents

(TEQs) or concentrations of specific congeners. Although all studies reporting TEQs based on PCBs were reviewed, those studies that reported TEQs based only on mono-ortho PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given very limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the World Health Organization (WHO) revised toxic equivalency factors (TEFs) of 2005 (La Rocca et al., 2008; van den Berg et al., 2006).

TYPE 2 DIABETES

Diabetes mellitus is a group of heterogeneous metabolic disorders characterized by hyperglycemia and a quantitative or qualitative deficiency in insulin action (Orchard et al., 1992) and classified as E08–E13 by the 10th revision of the *International Classification of Diseases* (ICD-10). Although all forms of diabetes share hyperglycemia, the pathogenic processes involved in the development of the various types of diabetes differ. Most cases of diabetes mellitus are in one of two categories: Type 1 diabetes [ICD-10 E10] is characterized by a lack of insulin caused by the destruction of insulin-producing cells in the pancreas (β cells), and type 2 diabetes [ICD-10 E1] is characterized by a combination of resistance to the actions of insulin and inadequate secretion of insulin (called relative insulin deficiency). In old classification systems, type 1 diabetes was called insulin-dependent diabetes mellitus or juvenile-onset diabetes mellitus, and type 2 was called non–insulin-dependent diabetes mellitus or adult-onset diabetes mellitus. Type 1 diabetes occurs as a result of the immunologically mediated destruction of β cells in the pancreas, which often occurs during childhood but can occur at any age. As in many autoimmune diseases, genetic and environmental factors both influence pathogenesis. Some viral infections are believed to be important environmental factors that can trigger the autoimmunity associated with type 1 diabetes. The modern classification system recognizes that type 2 diabetes can occur in children and can require insulin treatment. Long-term complications of both types can include cardiovascular disease (CVD), nephropathy, retinopathy, neuropathy, and increased vulnerability to infections. Keeping blood sugar concentrations within the normal range is crucial for preventing complications.

About 90 percent of all cases of diabetes mellitus are of type 2, and type 2 has been the type of diabetes that epidemiologic investigations relevant to Vietnam veterans have addressed. Onset can occur before the age of 30 years, and incidence increases steadily with age. The main risk factors are age, obesity, abdominal fat deposition, a history of gestational diabetes (in women), physical inactivity, ethnicity (prevalence is greater in blacks and Hispanics than in whites), and family history. The relative contributions of those features are not known. Prevalence and mortality statistics in the US population for 2009–2010 are presented in Table 12-1.

TABLE 12-1 Prevalence of and Mortality from Diabetes, Lipid Disorders, and Circulatory Disorders in the United States, 2009/2010

ICD-9 Range	Diseases of Circulatory System	Prevalence (% of Americans 20 years old and older)		Mortality (number of deaths, all ages)	
		Men	Women	Men	Women
250	Diabetes	nr	nr	38,324	35,507
	Physician-diagnosed	9.0[a]	8.0[a]	nr	nr
	Undiagnosed	4.4[a]	2.4[a]	nr	nr
	Prediabetes	42.4[a]	28.4[a]	nr	nr
	Lipid disorders				
	Total cholesterol ≥ 200 mg/dL	40.4	44.9	nr	nr
	Total cholesterol ≥ 240 mg/dL	11.6	14.4	nr	nr
	LDL cholesterol ≥ 130 mg/dL	31.0	32.0	nr	nr
	HDL cholesterol < 40 mg/dL	28.9	10.4	nr	nr
390–459	All circulatory disorders	36.4	33.7	388,606	398,035
390–398	Rheumatic fever and rheumatic heart disease	nr	nr	nr	nr
401–404[b]	Hypertensive disease	33.5	31.7	29,363	35,760
401	Essential hypertension	nr	nr	nr	nr
402	Hypertensive heart disease	nr	nr	nr	nr
403	Hypertensive renal disease	nr	nr	nr	nr
404	Hypertensive heart and renal disease	nr	nr	nr	nr
410–414, 429.2	Ischemic, coronary heart disease	7.6	5.0	206,908	168,387
410, 412	Acute, old myocardial infarction	4.0	1.8	66,765[a]	53,140[a]
411	Other acute, subacute forms of ischemic heart disease	nr	nr	nr	nr
413	Angina pectoris	3.4	3.2	nr	nr
414	Other forms of chronic ischemic heart disease	nr	nr	nr	nr
429.2	Cardiovascular disease, unspecified	nr	nr	nr	nr
415–417[b]	Diseases of pulmonary circulation	nr	nr	nr	nr
420-429	Other forms of heart disease (such as pericarditis, endocarditis, myocarditis, cardiomyopathy)	nr	nr	nr	nr
426–427	Arrhythmias	nr	nr	nr	nr
428	Heart failure	2.3	2.2	24,609	33,700
430–438[b]	Cerebrovascular disease (such as hemorrhage, occlusion, transient cerebral ischemia; includes mention of hypertension in ICD-401)	2.6	2.7	52,335	76,597
440–448[b]	Diseases of arteries, arterioles, capillaries	nr	nr	nr	nr

continued

TABLE 12-1 Continued

ICD-9 Range	Diseases of Circulatory System	Prevalence (% of Americans 20 years old and older)		Mortality (number of deaths, all ages)	
		Men	Women	Men	Women
451–459	Diseases of veins, lymphatics, other diseases of circulatory system	nr	nr	nr	nr

NOTE: dL, deciliter; HDL, high-density lipoprotein; ICD, *International Classification of Diseases*; LDL, low-density lipoprotein; nr, not reported.

[a]For all ages.

[b]Gap in ICD-9 sequence follows.

SOURCE: AHA, 2015.

The etiology of type 2 diabetes is unknown, but three major components have been identified: peripheral insulin resistance (thought by many to be primary) in target tissues (muscle, adipose tissue, and liver), a defect in β-cell secretion of insulin, and the overproduction of glucose by the liver. In states of insulin resistance, insulin secretion is initially higher for each concentration of glucose than in people who do not have diabetes. That hyperinsulinemic state is a compensation for peripheral resistance and in many cases keeps glucose concentrations normal for years. Eventually, β-cell compensation becomes inadequate, and there is a progression to overt diabetes with concomitant hyperglycemia. Why the β-cells cease to produce sufficient insulin is not known.

Pathogenic diversity and diagnostic uncertainty are among the important problems associated with the epidemiologic study of diabetes mellitus. There are multiple pathogenic mechanisms that are likely to play a role in the development of diabetes mellitus, including various genetic susceptibilities (as varied as autoimmunity and obesity) and all sorts of potential environmental and behavioral factors (such as viruses, nutrition, and activity). The multiplicity of contributing factors can lead to various responses to particular exposures. Because up to half the cases of diabetes are undiagnosed, the potential for ascertainment bias in population-based surveys is high (with more intensively followed groups or those with more frequent health care contact being more likely to get the diagnosis); this points to the need for formal standardized testing (to detect undiagnosed cases) in epidemiologic studies.

Scientists have named a clustering of cardiovascular risk factors—including hypertension, hyperglycemia, high triglycerides, abdominal obesity, and low high-density lipoprotein—as the "metabolic syndrome." Although it is not a disease entity itself, metabolic syndrome is associated with a five-fold increased risk of type 2 diabetes and a doubling of the risk of CVD (Alberti et al., 2009). There is a growing literature on the association between the COIs and metabolic syndrome and its components. Given its strong linkage with type 2 diabetes, new

literature that deals with metabolic syndrome as an outcome will be discussed primarily in this section.

Conclusions from *VAO* and Previous Updates

The committee responsible for *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*[1] (*VAO*; IOM, 1994) concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and diabetes mellitus. Additional information available to the committees responsible for *Update 1996* (IOM, 1996) and *Update 1998* (IOM, 1999) did not change that conclusion.

In 1999, in response to a request from the Department of Veterans Affairs, the Institute of Medicine called together a committee to conduct an interim review of the scientific evidence regarding type 2 diabetes. That review focused on information published after the deliberations of the *Update 1998* committee and resulted in the report *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (*Type 2 Diabetes*; IOM, 2000). The committee responsible for that report determined that there was limited or suggestive evidence of an association between exposure to at least one COI and type 2 diabetes. The committees responsible for *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), *Update 2004* (IOM, 2005), *Update 2006* (IOM, 2007), *Update 2008* (IOM, 2009), *Update 2010* (IOM, 2012), and *Update 2012* (IOM, 2014) upheld that finding.

Reviews of the pertinent studies are found in the earlier reports. Table 12-2 presents a summary.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Since *Update 2012*, epidemiologic publications emanated from two different study populations of veterans—female US Vietnam-era veterans and Korean Vietnam veterans.

Kang et al. (2014) reported on the mortality experience of women who served in the US military during the Vietnam era (July 4, 1965–March 28, 1973) who deployed to Vietnam (n = 4,734), served near Vietnam (n = 2,062), or were non-deployed (n = 5,313). Approximately two-thirds of the female Vietnam-era veterans were nurses, who perhaps experienced higher herbicide exposure than those deployed to Vietnam with other job assignments. The total and cause-specific

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

TABLE 12-2 Selected Epidemiologic Studies—Diabetes and Related Health Outcomes (Shaded entries are new information for this update)

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
AFHS—follow-up through 2004			Michalek and Pavuk, 2008
Calendar period in Vietnam			
During or before 1969	130	1.7 (p = 0.005)	
Background (serum TCDD ≤ 10 ppt)	39	1.3 (0.8–2.0)	
Low (10–91 ppt)	40	1.9 (1.2–2.9)	
High (> 91 ppt)	51	2.0 (1.3–3.1)	
After 1969	50	0.9 (p = 0.45)	
Spraying during tour			
≥ 90 days	170	1.3 (p = 0.04)	
Background (serum TCDD ≤ 10 ppt)	42	1.0 (0.7–1.4)	
Low (10–91 ppt)	60	1.5 (1.0–2.0)	
High (> 91 ppt)	68	1.6 (1.1–2.2)	
< 90 days	10	0.6 (p = 0.12)	
AFHS—Ranch Hand–comparison subject pairs—within-pair differences; lower Ranch Hand insulin sensitivity with greater TCDD levels			Kern et al., 2004
1997 examination (29 pairs)		(p = 0.01)	
2002 examination (71 pairs)		(p = 0.02)	
Air Force Ranch Hand veterans (n = 343)	92	ns	
AFHS—comparison veterans only, OR by quartiles of serum dioxin concentration			Longnecker and Michalek, 2000[b]
Quartile 1: < 2.8 ng/kg	26	1.0	
Quartile 2: 2.8–< 4.0 ng/kg	25	0.9 (0.5–1.7)	
Quartile 3: 4.0–< 5.2 ng/kg	57	1.8 (1.0–3.0)	
Quartile 4: ≥ 5.2 ng/kg	61	1.6 (0.9–2.7)	
AFHS—through 1992 examination cycle Ranch Hand veterans—high-exposure group			Henriksen et al., 1997[b]
Glucose abnormalities	60	1.4 (1.1–1.8)	
Diabetes prevalence	57	1.5 (1.2–2.0)	
Use of oral medications for diabetes	19	2.3 (1.3–3.9)	
Serum insulin abnormalities	18	3.4 (1.9–6.1)	

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (7/1/1965–3/28/1973)		**All COIs**	
Incidence— Self-reported diabetes diagnosed by doctor			
CATI survey of stratified sample: 1,499 deployed (795 with TCDD measured) vs 1,428 non-deployed (102 with TCDD measured)			Kang et al., 2006
Deployed vs non-deployed	226	1.2 (0.9–1.5)	
Sprayed herbicides in Vietnam (n = 662) vs never (n = 811)	123	1.5 (1.1–2.0)	
Mortality—diabetes			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)	27	1.8 (0.7–4.4)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray	ns	2.2 (0.6–8.0)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Follow-up—deployed vs non-deployed			CDC, 1988a
Interviewed—self-reported diabetes	155	1.2 ($p > 0.05$)	
Subset with physical examinations			
Self-reported diabetes	42	1.1 ($p > 0.05$)	
Fasting serum glucose		Geometric means 93.4 vs 92.4 mg/dL ($p < 0.05$)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Mortality			
Through 2010—Vietnam-era veterans	33	0.7 (0.4–1.5)	Kang et al., 2014
Vietnam nurses only	25	1.0 (0.4–2.2)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	

continued

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Incidence			
Validation Study— Expected number of exposed cases (95% CI)			
Men		*Cases expected*	CDVA, 1998a[b]
Self-report of doctor's diagnosis (proportion of respondents)	2,391 (6%)	1,780 (1,558–2,003)	
Women		*Cases expected*	CDVA, 1998a[b]
Self-report of doctor's diagnosis (proportion of respondents)	5 (2%)	10 (9–11)	
Mortality			
All branches, return–2001	55	0.5 (0.4–0.7)	ADVA, 2005a
Navy	12	0.5 (0.3–0.9)	
Army	37	0.5 (0.4–0.7)	
Air Force	6	0.5 (0.2–1.0)	
1980–1994			CDVA, 1997a
Sample of 1,000 Male Australian Vietnam Veterans–prevelance		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey	55	1.0 (0.8–1.3)	O'Toole et al., 2009
641 interviewed 1990–1993 vs respondents to 1989–1990 national survey (self-report of doctor diagnosis)	12	1.6 (0.4–2.7)	O'Toole et al., 1996b
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Mortality 1966–2001	6	0.3 (0.1–0.7)	ADVA, 2005c
Korean Vietnam Veterans		**All COIs**	
Korean veterans of Vietnam era: 1,224 deployed vs 154 non-deployed—incidence	154	2.7 (1.1–6.7)	Kim JS et al., 2003
Korean Vietnam Veterans Health Study—on basis of individual EOI scores categorized as high or low exposure [ICD-10]		**All COIs**	
Prevalence (2000–2005)			Yi et al., 2014a
Categorized high (n = 42,421) vs low (n = 69,305)			
All diabetes [E10–E14]	12,942 vs 19,891	1.0 (1.0–1.1) p = 0.006	
Type 1 diabetes [E10]	2,099 vs 2,981	1.1 (1.0–1.2) p = 0.001	

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Type 2 diabetes [E11]	10,881 vs 16,725	1.0 (1.0–1.1) p = 0.015	
OR per unit of $\log_{10}$ EOI (n = 111,726)			
All diabetes [E10–E14]	32,833	p = 0.014	
Type 1 diabetes [E10]	5,080	p = 0.120	
Type 2 diabetes [E11]	27,606	p = 0.029	
Mortality (1992–2005)			Yi et al., 2014b
All diabetes [E10–E14]			
Categorized high (n = 85,809) vs low (n = 94,442)	376 vs 327	1.0 (0.9–1.2) p = 0.859	
HR per unit of $\log_{10}$ EOI (n = 180,639)	703	p = 0.414	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Diabetes—mortality	33	2.3 (0.5–9.5)	Vena et al., 1998
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (*not* part of IARC)		**Focus on TCDD**	
Incidence			
BASF workers potentially exposed to TCDD following an accident involving trichlorophenol		p = 0.06	Ott et al., 1994
Through 1989 (n = 158 men exposed within 1 yr of accident vs 161 other BASF employees 1953–1969)	10	0.5 (0.2–1.0)	Zober et al., 1994
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
TCP production workers			
(Preliminary) NIOSH Cross-Sectional Medical Study		**Dioxin/phenoxy herbicides**	
Workers exposed to 2,4,5-T, derivatives			Calvert et al., 1999[b]
Serum TCDD pg/g of liquid			
< 20	7	2.1 (0.8–5.8)	

continued

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
20–75	6	1.5 (0.5–4.3)	
75–238	3	0.7 (0.2–2.6)	
238–3,400	10	2.0 (0.8–4.9)	
Dioxin-exposed workers in two chemical plants		1.1 (p = < 0.003)	Sweeney et al., 1997/1998
NIOSH/Ranch Hand Comparison—Ranch Hand veterans, workers exposed to TCDD-contaminated products compared with unexposed comparison cohorts		**Dioxin/phenoxy herbicides**	
Ranch Hands	147	1.2 (0.9–1.5)	Steenland
Workers	28	1.2 (0.7–2.3)	et al., 2001
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Highly exposed industrial cohort (n = 5,132)			Steenland
Diabetes as underlying cause	26	1.2 (0.8–1.7)	et al., 1999[b]
Diabetes among multiple causes	89	1.1 (0.9–1.3)	
Chloracne subcohort (n = 608)	4	1.1 (0.3–2.7)	
Dioxin exposed workers—mortality[c]			Steenland
Diabetes as underlying cause	16	1.1 (0.6–1.8)	et al., 1992[b]
Diabetes among multiple causes	58	1.1 (0.8–1.4)	Sweeney
NIOSH production workers	26	1.6 (0.9–3.0)	et al., 1992
Monsanto Plant—Nitro, WV		**Dioxin/phenoxy herbicides**	
2.4.5-T, TCP production workers with chloracne	22	2.3 (1.1–4.8)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	16	1.1 (0.6–1.8)	Collins et al., 2009b
1940–1982 (n = 2,187 men)	4	0.7 (0.2–1.9)	Cook et al., 1987
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	18	0.8 (0.5–1.2)	
PCP and TCP (n = 720)	8	1.1 (0.5–2.2)	
PCP (no TCP) (n = 1,402)	10	0.6 (0.3–1.2)	

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Dow PCP Production Workers (1937–1989 in Midland, MI) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins; 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	8	1.1 (0.5–2.2)	Collins et al., 2009a
Mortality 1940–1989 (n = 770)	4	1.2 (0.3–3.0)	Ramlow et al., 1996
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
Czechoslovakia Production Workers—Production workers admitted to hospital in Prague	11	**2,4,5-T, TCP** nr	Pazderova-Vejlupkova et al., 1981
German Production Workers—West German chemical production workers	nr	**Dioxin, phenoxy herbicides** nr	Von Benner et al., 1994
Japanese Waste-Incinerator Workers—Workers exposed to PCDD at municipal waste incinerator	8	**Dioxin, phenoxy herbicides** nr, but ns	Kitamura et al., 2000
United Kingdom Production Workers—TCP production workers	2	**Dioxin, phenoxy herbicides** nr	May, 1982
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 yr, mortality through July 1985	9	1.4 (0.7–2.7)	Henneberger et al., 1989
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916 men), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Self-reported incidence diabetes in 13,637 wives of licensed applicators (10 yr follow-up) (adjusted HR)			Starling et al., 2014
Ever use of 2,4,5-T or 2,4,5-TP	19	1.6 (1.0–2.5)	
Ever use of 2,5-D	185	1.1 (0.9–1.3)	

continued

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Self-reported incidence diabetes (1999–2003) in licensed applicators			Montgomery et al., 2008
2,4-D	73	0.9 (0.8–1.1)	
2,4,5-T	28	1.0 (0.9–1.2)	
Self-reported gestational diabetes in wives of licensed applicators			Saldana et al., 2007
Documented exposure during 1st trimester		ORs read from graph	
2,4-D	10	~1.0 (ns)	
2,4,5-T	3	~5 ($p < 0.05$)	
2,4,5-TP	2	~7 ($p < 0.05$)	
Dicamba	7	~3 ($p \sim 0.06$)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	98	0.5 (0.3–0.5)	
Spouses (n = 676)	42	0.4 (0.3–0.6)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	26	0.3 (0.2–0.5)	
Spouses of private applicators (> 99% women)	18	0.6 (0.4–1.0)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
Children residing in Seveso at time of incident—development of diabetes			Baccarelli et al., 2005b
101 with chloracne	1	nr	
211 without chloracne	2	nr	
Mortality			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
Zone A	3	1.0 (0.3–3.1)	
Zone B	26	1.3 (0.9–1.9)	
Zone R	192	1.3 (1.1–1.5)	
20-yr follow-up to 1996			Bertazzi et al., 2001
Zones A and B—men	6	0.8 (0.3–1.7)	
Zones A and B—women	20	1.7 (0.1–2.7)	
15-yr follow-up to 1991—men			Bertazzi et al., 1998[b]
Zone B	6	1.2 (0.5–2.7)	
15-yr follow-up to 1991—women			Bertazzi et al., 1998[b]
Zone A	2	1.8 (0.4–7.0)	
Zone B	13	1.8 (1.0–3.0)	

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
15-yr follow-up to 1991			Pesatori et al., 1998[b]
Zone R men	37	1.1 (0.8–1.6)	
Zone R women	74	1.2 (1.0–1.6)	
Seveso (Italy) Women's Health Study—981 women who were infants to 10–40 yrs of age when exposed—incidence		**TCDD**	
806 women with serum TCDD levels from 1976 followed through 2009			Warner et al., 2013
Diabetes —Log10 TCDD (ppt)	54	0.8 (0.5–1.3)	
Metabolic syndrome —Log10 TCDD (ppt)	172	1.1 (0.8–1.4)	
≤ 12 yrs of age	16	2.0 (1.3–3.3)	
> 12 yrs of age	156	1.0 (0.7–1.4)	
National Health and Nutrition Examination Survey		**Dioxin, dl PCBs**	
NHANES 1999–2004—2,588 participants (Total TEQ)			Everett and Thompson, 2014
Diabetes with nephropathy		2.4 (1.6–3.5)	
Diabetes without nephropathy		1.4 (1.1–1.9)	
NHANES 1999–2002 participants			Everett et al., 2007
Total diabetes (self-report or HbA1c > 6.1%)			
HxCDD (TEF = 0.1)			
> 42.0–99.1 pg/g		1.8 (1.1–2.8)	
> 99.1 pg/g		2.0 (0.9–4.4)	
PCB 126 (TEF = 0.1)			
> 31.3–83.8 pg/g		1.7 (1.0–2.7)	
> 83.8 pg/g		3.7 (2.1–6.5)	
NHANES 1999–2002 participants			Lee DH et al., 2006
HpCDD > 90th percentile vs nondetectable	46	2.7 (1.3–5.5)	
OCDD > 90th percentile vs nondetectable	31	2.1 (0.9–5.2)	
Anniston (AL) Community Health Survey—774 residents of Anniston, AL, an area with high level of PCBs		**PCBs**	
Association between diabetes and PCB levels in serum	202		Silverstone et al., 2012
Dioxin TEQs		1.2 (0.9–2.0)	
Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)—Prospective (cross-sectional) study of residents (≥ 70 yrs of age) living in Uppsala, Sweden between April 2001 and June 2004 (n = 989; 725 in diabetes analysis)		**Polychlorinated biphenyls, PCBs**	

continued

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Risk elevations compared to the lowest exposure quintiles:			Lee DH et al., 2011b
Second quintile, PCB 105		5.2 (1.3–84.4)	
Fourth quintile, PCB 118		10.7 (1.1–25.5)	
Fourth quintile, PCB 157		3.5 (1.0–12.4)	
Third quintile, PCB 189		3.5 (1.0–11.9)	
Coronary Artery Risk Development in Young Adults (CARDIA) Study		**Pesticides, PCBs**	
Nested case-control study within CARDIA study, relationship between persistant organic pollutants and type 2 diabetes (nested cases = 90 of 116 study participants who provided blood samples in 1987/88 exam and later developed diabetes)			Lee DH et al., 2010
Quartile 1 of PCB 156 (model 2, adjusted)		Referent	
Quartile 2		1.3 (0.5–3.5)	
Quartile 3		0.9 (0.3–2.6)	
Quartile 4		0.8 (0.2–2.9)	
Quartile 1 of PCB 157 (model 2, adjusted)		Referent	
Quartile 2		1.0 (0.4–2.5)	
Quartile 3		0.5 (0.2–1.5)	
Quartile 4		0.5 (0.1–1.7)	
Quartile 1 of PCB 167 (model 2, adjusted)		Referent	
Quartile 2		0.9 (0.4–2.2)	
Quartile 3		1.0 (0.4–2.5)	
Quartile 4		0.5 (0.2–1.3)	
Other Environmental Studies			
BELGIUM			
Belgium residents (142 women, 115 men) exposed to dioxin, PCBs		**Dioxin, PCBs**	Fierens et al., 2003a
Subjects in top decile for dioxin		5.1 (1.2–21.7)	
CANADA			
Fasting plasma levels (pg/ml) from non-diabetic, obese, postmenopausal women from Montreal—36 "metabolically healthy" vs 40 "metabolically abnormal," categorized on the basis of insulin sensitivity		**dl PCBs, OCDD**	Gauthier et al., 2014
Sum PCBs 105, 118, 156, 157, 189		$p < 0.001$	
OCDD		$p = 0.161$	
Population-based survey in Saskatchewan	28	**Herbicides** nr	Masley et al., 2000

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman	5	0.7 (0.1–1.0)	
Spouses	5	0.8 (0.3–1.9)	
GREENLAND			
Survey of Greenland Inuit—cross-sectional study		**dl PCBs**	Jørgensen et al., 2008
Quartile of dl PCBs (compared to Q1)		Adjusted prevalence OR	
Quartile 2		1.6 (0.6–4.1)	
Quartile 3		1.9 (0.7–5.1)	
Quartile 4		1.2 (0.4–3.2)	
JAPAN			
235 participants in the Saku Control Obesity Program (n = 15 participants with diabetes)—Association between PCB congener levels and definite diabetes		**PCBs**	Tanaka et al., 2011
PCB 118 and definite diabetes (total lipids)		1.0 (0.9–1.1)	
PCB 156 and definite diabetes (total lipids)		1.5 (0.9–2.7)	
Total dioxin (pg TEQ/g lipid)		**Dioxin**	Uemura et al., 2008a
≥ 20.00–31.00	17	2.1 (0.9–5.4)	
≥ 31.00	39	3.8 (1.6–10.1)	
2,216 Japanese from general population not occupationally exposed to dioxins, aged 15–76 yrs in 2002–2008		**Total Serum TEQ**	Nakamoto et al., 2013
Diabetes	113		
Quartile 1		1.0	
Quartile 2		8.9 (1.7–160)	
Quartile 3		14.0 (2.8–260	
Quartile 4		23.0 (4.6–430)	
		p-trend < 0.0001	
TAIWAN		**Dioxin, phenoxy herbicides**	
Residents around 12 municipal waste incinerators—prevalence of physician-diagnosed diabetes with TEQs for serum PCDD/Fs in logistic model adjusted for age, sex, smoking, BMI	29	2.4 (0.2–31.9)	Chen HL et al., 2006

continued

TABLE 12-2 Diabetes and Related Health Outcomes, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
UNITED STATES		**dl PCBs**	
Great Lakes sport fish consumers—cross sectional study		Adjusted prevalence OR	
Sum of dl PCBs			
< limit of detection		Reference	
0.2–0.3 ng/g lipid		1.2	
0.3–1.6 ng/g lipid		2.1 ($p < 0.05$) p-trend = 0.03	
Vertac/Hercules Superfund site residents (n = 62)—OR for high insulin in nondiabetic subjects at various times, levels for TCDD > 15 ppt compared with persons with TCDD < 15 ppt		**TCDD**	Cranmer et al., 2000[b]
Fasting (insulin > 4.5 µIU/ml)	3	8.5 (1.5–49.4)	
30-min (insulin > 177 µIU/ml)	3	7.0 (1.3–39.0)	
60-min (insulin > 228 µIU/ml)	4	12 (2.2–70.1)	
120-min (insulin > 97.7 µIU/ml)	6	56 (5.7–556)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, 2,4-dichlorophenoxypropanoic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; ACC, Army Chemical Corps; AFHS, Air Force Health Study; BMI, body-mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; EOI, Exposure Opportunity Index; HbA1c, hemoglobin A1c; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; HR, hazard ratio; HxCDD, 1,2,3,6,7,9-hexachlorodibenzo-*p*-dioxin; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; IU, international unit; MCPA, 2 methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; ml, milliliter; MOS, military occupational specialty; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupation Safety and Health; nr, not reported; ns, not significant; OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDD/Fs, chlorinated dioxins and furans combined; PCP, pentachlorophenol; pg/g, picogram per gram; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ppt, parts per trillion; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEF, toxicity equivalency factor; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]Given when available; results other than estimated risk explained individually.

[b]Study is discussed in greater detail in *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (IOM, 2000).

[c]Includes some subjects covered in other references cited in the category occupational cohorts.

mortality experience of these cohorts through 2010 (a mean of 37 years of follow-up) was ascertained through the National Death Index and a review of death certificates. When adjusted for age, race, military service duration, officer status, and nursing status, the relative risk of diabetes mortality was non-significantly lower for the female veterans deployed to Vietnam cohort compared with their non-deployed counterparts (relative risk [RR] = 0.72, 95% confidence interval [CI] 0.35–1.49). When this comparison was restricted to nurses only, the adjusted relative risk of diabetes mortality was effectively the same for deployed and non-deployed nurses (RR = 0.96, 95% CI 0.42–2.20). Thus, this study did not find evidence in support of an association between female veteran service in Vietnam and the risk of diabetes mortality.

An exceptionally large epidemiologic study of Korean veterans who served in the Vietnam War reported on diabetes prevalence (Yi et al., 2014a) and mortality (Yi et al., 2014b). In addition to exposure categories based on questionnaire responses concerning the veterans' own perceptions of their exposure to Agent Orange (or more precisely, the military herbicides sprayed in Vietnam), an objective quantification of potential herbicide exposure was calculated for each veteran using time and location information on his military unit from Korean military records as input to the Exposure Opportunity Index (EOI) model (Stellman et al., 2003b) based on US records of herbicide spray missions. For the purposes of this VAO update, exposure categorizations based on the EOI scores and validated reports of health outcomes are considered more reliable, and so the committee's evaluation focused on them in favor of self-reported measures.

For more than 111,000 Korean Vietnam veterans alive in 2000, Yi et al. (2014a) ascertained the prevalence of diabetes as validated by Korea National Health Insurance claims data through September 2005 by objective proximity-based assessment of exposure. With adjustment for age, rank, smoking, drinking, domestic herbicide exposure, physical activity, education, income, and BMI, the risk of type 2 diabetes [ICD-10 E11] mellitus was nominally higher for those with a high potential for herbicide exposure than for those with low EOI scores (odds ratio [OR] = 1.04, 95% CI 1.01–1.07). Adjusted for the same factors, logistic regression on the individual log-transformed EOI scores found a small, but marginally significant association ($p = 0.029$) for veterans with non–insulin-dependent diabetes mellitus. The findings for type 1 diabetes [ICD-10 E10] and for all forms of diabetes mellitus [ICD-10 E10-14] were effectively the same.

For 180,639 Korean Vietnam veterans, Yi et al. (2014b) ascertained mortality status and, when applicable, the underlying cause of death from the records of the National Statistical Office for 1992–2005. When examining diabetes mortality using the same categories of high- and low-potential herbicide exposure derived from the objective proximity-based EOI scores and adjustment for age at cohort entry (as of January 1, 1992) and military rank during service in Vietnam, high exposure (compared with low exposure) was not associated with mortality from all forms of diabetes [ICD-10 E10–E14] (HR = 0.99, 95% CI 0.85–1.15).

Occupational Studies

Starling et al. (2014) reported on a new analysis from the Agricultural Health Study (AHS), a large prospective cohort study of pesticide applicators and their spouses in Iowa and North Carolina. At enrollment, the subjects had been asked to report the number of years and average number of days per year that they personally mixed or applied particular pesticides. The herbicides 2,4,5-T and 2,4,5-TP were combined into a single variable because of their similar chemical structures and use patterns in the cohort and because both had been contaminated with TCDD at some time. A total of 45 pesticides were examined for possible association with a self-report of diabetes (type not specified, but type 2 would be expected among adults diagnosed during the 10 years following enrollment). The other COIs (picloram, cacodylic acid, and TCDD) were not examined. The subjects of this analysis were farmers' wives who had reported personally mixing or applying pesticides (n = 13,637). With adjustment for the state of residence and body mass index (BMI) at enrollment and using a binary classification of "ever use," the herbicide 2,4,5-T or 2,4,5-TP was associated with an increased risk of developing diabetes (HR = 1.59, 95% CI 1.00–2.51), whereas ever use of 2,4-D, which was much more prevalent than that of 2,4,5-T or 2,4,5-TP, was not associated with risk of diabetes (HR = 1.07, 95% CI 0.90–1.27). This study provides limited evidence suggestive of an association between exposure to the phenoxy herbicides and an increased risk of diabetes.

Environmental Studies

Warner et al. (2013) addressed the development of diabetes or metabolic syndrome between 1976 and 2009 in an updated analysis of the Seveso Women's Health Study. The members of this study population had been newborn to 40-year-old residents of Seveso, Italy, at the time of a major chemical explosion in 1976, which resulted in the highest known residential exposures to TCDD. This study, which has been reviewed in detail in previous VAO reports, made use of serum samples collected soon after the accident. The analysis of the occurrence of diabetes with respect to serum TCDD levels measured in the samples gathered in 1976 included 981 women. With adjustment for alcohol consumption, waist circumference, and family history, logarithms of the TCDD levels were non-significantly, inversely associated with development of diabetes (HR = 0.76, 95% CI 0.45–1.28). Similarly, the development of the metabolic syndrome in relation to the TCDD levels was evaluated with adjustment for age at interview, physical activity, family history, and medication use that might increase glucose levels. When all 806 women who had provided a fasting blood sample in 2008 were included, no association was evident (HR = 1.05, 95% CI 0.78–1.43). When this analysis was stratified by age at the time of the explosion, however, the serum TCDD levels of the 538 women who were at least 12 years of age at the time of

the explosion were not associated with the development of metabolic syndrome (OR = 0.96, 95% CI 0.68–1.35), while for those who were less than 12 years of age at the time of the explosion, the odds ratio per 10-fold increase in serum TCDD was associated with future development of metabolic syndrome (OR = 2.03, 95% CI 1.25–3.30). In summary, this analysis indicated no association between serum TCDD levels and development of diabetes in women, but an apparent association with future development of the metabolic syndrome when the female subjects had been exposed at a young age (< 12 years).

Nakamoto et al. (2013) conducted a cross-sectional study of 1,063 men and 1,201 women (aged 15–76 years) who were living throughout Japan and not occupationally exposed to dioxins from 2002 through 2010. Individual blood levels were measured for all dioxin, furan, and PCB congeners on the 2005 WHO list of DLCs. Quartiles were derived based on weight (picogram [pg]/g lipid) for individual congeners and for several groups of DLCs. With adjustments for age, sex, smoking, drinking, region, survey year, and BMI, a strong dose–response relationship was found between having a history of diabetes mellitus and all DLCs ($p < 0.0001$) and also the grouped dioxin-like dioxins and furans ($p = 0.002$) and the grouped dioxin-like PCBs ($p < 0.0001$). Although the prevalence of diabetes was low in this cohort (5.1 percent), persons in the upper quartile for all DLCs had 23-fold increased odds of having developed diabetes (95% CI 4.6–430) compared with persons in the lowest quartile. Although the evidence is indirect for TCDD itself, this study provides substantial evidence of dioxin-like activity being associated with the prevalence of diabetes.

Gauthier et al. (2014) studied 76 nondiabetic, obese (BMI > 30) postmenopausal women who had been subjects in two clinical studies conducted in Montreal from 2003 to 2007, in which information on cardiometabolic risk factors had been gathered. The participants were characterized as either metabolically healthy (n = 36) or metabolically abnormal (n = 40) based on an assessment of their insulin sensitivity. Among the persistent pollutants measured in fasting plasma samples were five mono-ortho dioxin-like PCBs 105, 118, 156, 157, and 189 (TEF = 0.00003) and a single dioxin (octachlorodibenzodioxin [OCDD]), which has 10 times more dioxin-like activity (TEF = 0.0003). The levels of OCDD did not differ between the two groups ($p = 0.161$). However, individually the levels of the dioxin-like PCBs were each significantly higher in the metabolically abnormal group than in the metabolically healthy group, as was the case for the sum of their levels ($p < 0.001$). This small study provides evidence that higher levels of dioxin-like PCBs in obese women are associated with lower insulin sensitivity.

Everett and Thompson (2014) examined the relationship between dioxins and dioxin-like PCBs and the prevalence of diabetes, stratified by separating those with and without nephropathy. The analysis was based on blood samples and self-report data on health status collected from the 1999–2004 National Health and Nutrition Examination Survey (NHANES, n = 2,588). Of the DLCs on the 2005 WHO list, 6 of the 7 polycholorinated dibenzo-*p*-dioxins (PCDDs),

9 of the 10 polychlorinated dibenzofuran (PCDFs), and 8 of the 12 PCBs were examined. For the 8 of these 23 DLCs with a reading that was at least 25 percent above the limit of detection, individual analyses on log-transformed TEQs were performed with adjustment made for age, sex, race, education, income, diet, physical activity, and family history. For diabetes without nephropathy, an association was evident for three of these eight DLCs, and the risk based on total TEQs was significantly elevated (OR = 1.44, 95% CI 1.11–1.87). For diabetes with nephropathy, seven of these eight DLCs were statistically associated, and the risk based on total TEQs was even more strongly elevated (OR = 2.35, 95% CI 1.57–3.52). These data are consistent with there being an association between serum levels of chlorinated compounds with dioxin-like activity and the prevalence of diabetes overall.

Case-Control Studies

No case-control studies of exposure to the COIs and type 2 diabetes have been published since *Update 2012*.

Biologic Plausibility

Several biologic mechanisms that have been studied in cell culture and animal models may explain the potential diabetogenic effects of TCDD in humans. TCDD is known to modify the expression of genes related to insulin transport and signaling and to inflammation (Kim MJ et al., 2012). In previous *VAO* updates, several studies have been reviewed that support the postulate that TCDD is mechanistically implicated in an increased risk of insulin resistance and the development of diabetes. C Wang et al. (2011) found that mice that lacked the aryl hydrocarbon receptor (AHR knockouts) had enhanced insulin sensitivity and glucose tolerance; this suggested that the AHR has a physiologic function in glucose metabolism and supported the speculation that sustained activation of the AHR by DLCs could contribute to diabetes. That would be consistent with results of a previous study by Kurita et al. (2009), who found that exposing mice to dioxin significantly reduced insulin secretion after a glucose challenge. In an in vitro study of differentiated adipocytes, TCDD significantly reduced insulin-stimulated glucose uptake (Hsu et al., 2010). Thus, the mechanisms associated with insulin signaling and glucose uptake may contribute to the diabetogenic effects of TCDD observed in humans.

Among the studies included in the current literature review, Kim et al. (2014) explored the relationships between 14 organochlorine insecticides and 22 PCBs in visceral adipose tissue and subcutaneous adipose tissue in 50 patients with or without type 2 diabetes who underwent surgery for either cancer or benign liver or gallbladder lesions. The researchers reported that persistent organic pollutants (POPs) in visceral or subcutaneous fat were significantly associated with both

diabetes and insulin resistance. These findings are consistent with experimental animal studies that have reported that exposure to POP mixtures through contaminated fish oil induces a severe impairment of whole-body insulin action (e.g., Ibrahim et al., 2011). Thus, on balance, there is biological plausibility of the COIs being causally implicated in the development of insulin resistance and diabetes.

Synthesis

A considerable amount of new evidence reviewed and considered by the committee in forming its judgment included studies on two sets of Vietnam veterans—female US Vietnam veterans and a very large group of Korean veterans who served in Vietnam, a report from the AHS with pesticide-specific information, an update from the Seveso Women's Health Study, and three additional environmental studies of DLCs.

The new reports on mortality in cohorts of Vietnam veterans showed no association between herbicide exposure and diabetes mortality, but epidemiologic evidence on diabetes mortality is generally of limited usefulness as an endpoint because it is the complications of diabetes, rather than diabetes itself, that are most often listed as the cause of death of those who have the disease, so many cases of diabetes would be missed if mortality data were used. However, the prevalence analyses on the Korean Vietnam veterans were quite supportive of there being an association between the herbicides sprayed in Vietnam and the occurrence of diabetes. Although self-reported use of 2,4-D was not associated with a risk of diabetes in the new AHS, the findings for 2,4,5-T and 2,4,5-TP are fully consistent with there being an increased risk of developing diabetes following exposure to TCDD-contaminated phenoxy herbicides. The new report from the Seveso Women's Health Study found no association between serum TCDD levels and the development of diabetes or the metabolic syndrome among those who were beyond puberty when exposed. Because all troops serving in Vietnam were in young adulthood or older at the time of exposure, this study is generally not supportive of an association between exposure to TCDD specifically and the future risk of diabetes. The three new studies examining exposure to compounds with dioxin-like activity provide indirect evidence suggestive of TCDD being potentially associated with the prevalence of diabetes and insulin resistance.

In the aggregate, the newly added studies support prior VAO committees' inclusion of diabetes in the limited and suggestive category.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee reaffirms its conclusion that there is limited or suggestive evidence of an association between exposure to at least one of the COIs and diabetes.

CIRCULATORY DISORDERS

This section covers a variety of conditions encompassed by the 9th and 10th revision of the ICD [ICD-9 390–459 and ICD-10 I00–I99, respectively], such as hypertension [ICD-9 401–404; ICD-10 I10–I13], ischemic heart disease (IHD) [ICD-9 410–414; ICD-10 I20–I25], heart failure [ICD-9 428; ICD-10 I50], cerebrovascular disease [ICD-9 430–438; ICD-10 I60–I69], and peripheral vascular disease [ICD-9 443; ICD-10 I73]. *Coronary heart disease* is related specifically to atherosclerosis; *ischemic heart disease* is broader and typically includes atherosclerosis and its symptoms. The American Heart Association reports mortality related to coronary heart disease, not to its symptoms, which include angina and myocardial infarction. Table 12-1 contains estimates of the prevalence of and mortality from individual disorders of the circulatory system in the US population in 2009–2010.

Circulatory diseases are a group of diverse conditions, of which hypertension, coronary heart disease, and stroke are the most prevalent, with these three conditions accounting for 75 percent of all deaths from circulatory diseases in the United States. In addition to family history, the major risk factors for circulatory diseases include age, race, smoking, serum cholesterol, BMI or percentage of body fat, and diabetes. Ideally, epidemiologic investigations of circulatory diseases would consider the conditions in this category separately rather than together because they have different patterns of occurrence and many have different etiologies. However, many mortality studies follow the ICD-9 rubric and report deaths from circulatory diseases together. Deaths from coronary or ischemic heart disease, heart failure, and, to a lesser extent, stroke predominate. Many of the reports also break out subcategories such as cerebrovascular disease and hypertension. The relative importance of heart failure is determined by the age of the cohort. In younger cohorts, most of the deaths in this category are expected to be from IHD. Cerebrovascular deaths are deaths from strokes, which can be classified as either ischemic or hemorrhagic. In the US population, the great majority of strokes are of the ischemic type.

The methods used in morbidity studies can involve the direct assessment of the circulatory system, including the analysis of symptoms or history, a physical examination of the heart and peripheral arteries, ultrasound measurements of the heart and arteries, electrocardiography (ECG), chest radiography, cardiac computed tomography (CT), and, more recently, cardiac magnetic resonance imaging (MRI). Ultrasonography, CT, and MRI can be used to visualize the heart and related vasculature directly. ECG can be used to detect heart conditions and abnormalities, such as arrhythmias (abnormal heart rhythms), heart enlargement, and heart attacks (myocardial infarctions). Chest radiography can be used to assess the consequences of IHD and hypertension, such as the enlargement of the heart seen in heart failure. It is sometimes difficult to determine the time of onset of clinical findings, so the temporal relationship between exposure and disease

occurrence may be uncertain. CVD epidemiologists prefer to observe cohorts over time for the incidence of discrete clinical events, such as acute myocardial infarction (ideally verified on the basis of changes in ECG readings and enzyme concentrations) and death due to heart disease. The onset of new angina symptoms or the performance of a revascularization procedure in a person who has no history of disease is also used as evidence of incident disease. In many occupational studies, only mortality information is available. The attribution of death to a vascular cause is often based on a death certificate, the accuracy of which can be uncertain.

The practice of evaluating the evidence on hypertension separately from that on other circulatory diseases was established in *Update 2006*; the separate consideration of IHD began in *Update 2008.* The number of studies with data on stroke and cerebrovascular disease is increasing, so this endpoint can be considered in its own right in this report separately from discussions of "other circulatory diseases."

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and circulatory disorders. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. The previously evaluated studies are summarized in Table 12-3, and those published since *Update 2012* are shaded.

The committee responsible for *Update 2006* reviewed new studies and intensively revisited all the studies related to IHD and hypertension that were discussed in previous updates and concluded that there is limited or suggestive evidence to support an association between exposure to the herbicides used in Vietnam and hypertension. That committee was unable to reach a consensus as to whether that was also the case for IHD, so that outcome remained in the category of inadequate evidence.

