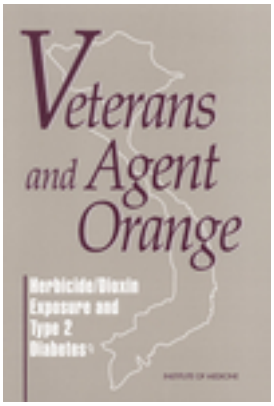

Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes

Committee to Review the Evidence Regarding the Link Between Exposure to Agent Orange and Diabetes, Division of Health Promotion and Disease Prevention

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Veterans and Agent Orange

Herbicide/Dioxin Exposure and Type 2 Diabetes

Committee to Review the Evidence Regarding the Link
Between Exposure to Agent Orange and Diabetes

Division of Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

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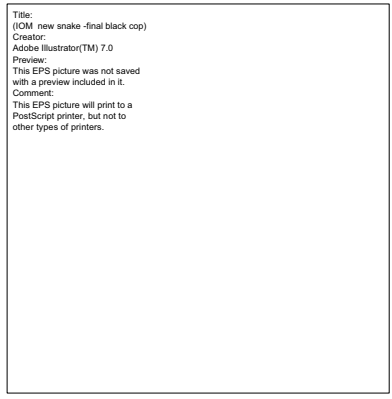
The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe



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Preface

In response to the concerns voiced by Vietnam veterans and their families, Congress called upon the National Academy of Sciences (NAS) to review the scientific evidence on the possible health effects of exposure to Agent Orange and other herbicides (Public Law 102-4, enacted on February 6, 1991). This call resulted in the creation of the first NAS Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides in 1992. The committee published its initial findings in the 1994 report *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*.

Public Law 102-4 also tasked the NAS to conduct biennial updates that would review newly published scientific literature regarding statistical associations between health outcomes and exposure to dioxin and other chemical compounds in these herbicides. The results of the first two of these efforts were published in *Veterans and Agent Orange: Update 1996* and *Update 1998*. Work on the *Update 2000* report is presently under way.

This report is the result of a 1999 request from the Department of Veterans Affairs (DVA) under the aegis of the *Veterans and Agent Orange* research program. DVA asked the Institute of Medicine to call together a committee to conduct a focused review of the scientific evidence regarding one of the medical conditions addressed in the report series in advance of the next scheduled biennial report. Specifically, DVA asked the committee to examine evidence regarding the association, if any, between Type 2 diabetes and exposure to dioxin and other chemical compounds in herbicides used in Vietnam.

David A. Butler served as the study director for this project and deserves credit for drafting the report. The committee would also like to acknowledge the

excellent work of IOM staff members James Bowers and Jennifer Cohen, and extend a special thanks to Susan Thaul for her work on this report. Thanks are also extended to Melisssa Goodwin, who handled the finances for the project; Florence Poillon who provided excellent editorial skills; Susan Fourt, who conducted data base searches; Michael Edington, who supervised the report through the editorial and publication phases; and Donna Thompson and Rita Gaskins, who provided administrative support to the project.

The committee also benefited from the assistance of several scientists and researchers who generously lent their time and expertise to help give committee members insight on particular issues, provide copies of newly released research, or answer queries concerning their work. Special thanks are extended to Drs. Geoffrey Calvert (National Institute for Occupational Safety and Health), Marilyn Fingerhut (National Institute for Occupational Safety and Health), Philip Kern (University of Arkansas for Medical Sciences), Bonnie LaFleur (The George Washington University School of Public Health and Health Services), Matthew Longnecker (National Institute for Environmental Safety and Health), Joel Michalek (Air Force Research Laboratory, Brooks Air Force Base), and Michael Stoto (The George Washington University School of Public Health and Health Services).