After consideration of the relative strengths and weaknesses of the evidence regarding the COIs and IHD and the relevant toxicologic literature, the committee responsible for *Update 2008* judged that the evidence was adequate to advance this health outcome from the "inadequate or insufficient" category into the "limited or suggestive" category, again acknowledging that bias and confounding could not be entirely ruled out. That conclusion was not changed in *Update 2010*.

The committee for *Update 2012* considered new evidence related to the COIs and the occurrence of stroke, and reexamined the literature reviewed by previous committees on this topic. A summary of the studies that committee considered most relevant in its deliberations is presented in Table 12-4. The committee was cognizant of the limitations in the literature, the relative imprecision in the

TABLE 12-3 Selected Epidemiologic Studies—Circulatory Disorders (Shaded entries are new information for this update)[a]

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Through 1999—Ranch Hand personnel (n = 1,262) vs SEA veterans (19,078)—circulatory disease—mortality			*Ketchum and Michalek, 2005*
Ranch Hand subjects vs all SEA veterans			
Pilots and navigators	18	1.1 (0.7–1.8)	Not adjusted for known risk factors
Administrative officers	2	1.8 (0.4–7.8)	
Enlisted flight engineers	6	0.5 (0.2–1.1)	
Ground crew	40	1.7 (1.2–2.4)	
Atherosclerosis	28	1.7 (1.1–2.5)	
Hypertensive disease	2	2.5 (0.6–10.8)	
Stroke	5	2.3 (0.9–6.0)	
Subjects with serum TCDD measures			Adjusted for smoking and family history of heart disease
SEA comparison group	31	1.0	
Background (0.6–10.0 ppt)	8	0.8 (0.4–1.8)	
Low (10.0–29.2 ppt)	12	1.8 (0.9–3.5)	
High (18.0–617.8 ppt)	9	1.5 (0.7–3.3)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (07/01/1965–03/28/1973)		**All COIs**	
Incidence—Self-reported circulatory disorders diagnosed by doctor			
CATI survey of stratified sample: 1,499 deployed (795 with TCDD measured) vs 1,428 non-deployed (102 with TCDD measured)			*Kang et al., 2006* Diagnoses not confirmed by medical record review. Adjusted for age, race, rank, BMI, smoking
Vietnam veterans vs non-Vietnam veterans			
Hypertension requiring medication	496	1.1 (0.9–1.3)	
Heart disease diagnosed by physician	243	1.1 (0.9–1.4)	
Sprayers vs nonsprayers			Serum TCDD levels measured in subset of subjects; self-reported
All (diabetics, nondiabetics)			
Hypertension requiring medication	247	1.3 (1.0–1.6)	
Heart disease diagnosed by physician	129	1.4 (1.1–1.9)	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
All veterans, contribution of spraying to logistic regression model			sprayers had significantly higher concentrations, so that category regarded as valid surrogate for elevated exposure
All (diabetics, nondiabetics)			
Hypertension requiring medication		1.3 (1.1–1.6)	
Heart disease diagnosed by physician		1.5 (1.2–1.9)	
Nondiabetics only			
Hypertension requiring medication		1.2 (1.0–1.5)	
Heart disease diagnosed by physician		1.5 (1.1–2.0)	
Controlling for diabetic status			
Hypertension requiring medication		1.3 (1.0–1.6)	
Heart disease diagnosed by physician		1.5 (1.1–1.9)	
Mortality—Circulatory disorders			
Vietnam veterans vs non-Vietnam veterans—through 2005			*Cypel and Kang, 2010*
Circulatory system disease	184	1.2 (0.9–1.6)	Deaths, causes of deaths from national death registries Adjustment for race, rank duration of service, and age
Hypertension	5	0.9 (0.2–3.9)	
Cerebrovascular disease	27	1.5 (0.7–3.3)	
Sprayers vs nonsprayers (subset studied in Kang et al., 2006)			
Circulatory system disease	ns	1.2 (0.6–2.3)	
Hypertension	ns	2.4 (0.2–28.5)	
Cerebrovascular disease	ns	2.1 (0.4–12.3)	
894 ACC members assigned to Vietnam in 1966–1971—1987 (vs US male population)			*Thomas and Kang, 1990*
Circulatory diseases (ICD 390–458)	6	0.6	Not adjusted for known risk factors
US CDC Vietnam Experience Study— Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Incidence			
Deployed vs non-deployed			*CDC, 1988a*
Hypertension after discharge			Not adjusted for known risk factors
Interviewed	2,013	1.3 ($p < 0.05$)	
Examined	623	1.2 ($p < 0.05$)	
Mortality			
Deployed vs non-deployed (1965–2000)	185	1.0 (0.8–1.2)	*Boehmer et al., 2004*
Circulatory disease			
Year of death			

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
1970–1984	nr	0.6 (0.3–1.2)	Adjusted for
1985–2000 (partition at 1970 arbitrary)	nr	1.1 (0.9–1.3)	age, race, military
Discharged before 1970	nr	0.8 (0.6–1.1)	occupation
Discharged after 1970	125	1.4 (1.0–2.0)	
Ischemic heart disease			
0–15 yrs since discharge	8	0.8 (0.3–1.6)	
> 15 yrs since discharge	117	1.1 (0.9–1.5)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988—mortality (PMR)			*Watanabe and Kang, 1996*
Served in Vietnam vs never deployed to SEA			
Circulatory disease			Not adjusted
Army	5,756	0.97 ($p > 0.05$)	for known risk
Marine Corps	1,048	0.92 ($p < 0.05$)	factors
US VA Study of Male Vietnam Veterans Wounded in Combat		**All COIs**	
Mortality through 1981—US wounded Vietnam veterans vs US men (focus on suicide)			*Bullman and Kang, 1996*
Circulatory disease	246	0.7 (0.6–0.9)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Mortality (deployed vs non-deployed)			
Through 2010—Vietnam-era veterans			*Kang et al., 2014*
Heart disease (angina pectoris, myocardial infarction, coronary artery disease, congestive heart failure) (n = 451)	167	0.8 (0.7–1.0)	
Cerebrovascular disease (total n = 94)	36	0.9 (0.6–1.3)	
Hypertension (total n = 12)	5	0.7 (0.2–2.3)	
Vietnam nurses only			
Heart disease (angina pectoris, myocardial infarction, coronary artery disease, congestive heart failure) (total = 343)	na	0.8 (0.6–1.0)	
Cerebrovascular disease (total n = 68)	na	0.8 (0.5–1.3)	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Hypertension (total n = 8)	na	0.7 (0.2–3.1)	
Through 2004—mortality			*Cypel and Kang, 2008*
Circulatory system diseases			
Vietnam vs non-SEA veterans	129	0.8 (0.6–1.0)	Adjusted for
Nurses only	102	0.8 (0.6–1.0)	duration of service, yr of birth, race
US American Legion Cohort		**All COIs**	
American Legionnaires serving during Vietnam era—morbidity			*Stellman SD et al., 1988b*
Service in SEA vs not, with medically diagnosed			Not age adjusted
High blood pressure	592	1.1 ($p > 0.05$)	
Heart disease	97	1.5 ($p < 0.05$)	Age adjusted
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans—(1958–1973)—mortality (1972–1983); deployed vs non-deployed			*Kogan and Clapp, 1985* (state report)
Deaths 1972–1983 (PMR)			Not adjusted
Circulatory system (except cerebrovascular)	139	0.9 ($p > 0.05$)	for age; VVs thought to be
Cerebrovascular	28	1.1 ($p > 0.05$)	younger
Deaths 1978–1983 (PMR)			Expected less
Circulatory system (except cerebrovascular)	85	0.8 ($p < 0.05$)	"diluted" effect for later time
Cerebrovascular	19	1.6 ($p < 0.05$)	
Wisconsin Vietnam-era veterans—923 white male Vietnam veteran's with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (all diseases of circulatory system)			*Anderson et al., 1986a,b*
White male Vietnam veterans vs:	100		
National population		0.69 ($p < 0.05$)	
State population		0.62 ($p < 0.05$)	
Nonveterans		0.58 ($p < 0.05$)	
All veterans		0.86 ($p > 0.05$)	
Vietnam-era veterans		1.0 (0.8–1.2)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Mortality—All branches, return–2001			
Circulatory disease	1,767	0.9 (0.8–0.9)	*ADVA, 2005a*
1963–1979	186	0.7 (0.6–0.8)	
1980–1990	546	0.9 (0.8–1.0)	Pattern of
1991–2001	1,035	0.9 (0.9–1.0)	increasing
Ischemic heart disease	1,297	0.9 (0.9–1.0)	risks with time
1963–1979	124	0.7 (0.6–0.8)	could indicate
1980–1990	421	1.0 (0.9–1.0)	dissipation of
1991–2001	753	1.0 (0.9–1.1)	healthy warrior
Stroke	223	0.8 (0.7–0.9)	effect
1963–1979	35	0.8 (0.5–1.1)	
1980–1990	59	0.7 (0.5–0.9)	
1991–2001	129	0.8 (0.7–1.0)	
1980–1994			*CDVA, 1997a*
Circulatory disease		1.0 (0.9–1.1)	Not adjusted
Ischemic heart disease		1.0 (0.9–1.1)	for known risk
Cerebral hemorrhage		0.8 (0.5–1.2)	factors
Sample of 1,000 Male Australian Vietnam Veterans–prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey			*O'Toole et al., 2009*
Hypertensive disease	192	1.1 (1.0–1.3)	
Ischemic heart disease			Prevalence
Angina	44	2.3 (1.7–3.0)	ratios
Without angina	59	4.1 (3.1–5.0)	calculated with
Cerebrovascular disease	12	2.4 (1.2–3.5)	age-adjustment
641 interviewed 1990–1993 vs respondents to 1989–1990 national survey			*O'Toole et al., 1996b*
Hypertensive disease	nr	2.2 (1.7–2.6)	
Heart disease	nr	2.0 (0.9–3.1)	
Other circulatory diseases	nr	2.4 (1.6–3.2)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Mortality			
1966–2001			*ADVA, 2005c*
Circulatory disease	208	1.1 (0.9–1.3)	
Ischemic heart disease	159	1.2 (0.9–1.5)	
Stroke	15	0.6 (0.3–1.2)	
1982–1994 (deployed vs non-deployed)			*CDVA, 1997b*

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Circulatory disease	77	1.0 (0.7–1.3)	Not adjusted for known risk factors
Ischemic heart disease	57	1.0 (0.7–1.4)	
Cerebral hemorrhage	3	1.0 (0.1–5.7)	
Other	17	0.9 (0.4–1.7)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975) (coronary heart disease)		**All COIs**	*McBride et al., 2013*
Mortality (1988–2008)	104	0.8 (0.7–1.0)	
Korean Vietnam Veterans Health Study		**All COIs**	
Prevalence (01/2000–09/2005) (n = 111,726)			*Yi et al., 2014a*
Diseases of the circulatory system [I00–I99]			
Categorized high (n = 42,421) vs low (n = 69,305)	25,613 vs 40,518	1.0 (1.0–1.0) p = 0.937	ORs adjusted for age, military rank, smoking, drinking frequency, physical activity, domestic herbicide experience, education, household income, BMI
Hypertensive disease [I10–I13]	19,597 vs 30,701	1.0 (1.0–1.0) p = 0.715	
Essential (primary) hypertension [I10]	18,946 vs 29,619	1.0 (1.0–1.0) p = 0.908	
Ischemic heart disease [I20–I25]	8,044 vs 12,226	1.0 (1.0–1.1) p = 0.025	
Acute myocardial infarction [I21–I23]	1,248 vs 1,891	1.0 (1.0–1.1) p = 0.539	
Heart failure [I50]	1,460 vs 2,156	1.0 (1.0–1.1) p = 0.769	
Stroke [I60–I64]	4,330 vs 6,024	1.1 (1.0–1.1) p < 0.001	
Atherosclerosis [I70]	1,036 vs 1,629	1.0 (0.9–1.1) p = 0.714	
Log EOI scores			
Diseases of the circulatory system [I00–I99]	66,131	p = 0.929	
Hypertensive disease [I10–I13]	50,298	p = 0.704	
Essential (primary) hypertension [I10]	48,565	p = 0.518	
Ischemic heart disease [I20–I25]	20,270	p = 0.012	
Acute myocardial infarction [I21–I23]	3,139	p = 0.699	
Heart failure [I50]	3,616	p = 0.402	
Stroke [I60–I64]	10,354	p < 0.001	
Atherosclerosis [I70]	2,665	p = 0.584	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Mortality (1992–2005) (n = 180,639)			*Yi et al., 2014b*
Diseases of the circulatory system [I00–I99]			
Categorized high (n = 85,809) vs low (n = 69,305)	1,716 vs 1,464	1.0 (1.0–1.1) p = 0.289	HRs adjusted for age at cohort entry, military rank during Vietnam service
Hypertension [I10–I13]	110 vs 82	1.2 (0.9–1.6) p = 0.278	
Ischemic heart disease [I20–I25]	437 vs 406	1.0 (0.9–1.1) p = 0.897	
Acute myocardial infarction [I21]	352 vs 347	0.9 (0.8–1.1) p = 0.383	
Cerebrovascular diseases [I60–I69]	879 vs 739	1.0 (0.9–1.1) p = 0.785	
Log EOI scores	3,180	p = 0.028	
Hypertensive disease [I10–I13]	192	p = 0.108	
Ischemic heart disease [I20–I25]	843	p = 0.729	
Acute myocardial infarction [I21]	699	p = 0.313	
Cerebrovascular diseases [I60–I69]	1,618	p = 0.353	
Korean Vietnam Veterans—morbidity		**All COIs**	*Kim JS et al., 2003*
Deployed vs non-deployed (unadjusted)			Concerns: selection bias, diagnosis quality, low participation, sample pooling made TCDD concentrations useless
Valvular heart disease	8	p = 0.0019	
Congestive heart failure	5	p = 0.5018	
Ischemic heart disease	34	p = 0.0143	
Hypertension	383	2.3 (1.3–4.0)	
Adjusted for age, smoking, alcohol, BMI, education, marital status			
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort— Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992 (ICD-9 390–459)			*Vena et al., 1998*
All male phenoxy herbicide workers			(same dataset as *Kogevinas et al., 1997* [emphasis on cancer])
All circulatory disease (ICD-9)	1,738	0.9 (0.9–1.0)	
Ischemic heart disease (410–414)	1,179	0.9 (0.9–1.0)	
Cerebrovascular disease (430–438)	254	0.9 (0.8–1.0)	
Other diseases of the heart (415–429)	166	1.1 (1.0–1.3)	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
All female phenoxy herbicide workers			
All circulatory disease (ICD-9)	48	1.0 (0.7–1.3)	Not adjusted
Ischemic heart disease (410–414)	24	1.1 (0.7–1.6)	for known risk
Cerebrovascular disease (430–438)	9	0.7 (0.3–1.4)	factors
Other diseases of the heart (415–429)	6	0.9 (0.3–2.0)	
Workers with phenoxy herbicide exposure only			
All circulatory disease (ICD-9)	588	0.9 (0.8–0.9)	
Ischemic heart disease (410–414)	394	0.9 (0.8–0.9)	
Cerebrovascular disease (430–438)	96	0.9 (0.7–1.1)	
Other diseases of the heart (415–429)	32	0.9 (0.8–0.9)	
TCDD-exposed workers			
All circulatory disease (ICD-9)	1,170	0.9 (0.9–1.0)	
Ischemic heart disease (410–414)	789	1.0 (0.9–1.0)	
Cerebrovascular disease (430–438)	162	0.8 (0.7–1.0)	
Other diseases of the heart (415–429)	138	1.2 (1.0–1.4)	
Contribution of TCDD exposure to Poisson regression analysis			Adjusted for age, timing of
All circulatory disease (ICD-9)	1,151	1.5 (1.2–2.0)	exposure
Ischemic heart disease (410–414)	775	1.7 (1.2–2.3)	
Cerebrovascular disease (430–438)	161	1.5 (0.8–2.9)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (*not* included in IARC cohort) (ICD-9)		**MCPA**	
Mortality through 1983 (hypertensive, ischemic heart disease) (401–414, 428–429)	337		*Coggon et al., 1986*
vs national rates		0.8 (0.7–0.9)	
vs rural adjustment		0.9 (0.8–1.0)	
British Production Workers at 4 plants (included in IARC cohort)		**Dioxins, but TCDD unlikely; MCPA**	*Coggon et al., 1991*
Mortality—circulatory disease	74	1.2 (0.9–1.5)	
Plant A (1975–1987)	34	1.7 (adjusted = 1.4, $p \approx 0.05$)	
Plant B (1969–1987)	5	0.95	
Plant C (1963–1987)	12	0.84	
Plant D (1969–1987)	23	0.97	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference/* Comments
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1987 (men only)			*Lynge, 1993*
Incidence 1943–1982			*Lynge, 1985*
Men			
Women			
Mortality			
Mortality 1955–2006			*Boers et al., 2012*
TCDD plasma level (HRs, by tertile)	93	1.2 (1.1–1.3)	
Background (≤ 0.4)	33	—	
Low (0.4–4.1)	6	0.9 (0.4–2.5)	
Medium (4.1–20.1)	6	1.5 (0.6–4.0)	
High (≥ 20.1)	7	2.7 (1.0–7.2)	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort) (ICD-9)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)			*Boers et al., 2012*
Ischemic heart disease (120–125)	60	1.2 (1.1–1.4)	
Cerebrovascular disease (160–167)	24	0.9 (0.7–1.1)	
Mortality 1955–2006			*Boers et al., 2010*
Ischemic heart disease	43	1.2 (0.7–2.0)	
Accident 1963	17	1.6 (0.7–3.6)	HRs adjusted
Main production workers	9	1.0 (0.5–2.2)	for age,
Occasionally exposed	17	1.1 (0.6–2.1)	yr of first
Cerebrovascular disease	17	1.2 (0.4–3.6)	employment.
Accident 1963	2	0.3 (0.1–1.4)	Referent group
Main production workers	5	1.3 (0.4–4.7)	are unexposed workers
Occasionally exposed	10	1.5 (0.5–4.3)	
Mortality 1955–1991 (549 exposed vs 482 unexposed male workers) (ICD-9)			*Hooiveld et al., 1998*
All circulatory disease (390–459)	45	1.4 (0.8–2.5)	
TCDD > 124 ng/kg	nr	1.5 (0.8–2.9)	Adjusted for
Ischemic heart disease (410–414)	33	1.8 (0.9–3.6)	age, timing of
TCDD > 124 ng/kg	nr	2.3 (1.0–5.0)	exposure

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Cerebrovascular disease (430–438)	9	1.4 (0.4–5.1)	
TCDD > 124 ng/kg	nr	0.8 (0.2–4.1)	
Other heart disease (415–429)	3	0.7 (0.1–4.3)	
TCDD > 124 ng/kg	nr	0.4 (0.0–4.9)	
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006			*Boers et al., 2010*
Ischemic heart disease	18	1.6 (0.8–3.1)	HRs adjusted
Main production workers	5	1.7 (0.6–4.6)	for age,
Occasionally exposed	13	1.6 (0.7–3.3)	yr of first
Cerebrovascular disease	7	1.0 (0.4–2.8)	employment
Main production workers	1	0.9 (0.1–7.1)	Referent group
Occasionally exposed	6	1.1 (0.4–3.2)	are unexposed workers
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results (ICD-9)		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992 (circulatory diseases, 390–458)	12	0.7 (0.4–1.3)	*Becher et al., 1996*
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results (ICD-9)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989 (circulatory diseases, 390–458)	3	0.3 (0.1–1.0)	*Becher et al., 1996*
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results (ICD-9)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989 (circulatory diseases, 390–458)	32	0.8 (0.5–1.1)	*Becher et al., 1996*
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (*not* part of IARC)		**Focus on TCDD**	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Mortality—1953–1992			*Ott and Zober, 1996b*
Circulatory diseases	37	0.8 (0.6–1.2)	
< 0.1 estimated TCDD µg/kg bw	13	0.8 (0.4–1.4)	
0.1–0.99	11	1.0 (0.5–1.7)	Reliability of estimated body burden is questionable
≥ 1.0	13	0.8 (0.4–1.3)	
Ischemic heart disease	16	0.7 (0.4–1.1)	
< 0.1 estimated TCDD µg/kg bw	7	0.9 (0.3–1.8)	
0.1–0.99	4	0.7 (0.2–1.7)	
≥ 1.0	5	0.6 (0.2–1.3)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007			*Manuwald et al., 2012*
Men			
Circulatory system disease		1.2 (1.0–1.3)	
Women			
Circulatory system disease		0.7 (0.6–0.9)	
Mortality 1952–1992; estimated blood PCDD, PCDF, TCDD from work history, measured in 190 of 1,189 men, divided into 4 lowest quintiles, top 2 deciles			*Flesch-Janys et al., 1995*
Estimated final PCDD, PCDF, TEQs (ng/kg)			
Circulatory disease (ICD-9 390–459)	156		Gas workers provide a more appropriate comparison group for the data on production workers than the national population data used in *Flesch-Janys, 1997; Flesch-Janys et al., 1998*
1.0–12.2		0.9 (0.6–1.5)	
12.3–39.5		0.9 (0.6–1.5)	
39.6–98.9		1.5 (1.0–2.2)	
99.0–278.5		1.6 (1.1–2.2)	
278.6–545.0		1.6 (1.0–2.6)	
545.1–4,361.9		2.1 (1.2–3.5)	
		p-trend < 0.01	
Ischemic heart disease (ICD-9 410–414)	76		
1.0–12.2		1.0 (0.5–2.0)	
12.3–39.5		1.0 (0.5–1.8)	
39.6–98.9		1.0 (0.5–1.8)	
99.0–278.5		1.1 (0.6–2.0)	
278.6–545.0		1.7 (0.9–3.3)	
545.1–4,361.9		2.7 (1.5–5.0)	
		p-trend < 0.01	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Estimated final TCDD (ng/kg)			
Circulatory disease (ICD-9 390–459)	156		
0–2.8		1.2 (0.8–1.8)	Not adjusted
2.81–14.4		0.9 (0.5–1.4)	for known risk
14.5–49.2		1.4 (0.9–2.0)	factors
49.3–156.7		1.6 (1.1–2.4)	
156.8–344.6		1.5 (1.0–2.4)	
344.7–3,890.2		2.0 (1.2–3.3)	
		p-trend = 0.01	
Ischemic heart disease (ICD-9 410–414)	76		
0–2.8		1.4 (0.8–2.4)	Potential for
2.81–14.4		0.8 (0.4–1.6)	exposure
14.5–49.2		1.2 (0.7–2.2)	misclassification
49.3–156.7		0.9 (0.5–1.8)	
156.8–344.6		1.6 (0.9–3.0)	
344.7–3,890.2		2.5 (1.3–4.7)	
		p-trend < 0.01	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			*McBride et al., 2009*
Ever-exposed workers—stroke	15	1.1 (0.6–1.9)	
Ever-exposed workers—ischemic heart disease	61	1.1 (0.9–1.5)	
Ischemic heart disease:			Adjusted for
TCDD exposure ppt-months			age, sex, hire yr,
0–68.3	14	1.0 (reference group)	birth yr
68.4–475.0	18	1.2 (0.6–2.6)	
475.1–2,088.7	15	1.3 (0.6–2.9)	
2,088.7+	14	0.9 (0.4–2.4)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000			*'t Mannetje et al., 2005*
Circulatory disease	51	1.0 (0.7–1.3)	
Hypertensive disease	0	0.0 (0.0–3.5)	Not adjusted
Ischemic heart disease	38	1.0 (0.7–1.4)	for known risk
All-causes (SMR)	nr	1.0 (0.8–1.2)	factors

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Sprayers 697 men and 2 women on register of New Zealand applicators, 1973–1984			
Mortality 1973–2000			*'t Mannetje et al., 2005*
Circulatory disease	33	0.5 (0.4–0.7)	
Hypertensive disease	1	0.8 (0.0–4.5)	Not adjusted for known risk factors
Ischemic heart disease	22	0.5 (0.3–0.8)	
All-causes (SMR)	nr	0.6 (0.5–0.8)	
(Preliminary) NIOSH Cross-Sectional Medical Study—490 workers from chemical plants in Newark, NJ, and Verona, MO, 1951–1969 (morbidity)		**Dioxin/phenoxy herbicides**	*Calvert et al., 1998*
Verified conditions			
TCDD-exposed (281) vs unexposed (260)			Not adjusted for known risk factors
Myocardial infarction	17	1.3 (0.6–2.8)	
Current systolic hypertension	64	1.1 (0.7–1.6)	
Current diastolic hypertension	77	1.2 (0.8–1.8)	
TCDD effect vs unexposed in logistic model. Self-reported, verified conditions combined			
Myocardial infarction			Adjusted for age, sex, BMI, smoking, drinking, diabetes, triglycerides, total cholesterol, HDL, family history of heart disease, and chemical plant
Serum TCDD < 238 pg/g of lipid	nr	1.1 (0.3–4.5)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.1 (0.2–5.1)	
Hypertension			
Serum TCDD < 238 pg/g of lipid	nr	1.3 (0.9–2.0)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.1 (0.6–1.9)	
Verified conditions			
Current systolic hypertension			
Serum TCDD < 238 pg/g of lipid	nr	1.1 (0.7–1.8)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.2 (0.6–2.3)	
Current diastolic hypertension			
Serum TCDD < 238 pg/g of lipid	nr	1.4 (0.9–2.1)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.0 (0.5–1.9)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997) (ICD-9)		**Dioxins, phenoxy herbicides**	
Through 1993			*Steenland et al., 1999*
Cerebrovascular disease (430–438)	69	1.0 (0.7–1.2)	Not adjusted for known risk factors
Ischemic heart disease (410–414)	456	1.1 (1.0–1.2)	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Chloracne subcohort (n = 608) vs US population; exposure subcohort (n = 3,538)	92		Adjusted for age
< 19 cumulative TCDD	nr	1.0	
19–138	nr	1.2 (0.8–2.0)	
139–580	nr	1.3 (0.8–2.2)	No units given for exposure derived from JEM
581–1,649	nr	1.3 (0.8–2.1)	
1,650–5,739	nr	1.4 (0.9–2.2)	
5,740–20,199	nr	1.6 (1.0–2.6)	
≥ 20,200	nr	1.8 (1.1–2.9) p-trend = 0.05 p-trend log < 0.001	
Monsanto workers (n = 240) involved in 2,4,5-T production (1948–1969) and 163 unexposed workers, results of clinical examination, July 1979—morbidity		**Dioxin, phenoxy herbicides**	*Suskind and Hertzberg, 1984*
Hypertension	70	(p > 0.05)	Adjusted for age
Coronary artery disease	22	(p > 0.05)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)			*Collins et al., 2009b*
Ischemic heart disease	218	1.1 (0.9–1.2)	No adjustment discussed
Cerebrovascular disease	37	1.0 (0.7–1.4)	
March 1955–1977 (n = 884 workers); mortality (ICD-9)			*Zack and Gaffey, 1983*
Circulatory disease (390–458)	92	1.11 (p > 0.05)	Not adjusted for known risk factors
Atherosclerosis and CHD (410–413)	79	1.33 (p > 0.05)	
March 1949–1978 (n = 121); mortality—121 TCP workers with chloracne (ICD-9)			*Zack and Suskind, 1980*
Circulatory disease (390–458)	17	0.68 (p > 0.05)	Not adjusted for known risk factors
Atherosclerosis and CHD (410–413)	13	0.73 (p > 0.05)	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL) (ICD-9)		**2,4,5-T; 2,4,5-TCP**	*Ruder and Yiin, 2011*
1940–2005 (n = 2,122)			
Rheumatic heart disease (390–398)	4	0.6 (0.2–1.6)	
Ischemic heart disease (410–414)	350	1.0 (0.9–1.2)	
Hypertension with heart disease (402, 404)	6	0.4 (0.2–1.0)	
Cerebrovascular disease (430–438)	64	1.0 (0.7–1.2)	
PCP and TCP (n = 720)			
Rheumatic heart disease (390–398)	0	0.0 (0.0–1.9)	
Ischemic heart disease (410–414)	120	1.1 (0.9–1.3)	
Hypertension with heart disease (402, 404)	0	0.0 (0.0–1.0)	
Cerebrovascular disease (430–438)	20	1.0 (0.6–1.5)	
PCP (no TCP) (n = 1,402)			
Rheumatic heart disease (390–398)	4	0.9 (0.3–2.3)	
Ischemic heart disease (410–414)	230	1.0 (0.9–1.1)	
Hypertension with heart disease (402, 404)	6	0.6 (0.2–1.3)	
Cerebrovascular disease (430–438)	44	0.9 (0.7–1.2)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1994 (n = 1,517), circulatory disease			*Burns et al., 2001*
0 yrs latency	158	1.0 (0.8–1.1)	
≥ 20 yrs latency	130	1.1 (0.9–1.2)	
Dow PCP Production Workers (1937–1989 in Midland, MI) (*not* in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)			*Collins et al., 2009a*
Ischemic heart disease	99	1.0 (0.8–1.3)	No adjustment discussed
Cerebrovascular disease	17	0.9 (0.5–1.2)	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Mortality 1940–1989 (n = 770) (ICD-9)			*Ramlow et al., 1996*
Circulatory disease (390–458)	115	1.0 (0.8–1.1)	
Arteriosclerotic heart disease (410–413)	86	1.0 (0.8–1.3)	
Cerebrovascular disease (430–438)	15	1.0 (0.6–1.7)	
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
Japanese Waste-Incinerator Workers—Workers exposed to PCDD at municipal waste incinerator		**Dioxin, phenoxy herbicides**	*Kitamura et al., 2000*
Hypertension by PCDD, PCDF	14 of 94	No increases observed	Adjusted for age, BMI, smoking
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			*McLean et al., 2006*
Exposure to nonvolatile organochlorine compounds—circulatory disease (mortality)			Not adjusted for known risk factors
Never	2,727	0.9 (0.8–1.0)	
Ever	2,157	1.0 (1.0–1.0)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Italian rice growers with documented phenoxy use, 1960–1980)—mortality (1957–1992) (n = 1,487)		**Phenoxy herbicides**	*Gambini et al., 1997*
Myocardial infarction	67	0.7 (0.6–0.9)	
Other ischemic heart diseases	72	0.4 (0.3–0.5)	
Stroke	155	1.0 (0.8–1.1)	
THE NETHERLANDS			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980		**Herbicides**	
Through 2000			*Swaen et al., 2004*
Circulatory disease	70	0.7 (0.5–0.9)	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference/* Comments
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916 men), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Study of myocardial infarction			*Mills et al., 2009*
Mortality among 54,069 male applicators			
2,4-D	73	0.9 (0.7–1.1)	Adjusted for age, state, smoking. Incidence analysis further adjusted for BMI
2,4,5-T	32	1.0 (0.8–1.2)	
2,4,5-TP	14	1.1 (0.8–1.4)	
Dicamba	42	0.9 (0.8–1.2)	
Non-fatal incidence among 32,024 male applicators—yr 5 survey			
2,4-D	78	1.2 (1.0–1.4)	
2,4,5-T	37	1.2 (1.0–1.4)	
2,4,5-TP	14	1.1 (0.9–1.4)	
Dicamba	47	1.1 (0.9–1.3)	
Enrollment through 2001—mortality			*Blair et al., 2005a,b*
Private applicators (farmers), spouses			Adjusted for age, race, state, sex, and calendar yr of death
Circulatory disease	619	0.5 (0.5–0.6)	
Enrollment through 2007, vs state rates			*Waggoner et al., 2011*
Applicators (n = 1,641)			
Rheumatic heart disease	8	0.7 (0.3–1.4)	
Hypertension with heart disease	40	0.5 (0.4–0.7)	
Hypertension without heart disease	15	0.4 (0.2–0.6)	
Ischemic heart disease	1,099	0.5 (0.5–0.6)	
Cerebrovascular disease	236	0.5 (0.5–0.6)	
Spouses (n = 676)			
Rheumatic heart disease	7	0.7 (0.3–1.5)	
Hypertension with heart disease	7	0.3 (0.1–0.6)	
Hypertension without heart disease	6	0.3 (0.1–0.7)	
Ischemic heart disease	211	0.5 (0.4–0.5)	
Cerebrovascular disease	105	0.6 (0.5–0.7)	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 (ICD-9)		**Herbicides**	
Forest conservationists		p-trend < over years worked	*Alavanja et al., 1989*
Ischemic heart disease (410–414)	543	1.0 (0.9–1.1)	Not adjusted
Cerebrovascular disease (430–438)	99	0.9 (0.8–1.1)	for known risk factors
Florida Licensed Pesticide Applicators		**Herbicides**	*Blair et al., 1983*
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976 (ICD-9)			Not adjusted for known risk factors
Circulatory diseases (390–458)			
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (All circulatory diseases [ICD-9 390–459])		**TCDD**	
25-yr follow-up to 2001			*Consonni et al., 2008*
Zone A, sexes combined	45	1.1 (0.8–1.4)	
Chronic rheumatic heart diseases (393–398)	3	5.7 (1.8–18.0)	Adjusted for gender, age,
Hypertension (400–405)	5	2.2 (0.9–5.3)	period
Ischemic heart diseases (410–414)	13	0.8 (0.5–1.4)	
Acute myocardial infarction (410)	6	0.6 (0.3–1.4)	
Chronic ischemic heart diseases (412, 414)	7	1.1 (0.5–2.3)	
Cerebrovascular diseases (430–438)	11	0.9 (0.5–1.6)	
Zone B, sexes combined	289	1.0 (0.9–1.1)	
Chronic rheumatic heart diseases (393–398)	1	0.3 (0.0–2.2)	
Hypertension (400–405)	11	0.7 (0.4–1.3)	
Ischemic heart diseases (410–414)	102	1.0 (0.8–1.2)	
Acute myocardial infarction (410)	54	0.9 (0.7–1.1)	
Chronic ischemic heart diseases (412, 414)	47	1.1 (0.8–1.4)	
Cerebrovascular diseases (430–438)	101	1.2 (1.0–1.5)	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Zone R, sexes combined	2,357	1.1 (1.0–1.1)	
Chronic rheumatic heart diseases (393–398)	24	1.0 (0.6–1.5)	
Hypertension (400–405)	144	1.2 (1.0–1.4)	
Ischemic heart diseases (410–414)	842	1.1 (1.0–1.1)	
Acute myocardial infarction (410)	447	1.0 (0.9–1.1)	
Chronic ischemic heart diseases (412, 414)	390	1.2 (1.0–1.3)	
Cerebrovascular diseases (430–438)	695	1.1 (1.0–1.2)	
National Health and Nutrition Examination Survey		**Dioxin, dl PCBs**	
NHANES 1999–2004—2,361 adults ≥ 40 yrs of age (1,176 males and 1,185 females) followed for mortality through 2006 (average 4.6 yrs)			*Lin et al., 2012* Adjusted for age, gender, BMI, race, smoking, drinking
CVD [ICD-10 I00–I78]—75 deaths			
< 25th percentile (13.3 pg TEQ/g lipid)		1.0	
25th–75th percentile (13.3–27.9 pg TEQ/g lipid)		1.5 (0.6–3.4)	
>75th percentile (≥ 27.9 pg TEQ/g lipid)		1.7 (0.6–4.5)	
		p-trend = 0.59	
increase per 1 pg in dioxin TEQ/g lipid		1.1 (0.8–1.5)	
NHANES 1999–2002—newly diagnosed hypertension; 524 adults (≥ 40 yrs of age) excluding treated hypertensives		≥ 75th percentile vs < 25th percentile	*Ha et al., 2009*
Men			
PCDDs	23	2.3 (0.7–7.8)	
		p-trend = 0.15	
PCDFs	21	1.9 (0.7–4.9)	
		p-trend = 0.17	
Dl PCBs	27	1.7 (0.8–6.6)	Adjusted for age, race, income, BMI, cigarette smoking, serum cotinine, alcohol, exercise
		p-trend = 0.11	
Women			
PCDDs	33	5.0 (1.2–21.5)	
		p-trend = 0.08	
PCDFs	30	4.2 (1.3–14.3)	
		p-trend = 0.01	
Dl PCBs	28	1.1 (0.3–3.5)	
		p-trend = 0.93	
26.1–59.1		1.1 (0.9–1.4)	
> 59.1		1.8 (1.2–2.6)	

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
PCB 156 (ng/g of lipid) (TEF = 0.0005)			
≤ 12.5		1.0	
12.6–15.4		1.3 (0.9–1.9)	
> 15.4		1.2 (0.8–1.9)	
PCB 169 (pg/g of lipid) (TEF = 0.01)			
≤ 27.0		1.0	
27.1–46.4		1.1 (0.9–1.5)	
> 46.4		1.3 (0.9–1.9)	
NHANES 1999–2002—self-reported cardiovascular disease (excluding hypertension)—889 nondiabetics ≥ 40 yrs of age		≥ 75th percentile vs < 25th percentile	*Ha et al., 2007*
Men			
HxCDD	18	2.5 (0.8–7.7)	Adjusted for age, race, income, BMI, cigarette-smoking, serum cotinine, alcohol, exercise HDL, total cholesterol, triglycerides hypertension, C-reactive protein
HpCDD	18	2.4 (0.5–10.3)	
OCDD	16	2.1 (0.6–7.7)	
PCDDs	23	2.2 (0.8–6.1)	
PCDFs	19	0.7 (0.3–1.7)	
Dl PCBs	22	1.7 (0.6–5.5)	
Women			
HxCDD	21	2.8 (0.9–8.6)	
HpCDD	14	1.9 (0.3–10.8)	
OCDD	17	0.7 (0.2–2.8)	
PCDDs	19	2.0 (0.7–6.4)	
PCDFs	15	1.0 (0.3–2.8)	
Dl PCBs	23	5.0 (1.2–20.4)	
NHANES 1999–2004—prevalent hypertension (self-report told by doctor ≥ 140/90 mmHg or antihypertensive medications)—3,398–3,712 individuals depending on congener			*Everett et al., 2008b* superseded *Everett et al. (2008a)* 1999–2002 and n = 2,074–2,556
PCB 126 (ng/g of lipid) (TEF = 0.1)			
≤ 26.1		1.0	
26.2–59.1		1.1 (0.9–1.4)	
> 59.1		1.8 (1.2–2.6)	
PCB 169 (ng/g of lipid) (TEF = 0.01)			Adjusted for age, gender, race-ethnicity, smoking status, BMI, exercise, total cholesterol, family history of myocardial infarction
≤ 27.0		1.0	
27.1–46.4		1.1 (0.9–1.5)	
> 46.4		1.3 (0.9–1.9)	
PCB 118 (ng/g of lipid) (TEF = 0.0001)			
≤ 12.5		1.0	
12.6–27.5		1.4 (1.1–1.8)	
> 27.5		2.0 (1.3–3.0)	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
PCB 156 (ng/g of lipid) (TEF = 0.0005)			
≤ 12.5		1.0	
12.6–15.4		1.3 (0.9–1.9)	
> 15.4		1.2 (0.8–1.9)	
NHANES 1999–2002—721 nondiabetics ≥ 20 with fasting blood samples and measured POPs high blood pressure (≥ 130/85 hg)	nr	≥ 75th percentile vs those with nondetectable level	*Lee et al., 2007c*
PCDDs		1.7 (1.0–3.1)	
HxCDD		1.2 (0.7–2.2)	Adjusted for
HpCDD		2.6 (1.3–5.0)	age, race,
OCDD		1.1 (0.6–2.0)	sex, income,
PCDFs		1.9 (1.2–3.3)	cigarette-
PeCDF		1.3 (0.7–2.4)	smoking, serum
HxCDF		2.3 (1.3–4.0)	cotinine, alcohol
HpCDF		1.4 (0.8–2.3)	consumption,
Dl PCBs		1.4 (0.8–2.7)	exercise
PCB 74		1.2 (0.6–2.4)	
PCB 118		1.8 (1.0–3.5)	
PCB 126		2.1 (1.2–3.7)	
PCB 169		0.6 (0.3–1.1)	
UNITED STATES			
Superfund site caused by wood-treatment facility in Pensacola, FL—47 workers, residents—prevalence		**Dioxin/phenoxy herbicides**	*Karouna-Renier et al., 2007*
Hypertension defined by self-report, medication use, or two readings of systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg		1.1 (1.1–1.2) [error likely; published OR, lower confidence limit identical to 3 decimal places]	Adjusted for age, race, sex, BMI, tobacco and alcohol use, worker status

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
Other International Environmental Studies			
CANADA		**dl PCBs**	
Inuit adults from Nunavik, Quebec (n = 315)		0.9 (0.8–1.1)	*Valera et al., 2013b* Adjusted
PCB 105 and hypertensive status		1.4 (1.1–1.9)	for age, sex, fasting glucose, total serum lipids, waist circumference, alcohol consumption, physical activity, Also adjusted for omega-3 fatty acid, mercury, lead levels
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**TCDD, PCBs, TEQs**	*Turunen et al., 2008*
Ischemic heart disease			Standardized
Men	269	0.7 (0.7–0.8)	mortality
Women	62	0.7 (0.5–0.8)	analysis—age
Cerebrovascular disease			adjusted
Men	67	0.7 (0.5–0.9)	
Women	46	1.0 (0.7–11.3)	

continued

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments
GREENLAND		**dl PCBs**	
Plasma levels of mono-ortho PCBs 105, 18, and 156 and hypertension status			
Inuit adults residing in Greenland (n = 1,614)	645	1.0 (0.9–1.2)	*Valera et al., 2013a*
Ages 18–39		1.3 (1.0–1.7)	Adjusting for age, sex, BMI, diabetes, physical activity, smoking
Ages ≥ 40 yrs		0.9 (0.8–1.1)	
JAPAN			
2,264 Japanese from general population not occupationally exposed to dioxins, aged 15–76 yrs in 2002–2008		**Total Serum TEQ**	*Nakamoto et al., 2013*
Hypertension	638		
Quartile 1		1.0	Adjusted for age, sex, smoking, drinking, region, survey yr, BMI
Quartile 2		1.3 (0.9–2.0)	
Quartile 3		1.5 (1.1–2.3)	
Quartile 4		2.3 (1.5–3.4)	
		p-trend < 0.0001	
Hyperlipidemia			
Quartile 1		1.0	
Quartile 2		1.7 (1.3–2.2)	
Quartile 3		2.4 (1.8–3.3)	
Quartile 4		3.4 (2.4–4.8)	
		p-trend < 0.0001	
TAIWAN			
Residents around 12 municipal-waste incinerators in Taiwan—prevalence		**Dioxin/phenoxy herbicides**	*Chen HL et al., 2006*
Hypertension diagnosed by a physician	118	5.6 (1.6–19.6)	
Serum PCDD/F (TEQs in logistic model)		0.9 (0.2–3.7)	
Serum PCDD/F (TEQs in logistic model)			

TABLE 12-3 Circulatory Disorders, continued

Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[c]	*Reference*/ Comments

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; BMI, body mass index; CATI, computer-assisted telephone interview; CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; EOI, Exposure Opportunity Index; HDL, high-density lipoprotein; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; HpCDF, 1,2,3,4,6,7,8-heptachlorodibenzofuran; HR, hazard ratio; HxCDD, 1,2,3,6,7,8-hexachlorodibenzo-*p*-dixion; HxCDF, 1,2,3,4,7,8-hexachlorodibenzofuran; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, months of service; na, not applicable; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDD/F, dioxins and furans combined; PCDF, polychlorinated dibenzofuran; PCP, pentachlorophenol; PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; PMR, proportional mortality ratio; POP, persistent organic pollutant; ppt, parts per trillion; SEA, Southeast Asia; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dixoin; TCP, trichlorophenol; TEF, toxicity equivalency factor for individual congener; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs; VV, Vietnam veteran.

[a]New citations labeled as such and bolded; section shaded for citations with dose–response information on TCDD.

[b]Subjects male unless otherwise noted.

[c]Given when available; results other than estimated risk explained individually.

estimates of effect due to the rarity of stroke as a result of the age of the cohorts, and the often incomplete control for confounding. After (1) a careful review of the new evidence of a statistically significant association in the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) cohort; (2) a careful consideration of the most appropriate prior literature, which shows an overall increase in stroke and cerebrovascular disease associated with exposure to the COIs in environmental, occupational, and Vietnam-veteran populations; (3) a demonstration of biologic plausibility in human and animal studies; and (4) observation of the strong connection between stroke and hypertension, CVD, and diabetes, three conditions already in the limited and suggestive category, the committee voted to move stroke to the limited and suggestive category.

TABLE 12-4 Epidemiologic Studies Providing Best Evidence in Terms of Design, Sample Size, and Relevance—Cerebrovascular Disorders/Stroke

Reference	Population	Cases/N	Finding (maximally adjusted OR/RRs shown)	Strengths	Weaknesses
VIETNAM VETERANS					
US Air Force Health Study—Ranch Hand veterans vs SEA veterans					
Ketchum and Michalek, 2005	Ranch Hands, through 1999	5/1,262 RH 34/19,078 SEA	RH vs SEA: 2.3 (0.9–6.0)	• Prospective design • Population of interest • Exposure to chemicals of interest documented	• Small number of cases • Mortality not incidence • Case ascertainment based on reported cause of death • Subtype not determined • Adjusted only for military occupation, year of birth, smoking, and family history of heart disease
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (07/01/1965–03/28/1973)					
Cypel and Kang, 2010	Army Chemical Corp, 32 yrs of follow-up	36/4661 27/2872 6/1473	Vietnam service: Yes/No: 1.48 (0.67–3.62) Vietnam service vs US pop: 1.47 (0.97–2.13) Sprayers: Yes/No: 2.12 (0.37–12.3)	• Prospective design • Population of interest • Sprayers were exposed to chemicals of interest • Sprayer association adjusted for age, duration of service, rank, BMI, race, smoking status	• Small number of cases • Mortality not incidence • No direct exposure measurement • Case ascertainment based on reported cause of death • Subtype not determined

OCCUPATIONAL					
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates					
Vena et al., 1998	IARC cohort, variable follow-up	263/26,976; Internal comparison	TCDD exposure: Yes/No: 1.54 (0.83–2.66)	• Prospective design • Exposure to chemicals of interest documented • Evidence of increased risk with increased duration of exposure	• Mortality not incidence • Case ascertainment based on reported cause of death • Subtype not determined • Adjusted only for age, gender, country, calendar period, employment status, age at first exposure, duration of exposure
ENVIRONMENTAL					
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)					
Consonni et al., 2008	Seveso cohort, 25-yr follow-up	Zone A: 11/723 Zone B: 101/4821 Zone R: 695/31,643	Zone A vs Ref: 0.9 (0.5–1.63) Zone B vs Ref: 1.21 (0.99–1.48) Zone R vs Ref: 1.09 (1.0–1.38)	• Prospective design • Exposed to TCDD documented	• Dose extrapolated from geography • Mortality • Subtype not determined • Only adjusted for gender, age, presence at time of accident, and time period
Other Environmental					
Lee DH et al., 2012b	PIVUS, 5-yr incidence	35/ 898	$TEQ_{(75\%/25\%)}$: 3.8 (1.2–12.22)	• Prospective design • Stroke incidence • Direct exposure assessment • TEQ used • Adjustment for multiple confounders • Dose–response • Stronger effect for TEQ than all PCBs	• Small sample size • No measureable TCDD exposure (all TEQs for DLCs) • Subtype not determined • "Metabolic" confounding cannot be ruled out

NOTE: BMI, body mass index; DLC, dioxin-like chemical; IARC, International Agency for Research on Cancer; MOS, months of service; OR, odds ratio; PCB, polychlorinated biphenyl; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; Ref, reference; RH, Ranch Hand; RR, relative risk; SEA, Southeast Asia (AFHS subjects servicing elsewhere in SEA than Vietnam); TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dixoin; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

Update of the Epidemiologic Literature

Hypertension

Vietnam-Veteran Studies Three studies were published since *Update 2012* concerning the experience of two cohorts of Vietnam-era veterans with hypertension. Kang et al. (2014) reported the mortality experience through 2010 of Vietnam-era female veterans. After adjusting for age, race, military service duration, officer status, and nursing status, women deployed to Vietnam were somewhat less likely to have died from hypertension than women serving in the United States (RR = 0.70, 95% CI 0.22–2.26). This estimate was based on 12 deaths attributed to hypertension (5 in those deployed to Vietnam and 7 serving in the United States). When the analysis was limited to just the nurses, the result for this internal comparison was effectively the same (RR = 0.70, 95% CI 0.16–3.13).

Yi et al. (2014a) examined the health insurance claims of Korean Vietnam veterans filed from January 1, 2000, to September 20, 2005. The design of this study is described in detail in Chapter 6. For 111,726 veterans, records on the dates and locations of their units were available to generate individual-specific estimates of opportunity for herbicide exposure using a model developed using US flight records of the missions that sprayed herbicides. The resulting scores were partitioned into high-exposure (n = 42,421) and low-exposure (n = 69,305) groups. The prevalence of hypertensive diseases [ICD-10 I10–I13] among those veterans serving in units with low exposure potential was 44.3 percent compared to 46.2 percent in those with high exposure potential ($p < 0.0001$). After adjusting for multiple behavioral, demographic, and service-related factors, however, no association between potential herbicide exposure and hypertension prevalence was evident ($p = 0.715$).

Yi et al. (2014b) also examined the mortality experience of the Korean Vietnam veterans from 1992 to 2005. In 2000, a cohort of 187,897 veterans was located from approximately 320,000 Korean who had served in Vietnam from1964 to 1971. From this list, 7,258 individuals who died, emigrated, or had no known residence by 1992 were excluded. The vital status and, when applicable, cause of death were determined for the remaining 180,639 veterans from the death records of the National Statistical Office. One hundred ninety-two deaths were attributed to hypertension. The relative rate of mortality from hypertension adjusted for age and military rank was weakly associated with herbicide exposure either when expressed as the log of estimated exposure ($p = 0.108$) or when contrasting those with high estimated exposure to those in the lower category, but chance could not be ruled out as an explanation (HR = 1.18, 95% CI 0.88–1.58).

Occupational and Case-Control Studies No occupational or case-control studies addressing exposure to the COIs and hypertension have been published since *Update 2012*.

Environmental Studies Several studies relating the compounds of interest to hypertensive status were published since *Update 2012.*

Nakamoto et al. (2013) assembled a sample of 2,264 adult Japanese who were not occupationally exposed to dioxins. The researchers measured the lipid-adjusted blood levels of many dioxin, furan, and PCB congeners with dioxin-like activity and derived the associated TEQs. Hypertension status was determined by resting blood pressure measurements (systolic blood pressure of 140 mmHg and above or diastolic blood pressure of 90 mmHg or above) or a self-report of a physician diagnosis of hypertension. Contrasting extreme exposure quartiles, TEQs for PCDD/Fs and for PCBs and their total were all significantly associated with hypertensive status after adjusting for age, sex, smoking, drinking, region, survey year, and BMI (OR = 1.7, 95% CI 1.2–2.6; OR = 2.4, 95% CI 1.6–3.7; and OR = 2.3, 95% CI 1.5–3.4, respectively). There was strong statistical evidence of a linear dose–response across the exposure range for each of these categories ($p = 0.001$, $p < 0.0001$, $p < 0.0001$, respectively).

Defining hypertension as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or receiving antihypertensive treatment, Valera et al. (2013a) conducted a survey that assessed the cross-sectional association between hypertension and plasma levels of POPs in 1,614 Inuit adults residing in Greenland. The Inuit population is of interest because its diet is rich in food sources that can concentrate organic pollutants. The authors measured three mono-ortho PCBs (105, 118, and 156), which have modest dioxin-like activity. In the overall sample, neither the concentrations of these individual congeners nor their sum was associated with hypertensive status after adjusting for age, sex, BMI, diabetes, physical activity, and smoking. The investigators stratified the sample by age (18–39 versus ≥ 40 years) after detecting statistical evidence of an age interaction. There was an association with the sum of dioxin-like PCBs and hypertensive status in the younger group (OR = 1.34, 95% CI 1.03–1.74), but not in the older group (OR = 0.93, 95% CI 0.77–1.12) after adjustment for the covariates listed above. Valera et al. (2013b) also surveyed 315 adult Inuits from Nunavik (Quebec, Canada). After adjusting for age, sex, fasting glucose, total lipids, waist circumference, drinking, smoking, and physical activity, none of the same three mono-ortho dioxin-like PCBs measured in the Inuits from Greenland showed any indication of association individually or when summed (OR = 0.94, 95% CI 0.78–1.13). Only PCB 105, when also adjusted for omega-3 fatty acid levels, mercury, and lead levels, was moderately associated with hypertensive status (OR = 1.44, 95% CI 1.11–1.86).

Peters et al. (2014) added NHANES data for 2005–2008 to the sets for 1999–2002 and 2003–2004 previously analyzed by Everett et al. (2008a,b) for association of blood pressure with blood concentrations of dioxin-like PCBs 126 and 169 and mono-ortho PCBs 118 and 156. Using this expanded dataset, they developed a structural equations model for the prediction of blood pressure involving PCB, lead, and cadmium blood levels, in combination with generally

available variables such as age, sex, and ethnicity. PCB concentrations were most predictive for systolic blood pressure and pulse pressure, while lead levels were most predictive for diastolic blood pressure and arterial pressure. The PCBs metric used in this modeling effort was the total blood concentration by weight of PCBs 66, 101, 118, 128, and 187, so for VAO purposes this work does not augment the results previously published by Everett et al. (2008a,b).

Ischemic Heart Disease

Vietnam-Veteran Studies A number of relevant studies of veteran populations were published since *Update 2012*. McBride et al. (2013) reported the mortality experience of New Zealand Vietnam veterans. The investigators identified 3,394 personnel with service in Vietnam between 1964 and 1975. The study tracked mortality from 1998 to 2008, and the veterans' mortality experience was compared with that of the general New Zealand population. The number of observed coronary heart disease deaths among the veterans was 16 percent lower than expected (SMR = 0.84, 95% CI 0.69–1.02, n = 104). There was no information on possible exposure to the COIs, nor were any risk factors except age considered in the analysis.

Kang et al. (2014) reported the mortality experience of Vietnam-era female veterans. After adjusting for age, race, duration of service, officer status, and nursing status, women deployed to Vietnam were found to have experienced significantly lower mortality from heart disease (including angina pectoris, myocardial infarction, coronary artery disease, and congestive heart failure) than women who were not deployed overseas (RR = 0.79, 95% CI 0.65–0.96). This was also the case when only the nurses were included in the analysis (RR = 0.80, 95% CI 0.63–1.00).

The heart disease experience of Korean Vietnam-era veterans was reported by Yi et al. (2013a, 2014a,b). Using health insurance claims data, the adjusted prevalence of IHD [ICD-10 I20–I25] was 4 percent higher in those with high putative herbicide exposure compared with those with low exposure (OR = 1.04, 95% CI 1.00–1.07) after adjusting for several behavioral, demographic, and service-related factors. The log-transformed individual scores for potential herbicide exposure also showed a positive association (p = 0.012). In the mortality study in the same cohort, however, Yi et al. (2014b) found differences between the groups with high and low potential exposure (HR = 0.99, 95% CI 0.86–1.14) and no association between putative log-transformed exposure and ischemic heart disease mortality (p = 0.729).

Kim KH et al. (2014) assembled two groups of patients undergoing cardiac angiography: 1,245 male Vietnam veterans recruited from two Korean veterans' hospitals and 506 recruited from two university hospitals. Exposure to herbicide was not assessed. Although the nature of coronary lesions detected at the initial angiography differed slightly between the two groups, the time until a future

revascularization procedure did not differ. The research objective of this work concerned the prognostic value of presumed herbicide exposure on the course of the disease rather than the risk of developing coronary artery disease, so this study does not contribute useful information to the VAO task.

Occupational and Case-Control Studies No occupational or case-control studies addressing exposure to the COIs and IHD have been published since *Update 2012.*

Environmental Studies Lin et al. (2012) reported the mortality experience of 2,361 NHANES participants 40 years of age or older. The blood levels of chlorinated dioxins, furans, and PCBs with dioxin-like activity were measured between 1999 and 2004, and deaths among cohort members were ascertained through 2006. During follow-up 75 participants died from CVD [ICD-10 I00–I78], which includes hypertension, IHD, and stroke. Mortality rate ratios in terms of TEQs were adjusted for age, gender, BMI, race, cigarette smoking, and alcohol consumption. Compared to those with the lowest TEQ levels, those with the highest TEQ levels were estimated to be roughly 1.67 times more likely to die from CVD (HR = 1.67, 95% CI 0.62–4.47). Analysis of the individual TEQs also found a non-significant increase in the CVD death rate (HR = 1.07, 95% CI 0.78–1.46).

Other Reviewed Studies In addition to hypertension, which was discussed separately above, several other risk factors for heart disease were addressed in relation to dioxin-like PCBs in recent studies.

Turunen et al. (2012) measured serum concentrations of 17 PCDD/F and 37 PCB congeners in samples gathered from Finnish fishermen and their wives in a larger study (Turunen et al., 2008), and calculated total TEQs. Information on several risk factors for CVD (BMI, blood pressure, lipids, and glucose metabolism) was gathered for 123 men and 132 women. Vascular measurements (intima-media thickness, arterial diameter change, and atherosclerotic plaques in the carotid artery) were made by ultrasound in 84 of the men and 90 of the women; three measures of carotid artery stiffness (compliance, elastic modulus, and β-stiffness index) were derived from the value for arterial diameter change. All these variables were analyzed with respect to TEQs after adjustment for age, smoking, physical activity, dietary factors, alcohol consumption, and medications. In the women, none of these factors showed an association with TEQ levels. In the men, indications of trend were strongest for insulin resistance ($p = 0.09$) and β-stiffness ($p = 0.10$) with increasing TEQs.

Sjöberg Lind et al. (2013a,b) examined the cross-sectional relationship between POPs and left ventricular remodeling and systolic and diastolic heart function in the PIVUS study, which recruited 70-year-old residents of Uppsala, Sweden. Hypertension can lead to ventricular remodeling, and changes in heart function are early indications of heart failure. PCBs with dioxin-like activity were

not associated with ventricular geometry after adjustment for covariates. Blood levels of OCDD were inversely associated with the left ventricular ejection fraction after adjusting for gender, smoking, systolic blood pressure, antihypertensive medications, BMI, and left ventricular hypertrophy ($p = 0.0048$). A consistent pattern did not emerge for the PCBs; some with dioxin-like activity (mono-ortho PCBs 105 and 189), but not all (non-ortho PCB 126, mono-ortho PCBs 156 and 157), were inversely associated with ejection fraction, while other PCBs with no dioxin-like activity were also associated.

Kumar et al. (2014b) also analyzed data from the PIVUS study to examine the relationship between TEQs and components of the complement system, which is involved in clotting and hemostasis. TEQs were associated with a significantly elevated C3a and an elevated C3a/C3 ratio (both $p = 0.01$) after adjusting for many potential confounding variables. An elevated ratio indicates an activated complement system, which is a risk factor for heart disease and stroke. Levels of PCB 126, which has high dioxin-like activity, were most strongly correlated with the ratio.

In the Japanese community survey previously described, Nakamoto et al. (2013) found a strong cross-sectional relationship between hyperlipidemia and quartiles of blood concentrations of DLCs. When adjusted for age, sex, smoking, drinking, region, survey year, and BMI, those in the highest TEQ quartile were 3.4 times more likely than those in the lowest quartile to report hyperlidemia (OR = 3.4, 95% CI 2.4–4.8). There was strong evidence for a linear trend in the prevalence of hyperlipidemia with increasing levels of circulating TEQs ($p < 0.0001$).

In the Korean Veterans Health Study, Yi et al. (2014a) found that veterans of the Vietnam War with high potential herbicide exposures were not more likely than those in the low-exposure group to have made health insurance claims for lipid abnormalities (OR = 1.02, 95% CI 0.99–1.05).

Aminov et al. (2013) studied the cross-sectional relationship between levels of several PCB congeners and serum lipid levels in 575 residents of Anniston, Alabama, a site of previous industrial contamination. Residents taking lipid-lowering drugs were excluded. The 35 ortho-substituted PCB congeners studied did not, of course, include the four most potent dioxin-like PCBs, which are characterized by non-ortho substitution. Six of the eight mono-ortho PCBs with dioxin-like activity (PCBs 105, 118, 156, 157, 167, and 189) were measured. For analyses of association with the levels of various lipids, PCB congeners were grouped by their number of chlorine atoms, which does not correspond to dioxin-like activity. Consequently, this study is not informative for the VAO objective.

Cerebrovascular Disease and Stroke

Vietnam-Veteran Studies Kang et al. (2014) reported the mortality experience of Vietnam-era female veterans as described above. Analyzing 68 deaths, after adjusting for age, race, military service duration, officer status and nursing status,

they concluded that women deployed to Vietnam appeared somewhat less likely to die from cerebrovascular disease (primarily stroke) than women who served in the United States (RR = 0.87, 95% CI 0.56–1.34). The same was the case for just the nurses (RR = 0.80, 95% CI 0.48–1.34).

The stroke experience of Korean Vietnam-era veterans has been reported by Yi et al. (2014a,b). With adjustment for multiple behavioral, demographic, and service-related factors, the more highly exposed cohort members had a 9 percent higher stroke [ICD-10 I60–I64] prevalence (OR = 1.09, 95% CI 1.04–1.13). The association was seen for both major stroke types: cerebral infarction [ICD-10 I63] (OR = 1.09, 95% CI 1.04–1.14) and cerebral hemorrhage [ICD-10 I60–I62] (OR = 1.11, 95% CI 1.00–1.23). In the mortality study in the same cohort, adjusting for only age and rank, Yi et al., 2014b) found no difference in mortality from cerebrovascular disease [ICD-10 I60–I69] between the groups with high and low potential for herbicide exposure (HR = 1.01, 95% CI 0.92–1.12) and no association with individual exposure potential (HR per 1 log unit increase in EOI score = 1.01, 95% CI 0.99–1.04).

Occupational Studies No occupational studies addressing exposure to the COIs and IHD have been published since *Update 2012.*

Environmental Studies Lin et al. (2012) reported a positive, but non-significant, association between DLCs in the blood and mortality from CVD in the NHANES study. The endpoint definition included stroke, and its results are summarized above.

Case-Control Studies

Other Reviewed Studies Rinsky et al. (2013) examined agricultural exposures and stroke mortality in the Agricultural Health Study, but did not consider exposure to specific COIs.

Biologic Plausibility

Studies have demonstrated that both the vasculature and adipose tissue are targets of TCDD toxicity and have provided a mechanistic understanding of how TCDD exposure increases the risk of circulatory diseases, such as hypertension, IHD, and stroke. TCDD exposure of cultured endothelial cells or cultured adipocytes induces major changes in gene expression and leads to substantial increases in oxidative stress and inflammatory markers (Andersson et al., 2011; Han SG et al., 2012; Ishimura et al., 2009; Kerley-Hamilton et al., 2012a; Kim MJ et al., 2012; Kopf and Walker, 2010; Majkova et al., 2009; Puga et al., 2004). Notably, the loss of the AHR, as happens in AHR knockout mice, is associated with decreases in blood pressure (modeling hypotension), while sustained

activation of the AHR resulting from dioxin exposure leads to increases in blood pressure (Agbor et al., 2011). L Zhang et al. (2010) showed that the genetic loss of AHR from all tissues or solely from endothelial cells results in hypotension. In contrast, Kopf et al. (2010) demonstrated that the chronic exposure of mice to TCDD induces hypertension that is associated with significant increases in vascular oxidative stress and decreases in vascular relaxation. Those changes in vascular function and blood pressure could be mediated in part by increases in the metabolism of arachidonic acid to vasoconstrictive and inflammatory eicosanoids (Bui et al., 2012). Studies have also demonstrated that exposure to AHR agonists, including TCDD and benzo[a]pyrene, increases the incidence, severity, and progression of atherosclerosis, a primary cause of IHD and stroke (Dalton et al., 2001; Kerley-Hamilton et al., 2012a; Wu et al., 2011). Furthermore, Wu et al. (2011) demonstrated that TCDD mediates those effects in part by increasing vascular inflammation. In addition to the vasculature, studies have suggested that the heart is a target of TCDD. TCDD exposure increases hypertrophy of rat cardiac cells in culture (Zordoky and El-Kadi, 2010) and impairs the differentiation of mouse embryonic stem cells into cardiomyocytes (Neri et al., 2011).

In addition to the direct effects of TCDD on the vasculature and heart, there is evidence that TCDD influences other CVD risk factors, for example, by promoting obesity (Kerley-Hamilton et al., 2012b), accumulating macrophage lipid, inducing lipid mobilization, and altering lipid metabolism. Thus, on the basis of animal models, there appear to be several overlapping and potentially contributing pathways that link TCDD exposure and increased CVD risk.

Synthesis

In this section, the committee synthesizes information on circulatory disorders from the new studies described above and reconsiders studies that were reviewed in previous updates. Because circulatory diseases constitute a broad group of diverse conditions, hypertension, IHD, and stroke are discussed separately so that the new studies can be adequately synthesized and integrated with the earlier studies.

Hypertension

Hypertension, typically defined as blood pressure above 140/90 mmHg, affects more than 70 million adult Americans and is a major risk factor for coronary heart disease, myocardial infarction, stroke, and heart and renal failure. The major quantifiable risk factors for hypertension are well established and include age, race, BMI or percentage of body fat, and diabetes; the strongest conclusions regarding a potential increase in the incidence of hypertension come from studies that have controlled for these risk factors. The committee responsible for *Update 2006* concluded that the available evidence was consistent with the placement of

hypertension in the limited or suggestive category. Additional evidence reviewed in *Updates 2008*, *2010*, and *2012* reaffirmed this conclusion.

The new studies looking at mortality are not helpful in understanding the relationship between herbicide exposure and hypertension (Kang et al., 2014; Yi et al., 2014b). Many more people die with hypertension than from hypertension, and it is uncertain how representative those dying from hypertension are of all of those who may have developed it. In addition, many important confounding variables were not accounted for. The two prevalence studies of Korean Vietnam veterans are of interest (Yi, 2013; Yi et al., 2014a), but suffer because not all persons of relevance to the analysis could be included. Specifically, the health experiences of veterans who died or relocated between their Vietnam service and the start of the investigation are not included. Thus, the validity of the calculated exposure–outcome relationship is based on the strong assumption that the observed relationships in those included are similar to those who were not included. In some cases, 40 percent of the relevant data is missing. In addition, the determination of hypertension was either by self report or through health insurance claims. It cannot be assured that all participants with hypertension were detected because no standardized blood pressure assessment was done. The environmental surveys had conflicting results, with one study showing a strong association with dioxin-like activity (Nakamoto et al., 2013), and two smaller studies showing no associations or associations limited to a single congener or age group (Valera et al., 2014a,b). All three studies were based on measured blood pressure and adjusted for relevant confounders, but the study by Nakamoto was designed to calculate TEQs for all chlorinated DLCs, while the two other studies assessed only three PCBs with low dioxin-like activity. Nevertheless, as with all cross-sectional studies, those available to participate in the study may not represent all persons who develop hypertension, which limits the ability to draw strong inferences in such studies.

Because a variety of weaknesses in the relevant studies reviewed, the committee found no compelling reason to consider a change in category. The new relevant data are consistent with a relationship between the COIs and elevated blood pressure. Thus, the committee reaffirms placement of hypertension in the limited and suggestive category.

Ischemic Heart Disease

The committee responsible for *Update 2008* revisited the entire body of evidence on TCDD exposure and heart disease and concluded that the evidence supported moving IHD to the limited and suggestive category. That conclusion was based on evidence of a dose–response relationship in the occupational cohorts, evidence of increased risk of myocardial infarction in Vietnam veterans, supporting cross-sectional survey data, and a strong biologic rationale. Evidence reviewed for *Update 2010* and *Update 2012* supported that classification.

Several studies of potential relevance were reviewed for *Update 2014*. The studies of New Zealand, Korean, and female US veterans did not find an increase in IHD mortality. IHD is not a uniformly fatal disease, and therefore mortality rates represent not only disease occurrence but also disease severity and access to appropriate medical care. The validity of the point estimate depends on those dying of disease being a fair representation of all persons developing IHD. The mortality experience of the New Zealand veterans was compared to the general New Zealand population. Such comparisons often show that veterans have a health advantage over the general population across a range of health outcomes. This "healthy soldier" effect may reflect the fact that persons serving in the military are required to have a certain minimal level of health in order to serve. Furthermore, in neither the New Zealand nor the US study was there direct assessment of herbicide exposure. The Korean veterans study did quantify possible herbicide exposure. Not all relevant confounding variables were accounted for, and about 10 percent of potentially eligible participants were not included. The mortality study included 843 deaths from IHD. The studies of disease prevalence in the same population identified more than 20,000 persons with this condition. This contrast highlights the possibility that IHD deaths may not fairly represent all cases of the disease. The Korean veterans study found an association between putative herbicide exposure and disease prevalence. However, as mentioned above, given the cross-sectional design and the large number of relevant veterans who were not included in the analytic sample, bias might explain the findings. The study from NHANES (Lin et al., 2012) was well conducted and showed an increase in the risk of CVD death in those with higher levels of dioxin TEQs, but because of the small number of events the study's estimate of effect was imprecise and chance could not be ruled out. Data from Nakamoto et al. (2013) and from the PIVUS cohort provide data that show differences in risk factors consistent with an increased risk of CVD. Other population cross-sectional studies did not demonstrate such relationships.

The committee reaffirmed the decision of previous VAO committees to put IHD in the limited and suggestive category.

Cerebrovascular Disease and Stroke

Several studies of potential relevance were reviewed for *Update 2014*. As discussed above, the value of the information from women who served in Vietnam is limited by the lack of information related to actual exposure to herbicides and the lack of adjustment for potential confounders. Additionally, the small number of stroke deaths means that the estimate of the relationship between Vietnam service and stroke mortality is very imprecise. The data from the Korean veterans provide information on herbicide exposure, and the prevalence studies account for many relevant risk factors. There is evidence of increased stroke prevalence associated with exposure. The associations are modest, and it is possible that

selection bias or residual confounding could account for them. The mortality data from the Korean veterans did not find an association. As with heart disease, fatal cases of stroke may not fairly represent the full spectrum of cases. The Korean mortality study included 875 deaths from cerebral hemorrhage and 309 deaths from cerebral infarction. The prevalence study included 1,606 cases of cerebral hemorrhage and 9,210 cases of cerebral infarction. Thus, the observed association between herbicide exposure and total stroke incidence could have been different if the exposure history of the non-fatal cases differed even modestly from those dying of the disease.

The committee believed that the new evidence reviewed did not strongly refute or confirm a relationship between herbicide exposure and stroke occurrence. Thus, it decided to leave the current category unchanged—there is limited and suggestive of a relationship between herbicide exposure and the occurrence of stroke.

Conclusion

After carefully examining the new evidence, the present committee concurred with those for previous updates that there is limited or suggestive evidence that hypertension, ischemic heart disease, and stroke are associated with herbicide exposure. Other forms of circulatory disease should remain in the inadequate or insufficient category.

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Other Chronic Health Outcomes

Chapter Overview

Based on new evidence and a review of prior studies, the committee for Update *2014 found:*

- *There is now limited or suggestive evidence of an association between hypothyroidism and exposure to the chemicals of interest (COIs) in this report.*

In previous updates that considered short-term adverse outcomes (see Appendix B), the committees found:

- *There is sufficient evidence of an association between the COIs and chloracne.*
- *There is limited or suggestive evidence of an association between the COIs and early onset peripheral neuropathy and porpohyria cutanea tarda.*

No additional scientifically relevant associations between the exposures of concern and adverse chronic health outcomes were noted. The current evidence supports the findings of earlier studies that:

- *No other adverse outcomes had sufficient evidence of an association with the COIs.*

- *No other adverse outcomes had limited or suggestive evidence of an association with the COIs.*
- *There is inadequate or insufficient evidence to determine whether there is an association between the COIs and respiratory disorders, gastrointestinal and digestive disease (including liver toxicity), kidney disease, adverse effects on endocrine function (other than hypothyroidism), eye problems, or bone conditions.*

This chapter discusses data on the possible association between exposure to the herbicides used in Vietnam—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid—and several non-cancer health outcomes: respiratory disorders, gastrointestinal and digestive disease (including liver toxicity), adverse effects on thyroid homeostasis, kidney disease, eye problems, and bone conditions. The committee also considers the results of studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like chemicals (DLCs) to be informative if they were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of dioxin-like specific congeners. Although all studies reporting TEQs based on PCBs were reviewed, those studies that reported TEQs based only on mono-ortho PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given very limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the World Health Organization (WHO) revised toxicity equivalency factors (TEFs) of 2005 (La Rocca et al., 2008; van den Berg et al., 2006).

In previous updates, chloracne and porphyria cutanea tarda were considered with the chronic non-cancer conditions. They are accepted as being associated with dioxin exposure, but when they occur, it happens within a matter of months of the exposure. In *Update 2010*, the two health outcomes were moved to an appendix on short-term effects along with transient early-onset peripheral neuropathy, which had previously been discussed in the chapter on neurologic disorders.

For each type of health outcome, background information is followed by a brief summary of the findings described in earlier reports by the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. In the discussion of the most recent scientific literature, the studies are grouped by exposure type (Vietnam veteran, occupational, or environmental). For articles that report on only a single health outcome and are not revisiting a previously studied population, the design information is summarized with the results; the design information on other studies can be found in Chapter 6. A synopsis of toxicologic and clinical information related to the biologic plausibility that the COIs can influence the occurrence of a health outcome is presented next and followed by a synthesis of all the material reviewed. Each health-outcome section ends with the present committee's conclusions regarding the strength of

the evidence that supports an association with the COIs. The categories of association and the committee's approach to categorizing the health outcomes are discussed in Chapters 1 and 2.

RESPIRATORY DISORDERS

For the purposes of this report, "non-cancerous respiratory disorders" are all acute and chronic lung diseases (other than cancers), a variety of conditions encompassed by the *International Classification of Diseases* (ICD), Ninth Revision (ICD-9 460–519) or Tenth Revision [ICD-10 J00–J99]. Acute non-cancerous respiratory disorders include pneumonia and other respiratory infections; they can increase in frequency and severity when the normal defense mechanisms of the lower respiratory tract are compromised. Chronic non-cancerous respiratory disorders generally take two forms: airways diseases and parenchymal diseases. Airway diseases are disorders—among them asthma and chronic obstructive pulmonary disease (COPD)—characterized by an obstruction of the flow of air out of the lungs. COPD, which is also known as chronic obstructive airways disease, includes such disorders as emphysema and chronic bronchitis. Parenchymal disease, or interstitial disease, generally includes disorders that cause inflammation and scarring of the deep lung tissue, including the air sacs and supporting structures. Parenchymal disease is less common than airways disease and is characterized by reductions in lung capacity, although it can include a component of airway obstruction. Some severe chronic lung disorders, such as cystic fibrosis, are hereditary. Because Vietnam veterans received health screenings before entering military service, few severe hereditary chronic lung disorders are expected in that population.

The most important risk factor for many non-cancerous respiratory disorders is inhalation of cigarette smoke. Although exposure to cigarette smoke is not associated with all diseases of the lungs, it is the major cause of many airways disorders, especially COPD; it contributes to some interstitial disease; and it compromises host defenses in such a way that people who smoke are generally more susceptible to some types of pneumonia. Cigarette smoking also makes almost every respiratory disorder more severe and symptomatic than it would otherwise be. The incidence rates of habitual cigarette smoking vary with occupation, socioeconomic status, and generation. For those reasons, cigarette smoking can be a major confounding factor in interpreting the literature on risk factors for respiratory disease. Vietnam veterans are reported to smoke more heavily than non-Vietnam veterans (Kang et al., 2006; McKinney et al., 1997).

It is well known that the causes of death from respiratory diseases, especially chronic diseases, are often misclassified on death certificates. Grouping various respiratory diseases for analysis, unless they all are associated with a given exposure, will lead to an attenuation of the estimates of relative risk (RR) and to a diminution of statistical power. Moreover, the diagnosis of the primary cause

of death from respiratory and cardiovascular diseases is often inconsistent. In particular, when a person had both conditions concurrently and both contributed to death, there may be some uncertainty about which cause should be selected as the primary underlying cause. In other instances, errors may arise in selecting one underlying cause in a complex chain of health events (for example, if COPD leads to congestive heart failure and then to respiratory failure).

Many study populations are small, so investigators group deaths from all non-cancerous respiratory diseases into one category that combines pneumonia, influenza, and other diseases with COPD and asthma. The committee notes that an association between the group of all non-cancerous respiratory diseases with any of the COIs would be too nonspecific to be clinically meaningful; at most, such a pattern would be an indication that within this broad classification the incidence of some particular disease entity might be affected by an exposure to a COI.

Conclusions from *VAO* and Previous Updates

The committee responsible for *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*,[1] hereafter referred to as *VAO* (IOM, 1994), concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and the respiratory disorders specified above.

Additional information available to the committees responsible for *Veterans and Agent Orange: Update 1996* (IOM, 1996) and *Update 1998* (IOM, 1999) did not change that finding. *Update 2000* (IOM, 2001) drew attention to findings in the Seveso cohort that suggested a higher mortality from non-cancerous respiratory disorders in study subjects, particularly males, who were more heavily exposed to TCDD. The committee concluded that although new evidence suggested an increased risk of non-cancerous respiratory disorders, particularly COPD, in people exposed to TCDD, the observation was tentative. Additional information that was available to the committees responsible for *Update 2002* (IOM, 2003) and *Update 2004* (IOM, 2005) did not change that finding.

Update 2006 (IOM, 2007) reviewed a number of studies of veterans of the Vietnam War. Mortality from respiratory diseases was not found to be higher than expected in the Centers for Disease Control and Prevention Vietnam Experience Study (Boehmer et al., 2004), in the Air Force Health Study (AFHS) (Ketchum and Michalek, 2005), or in two Australian studies of Vietnam veterans (ADVA, 2005b,c). In contrast, in the US Army Chemical Corps (ACC) cohort of Vietnam

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

veterans, Kang et al. (2006) found that the prevalence of self-reported non-cancerous respiratory problems diagnosed by a doctor was significantly increased by about 40 to 60 percent, although no differences in the prevalence of respiratory problems were found in the subset of veterans whose serum TCDD was above 2.5 parts per trillion (ppt). However, in new studies of occupational cohorts, no associations were observed with respiratory mortality in a small subcohort of New Zealand phenoxy-herbicide sprayers ('t Mannetje et al., 2005) or with mortality from COPD in private applicators or their spouses in the Agricultural Health Study (AHS) (Blair et al., 2005a).

The committee for *Update 2008* (IOM, 2009) evaluated several AHS publications concerning morbidity from particular self-reported respiratory health problems: analyses concerning wheeze (Hoppin et al., 2006c), asthma (Hoppin et al., 2008), "farmer's lung" or hypersensitivity pneumonitis (Hoppin et al., 2007b), and chronic bronchitis (Hoppin et al., 2007a; Valcin et al., 2007). The 25-year follow-up of mortality in the Seveso population (Consonni et al., 2008) reported some increase in mortality from COPD as had been seen in the 15- and 20-year-mortality follow-ups (Bertazzi et al., 1998, 2001).

New literature considered in *Update 2010* raised considerable concern that a pattern of COPD might be coming into focus. Cypel and Kang (2010) reported cause-specific mortality through 2005 in an ACC cohort of deployed and non-deployed Vietnam-era veterans and in a subset of the original deployed ACC veterans who had reported in an earlier morbidity study whether they had sprayed herbicide (Kang et al., 2006). Cypel and Kang (2010) reported a statistically significant excess mortality from COPD (RR = 4.82, 95% confidence interval [CI] 1.10–21.18) when comparing the deployed and non-deployed groups. A similar pattern in the deployed ACC veterans was observed when they were compared with the US male population (standardized mortality ratio [SMR] = 1.62, 95% CI 0.99–2.51). When the subgroups of deployed ACC veterans who had and had not reported spraying herbicides were compared, the sprayers had an elevated risk for death due to the less specific category of "non-cancerous respiratory system disease" (RR = 2.24, 95% CI 0.42–11.83); this was the only one of these comparisons in which the researchers were able to control for self-reported herbicide exposure, body mass index (BMI), and smoking status. Deaths due to COPD were lower in non-deployed ACC veterans than in males in the US population (SMR = 0.3, 95% CI 0.04–1.07); this is noteworthy because the prevalence of smoking in the non-deployed ACC veterans was about twice that in men in the US population (Kang et al., 2006). Publications evaluated in *Update 2010* that studied industrial cohorts did not report on COPD specifically but did not find increased mortality from non-cancerous respiratory diseases overall (Boers et al., 2010; Collins et al., 2009a,c; McBride et al., 2009a). In the AHS cohort, Hoppin et al. (2009) did not find increased morbidity from asthma associated with 2,4-D or 2,4,5-T use; Slager et al. (2009) found the current use of 2,4-D to be associated with an increase in current rhinitis.

Several new occupational studies were evaluated in *Update 2012*. An update of the National Institute of Occupational Safety and Health (NIOSH) cohort of pentochlorophenol (PCP) workers (Ruder and Yin, 2011) did not find an association of exposure to the COIs with deaths from all nonmalignant respiratory diseases; however, an excess in COPD deaths (possibly related to duration of employment) was observed in the entire cohort (63 deaths, SMR = 1.38, 95% CI 1.06–1.77), which was reflected in the subgroup exposed to PCP only, but not in the subgroup exposed to both TCDD and PCP. Updated mortality data on workers in two chlorphenoxy herbicide plants in the Netherlands (discussed in *Update 2010*) were re-analyzed by Boers et al. (2012) using serum measurements from a subcohort of 187 workers to construct a model of TCDD exposure, but no association of TCDD exposure with respiratory diseases was observed. An updated mortality study of workers in a pesticide factory with TCDD contamination (Manuwald et al., 2012) showed no association of nonmalignant respiratory disease with exposure, although an association of respiratory cancers with exposures was found. These cohort studies were unable to control for smoking.

Table 13-1 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Since the prior update, Kang et al. (2014) have reported the results of a retrospective study of 4,734 women who served in Vietnam, along with 2,062 women who were stationed in countries near Vietnam and 5,313 women who were not deployed during the Vietnam War. These veterans were identified through military records and followed for 40 years. In a comparison between the Vietnam cohort and the non-deployed cohort, 195 respiratory system disease deaths (SMR = 0.78, 95% CI 0.58–1.05) and 87 cases of COPD (SMR = 0.82, 95% CI 0.52–1.28) were observed. A sub-analysis of nurses who served in Vietnam compared with non-deployed nurses identified 130 cases of respiratory system disease (SMR = 0.73, 95% CI 0.50–1.06) and 56 cases of COPD (SMR = 0.71, 95% CI 0.40–1.28). As in many other cohort studies of mortality, the possibility of Type I statistical errors (i.e., false positives) was considerable due to numerous comparisons, and adjustment for tobacco use was not possible.