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making the published report as sound as possible and to ensure that the report meets institutional standards for 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 wish to thank the following individuals for their participation in the review of this report: John C. Bailar, The University of Chicago; Daniel W. Foster, University of Texas Southwestern Medical Center at Dallas; Kristine M. Gebbie, Columbia University; Barbara C. Hansen, University of Maryland at Baltimore; Paul D. Stolley, University of Maryland at Baltimore; Martha Vaughan, National Heart, Lung, and Blood Institute; M. Donald Whorton, M. Donald Whorton, Inc. While the individuals listed above have provided constructive comments and suggestions, it must be emphasized that responsibility for the final content of this report rests entirely with the authoring committee and the institution.

David Tollerud
Chair

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Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes

EXECUTIVE SUMMARY

In 1999, in response to a request from the Department of Veterans Affairs (DVA), the Institute of Medicine (IOM) called together a committee to conduct a review of the scientific evidence regarding the association, if any, between Type 2 diabetes[1] and exposure to dioxin[2] and other chemical compounds in herbicides used in Vietnam. The committee was asked to determine, to the extent that available data permitted meaningful determinations, (1) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association; (2) the increased risk of the disease among those exposed to herbicides during Vietnam service; and (3) whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The work performed by the committee adheres to the format of a set of studies performed by the IOM at the behest of DVA under Public Law 102-4, the "Agent Orange Act of 1991." The conclusions in this report are based on cumulative evidence from the scientific literature reviewed in these studies—*Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*; *Veterans and Agent Orange: Update 1996*; and *Veterans and Agent Orange:*

[1]Also referred to as Type II diabetes, diabetes mellitus, non-insulin-dependent diabetes mellitus, and adult-onset diabetes.

[2]2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, commonly referred to as TCDD or "dioxin," was an unintentional contaminant of one of the herbicides used in Vietnam.

Update 1998—and relevant papers published since the deliberations of the *Update 1998* committee were completed.

Strength of Evidence in Epidemiologic Studies

Based on the scientific evidence reviewed in this report as well as the cumulative findings of research reviewed in the previous *Veterans and Agent Orange* reports, the committee finds that **there is limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and Type 2 diabetes**. This is a change in classification from previous *Veterans and Agent Orange* reports, which found inadequate/insufficient evidence to determine whether an association existed.[3]

No one paper or study was determinative in reaching this decision. Instead, the committee found that the information accumulated over years of research now meets the definition established for limited/suggestive evidence—that is, *evidence is suggestive of an association between herbicides and the outcome, but limited because chance, bias, and confounding could not be ruled out with confidence*. In reaching this decision, the committee observed the following:

- **Positive associations are reported in many mortality studies, which may underestimate the incidence of diabetes.** Morbidity (the rate of incidence of a disease) is thought to be a more informative end point than mortality (the rate of death) when conducting epidemiologic studies of Type 2 diabetes because the disease is not typically fatal, its known complications may be more likely to be implicated as the underlying cause of death, and reporting of contributory causes of death on death certificates may be spotty. These reasons also lead epidemiologists to suspect that mortality studies may underestimate the incidence of diabetes. Four mortality studies were reviewed in this report. Individuals living near the site of a 1976 industrial accident involving dioxin were found to have a higher risk of diabetes death than a reference population in all exposure zones where diabetes deaths were recorded. Two studies of a TCDD-exposed cohort of workers at 12 U.S. plants found positive but non-statistically significant associations between measures of exposure and notations of diabetes on death certificates. The fourth study, which examined workers in 12 countries who produced or sprayed phenoxy herbicides and chlorophenols, reported an elevated relative risk of mortality from diabetes in exposed workers versus non-exposed referents. Studies reviewed in previous *Veterans and Agent Orange* reports show an inconsistent but weakly positive association between exposure measures and Type 2 diabetes mortality.

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[3]The categories of association mentioned here were established in the original (1994) *Veterans and Agent Orange* report and have been used in all subsequent reports. A complete list of categories is contained in the "Organization and Framework" section of this report.

- **Positive associations are reported in most of the morbidity studies identified by the committee.** Several studies that used Type 2 diabetes morbidity as an outcome measure have been published since the last *Veterans and Agent Orange* review: studies of male and female Vietnam veterans from Australia; a National Institute for Occupational Safety and Health (NIOSH) study of U.S. chemical workers; the Air Force Health Study (Ranch Hand study); and a separate examination of the Ranch Hand comparison group. One of these studies did not show a positive association: the survey of female veterans from Australia indicated 5 self-reported cases of diabetes where 10 were expected. However, the survey of male Australian veterans of Vietnam did find a statistically significant excess of self-reported diabetes—2,391 cases were reported when 1,780 were expected. The Ranch Hand comparison group and NIOSH studies each reported an elevated incidence of diabetes in individuals who had high levels of serum dioxin relative to others examined in that study. The primary analysis in the Air Force Health Study showed nearly identical diabetes incidence in Ranch Hand veterans and the matched comparison group. Despite this negative finding, the study is considered suggestive because dose–response relationships between dioxin levels and diabetes incidence were observed in several other analyses of the Ranch Hand veterans and comparison group that controlled for confounding variables.

Although some of the risk estimates in the studies examined by the committee are not statistically significant and, individually, studies can be faulted for various methodological reasons, the accumulation of positive evidence is suggestive. The committee does not believe that publication bias plays a crucial role in this tendency in the data.

Increased Risk of Diabetes Among Vietnam Veterans

Presently available data allow for the possibility of an increased risk of Type 2 diabetes in Vietnam veterans. It must be noted, however, that these studies indicate that the increased risk, if any, from herbicide or dioxin exposure appears to be small. The known predictors of diabetes risk—family history, physical inactivity, and obesity—continue to greatly outweigh any suggested increased risk from wartime exposure to herbicides.

Biologic Plausibility

Animal, laboratory, and human data reviewed in *Update 1998* provide reasonable evidence that exposure to dioxin could affect Type 2 diabetes risk in humans. TCDD's associations with altered triglyceride and high-density lipoprotein (HDL) concentrations are generally consistent with a diabetes effect because these are the hallmarks of altered lipid metabolism in the disease and fatty acid metabolism, insulin resistance, and glucose metabolism are closely linked. How-

ever, it is not at present known whether or not such associations are indicative of a causal pathway from dioxin exposure to Type 2 diabetes. Other observed effects include alteration of glucose transport in a variety of cells, modulation of protein kinase C activity, reduction in adipose tissue lipoprotein lipase in guinea pigs, hypertriglyceridemia in rabbits, and down-regulation of low-density lipoprotein receptors on the plasma membrane in guinea pig hepatocytes.

Three recent studies of humans add to that evidence by reporting a compensatory metabolic relation between dioxin and insulin regulation in Air Force Health Study (AFHS) participants, an apparent association between serum dioxin levels and fasting glucose levels among nondiabetic AFHS comparison group members with less than 10 parts per trillion (ppt) serum dioxin, and an elevated incidence of hyperinsulinemia among a group of nondiabetics with serum TCDD levels greater than 15 ppt. These studies, however, have methodologic limitations—primarily, inadequate measures of individual characteristics such as percentage of body fat at the time of exposure—that prevent more definitive conclusions from being drawn.

INTRODUCTION

Background

Because of continuing uncertainty about the long-term health effects of exposure to the herbicides used in Vietnam, Congress passed Public Law 102-4, the Agent Orange Act of 1991. This legislation directed the Secretary of Veterans Affairs to request the National Academy of Sciences (NAS) to conduct a comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of these herbicides, including dioxin. A committee convened by the Institute of Medicine of the NAS conducted this review and in 1994 published a comprehensive report entitled *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (henceforth called *VAO*) (IOM, 1994).

Public Law 102-4 also called for the NAS to conduct subsequent reviews at least every 2 years for a period of 10 years from the date of the first report. The NAS was instructed to conduct a comprehensive review of the evidence that had become available since the previous IOM committee report and to reassess its determinations and estimates of statistical association, risk, and biological plausibility. On completion of *VAO*, successor committees were formed that produced *Veterans and Agent Orange: Update 1996* (IOM, 1996) and *Veterans and Agent Orange: Update 1998* (IOM, 1999). IOM is now convening a committee to review publications from 1998 to 2000 to form revised assessments, if indicated, of the cumulative evidence and issue a 2000 update.