Two additional cohort studies of Vietnam War veterans (majority males) from New Zealand and Korea recently reported on respiratory mortality. Starting with a complete roster of New Zealand veterans who served in Vietnam between 1964 and 1972, McBride et al. (2013) determined that 2,783 of these men were alive and residing in New Zealand in 1988, which represented 84 percent of the 3,322 male New Zealand troops who had survived their service in Vietnam. Their mortality experience from 1988 through 2008 and underlying cause of death were obtained from the national verified Mortality Collection. Comparing the veterans

TABLE 13-1 Selected Epidemiologic Studies—Non-Cancer Respiratory Disease (Shaded entries are new information for this update)

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Mortality			
Through 1999—Ranch Hand personnel (n = 1,262) vs SEA veterans (19,078) (respiratory disease, ICD-9 460–519)	8	1.2 (0.6–2.5)	Ketchum and Michalek, 2005
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (07/01/1965–03/28/1973)		**All COIs**	
Incidence—Self-reported respiratory disease diagnosed by doctor			
CATI survey of stratified sample: 1,499 deployed (795 with TCDD measured) vs 1,428 non-deployed (102 with TCDD measured)			Kang et al., 2006
Deployed vs non-deployed	267	1.4 (1.1–1.8)	
Sprayed herbicides in Vietnam (n = 662) vs never (n = 811)	140	1.6 (1.2–2.1)	
Mortality—respiratory disease			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)			
Respiratory system disease	32 vs 8	2.2 (1.0–4.9)	
Pneumonia, influenza	12 vs 6	1.3 (0.5–3.6)	
COPD	20 vs 2	4.8 (1.1–21.2)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray			
Respiratory system disease	8	2.2 (0.4–11.8)	
Pulmonary disease (COPD)	6	3.6 (0.4–32.1)	
Through 1991 (respiratory system disease)	11 vs 2	2.6 (0.5–12.2)	Dalager and Kang, 1997
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	

continued

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Incidence			
Physical health— ORs from pulmonary-function tests (case definition: ≥ 80% predicted value)			CDC, 1988a
FEV_1	254	0.9 (0.7–1.1)	
FVC	177	1.0 (0.8–1.3)	
FEV_1/FVC	152	1.0 (0.8–1.3)	
Mortality			
1965–2000 (non-cancerous respiratory mortality, ICD-9 460–519)	20	0.8 (0.5–1.5)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs non-deployed (n = 31,757)	648	0.8 ($p < 0.05$)	
Marine Corps, deployed (n = 6,237) vs non-deployed (n = 5,040)	111	0.7 ($p < 0.05$)	
US VA Study of Male Vietnam Veterans Wounded in Combat		**All COIs**	
Mortality through December 1991			Bullman and Kang, 1996
Non-cancerous respiratory mortality (ICD-9 460–519)	43	0.9 (0.7–1.2)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only = 3,282)		**All COIs**	Kang et al., 2014
Mortality (through 2004)			
Respiratory system disease	195	0.8 (0.6–1.1)	
COPD	87	0.8 (0.5–1.3)	
Vietnam nurses only			
Respiratory system disease	130	0.7 (0.5–1.1)	
COPD	56	0.7 (0.4–1.3)	
US VA Cohort of Monozygotic Twins—Vietnam-era		**All COIs**	
Incidence of respiratory conditioins, deployed vs non-deployed			Eisen et al., 1991
Present at time of survey	nr	1.4 (0.8–2.4)	
At any time since service	nr	1.4 (0.9–2.0)	
Required hospitalization	nr	1.8 (0.7–4.2)	

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
State Studies of US Vietnam Veterans			
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (mortality from non-cancerous respiratory disease, ICD-8 460–519)			Anderson et al., 1986a,b
Vietnam veterans vs expected deaths calculated from proportions for:	10		
Non-veterans		0.5 (0.3–0.8)	
All veterans		0.8 (0.4–1.5)	
Vietnam-era veterans		1.0 (0.5–1.8)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Mortality			
All branches, return–2001			ADVA, 2005a
Respiratory system disease	239	0.8 (0.7–0.9)	
COPD	128	0.9 (0.7–1.0)	
Navy			
Respiratory system disease	50	0.8 (0.6–1.0)	
COPD	28	0.9 (0.6–1.3)	
Army			
Respiratory system disease	162	0.8 (0.7–0.9)	
COPD	81	0.9 (0.7–1.0)	
Air Force			
Respiratory system disease	28	0.6 (0.4–0.9)	
COPD	18	0.8 (0.4–1.2)	
1980–1994			CDVA, 1997a
Non-cancerous respiratory mortality (ICD-9 460–519)			
1964–1979	3	0.1 (0.0–0.3)	
1980–1994	92	0.9 (0.7–1.1)	
Chronic obstructive airways disease (ICD-9 460–496)	47	0.9 (0.7–1.2)	
Sample of 1,000 Male Australian Vietnam Veterans—prevalance		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey			O'Toole et al., 2009

continued

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Chronic lower respiratory disease	nr		
Bronchitis	nr	2.9 (2.2–3.6)	
Emphysema	nr	2.0 (1.3–2.7)	
Asthma	nr	1.3 (1.0–1.6)	
Hay fever, allergic rhinitis	nr	1.2 (0.96–1.4)	
Chronic sinusitis	nr	1.7 (1.5–2.0)	
Other diseases of respiratory system	nr	15.4 (11.7–19.1)	
641 interviewed 1990–1993 vs respondents to 1989–1990 national survey			O'Toole et al., 1996b
Asthma	nr	0.9 (0.5–1.4)	
Bronchitis, emphysema	nr	4.1 (2.8–5.5)	
Other	nr	4.0 (2.2–5.9)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Mortality			
1966–2001			ADVA, 2005c
Respiratory diseases	18	1.1 (0.6–2.2)	
COPD	8	1.0 (0.3–2.8)	
1982–1994			CDVA, 1997b
1965–1982	2	2.6 (0.2–30.0)	
1982–1994	6	0.9 (0.3–2.7)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Mortality (1988–2008)			
Respiratory disease (not COPD)	12	0.4 (0.2–0.7)	
COPD	18	0.8 (0.5–1.2)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs)		**All COIs**	
Prevalence (01/2000–09/2005)—log EOI scores			Yi et al., 2014a
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.0)	
Pneumonia not due to influenza (J12–J18)		1.0 (1.0–1.0)	
COPD (J40–J44, J47)		1.0 (1.0–1.0)	
Chronic bronchitis (J41–J42)		1.0 (1.0–1.0)	
Emphysema (J43)		1.0 (1.0–1.0)	
Bronchiectasis (J47)		1.0 (1.0–1.1)	
Asthma (J45–J46)		1.0 (1.0–1.0)	

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Prevalence (01/2000–09/2005)—categorized high (n = 36,813) vs low (n = 59,615) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.1)	
Pneumonia not due to influenza (J12–J18)		1.0 (1.0–1.1)	
COPD (J40–J44, J47)		1.0 (1.0–1.0)	
Chronic bronchitis (J41–J42)		1.1 (1.0–1.1)	
Emphysema (J43)		0.9 (0.8–1.1)	
Bronchiectasis (J47)		1.2 (1.1–1.3)	
Asthma (J45–J46)		1.0 (1.0–1.1)	
Mortality (1992–2005) (adjusted HRs)			Yi et al., 2014b
Diseases of the respiratory system (J00–J98)	446	1.0 (1.0–1.1)	
Pneumonia not due to influenza (J12–J18)	107	1.0 (0.9–1.1)	
COPD (J40–J44, J47)	115	1.0 (1.0–1.3)	
Asthma (J45–J46)	75	1.0 (0.9–1.1)	
Mortality (01/2000–09/2005)—categorized high (n = 266) vs low (n = 180) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J98)		1.2 (1.0–1.5)	
Pneumonia not due to influenza (J12–J18)		1.0 (0.7–1.5)	
COPD (J40–J44, J47)		1.7 (1.2–2.6)	
Asthma (J45–J46)		0.9 (0.6–1.4)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992		**Phenoxy herbicides, chlorophenols**	Kogevinas et al., 1997
21,863 exposed workers			
Men	252	0.8 (0.7–0.9)	
Women	7	1.1 (0.4–2.2)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (*not* included in IARC cohort)		**MCPA**	
Mortality through 1983 (non-cancerous respiratory diseases, ICD-9 460–519)	93	0.6 (0.5–0.8)	Coggon et al., 1986

continued

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
British Production Workers at 4 plants (included in IARC cohort)		**Dioxins, but TCDD unlikely; MCPA**	Coggon et al., 1991
Mortality 1963–1985 (non-cancerous respiratory diseases, ICD-9 460–519)	8	0.7 (0.3–1.3)	
Dutch production workers in Plant A and Plant B, combined (Plant A, 1,020 workers; Plant B, 1,036 workers) (in IARC cohort)		**Dioxins, 2,4-D, 2,4-DP, 2,4,5-T, 2,4,5-TCP MCPA, MCPP**	
Mortality 1955–2006 (diseases of the respiratory system)	52	1.0 (0.8–1.2)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)			Boers et al., 2012
Diseases of the respiratory system	31	1.0 (0.8–1.3)	
Mortality 1955–2006	19 vs 12	1.0 (0.4–2.3)	Boers et al., 2010
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	6 vs 15	0.5 (0.2–1.2)	Boers et al., 2010
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 mo in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992 (ICD-9 460–519)	2	0.9 (0.1–3.1)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 mo in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989 (ICD-9 460–519)	0	0.0	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 mo in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989 (ICD-9 460–519)	4	0.6 (0.2–1.6)	Becher et al., 1996

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (*not* part of IARC)		**Focus on TCDD**	
Incidence			
Through 1989 (n = 158 men exposed within 1 yr of accident vs 161 other BASF employees 1953–1969)			Zober et al., 1994
All non-cancerous respiratory diseases (ICD-9 460–419)	nr	33.7/31.0 (p = 0.22)	
Upper respiratory tract infections (ICD-9 460–478)	nr	12.0/9.0 (p = 0.00)	
Pneumonia, influenza (ICD-9 480–487)	nr	17.4/18.8 (p = 0.08)	
COPD (ICD-9 490–496)	nr	8.0/7.5 (p = 0.31)	
Mortality			
1953–1992 (non-cancerous respiratory)	1	0.1 (0.0–0.8)	Ott and Zober, 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 mo in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 codes 460–519)	33	0.6 (0.4–0.9)	Manuwald et al., 2012
Men	25	0.6 (0.4–0.9)	
Women	8	0.7 (0.3–1.4)	
Mortalilty 1952–1989 (ICD-9 460–519)	10	0.5 (0.3–1.0)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	12	0.8 (0.4–1.4)	
Never-exposed workers	2	0.4 (0.0–1.5)	
Production Workers (713 men and 100 women worked > 1 mo in 1969–1984)			
Mortality 1969–2000	9	0.9 (0.4–1.8)	‘t Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			

continued

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Mortality 1973–2000	6	0.7 (0.2–1.2)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993 (non-cancerous respiratory, ICD-9 460–519)	86	0.9 (0.7–1.1)	Steenland et al., 1999
Monsanto workers (n = 240) involved in 2,4,5-T production (1948–1969) and 163 unexposed workers, results of clinical examination July 1979—morbidity			Suskind and Hertzberg, 1984
"Abnormal" outcome on pulmonary-functions tests:			
FEV_1 (< 80% predicted)	32	2.81 (p = 0.02)	
FVC (< 80% predicted)	35	2.25 (p = 0.03)	
FEV_1/FVC (< 70%)	32	2.97 (p = 0.01)	
$FEF_{25–75}$ (< 80% predicted)	47	1.86 (p = 0.05)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, MI) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	44	0.8 (0.6–1.0)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
Respiratory disorders (ICD-9 460–466, 470–478, 480–487, 490–519)			
1940–2005 (n = 2,122)	94	1.0 (0.8–1.3)	
PCP and TCP (n = 720)	21	0.7 (0.5–1.1)	
PCP (no TCP) (n = 1,402)	73	1.2 (0.9–1.5)	
Pneumonia (ICD-9 480–486)			
1940–2005 (n = 2,122)	19	0.7 (0.4–1.0)	
PCP and TCP (n = 720)	8	0.9 (0.4–1.8)	
PCP (no TCP) (n = 1,402)	11	0.5 (0.3–1.0)	
COPD (ICD-9 490–492, 496)			
1940–2005 (n = 2,122)	63	1.4 (1.1–1.8)	
PCP and TCP (n = 720)	10	0.7 (0.3–1.3)	
PCP (no TCP) (n = 1,402)	53	1.7 (1.3–2.2)	
Dow 2,4-D Production Workers (1945–1982 in Midland, MI) (subset of all TCP-exposed workers) excluded		**2,4-D, lower chlorinated dioxins**	

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Through 1994 (n = 1,517)			Burns et al., 2001
Non-cancerous respiratory (ICD-8 460–519)	8	0.4 (0.2–0.7)	
Pneumonia	4	0.6 (0.2–1.4)	
Dow PCP Production Workers (1937–1989 in Midland, MI) (*not* in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	19	0.7 (0.4–1.2)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
Non-cancerous respiratory mortality (ICD-8 460–519)	14	0.9 (0.5–1.5)	
Cumulative PCP exposure			
< 1 unit	3	0.6 (0.2–1.9)	
≥ 1 unit	11	0.4 (0.8–2.5)	
Pneumonia (ICD-8 480–486)	6	1.1 (0.4–2.4)	
Emphysema (ICD-8 492)	4	1.3 (0.4–3.3)	
Preliminary NIOSH Cross-Sectional Medical Study—workers in production of sodium trichlorophenol, 2,4,5-T ester contaminated with TCDD—morbidity			
Chronic bronchitis and COPD	2	nr	Sweeney et al., 1997/98
ORs for increase in 1 ppt of serum TCDD compared to unexposed workers			Calvert et al., 1991
Chronic bronchitis	nr	0.5 (0.1–2.6)	
COPD	nr	1.2 (0.5–2.8)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Cross-sectional study of self-reported prevalence of self-reported asthma (n = 83) in male farmers (n = 1,939) in Saskatchewan (1982–1983)		**Phenoxy herbicides** *Asthmatics vs non-asthmatics*	Senthilselvan et al., 1992
Phenoxyacetic herbicide use	71	85.5% vs 88.5%	
Saskatchewan Rural Health Study—8,153 adults completed mailed questionnaires; 482 self-reported cases of doctor-diagnosed chronic bronchitis		**Herbicides**	Pahwa et al., 2012b
Herbicide—ever exposed occupationally	264	1.2 (1.0–1.5)	

continued

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916 men), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Prevalence of allergic (n = 127) and nonallergic (n = 314) asthma in male farmers and commercial applicators			Hoppin et al., 2009
Men with allergic asthma exposed to:			
2,4,5-T	38	1.4 (1.0–2.2)	
2,4-D	110	1.6 (0.9–2.7)	
Men with nonallergic asthma exposed to:			
2,4,5-T	88	1.2 (0.9–1.6)	
2,4-D	264	1.2 (0.9–1.6)	
Prevalence of atopic (n = 282) or nonatopic asthma (n = 420) reported by women (> 19 yrs of age) at enrollment (1993–1997)			Hoppin et al., 2008
Women reporting atopic asthma exposed to:			
2,4-D	52	1.5 (1.1–2.1)	
Dicamba	11	1.1 (0.6–2.1)	
Women reporting nonatopic asthma exposed to:			
2,4-D	66	1.1 (0.8–1.4)	
Dicamba	13	0.7 (0.4–1.3)	
Prevalence of chronic bronchitis at enrollment (n = 654) in private applicators exposed to:			Hoppin et al., 2007a
2,4-D	78	1.1 (0.9–1.4)	
2,4,5-T	28	1.5 (1.3–1.8)	
2,4,5-TP	9	1.7 (1.3–2.3)	
Dicamba	48	1.0 (0.8–1.2)	
Prevalence of chronic bronchitis at enrollment in nonsmoking farm women (n = 21,541) exposed to:		0.9 (0.7–1.1)	Valcin et al., 2007
2,4-D	16	1.2 (0.9–1.6)	
2,4,5-T	1	1.0 (0.4–2.5)	
Dicamba	5	1.1 (0.6–2.0)	

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Respiratory system diseases			
Applicators (n = 1,641)	346	0.4 (0.3–0.4)	
Spouses (n = 676)	92	0.3 (0.2–0.4)	
Pneumonia			
Applicators (n = 1,641)	76	0.4 (0.3–0.5)	
Spouses (n = 676)	17	0.3 (0.2–0.5)	
COPD			
Applicators (n = 1,641)	165	0.3 (0.3–0.4)	
Spouses (n = 676)	50	0.3 (0.2–0.4)	
Asthma			
Applicators (n = 1,641)	8	0.8 (0.3–1.6)	
Other respiratory diseases			
Applicators (n = 1,641)	97	0.6 (0.5–0.7)	
Spouses (n = 676)	21	0.4 (0.3–0.6)	
Enrollment through 2000, vs state rates			Blair et al., 2005a,b
Private applicators (men and women)	50	0.2 (0.2–0.3)	
Spouses of private applicators (> 99% women)	15	0.3 (0.2–0.7)	
US Department of Agriculture Workers— nested case-control study of white men dying 1970–1979 of non-cancerous respiratory diseases (ICD-8 460–519)		**Herbicides**	
Forest conservationists	80	0.8 (0.6–1.0)	Alavanja et al., 1989
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976 from non-cancerous respiratory diseases (ICD-8 460–519)	2	**Herbicides** 0.9 (nr)	Blair et al., 1983
Any pesticide (dose–response by length of licensure)			
< 10 yrs	8	0.6 (nr)	
10–19 yrs	8	1.5 (nr)	
≥ 20 yrs	4	1.7 (nr)	

continued

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Mortality (ICD-9)			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
Respiratory disease (460–519)			
Zone A	9	1.4 (0.7–2.7)	
Zone B	48	1.0 (0.8–1.4)	
Zone R	341	1.0 (0.9–1.1)	
COPD (490–493)			
Zone A	7	2.5 (1.2–5.3)	
Zone B	26	1.3 (0.9–1.9)	
Zone R	175	1.2 (1.0–1.4)	
20-yr follow-up to 1996			Bertazzi et al., 2001
Respiratory disease (460–519)	44	1.0 (0.8–1.4)	
Zone A	9	1.9 (1.0–3.6)	
Zone B	35	1.3 (0.9–2.0)	
COPD (490–493)	29	1.5 (1.1–2.2)	
Zone A	7	3.3 (1.6–6.9)	
Zone B	22	1.3 (0.9–2.0)	
15-yr follow-up to 1991—men			Bertazzi et al., 1998
Respiratory disease (460–519)			
Zone A	5	2.4 (1.0–5.7)	
Zone B	13	0.7 (0.4–1.2)	
Zone R	133	1.1 (0.9–1.3)	
COPD (490–493)			
Zone A	4	3.7 (1.4–9.8)	
Zone B	9	1.0 (0.5–1.9)	
Zone R	74	1.2 (0.9–1.5)	
15-yr follow-up to 1991—women			Bertazzi et al., 1998
Respiratory disease (460–519)			
Zone A	2	1.3 (0.3–5.3)	
Zone B	10	1.0 (0.5–1.9)	
Zone R	84	1.0 (0.8–1.2)	
COPD (490–493)			
Zone A	1	2.1 (0.3–14.9)	
Zone B	8	2.5 (1.2–5.0)	
Zone R	37	1.3 (0.9–1.9)	

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
10-yr follow-up to 1986—men (Zones A, B, R)			Bertazzi et al., 1989a
Respiratory disease (460–519)	55	1.0 (0.7–1.3)	
Pneumonia (480–486)	14	0.9 (0.5–1.5)	
COPD (490–493)	31	1.1 (0.8–1.7)	
10-yr follow-up to 1986—women (Zones A, B, R)			Bertazzi et al., 1989a
Respiratory disease (460–519)	24	1.0 (0.7–1.6)	
Pneumonia (480–486)	9	0.8 (0.4–1.6)	
COPD (490–493)	8	1.0 (0.5–2.2)	
Cross-sectional study of residents near wood treatment plant (creosote, PCP) in Mississippi, who were plaintiffs (n = 199) in lawsuit vs subjects in comparable area (n = 115) without known exposures		**Dioxin, furans** Prevalence in exposed vs unexposed	Dahlgren et al., 2003b
Chronic bronchitis			
By history		21.7% vs 4.3% ($p < 0.0001$)	
Diagnosed by physician		17.8% vs 5.8% ($p < 0.0001$)	
Chronic bronchitis			
By history		40.5% vs 11.0% ($p < 0.0001$)	
Diagnosed by physician		13.1% vs 12.0% ns	
Other International Environmental Studies			
JAPAN			
2,253 Japanese from general population not occupationally exposed to dioxins, aged 15–76 yrs in 2002–2008,		**Total Serum TEQ**	Nakamoto et al., 2013
Asthma (40 cases in men; 53 cases in women)	93		
Quartile 1		1.0	
Quartile 2		1.1 (0.6–2.0)	
Quartile 3		1.0 (0.5–1.9)	
Quartile 4		1.1 (0.5–2.4) p-trend = 0.88	

continued

TABLE 13-1 Non-Cancer Respiratory Disease, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Mortality			
East coast	4	0.5 (0.1–1.2)	
West coast	43	0.8 (0.6–1.1)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, US Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; COPD, chronic obstructive pulmonary disease; EOI, Exposure Opportunity Index; FEF_{25-75}, forced midexpiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD-8, *International Classification of Diseases, 8th revision*; ICD-9, *International Classification of Diseases, 9th revision*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, months of service; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; OR, odds ratio; PCP, pentachlorophenol; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Given when available; results other than estimated risk explained individually.

to the general male population of New Zealand, the risk of death from all nonmalignant respiratory diseases (excluding COPD) was significantly lower (SMR = 0.40, 95% CI 0.21–0.70), but for COPD specifically no difference was apparent (SMR = 0.78, 95% CI 0.46–1.23). These authors were also unable to adjust for potential confounders, particularly tobacco use.

Yi et al. (2014a,b) applied the Stellman model (Stellman et al., 2003b) in an effort to quantify exposures in the Korean Veterans Health Study. With 446 deaths from respiratory disease, an analysis of the individual Exposure Opportunity Index (EOI) scores found a slightly elevated hazard ratio (HR = 1.04, 95% CI 0.99–1.09) after adjusting for age and rank in Vietnam (Yi et al., 2014b). A comparison of the 180 deaths in the low-exposure category with the 266 deaths in the high-exposure category generated a significant risk (HR = 1.24, 95% CI 1.02–1.50). The authors further explored specific respiratory diseases by exposure category and found 115 total deaths associated with COPD, with 80 of these occurring in the high-exposure group (HR = 1.73, 95% CI 1.16–2.60). No significant associations of exposure to the COIs were seen for pneumonia (HR = 1.02, 95% CI 0.69–1.50, 57 cases in high, 50 in low) or asthma (HR = 0.88, 95% CI 0.55–1.42, 36 cases in high, 39 in low). Importantly, information on smoking habits was not available for this cohort during follow-up through 2003.

Yi et al. (2014a) used insurance claim data from January 2000 through September 2005 to evaluate disease prevalence in Korean Veterans Health Study participants. Diseases of the respiratory system were positively associated with the log of EOI scores (odds ratio [OR] = 1.01, 95% CI 1.00–1.01), but a comparison between the high-exposure group and the low-exposure group found no significant association (OR = 1.02, 95% CI 0.99–1.06). COPD was positively associated with the log EOI scores (OR = 1.01, 95% CI 1.00–1.01) and when the high- and low-exposure groups were compared (OR = 1.04, 95% CI 1.01–1.07). Significant findings were also reported in comparisons between the high- and low-exposure groups for pneumonia not due to influenza (OR = 1.04, 95% CI 1.00–1.09), chronic bronchitis (OR = 1.05, 95% CI 1.02–1.08), bronchiectasis (OR = 1.06, 95% CI 1.06–1.27), and asthma (OR = 1.04, 95% CI 1.01–1.08), but the findings for emphysema were not statistically significant (OR = 0.94, 95% CI 0.83–1.05).

Occupational Studies

As part of the Saskatchewan Rural Health Study, Pahwa et al. (2012b) examined the prevalence of chronic bronchitis (CB) in farm and non-farm rural residents of Saskatchewan, Canada. This two-phase, prospective study collected baseline health data on 8,261 males and females at least 18 years of age using self-administered, mailed questionnaires. The authors report on 8,153 subjects, finding 482 who reported doctor-diagnosed CB. The prevalence of CB in farm residents was 5.3 percent versus 6.4 percent in non-farm residents. Although some information on herbicide exposure was gathered (unadjusted OR = 1.24, 95% CI 1.02–1.50), there was essentially no exposure specificity, making this study of minimal use to the committee.

The above results in terms on exposures no more specific than "herbicide exposure" are of only marginal relevance in assessing the relationship between respiratory disease and exposure to the COIs for VAO's purposes. The committee notes three additional new publications (de Jong et al., 2014; Sapbamrer and Nata, 2014; Tual et al., 2013) that assessed relationships between adverse respiratory outcomes and various agricultural risk factors with exposure characterizations that are not informative for this report.

Environmental Studies

In a cross-sectional study of 1,063 men and 1,201 women living throughout Japan (who had not been occupationally exposed to dioxins), Nakamoto et al. (2013) gathered fasting blood samples between 2002 and 2010 for assessment of environmental exposure to DLCs. Blood levels and the corresponding TEQs were determined for dioxin-like polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and PCBs. In addition to estimating a trend across all quartiles (pg/g lipid), logistic regression adjusted for age, sex, smoking

habit, drinking habit, regional block, and survey year was used to estimate the odds of self-reported asthma in the upper three quartiles versus the lowest quartile for PCDDs and PCDFs combined (PCDD/Fs), PCBs, and all DLCs. None of the results for self-reported asthma were at all indicative of association with any of these three exposure groupings.

Biologic Plausibility

An evaluation of the biologic plausibility of the induction of or contribution to the development of lung diseases by the COIs is hampered by a lack of animal models for studing such endpoints as COPD or asthma because these diseases usually develop in humans in response to additional co-factors (smoking and air pollution).

2,4-D has been shown to be toxin to a human fibroblast cell line (WI-38) in culture via disruption of the tubulin-microtubule network (Ganguli et al., 2014). Activation of the aryl hydrocarbon receptor (AHR) by TCDD has been shown to modify the expression of six genes in human bronchial epithelial cells in culture, although this study used a low-throughput analysis that likely missed many AHR targets (Jin et al., 2012). In both human cell line (NCI H441, derived from Clara cells from a bronchiolar adenocarcinoma) and the lungs of C57BL/6 mice, TCDD exposure induced genes that code for inflammatory cytokines, matrix metalloproteases, and mucin production (Wong PS et al., 2010). AHR activation in the NCI H441 cells also activates a process involving IL-1b and COX-2, which leads to increased mucin production. That process might be facilitated via differentiation of the Clara cell to a mucin-producing, goblet-like cell phenotype. One of the major clinical characteristics of COPD is mucous-cell or goblet-cell hyperplasia in the airways. MUC5AC is a major gel-forming mucin that is frequently elevated in various airway diseases (Rose and Voynow, 2006; Voynow et al., 2006). JH Lee et al. (2010) reported TCDD-induced time-dependent increases in MUC5AC mRNA and protein synthesis in primary normal human bronchial epithelial cells and in an immortalized normal human bronchial epithelial cell line (HBE1). YC Lee et al. (2011) reported that TCDD induced the expression of MUC5AC mRNA and protein and the expression of CYP1A1 in both primary normal human bronchial epithelial cells and the immortalized cell line HBE1. TCDD-induced expression of the mucin gene is consistent with mucous-cell or goblet-cell hyperplasia, which in turn is an element of the pathogenesis of COPD. These results are consistent with changes associated with a variety of lung diseases—such as bronchitis, asthma, small-airways disease, and lung remodeling (fibrosis)—and support the role of AHR activation in the development of lung injury (Beamer and Shephard, 2013).

Acute non-cancerous respiratory disorders, including pneumonia and other respiratory infections, can also be increased in frequency and severity when the normal defense mechanisms of the lower respiratory tract are compromised. Thus, an exposure to chemicals that affect those mechanisms could exacerbate respiratory

disorders. There is no evidence that the specific herbicides used in Vietnam alter such defense mechanisms. However, several laboratory studies have shown that the treatment of mice with TCDD increases their mortality after infection with the influenza virus (Burleson et al., 1996; Warren et al., 2000). Treatment with TCDD also suppressed the animals' ability to generate an immune response to the virus (Mitchell and Lawrence, 2003). The mechanism underlying increased influenza mortality was not related to the suppression of the immune response to influenza by TCDD, but appeared to involve an increase in the inflammatory response associated with an increased flow of neutrophils into the lung (Mitchell and Lawrence, 2003). Teske et al. (2008) investigated the mechanism by which AHR activation influences the pulmonary immune response to viral infection. They demonstrated that the enhanced migration of neutrophils to the infected lung is caused by AHR-driven events extrinsic to the immune system; this suggests that AHR-mediated events within the lung influence neutrophil recruitment and thereby alter the outcome of respiratory viral infection. Neutrophils produce several toxic products (which kill pathogens), so it is possible that excess neutrophils in the lung produce excess collateral damage and pathologic changes that increase mortality.

It is also plausible that the induction of CYP1A1 and CYP1B1 enzymes in the lung by TCDD could result in the metabolism of other chemicals into more toxic intermediates. Exposure to TCDD could thus increase the toxic effects of several components of tobacco smoke and thus increase respiratory disease. In practice, however, this is not always the case, as Uno et al. (2006) demonstrated in mouse strains with the genes for CYP1A1 and CYP1B1 knocked out that showed increased sensitivity to benzo[a]pyrene (B[a]P). Chiba et al. (2012) recently reviewed the role of the AHR in the pathology of asthma and COPD. The authors suggest that AHR activation by TCDD and DLCs in cigarette smoke promotes inflammation and the exacerbation of asthma and COPD through the arachidonic acid cascade, cell differentiation, cell–cell adhesion interactions, cytokine expression, and mucin production. A recent systemic review that examined the results from 23 papers (chosen from an initial set of more than 4,000 publications) identified pesticides as contributing to asthma, particularly in children, and perhaps to COPD, as well. This review, however, did not shed specific insight into TCDD or the other COIs (Doust et al., 2014). Thus, it is biologically plausible that exposure to TCDD results in the exacerbation of acute lung disease that is associated with reduced immune responses or of chronic lung diseases, including COPD, that are associated with increased inflammatory responses.

Synthesis

Non-Cancerous Respiratory Disease (Without Further Specification)

Results of the studies of mortality from non-cancerous respiratory diseases reported in *Update 2008* and earlier VAO reports (ADVA, 2005b,c; Anderson et

al., 1986a; Becher et al., 1996; Blair et al., 1983, 2005a; Boehmer et al., 2004; Bullman and Kang, 1996; Burns et al., 2001; Coggon et al., 1986, 1991; Consonni et al., 2008; Crane et al., 1997a; Ketchum and Michalek, 2005; Kogevinas et al., 1997; Ott and Zober, 1996a; Ramlow et al., 1996; Steenland et al., 1999; Svensson et al., 1995b; 't Mannetje et al., 2005; Zober et al., 1994) did not support the hypothesis that exposures to herbicides or TCDD are associated with the general category of non-cancerous respiratory diseases.

A study of the prevalence of self-reported physician-confirmed respiratory problems in a subset of ACC personnel (Kang et al., 2006) was reviewed in *Update 2006*. Comparison of deployed with non-deployed veterans indicated an association (odds ratio [OR] = 1.41, 95% CI 1.13–1.76), as did a comparison of those who reported spraying herbicides in Vietnam with those who did not (OR = 1.62, 95% CI 1.26–2.05). In the subset of subjects whose serum TCDD concentrations had been determined, however, people who had respiratory problems were evenly distributed above and below the median, which argues against the association with herbicide exposure.

Another study of the ACC cohort (Cypel and Kang, 2010) that addressed the mortality experience of the entire cohort was considered in *Update 2010*. An increase in mortality due to respiratory disease was statistically significant when the deployed veterans were compared with men in the US population (SMR = 1.58, 95% CI 1.08–2.23). That observation contrasts with four occupational studies that did not report an association of death due to non-cancerous respiratory disease with exposures to herbicides or TCDD (Boers et al., 2010; Collins et al., 2009b,c; McBride et al., 2009a). Similarly, a study of Finnish fisherman found that an increase in serum dioxin TEQs was not associated with mortality from non-cancerous respiratory disorders (Turunen et al., 2008).

In *Update 2012*, four occupational studies of exposures to the COIs were consistent in reporting no increase in mortality due to pneumonia and the broad category of nonmalignant diseases of the respiratory system (Boers et al., 2012; Manuwald et al., 2012; Ruder and Yiin, 2011; Waggoner et al., 2010).

Finally in the current update, there were studies of three cohorts of Vietnam-era veterans (Kang et al., 2014; McBride et al., 2013; Yi et al., 2014a,b) and several new environmental and occupational studies, but no additional data convincingly contributed consistent evidence of either enhanced mortality or an increased risk associated with exposures to the COIs for specific or nonspecific nonmalignant respiratory diseases.

The committee does not believe that scientific conclusions (other than that the evidence is inadequate) can be reached with regard to health outcomes that are defined vaguely, for example, by combining a wide array of disparate respiratory health outcomes into one large category of non-cancerous respiratory disease. The nonspecificity of the respiratory conditions reported in these studies makes it exceedingly difficult to draw any conclusions regarding specific respiratory conditions.

Chronic Obstructive Pulmonary Disease

Ruder and Yiin (2011) reported a significant increase in COPD mortality, relative to US referent rates, in a cohort of 2,122 US PCP production workers in four plants in the NIOSH Dioxin Registry. The workers in all four plants were exposed to PCP and to its contaminating PCDD/Fs. The fact that no information on smoking was available, however, greatly limits the possible conclusions regarding the contribution of these agents to the increase in mortality due to COPD. Table 13-2 summarizes the findings with the relevant information from previous studies.

In an earlier study of mortality in a cohort of Vietnam-era veterans who had service in the ACC, as of 1991, the deployed ACC veterans had a non-significant adjusted RR of 2.59 for death due to non-cancerous respiratory diseases compared with their non-deployed peers (Dalager and Kang, 1997). The study by Cypel and Kang (2010) added 14 years of observation and found an increased risk of death from non-cancerous respiratory diseases on the cusp of statistical significance (RR = 2.20, 95% CI 0.99–4.91). For COPD in particular, they reported a statistically significant excess mortality in deployed ACC veterans (RR = 4.82, 95% CI 1.10–21.18) compared with non-deployed ACC veterans. A similar pattern of excess COPD mortality in the deployed veterans persisted when comparisons were made with the US male population (SMR = 1.58, 95% CI 1.08–2.23). In accord with those mortality data, a morbidity survey of 2,927 of the ACC veterans (deployed and non-deployed) conducted in 1999–2000 (Kang et al., 2006) found a significant increase in the broader category of self-reported non-cancerous respiratory conditions in deployed ACC veterans (OR = 1.41, 95% CI 1.13–1.76), which was also significantly related to the reported use of herbicides in Vietnam (OR = 1.62, 95% CI 1.28–2.05); the study used a multiple logistic regression model with adjustment for age, race, BMI, rank, and smoking. Among the deployed ACC veterans who had particated in the morbidity study, only 120 deaths had occurred by the end of 2005, so when Cypel and Kang (2010) assessed mortality associated with self-reported herbicide use, adjusted for smoking status, the estimated increase in COPD (adjusted RR = 3.55) had a 95% CI spanning 2 orders of magnitude (0.39–32).

Other studies of US Vietnam veterans, including the Ranch Hand cohort, found no significant increase in mortality due to the broader classification of non-cancerous respiratory mortality (Anderson et al., 1986a; Boehmer et al., 2004; Ketchum and Michalek, 2005) but did not address causes of death as specific as COPD. The Vietnam Experience Study (CDC, 1988a) did not find evidence of compromised lung function; there have been no integrated publications on specific aspects of respiratory morbidity in the Ranch Hand cohort. Studies of the full cohort of male Australian Vietnam veterans versus the general population (ADVA, 2005b; CDVA, 1997a) and of deployed versus non-deployed Australian Army National Service (conscripted) veterans (ADVA, 2005c; CDVA, 1997b)

TABLE 13-2 Selected Epidemiologic Studies—COPD and Pulmonary Function (Shaded entries are new information for this update)

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 non-deployed) serving during Vietnam era (07/01/1965–03/28/1973)		**All COIs**	
Through 2005—Mortality			Cypel and Kang, 2010
Deployed veterans (2,872) vs non-deployed (2,737)			
Respiratory system disease	32 vs 8	2.2 (1.0–4.9)	
COPD	20 vs 2	4.8 (1.1–21.2)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray			
Respiratory system disease	8	2.2 (0.4–11.8)	
Pulmonary disease (COPD)	6	3.6 (0.4–32.1)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 non-deployed		**All COIs**	
Incidence			
Physical health—ORs from pulmonary-function tests (case definition: ≥ 80% predicted value)			CDC, 1988a
FEV_1	254	0.9 (0.7–1.1)	
FVC	177	1.0 (0.8–1.3)	
FEV_1/FVC	152	1.0 (0.8–1.3)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); non-deployed (n = 5,325; nurses only = 3,282)		**All COIs**	Kang et al., 2014
Mortality (through 2004)			
Through 2004—COPD	87	0.8 (0.5–1.3)	
Vietnam nurses only—COPD	56	0.7 (0.4–1.3)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters 5/23/1962–7/1/1973 vs Australian population		**All COIs**	

TABLE 13-2 COPD and Pulmonary Function, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Mortality			
All branches, return–2001			ADVA, 2005a
Respiratory system disease	239	0.8 (0.7–0.9)	
COPD	128	0.9 (0.7–1.0)	
Navy			
Respiratory system disease	50	0.8 (0.6–1.0)	
COPD	28	0.9 (0.6–1.3)	
Army			
Respiratory system disease	162	0.8 (0.7–0.9)	
COPD	81	0.9 (0.7–1.0)	
Air Force			
Respiratory system disease	28	0.6 (0.4–0.9)	
COPD	18	0.8 (0.4–1.2)	
1980–1994			CDVA, 1997a
Non-cancerous respiratory mortality (ICD-9 460–519)			
Chronic obstructive airways disease (ICD-9 460–496)	47	0.9 (0.7–1.2)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 non-deployed)		**All COIs**	
Mortality			
1966–2001			ADVA, 2005c
Respiratory diseases	18	1.1 (0.6–2.2)	
COPD	8	1.0 (0.3–2.8)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Mortality (1988–2008)			
Respiratory disease (not COPD)	12	0.4 (0.2–0.7)	
COPD	18	0.8 (0.5–1.2)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs; ICD-10)		**All COIs**	
Prevalence (01/2000–09/2005)—log EOI scores			Yi et al., 2014a
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.0)	
COPD [J40–J44, J47]		1.0 (1.0–1.0)	

continued

TABLE 13-2 COPD and Pulmonary Function, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Prevalence (01/2000–09/2005)—categorized high (n = 36,813) vs low (n = 59,615) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.1)	
COPD [J40–J44, J47]		1.0 (1.0–1.0)	
Mortality (1992–2005) (adjusted HRs)			Yi et al., 2014b
Diseases of the respiratory system (J00–J98)	446	1.0 (1.0–1.1)	
COPD [J40–J44, J47]	115	1.0 (1.0–1.3)	
Mortality (01/2000–09/2005)—categorized high (n = 266) vs low (n = 180) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J98)		1.2 (1.0–1.5)	
COPD [J40–J44, J47]		1.7 (1.2–2.6)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (*not* part of IARC)		**Focus on TCDD**	
Incidence			
Through 1989 (n = 158 men exposed within 1 yr of accident vs 161 other BASF employees 1953–1969)			Zober et al., 1994
All non-cancerous respiratory diseases (ICD-9 460–419)	nr	33.7/31.0 (p = 0.22)	
COPD (ICD-9 490–496)	nr	8.0/7.5 (p = 0.31)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Monsanto workers (n = 240) involved in 2,4,5-T production (1948–1969) and 163 unexposed workers, results of clinical examination July, 1979—morbidity			Suskind and Hertzberg, 1984
"Abnormal" outcome on pulmonary-functions tests:			
FEV_1 (< 80% predicted)	32	2.81 (p = 0.02)	
FVC (< 80% predicted)	35	2.25 (p = 0.03)	
FEV_1/FVC (< 70%)	32	2.97 (p = 0.01)	
$FEF_{25–75}$ (< 80% predicted)	47	1.86 (p = 0.05)	

TABLE 13-2 COPD and Pulmonary Function, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, WA, and Wichita, KS) and workers who made PCP and TCP at two additional plants (in Midland, MI, and Sauget, IL)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	63	1.4 (0.1–1.8)	
PCP and TCP (n = 720)	10	0.7 (0.3–1.3)	
PCP (no TCP) (n = 1,402)	53	0.7 (0.3–2.2)	
Preliminary NIOSH Cross-sectional Medical Study—workers in production of sodium trichlorophenol, 2,4,5-T ester contaminated with TCDD—morbidity			
Chronic bronchitis and COPD	2	nr	Sweeney et al., 1997/98
ORs for increase in 1 ppt of serum TCDD compared to unexposed workers			Calvert et al., 1991
Chronic bronchitis	nr	0.5 (0.1–2.6)	
COPD	nr	1.2 (0.5–2.8)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916 men), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Mortality (COPD)			
Enrollment through 2007, vs state rates		SMR	Waggoner et al., 2011
Applicators (n = 1,641)	165	0.3 (0.3–0.4)	
Spouses (n = 676)	50	0.3 (0.2–0.4)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	50	0.2 (0.2–0.3)	
Spouses of private applicators (> 99% women)	15	0.3 (0.2–0.7)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	

continued

TABLE 13-2 COPD and Pulmonary Function, continued

Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Relative Risk (95% CI)[a]	Reference
Mortality			
25-yr follow-up to 2001—men and women			Consonni et al., 2008
COPD (ICD-9 490–493)			
Zone A	7	2.5 (1.2–5.3)	
Zone B	26	1.3 (0.9–1.9)	
Zone R	175	1.2 (1.0–1.4)	
20-yr follow-up to 1996			Bertazzi et al., 2001
COPD (ICD-9 490–493)	29	1.5 (1.1–2.2)	
Zone A	7	3.3 (1.6–6.9)	
Zone B	22	1.3 (0.9–2.0)	
15-yr follow-up to 1991—men			Bertazzi et al., 1998
COPD (ICD-9 490–493)			
Zone A	4	3.7 (1.4–9.8)	
Zone B	9	1.0 (0.5–1.9)	
Zone R	74	1.2 (0.9–1.5)	
15-yr follow-up to 1991—women			Bertazzi et al., 1998
COPD (ICD-9 490–493)			
Zone A	1	2.1 (0.3–14.9)	
Zone B	8	2.5 (1.2–5.0)	
Zone R	37	1.3 (0.9–1.9)	
10-yr follow-up to 1986—men (Zones A, B, R)			Bertazzi et al., 1989a
COPD (ICD-9 490–493)	31	1.1 (0.8–1.7)	
10-yr follow-up to 1986—women (Zones A, B, R)			Bertazzi et al., 1989a
COPD (ICD-9 490–493)	8	1.0 (0.5–2.2)	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; COPD, chronic obstructive pulmonary disease; EOI, Exposure Opportunity Index; FEF_{25-75}, forced midexpiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD-9, *International Classification of Diseases, 9th revision*; MOS, months of service; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; OR, odds ratio; PCP, pentachlorophenol; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Given when available; results other than estimated risk explained individually.

also showed no suggestion of increased mortality from COPD or non-cancerous respiratory disorders.

Almost all the studies of mortality in industrial cohorts considered in the VAO updates assessed only the nonspecific category of mortality due to non-cancerous respiratory disease, and no significant excesses were reported (Becher

et al., 1996; Burns et al., 2001; Kogevinas et al., 1997; Ott and Zober, 1996a; Steenland et al., 1999; 't Mannetje et al., 2005). Only an earlier mortality study of Dow 2,4,5-trichlorophenol (2,4,5-TCP) workers (Ramlow et al., 1996) reported on a more specific type of respiratory death, emphysema, which was not significantly increased. Only three studies of morbidity related to COPD in industrial populations have been considered in the VAO updates. Increases in the ORs for measures of abnormal pulmonary function were reported in workers at a 2,4,5-T plant in Nitro, West Virginia (Suskind and Hertzberg, 1984), but the other two cross-sectional studies of COPD prevalence had negative findings. Zober et al. (1994) found that episodes of COPD in workers at a BASF plant in Germany were not associated with TCDD exposure. The NIOSH Cross-sectional Study of production workers exposed to TCDD (Calvert et al., 1991) did not show an increase in COPD or chronic bronchitis or in altered pulmonary function measures associated with increased serum TCDD concentration in workers compared with a community-based referent population.

Waggoner et al. (2011) reported mortality in the AHS from the time of enrollment (1993–1997) through 2007. Death due to COPD was significantly decreased in applicators and their spouses. An early agricultural study (Senthilselvan et al., 1992) found no relationship between self-reported asthma and the use of phenoxy herbicides. Recently, the AHS has generated a number of publications with COPD-related findings. First, Blair et al. (2005a) found significant *decreases* in mortality due to COPD in private applicators and their spouses compared with state rates, which may have been due to the healthy-worker effect and the inability to adjust for low tobacco use. Analyses, with adjustment for smoking, of self-reported prevalence at enrollment (1993–1997) and prior exposure to phenoxy herbicides found indications of associations with chronic bronchitis in farmers (mostly men) that were significant for 2,4,5-T and 2,4,5-TP (Hoppin et al., 2007a) but only a 20 percent non-significant increase in nonsmoking farm women (Valcin et al., 2007); some association of phenoxy herbicide exposure with allergic asthma was evident (significant for 2,4-D in women and 2,4,5-T in men), but the association with nonallergic asthma in men (Hoppin et al., 2009) or women (Hoppin et al., 2008) was not so clear. The AHS has been generating valuable information on the COIs for a number of years, but these results, like those in Alavanja et al. (2005) and Blair et al. (2005a), are not herbicide-specific and so are not regarded as being fully informative for the committee's task.

Mortality studies of the Seveso incident have reported an emerging picture of increased risk of death from COPD (Bertazzi et al., 1998, 2001; Consonni et al., 2008; Pesatori et al., 1998) with higher and significant RRs found in the zone (A) closest to the accident and somewhat lower RRs in the outlying zones. Adjustment for smoking has not been possible for the Seveso cohort. In the only other relevant environmental study, Svensson et al. (1995b) assumed that TCDD exposure was higher in Swedish fishermen because of fish consumption but found no increase in mortality from bronchitis or emphysema. Dahlgren et al. (2003b)

reported that the prevalance of chronic bronchitis was positively associated with an environmental exposure to creosote and PCP emissions from a wood-processing plant, but strong concerns about bias are raised by the fact that the study sample was composed of plaintiffs in a law suit. There have been no other studies of environmental exposure to the COIs and COPD-related morbidity.

The large increase in relative risk of mortality from COPD in the ACC cohort that served in Vietnam (Cypel and Kang, 2010) motivated the committee to request additional information from Cypel and Kang (March 3, 2011, reply is available on request from the VAO public-access file). The committee learned that the six deaths from "pulmonary disease" among the deployed ACC veterans in the morbidity study (Table 5 in the 2010 paper) were indeed COPD cases; among the non-deployed ACC veterans in the morbidity study, there had been only one death from respiratory disease, and it had not been from COPD, and all the respiratory deaths had been in smokers. Conclusions from an analysis of COPD mortality in the ACC morbidity-study subset are limited by the very small number of deaths that had occurred by the end of 2005 and by the fact that this subset cannot be considered representative of the entire ACC cohort in that its members were all alive in 1999. Information on smoking status is available only on the people who participated in the 1999–2000 morbidity survey (of the 2,972 subjects, 71.5 percent of the deployed versus 60.1 percent of the non-deployed smoked), so the researchers lacked the ability to adjust the RR of COPD mortality in the entire ACC cohort (5,609). Because cigarette smoking is the major cause of COPD, the committee viewed this as strongly constraining the conclusions that could be drawn from the ACC data overall.

The committee for *Update 2010* consulted with Paul Enright of the University of Arizona, a medical expert on COPD. That consultation increased concern (as delineated at the beginning of this section on respiratory diseases) that the causes of death from COPD are frequently misclassified on death certificates. The common presence of comorbid conditions in people who have COPD makes it difficult to deduce a single contributing cause of death. Furthermore, it was emphasized that COPD is often incorrectly diagnosed in prevalence investigations, and there is considerable debate about the appropriate diagnosic criteria for COPD, particularly in relation to the normal decrease in capacity with age (Celli and Halbert, 2010a,b; Enright and Brusasco, 2010a,b).

Thus, the committee for *Update 2010* concluded that it could not base a conclusion about an association with COPD on mortality data, given the questionable nature of death-certificate information on COPD and the routine inability to adjust for smoking. That committee said that additional studies of the incidence of COPD, based on rigorous criteria for its diagnosis and adjustment for smoking, would be particularly valuable in resolving whether there is evidence to support an association with exposure to the COIs. The small amount of new data available to the committee for *Update 2012* did not alter its concurrence with the conclusions of the *Update 2010* committee.

This update includes new data that do not add coherence to this issue; Kang et al. (2014) and McBride et al. (2013) report data that are not suggestive of an association of exposure to herbicides in Vietnam with COPD, while the data from the Korean Veterans Health Study (Yi et al., 2014a,b) report an exposure-associated increase in both COPD mortality and prevalence after applying the Stellman model to assess exposure to herbicides. In view of this, we are unable to alter our prior stance. We are mindful of a prior commitment by the US Department of Veterans Affairs to undertake a morbidity follow-up on the ACC cohort, but the status of this work remains unknown to the committee and its results have yet to be published. Accordingly, we continue to concur with prior committee findings.

Other Specific Respiratory Diseases

There is still not a coherent body of epidemiology evidence to support conclusions as to whether the risks of other particular respiratory problems are associated with exposure to the COIs.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the COIs and mortality from all non-cancerous respiratory diseases or from COPD specifically. There is also inadequate or insufficient evidence of an association between exposure to the COIs and the prevalence of respiratory diseases, such as wheeze or asthma, COPD, and farmer's lung.