In 1999, in response to a request from the Department of Veterans Affairs, IOM called together a committee to conduct an interim review of the scientific evidence regarding one of the conditions addressed in the *Veterans and Agent*

Orange series of reports: Type 2 diabetes. The committee consisted of individuals responsible for the *Update 1998* report plus recognized experts in the field of Type 2 diabetes. They conducted two workshops to hear researchers in the field present information on their past and ongoing investigations, and reviewed material published since the deliberations of the *Update 1998* committee.

While limited to one health outcome, this report adheres to the format of the update series' directions from Congress via the Secretary of Veterans Affairs. In conducting its study, the IOM committee operated independently of the DVA and other government agencies. The committee was not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. Rather, the study provides scientific information for the Secretary of Veterans Affairs to consider as the DVA exercises its responsibilities to Vietnam veterans.

Organization and Framework

The conclusions in this report are based on cumulative evidence from the scientific literature reviewed in *VAO*, *Update 1996,* and *Update 1998* and relevant papers published since the deliberations of the *Update 1998* committee were completed. This present update is intended to supplement rather than replace the previous reports; therefore, not all of the information on studies reviewed in those reports has been repeated. Appendix B of this report reproduces the review of diabetes studies presented in *Update 1998*.

The report begins with a brief overview of the study methodology and the considerations underlying the assessment of research reviewed. This is followed by an evaluation of the epidemiologic evidence, which includes background on the scientific data reviewed in *VAO*, *Update 1996,* and *Update 1998,* and a more thorough discussion of the newly published data and their interpretation. The reader is referred to relevant sections of the previous reports for additional detail and explanation.

In the *Veterans and Agent Orange* series of reports, committees have focused most of their efforts on reviewing and interpreting epidemiologic studies in order to evaluate the extent to which the scientific literature does or does not suggest that particular human health effects are associated with exposure to herbicides or dioxin. In this report, the committee weighed the strengths and limitations of the scientific data in *VAO*, *Update 1996,* and *Update 1998,* as well as the newly published scientific data, and reached its conclusions by interpreting the new evidence in the context of the whole of the literature. Earlier committees have placed each disease into one of four categories, depending on the strength of evidence for an association (see "Categories of Association," below). Here, the discussion and category relate only to Type 2 diabetes, using the same criteria to categorize health outcomes as used in the previous reports.

Categories of Association

Consistent with the charge to the Secretary of Veterans Affairs in Public Law 102-4, the categories of association used by the committee are based on "statistical association," not on causality. Thus, standard criteria used in epidemiology for assessing causality (Hill, 1971) do not strictly apply. The categories are as follows:

- *Sufficient Evidence of an Association.* Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, this may constitute sufficient evidence for an association.
- *Limited/Suggestive Evidence of an Association.* Evidence is suggestive of an association between herbicides and the outcome, but it is limited because chance, bias, and confounding could not be ruled out with confidence. For example, if at least one high-quality study shows a positive association, but the results of other studies are inconsistent, this may constitute limited/suggestive evidence of an association.
- *Inadequate/Insufficient Evidence to Determine Whether an Association Exists*. The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, if studies fail to control for confounding, contain inadequate exposure assessment, or have inadequate sample size, this may constitute inadequate/insufficient evidence to determine whether an association exists.
- *Limited/Suggestive Evidence of No Association.* There are several adequate studies, covering the full range of exposure levels that humans are known to encounter, that are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

Methodologic Considerations in Evaluating the Evidence

Questions Addressed

The committee was charged with the task of summarizing the strength of the scientific evidence concerning the association between herbicide exposure during Vietnam service and Type 2 diabetes. Public Law 102-4 specifies three

scientific determinations concerning diseases that must be made. It charges the committee to:

> . . . determine (to the extent that available scientific data permit meaningful determinations):
>
> 1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
>
> 2. the increased risk of each disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
>
> 3. whether there exists a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The committee's judgments have both quantitative and qualitative aspects; they reflect both the evidence examined and the approach taken to evaluate it. The primary considerations are delineated below.