GASTROINTESTINAL AND DIGESTIVE DISEASES, INCLUDING LIVER TOXICITY

This section discusses a variety of conditions specified by ICD-9 520–579 or ICD-10 K00–K95: diseases of the esophagus, stomach, intestines, rectum, liver, and pancreas. Details on peptic ulcer and liver disease, the two conditions most often discussed in the literature reviewed, are provided below. The symptoms and signs of gastrointestinal disease and liver toxicity are highly varied and often vague.

The essential functions of the gastrointestinal tract are to absorb nutrients and eliminate waste. Those complex tasks involve numerous chemical and molecular interactions on the mucosal surface and complex local and distant neural and endocrine activity. One common condition of the gastrointestinal tract is motility disorder, which is present in about 15 percent of adults. The most convenient way to categorize diseases that affect the gastrointestinal system is according to the effected anatomic segment. Esophageal disorders predominantly affect swallowing,

gastric disorders are related to acid secretion, and conditions that affect the small and large intestines are reflected in alterations in nutrition, mucosal integrity, and motility. Some systemic disorders (inflammatory, vascular, infectious, and neoplastic conditions) also affect the gastrointestinal system.

Peptic-Ulcer Disease

Peptic-ulcer disease refers to ulcerative disorders of the gastrointestinal tract that are caused by the action of acid and pepsin on the stomach or duodenal mucosa. Peptic-ulcer disease is characterized as gastric or duodenal ulcer, depending on the site of origin. Peptic-ulcer disease occurs when the corrosive action of gastric acid and pepsin overcomes the normal mucosal defense mechanisms that protect against ulceration. About 10 percent of the population has clinical evidence of duodenal ulcer at some time in their life; a similar percentage is affected by gastric ulcer. The incidence of duodenal ulcer peaks in the fifth decade, and the incidence of gastric ulcer about 10 years later.

Evidence increasingly indicates that the bacterium *Helicobacter pylori* is linked to peptic-ulcer disease (both duodenal and gastric). *H. pylori* colonizes the gastric mucosa in 95 to 100 percent of patients who have duodenal ulcer and in 75 to 80 percent of patients who have gastric ulcer. Healthy people in the United States under 30 years old have gastric colonization rates of about 10 percent. Over the age of 60 years, colonization rates exceed 60 percent. Colonization alone, however, is not sufficient for the development of ulcer disease; only 15 to 20 percent of subjects who have *H. pylori* colonization will develop ulcers in their lifetimes. Other risk factors include genetic predisposition (such as some blood and human leukocyte antigen [HLA] types), cigarette smoking, and psychologic factors (chronic anxiety and stress).

Liver Disease

Blood tests that reflect liver function are the mainstay of diagnosis of liver disease. Increases in serum bilirubin and in the serum concentrations of some hepatic enzymes—aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, and γ-glutamyltransferase (GGT)—are commonly noted in liver disorders. The relative sensitivity and specificity of those enzymes for diagnosing liver disease vary, and a diagnosis can require several tests. The only regularly reported abnormality in liver function associated with TCDD exposure in humans is an increase in GGT. Estimated serum activity of that enzyme is a sensitive indicator of a variety of conditions, including alcohol and drug hepatotoxicity, infiltrative lesions of the liver, parenchymal liver disease, and biliary tract obstruction. Increases are noted after many chemical and drug exposures that are not followed by evidence of liver injury. The confounding effects of alcohol use (often associated with increased GGT) make the interpretation of changes

in GGT in exposed people difficult (Calvert et al., 1992). An increase in GGT can be considered a normal biologic adaptation to chemical, drug, or hormone exposure.

Cirrhosis is the most commonly reported liver disease in epidemiologic studies of herbicide or TCDD exposure. Cirrhosis is irreversible chronic injury of the liver with extensive scarring and a resulting loss of function. Clinical symptoms and signs include jaundice, edema, abnormalities in blood clotting, and metabolic disturbances. Cirrhosis can lead to portal hypertension with associated gastroesophageal varices, an enlarged spleen, abdominal swelling attributable to ascites, and, ultimately, hepatic encephalopathy that can progress to coma. It generally is impossible to distinguish the various causes of cirrhosis by using clinical signs and symptoms or pathologic characteristics. The most common cause of cirrhosis in North America and many parts of western Europe and South America is excessive alcohol consumption. Other causes are chronic viral infection (hepatitis B or hepatitis C), the poorly understood condition primary biliary cirrhosis, chronic right-sided heart failure, and a variety of less common metabolic and drug-related conditions.

Conclusions from *VAO* and Previous Updates

Some studies that have been reviewed by previous VAO committees focused on liver enzymes, and others reported specific liver diseases. An evaluation of the effects of herbicide and TCDD exposure on non-cancer gastrointestinal ailments is challenging in that clinical experience suggests that medical history and physical examination are undependable diagnostic tools for some ailments, so incidence data are sometimes problematic. The strong interdependence among the characteristics of a given person (such as weight and laboratory indexes of hepatic function and health) and TCDD body burden complicates the already difficult task of assessing association.

Most of the analyses of occupational or environmental cohorts have had insufficient numbers of cases to support confident conclusions. A study of the International Agency for Research on Cancer cohort of phenoxy-herbicide and chlorophenol production workers and sprayers (Vena et al., 1998), the only study that had a relatively large number of observations, found less digestive system disease and cirrhosis mortality in exposed workers than in non-exposed controls. A study that compared Australian veterans with the general population (O'Toole et al., 1996b) suggested a higher incidence of stomach and duodenal ulcers in both men and women, but the information was self-reported, and the analyses were not controlled for confounding influences.

A report from the AFHS (2000) found a significantly higher percentage of Ranch Hand veterans in the high-dioxin category had excesses of transaminase and other nonspecific laboratory measures of liver function than Southeast Asia comparison subjects. The data were consistent with an interpretation of a

dose–response relationship, but other explanations were also plausible. There have been later reports (AFHS, 2005) of some abnormalities in liver enzymes in the Ranch Hand cohort, including decreasing C4 complement as dioxin increased; abnormal triglyceride concentrations also increased as the 1987 dioxin concentration increased. However, mortality studies of the Ranch Hand cohort have not found increased mortality related to gastrointestinal or liver disease (Ketchum and Michalek, 2005).

A study of ACC Vietnam veterans found an increased rate of hepatitis associated with Vietnam service but not with a history of spraying herbicide (Kang et al., 2006). Additional analyses of the mortality experience of the ACC veterans were reviewed in *Update 2010* (Cypel and Kang, 2010). There was about an 80 percent excess of digestive system or cirrhosis deaths observed in veterans who handled or sprayed herbicides in Vietnam compared with non-Vietnam veteran peers, but chance could not be excluded as an explanation.

Likewise, the Australian Vietnam-veterans study (ADVA, 2005b) did not find an increase in liver disease in military personnel who served in Vietnam compared with the general population of Australia. A survey of self-reported health problems of Australian veterans indicated an excess of a variety of gastrointestinal problems, including diseases of the esophagus, ulcer, and irritable bowel syndrome but not gallstones (O'Toole et al., 2009); however, multiple methodologic weaknesses—including a low response rate, a lack of specific exposure information, and the inherent problems associated with self-reported health conditions—make the findings of this study unpersuasive.

The mortality results through 2001 for the Seveso cohort in Italy (Consonni et al., 2008) found no excess of deaths related to digestive diseases or related specifically to cirrhosis.

Several mortality studies of various occupational cohorts exposed to the COIs were reviewed (Boers et al., 2010, 2012; Collins et al., 2010a,b; Manuwald et al., 2012; McBride et al., 2009a,b; Ruder and Yiin, 2011). Those studies have been inconsistent but generally found no statistically significant increases in deaths from either ulcers or cirrhosis, although Collins et al. (2009c) found an increase in stomach and duodenal ulcer deaths in 773 workers who were exposed to chlorinated dioxins other than TCDD in the production of PCP.

Thus, the reports have been inconsistent, and interpreting individual studies is difficult because of a lack of information on alcohol consumption and other risk factors. In the studies that showed the strongest association between potential exposure and gastrointestinal disease (specifically cirrhosis), there was strong evidence that excess alcohol consumption was the cause of the cirrhosis.

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the COIs and gastrointestinal and digestive disease, including liver toxicity. Additional information available to the committees responsible for subsequent updates did not change that conclusion.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

The relationship between possible herbicide exposure and liver and gastric-ulcer disease was described in a sample of Korean Vietnam-era veterans in three publications by Yi et al. (2013, 2014a,b). The study is described in detail in Chapter 6. Using health insurance claims data, the adjusted prevalence of peptic-ulcer disease was found to be 3 percent higher in those with high putative exposure compared to low exposure (OR = 1.03, 95% CI 1.01–1.06) after adjusting for several behavioral, demographic and service-related factors. For liver disease, there was a small but statistically significant elevation in the prevalence of liver cirrhosis (OR = 1.08, 95% CI 1.01–1.16) and a significant log-linear relationship between an exposure opportunity score and the odds of having cirrhosis ($p = 0.007$). When using self-reported health information, herbicide exposure was weakly but significantly associated with chronic hepatitis and enterocholitis (ORs ≤ 1.12) when the exposures were based on the division-/brigade-level exposure data, but not when using data derived from battalion/company data.

In the mortality study in the same cohort (Yi et al., 2014b) there was no association between putative log-transformed exposure and mortality from peptic ulcers (hazard ratio [HR] per 1 log unit increase in estimated exposure = 0.98, 95% CI 0.84–1.15). However, there was a statistically significant relationship between the estimated exposure and deaths from liver cirrhosis (HR per 1 log unit increase in estimated exposure = 1.05, 95% CI 1.02–1.08). Highly exposed veterans had a 17 percent elevation in the mortality from cirrhosis compared with those with low exposure (HR = 1.17, 95% CI 1.05–1.30). Deaths from alcoholic liver disease were also elevated in the more highly exposed veterans (HR = 1.43, 95% CI 1.16–1.77).

Environmental Studies

Nakamoto et al. (2013) assembled a sample of 2,264 adult Japanese who were not occupationally exposed to dioxins. The presence of gastric ulcers was determined by self-report. There were no statistically significant associations with ulcer disease and either serum levels of dioxin-like PCDD/Fs, dioxin-like PCBs, or total TEQs after adjusting for age, sex, smoking, drinking, region, survey year, and BMI ($p = 0.07$, $p = 0.22$, and $p = 0.29$, respectively).

Yorita Christensen et al. (2013) reported the association between blood levels of 37 environmental pollutants and ALT levels in the National Health and Nutrition Examination Survey (NHANES) data. The analytic sample included 1,345 persons aged 12 years and older. Those who reported high alcohol intake or self-reported liver disease were excluded as were persons who had ALT levels greater than 81 U/L. In general, blood levels of DLCs were not significantly correlated

with ALT levels. The exception was 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin, which was associated with only a slight elevation (< 1 percent).

Occupational and Case-Control Studies

No occupational or case-control studies of exposure to the COIs and gastrointestinal and digestive disease have been published since *Update 2012*.

Biologic Plausibility

The liver is a primary target for the toxicity of many chemicals. It is the first organ that encounters chemicals absorbed from the gastrointestinal tract, and it is responsible for metabolizing them to water-soluble chemicals that can be excreted in the urine. Because the liver has many detoxifying enzymes that efficiently metabolize many chemicals, liver toxicity is usually associated only with high-dose acute exposure or lower-dose chronic exposure. The liver can be damaged if metabolism of a chemical results in the production of a reactive intermediate that is more toxic than the parent chemical. Changes in the serum concentrations of liver enzymes are biomarkers of liver toxicity, and their magnitudes correlate with the degree of liver damage. The exposure of laboratory animals to high doses of 2,4-D, 2,4,5-T, and TCDD is known to cause liver damage. The mechanisms by which the phenoxy herbicides damage the liver are based on the inhibition of mitochondrial function by the blocking of oxidative phosphorylation; this leads to a loss of generation of adenosine triphosphate, the death of cells, and hepatic necrosis and fibrosis. TCDD-induced hepatotoxicity is mediated by activation of the AHR, which leads to changes in gene transcription and associated changes in cell function. Changes in gene expression are associated with several physiologic processes, oxidative stress, and apoptosis (Boverhof et al., 2005, 2006). TCDD-mediated hepatic steatosis is characterized by the accumulation of triglyceride caused by the combined up-regulation of CD36/fatty acid translocase and fatty acid transport proteins, suppression of fatty acid oxidation, inhibition of hepatic export of triglycerides, increase in peripheral fat mobilization, and increase in hepatic oxidative stress (Lee JH et al., 2010). Recent evidence suggests that hepatic steatosis produced by TCDD might be mediated by the mitochondria (He et al., 2013). The exposure of rats to TCDD over a 2-year period (NTP, 2004) also produced several changes in the liver, including hepatocyte hypertrophy, multinucleated hepatocytes, inflammation, pigmentation, diffuse fatty change, necrosis, bile duct hyperplasia, bile duct cyst, nodular hyperplasia, portal fibrosis, and cholangiofibrosis.

The AHR displays species differences; for example, amino acid sequences in the C-terminal region of human and mouse AHR are only 58 percent identical. Compared with the mouse AHR, the human AHR has about a 10-fold lower

relative affinity for TCDD; the difference has been attributed to the amino acid residue valine 381 in the ligand-binding domain of the human AHR (Flaveny et al., 2009; Ramadoss and Perdew, 2004). The existence of species differences associated with AHR activation is supported by the divergence in the transcriptomic and metabolomic responses to TCDD in mouse, rat, and human liver (Boutros et al., 2008, 2009; Carlson et al., 2009; Forgacs et al., 2012, 2013; Kim et al., 2009; Nault et al., 2013). In a recent study, gene-expression changes were compared in adult female primary human and rat hepatocytes exposed to TCDD in vitro (Black et al., 2012). Whole-genome microarrays found that TCDD produced divergent gene-expression profiles in rat and human hepatocytes, both on an ortholog basis (conserved genes in different species) and on a pathway basis. For commonly affected orthologs or signaling pathways, the human hepatocytes were about 15-fold less sensitive than rat hepatocytes. Another recent microarray study examining species-specific transcriptomic differences in primary hepatocytes from humans, mice, and rats only identified 16 orthologous genes that were dysregulated by TCDD in all three species (Forgacs et al., 2013). Such findings are consistent with epidemiologic studies that have shown humans to be less sensitive to TCDD-induced hepatotoxicity. However, it should be noted that in vitro human hepatocyte studies may not reflect the in vivo response of human liver to TCDD.

Few health-relevant effects of phenoxy herbicides or TCDD on the gastrointestinal tract, even after high exposure, have been reported. Thus, the animal data do not support a plausible link between herbicide exposure and gastrointestinal toxicity in Vietnam veterans.

Synthesis

Prior to this update there was little convincing evidence of liver toxicity associated with exposure to the COIs. The publications from the Korean veterans study suggest a link between herbicide exposure and liver cirrhosis but not other GI diseases. Korea is notable for its very high rates of liver cirrhosis, which is related to both very high per capita alcohol consumption and high rates of hepatitis B and C infection. Thus, it is imperative that studies of cirrhosis be controlled for the potential confounding effects of these strong and prevalent factors. The prevalence data did control for self-reported alcohol consumption but not for prior infection with viral hepatitis. Possibly, herbicide exposure could potentiate the effect of viral exposures, but this hypothesis cannot be tested without data on infection status of the subjects. Given the absence of any supporting evidence that the COIs cause liver damage and the lack of control for critical potential confounders in the Korean veterans study, the committee concluded that there was inadequate or insufficient evidence to link herbicide exposure to liver cirrhosis.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and gastrointestinal and digestive diseases.

KIDNEY DISEASE

This is the first update for which the literature search identified studies reporting results concerning a possible association between exposure to the COIs and kidney diseases, which are grouped in ICD-9 580–589 or in ICD-10 N00–N29. An average person has two kidneys located in the lower back region; their main function is to use nephrons to filter wastes and excess water out of blood, which results in the production of urine. Kidneys are also responsible for helping to maintain the body's chemical balance, helping to control blood pressure, and making hormones. When problems arise with kidney function, it is often the result of damaged nephrons, which may leave the kidneys unable to filter blood and thus unable to remove wastes. A disorder characterized by gradual and usually permanent loss of kidney function, resulting in renal failure, is called chronic kidney disease. Diabetes, hypertension, and glomerulonephritis (acute inflammation) can all increase the risk of kidney disease.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Publications from the Korean Veterans Health Study included findings for non-malignant kidney disease. This study derived EOI scores based on the proximity of the veteran's unit to sprayed areas using a geographical information system–based model (Stellman et al., 2003b) developed flight records of the US spray missions. In the first article, Yi et al. (2013a) examined the prevalence of self-reported diseases from a postal survey of 114,562 Korean Vietnam veterans with respect to their perceived herbicide exposure as assessed by a six-item questionnaire. Self-reported kidney failure was found to be significantly increased in terms of the perceived exposures, but not when analysis was based on the EOI scores. The more reliable information on the occurrence of disease from 2000 to 2005 gathered from the Insurance Review and Assessment Service of Korea and the Veterans Health Service was analysed in Yi et al. (2014a), but no findings were presented for any form of kidney disease.

Data on vital status and cause of death through 2005 for 180,639 Korean Veterans alive in 1992 were assembled from death records at the National Statistical Office and analyzed by Yi et al. (2014b). The causes of death were classified

according to ICD-10 in all instances where 10 or more cases were documented. With adjustment for the veteran's age in 1992 and rank, no differences were observed in the hazard ratios for acute renal failure [ICD-10 N17] or for chronic renal failure [ICD-10 N18] when analyses were based on the EOI scores either used individually in regression or grouped for a high- versus low-exposure comparison.

Environmental Studies

In a cross-sectional study of 1,063 men and 1,201 women living throughout Japan (who had not been occupationally exposed to dioxins), 47 cases of kidney disease (not otherwise characterized) were reported (Nakamoto et al., 2013). Fasting blood samples were gathered from 2002 to 2010 for assessment of environmental exposure to DLCs. Blood concentrations and the corresponding TEQs were determined individually for dioxin-like PCDDs, PCDFs, and PCBs. With adjustment for age, sex, smoking, drinking, regional block, and survey year, logistic regression on concentration (pg/g lipid) was used to estimate the odds of self-reported kidney disease in the upper three quartiles versus the lowest quartile for dioxin-like PCDD/Fs, for dioxin-like PCBs, and combined for all DLCs. None of these paired comparisons approached significance, but all the estimated ORs versus the lowest quartile were consistently less than one. In addition, trend in concentration across all quartiles was assessed for each grouping of DLCs (p for trend = 0.21, 0.90, and 0.28 for PCDD/Fs, PCBs, and total DLCs, respectively). Overall, there was no indication of association between dioxin-like activity in blood and self-reported kidney disease.

Jayatilake et al. (2013) sought to determine the factors contributing to a form of kidney disease not related to diabetes, hypertension, or any other recognized cause. Recent studies had found chronic kidney disease of uncertain etiology to be prevalent in 2 to 3 percent of adults in Sri Lanka. Screening of endemic areas in the northern interior of the island identified 733 cases, and 4,044 individuals without diabetes or any kidney disease were retained as controls; another 250 controls were gathered in non-endemic coastal areas. In addition to consideration of environmental metal levels, pesticide exposure was addressed by gathering urine samples from 57 cases and 39 controls from non-endemic areas. The samples were analyzed for 11 biomarkers of pesticides, including the COIs 2,4-D, 2,4,5-T, and 2,4,5-TCP. Of these, only 2,4-D was among the seven biomarkers found at concentrations above the limit of detection; 3.5 percent of the cases had 2,4-D concentrations above the reference limit of 0.3 µg/l. Since urinary pesticide results were presented for only the cases, no inference can be made about relative risk for this kidney condition in association with 2,4-D.

Occupational and Case-Control Studies

No occupational or case-control studies of exposure to the COIs and kidney disease have been published since *Update 2012*.

Biologic Plausibility

Currently, there are no toxicologic studies relevant to exposure to any of the COIs and the occurrence of any form of nonmalignant kidney disease.

Synthesis

No statistical findings from epidemiology studies concerning kidney disease have been reported previously in the VAO series. The few findings on this health outcome reviewed by the current committee do not present any coherent pattern of an association between exposure to the COIs and kidney disorders.

Conclusion

The committee found that these first epidemiologic results addressing kidney disease in relation to exposure to the COIs constituted inadequate or insufficient evidence of an association between nonmalignant kidney diseases and exposure to the herbicides sprayed in Vietnam.

THYROID HOMEOSTASIS OR OTHER ENDOCRINE FUNCTIONS

This section discusses a variety of conditions related to endocrine function, excluding diabetes and other pancreatic disorders [ICD-9 250–251 or ICD-10 E08–E16], which were discussed in Chapter 12. Clinical disruptions of thyroid function in particular are grouped as ICD-9 240–246 or as ICD-10 E00–E07, E20–21, while the remaining endocrine disorders are grouped as ICD-9 252–259 or as ICD-10 E22–E35.

The thyroid secretes the hormones thyroxine (T_4) and triiodothyronine (T_3), which stimulate and help to regulate metabolism throughout the body. The thyroid also secretes calcitonin, a hormone that controls calcium concentration in the blood and the storage of calcium in bones. Secretion of T_4 and T_3 is under the control of thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary. Iodine operates in thyroid physiology both as a constituent of thyroid hormones and as a regulator of glandular function. Concentrations of those circulating hormones are regulated primarily by a negative-feedback pathway that involves three organs: the thyroid, the pituitary, and the hypothalamus. In the hypothalamus–pituitary–thyroid feedback scheme, the hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the pituitary to produce TSH, which triggers the thyroid to produce T_4 and T_3. Cells in the hypothalamus and pituitary respond to concentrations of circulating T_4 and T_3. When T_4 and T_3 are low, the pituitary is stimulated to deliver more TSH to the thyroid, which increases T_4 and T_3 output. When circulating T_4 and T_3 are high, it triggers a

reduction in the output of TRH and TSH. The negative-feedback loop maintains hormone homeostasis.

A disruption of thyroid homeostasis can be stimulatory (hyperthyroidism) or suppressive (hypothyroidism). Both conditions are diagnosed on the basis of blood concentrations of thyroid hormones, TSH, and other proteins (antithyroid antibodies). The prevalence of thyroid dysfunction in adults in the general population ranges from 1 percent to 10 percent, depending on the group, the testing setting, sex, age, the method of assessment, and the presence of conditions that affect thyroid function. People who have subclinical (biochemical) conditions may or may not show other evidence (signs or symptoms) of thyroid dysfunction.

In *hypothyroidism*, the body lacks sufficient thyroid hormone. Overt hypothyroidism is seen as a high serum concentration of TSH and a low serum concentration of free T_4. Subclinical hypothyroidism is defined as a high serum concentration of TSH and a normal serum concentration of free T_4. People who have hypothyroidism typically have symptoms of low metabolism. Studies consistently show that subclinical hypothyroidism is common and occurs more frequently in women than in men (Canaris et al., 2000; Hollowell et al., 2002; Sawin et al., 1985). In the Framingham study, for example, among 2,139 people 60 years old or older, 14 percent of women and 6 percent of men had subclinical hypothyroidism (Sawin et al., 1985). Subclinical hypothyroidism is a risk factor for overt hypothyroidism. Studies have reported associations of hypothyroidism with a wide variety of other conditions. Chemically induced hypothyroidism can develop because of direct effects on the functional cell types in the thyroid gland or because of an induction of auto-antibodies that destroy thyroid tissue, such as in Hashimoto's disease, an auto-immune form of thyroiditis.

The term *hyperthyroidism* may involve any disease that results in overabundance of thyroid hormone. Clinical or overt hyperthyroidism is characterized as a low serum concentration of TSH and a high serum concentration of free T_4. Subclinical hyperthyroidism is defined as a low serum concentration of TSH and a normal serum concentration of free T_4. The prevalence of subclinical hyperthyroidism has been estimated at about 1 percent in men and 1.5 percent in women over 60 years old (Helfand and Redfern, 1998). Conditions associated with hyperthyroidism include diffuse toxic goiter and Graves disease, an autoimmune disease in which antibodies are produced that mimic the activity of TSH. Like hypothyroidism, hyperthyroidism is more common in women than in men, and, although it occurs at all ages, it is most likely to occur in people more than 15 years old. A form of hyperthyroidism called neonatal Graves disease occurs in infants born to mothers who have Graves disease. Occult hyperthyroidism may occur in patients more than 65 years old and is characterized by a distinct lack of typical symptoms.

It is important to distinguish between potential effects on adults and effects that may occur during development. In adults, the thyroid is able to compensate, within reasonable limits, for mild or moderate disruption (such as that caused by hyperplasia or goiter). In contrast, the fetus is highly sensitive to alterations in

thyroid hormones, and alterations in thyroid homeostasis can hamper the development of many organ systems, including the nervous and reproductive systems; such findings are discussed in Chapter 10, which addresses the potential effects of Vietnam veterans' exposure to herbicides on their offspring. Only observations on adults are considered here.

Summary of Previous Updates

Thyroid homeostasis in humans was first addressed with respect to the COIs by the VAO committee for *Update 2002*.

Extensive assessment of endocrine function in clinical examinations, including a series of thyroid-function tests, failed to show systematic differences in thyroid function when contrasting veterans who participated in Operation Ranch Hand and control veterans (AFHS, 1991a). In analyzing individual TCDD readings obtained for subjects in the AFHS, however, Pavuk et al. (2003) found statistically significantly increased TSH measures from the 1985 and 1987 examinations in the high-exposure category and a significantly increasing trend across the three TCDD categories in data gathered during the 1982, 1985, 1987, and 1992 examinations. Other studies of veterans of the Vietnam War have not documented an increased risk of thyroid disease.

Calvert et al. (1999) provided evidence of higher adjusted mean free-T_4 concentrations in TCDD-exposed workers in the NIOSH Cross-sectional Medical Study, but there was no dose–response relationship with serum TCDD. Bloom et al. (2006) found indications of an inverse relationship between the sum of DLCs and the concentration of free T_4 in anglers in New York State but no association between the sum of DLCs and TSH or T_3. Abdelouahab et al. (2008) described thyroid function in adult freshwater-fish consumers in Canada; dioxin-like congeners were associated with an increase in TSH and a decrease in T_4 but below the threshold at which clinical symptoms would be present. An analysis of 1999–2002 NHANES data (Turyk et al., 2007) found total T_4 to have a weak inverse relationship with serum TEQs; the effect was somewhat stronger in people over 60 years old and in women as compared with men. Clear effects of DLCs on thyroid function were not apparent in Inuit adults (Dallaire et al., 2009) or in a cross-sectional study of a Chinese community exposed to an electronic-waste recycling plant (Zhang J et al., 2010).

In a study focusing on pesticide use, Chevrier et al. (2008) did not find evidence of effects on thyroid function among women enrolled at the Center for the Health Assessment of Mothers and Children of Salinas in California. Goldner et al. (2010) also published negative results for an association between phenoxy-herbicide exposures and self-reported history of physician-diagnosed thyroid disease in women in the AHS. Schreinemachers (2010) did not find associations of recent exposure to 2,4-D with T_4 and TSH concentrations in subjects in NHANES III (1988–1994).

Table 13-3 summarizes findings of studies that have examined the association between dioxin-like congeners and markers of thyroid function. Shaded entries are new findings in this update.

As early as 1994, Koopman-Esseboom et al. noted an inverse association between dioxin-like congeners and markers of disrupted thyroid homeostasis in pregnant women. There has been considerable further study of maternal exposure and perinatal effects on thyroid function, which is not directly applicable to the adult exposure of the mostly male Vietnam veterans whose own health is the primary concern of these updates. A discussion of that material can be found in Chapter 10, on possible adverse effects on the offspring of Vietnam veterans.

Update of the Scientific Literature

Several new epidemiologic studies of occupational or environmental exposure to the COIs or of Vietnam veterans and effects on thyroid homeostasis have been published since *Update 2012*. Mass media coverage of conference presentations in 2010 created an expectation of results from a study of Graves disease, an autoimmune hyperthyroid condition. Two papers in preparation were mentioned in a descriptive article lacking actual data (Spaulding, 2011); however, because peer-reviewed publications derived from the preliminary findings still have not appeared, VAO committees have had to disregard this study.

Vietnam-Veteran Studies

In an effort to quantify herbicide exposures experienced during the Vietnam War, Yi et al. (2014a,b) generated EOIs for 111,726 men in the Korean Veterans Health Study by applying the Stellman model (Stellman et al., 2003b).

Yi et al. (2014a) gathered morbidity information for January 2000 through September 2005 on 111,726 of these veterans who had responded to a postal questionnaire in 2004. Claims data from the Health Insurance Review and Assessment of Korea and from the Veterans Health Service were searched for ICD-10 diagnoses corresponding to this set of subjects. With adjustment for age, military rank, smoking, drinking, physical activity, household income, herbicide exposure at home, and BMI, logistic regression on the logarithms of the individual EOI scores was performed. The EOI scores were also partitioned into groups with high or low potential for herbicide exposure. Adjusting for the same factors, the prevelances in the high and low groups were compared. Thyroid conditions overall [ICD-10 E00–E07] showed an indication of increased risk with herbicide exposure both in the internal comparison (OR = 1.06, 95% CI 1.00–1.12) and with analysis of individual scores (OR = 1.01, 95% CI 1.00–1.03). The pattern was very similar for both non-iodine-deficiency hypothyroidism [ICD-10 E03]: for high versus low (OR = 1.13, 95% CI 1.01–1.25) and for individual scores

TABLE 13-3 Selected Epidemiologic Studies—Thyroid Homeostasis (Shaded entries are new information for this update)

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Cross-sectional analysis of Ranch Hand personnel (n = 1,009) and SEA veterans (n = 1,429); TSH, total T4, T3%			Pavuk et al., 2003
TSH uptake by TCDD category			
Comparisons (SEA veterans—no TCDD spraying)	1,247	Normal = 0–3 µIU/ml	
RH background (TCDD ≤ 10 ppt)	409	0.84 (p = 0.88)	
RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	0.87 (p = 0.16)	
RH high (TCDD > 94 ppt)	275	0.90 (p = 0.04)	
T4 (thyroxine) means by TCDD category		Normal = 4.5–11.5 µg/dl	
Comparisons (SEA veterans—no TCDD spraying)	1,247	7.47	
RH background (TCDD ≤ 10 ppt)	409	7.56 (p = 0.19)	
RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	7.54 (p = 0.38)	
RH high (TCDD > 94 ppt)	275	7.56 (p = 0.28)	
T3% (triiodothyronin) uptake by TCDD category		Normal 25%–35%	
Comparisons (SEA veterans—no TCDD spraying)	1,247	30.7	
RH background (TCDD ≤ 10 ppt)	409	30.7 (p = 0.19)	
RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	30.7 (p = 0.98)	
RH high (TCDD > 94 ppt)	275	30.5 (p = 0.24)	
International Vietnam-Veteran Study			
Sample of 1,000 Male Australian Vietnam Veterans—prevalance		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey (disorders of the thyroid gland)	450	1.4 (0.5–2.2)	O'Toole et al., 2009
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 42,421) vs low exposure (n = 69,305) (individual EOI scores) (HRs; ICD-10)		**All COIs**	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
Prevalence (01/2000–09/2005)—log EOI scores			Yi et al., 2014a
Disorders of the thyroid gland [E00–E07]	5,408	1.0 (1.0–1.0)	
Non-iodine-deficiency hypothyroidism [E03]	1,444	1.0 (1.0–1.1)	
Other nontoxic goiter [E04]	953	1.0 (1.0–1.0)	
Thyrotoxicosis (hyperthyroidism) [E05]	2,476	1.0 (1.0–1.0)	
Thyroiditis [E06]	423	1.0 (1.0–1.1)	
Autoimmune thyroiditis [E06.3]	92	1.2 (1.1–1.3)	
Prevalence (01/2000–09/2005)—categorized high (n = 2,134) vs low (n = 3,274) (5.0% vs 4.7%)			
Disorders of the thyroid gland [E00–E07] (2,134 vs 3,274)		1.1 (1.0–1.1)	
Non-iodine-deficiency hypothyroidism [E03] (598 vs 846)		1.1 (1.0–1.3)	
Other nontoxic goiter [E04] (386 vs 567)		1.1 (1.0–1.3)	
Thyrotoxicosis (hyperthyroidism) [E05] (951 vs 1,525)		1.0 (0.9–1.1)	
Thyroiditis [E06] (175 vs 248)		1.2 (1.0–1.4)	
Autoimmune thyroiditis [E06.3] (48 vs 92)		1.9 (1.3–2.9)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort— Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
NIOSH Cohort—TCDD-exposed workers from 2,4,5-T plants in Newark, NJ, and Verona, MO, employed > 15 yrs earlier and matched controls (n = 260)			Calvert et al., 1999
TSH mU/1		Adjusted mean (SE)	
All workers	278	2.0 (0.1) p = 0.66	
TCDD < 20	75	2.2 (0.3) p = 0.28	
20 ≤ TCDD < 75	66	2.0 (0.3) p = 0.88	
75 ≤ TCDD < 238	66	1.9 (0.3) p = 0.94	
238 ≤ TCDD < 3,400	64	1.8 (0.3) p = 0.65	
Referents (< 20)	257	1.9 (0.1)	

continued

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
T4 nmol/l		Adjusted mean (SE)	
All workers	278	101.4 (1.0) p = 0.07	
TCDD < 20	75	102.7 (2.0) p = 0.08	
20 ≤ TCDD < 75	66	99.4 (2.1) p = 0.79	
75 ≤ TCDD < 238	66	102.7 (2.1) p = 0.09	
238 ≤ TCDD < 3,400	64	100.1 (2.2) p = 0.58	
Referents (< 20)	257	98.8 (1.1)	
Free T4 index nmol/l		Adjusted mean (SE)	
All workers	278	27.8 (0.3) p = 0.02	
TCDD < 20	75	27.7 (0.5) p = 0.15	
20 ≤ TCDD < 75	66	27.4 (0.6) p = 0.36	
75 ≤ TCDD < 238	66	28.2 (0.6) p = 0.03	
238 ≤ TCDD < 3,400	64	27.7 (0.6) p = 0.19	
Referents (< 20)	257	26.8 (0.3)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
AUSTRALIAN 2,4,5-T in Victoria, Australia (n = 37)		**2,4-D, 2,4,5-T**	Johnson et al., 2001
TSH vs estimated serum TCDD level	32	Normal = 0.3–5.0 µIU/ml	
Based on local levels		0.2	
Based on individual sampling LDs		–.03	
Based on back extrapolation		–1.4 (p < 0.05)	
T4 vs estimated serum TCDD level	32	Normal = 0.045–2.125 µg/ml	
Based on local levels		0.1	
Based on individual sampling LDs		–0.0	
Based on back extrapolation		–0.0	
T3 vs estimated serum TCDD level	32	Normal = 0.9–1.9 µg/ml	
Based on local levels		–0.1	
Based on individual sampling LDs		–0.4 (p < 0.05)	
Based on back extrapolation		–0.5 (p < 0.01)	
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916 men), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
Incidence			
Thyroid disease among male pesticide sprayers (n = 22,327) in Iowa and North Carolina (1993–2010)			Goldner et al., 2013
Self-reported hypothyroid disease (n = 461)			
Self-reported 2,4-D exposure	392	1.4 (1.0–1.8)	
Self-reported 2,4,5-T exposure	153	1.4 (1.1–1.7)	
Self-reported 2,4,5-TP exposure	67	1.4 (1.1–1.8)	
Self-reported dicamba exposure	289	1.4 (1.1–1.7)	
Hypothyroid disease			
Self-reported 2,4-D use, higher than median	207	1.4 (1.1–1.9)	
Self-reported 2,4-D use, less than median	177	1.2 (1.0–1.8)	
Incidence			
Thyroid disease among female spouses (n = 19,529) in Iowa and North Carolina (1993–2003)			Goldner et al., 2010
Hyperthyroid			
Self-reported 2,4-D exposure	46	0.9 (0.7–1.3)	
Self-reported 2,4,5-T exposure	3	NA	
Self-reported dicamba exposure	17	0.8 (0.8–2.1)	
Hypothyroid			
Self-reported 2,4-D exposure	147	1.0 (0.8–1.1)	
Self-reported 2,4,5-T exposure	7	1.0 (0.5–2.2)	
Self-reported dicamba exposure	27	0.7 (0.5–1.0)	
Other thyroid conditions			
Self-reported 2,4-D exposure	87	1.2 (1.0–1.5)	
Self-reported 2,4,5-T exposure	4	NA	
Self-reported dicamba exposure	19	1.0 (0.6–1.5)	
ENVIRONMENTAL			
National Health and Nutrition Examination Survey		2,4-D	
NHANES III—analysis of data from subjects with detectable limits of urinary 2,4-D			Schreinemachers, 2010
TSH			
Detectable 2,4-D	102	1.6 mU/L	
Non-detectable 2,4-D	625	1.7 mU/L	

continued

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
T4			
Detectable 2,4-D	102	8.5 µg/dl	
Non-detectable 2,4-D	625	8.6 µg/dl	
NHANES (1999–2002, 2001–2002)—Associations with TEQs in individuals without thyroid disease			Turyk et al., 2007
Men (1999–2000)			
T4	402	–0.12 (–0.61 to 0.37)	
TSH	402	–0.09 (–0.38 to 0.20)	
Men (2000–2001)			
T4	497	–0.47 (–0.97 to 0.04)	
TSH	497	–0.02 (–0.20 to 0.16)	
Women (1999–2000)			
T4	310	–0.19 (–0.70 to 0.33)	
TSH	309	–0.15 (–0.14 to 0.44)	
Men (1999–2000)			
T4	386	–0.58 (–1.26 to 0.10)	
TSH	385	–0.06 (–0.15 to 0.35)	
Other Environmental Studies			
CANADA			
Cross-sectional study of Inuit residents (≥ 18 yrs of age) of Nunavik (Québec, Canada)	607	**dl PCBs**/correlation of dl-congeners (adjusted)	Dallaire et al., 2009
TSH		0.02	
fT4		–0.01	
fT3		–0.03 ($p < 0.05$)	
Cross-sectional study of freshwater fish consumers from two Canadian communities		**dl PCBs**/ dl-PCB congeners ß estimates	Abdelouahab et al., 2008
Men	124		
TSH		0.55 ($p < 0.001$)	
T4		–2.19 ($p < 0.05$)	
T3		–0.01	
Women	87		
TSH		0.04	
T4		0.04	
T3		–0.01	
Cross-sectional examination of serum from pregnant women attending Canadian prenatal diagnosis clinic	150	**dl compounds**	Foster et al., 2005
TSH correlation coefficient		ns (value nr)	
T4 correlation coefficient		ns (value nr)	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
CHINA—cross-sectional study of a Chinese community in the vacinity of an electronic-waste recycling plant—maternal serum T4 levels at 16 weeks gestation (correlations with contaminant levels in cord blood)		**PCDDs, PCDFs, dl PCBs**	Zhang J et al., 2010
dl PCBs		r = –0.413 (p = 0.01)	
PCDD/Fs		r = –0.198 (p = 0.21)	
ITALY—Seveso Women's Health Study—Industrial accident July 10, 1976; 981 women between infancy and 40 yrs of age at time of accident, who resided in Zones A and B		**TCDD**	Chevrier et al., 2014
1996 thyroid hormone measurements (postmenarche at exposure):			
TSH	637	9.3 (–0.8–20.3)	
Total T4	629	–0.1 (–0.4–0.1)	
Free T4	634	0.0 (–0.1–0.1)	
Free T3	635	–0.0 (–0.0–0.0)	
JAPAN			
2,253 Japanese from general population not occupationally exposed to dioxins, aged 15–76 yrs in 2002–2008,		**Total Serum TEQ**	Nakamoto et al., 2013
Thyroid disease (10 cases in men; 63 cases in women)	73		
Quartile 1		1.0	
Quartile 2		1.0 (0.5–2.4)	
Quartile 3		1.2 (0.5–2.7)	
Quartile 4		0.7 (0.3–1.9)	
		p-trend = 0.32	
Yusho patients exposed in 1968 during Yusho incident; blood collection from participants 1996 and 1997	16	**PCDDs, PCDFs, dl PCBS**	Nagayama et al., 2001
TSH correlation coefficient		0.01 (p = 0.97)	
T4 correlation coefficient		0.03 (p = 0.90)	
T3 correlation coefficient		–0.09 (p = 0.74)	

continued

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
KOREA—105 pregnant Korean women provided blood samples the day before delivery		**dl mono-ortho PCB 118**	Kim et al., 2013
		β (95% CI)	
Free T_3		–0.020 (–0.091–0.005)	
Total T_3		–0.114 (–0.223–0.005)	
Free T_4		–0.049 (–0.136–0.038)	
Total T_4		–0.047 (–0.134–0.040)	
TSH		0.389 (–0.183–0.960)	
THE NETHERLANDS—Part of the prospective longitudinal Dutch PCB/Dioxin study; 105 health mother-infant pairs living in or around Rotterdam, recruited June 1990–February 1992		**Dioxins, PCBs**	Koopman-Esseboom et al., 1994
Maternal serum correlations with dioxin TEQs	78		
T4		–0.4 ($p \leq 0.001$)	
T3		–0.5 ($p \leq 0.001$)	
UNITED STATES			
CHAMACOS Study—334 pregnant women from Salinas Valley, CA, providing blood at 26 wks gestation		**dl PCBs** ß (95% CI)	Chevrier et al., 2008
Free T4 vs:			
PCB TEQs (pg/g)		–0.05 (–0.16 to 0.06)	
Mono-ortho PCBs (ng/g)		–0.09 (–0.19 to 0.01)	
PCB 118 (ng/g)		–0.05 (–0.15 to 0.06)	
PCB 156 (ng/g)		–0.06 (–0.13 to 0.01)	
Total T4 vs:			
PCB TEQs (pg/g)		0.26 (–0.45 to 0.96)	
Mono-ortho PCBs (ng/g)		–0.13 (–0.78 to 0.53)	
PCB 118 (ng/g)		–0.26 (–0.43 to 0.95)	
PCB 156 (ng/g)		–0.05 (–0.52 to 0.42)	
Adult men recruited from Massachusetts infertility clinic (2000–2003)	341	**dl PCBs** Estimated risk (95% CI)	Meeker et al., 2007
T3		0.02 (0.05–0.01)[a]	
fT4		0.01 (0.01–0.05)[a]	
fTSH		0.93 (0.84–1.03)[a]	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
Sportfish anglers from New York exposed to dioxin-like compounds in diet	38	**PCDDs, PCDFs, dl PCBs** mean/median (range)	Bloom et al., 2006
TSH µUL/ml		2.0/1.4 (0.2–15.7)	
T4 µg/dL		6.3/6.4 (3.2–10.0)	
Free T4 ng/ml		1.1/1.1 (0.9–1.6)	
T3 ng/dL		92.6/87.5 (56.0–181.0)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; dL, deciliter; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; LD, level of detection; ml, milliliter; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, nonsignificant; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDD/Fs, chlorinated dioxins and furans combined; PCDF, polychlorinated dibenzofurans; ppt, parts per trillion; SE, standard error; SEA, Southeast Asia; RH, Ranch Hand; T3, triiodothyronine; T4, tetraiodothyronine; TCDD, tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; TSH, thyroid stimulating hormone.

[a]Adjusted coefficients for change in thyroid hormone level associated with an interquartile range increase in serum dioxin-like congeners.

(OR = 1.02, 95% CI 1.00–1.05), and for other nontoxic goiter [ICD-10 E04]: for high versus low (OR = 1.14, 95% CI 1.00–1.31) and for individual scores (OR = 1.01, 95% CI 0.98–1.04). The risk of thyroiditis [ICD-10 E06] overall was not found to be significantly associated with heribicide exposure. The strongest endocrine-related results, however, were for the specific subtype of thyroiditis, auto-immune thyroiditis [ICD-10 E06.3]: for high versus low (OR = 1.93, 95% CI 1.27–2.94) and for individual scores (OR = 1.16, 95% CI 1.05–1.28). The risk of hyperthyroidism [ICD-10 E05] was not significantly different from 1.00.

Yi et al. (2014b) screened the death records of the National Statistical Office for 1992–2005 to establish vital status for 180,639 of these Korean veterans of the Vietnam War. Results for deaths from endocrine diseases were presented only for the broad range of ICD-10 E00–E88, for which no significant association with herbicide exposure was noted for either the high versus low comparison or for the analysis based on individual scores. No information was provided on mortality for subtypes of endocrine conditions, so nothing was revealed about mortality from disorders specifically involving thyroid dysfunction.