Is Herbicide Exposure Statistically Associated with the Health Outcome?

The committee necessarily focused on a pragmatic question: What is the nature of the relevant evidence for or against a statistical association between exposure and the health outcome? The evidentiary base that the committee found to be most helpful derived from epidemiologic studies of populations—that is, investigations in which large groups of people are studied to determine the association between the occurrence of particular diseases and exposure to the substances at issue. To determine whether an association exists, epidemiologists estimate the magnitude of an appropriate quantitative measure (such as the relative risk or the odds ratio) that describes the relationship between exposure and disease in defined populations or groups. However, the use of terms such as "relative risk," "odds ratio," or "estimate of relative risk" is not consistent in the literature. In this report, the committee intends *relative risk* to refer to the results of cohort studies and *odds ratio* (an estimate of relative risk) to refer to the results of case-control studies. Values of relative risk greater than 1 may indicate a positive or direct association—that is, a harmful association—whereas values between 0 and 1 may indicate a negative or inverse association—that is, a protective association. A "statistically significant" difference is one that, under the assumptions made in the study and the laws of probability, would be unlikely to occur if there was no true difference.

Determining whether an observed statistical association between exposure and a health outcome is "real" requires additional scrutiny because there may be alternative explanations for the observed association. These include: *error* in the design, conduct, or analysis of the investigation; *bias*, or a systematic tendency

to distort the measure of association so that it may not represent the true relation between exposure and outcome; *confounding*, or distortion of the measure of association because another factor related to both exposure and outcome has not been recognized or taken into account in the analysis; and *chance*, the effect of random variation, which produces spurious associations that can, with a known probability, sometimes depart widely from the true relation.

Therefore, in deciding whether an association between herbicide exposure and a particular outcome existed, the committee examined the quantitative estimates of risk and evaluated whether these estimates might be due to error, bias, confounding, or chance, or were likely to represent a true association.

In pursuing the question of statistical association, the committee recognized that an absolute conclusion about the absence of association may never be attained. As in science generally, studies of health outcomes following herbicide exposure are not capable of demonstrating that the purported effect is impossible or could never occur. Any instrument of observation, including epidemiologic studies, has a limit to its resolving power. Hence, in a strict technical sense, the committee could not prove the absolute absence of a health outcome associated with herbicide or dioxin exposure.

What Is the Increased Risk of the Outcome in Question Among Those Exposed to Herbicides in Vietnam?

This question, which is pertinent principally (but not exclusively) if there is evidence for a positive association between exposure and a health outcome, concerns the likely magnitude of the association in Vietnam veterans exposed to herbicides. The most desirable evidence in answering this type of question involves knowledge of the rate of occurrence of the disease in those Vietnam veterans who were actually exposed to herbicides, the rate in those who were not exposed (the "background" rate of the disease in the population of Vietnam veterans), and the degree to which any other differences between exposed and unexposed groups of veterans influence the difference in rates. When exposure levels among Vietnam veterans have not been adequately determined, which has been the case in most studies, this question is very difficult to answer. The committees have found the available evidence sufficient for drawing conclusions about the association between herbicide exposure and a number of health outcomes. However, the lack of good data on Vietnam veterans per se, especially with regard to herbicide exposure, has complicated the assessment of the increased risk of disease among individuals exposed to herbicides during service in Vietnam. By considering the magnitude of the association observed in other cohorts, the quality and results of studies that have been made of veterans, and other principles of epidemiologic research, the present committee has formulated a qualitative judgment regarding the risk of disease among Vietnam veterans. Indeed, most of the evidence on which the findings in this and other reports are based comes from studies of people exposed to dioxin or herbicides in occupational and environmental settings rather than from studies of Vietnam veterans.

Is There a Plausible Biologic Mechanism?

Chapters 3 and 11 of *Update 1998* include reviews of the previously available cellular, animal, and human evidence that provides the basis for the assessment of biologic plausibility—the extent to which a statistical association is consistent with existing biological or medical knowledge. The likelihood that a given chemical exposure–health outcome relationship reflects a true association in humans is addressed in the context of research regarding the mechanism of interaction between the chemical and biological systems, evidence in animal studies, evidence of an association between exposure and health outcome occurrence in humans, and/or evidence that a given outcome is associated with occupational or environmental chemical exposures. It must be recognized, however, that a lack of data in support of a plausible biologic mechanism does not rule out the possibility that a causal relationship does exist.

Publication Bias

It has been well documented (Song et al., 2000) in biomedical research that studies with a statistically significant finding are more likely to be published than studies with nonsignificant results. Thus, evaluations of disease–exposure associations that are based solely on the published literature could be biased in favor of a positive association. In general, however, for reports of overall associations with exposure, the committee did not consider the risk of publication bias to be high among studies of herbicide exposure and health risks. The committee took this position because there are numerous published studies showing no positive association; because it examined a substantial amount of unpublished material; and because the committee felt that publicity surrounding the issue of exposure to herbicides, particularly regarding Vietnam veterans, has been so intense that any studies showing no association would be unlikely to be viewed as unimportant by the investigators. In short, the pressure to publish such "negative" findings would be considerable.

Exposure Assessment

Assessment of individual exposure to herbicides and dioxin is a key element in determining whether specific health outcomes are linked to these compounds. The committee responsible for producing *VAO* found that the definition and quantification of exposure are the weakest methodologic aspects of the epidemiologic studies. Although different approaches have been used to estimate exposure among Vietnam veterans, each approach is limited in its ability to determine precisely the intensity and duration of individual exposure.

A separate effort by another Institute of Medicine committee is facilitating the development and evaluation of models of herbicide exposure for use in studies of Vietnam veterans. That committee authored and disseminated a Re-

quest for Proposals for exposure assessment research in 1997 (IOM, 1997) and is carrying out scientific oversight of the research.

Although definitive data are presently lacking, the available evidence suggests that Vietnam veterans as a group had substantially lower exposure to herbicides and dioxin than did the subjects in many occupational studies. Participants in Operation Ranch Hand and members of the Army Chemical Corps are exceptions to this pattern, and it is likely that there are others who served in Vietnam who had exposures comparable in intensity to members of the occupationally exposed cohorts. Although it is currently not possible to identify this heavily exposed fraction of Vietnam veterans, the exposure assessment research effort presently under way may allow progress to be made on this important question.

Issues Related to the Epidemiologic Study of Exposure to Herbicides and Type 2 Diabetes

In addition to the difficulties of exposure ascertainment common to nearly all studies of herbicide exposure and human health effects, some research issues relate specifically to the study of diabetes. These begin with the case definition of diabetes itself. Unlike certain tumors whose diagnosis is defined by the presence of specific cell types, a diagnosis of diabetes is based on a continuum of metabolic activity, with a threshold set at a specific value for purposes of definition. The accepted normative value has been reset in recent years, from a fasting plasma glucose level of ≥140 mg/dl to a level of ≥126 mg/dl (WHO, 1980; ADA, 1997). Additional uncertainty is added by normal laboratory measurement and intraindividual variability that create an error range around the cut-off. Also, heath care providers use an array of interrelated assessment tools and acquire differing amounts of interview information from patients. The "Background" section of the diabetes discussion in Chapter 11 of *Update 1998*—reproduced in Appendix B in this report—provides more detailed information on the disease itself.

The accuracy of death certificate coding of diabetes compounds the issue of diagnostic definition. Underlying cause and associated causes of death are coded according to internationally endorsed guidelines based on information written on the death certificate by the medical authority present at or soon after the death. For all diseases, the extent to which that person knows the medical history of the decedent influences the assignment of the underlying cause of death and the nature of associated, contributing, and otherwise present medical conditions that are noted on the death certificate. Prevalence of diabetes at death substantially exceeds its designation as underlying cause of death, a methodologic challenge addressed by Steenland and colleagues (1992, 1999) and discussed later in this report.