Occupational Studies

Goldner et al. (2013) reported on new results of the prospective AHS in which male private pesticide applicators were asked (by questionnaire) about their use between 1993 and 1997 of 50 specific agents, including 2,4-D, 2,4,5-T, 2,4,5-triphenoxy-proprionic acid (2,4,5-TP) and about any history of physician-diagnosed thyroid disease between 2005 and 2010 (by phone interview). Of 35,505 men with complete pesticide use data, 22,854 provided the requested data about thyroid disease. Among the 22,246 who had data on all the covariates needed for analysis, 175 reported hyperthyroidism, 461 reported hypothyroidism, and 283 reported other thyroid conditions. After adjusting for age, education, and BMI, the ORs of hypothyroidism for ever-use versus never-use were significantly elevated for 2,4-D (OR = 1.35, 95% CI 1.04–1.76, 392 cases), for 2,4,5-T (OR = 1.38, 95% CI 1.12–1.69, 153 cases), and for 2,4,5-TP (OR = 1.39, 95% CI 1.06–1.82, 67 cases). Intensity-weighted data (cumulative days of use) were available for 2,4-D. In comparison with those who had never used 2,4-D, an increased risk of hypothyroidism was seen in both those who had used 2,4-D for more than the median number of days (OR = 1.40, 95% CI 1.06–1.85, 207 cases) and those whose days of 2,4-D use were fewer than the median (OR = 1.34, 95% CI 1.01–1.78, 177 cases), and the p-value for the trend was 0.025. The use of 2,4,5-TP was found to be inversely related to having a history of hyperthyroidism (OR = 0.46, 95% CI 0.23–0.90). None of the phenoxy herbicides was found to be related to having histories of other thyroid diseases. No analyses of arsenic-based herbicides were presented in this paper.

Environmental Studies

In a cross-sectional study of 1,063 men and 1,201 women living throughout Japan (who had not been occupationally exposed to dioxins), 73 cases of thyroid diseases were reported (Nakamoto et al., 2013). Fasting blood samples were gathered from 2002 to 2010 for an assessment of environmental exposure to DLCs. Blood levels and the corresponding TEQs were determined for dioxin-like PCDD/Fs and PCBs. In addition to estimating trend across all quartiles (pg/g lipid), logistic regression with adjustment for age, sex, smoking, drinking, regional block, and survey year was used to estimate the odds of self-reported thyroid diseases in the upper three quartiles versus the lowest quartile for PCDD/Fs, for PCBs, and combined for all DLCs. The results for thyroid diseases showed no association with any of these three exposure groupings (p for trend over the quartiles = 0.75, 0.24, and 0.32, respectively). Because of the lack of information about the particular type of thyroid disorder, these results are not useful for assessing the prevalance of hypothyroidism specifically.

Among women exposed in the Seveso incident, Chevrier et al. (2014) found a significant inverse association between serum concentrations of TCDD in 1976

(n = 981) and 1996 (n = 260) with serum total thyroxine (T_4), but not with TSH or free T_3, which were measured in 1996 (n = 909). This association was stronger for women who were exposed before menarche than for women exposed after menarche. When thyroid hormones were measured again in 2008 (n = 724) and compared with TCDD levels in 1976 and 1996, the association was no longer present.

In their endeavor to derive individual TEFs for DLCs on a more relevant basis than the responses of acutely exposed laboratory animals, Trnovec et al. (2013) generated a set of input data by measuring two aspects of thyroid function (thyroid gland volume and free T_4) in 320 adults from an organochlorine-contaminated area in Slovakia. These measures were chosen for the consistency of their response to dioxin-like activity in both animals and humans. Blood samples from these subjects produced readings above the limits of detection (LODs) for all 7 dioxins, 8 of 10 furans, and all but 1 of the 12 PCBs on the 2005 WHO list of DLCs. Unfortunately, for 3 of the 4 non-ortho PCBs (which have stronger dioxin-like activity than the mono-ortho PCBs), so many of the samples had concentraions below the LODs that analyses could not be performed on these congeners. The article focused on describing the derivation of the TEFs and did not present the statistical properties of the assembled input data, but Trnovec et al. (2013) did note that the two thyroid response variables were selected for this human TEF project because they have consistently shown significant inverse relationships with the DLCs.

During 2011, Kim et al. (2013) collected blood samples from 138 pregnant women during the day before delivery at five Korean hospitals. These samples were analyzed for free T_3, total T_3, free T_4, total T_4, and TSH and for concentrations of 19 PCB congeners, of which only the mono-ortho PCB 118 has dioxin-like activity. The pattern for PCB 118 was very similar to that of the non–dioxin-like PCBs measured: a positive relationship with TSH and negative associations with the T_3 and T_4 variables. For PCB 118, only the association with total T_3 levels was statistically significant ($\beta = -0.114$, 95% CI –0.223 to –0.005), so evidence favoring hypothyroidism was not limited to dioxin-like activity specifically.

In an Italian study that compared urban and rural workers, Ciarrocca et al. (2012) found that their urinary arsenic levels differed by a factor of between 2 and 4. Urinary arsenic was positively correlated with serum TSH and thyroglobulin and negatively with free T_3 and T_4. In addition to reports on thyroid function, there were some reports on other endocrine measures in humans.

Manh et al. (2013) and Kido et al. (2014) studied steroid hormone levels in the serum and saliva and dioxin concentrations in the breast milk of lactating Vietnamese women living in a so-called "Agent Orange hot spot" (n = 51) or in an area with no suspected exposure (n = 58). Levels of cortisol and corticosterone in serum and saliva were higher in women living in the hot spot area and were positively correlated with breast-milk dioxin concentrations.

Pituitary and adrenal disorders were reported on in the Korean Vietnam Veterans Health Study (Yi et al., 2014a) (see above in the discussion of results on thyroid function). Comparing the high-EOI-exposure group (95 cases) with the low-exposure group (110 cases), a significantly ($p = 0.011$) elevated risk was observed for pituitary hypofunction (OR= 1.44, 95% CI 1.09–1.90), while the risk of pituitary hyperfunction was non-significantly elevated (OR = 1.44, 95% CI 0.90–2.30) for 34 and 37 cases, respectively. The odds ratio for hyperaldosteronism was also non-significantly elevated (OR = 1.94, 95% CI 0.66–5.66), but it was based on a very small number of cases (14 total). Analyses using the one unit increase in the EOI approach yielded similar results, although none of the odds ratios was significant.

Biologic Plausibility

The influence of TCDD on thyroid-hormone homeostasis has been measured in numerous animal studies, and exposure has been associated with changes in serum concentrations of T_4, T_3, and TSH. In most studies, TCDD exposure is associated with a hypothyroid state, including reduced circulating T_3 and T_4 and increased TSH, especially after chronic exposure. The reduction in circulating T_4 concentrations is robust and has recently been proposed as a biomarker of the effect of DLCs (Yang JM et al., 2010). Female rats exposed chronically to TCDD showed follicular-cell hyperplasia and hypertrophy of thyroid follicles that were consistent with an overstimulation of the thyroid by TSH (TSH increases as a homeostatic response to low T_4 levels) (Yoshizawa et al., 2010). TCDD enhances the metabolism of thyroid hormones primarily through an AHR-dependent induction of glucuronyl transferase activity (Gessner et al., 2012; Kato et al., 2010; Martin et al., 2012; Nishimura et al., 2005). An enhanced accumulation of T_4 in hepatic tissue of TCDD-treated mice may also contribute to the reduction in circulating T_4 (Kato et al., 2010).

The possibility that arsenic could act as an endocrine disruptor on thyroid hormone–mediated processes has been proposed on the basis of cell culture studies and experiments with the ex vivo amphibian tail metamorphosis assay (Davey et al., 2008). In guinea pigs fed diets containing 50 ppm arsenic as sodium arsenite or arsenic trioxide for 11 weeks, serum (total) T_3 and T_4 were reduced compared to controls by about 20 to 25 percent and 33 percent, respectively (Mohanta et al., 2014). These data raise the possibility that cacodylic acid may also disrupt thyroid homeostasis, but there are no published epidemiologic studies that have addressed this.

Synthesis

Numerous animal experiments and several epidemiologic studies have shown that TCDD and DLCs exert some influence on thyroid homeostasis, with findings

being most consistently indicative of hypothyroidism (Boas et al., 2006, 2012). The underlying molecular mechanisms resulting in these effects on thyroid hormone and TSH concentrations in humans, however, are not as yet fully characterized (Langer, 2008).

Several prior studies of populations environmentally exposed to PCBs found some combination of elevated TSH concentrations and depressed T_4 and T_3 levels (Bloom et al., 2006; Hagmar et al., 2001a; Persky et al., 2001; Schell et al., 2004), although some (Hagmar et al., 2001b; Sala et al., 2001) found no significant effect. Although the findings in the infants in studies of women and their children are not relevant to effects arising from adult exposure, observations in the mothers themselves contribute to the findings of this chapter. Such studies have tended to support the hypothesis that exposure to DLCs is associated with hypothyroidism (Koopman-Esseboom et al., 1994; Takser et al., 2005), although the recent study on Korean mothers (Kim et al., 2013) did not report strong evidence of this. The new findings concerning thyroid hormones in women from Seveso presented a result fairly consistent with hypothyroidism 20 years after the accident, which had dissipated after another 12 years (Chevrier et al., 2014).

Pavuk et al. (2003) had reported a trend of higher TCDD serum concentrations being associated with increasing concentrations of TSH that was not accompanied by changes in circulating T_4 or T_3 (which would be interpreted as subclinical hypothyroidism) in participants in the AFHS. This finding in US Vietnam veterans is complemented by the new results from the Korean Vietnam Veterans Health Study. Yi et al. (2014a) found evidence of an increased occurrence of clinical hypothyroid disease, possibly associated with autoimmune hypothyroidism, in association with higher estimated potential herbicide exposure. In addition, the report from the AHS of increased physician-diagnosed hypothyroidism in herbicide applicators with phenoxy herbicide exposure (Golden et al., 2013) supports the notion that this association is real.

An overall assessment of the studies suggests some variation in thyroid-hormone concentrations in relation to exposure to DLCs and possibly the phenoxy compounds themselves. Although the functional importance of the changes may be unclear in some cases, it should be noted that in the new epidemiological studies identified in this update, clinical hypothyroidism was the endpoint. Because of the consistent observations of exposures to the COIs being related to perturbations of thyroid function, and to clinical hypothyroidism in particular, the committee considered the body of epidemiologic data, in combination with strong biologic plausibility, to represent limited or suggestive evidence.

New data from the Korean Vietnam Veterans Health Study suggest that adrenal and possibly pituitary function may also be affected by exposure to DLCs supporting some older literature data. In addition, there are some data to suggest the possibility that arsenic-based herbicides may also affect thyroid function.

Conclusions

There is limited or suggestive evidence of an association between exposure to the COIs and hypothyroidism. Additional endocrine effects have been observed in conjunction with exposure to the COIs in both humans and animals, but the evidence is inadequate or insufficient to establish an association with herbicide exposure for them.

EYE PROBLEMS

This section discusses eye problems, which are grouped in ICD-9 360–379 or ICD-10 H00–H59. The loss of vision is increasingly common with advanced age, and about one-sixth of people over 70 years old have substantial impairment, with men and women being similarly affected (NCHS, 2010). The most prevalent ocular problems in the current age range of Vietnam veterans are age-related macular degeneration, cataracts, glaucoma, and diabetic retinopathy. Ocular problems involving chemical agents most often arise from acute, direct contact with caustic or corrosive substances that may have permanent consequences. Ocular impairment arising from systemic exposure to toxic agents may be mediated by nerve damage. Cataracts can be induced by a chronic internal exposure of the lens to such chemicals as 2,4-dinitrophenol, corticosteroids, and thallium; glaucoma may be secondary to any toxic inflammation and from topical or systemic treatment with anti-inflammatory corticosteroids (Casarett and Doull, 1995).

Conclusions from *VAO* and Previous Updates

Update 2010 considered one study of Australian Vietnam veterans that found that the veterans had a higher prevalence of all the eye conditions assessed—cataracts, presbyopia, color blindness, and other diseases of the eye—than the Australian population (O'Toole et al., 2009). However, the committee noted a lack of information on exposure to the COIs and a lack of clinical confirmation of the eye conditions, and it had serious concerns about the possibility that recall bias played a role in the findings. On the basis of the evidence reviewed, *Update 2010* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and eye conditions. In *Update 2012*, the committee noted that no epidemiologic studies of exposure to the COIs and eye problems had been published since *Update 2010*, and they concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and eye conditions.

Update of Epidemiologic Evidence

No epidemiologic studies of exposure to the COIs and eye problems have been published since *Update 2012*.

Biologic Plausibility

There have been several recent reports of ocular activity associated with AHR induction in or with TCDD exposure of rats (Sugamo et al., 2009), mice (Takeuchi et al., 2009), and human nonpigmented ciliary epithelial cells (Volotinen et al., 2009). Since *Update 2012*, Hu et al. (2013) reported that mice harboring the null allele at the AHR locus developed macular age-related degeneration-like pathology.

Synthesis

Since *Update 2012*, no additional epidemiologic results have supported the increase in risk of several eye conditions in the Australian Vietnam veterans reported by O'Toole et al. (2009). The reliability of those findings were of concern to the committee for *Update 2012* because of the lack of information on exposure to the COIs, the lack of clinical confirmation of the eye conditions, and the considerable likelihood of recall bias.

Conclusion

Given the lack of additional evidence, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and eye conditions.

BONE CONDITIONS

This section discusses osteoporosis, or decreased bone density, which is coded as ICD-9 733.0–733.1 or ICD-10 M80–M81. Osteoporosis is a skeletal disorder characterized by a decrease in bone mineral density (BMD) and a loss of the structural and biomechanical properties of the skeleton, which leads to an increased risk of fractures. Although there are no practical methods for assessing overall bone strength, BMD correlates closely with skeletal load-bearing capacity and fracture risk (Lash et al., 2009). The WHO has defined osteoporosis based on BMD measurements. The diagnostic T-score derived by dual energy x-ray absorptiometry is the number of standard deviations from the mean BMD for healthy women. In women, readings greater than −1.0 are normal, whereas osteopenia is defined by a T-score between −1.0 and −2.5, osteoporosis is defined by a T-score between −2.5 and −5.0, and severe osteoporosis corresponds to a T-score of −5.0 or lower. Diagnostic criteria have not been standardized for osteoporosis in men. Although men have much higher baseline BMD than women, they seem to have a similar fracture risk for a given BMD (Lash et al., 2009), so most authorities apply the same WHO ranges for T-scores calculated relative to normal young women.

Sex is an important risk factor for osteoporosis; about 56 percent of postmenopausal women have decreased BMD, and 6 percent have osteoporosis (CDC, 2002). The effects of aging on bone loss in women are well known, but many health care providers and patients are less familiar with the prevalence and effects of bone changes in older men (Orwoll et al., 2010). Individual patients have genetic and acquired risks of osteoporosis, and the osteoporosis disease process can be without symptoms for decades. It is well known that hormones, vitamins, and pharmaceuticals can have adverse effects on bone. Drug-induced osteoporosis occurs primarily in postmenopausal women, but premenopausal women and men are also significantly affected. Glucocorticoids are the most common cause of drug-induced osteoporosis (Mazziotti et al., 2010). Other risk factors for loss of BMD include the use of long-acting benzodiazepine or anticonvulsant drugs, previous hyperthyroidism, excessive caffeine intake, and routinely standing for less than 4 hours per day (Lash et al., 2009).

Several studies have described a link between organochlorine exposure and effects on bone growth, most notably reports of infants exposed in utero to high concentration of PCBs and PCDFs who developed irregular calcifications of their skulls (Miller, 1985) and reports of accidental organochlorine poisoning that resulted in osteoporosis (Cripps et al., 1984; Gocmen et al., 1989). However, epidemiologic studies of the association between environmental exposures to organochlorine compounds and bone disorders have had inconsistent results.

Summary of Previous Updates

Update 2010 was the first VAO update that reviewed studies of the association between exposures to the COIs and a decrease in BMD. Results from Hodgson et al. (2008) motivated the inclusion of this health outcome. The researchers studied the relationship between environmental exposures and BMD in a set of 325 members of the Osteoporosis Cadmium as a Risk Factor (OSCAR) cohort who were at least 60 years old. Forearm BMD was measured, blood samples were analyzed for the five dioxin-like mono-ortho PCB congeners (PCB 105, 118, 156, 157, and 167), and TEQs were calculated. In men, PCB 118 had a marginally significant negative association with BMD, but the TEQ for all five dioxin-like mono-ortho PCBs did not show an association. In women, PCB 118 alone and the TEQ for all five dioxin-like mono-ortho PCBs were positively associated with BMD (slope $\beta = 0.00008$, $p = 0.045$; $\beta = 1.652$, $p = 0.057$, respectively). When the risk of low BMD (more than 1 standard deviation below the mean) was treated as a binary variable in an adjusted logistic model, there was a significant association with PCB 118 in men, but none of the measured compounds (also including non–dioxin-like PCBs 138, 153, and 180) was predictive in women.

Little additional data were available for review in *Update 2012*. There were no new studies of Vietnam-era veterans, and neither the single occupational study (Waggoner et al., 2011) nor the environmental study (Cho et al., 2011) reported

results with enough exposure specificity to be fully informative for VAO consideration. Furthermore, the category of "bone and connective tissue disorders" reported in Waggoner is difficult to clearly interpret.

Update of the Scientific Literature

Vietnam-Veteran, Occupational, and Case-Control Studies

No Vietnam veteran, occupational, or case-control studies of exposure to the COIs and BMD or osteoporosis have been published since the *Update 2012*.

Environmental Studies

A recent study of 350 women who were exposed to TCDD as a result of living in Seveso, Italy, during the 1976 chemical explosion examined the relationship of DEXA-assessed bone mineral density and TCDD serum levels (Eskenazi et al., 2014). The results suggested that TCDD levels were associated with some evidence of better bone structure in the 48 women for whom exposure occurred after their age or peak bone mass, which is estimated to happen 2 years after menarche. The study did not support the hypothesis that postnatal TCDD exposure adversely affects adult bone health.

There were two cross-sectional studies recently published addressing the association of exposure to DLCs and bone quality in residents of Canada's northern regions who are known to be exposed to these compounds as a result of their diet, which includes marine mammals and predatory fish (Paunescu et al., 2013a,b). The cross-sectional study of 249 adult Cree women in James Bay, Canada, reported an increase in dioxin-like PCBs 105 and 108 to be negatively associated with a "stiffness index." In a similar cross-sectional study of 194 Inuit women aged 35–72 years, neither total plasma DLC levels nor any specific dioxin-like PCB level was associated with ultrasonography-assessed bone strength.

Biologic Plausibility

Animal studies suggest that TCDD may have some influence on bone formation and maintenance. Recent work from Herlin et al. (2013) has shown that the exposure of adult mice to TCDD resulted in harder bone matrix, thinner cortical bone, mechanically weaker bones, and, most notably, increased trabecular bone volume fraction in *Ahr(+/+)* mice. It is known that TCDD can induce chondrocyte apoptosis in culture, which could be an initial event leading to cartilage degradation as observed in arthritis (Yang and Lee, 2010). Lee and Yang (2012) recently demonstrated that this is mediated by reactive oxygen species. In addition, TCDD exposure via the dam's milk impaired bone mineralization during postnatal development in mice because of a reduction in osteoblastic activity as

a result of TCDD-induced up-regulation in the active form of vitamin D in serum (Nishimura et al., 2009). TCDD altered osteogenesis (bone formation) in an in vitro osteoblast model and led to alterations in proteins associated with cytoskeleton organization and biogenesis, a decrease in the expression of calcium-binding proteins, and a decrease in osteoblast calcium deposition (Carpi et al., 2009). In adult rats, TCDD exposure reduced trabecular bone cross-sectional area, but significantly increased total BMD; it was further noted that TCDD decreased the expression of the bone-formation marker procollagen type I *N*-terminal propeptide and increased the expression of the bone-resorption marker carboxy-terminal collagen cross-link, suggesting a net loss of bone tissue (Lind et al., 2009). It is also known that exposure to polyaromatic hydrocarbons (such as those in tobacco smoke) can affect bone health, and some of these alterations have been shown to be mediated, at least in part by the AHR. That implies that TCDD may alter or modify the effects (Kung et al., 2012; Yan et al., 2011). Iqbal et al. (2013) recently addressed this, studying genetically altered mice so that they could understand the contributions of tobacco carcinogens and TCDD. In their work, mice in which the *Ahr* or *Cyp1a1*, *Cyp1a2*, and *Cyp1b1* genes were deleted displayed reduced resorption and high bone mass. In contrast, AHR activation by administering B[a]P to wild-type mice increased osteoclastogenesis and bone resorption.

Synthesis

The small amount of available epidemiologic information on the possible adverse effects of exposure to the COIs on bone structure is based entirely on dioxin-like mono-ortho PCBs, which contribute a small percentage to total TEQs based on all dioxin-like PCBs. The biological data confirm that TCDD is active in bone metabolism, but the pattern of association of exposure to the COIs and subsequent disease is not consistent in the current literature.

Conclusion

There is inadequate or insufficient evidence of an association between exposure to the COIs and clinical or overt adverse effects of osteoporosis or loss of BMD.

14

Conclusions and Recommendations

Chapter Overview

The current committee reviewed and updated the scientific evidence published in the 2 years following the set of new studies considered in Veterans and Agent Orange: Update 2012[1] *(IOM, 2014) regarding statistical associations between diseases and possible exposure to dioxin and other chemical compounds in herbicides used in Vietnam. The publication period reviewed for this update was from October 1, 2012, to September 30, 2014. In addition, the committee evaluated the risk of disease among individuals potentially exposed to herbicides during service in Vietnam, as well as scientific studies related to plausible biologic mechanisms or causal relationships between exposure and a disease.*

SYNOPSIS OF COMMITTEE CONCLUSIONS

The committee weighed the strengths and limitations of the epidemiologic evidence reviewed in its report and in previous Veterans and Agent Orange (VAO) reports. Although the studies published since *Update 2012* are the subject of detailed evaluation here, the committee drew its conclusions in the context of the entire body of literature. The contribution of recent publications to the evidence database is emphasized in this report, but the totality of the weight

[1]Despite loose usage of "Agent Orange" by many people, in numerous publications, and even in the title of this series, this committee uses "herbicides" to refer to the full range of herbicide exposures experienced in Vietnam, while "Agent Orange" is reserved for a specific one of the mixtures sprayed in Vietnam.

of the evidence was the primary consideration guiding the evaluation of health outcomes. Although the study subjects in the new literature reviewed here were not the male American Vietnam veterans who constitute most of the population affected by the VAO reports, the new studies of female American Vietnam veterans and male Vietnam veterans from Korea and New Zealand provided extremely pertinent information. The findings of these investigations are especially relevant because they consisted of observations in the aging population of primary concern, Vietnam veterans.

Epidemiologic methods and analytic capabilities have continued to improve over the period in which these 10 biennial VAO updates have been conducted. As has been the case for recent updates, a considerable number of new studies presented results in terms of serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) concentrations or total toxic equivalents (TEQs), which are particularly useful for the committee's purpose because they provide a cumulative measure of exposure to all dioxin-like chemicals. It was particularly gratifying that the literature identified for the current update contained a series of papers based on an investigation of a large cohort of Korean veterans who served in Vietnam. Their health experience was analyzed in terms of several exposure metrics, including the simple proxy for herbicide exposure of deployment status and the bias-prone measure of self-perceived exposure. In addition, however, the Korean Veterans' Health Study is the first epidemiological application of the model for generating exposure opportunity scores based on how troop movements intersected the herbicide spray missions in time and location, the development of which was fostered by early VAO committees.

In the course of reviewing the recent epidemiology literature, the committee noticed that several studies at Department of Veterans Affairs (VA) medical centers based exposure characterization upon indications of "Agent Orange exposure" in the medical records. While it is gratifying that data generated in the course of VA's medical services are being used for research, the committee is concerned that undue confidence may be placed upon these data given the lack of validation of exposure classifiers. The committee has been unable to obtain documentation of the source of and manner in which such exposure classifiers are coded into patients' electronic records. In the absence of standardized designations that rely on reliable methods, herbicide exposure designations derived from medical records are no more reliable than entries based on the Agent Orange Registry or simply service during the Vietnam conflict.

The committee also notes that considerable experimental data related to the biologic plausibility of the health conditions statistically associated with exposure to the components of the herbicides sprayed in Vietnam have emerged since the beginning of this series of VAO reports. These findings help to inform decisions about how to categorize the degree of association for individual conditions.

On the basis of its evaluation of epidemiology studies of Vietnam-veteran, occupational, and environmental populations, and aided by experimental studies

on biologic plausibility, the committee assigned each health outcome to one of four categories of relative certainty of association with exposure to the herbicides used in Vietnam or to any of their components or contaminants. The assignments were not based on a particular one of the chemicals of interest being specified as the responsible agent. This committee's deliberations led to the addition of two findings of "limited or suggestive" evidence of association to those of previous VAO committees and modifications to two prior findings.

The committee for *Update 2014* concluded that the information now assembled constituted compelling evidence for moving both bladder cancer and hypothyroid conditions into the category of limited or suggestive evidence of association with herbicide exposure from their previous positions in the inadequate or insufficient evidence category. For each of these conditions, new results from the large study of Korean veterans who served in the Vietnam War were compellingly suggestive. In the case of hypothyroid conditions, there were also new supportive epidemiologic observations. In combination with some pre-existing supportive epidemiologic findings and substantial biologic plausibility, the new information provided enough evidence to merit a change in category of association.

There has been no additional epidemiologic evidence to support the placement of spina bifida in the category of limited or suggestive evidence of association, and plausibility for paternal transmission of health problems to their offspring remains quite uncertain. Although animal studies have shown epigenetic modifications to be passed along through the male germline, as yet, this has only been the result of perinatal exposure (in utero and by lactation) in which the exposed parent is the mother. The perinatal period clearly represents a period of susceptibility for impacts on the development of both male and female fetuses and on their germlines, but this exposure scenario is not relevant for the offspring of male Vietnam veterans who were adults when the exposure of concern would have taken place. Epigenetic research has provided insights into biologic mechanisms underlying the transmission of adverse effects to offspring when an adult female is exposed, but it has not been convincingly established that harm to offspring may arise from paternal exposures experienced as an adult. Therefore, the committee concluded that spina bifida in children of male Vietnam veterans should be moved to the insufficient category. This decision reflects the committee's conviction that it would be inappropriate to let the very uncertain dataset on the chemicals of interest and spina bifida remain as a formally documented instance of the questionable phenomenon of paternal transmission. Although the biologic plausibility of maternal exposure to toxic agents, specifically including the chemicals of interest, is well established, there are no existing epidemiologic data supporting increased incidence of spina bifida specifically following maternal exposure to the components of the herbicides sprayed in Vietnam as is required for identifying an association under the Agent Orange Act. Consequently, spina bifida in the offspring of both male and female veterans has been moved to the category of inadequate or insufficient evidence of an association with

herbicide exposure from its prior categorization as having limited or suggestive evidence of an association.

VA also charged the committee for *Update 2014* to address the specific question of whether various conditions with Parkinson-like symptoms should be considered covered under the assignment of Parkinson disease to the limited-or-suggestive category of association with herbicide exposure. The committee noted that the diagnostic standards for this condition should not be assumed to have been uniform in the epidemiologic studies that constitute the basis for this association or in the claims submitted by veterans, so there is no rational basis for exclusion of individuals with Parkinson-like symptoms from the service-related category denoted as Parkinson disease. To exclude a claim for a condition with Parkinson-like symptoms, the onus should be on VA on a case-by-case basis to definitively establish the role of a recognized etiologic factor other than the herbicides sprayed in Vietnam.

Although VA has not found hypertension [Health Effects Not Associated with Exposure to Certain Herbicide Agents, 75 Fed. Reg. 109 (June 8, 2010)] or stroke [Determinations Concerning Illnesses Discussed in National Academy of Sciences Report: Veterans and Agent Orange: Update 2012, 79 Fed. Reg. 70 (April 11, 2014)] to be presumptively related to service in Vietnam, on the basis of the total weight of available evidence the current committee reaffirmed the conclusions of previous VAO committees that these two health outcomes should be placed in the category of limited or suggestive evidence of association.

The changes made by the current committee to the categorizations determined by the committee for *Update 2012* (as presented in Table 1-1) are noted in boldface in Table 14-1. As mandated by Public Law (PL) 102-4, the distinctions among categories are based on statistical association and not on strict causality. The committee was directed to review the scientific data, not to recommend VA policy, and, therefore, the conclusions presented in Table 14-1 are not intended to imply or suggest policy decisions. Instead, the conclusions are based on observed associations between exposure and health outcomes in human *populations*. These categorizations do not address the likelihood that the health problems of any one *individual* are associated with or caused by the chemicals in question.

COMMITTEE RECOMMENDATIONS

As part of their charge, all VAO committees have been asked to offer recommendations concerning the need for additional scientific studies and research to resolve areas of continuing scientific uncertainty concerning the health effects of the chemicals of interest sprayed in Vietnam: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant TCDD, picloram, and cacodylic acid. Because *Update 2014* is the last of the reports mandated by the Agent Orange Act (PL 102-4, and renewed as PL 107-103), this committee considered it appropriate to review the recommendations made

TABLE 14-1 Summary of *Tenth Biennial Update* of Findings on Vietnam-Veteran, Occupational, and Environmental Studies Regarding Scientifically Relevant Associations Between Exposure to Herbicides and Specific Health Outcomes[a]

Sufficient Evidence of an Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.[b] For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Soft-tissue sarcoma (including heart)
* Non-Hodgkin lymphoma
* Chronic lymphocytic leukemia (including hairy cell leukemia and other chronic B-cell leukemias)
* Hodgkin lymphoma
Chloracne

Limited or Suggestive Evidence of an Association

Epidemiologic evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.[b] For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Laryngeal cancer
Cancer of the lung, bronchus, or trachea
Prostate cancer
Cancer of the urinary bladder (category change from Inadequate or Insufficient in *Update 2012*)
* Multiple myeloma
* AL amyloidosis
Early-onset peripheral neuropathy
Parkinson disease (including Parkinsonism and Parkinson-like syndromes) (category clarification from *Update 2012*)
Porphyria cutanea tarda
Hypertension
Ischemic heart disease
Stroke
Type 2 diabetes (mellitus)
Hypothroidism (category change from Inadequate or Insufficient in *Update 2012*)

Inadequate or Insufficient Evidence to Determine an Association

The available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes that were explicitly reviewed:

continued

TABLE 14-1 Continued

Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)
Cancers of the pleura, mediastinum, and other unspecified sites in the respiratory system and intrathoracic organs
Esophageal cancer
Stomach cancer
Colorectal cancer (including small intestine and anus)
Hepatobiliary cancers (liver, gallbladder, and bile ducts)
Pancreatic cancer
Bone and joint cancer
Melanoma
Non-melanoma skin cancer (basal-cell and squamous-cell)
Breast cancer
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
Renal cancer (kidney and renal pelvis)
Cancers of brain and nervous system (including eye)
Endocrine cancers (thyroid, thymus, and other endocrine organs)
Leukemia (other than chronic B-cell leukemias, including chronic lymphocytic leukemia and hairy cell leukemia)
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than after paternal exposure to TCDD, which appears *not* to be associated)
Neonatal or infant death and stillbirth in offspring of exposed people
Low birth weight in offspring of exposed people
Birth defects in offspring of exposed people (category change from Limited or Suggestive in *Update 2012* for spina bifida)
Childhood cancer (including acute myeloid leukemia) in offspring of exposed people
Neurobehavioral disorders (cognitive and neuropsychiatric)
Neurodegenerative diseases, excluding Parkinson disease
Chronic peripheral nervous system disorders
Hearing loss
Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
Gastrointestinal, metabolic, and digestive disorders (changes in hepatic enzymes, lipid abnormalities, and ulcers)
Immune system disorders (immune suppression, allergy, and autoimmunity)
Circulatory disorders (other than hypertension, ischemic heart disease, and stroke)
Endometriosis
Disruption of thyroid homeostasis (other than hypothyroidism) (category modification from *Update 2012*)
Eye problems
Bone conditions

This committee used a classification that spans the full array of cancers. However, reviews for non-malignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. *By default, any health outcome on which no epidemiologic information has been found falls into this category.*

TABLE 14-1 Continued

Limited or Suggestive Evidence of *No* Association

Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to a component of the herbicides of interest and the outcome. A conclusion of "no association" is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. *In addition, the possibility of a very small increase in risk at the exposure studied can never be excluded.* There is limited or suggestive evidence of *no* association between exposure to the herbicide component of interest and the following health outcome:

Spontaneous abortion after paternal exposure to TCDD

[a]*Herbicides* indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from occupational, environmental, and veteran studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.

[b]Evidence of an association is strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.

*The committee notes the consistency of these findings with the biologic understanding of the clonal derivation of lymphohematopoietic cancers that is the basis of the World Health Organization classification system (Campo et al., 2011; see table here http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109529/table/T1, accessed December 2, 2015).

by prior VAO committees and, in light of the lessons learned in this process, to consider what would be the most important activities to undertake in the future. This committee has endeavored to factor the constraints of feasibility into its judgments. Table 14-2 is a compendium of the recommendations of prior committees condensed and sorted into several topic areas, with comments on what response these recommendations received from VA, Department of Defense (DOD), and other parties. In Table 14-3, this committee summarizes the future activities it considers most important for monitoring and evaluating the health issues of Vietnam veterans and other veterans who might experience service-related health problems long after discharge.

As evidenced in Table 14-2, the recommendations of previous VAO committees fall into four primary areas:

- Management of information under the auspices of DOD and VA
- Additional epidemiologic work
- Improvement of exposure estimation
- Priority areas for toxicologic research

In instances in which the VAO committees have been aware of actions taken after a recommendation was made, the events are briefly delineated in the rightmost column of Table 14-2. After encouragement of the effort that matured into the model to estimate individual opportunity of herbicide exposure based

TABLE 14-2 Compendium of Research Recommendations from Previous and Current Veterans and Agent Orange Reports

Recommendation Focus	Report of Initial Recommendation	Follow-up
DATA MANAGEMENT		
DOD and VA databases should be linked to identify, record, and/or monitor trends in diseases of aging Vietnam veterans for evaluation of possible associations with military service in Vietnam (Vietnam or in the Vietnam theater during the Vietnam era).	*VAO*	Although it is most probably no longer possible to do this for Vietnam veterans, this type of linkage still has not been successfully established to manage follow-up of more recent deployments (e.g., "Returning Home" [IOM, 2013])
The VA should make more effective use of its databases to determine health effects that may have resulted from exposures in Vietnam:		No known follow-up
Link the EMR and associated administrative databases, such as discharge-diagnosis and pharmacy-use records	*Update 2006*	
Establish systematic review of the distribution of health outcomes	*Update 2008*	
Combine information from the Neurotoxin Exposure Treatment Parkinson Research program with the resources of the VA's appeals and medical records	*Update 2008*	
Commission an independent panel to identify and assign priorities	*Update 2010*	
Involve external analysts	*Update 2010*	
Investigations of VA data sources should be conducted on:		
COPD	*Update 2010*	Other than the work in progress on COPD in the ACC study population discussed below, the committee is not aware of epidemiologic efforts undertaken by VA to assess a possible role for herbicides in the occurrence of the other conditions listed here.
Brain cancer	*Update 2002*	
Breast cancer	*Update 2006*	
Tonsil cancer (squamous cell carcinomas of the head and neck)	*Update 2006*	
Melanoma	*Update 2006*	
Amyotrophic lateral sclerosis	*Update 2002*	
Parkinson disease	*Update 2002*	Several small studies have been published by individual researchers using the "AO exposed" variable in VA medical records without explanation of its derivation.
Alzheimer disease	*Update 2010*	
Metabolic syndrome	*Update 2006*	
Paternally mediated effects on health of offspring	*Update 2006*	

EPIDEMIOLOGIC STUDIES

VA Studies

Mortality Cohort of Male Vietnam–era Veterans		
VA should continue epidemiologic studies (morbidity and mortality) of Vietnam Veterans, especially as the VV population grows older and the incidence of many health outcomes increases with age.	*Update 2004*	
Army Chemical Corps (ACC)		
Study ACC members to increase the size of the highly exposed population of Vietnam veterans and gain greater statistical power to detect less common health outcomes.	*VAO*	Kang et al. (2006) examined health status of ACC VVs. Cypel and Kang (2010) presented updated mortality findings on a limited number of cancers, diabetes, circulatory conditions, respiratory conditions, and cirrhosis of the liver.
Collect and store biological samples and determine serum TCDD levels.	*VAO*	TCDD serum levels were determined in a subset of the ACC cohort (Kang et al., 2006), but not aware of collection of other biospecimens
Augment update mortality of ACC with assembly of clinical information on morbidity associated with COPD and HT.	*Update 2010*	In 2010, VA launched the ACC Vietnam-era Veterans Health Study to investigate the relationship between herbicide exposure during the Vietnam War and morbidity from hypertension and COPD in ACC veterans [results have not yet been reported].

continued

TABLE 14-2 Continued

Recommendation Focus	Report of Initial Recommendation	Follow-up
Female Vietnam-era Veterans		
Women Vietnam veterans should be included in Vietnam veteran studies whenever appropriate.	*VAO*	A cohort of female US Vietnam-era veterans (primarily nurses) was developed and reported on by Kang et al. (2000). Since then, Cypel and Kang (2008) and Kang et al. (2014) have updated mortality. In 2009, VA announced the start of a 4-year undertaking to investigate the mental and physical health of this cohort, but any results remain outstanding.
US Air Force—Air Force Health Study (AFHS)		
Data Analysis		
The AFHS could benefit from improved methods of analysis and presentation of results both for existing data and for data obtained in the future.	*VAO*	No known follow-up
Establish an independent, non-governmental scientific panel to oversee analysis of resulting data to satisfy the public's concern about impartiality and scientific credibility.	*VAO*	No known follow-up
Study the potential for paternally mediated effects on health outcomes in offspring.	*Update 2006*	No known follow-up
Comprehensive longitudinal analysis of the AFHS data collected in the six intensive medical-cycle examinations (particularly concerning medical interventions, cancer incidence, mortality, birth defects in veterans' offspring) making use of the available exposure data.	*Update 2008*	No known follow-up
Perform a comprehensive analysis of melanoma in the entire AFHS dataset to resolve ambiguity remaining in currently published results.	*Update 2010*	No known follow-up
Combine existing data from AFHS with new results derived by assays of the curated biological samples.	*Update 2010*	No known follow-up

Future		
Consideration should be given to whether it is appropriate to continue the AFHS study past its planned completion date because AFHS cohorts are only now reaching the age where several health outcomes of interest may be expected to manifest.	*VAO*	Following the last AFHS physical exam in 2002, the IOM was asked to form a committee to provide guidance on the future of the AFHS.
Retain and maintain AFHS medical records and biological samples with oversight that could be established for future use and research, while respecting the privacy of participants.	*VAO*	The IOM committee's final report, *Disposition of the Air Force Health Study*, concluded that the medical records, data, and biological specimens collected in the study, which closed on September 30, 2006, were a trove of valuable research material. It recommended that—after the AFHS's scheduled end—these assets be made available to researchers, through a custodian that takes an active role in fostering their use. No matter where the AFHS materials go, that custodian would need a secure source of funding. The report also recommended that Congress allocate at least $250,000 annually for 3 years to promote research using the data and specimens.
Dedicated funding is required so that focused analyses can be carried out by independent investigators using the AFHS data and biospecimens.	*Update 2008*	In spring 2012, the Committee on the Management of the Air Force Health Study Data and Specimens issued a request for proposals to use the AFHS materials (data or specimens) for innovative research. Each submission was subject to an intensive review by the entire committee to ensure that it was scientifically sound and feasible. Seven proposals were approved. The investigations have begun only fairly recently, so no results are available. A second request for proposals was issued in May 2013. The committee enthusiastically supports these new and continuing research efforts.

continued

TABLE 14-2 Continued

Recommendation Focus	Report of Initial Recommendation	Follow-up
CDC—National Vietnam Veterans Readjustment Study (NVVRS)/National Vietnam Veterans Longitudinal Study (NVVLS)		
As mandated by Congress (PL 106-419), the cohort from the NVVRS should be updated as the NVVLS. As directed by VA's Inspector General (VAOIG, 2005), the aborted update of the NVVRS should be started again. The committee recommends that, in addition to the largely psychological outcomes that were the focus of the NVVRS, the physical health (and Alzheimer disease) of the members of this carefully selected cohort should be assessed in the NVVLS. Outcomes considered most important for data gathering are those for which current evidence is inadequate or insufficient to determine whether there is an association with herbicide exposure, such as COPD, brain cancer, tonsil cancer, melanoma (with particular attention given to ocular types), and Alzheimer disease. Even an up-to-date estimate of overall mortality would be quite helpful.	*Update 2010*	In 2010, VA announced that a contractor had been engaged to conduct the study, with an expected completion date of 2013. Unfortunately from the perspective of VAO committees, the questionnaires and interviews are focusing on PTSD/psychologic issues rather than expanding the data gathering to include the physical health status of this well-defined cohort. *Update: The NVVLS was completed in 2014—IOM is working to obtain the full report (See Schlenger et al., 2015 for methods).*
National Institute for Occupational Safety and Health (NIOSH)		
Conduct epidemiologic studies—with adequate sample size to detect elevated associations—of the reproductive history of individuals with occupational or environmental exposure to herbicides and dioxin.	*VAO*	No known follow-up
Continue the NIOSH studies.	*Update 2006*	No known follow-up
Agricultural Health Study (AHS)		
Researchers should try to resolve known inconsistencies in results for incident and prevalent PD cases (possibly using the analytic method described in Copas and Farewell, 2008).	*Update 2008*	No known follow-up
International Agency for Research on Cancer (IARC)		
Carefully conducted epidemiologic studies—with adequate sample size to detect elevated associations—of the reproductive history of individuals with occupational or environmental exposure to herbicides and dioxin are recommended.	*VAO*	No known follow-up

Other Recommended Epidemiologic Studies and Analyses:		
Studies of individual characteristics and other factors affecting TCDD metabolism are particularly important and should be encouraged.	*VAO*	No known follow-up
Biomarkers for herbicide exposure should be developed further.	*VAO*	No known follow-up
Studies of the Vietnamese population exposed to herbicides (including both those who served in the military during the war and civilians) are possible and potentially useful. Before significant resources are committed, the committee recommends that feasibility studies of both exposure reconstruction and disease outcome monitoring be conducted. The committee supports further steps toward collaborative programs of research. Studies should include sufficient exposure measures, such as tissue TCDD concentrations.	*VAO*	No known follow-up [Given the chronic nature of exposure of the entire population, it now seems that such studies of the Vietnamese would not be particularly enlightening (particularly for question of paternal transmission of adverse effects).]
Future epidemiologic studies should be as specific as possible, rather than generic findings such as "all respiratory disorders."	*Update 2006*	No known follow-up
An ad hoc group should conduct a meta-analysis of the current epidemiologic studies of male populations exposed to the COIs and the risk of birth defects in offspring.	*Update 2006*	No known follow-up [Given the paucity of studies of only paternal transmission and the extremely heterogeneous study designs and exposures, meta-analyses no longer seems a plausible approach to evaluating birth defects (or any other health outcome).]
Additional studies of the COIs and conditions that have been noted to be of special interest but on which the current evidence is inadequate or insufficient (such as COPD, brain cancer, breast cancer, tonsil cancer, melanoma, amyotrophic lateral sclerosis, Parkinson disease, and Alzheimer disease). For very uncommon health outcomes, a case-control design would probably be most appropriate.	*Update 2006*	No known follow-up
Investigate possible effects in offspring of VVs (especially for birth defects or developmental disease, including cognitive and developmental effects in children and possibly grandchildren), especially those associated with paternal exposures.	*Update 2006*	No known follow-up
Conduct studies of defined clinical health conditions in mature offspring following exposure of either parent, rather than more investigations of physiological biomarkers that may merely be predictive of disease development later in life.	*Update 2010*	No known follow-up

continued

TABLE 14-2 Continued

Recommendation Focus	Report of Initial Recommendation	Follow-up
Develop epidemiologic protocols to address whether adverse effects are being manifested in later generations as a result of paternal exposure (in the absence of maternal exposure, focusing on those organ systems that have shown the greatest impact following maternal exposure, including neurologic, immune, and endocrine effects). Consideration must be given to the minimum sample size needed to detect changes if present, and to which outcome measures would be most sensitive and reliable.	*Update 2010*	No known follow-up
Case-control study should be used to explore whether information about Vietnam exposure or specific herbicide exposure could be ascertained in any of the many birth cohorts that have been established in the last several decades (especially for very uncommon health outcomes). To hone in on a paternal effect, however, it will be necessary to establish that the mothers did not have the opportunity for other than background exposure to the COIs.	*Update 2010*	No known follow-up
New studies in additional populations of COPD diagnosed using appropriate functional tests with adjustment for smoking status and consideration of comorbidities that could contribute to death from COPD.	*Update 2010*	No known follow-up
Epi studies to explore the relationship between exposure to the chemicals of interest and meaningful biomarkers of immune/inflammatory diseases, such as Fox p3+ T regulatory cells, Th17 cells, and dendritic cells; interleukin 6 elevations; frequency and duration of specific types of infections; and inflammatory cytokines under resting and challenged conditions.	*Update 2010*	No known follow-up
EXPOSURE ESTIMATION		
A non-governmental organization with appropriate experience in historical reconstruction should be commissioned to develop and test models of herbicide exposure for use in studies of Vietnam veterans. If it is determined that a valid exposure reconstruction model is feasible, then the VA and other government agencies should facilitate additional epidemiologic studies of veterans.	*VAO*	Stellman model developed

TOXICOLOGOC STUDIES		
Animal studies of multiple exposures (for example, examining the interaction of smoking and TCDD exposure with the health outcomes of interest) would be useful for interpreting the results of epidemiologic studies.	*Update 2002*	No known follow-up
Studies are needed to examine and clarify the role of genetic factors, in particular studies addressing the identification, distribution, and functional consequences of polymorphisms of the aryl-hydrocarbon receptor.	*Update 2004*	Additional studies of genetic factors and AHR polymorphisms have been published.
Animal models are needed to elucidate disease mechanisms and progression (particularly cardiovascular disease, B-cell cancers, obesity and the components of metabolic syndrome, and transgenerational or paternally mediated effects).	*Update 2006*	No known follow-up
There is a need for a biphasic physiologically based pharmacokinetic model for TCDD. There is also a need for additional validation of the PBPK models and direct comparisons of the resulting exposure classifications when the new models and the standard first-order elimination models are applied to larger datasets.	*Update 2006*	Additional studies of pharmacokinetic modeling have been published.
An investigation of mitochondrial disease is needed and could have important implications for health effects of concern in VVs.	*Update 2008*	No known follow-up
Toxicological investigations of the potential for the COIs (particularly TCDD) to induce epigenetic modifications, with special attention to the capacity for paternal transmission of such effects, should be conducted.	*Update 2010*	No known follow-up
Animal studies of the mechanisms of inhibition of fetal growth, particularly in male offspring, after maternal exposure could help to elucidate findings seen in some epidemiologic studies that examined maternal exposure and birth weight.	*Update 2012*	No known follow-up

NOTE: ACC, US Army Chemical Corps; AFHS, Air Force Health Study; AHS, Agricultural Health Study; AO, Agent Orange; COI, chemical of interest; COPD, chronic obstructive pulmonary disease; DOD, US Department of Defense; EMR, electronic medical record; HT, hypertension; IARC, International Agency for Research on Cancer; IOM, Institute of Medicine; NIOSH, National Institute for Occupational Safety and Health; NVVLS, National Vietnam Veterans Longitudinal Study; NVVRS, National Vietnam Veterans Readjustment Study; PBPK model, physiologically based pharmacokinetic model; PD, Parkinson disease; PTSD, posttraumatic stress disorder; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, Veterans Administration; VAO, Veterans and Agent Orange: VV, Vietnam veteran.

TABLE 14-3 Suggested Activities to Follow the Completion of the Veterans and Agent Orange Report Series Mandated by the Agent Orange Act

OVERSIGHT OF LONG-TERM HEALTH STATUS OF DEPLOYED SERVICE MEMBERS

A single overarching body is needed to review all deployment-related issues of veteran's health regularly and in a uniform fashion. (Numerous points concerning appointment of members and other procedural matters would need to be addressed in advance.)

Very careful review of evidence concerning whether **paternal exposure** to any toxicant has definitively been demonstrated to result in abnormalities in even the first generation of offspring.

Careful assessment of the risks to offspring that may arise from **maternal exposure** is also merited given the greatly increased number women now serving in the military.

DATA COLLECTION

DOD should create and maintain **rosters of individuals deployed** on every mission.

DOD should create and maintain a **matrix of potentially toxic exposures** by time and location for every deployment.

DOD's collection of **biological specimens** should be expanded to occur at regular intervals for all service members, as well as before and after deployments. Storage should be established on a permanent basis, with samples being accessible to researchers

Documentation of vaccination and other **medical procedures performed during service** need to be included in the records of each service person, and automatically transferred to VA upon discharge from the military.

DATA MANAGEMENT

DOD and VA databases should be linked to systematically identify, record, and/or monitor trends in diseases of soldiers and veterans for evaluation of possible associations with military service deployments.

VA should routinely (probably quarterly) obtain **frequency distributions of health conditions treated at its medical facilities** for participants in each deployment in contrast to those observed among their non-deployed contemporaries.

It would be worthwhile to conduct similar monitoring of VA claims data even though it might be less objective than treatment records and does not have an obvious comparison group.

EPIDEMIOLOGIC STUDIES

Air Force Health Study (AFHS)

Comprehensive **longitudinal analysis** of the AFHS data collected in the six intensive medical-cycle examinations (particularly concerning medical interventions, **cancer** incidence, mortality, **birth defects** in veterans' offspring) making use of the available exposure data.

Use AFHS samples for study of epigenetic changes and definition of biomarkers of exposure and effect. (See Table 14-4 from the recent report of the Committee on the Management of the Air Force Health Study Data and Specimens [IOM, 2015].)

Dedicated funding should be continued for focused analyses by independent investigators.

Army Chemical Corps (ACC)

Analysis and release of findings gathered by following up on the ACC mortality study to assemble clinical information on morbidity associated with **COPD** and **HT.**

TABLE 14-3 Continued

Vietnam Era-Health Evaluation Retrospective Observational Study (VE-HEROeS)
VA should continue epidemiologic studies (morbidity and mortality) of Vietnam veterans, especially as this population grows older and the incidence of many health outcomes increases with age.
Clinical examination and collection of biologic specimens from a subsample would provide a basis for establishing the reliability of self-reported information and deepen the value of hypotheses that could be explored.
Foster **cooperation with veterans' service organizations** in conducting studies.

Other Epidemiology Goals
Pursue development of protocols that could feasibly and efficiently investigate **paternal transmission** of adverse effects to offspring at birth or manifesting with maturation that have sufficient power for convincing findings. The logistics of attempting to detect adverse effects in the grandchildren of Vietnam veterans would be considerably more challenging.
Design a study to focus on specific manifestations in humans of dioxin exposure and **compromised immunity**, which has been so clearly demonstrated in animal models.

TOXICOLOGIC RESEARCH
Foster investigation of epigenetic changes in both somatic tissues and germ cells and during gestation.
Without sophisticated and specific **markers of environmentally induced epigenetic activity**, epidemiologic investigations will not be able to distinguish the mechanisms inducing any observed adverse health effects in exposed people or their offspring.
Fully investigate whether **paternally transmitted adverse effects** occur in animal models.
Continue exploration of the constellation of effects involved with the **metabolic syndrome**, which appear to represent a node of dioxin-related conditions.
Explore the role of **B-cell responses** to dioxin-like activity.
Resolve whether toxicology results for direct exposure to organic arsenic compounds are applicable to human exposure to such compounds.

on merging records of troop movements and flight records of Operation Ranch Hand herbicide spray missions, innovative ideas for exposure assessment that might improve the evaluation of health effects in Vietnam veterans appear to have been exhausted. In the other areas, however, VAO committees repeatedly proposed variations of several suggestions. VAO committees have been gratified by some of the responses to their encouragement of following up on established cohorts of Vietnam veterans, as embodied by additional epidemiology studies of female Vietnam veterans and the Army Chemical Corps. For example, the committee for *Update 2010* placed a high priority on research to address COPD from a morbidity perspective with an appropriate functional diagnosis of COPD and a collection of data to permit adjustments for smoking and other relevant confounders. The committee for *Update 2012* was pleased to note that VA had started such a study on its ACC cohort; the results from any such investigation, however, were not available to the present committee for review.

Similarly, previous VAO committees strongly recommended that measures of physical health be included along with the psychological endpoints when the congressionally mandated update of the carefully selected sample of the National Vietnam Veterans Readjustment Study (1986–1988) was conducted. Although the committee asked repeatedly about the status of this effort, it was not until a terse summary of the findings of the National Vietnam Veterans Longitudinal Study appeared in the Summer 2015 issue of VA's erratically published *Agent Orange Newsletter*, it became evident that this advice had not been incorporated into the experimental design.

In retrospect, it appears that the implementation of some of these suggestions was not feasible. A lack of comprehensive rosters of who had been deployed to Vietnam impeded the conducting of epidemiologic studies in an optimal fashion, and the difficulty of establishing retrospective methods to reliably estimate individual exposure has proved frustrating. With the passage of time, some opportunities have been missed and other suggestions no longer seem to have high priority, but a considerable number remain that merit serious consideration.

Although progress has been made in understanding the health effects of exposure to the chemicals of interest and the mechanisms underlying these effects, significant gaps in our knowledge remain. The scope of potential research is far-reaching, and what follows here is not an exhaustive list of future research that would be worthwhile. Many additional opportunities for progress in toxicology research, the conduct of continuing or new epidemiologic studies, and a systematic and comprehensive integration of existing datasets have not been explicitly noted here. As Table 14-2 illustrates, a number of the recommendations detailed below have been mentioned in previous VAO updates, but they are restated here to emphasize the committee's conviction that more progress should be made in the research fields noted.

Several themes underlie the points raised for future action in Table 14-3. A uniform, equitable, and evidence-based approach to meeting this country's obligation associated with delayed service-related health problems is a high priority not only for Vietnam veterans, but also for all US veterans. Improved cooperation between the organizations that place new recruits in service and those that are responsible for their care after discharge has been recommended repeatedly, and this represents an essential element to having a functional system. These individual suggestions fall into five categories, as discussed below.

Oversight of the Long-Term Health Status of Deployed Service Members

This is an area in which the VAO charge does not allow for specific recommendations. This committee simply notes that its experience suggests that, as the mandate of the Agent Orange Act expires, concern about service-related health problems in the Vietnam veterans continues. As adjustment to government policy about Vietnam veterans is made at this point of transition, it seems an opportune

time to allocate resources toward addressing how this issue will be handled in the future for all veterans. Rather than simply continuing regular periodic updates on literature related to the health of Vietnam veterans and addressing, on a case-by-case basis, health problems in other veterans that might involve harmful exposures suffered while in the military, a more effective approach would be a standing, overarching body to review all deployment-related issues of veteran's health regularly and in a uniform fashion. (Of course, numerous points concerning the appointment of members and other procedural matters would need to be addressed in advance.)

More specifically, before committing extensive resources to ameliorating adverse health consequences in the descendants of veterans, both male and female, it would be appropriate to conduct a very careful review of evidence concerning whether paternal exposure to any toxicant has definitively been demonstrated to result in abnormalities in even the first generation of offspring.

Data Collection

It is too late for Vietnam veterans and other more recently deployed veterans, but DOD should prepare the way for addressing the issue of delayed service-related health conditions in a more coherent and better documented fashion for future veterans. The compilation of rosters of individuals sent on various deployments is a rudimentary starting point for any subsequent epidemiologic investigations. Documentation of medical procedures such as vaccinations should also be maintained for such cohorts.

The committee endorses DOD's efforts to improve the collection of exposure data during current deployments so that the impasses associated with missing exposure information will not impede investigations of health consequences in future veterans. It notes, however, that more regular collection of biological samples from military personnel and storage without analysis might prove a more flexible tool for investigation in the event of a health issue involving possible toxic exposure.

In general, improved data linkage and data sharing between DOD and VA would greatly enhance the conduct of military epidemiology to guide health care delivery for veterans of all conflicts.

Data Management

It is recognized that those who use VA services will not constitute a representative sample of the full cohort of veterans from a given deployment. VA could make extremely substantial contributions by the identification of possible service-related health problems through regular and systematic processing of the data accumulated in the course of fulfilling its health care responsibilities. Routine comparisons of health care use by deployed veterans and suitably matched

non-deployed veterans from each deployment could provide early alerts of impending relevance in the very population of interest. Although applications for compensation and appeals constitute a non-representative, self-selected sample that is influenced by which conditions are already judged to be service-related, even a periodic determination of the distribution of health conditions for which claims are filed could be informative. More rigorous investigation could then be directed at the confirmation or dismissal of such conditions as being service-related, such as a case-control approach that addresses deployment status and other emerging risk factors nested within VA's patient population.

Linkage of occupational, health, and socioeconomic data from DOD with VA electronic medical-record system and associated administrative databases, such as discharge diagnoses and pharmacy-use records, would afford VA the opportunity to assemble an expansive epidemiologic database for a more rigorous evaluation of possible associations with military service in Vietnam. Particular attention should be paid to the feasibility of conducting epidemiologic studies of conditions that have been noted to be of special interest, but for which the current evidence is inadequate or insufficient to determine whether there is an association with herbicide exposure (see list in Table 14-2). A creative analysis of VA's own data resources may well be the most effective way to address those outcomes and to gain a better understanding of the role, if any, of herbicide exposure in chronic diseases of Vietnam veterans. Perceptions that VA would have a conflict of interest in surveying its own databases might be alleviated by recruiting external analysts to evaluate the contents of VA's medical databases. For example, an independent panel could be commissioned to identify and assign priorities to database information that would aid future evaluation of the evidence.

In addition, VA should establish an external advisory group to identify effective mechanisms for mining VA medical database information and to establish guidelines for the creation of a grants program focused on proposals for the conduct of analytic studies related to specific health outcomes of interest.

Epidemiologic Studies

The committee notes that future analyses of health outcomes in any future epidemiology studies should be as specific as possible because generic findings, such as those for "all respiratory outcomes," are not useful in determining associations of herbicide exposures with specific health conditions.

The Institute of Medicine (IOM) Medical Follow-up Agency (MFUA) has become the custodian of the data and biologic specimens generated by the Air Force Health Study (AFHS) (PL 109-364; 120 Stat. 2290); the specimens are held in storage at the Wright–Patterson Air Force Base under MFUA's aegis, and funding has been provided for the IOM to maintain and manage the materials and to make these invaluable data and biospecimens available to independent researchers. Such research could clarify the various issues and would generate substantial

benefits in the understanding of health issues of Vietnam veterans exposed to herbicides. Comprehensive longitudinal analyses of the data collected in the six intensive medical examinations—which include data on medical interventions (such as hospitalizations and emergency-department visits), cancer incidence, mortality, and exposures—should be conducted to investigate, if not all the health outcomes, at least those for which a possible association with herbicide exposure remains contentious. The distillation of existing data could be enhanced by the incorporation of new results derived from study of the biologic samples. For example, an analysis of banked semen samples for epigenetic markers on sperm DNA and the measurement of TCDD in seminal fluid, particularly in comparison with the subjects' serum TCDD concentrations, could provide insight into the likelihood of male Vietnam veterans' transmitting effects to their offspring, as well as supplementing general knowledge on paternal transmission. Through January 2015, 13 projects using the AFHS resources have been approved and initiated. Although the program does not require that these research projects necessarily investigate issues related to the health of Vietnam veterans specifically, most of them do address topics that are relevant to questions VAO committees have posed. Table 14-4 reproduces a table from the recent report of the Committee on the Management of the Air Force Health Study Data and Specimens (IOM, 2015), which summarized the diverse efforts undertaken. The committee enthusiastically supports these new and continuing research efforts and believes dedicated funding should be continued for focused analyses of these invaluable AFHS data and biospecimens by independent investigators.

Members of the ACC constitute the largest cohort of Vietnam veterans exposed directly to herbicides and TCDD. They were involved in the handling and distribution of the chemicals in Vietnam. ACC veterans who reported spraying herbicides as part of their duties have increased serum TCDD concentrations; this highly exposed population has also been shown to be at increased risk for several diseases. Previous VAO committees recommended that VA conduct additional studies of ACC veterans because the population presents a unique opportunity to examine the association between the health effects of exposure to TCDD and the herbicides used in Vietnam. Recently, VA launched the ACC Vietnam-Era Veterans Health Study to investigate the relationship between herbicide exposure during the Vietnam War and hypertension and COPD in ACC veterans. Information garnered from the study could benefit VA and future VAO committees as potential associations between exposure to the chemicals of interest and respiratory outcomes are evaluated.

Although about 250,000 US women served in the military during the Vietnam War and 5,000–7,000 women served in Vietnam, few data on the health of the deployed and non-deployed female veterans are available. More than a decade ago, Kang et al. (2000a,b) examined the prevalence of gynecologic cancers in female Vietnam veterans and of birth defects in their children. Kang et al. (2014) extended information on vital status in this population through 2010, adding

TABLE 14-4 Studies Approved for Use of the AFHS Data or Biospecimens Since 2012[a,b]

Principal Investigator	Institution	Proposal Title	Request Type
Batty	University of Edinburgh	Cognitive function in middle age as a predictor of later life health: Analyses of data from the Air Force Health Study	Data only
Boekelheide[c]	Brown University	Identifying epigenetic molecular markers of dioxin exposure in Vietnam veterans	Data and biospecimens
Chambers[c]	Mississippi State University	A longitudinal study of paraoxonase 1 (PON1) in relationship to type 2 diabetes and aging	Data and biospecimens
Haws	ToxStrategies, Inc.	Exposure–response relationship for dioxin and cancer and non-cancer health outcomes in the Air Force Health Study cohort using physiologically based pharmacokinetic modeling of exposure and updated mortality	Data only
Knafl	University of North Carolina at Chapel Hill	Effects of dioxin exposure for male Air Force Vietnam veterans on reproductive outcomes	Data only
Mandel	Exponent, Inc.	The reanalysis of the Ranch Hand data	Data only
Mazur	Syracuse University	Testosterone changes	Data only
Mitchell	Emory University and Atlanta VA Medical Center	Identifying novel biomarkers of vulnerable coronary artery disease: The Air Force Health Study	Data and biospecimens
Ramos[c]	University of Louisville	Detection of L1 protein in Ranch Hand biospecimens	Data and biospecimens
Ross[c]	Pacific Health Research and Education Institute, VA	Parkinson's disease and pre-motor features of Parkinson's disease in the Air Force Health Study	Data only
Roth[c]	VA San Diego Healthcare System	Caveolin's role during healthy aging	Data and biospecimens
Seldin[c]	Boston University	Incidence of abnormal free light chains and other markers of light chain amyloidosis in veterans exposed to Agent Orange: A pilot study	Data and biospecimens
Shim[y]	Centers for Disease Control and Prevention	Monoclonal gammopathy of undetermined significance (MGUS) and microRNAs in Ranch Hand veterans	Data and biospecimens

[a]This list represents studies approved as of February 1, 2015.

[b]The date that a proposal was approved and the date that the study was able to start varied depending on the type and extensiveness of the requested assets. For example, studies that requested more biospecimens (for example, more than 100) took longer to process than those requesting fewer samples.

[c]Denotes studies that were awarded pilot funding.

SOURCE: IOM, 2015.

6 years of follow-up to the previous mortality study (Cypel and Kang, 2008). However, no additional information on the health status of the survivors in this group has become available. In 2009, VA announced the start of the Health of the Vietnam Era Veteran Women's Study, a 4-year undertaking to investigate the mental and physical health of deployed and non-deployed US women who served during the Vietnam War. Although findings from the study have yet to be published, the committee supports these VA efforts and hopes that the findings will help to elucidate how military service in Vietnam may have affected the health of female veterans who served.

There has not been a sizable survey of the health of Vietnam veterans since CDC's Vietnam Experience Study was conducted 30 years ago in the mid-1980s, so the committee was pleased to learn that VA has already done considerable preparation for a study to monitor the health of Vietnam veterans as they age, the Vietnam Era Health Evaluation Retrospective Observational Study (VE-HEROeS). Table 14-3 contains several suggestions about maximizing the rate of participation, validating self-reported health outcomes, and gathering biological samples that would strengthen and increase the utility of the results generated by this endeavor.

VAO committees have been monitoring studies of morphologic birth defects and cancers in the offspring of exposed individuals, but systematic review of defined clinical health conditions that are manifested later in the offspring's lives remains difficult because most studies report on physiologic biomarkers that might or might not predict the potential for disease development later in life, rather than investigating specific diseases. A longstanding major concern is the possible association between the exposure of male Vietnam veterans to the chemicals of interest and health problems in their offspring, but there are few epidemiology studies of these endpoints that have addressed paternal exposure in the absence of maternal exposure. The few data on toxic contaminants in seminal fluid suggest that fetal exposure due to paternal transmission during later acts of intercourse is highly unlikely, but it now appears more physiologically possible that epigenetic modifications of sperm, including alterations in sperm mRNAs, microRNAs, and DNA after paternal exposure, might lead to changes in the offspring. The last of the few publications on birth defects in the offspring of male Vietnam veterans was published before the report on the children of female Vietnam veterans (Kang et al., 2000b), and no recently reviewed epidemiologic studies have assessed the role of paternal exposure in the occurrence of such effects. Thus, most of the available epidemiologic studies of effects in offspring are not relevant to the primary exposure group of concern: male Vietnam veterans.

Toxicologic Research

The committee believes that experimental research on the mechanisms that underlie human health outcomes (particularly cardiovascular disease, B-cell

cancers, and paternally mediated effects in offspring) could provide valuable information related to the risk of disease in Vietnam veterans and their children. Specifically, determining the mechanism by which dioxin-like chemicals induce B-cell cancers and how exposure to dioxin-like chemicals alters susceptibility to obesity and components of metabolic syndrome would fill important knowledge gaps. The development of animal models of neurologic outcomes and various chronic health conditions and their progression would also be useful for understanding the possible contributions of the chemicals of interest to impacting the health of aging Vietnam veterans.

The rapidly expanding field of epigenetics is revealing the molecular mechanisms by which environmental agents can modify gene expression without changing DNA sequence long after exposure occurs, even in later generations—at least in the case of maternal exposure to some chemicals. Animal studies of the mechanisms of inhibition of fetal growth, particularly in male offspring, after maternal exposure could help to elucidate findings seen in some epidemiologic studies that examined maternal exposure to the chemicals of interest and birth weight. There is a growing body of evidence that TCDD can induce epigenetic changes in animal models, and continuing research could characterize the timing and duration of exposure that are most critical as well as the susceptibility of specific organ systems to disease development in offspring later in life. The occurrence of adverse effects in offspring following maternal exposure to numerous agents, including TCDD, has been amply documented, and experimental results have shown that effects on male offspring following maternal exposure to TCDD can be passed even to the second generation, but to date there has been minimal investigation of whether paternal exposure poses a risk of adverse effects in their offspring, for xenobiotics in general and the VAO chemicals of interest in particular. Given the current concern among male veterans about the transmission of adverse effects to their descendants, focused use of animal models to investigate the possibility of paternal exposure contributing to the development of disease in offspring would be very informative. In fact, it might be wise to delay the initiation of epidemiologic studies on these endpoints until such effects have been demonstrated in the offspring of exposed male laboratory animals.

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Appendix A

Issues Raised by the Public and Agendas of Public Meetings Held by the Committee and Other Written Submissions to the Committee

MAIN ISSUES RAISED BY THE PUBLIC

Following the delivery of the committee's charge by a Department of Veterans Affairs representative at the first meeting, the open session continued with brief presentations by other members of the public. It has been the practice of Veterans and Agent Orange committees to conduct open sessions, not only to gather additional information from people who have particular expertise on points that arise during deliberations but also especially to hear from individual Vietnam veterans and others concerned about aspects of their health experience that may be service-related. Open sessions were held during the first three of the committee's five meetings. Following the agendas for these public meeting is a complete list of written submissions to and considered by the committee, which are all available from this study's Public Access File.

Having solicited input, the committee feels a responsibility to note the concerns raised, even if it is only to the extent of noting that a topic does not fall within the committee's charge. The main issues raised by veterans or their advocates during the current updating period fell into four general categories. The following is a summary of the four main topics (in no particular order) that were raised at the open sessions and/or in submitted written statements.

- **Veterans exposed to Agent Orange in places other than Vietnam:** Veterans noted several locations or situations outside of Vietnam where they believe they were exposed to Agent Orange and so are entitled to coverage of those diseases recognized as service-related for veterans who had "boots on the ground" in Vietnam. Evaluating data on the basis of *where*

veterans may have experienced herbicide exposure is not within the scope of this committee's charge.

- **Health problems in children and grandchildren of Vietnam veterans:** Veterans noted numerous concerns about the general phenomenon of the transmission of adverse effects to offspring following paternal exposure to toxic agents. Chapter 10 addresses evidence related to the possibility that the herbicide exposure of Vietnam veterans has had adverse consequences for their progeny.
- **Bladder cancer:** Veterans brought the issue of bladder cancer to the committee's attention on multiple occasions during this update, drawing particular attention to decisions from regulatory bodies concerning organic arsenic compounds, including dimethyl arsenic acid, also known as DMA or cacodylic, one of the four herbicides sprayed by the US military in Vietnam. With addition of some new findings, the relevant epidemiologic evidence (although not specifically related to exposures to cacodylic acid) now shows that there is limited or suggestive evidence of an association between the chemicals of interest and bladder cancer. Chapter 8 contains a specific discussion on the new information informing the committee's decision to change this category of association.
- **Myelodysplastic syndrome (MDS):** Epidemiologic studies addressing risk factors for MDS were identified in the recent update period, but the available evidence remains insufficiently specific with respect to the four herbicides sprayed in Vietnam and their dioxin contaminant to provide a basis of a decision concerning an association other than the default decision of inadequate or insufficient. In addition, exposure to benzene is recognized as being a risk factor for MDS, and it is a component of the petroleum products used as dispersants with the herbicides. Benzene is so highly volatile that it would no longer be part of the sprayed herbicides as they reached ground level, so it is not covered under the committee's charge. The relevant available epidemiologic evidence remains inadequate and insufficient to support an association of MDS with exposure to the committee's chemicals of interest. See Chapter 8 for specific discussion.

FIRST PUBLIC MEETING

November 17, 2014
The National Academies' Keck Center
500 Fifth Street, NW
Washington, DC 20001

Open Session

1:30 p.m. **Welcome, goals/conduct of the open session, committee member introductions**
Kenneth Ramos, Committee Chair

1:35 p.m. **Charge to the committee**
- Origins of Study
- Study Scope
- Expected Outcomes

R. Loren Erickson, US Department of Veterans Affairs

2:00 p.m. **Vietnam Veterans of America statement**
Rick Weidman, Executive Director, Policy and Government Affairs, Vietnam Veterans of America

2:10 p.m. **New Jersey State Council, Vietnam Veterans of America statement**
Michael Eckstein, Chair, Agent Orange/Dioxin Committee

2:20 p.m. **Assumed association of long-term adverse health conditions from exposures and related presumptive illnesses—Veteran statements**
Carlo Albanese, Veteran (tentative)
Helene Van Clief, Army Staff Sergeant

2:40 p.m. **Recent literature addressing presumptive illnesses and post-Vietnam exposures, and VA redefinition of "exposure" in the light of post-Vietnam concerns**
Major Wes Carter, Chair, The C-123 Veterans Association

2:50 p.m. **Open comment period**

3:00 p.m. **Open session adjourns**

SECOND PUBLIC MEETING

January 20, 2015
National Academies' Beckman Conference Center
100 Academy Way
Irvine, CA 92612

Open Session

1:00 p.m. **Welcome, goals/conduct of the open session, committee member introductions**
Kenneth Ramos, Committee Chair

1:15 p.m. **Open comment period**

3:00 p.m. **Open session adjourns**

THIRD PUBLIC MEETING

March 9, 2015
JW Marriott Tucson Starr Pass Resort
3800 West Starr Pass Boulevard
Tucson, AZ 85745

Open Session

1:00 p.m. **Welcome, goals/conduct of the open session, committee member introductions**
Kenneth Ramos, Committee Chair

1:15 p.m. **Discussion on grouping B-cell neoplasms**
Moderator: Karl Kelsey, Brown University

Experts in attendance:

- **Recent classification paradigms**
  Lisa Rimsza, MD, University of Arizona
- **Role of biological mechanism in clinical applications**
  Dan Persky, MD, University of Arizona

Experts participating remotely:

- *Elaine Jaffe, MD, IOM, National Cancer Institute*
- Members of InterLymph Project team:
  - *Annaclaire De Roos, PhD, MPH, Drexel University*
  - *Martha Linet, MD, MPH, National Cancer Institute*
  - *Lindsay Morton, PhD, National Cancer Institute*

2:00 p.m. **Comments from Vietnam veterans and their representatives**

3:00 p.m. **Open session adjourns**

Written Statements Received from Public

1. Carlo Albanese, Veteran Spokesperson
Submitted: 11/14/2014
Letter via email: Letter Re: Mtg. 1

2. Placido Salazar, Vietnam Veteran
Submitted: 11/16/2014
Letter via email: Letter to Mary Paxton, Study Director, Re: Meeting 1

3. Leroy Foster, Vietnam Veteran
Submitted: 11/16/2014
Letter via email: Letter to Mary Paxton, Study Director, Re: Meeting 1

4. Ralph (Loren) Erickson, Pre-9/11 Era Environmental Health Program, Veterans Health Administration
Submitted: 11/17/2014
PPT: Charge to the Committee: "INSTITUTE OF MEDICINE AGENT ORANGE COMMITTEE: Veterans and Agent Orange, Biennial Update"

5. Major Wesley Carter, C-123 Veterans Association
Submitted: 11/17/2014
PPT: C-123 Veterans Association Presentation

6. Major Wesley Carter, C-123 Veterans Association
Submitted: 11/17/2014
PDF: Written Statement: "Statement of the C-123 Veterans Association by Wesley T. Carter, Chair"

7. Major Wesley Carter, C-123 Veterans Association
Submitted: 11/17/2014
USB/Zip File (44 items): Compilation of documents submitted to the Committee by the C-123 Veterans Association

8. Helene Van Clief, Vietnam Veteran
Submitted: 11/17/2014
Email+ 1 attachment PDF: Information on Women Veterans and Stateside Exposures at Fort McClellan

9. Placido Salazar, Vietnam Veteran
Submitted: 11/17/2014
Letter via email: Letter to Mary Paxton, Study Director

10. Michael Eckstein, Agent Orange/Dioxin Committee, New Jersey State Council, VVA
Submitted: 11/17/2014
PDF: Written statement: Written version of oral presentation to the committee

11. Michael Eckstein, Agent Orange/Dioxin Committee, New Jersey State Council, VVA
Submitted: 11/17/2014
PDF: VAO Report Series Stats Spreadsheet

12. Carlo Albanese, Veteran Spokesperson
Submitted: 11/17/2014
2 DVDs: Video Statement by Carlo Albanese on behalf of the Veterans and Agent Orange Movement Group

13. Charles Kelley, Vietnam Veteran
Submitted: 11/19/2014
Letter via email: Letter to Mary Paxton, Study Director

14. Placido Salazar, Vietnam Veteran
Submitted: 11/23/2014
Letter via email + 1 attachment PDF: Letter to Mary Paxton, Study Director and a Leaked 1990 EPA Memo

15. Michael Eckstein, Agent Orange/Dioxin Committee, New Jersey State Council, VVA
Submitted: 11/25/2014
Excel: VAO Report Series Stats Spreadsheet (full electronic version of item #11 above)

16. Peter Sullivan, The Thomas Joseph Sergeant Sullivan Center
Submitted: 1/23/2015
Email: Fwd: Agent Orange report comes after years of VA denials

17. John J. Bury, Vietnam Veteran
Submitted: 2/23/2015
Email: John Bury Letter Agent Orange Effects

18. Donald Wilbur
Submitted: 3/4/2015
Email: Donald Wilbur Written Statement

19. Rae Grisius, Bladder Cancer Advocacy
Submitted: 3/5/2015
Email: Statement of Rae Grisius

20. John McClun, US Army (Retired)
Submitted: 3/6/2015
Email: John McClun Written Statement

21. Gwendolyn Krossfik
Submitted: 3/6/2015
Email: Statement of Gwendolyn Krofssik

22. Carla Dean, Bladder Cancer Foundation of Florida
Submitted: 3/9/2015
Email: Statement of Carla Dean

23. Carla, Dean, Bladder Cancer Foundation of Florida
Submitted: 3/9/2015
PDF: Carla Dean Attachment EPA Organic Arsenicals

24. Carla Dean, Bladder Cancer Foundation of Florida
Submitted: 3/9/2015
Email: Carla Dean Attachments on Arsenic Exposures (A-–H)

A. Carla Dean Attachment A Hazardous Substances
B. Carla Dean Attachment B EPA Arsenic Compounds
C. Carla Dean Attachment C EPA Cacodylic Acid
D. Carla Dean Attachment D Thesis Arsenic Contamination in Ground Water in Vietnam
E. Carla Dean Attachment E Full Report Arsenic Contamination in Ground Water in Vietnam
F. Carla Dean Attachment F Environmental Health Criteria 224 Arsenic and Arsenic Compounds Link to Full Report
G. Carla Dean Attachment G Abstract Increased Lung and Bladder Cancer Incidence in Adults after In Utero and Early-Life Arsenic Exposure
H. Carla Dean Attachment H Mortality study of chemical workers exposed to dioxins

25. Judy Bryant, Alderson Broaddus University
Submitted: 3/9/2015 Email: Judy Bryant Statement to Institute of Medicine Committee reviewing the Health Effects in Vietnam Veterans of Exposure to Herbicides

26. Lisa Rimsza, MD University of Arizona, Tucson
Submitted: 3/10/2015
Presentation: Lymphoma Classification

27. Daniel O. Persky, MD University of Arizona Cancer Center
Submitted: 3/10/2015
Presentation: Biological mechanisms in clinical applications for B-cell neoplasms cell of origin in diffuse large B-cell lymphoma

28. Bill Colberg, Vietnam Veterans of America
Submitted: 3/10/2015
Letter: Bill Colberg Statement VVA Presentation Before the IOM Committee

29. Dennis St. Germaine, Vietnam Veterans for America
Submitted: 3/10/2015
A. Audio Vietnam Veterans for America Agent Orange

30. Carolyn C. McGrath
Submitted: 3/18/2015
Letter: Carolyn C. McGrath Statement and Materials

31. Toby Watson, MD
Submitted: 3/27/2015
Letter: Rates of Missing Conditions: It Looks Like Psychiatric Disorders

32. Charles Kelley
Submitted: 3/31/2015
Letter: Concerning TCDD's role in all cancers

33. Carla Dean, Bladder Cancer Foundation of Florida
Submitted: 5/29/2015
Article: Agent Blue Arsenic Laced Rainbow

34. Jamie Chadwick
Submitted: 6/23/2015
Letter: Jamie Chadwick Statement on Bladder Cancer

35. Cindy Fabbri
Submitted: 7/17/2015
Letter: Cindy Fabbri Statement On Esophageal Cancer

Appendix B

Short-Term Adverse Health Responses

The committee responsible for *Update 2008* advised the removal of chloracne, porphyria cutanea tarda (PCT), and early-onset peripheral neuropathy from the body of the Veterans and Agent Orange (VAO) reports, and the committee for *Update 2010* removed them. The three conditions that occur in temporal proximity to exposure have little relevance to new claims from Vietnam veterans, and there has been minimal new evidence since they were classified as having evidence of an association with herbicide exposure

The three conditions have long been recognized by the Department of Veterans Affairs as presumptively related to service in Vietnam. This appendix has been retained in subsequent volumes in the VAO series to provide easy access to the distilled body of biomedical evidence upon which these decisions were made.

CHLORACNE

Chloracne is a skin disease that is characteristic of exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other diaromatic organochlorine chemicals. It shares some pathologic processes (such as the occlusion of the orifice of the sebaceous follicle) with more common forms of acne (such as acne vulgaris), but it can be differentiated by the presence of epidermoid inclusion cysts, which are caused by proliferation and hyperkeratinization (horn-like cornification) of the epidermis and sebaceous gland epithelium. Although chloracne is typically distributed over the eyes, ears, and neck, it can also occur on the trunk, genitalia, and buttocks of chemical-industry workers exposed to TCDD (Neuberger et al., 1998). It is resistant to acne treatments, but it usually regresses.

Chloracne has been used as a marker of exposure in epidemiologic studies of populations exposed to TCDD and related chemicals. It is one of the few findings in humans that are consistently associated with such exposure, and it is a well-validated indicator of high-dose exposure to TCDD and related chemicals (Sweeney et al., 1997/98). If chloracne occurs, then it appears shortly after the chemical exposure, not after a long latent period; therefore, new cases of chloracne among Vietnam veterans would not be the result of exposure during the Vietnam War. It should be noted that the absence of chloracne does not necessarily indicate an absence of substantial exposure to TCDD, as is apparent from studies of people who had documented exposure to TCDD after the Seveso incident in 1976 in Italy (Baccarelli et al., 2005a), nor is there necessarily a correlation between serum TCDD concentration and the occurrence or severity of chloracne. Susceptibility to the development of chloracne varies among individuals.

Recent data released following the poisoning of Victor Yushchenko have provided evidence suggesting that chloracne may be a detoxification mechanism. Close examination of the lesions over time demonstrate that the lesions are hamartomas, characterized by the loss of the sebaceous glands. These lesions concentrate the level of TCDD 10-fold, and show increased expression of enzymes involved in toxicant metabolism (Saurat et al., 2012). This suggests the hypothesis that chloracne lesions are an adaptive skin response to the exposure to dioxin and related compounds and that they play a functional role in the detoxification pathway for these compounds.

Conclusions from *VAO* and Previous Updates

The committee responsible for *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (referred to as *VAO*; IOM, 1994) determined that there was sufficient evidence of an association between exposure to at least one chemical of interest (TCDD) and chloracne. Additional information available to the committees responsible for *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003a), *Update 2004* (IOM, 2005), *Update 2006* (IOM, 2007), *Update 2008* (IOM, 2009), *Update 2010* (IOM, 2011a), and *Update 2012* (IOM, 2014) has not modified that conclusion.

Even in the absence of a full understanding of the cellular and molecular mechanisms that lead to the disease, several notable reviews (Panteleyev and Bickers, 2006; Sweeney and Mocarelli, 2000) have deemed the clinical and epidemiologic evidence of dioxin-induced chloracne to be strong. The occupational epidemiologic literature has many examples of chloracne in workers after reported industrial exposures (Beck et al., 1989; Bond et al., 1987, 1989a,b; Cook et al., 1980; Goldman, 1972; May, 1973, 1982; Oliver, 1975; Pazderova-Vejlupkova et al., 1981; Poland et al., 1971; Suskind and Hertzberg, 1984; Suskind et al., 1953; Zober et al., 1990). With relative-risk estimates as high as 5.5 in exposed

workers compared with referent non-exposed workers, Bond et al. (1989a) identified a dose–response relationship between probable exposure to TCDD and chloracne. Not everyone exposed to relatively high doses develops chloracne, and some with lower exposure may acquire it (Beck et al., 1989).

Almost 200 cases of chloracne were recorded in those residing in the vicinity of the accidental industrial release of dioxin in Seveso. Most cases occurred in children, particularly those who lived in the highest-exposure zone, and most cases resolved within 7 years (Assennato et al., 1989a,b; Caramaschi et al., 1981; Mocarelli et al., 1991). No cases of chloracne were identified in conjunction with the non-extreme environmental dioxin contamination at Times Beach, Missouri (Webb et al., 1987).

Exposures of Vietnam veterans were substantially lower than those observed in occupational studies and in environmental disasters, such as the one in Seveso. The long period since the putative exposure has imposed methodologic limitations on studies of Vietnam cohorts for chloracne. Nonetheless, the Vietnam Experience Study (CDC, 1988) found that chloracne was self-reported more often by Vietnam veterans than by Vietnam-era veterans (odds ratio [OR] = 3.9). An excess incidence was also found in Vietnam versus era veterans among subjects who were physically examined (OR = 7.3). In comparison with a non-exposed group, Air Force Ranch Hand personnel potentially exposed to Agent Orange reported a significant excess of acne (OR = 1.6) (Wolfe et al., 1990), but no cases of chloracne or postinflammatory scars were found on physical examination 20 years after possible herbicide exposure (AFHS, 1991b).

Biologic Plausibility

Previous updates have reported that chloracne-like skin lesions have been observed in several animal species in response to exposure to TCDD but not to purified phenoxy herbicides. Data accruing over the past several decades demonstrated that TCDD alters the differentiation of human keratinocytes, and more recent studies have illuminated how. Geusau et al. (2005) found that TCDD accelerates the events associated with early differentiation but also obstructs the completion of differentiation. Panteleyev and Bickers (2006) proposed that the major mechanism of TCDD induction of chloracne is activation of the stem cells in the basal layer of the skin to differentiate and inhibition of their ability to commit fully to a differentiated status. Ikuta et al. (2010) have investigated the expression of B-lymphocyte maturation protein 1 in epidermal keratinocytes and sebocytes in mice after induction of the aryl hydrocarbon receptor (AHR). Using a constitutively activated form of the AHR, Tauchi et al. (2005) demonstrated that TCDD-mediated chloracne involves inflammatory processes, which was confirmed by a recent finding that reactive oxygen species (ROS) can accelerate keratinocyte differentiation (Kennedy et al., 2012). Recent studies using an in vitro model of normal human epidermal keratinocytes confirmed the involvement

of the AHR in chloracne development (Forrester et al., 2014). The data support a biologically plausible mechanism for the induction of chloracne by TCDD.

Synthesis

No epidemiologic data in the past decade have refuted the conclusion of prior VAO committees that the evidence of an association between exposure to dioxin and chloracne is sufficient. The 2004 poisoning case of Ukrainian politician Victor Yushchenko has provided a high-profile instance that supports the idea that this condition can be a response to high-level exposure to TCDD, and the careful monitoring of his case has demonstrated the course of chloracne's resolution in conjunction with subsiding serum concentrations (Sorg et al., 2009). The formation of chloracne lesions after the administration of TCDD has been observed in some species of laboratory animals.

Conclusion

On the basis of numerous epidemiologic studies of occupationally and environmentally exposed populations and supportive toxicologic information, the committee for *Update 2014* concurs with all previous VAO committees that there is sufficient evidence of an association between exposure to at least one chemical of interest and chloracne. Because TCDD-associated chloracne becomes evident shortly after exposure, there is no risk of new cases long after service in Vietnam.

PORPHYRIA CUTANEA TARDA (PCT)

Porphyrias are uncommon disorders caused by deficiencies of enzymes involved in the pathway of biosynthesis of heme, the iron-containing nonprotein portion of the hemoglobin molecule. PCT, the most common of the porphyrias, is a heterogeneous group of disorders caused by a deficiency of a specific enzyme, uroporphyrinogen decarboxylase. It can be inherited but usually is acquired. Type I PCT, which accounts for 80 to 90 percent of all cases, is an acquired disease that typically becomes evident in adulthood. It can occur spontaneously but usually occurs in conjunction with environmental factors, such as alcohol consumption, exposure to estrogens, or use of some medications.

The most important clinical finding in PCT is cutaneous photosensitivity. Sensitivity to sunlight is thought to result from the excitation of excess porphyrins in the skin by long-wave ultraviolet radiation, which leads to cell damage. Fluid-filled vesicles and bullae develop on sun-exposed areas of the face and on the dorsal surfaces of the hands, feet, forearms, and legs. Other features include hypertrichosis (excess hair) and hyperpigmentation (increased pigment), especially on the face. People with PCT have increased porphyrins in the liver, plasma, urine, and stools. Iron, estrogens, alcohol, viral hepatitis, and chlorinated

hydrocarbons can aggravate the disorder. Iron overload is almost always present in people who have PCT.

Conclusions from *VAO* and Previous Updates

On the basis of strong animal studies and case reports demonstrating TCDD-induced PCT and resolution after cessation of exposure, the committee responsible for *VAO* determined that there was sufficient evidence of an association between exposure to TCDD and PCT in genetically susceptible people.