Type 2 diabetes, also called non-insulin-dependent diabetes mellitus, is usually an adult-onset condition with incidence rates increasing with age. Type 2 diabetes prevalence per 1,000 males is 12.2 at ages 25–44 and 101.4 at ages 65 and older (Kenny et al., 1995). The Vietnam veteran cohort has only recently entered the age range with sufficient incidence for accurate study. Therefore, past studies

of association between dioxin and diabetes have been hampered by the relatively low prevalence of diabetes and the even lower death rate attributed to it.

Perhaps the greatest challenge faced by researchers examining the possibility of a link between herbicide exposure and diabetes is the time-dependent influence of age, percentage body fat, weight, dioxin dose, and serum dioxin measures. The interrelationships among these variables are complex, making it difficult to ascertain valid estimates of relationships between past dioxin exposure and current diabetes status.

SUMMARIES OF EPIDEMIOLOGIC EVIDENCE

In seeking evidence for associations between health outcomes and exposure to herbicides and 2,3,7,8-TCDD (also abbreviated as TCDD and commonly referred to as "dioxin"), many different kinds of epidemiologic studies must be considered. Each study has various strengths and weaknesses and contributes evidence to an association between exposure and the health outcome. The three main groups of individuals studied with respect to herbicide exposure are those with occupational, environmental, and military exposures. The historical basis for the groups studied was examined in Chapter 2 of *VAO*. A discussion of the criteria for inclusion in the review is detailed in Appendix A of that report.

The epidemiologic studies and reports reviewed by the committee are summarized below. Each subsection begins with an overview of earlier studies (reviewed in greater detail in *VAO*, *Update 1996*, or *Update 1998*) and continues with a more detailed discussion of the most recently published literature. Table 1 gives a brief overview of the epidemiologic studies reviewed.

Occupational Cohorts

National Institute for Occupational Safety and Health (NIOSH)

Background In 1978, NIOSH began a study to identify all U.S. workers potentially exposed to TCDD between 1942 and 1984 (Fingerhut et al., 1991). In a total of 12 chemical companies, 5,000 workers were identified from personnel and payroll records as having been involved in production or maintenance processes associated with TCDD contamination. Their exposure resulted from working with certain chemicals in which TCDD was a contaminant, including 2,4,5-trichlorophenol (TCP) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), Silvex, Erbon, Ronnel, and hexachlorophene. An additional 172 workers identified previously by their employers as being exposed to TCDD were also included in the study cohort. The 12 plants involved were large manufacturing sites of major chemical companies. Thus, many study subjects probably were exposed to a variety of other chemicals.

TABLE 1 Selected Epidemiologic Studies Reviewed in this Report

Reference	Study Population and Outcome Studied (if not Type 2 diabetes)	Exposed Cases	Estimated Relative Risk (95% CI)
OCCUPATIONAL			
Calvert et al., 1999	Workers exposed to 2,4,5-T and derivatives		
	All workers	26	1.49 (0.77–2.91)
	Serum TCDD < 20 pg/g (ng/kg) lipid	7	2.11 (0.77–5.75)
	20 < TCDD < 75	6	1.51 (0.53–4.27)
	75 < TCDD < 238	3	0.67 (0.17–2.57)
	238 < TCDD < 3,400	10	1.97 (0.79–4.90)
Steenland et al., 1999	Highly exposed industrial cohorts (N = 5,132)		
	Diabetes as underlying cause	26	1.18 (0.77–1.73)
	Diabetes among multiple causes	89	1.08 (0.87–1.33)
	Chloracne subcohort (N = 608)	4	1.06 (0.29–2.71)
Vena et al., 1998	Exposed production workers and sprayers in 12 countries*	33	2.25 (0.53–9.5)
Calvert et al., 1996	Workers (N = 273) exposed to 2,4,5-T and derivatives vs. matched referents (N = 259)		
	OR for abnormal total cholesterol concentration	95	Overall: 1.1 (0.8–1.6)
		18	High TCDD[a]: 1.0 (0.5–1.7)
	OR for abnormal HDL cholesterol concentration	46	Overall: 1.2 (0.7–2.1)
		16	High TCDD[a]: 2.2 (1.1–4.7)
	OR for abnormal mean total/HDL cholesterol ratio	131	Overall: 1.1 (0.8–1.6)
		36	High TCDD[a]: 1.5 (0.8–2.7)
	OR for abnormal mean triglyceride concentration	20	Overall: 1.0 (0.5–2.0)
		7	High TCDD[a]: 1.7(0.6–4.6)