Epidemiologic studies of occupational populations have indicated inconsistent associations between the chemicals of interest and increased urinary uroporphyrin. Bleiberg et al. (1964) reported increased urinary uroporphyrin in 11 of 29 workers in a factory that manufactured 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), with the manifestation of some clinical evidence of PCT in three of them. In a follow-up study of the same facility 6 years later, no abnormalities in urinary porphyrins were observed (Poland et al., 1971). Calvert et al. (1992) reported no difference in porphyrinuria or the occurrence of PCT between 281 workers in the National Institute for Occupational Safety and Health (NIOSH) cohort who were involved in the production of trichlorophenol and were exposed to TCDD and 260 non-exposed workers. Serum TCDD concentration was not associated with uroporphyrin or coproporphyrin concentrations.

Among people who were exposed to TCDD as a result of the 1976 chemical-plant explosion in Seveso, Italy, clinical PCT was observed only in a brother and a sister who had a mutant enzyme that confers susceptibility in the heterozygous state. In 1977, 60 Seveso residents were tested for increased porphyrins, and 13 had secondary coproporphyrinuria; increased concentrations persisted in only three cases, and this was thought to be due to liver damage and alcohol consumption (Doss et al., 1984). In the Quail Run mobile-home park in Missouri, residents exposed to dioxin as a result of the spraying of waste oil contaminated with TCDD were found to have higher urinary uroporphyrins than controls, but no cases of clinical PCT were diagnosed (Hoffman et al., 1986; Stehr-Green et al., 1987).

The baseline study of the US Air Force Ranch Hands (AFHS, 1984) showed no difference in uroporphyrin or coproporphyrin concentrations in urine between Ranch Hands and controls. There were no indications of the clinical appearance of PCT in Ranch Hands. Follow-up studies of the Ranch Hand cohort revealed that mean uroporphyrin was greater in the comparison group than in the Ranch Hands, whereas mean coproporphyrin was higher in Ranch Hands. The clinical significance of the small differences between the Ranch Hands and the comparison groups was uncertain.

The committee responsible for *Update 1996* considered three additional non-positive citations of populations that had substantial exposure to TCDD. Jung et

al. (1994) presented porphyrin data on former workers in a German pesticide plant that had manufactured 2,4-D and 2,4,5-T. Of 170 men tested, 27 had present or past chloracne. The study found no difference in porphyrin concentrations between subjects with and without chloracne. There was also no relationship between abnormal results of liver-function tests or porphyrin concentrations and the presence of chloracne. In addition, there was no relationship between porphyrin concentrations in urine, red blood cells, or plasma and TCDD concentrations in adipose tissue. Three cases of chronic hepatic porphyria (none with overt PCT and none with chloracne) were identified—a number that did not exceed the expected prevalence in this population. Von Benner et al. (1994) found no indication of clinical porphyria in self-referred workers in six other German chemical plants. Another report on the NIOSH cohort (Calvert et al., 1994) was negative. On the basis of the cumulative findings, the committee responsible for *Update 1996* concluded that there was only limited or suggestive evidence of an association. The committees for later updates have not changed the revised conclusion.

Because PCT is manifested shortly after exposure to TCDD, new cases of PCT attributable to exposure during the Vietnam War are not expected to occur.

Biologic Plausibility

PCT has not been exactly replicated in animal studies of the effects of TCDD although other porphyrin abnormalities have been reported. Administration of TCDD to mice results in an accumulation of uroporphyrin that occurs in a manner that requires the AHR, cytochrome P450 1A1 (CYP1A1), and CYP1A2 (Robinson et al., 2002; Smith et al., 2001; Uno et al., 2004), but the underlying mechanism of action has not been fully illuminated (Smith and Chernova, 2009; Smith and Elder, 2010). In a recent study, Chavan and Krishnamurthy (2012) treated human liver–derived cell lines with TCDD, showing that this activated ABCB6 expression, an important requirement to support the increased heme demand that occurs when animals are exposed to xenobiotics.

Synthesis

No epidemiologic data have emerged in the past decade that refute the conclusion of previous VAO committees that there is limited or suggestive evidence of an association between the chemicals of interest and PCT.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee for *Update 2014* concurs with prior VAO committees that there is limited or suggestive evidence of an association between exposure to at least one chemical of interest and PCT. PCT is rare, and its occurrence may be influenced

by a genetic predisposition in people who have low concentrations of protoporphyrinogen decarboxylase.

EARLY-ONSET PERIPHERAL NEUROPATHY

Since *Update 1996*, VAO committees have partitioned their consideration of peripheral neuropathy into early-onset (implicitly transient) peripheral neuropathy and chronic peripheral neuropathy. Primarily on the basis of reports of short-term health effects after industrial accidents, the committee responsible for *Update 1996* concluded that there was limited or suggestive evidence of an association between exposure to the chemicals of interest and "acute and subacute" neuropathy, which was redesignated early-onset transient peripheral neuropathy by the committee responsible for *Update 2004*. The committee for *Update 2010* recognized the imprecision in the nomenclature that had been used to characterize the type of peripheral neuropathy that is regarded as service-connected. The diagnosis in question is, in fact, contingent on the *proximity of its occurrence to the time of exposure* rather than on the transitory nature of the adverse outcome. Clinically, in cases of an immediate response of peripheral neuropathy after toxicant exposure, stabilization or improvement is the rule after the exposure ends. However, the recovery may not be complete; the degree of recovery can depend on the severity of the initial deficits and the particular exposure. Furthermore, there is a possibility of "subclinical" effects, and a person might be unaware of symptoms, although evidence of nerve dysfunction can be found through a detailed neurologic examination or electrodiagnostic testing. Thus, the committee chose to delete the word *transient* to recognize that symptoms of early-onset peripheral neuropathy may be protracted and that recovery from them may be incomplete.

The information about peripheral neuropathy presented in this appendix demonstrates that it may occur soon after an exposure to extremely high concentrations of dioxin. In addition, this appendix addresses the evidence that some people who experience early-onset peripheral neuropathy (that is, during or shortly after dioxin exposure) may continue to manifest the problem long after the exposure has ceased; this would show that early-onset peripheral neuropathy is not necessarily transient.

Conclusions from *VAO* and Previous Updates

Several occupational studies have evaluated whether herbicide exposure or production may lead to early-onset neuropathy. In March 1949, an explosion occurred in a reactor vessel in a chemical plant in Nitro, West Virginia, where 2,4,5-T was being produced. Many workers reported health effects (toxic hepatitis, increased serum lipids, and central nervous system involvement), including a severe acute neuropathy in four workers who had chloracne (Ashe and Suskind,

1949, 1950). Thirty years later, an attempt was made to identify workers who had been exposed during that accident and workers who may have been chronically exposed from 1948 through 1969 (Suskind and Hertzberg, 1984). Neurologic examination and nerve-conduction studies did not demonstrate abnormalities compared with a cohort of non-exposed controls; however, the procedure for obtaining controls did not ensure equivalence. It is unclear whether the four subjects who had acute neuropathy were included in the effort.

In April 1979, chlorinated dibenzo-*p*-dioxin contamination was found in a community in Arkansas that was close to a plant where 2,4,5-T and 2,4-D had been produced since 1957. Fifty-five workers in that plant who had no history of diabetes or alcohol abuse were identified from the total workforce; they underwent neurologic examination and nerve-conduction studies (Singer et al., 1982). Both median motor and calf sensory nerve-conduction studies showed significantly lower conduction velocity in the plant workers than in control subjects.

Other industrial accidents have also suggested a link between the chemicals of interest and early-onset neuropathic symptoms, which persisted in some people. Jirasek et al. (1974) studied 55 of 80 workers who complained of a variety of symptoms after chronic exposure to 2,4,5-T in a manufacturing facility in the Czech Republic; of the 55, the results of physical examinations of 17 suggested neuropathy that was said to have been confirmed with electromyographic abnormalities. A follow-up of 44 of the 55 was conducted 10 years after the exposure had ceased; about 30 percent of them were reported to have continued neuropathic symptoms (Pazderova-Vejlupkova et al., 1981). More recently, Urban et al. (2007) evaluated long-term sequelae in subjects who developed neuropathy after the original exposure. Subjects had increased serum TCDD concentrations more than 30 years after exposure, and evidence of continued neuropathy was noted in 9 of 15 subjects who were available for study.

Acute neuropathic symptoms were reported after the Seveso accident, and persistent signs were noted. Gilioli et al. (1979) evaluated 35 subjects who had been exposed during the accident and noted abnormalities in a variety of neurophysiologic measures compared with age-matched controls 2 years after the exposure. However, it is unclear how the exposed subjects were selected for study. In a more complete survey, Boeri et al. (1978) studied 470 subjects from two exposure zones about a year after the accident and found a higher incidence of neurophysiologic abnormalities in the exposed subjects than in non-exposed controls; the residents of the zone of greater exposure were more severely affected than those of the less exposed zone. The same group (Filippini et al., 1981) found an increased prevalence of peripheral neuropathy in residents who had indicators of exposure compared with those who did not (relative risk [RR] = 2.6, 95% confidence interval [CI] 1.0–7.2 for those with choracne; RR = 3.6, 95% CI 1.3–10.2, for those with increased hepatic enzymes) when they were evaluated 21 months after the accident. Improvement may have occurred in the years following the accident. For example, Assennato et al. (1989a,b) studied 193 exposed

residents of the area 9 years after the accident and did not find neurophysiologic abnormalities; however, the number of residents in the group who originally complained of neuropathic symptoms was not discussed. Similarly, 6 years after the accident, Barbieri et al. (1988) examined 153 residents who had developed chloracne. World Health Organization criteria for neuropathy were not fulfilled for any subjects, but there was a statistically significant increase in neurophysiologic abnormalities compared with those in non-exposed age-matched controls.

There have been a number of case reports of exposure-associated early-onset neuropathy. Goldstein et al. (1959) reported the cases of three patients seen at the Mayo Clinic who had acute weakness and sensory loss demonstrated to be due to peripheral neuropathy; symptoms occurred within hours of an exposure to 2,4-D sufficient to wet both clothes and skin. The three patients recovered incompletely; in one, a cerebrospinal fluid (CSF) examination was normal except for minimally increased protein. Todd (1962) reported another case of neuropathy that occurred about 4 days after 2,4-D exposure, again in sufficient quantities to cause large areas of skin to be wet. Clinical examination demonstrated a sensory motor polyneuropathy; CSF examination showed slightly increased protein but was otherwise normal. The patient recovered substantially but not completely over 2 years. Finally, Berkley and Magee (1963) reported a case of a 39-year-old man who had symptoms of acute neuropathy that progressed to an inability to walk starting 4 days after 2,4-D exposure; CSF analysis was normal, including normal protein concentrations, and he recovered nearly completely over the course of 8 months.

Case reports do not provide conclusive evidence of causal relationships, but the cases discussed above showed a close temporal relationship between a high exposure to 2,4-D and neuropathy. The most likely non-toxicant-related acute neuropathy is Guillain-Barré syndrome; however, this syndrome is associated with characteristic findings on clinical neurophysiologic examination and highly increased protein in CSF. In the three cases above that had CSF evaluation, protein concentrations were either normal or increased to a minimal extent not consistent with Guillain-Barré syndrome. In addition, patients who had clinical neurophysiologic studies also showed abnormalities not consistent with Guillain-Barré. Thus, it seems likely that the cases represent the results of 2,4-D exposure.

Biologic Plausibility

Neuronal cell cultures treated with 2,4-D showed a decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis (Rosso et al., 2000a,b). Those mechanisms are important for maintaining synaptic connections between nerve cells and supporting the mechanisms involved in axon regeneration during recovery from peripheral neuropathy. Grahmann et al. (1993) and Grehl et al. (1993) reported observing, respectively, electrophysiologic and pathologic abnormalities in the

peripheral nerves of rats treated with TCDD. When the animals were sacrificed 8 months after exposure, there was pathologic evidence of axonal nerve damage and histologic findings typical of toxicant-induced injury. Those results constitute evidence of the biologic plausibility of an association between exposure to the chemicals of interest and peripheral neuropathy.

Conclusions

On the basis of studies of health effects after industrial accidents and the well-documented cases reported above, the current committee reaffirms the conclusion of VAO committees since *Update 1996* that there is limited or suggestive evidence of an association between exposure to the chemicals of interest and early-onset peripheral neuropathy. Inasmuch as new data on this subject, especially with regard to Vietnam veterans, are unlikely to emerge, the committee for *Update 2014* reaffirms that finding.

REFERENCES

The Appendix B references can be found in the References chapter.

Appendix C

Clarification of Cancer Groupings Used in Reporting Results, with Correspondence to National Institute for Occupational Safety and Health Cause-of-Death Codes and *International Classification of Diseases* Codes for Cancers

In response to a request from the Department of Veterans Affairs, the committee responsible for *Update 2006* prepared Table C-1 to demonstrate how conclusions provided for the full range of cancer types and to clarify into which groupings any specific cancer diagnosis falls. The committee for *Update 2010* reframed its overview of lymphohematopoietic neoplasms according to the World Health Organization (WHO) classification system (WHO, 2008), which partitions these disorders first according to the lymphoid or myeloid lineage of the transformed cells rather than as lymphomas or leukemias; this emphasizes the close etiologic relationship of chronic lymphocytic leukemia and hairy-cell leukemia with Hodgkin and non-Hodgkin lymphomas and with the neoplasm multiple myeloma and its related condition AL amyloidosis.

The major portion of evidence compiled for review in the Veterans and Agent Orange (VAO) series comes from cohort studies, primarily of mortality but also some of incidence. Other data have been generated by case-control studies, which follow the only design amenable to studying very infrequent or very specific health outcomes. How researchers are able to group, analyze, and report their findings is influenced by the distribution of cases that they observe, so the data that VAO committees have had available for review reflect mortality experience at a level of specificity concordant with statistical analysis.

The *International Classification of Diseases* (ICD) system is used by physicians and researchers around the world to group related diseases and procedures so that morbidity and mortality information can be classified for statistical purposes in a standard form that is amenable to data storage and retrieval. It is a comprehensive hierarchic system that permits great detail but that can be collapsed into broad categories. Codes mentioned in VAO reports are stated in terms

TABLE C-1 Mapping of Groupings of Malignant Neoplasms That Are the Subjects of Conclusions in the *Veterans and Agent Orange* Series with ICD-9 Codes

NIOSH Category for Cause of Death		NIOSH Groupings of Cancer Sites	"VAO Characterization of Grouping"[a] Subsites	ICD-9 Codes
Major	**Minor**			
02		Buccal cavity and pharynx	**"Oral, nasal, and pharyngeal"**	
	004	Lip		140
	005	Tongue		141
	006	Other parts of buccal cavity		
			Salivary glands	142
			Floor of mouth	144
			Gum and other mouth	143, 145
	007	Pharynx		
			Oropharynx	146
			Tonsil	146.0–146.2
			Nasopharynx	147
			Hypopharynx	148
			Other buccal cavity and pharynx	149
				(160 = nasal below)
03		Digestive organs and peritoneum		
	008	Esophagus	**"Esophagus"**	150
	009	Stomach	**"Stomach"**	151
	010	Intestine except rectum	**"Colorectal"**	
			Small intestine	152
			Colon (large intestine)	153
	011	Rectum		154
	012	Biliary passages, liver, and gall bladder	**"Hepatobiliary"**	
			Liver and intrahepatic bile ducts	155
			Gallbladder and extrahepatic bile ducts	156
	013	Pancreas		157

	014	Retroperitoneum and other and unspecified digestive organs		158–159
04		Respiratory system	**"Respiratory"**	
	015	Larynx	**"Larynx"**	161
	016	Trachea, bronchus, and lung	**"Lung"**	162
			Trachea	162.0 (there is no ICD 162.1)
			Lung and bronchus	162.2–162.9
	017	Pleura		163
	018	Other respiratory		
			Nasal cavity, middle ear, and accessory sinuses	(160, above with oral and pharyngeal)
			Thymus, heart, and mediastinum	164 (164.0, below with endocrine; 164.1, below with soft tissue sarcoma)
			Other respiratory, unspecified	165 (discontinuity with ICD codes)
05	019	Breast (male and female)	**"Breast"**	174, 175
06		Female genital organs	**"Female reproductive"**	
	020	Cervix uteri		180
	021	Other unspecified parts of uterus		179, 181, 182
			Uterus, parts unspecified	179
			Placenta	181
			Body of uterus	182
	022	Ovary, fallopian tube, and broad ligament		183
			Ovary	183.0 (there is no ICD 183.1)
			Fallopian tube and other uterine adnexa	183.2–183.9
	023	Other female genital organs		184
07		Male genital system		185, 186
	024	Prostate	**"Prostate"**	185
	025	Testis	**"Testicular"**	186
		Penis and other male genital organs	[for NIOSH in minor group 036]	187

continued

TABLE C-1 Continued

NIOSH Category for Cause of Death		NIOSH Groupings of Cancer Sites	"VAO Characterization of Grouping"[a] Subsites	ICD-9 Codes
Major	**Minor**			
08		Urinary system		
	026	Kidney (including renal pelvis and ureter)	**"Renal"**	189.0–189.2
	027	Bladder and other urinary organs	**"Urinary bladder"**	188, 189.3–189.9
			Bladder	188
			Urethra, paraurethral glands, other and unspecified urinary	189.3–189.9
				(discontinuity with ICD codes)
09		Other and unspecified sites		
	028	Bone ("and articular cartilage" in ICD nomenclature)	**"Bone and joint"**	170
	029	Melanoma	**"Melanoma"**	172
	030	Other malignant skin neoplasm	**"Non-melanoma skin"**	173
	031	Mesothelioma		No codes (new minor code, above with lung)
	032	Connective ("and other soft" in ICD nomenclature) tissue	**"Soft-tissue sarcomas"**	171
			(heart)	(164.1)
	033	Brain and other parts of nervous system (ICD "soft tissue" includes peripheral nerves and autonomic nervous system)	**"Brain"**	191–192
	034	Eye		190
	035	Thyroid		193
			(thymus)	164.0
	036	Other and unspecified sites	Other endocrine cancers	194
			Other and ill-defined sites	195

			Stated or assumed to be secondary of specified sites	196–198
			Site unspecified	199
10		Lymphatic and hematopoietic tissue		
		Lymphoma		
	037	**Hodgkin disease**		201
	038	**Non-Hodgkin lymphoma**		200, 202 (excluding 202.4), 273.3
	039	**Multiple myeloma**		203 (excluding 203.1)
	040	Leukemia and aleukemia	**"Leukemias (other than chronic B-cell leukemias)"**	204–208
		Lymphocytic	primary grouping now with other neoplasms of lymphocytic origin, lymphomas and multiple myeloma	
			Acute lymphocytic	204.0
			"Chronic lymphocytic (including hairy cell leukemia)"	204.1
			Other lymphocytic	202.4; 204.2–204.9
		Myeloid (granulocytic)		
			Acute myeloid	
			Acute	205.0
			Acute erythremia and erythroleukemia	207.0
			Megakaryocytic leukemia	207.2
			Chronic myeloid	205.1
			Other myeloid	205.2–205.3, 205.8–205.9
		Monocytic		
			Acute monocytic	206.0
			Chronic monocytic	206.1
			Other monocytic	206.2–206.9
		Other leukemias		
			Other acute	208.0
			Other chronic	207.1, 208.1
			Aleukemic, subleukemia and "not otherwise specified"	203.1, 207.2, 207.8, 208.2–208.9

[a]**Boldface cancer (sub)site:** most comprehensive grouping for which a conclusion has been drawn.

of ICD, Revision 9 (ICD-9). ICD-7, ICD-8, and ICD-9 were in effect for deaths that occurred in 1960–1967, 1968–1978, and 1979–1998, respectively; the differences among them are fairly subtle. Although ICD-10, which went into effect for coding causes of deaths that occurred from 1999 on, appears radically different from the earlier versions, it corresponds in large part to basically the same disease entities (see Table C-2). Most published epidemiologic studies considered in the VAO series have been related to health outcomes that occurred and were encoded before ICD-10 went into effect.

Since 1983, the National Institute for Occupational Safety and Health (NIOSH) has maintained software for generating standardized expectations, as derived from US mortality data assembled by the National Center for Health Statistics, for ICD-encoded mortality datasets. An article by Robinson et al. (2006) discusses revisions to that standard software to incorporate deaths coded according to ICD-10 and includes conversions and equivalences among ICD-7, ICD-8, ICD-9, and ICD-10 for 119 exhaustive categories of cause of death. Codes for malignant neoplasms span the ICD-9 range 140.0–208.9, NIOSH's major categories 02–10, or NIOSH's more specific minor categories 004–040.

The NIOSH death codes for neoplasms provide a comprehensive scaffolding for organizing the committee's reviews and conclusions by cancer type, which is somewhat simpler than ICD classifications but maps completely to the ICD system as it has evolved. Because the NIOSH system has been used to mediate analysis of many sets of cohort data, its groupings correspond quite closely to the published research findings available for review by VAO committees. In general cohort studies, one is unlikely to encounter results on more specific groupings than NIOSH's minor categories.

As discussed in Chapter 2, the VAO committees have not framed its conclusions strictly in terms of ICD codes, but the ICD system has been a valuable tool for the work of VAO committees. There can be coding errors on hospital records or death certificates, but when researchers present their results labeled with ICD codes, there can be little ambiguity about what they intended. When their most definitive indication is something like "respiratory cancers," however, there can be uncertainty about where the evidence should be considered. In such cases, the committee has done its best to follow the hierarchy laid out in Table C-1.

As indicated above, many of the studies reviewed by the committee use or were written up at a time when ICD-9 was in place. Accordingly, ICD references in this report use that scheme. ICD-10 began to be implemented in the United States in 1999. It differs from ICD-9 in level of detail (about 8,000 categories versus about 5,000 in ICD-9) and nomenclature (alphanumeric versus the numeric codes of ICD-9); additions and modifications were also made with regard to some coding rules and the rules for selecting an underlying cause of death (Anderson et al., 2001). Table C-2 lists the ICD-9 and ICD-10 codes for the various forms of malignant neoplasm addressed in this report. In situ neoplasms, benign neoplasms, neoplasms of uncertain behavior, and neoplasms of unspecified behavior have separate codes in both schemes.

TABLE C-2 Surveillance, Epidemiology, and End Results (SEER) Program Malignant Neoplasm Site Groupings for ICD-9 and ICD-10

Cancer Site	ICD-9 Codes	ICD-10 Codes
Buccal cavity and pharynx		
Lip	140.0–140.9	C00.0–C00.9
Tongue	141.0–141.9	C01, C02.1–C02.9
Salivary glands	142.0–142.9	C07, C08.0–C08.9
Floor of mouth	144.0–144.9	C04.0–C04.9
Gum and other mouth	143.0–143.9, 145.0–145.6, 145.8–145.9	C03.0–C03.9, C05.0–C05.9, C06.0–C06.9
Nasopharynx	147.0–147.9	C11.1–C11.9
Tonsil	146.0–146.2	C09.0–C09.9
Oropharynx	146.3–146.9	C10.1–C10.9
Hypopharynx	148.0–148.9	C12, C13.0–C13.9
Other buccal cavity and pharynx	149.0–149.9	C14.0–C14.9
Digestive system		
Esophagus	150.0–150.9	C15.0–C15.9
Stomach	151.0–151.9	C16.0–C16.9
Small intestine	152.0–152.9	C17.0–C17.9
Colon excluding rectum	153.0–153.9, 159.0	C18.0–C18.9, C26.0
Rectum and rectosigmoid junction	154.0–154.1	C19, C20
Anus, anal canal, and anorectum	154.2–154.3, 154.8	C21.0–C21.9
Liver and intrahepatic bile duct		
Liver	155.0,155.2	C22.0, C22.2–C22.4, C22.7–C22.9
Intrahepatic bile duct	155.1	C22.1
Gallbladder	156.0	C23
Other biliary	156.1–156.9	C24.0–C24.9
Pancreas	157.0–157.9	C25.0–C25.9
Retroperitoneum	158.0	C48.0
Peritoneum, omentum, and mesentery	158.8–158.9	C48.1–C48.2
Other digestive organs	159.8–159.9	C26.8–26.9, C48.8
Respiratory system		
Nasal cavity, middle ear, and accessory sinuses	160.0–160.9	C30.0, C30.1, C31.0–C31.9
Larynx	161.0–161.9	C32.0–C32.9
Lung and bronchus	162.2–162.9	C34.0–C34.9
Pleura	163.0–163.9	C38.4
Trachea, mediastinum, and other respiratory organs	162.0, 164.2–165.9	C33, C38.1–C38.3, C38.8, C39
Bones and joints	170.0–170.9	C40.0–C40.9, C41.0–C41.9
Soft tissue (including heart)	171.0–171.9, 164.1	C38.0, C47.0–C47.9, C49.0–C49.9

continued

TABLE C-2 Continued

Cancer Site	ICD-9 Codes	ICD-10 Codes
Skin		
Malignant melanomas	172.0–172.9	C43.0–C43.9
Other malignant skin neoplasms	173.0–173.9	C44.0–C44.9
Breast (male and female)	174.0–174.9, 175	C50.0–C50.9
Female genital system		
Cervix	180.0–180.9	C53.0–C53.9
Corpus	182.0–182.1, 182.8	C54.0–C54.9
Uterus, not otherwise specified	179	C55
Ovary	183.0	C56.0–C56.9
Vagina	184.0	C52
Vulva	184.1–184.4	C51.0–C51.9
Other female genital organs	181, 183.2–183.9, 184.8, 184.9	C57.0–C57.9, C58
Male genital system		
Prostate	185	C61
Testis	186.0–186.9	C62.0–C62.9
Penis	187.1–187.4	C60.0–C60.9
Other male genital organs	187.5–187.9	C63.0–C63.9
Urinary system		
Urinary bladder	188.0–188.9	C67.0–C67.9
Kidney and renal pelvis	189.0, 189.1	C64.0–C64.9, C65.0–C65.9
Ureter	189.2	C66.0–C66.9
Other urinary organs	189.3–189.4, 189.8–189.9	C68.0–C68.9
Eye and orbit	190.0–190.9	C69.0–C69.9
Brain and other nervous system		
Brain	191.0–191.9	C71.0–C71.9
Meninges	192.1	C70.0–C70.9
Other nervous system [a]	192.0, 192.2–192.9	C72.0–C72.9
Endocrine system		
Thyroid	193	C73
Other endocrine (including thymus)	164.0, 194.0–194.9	C37, C74.00–C74.92, C75.0–C75.9
Lymphomas		
Hodgkin's disease	201.0–201.9	C81.0–81.9
Non-Hodgkin's lymphomas	200.0–200.8, 202.0–202.2, 202.8–202.9	C82.0–C82.9, C83.0–C83.9, C84.0–C84.5, C85.0–C85.9, C96.3
Multiple myeloma	203.0, 238.6	C90.0, C90.2

TABLE C-2 Continued

Cancer Site	ICD-9 Codes	ICD-10 Codes
Leukemias		
Lymphocytic		
Acute lymphocytic	204.0	C91.0
Chronic lymphocytic	204.1	C91.1
Other lymphocytic	202.4, 204.2–204.9	C91.2-C91.4, C91.7, C91.9
Myeloid (granulocytic)		
Acute myeloid	205.0, 207.0, 207.2	C92.0, C92.4–C92.5, C94.0, C94.2
Chronic myeloid	205.1	C92.1
Other myeloid	205.2–205.3, 205.8–205.9	C92.2–C92.3, C92.7, C92.9
Monocytic		
Acute monocytic	206.0	C93.0
Chronic monocytic	206.1	C93.1
Other monocytic	206.2–206.9	C93.2, C93.7, C93.9
Other leukemias		
Other acute	208.0	C94.4, C94.5, C95.0
Other chronic	207.1, 208.1	C94.1, C95.1
Aleukemic, subleukemic and "not otherwise specified"	203.1, 207.2, 207.8, 208.2–208.9	C90.1, C91.5, C94.3, C94.7, C95.2, C95.7, C95.9
Miscellaneous malignant neoplasms	159.1, 195.0–195.8, 196.0–196.9, 199.0–199.1, 202.3, 202.5–202.6, 203.8	C26.1, C76.0–C76.8, C77.0–C77.9, C78.0–C78.8, C79.0–C79.8, C80, C88.0–C88.9, C96.0–C96.2, C96.7, C96.9, C97

[a] Cancers of the peripheral nerves and the autonomic nervous system are classified as "soft tissue" in ICD.

SOURCE: Adapted from Ries et al., 2003, Table A-4.

REFERENCES

The Appendix C references can be found in the References chapter.

Appendix D

Committee and Staff Biographies

COMMITTEE BIOGRAPHIES

Kenneth S. Ramos, MD, PhD (*Chair*), is the Associate Vice President for Precision Health Sciences and a professor of medicine in the Division of Pulmonary, Allergy, Critical Care and Sleep Medicine at the Arizona Health Sciences Center. Dr. Ramos also serves as the Director of the Center for Applied Genetics and Genomic Medicine and Director of the College of Medicine MD-PhD Program. He is responsible for developing precision-health strategies and approaches to health outcomes and health care delivery and provides senior leadership in the development of personal diagnostics and therapeutics for complex diseases, including cancers, cardiopulmonary disorders, and diabetes. Dr. Ramos' research program integrates diverse approaches ranging from molecular genetics to population-based public health studies in efforts to understand the genomic bases of human disease and to advance the goals of personalized genomic medicine. He is regarded as a leading expert in the study of gene–environment interactions and personalized medicine and directs a competitive and innovative research program in translational and clinical genetics and genomics at the University of Arizona. Dr. Ramos completed a BS in pharmaceutical sciences and chemistry (magna cum laude) at the University of Puerto Rico, a PhD in biochemical pharmacology at the University of Texas at Austin, and an MD with postgraduate training in internal medicine at the University of Louisville Health Sciences Center. He has held faculty positions at the University of the Sciences in Philadelphia, Texas Tech University Health Sciences Center, Texas A&M University, the University of Louisville School of Medicine, and the University of Arizona. He is currently

affiliated with the Arizona Cancer Center and the Arizona Respiratory Center. Dr. Ramos is former President of the Society of Toxicology (2008–2009) and has served on numerous National Academies of Sciences, Engineering and Medicine committees, including the committees responsible for the *Veterans and Agent Orange: Update 1996* and *Update 1998* reports, the Committee on Application of Toxicogenomics Technologies to Predictive Toxicology, the Committee on Emerging Issues and Data on Environmental Contaminants, and the Committee on Application of Genomic Signatures: A Workshop. He is currently serving on the Roundtable on Public Interfaces of Life Sciences and was co-chair of the Committee on Sustainable Infrastructures for Public Communication of the Life Sciences: A Workshop.

Ilir Agalliu, MD, ScD, is an assistant professor in the Department of Epidemiology and Population Health and the Department of Urology at Albert Einstein College of Medicine. His main research interests are directed toward understanding the contribution of genetic and lifestyle/environmental risk factors in the etiology and progression of cancers. Dr. Agalliu received his training at the University of Massachusetts at Lowell, University of Manchester, and the University of Tirana, Medical School. He was a post-doctoral fellow at the Fred Hutchinson Cancer Research Center. He is a member of multiple organizations, including the American Public Health Association and the Society for Epidemiologic Research.

Erin M. Bell, PhD, is associate professor in the Departments of Epidemiology and Biostatistics and the Department of Environmental Health Sciences in the School of Public Health of the University at Albany. She received her undergraduate degree in biology with honors from Hartwick College and her MS and PhD degrees in epidemiology from, respectively, the University of Massachusetts–Amherst and the University of North Carolina at Chapel Hill. Between her master's and doctoral studies, she was a Research Associate for the Institute of Medicine's (IOM's) Medical Follow-up Agency. Her epidemiology research focuses on environmental exposures, particularly to pesticides, as they are related to reproductive, immune, and cancer outcomes. She previously served on the IOM Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides: Seventh and Eighth Biennial Updates.

Maarten C. Bosland, PhD, DVSc, is a professor of pathology at the University of Illinois, College of Medicine, at Chicago. He earned his DVSc (1978) and PhD (1989) from the University of Utrecht in The Netherlands. Dr. Bosland's research interests include hormonal carcinogenesis, particularly prostate carcinogenesis, and clinical and preclinical cancer chemoprevention, particularly prostate cancer prevention. He has served on four panels of the World Health Organization's International Agency for Research on Cancer because of his expertise in the mechanisms of hormonal carcinogenesis.

Robert Canales, PhD, MS, is an assistant professor in the Community, Environment and Policy Division at the Mel & Enid Zuckerman School of Public Health at the University of Arizona. He received his MS in statistics and PhD in environmental engineering and science from Stanford University and was a post-doctoral fellow at the Harvard School of Public Health. Dr. Canales applies principles in the natural sciences and mathematics to explore environmental health issues, particularly human exposure to environmental contaminants. With a background in environmental engineering, public health, and statistics, his research focuses on creating models/simulations and exploring data to improve human health, and has included a variety of projects, including modeling the fate and transport of contaminants in indoor environments, simulating children's behavior and contaminant intake levels, and distinguishing demographic variables for identifying households with high indoor pesticide concentrations. Dr. Canales recently served on the IOM's Committee to Evaluate the Potential Exposure of Agent Orange/TCDD Residue and Level of Risk of Adverse Health Effects for Aircrew of Post-Vietnam C-123 Aircraft.

Michael J. Carvan III, PhD, MS, is a Shaw Professor at the School of Freshwater Sciences and School of Public Health, both of the University of Wisconsin–Milwaukee. He earned his MS in biologic oceanography at the University of Miami's Rosenstiel School of Marine and Atmospheric Science in Coral Gables and his PhD in veterinary anatomy and public health with a focus in toxicology from Texas A&M University's College of Veterinary Medicine in College Station. After obtaining his doctorate, Dr. Carvan held National Institute of Environmental Health Sciences molecular toxicology fellowships at the University of Cincinnati Medical Center. His research uses zebrafish as a genetic system for identifying genes that influence susceptibility of response to xenobiotics. He has served on the National Academies of Sciences, Engineering, and Medicine Board on Life Sciences and, most recently, on the IOM Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides: Ninth Biennial Update.

Melissa Gonzales, PhD, is an associate professor in the Division of Epidemiology at the University of New Mexico (UNM) School of Medicine. She received her doctorate in environmental health from the University of California, Berkeley, School of Public Health, and her master's in toxicology/industrial hygiene from the University of Arizona College of Pharmacy. Dr. Gonzales's research focuses on characterizing complex environmental exposures for population and laboratory health effects studies, and the translation and communication of scientific findings to affected communities, regulatory agencies and health care providers. Currently, Dr. Gonzales co-directs the Center for Native American Environmental Health Equity, an academic-tribal partnership; and is a founding member of the UNM Metal Exposure Toxicity Assessment on Tribal Lands in the Southwest (METALS) Team investigating transdisciplinary approaches to understanding the

unique exposure and response mechanisms in tribal communities that contribute to health disparities. Her work includes the Albuquerque Hispanic Moms Study, the Zuni Exposure Study, the Colorectal Disease Prevention Study, occupational exposure and DNA repair in melanoma, and the Environmental Protection Agency El Paso Children's Health Study and the ARCH study of asthma and air pollution among children living on the US/Mexico border. She previously served on the IOM Committee to Evaluate the Potential Exposure of Agent Orange/TCDD Residue and Level of Risk of Adverse Health Effects for Aircrew of Post-Vietnam C-123 Aircraft.

Karl T. Kelsey, MD, MOH, is a professor of epidemiology and pathology and laboratory medicine at Brown University. He received his MD from the University of Minnesota and a master's degree in occupational health from Harvard University. Until 2007 he was on the faculty of the Harvard School of Public Health and Harvard Medical School. He is interested in the application of laboratory-based biomarkers in chronic-disease epidemiology and tumor biology and in characterizing individual susceptibility to cancers. He is an author of more than 200 publications and has served on the National Academies of Sciences, Engineering, and Medicine Committee on Toxicity Testing and Assessment of Environmental Agents, Committee on Copper in Drinking Water, Committee on the Evaluation of the Department of Veterans Affairs Uniform Case Assessment Protocol, Committee to Review the Health Consequences of Service During the Persian Gulf War, Committee to Conduct a Study on Curriculum Development in Environmental Medicine, Committee on the Health Effects of Mustard Gas and Lewisite, and, most recently, on the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides: Eighth and Ninth Biennial Updates.

Kevin E. Kip, PhD, FAHA, is a professor of epidemiology and biostatistics in the College of Nursing, and Executive Director of the Research Center in the College of Nursing at the University of South Florida. Dr. Kip has substantial experience in directing observational epidemiological studies and clinical trials principally in the areas of cardiovascular diseases and psychotherapy. He also has research interests in complementary and alternative medicine, gastroenterology, epidemiological methods, and veterans' health. He received his MS degree from the University of Central Florida, his MSPH from the University of Alabama, and his PhD from the University of Pittsburgh.

Stephen Kritchevsky, PhD, is a professor of internal medicine and translational science and the director of the Sticht Center on Aging of Wake Forest School of Medicine. After receiving both his MSPH and PhD in epidemiology from the University of North Carolina at Chapel Hill, he joined the Departments of Biostatistics and of Epidemiology at the University of Tennessee Health Science Center, where he founded that school's Masters of Clinical Epidemiology

Program. Dr. Kritchevsky's research interests are related to conditions that compromise the health of aging populations, particularly inflammation, obesity, metabolic syndrome, and cardiovascular disease. He has published more than 300 articles in peer-reviewed scientific journals. He is a fellow of the Gerontological Society of America and editor-in-chief of the *Journal of Gerontology: Medical Sciences*. Most recently, he served on the IOM Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides: Seventh, Eighth, and Ninth Biennial Updates.

Elan D. Louis, MD, MSc, is a professor of Neurology and Epidemiology and Chief of the Division of Movement Disorders at Yale University. His principal academic interest is in degenerative diseases of the central nervous system, focusing on disorders of involuntary movement, including their epidemiology, distribution within populations, genetic basis, etiology, and pathogenesis. He has a particular interest in essential tremor (ET), one of the most common neurological disorders, and his research efforts have focused on the familial aggregation of ET; the environmental epidemiology of ET; the role of lead, beta-carboline alkaloids and other neurotoxins in ET, the relationships between ET and Parkinson's and Alzheimer's diseases; and the pathological basis of ET. Dr. Louis currently leads the Essential Tremor Centralized Brain Repository at Columbia University, which is a national centralized brain bank for the study of ET, and he has established a large DNA bank for patients with the disorder. He collaborates with investigators in Mexico, Spain, and Turkey examining the epidemiology of ET in these populations, and he has received continuous funding from the National Institutes of Health (NIH) since 1995, as well as funding from the International Essential Tremor Foundation, the Charles A. Dana Foundation, the Parkinson's Disease Foundation, and a Paul Beeson Physician Faculty Scholars Award from the American Federation for Aging Research. Since 2008 he has been the Principal Investigator of the Neuroepidemiology Training Program, which is a postdoctoral training program at Columbia University funded by NIH through a T32 mechanism. The program provides training in a research environment for developing neurologists/neuroscientists who wish to use epidemiologic methods to study diseases of the nervous system and have as a career goal, a research or academic position. Dr. Louis is the author of more than 400 peer-reviewed publications and has been invited to write editorials and reviews for *Annals of Neurology*, *Movement Disorders*, *Archives of Neurology*, *New England Journal of Medicine*, *Lancet*, and *Lancet Neurology*.

David Richardson, PhD, MSPH, is an associate professor of epidemiology in the School of Public Health at the University of North Carolina at Chapel Hill. His research focuses on the health effects of exposure to ionizing radiation. He has conducted studies of cancers among nuclear workers at several US Department of Energy facilities as well as studied cancers among the Japanese survivors

of the atomic bombings of Hiroshima and Nagasaki. He has served as a visiting scientist at the World Health Organization's International Agency for Research on Cancer in Lyon, France, and at the Radiation Effects Research Foundation in Hiroshima, Japan. He is an associate editor of the journals *Occupational and Environmental Medicine* and *Environmental Health Perspectives*, and he is a member of the President's Advisory Board on Radiation and Worker Health.

Mitchell Turker, PhD, JD, is a Senior Scientist at the Oregon Institute of Occupational Health Sciences and a Professor of Molecular and Medical Genetics at Oregon Health & Science University. Dr. Turker received his PhD in pathology from the University of Washington (UW) and was a post-doctoral fellow at the University of Colorado Health Sciences Center. He served as a Research Instructor in the Department of Pathology at UW. He went on to the University of Kentucky, where he served as an assistant professor and associate professor in the Departments of Pathology and Microbiology/ Immunology and as the Director of Experimental Pathology. Prior to joining the Center for Research on Occupational and Environmental Toxicology, he was a visiting Associate Professor in the Department of Genetics and Development at Columbia University. Dr. Turker received a JD from Lewis and Clark Law School in May 2008 with a certificate in environmental law. He was a Jefferson Science Fellow at the US Department of State from 2010 to 2011.

Lori White, PhD, MS, is an associate professor in the Department of Biochemistry and Microbiology of the School of Environmental and Biological Sciences of Rutgers, the State University of New Jersey. She received a master's degree in zoology from the University of Maine, earned a PhD in biochemistry from Dartmouth Medical School, and did post-doctoral work at the University of Wisconsin. She has been active in Gordon Conference programs and was the chairperson for the Mechanisms of Toxicology summer session in 2008. Her research interests include the elucidation of dioxin's carcinogenic activity and the use of the zebrafish as a model for investigating the effects of environmental chemicals on development. She recently served on the IOM Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides: Ninth Biennial Update.

STAFF BIOGRAPHIES

Mary Burr Paxton, PhD, is a Senior Program Officer in the National Academies of Sciences, Engineering, and Medicine Board on the Health of Select Populations. Before joining the Academies, she worked as a consultant on the regulation of toxic substances and managed the conduct and analysis of several epidemiologic studies on veterans' health. She received an MS in biostatistics from the Johns Hopkins School of Hygiene and Public Health and a doctorate in genetics

from the George Washington University. She was a diplomate of the American Board of Toxicology (1993–2013). Dr. Paxton has worked on several Academies reports, including *Issues in Risk Assessment*; *Environmental Neurotoxicology*; *Gulf War and Health: Insecticides and Solvents*; *Gulf War and Health: Fuels, Combustion Products, and Propellants*; *Asbestos: Selected Cancers*; *Veterans and Agent Orange: Update 2004*; *Veterans and Agent Orange: Update 2006*; *Veterans and Agent Orange: Update 2008*; *Veterans and Agent Orange: Update 2010; Veterans and Agent Orange: Update 2012*; and *Post-Vietnam Dioxin Exposure in Agent Orange–Contaminated C-123 Aircraft.*

Jennifer A. Cohen, MPH, is a Program Officer in the National Academies of Sciences, Engineering, and Medicine Board on the Health of Select Populations. She received her undergraduate degree and her MPH from the University of Maryland. She has been involved with the Academies committees that produced O*rgan Procurement and Transplantation*; *Clearing the Air: Asthma and Indoor Air Exposures*; *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*; *Veterans and Agent Orange: Update 2000*; *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans*; *Veterans and Agent Orange: Update 2004*; *Veterans and Agent Orange: Update 2006*; *Veterans and Agent Orange: Update 2008*; *Veterans and Agent Orange: Update 2010*; *Veterans and Agent Orange: Update 2012*; and *Post-Vietnam Dioxin Exposure in Agent Orange–Contaminated C-123 Aircraft.* She was also rapporteur for the Institute of Medicine report *Challenges and Successes in Reducing Health Disparities*.

Heather L. Chiarello, MA, joined the staff of the US National Academies of Sciences, Engineering, and Medicine in July 2008. She graduated magna cum laude from Central Michigan University in 2007 with a BS in political science accompanied by a concentration in public administration and a minor in legal studies. She obtained a master's degree in sociology with a focus on military sociology in 2014 from The Catholic University of America in Washington, DC. Ms. Chiarello has worked on numerous studies throughout the Academies and is currently a research associate focusing on military and veteran studies with the Board on the Health of Select Populations at the Academies.

Nicole Freid is a Senior Program Assistant at the National Academies of Sciences, Engineering, and Medicine Board on the Health of Select Populations. She is working on several studies at the Academies addressing occupational and environmental exposures among the veteran population. She earned her bachelor's degree in economics and political science at American University in Washington, DC. Before joining the Academies, she worked at Avalere Health; a health care consulting firm, where she incorporated health policy analysis in final deliverables for pharmaceutical and medical device manufacturers.