Steenland et al., 1992[b]	Dioxin-exposed workers—mortality rates		
	Diabetes as underlying cause	16	1.07 (0.61–1.75)
	Diabetes among multiple causes	58	1.05 (0.80–1.36)
ENVIRONMENTAL			
Cranmer et al., 2000	Vertac/Hercules Superfund site nondiabetic residents		
	OR for "high" fasting insulin—subjects with serum TCDD >15 ppt vs. < 15 ppt	7: >15 ppt 62: <15 ppt	8.5 (1.49–49.4)
	. . . "high" 30-minute insulin . . .	" "	7 (1.26–39.0)
	. . . "high" 60-minute insulin . . .	" "	12 (2.23–70.1)
	. . . "high" 120-minute insulin . . .	" "	56 (5.7–556)
Pesatori et al., 1998[c]	Seveso residents 15-year (1976–1991) mortality rates		
	Zone A ($N = 805$)		
	Males	0	N/A
	Females	2	1.8 (0.4–7.3)
	Zone B ($N = 5,943$)		
	Males	6	1.3 (0.6-2.9)
	Females	13	1.9 (1.1–3.2)
	Zone R ($N = 38,625$)		
	Males	37	1.1 (0.8–1.6)
	Females	74	1.2 (1.0–1.6)
VIETNAM VETERANS			
AFHS (Air Force Health Study), 2000	Ranch Hand veterans and comparisons	(Numerous analyses discussed in text)	

Continued

TABLE 1 *Continued*

Reference	Study Population and Outcome Studied (if not Type 2 diabetes)	Exposed Cases	Estimated Relative Risk (95% CI)
VIETNAM VETERANS (*continued*)			
Longnecker and Michalek, 2000	Ranch Hand unexposed referents only, OR by quartile and serum dioxin concentration		
	Quartile 1: <2.8 ng/kg (pg/g)	26	1.00—referent
	Quartile 2: 2.8–<4.0 ng/kg	25	0.91 (0.50–1.68)[d]
	Quartile 3: 4.0–<5.2 ng/kg	57	1.77 (1.04–3.02)[d]
	Quartile 4: ≥5.2 ng/kg	61	1.56 (0.91–2.67)[d]
Commonwealth Department of Veterans' Affairs, 1998a,b	Australian Vietnam veterans—male	2,391 reported[e] (6% of respondents)	1,780 expected (1,558–2,003)
	Australian Vietnam veterans—female	5 reported[e] (2% of respondents)	10 expected (9–11)
Henriksen et al., 1997	Ranch Hands—high-exposure group		
	Glucose abnormalities		1.4 (1.1–1.8)
	Diabetes prevalence		1.5 (1.2–2.0)
	Use of oral medications for diabetes		2.3 (1.3–3.9)
	Serum insulin abnormalities		3.4 (1.9–6.1)

NOTE: HDL = high-density lipoprotein; N/A = not available; OR = odds ratio; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid.
*May include some of the same subjects covered in the NIOSH cohorts addressed in the other references cited in the Occupational cohorts category.

[a]The high TCDD category comprises workers with TCDD levels between 1,516 and 19,717 fg/g serum.
[b]This is listed as a "new" study because it was not previously reviewed in a *Veterans and Agent Orange* series report.
[c]Very similar data are reported in Bertazzi et al., 1998.
[d]Adjusted for age, race, body mass index, waist size, family history of diabetes, body mass index at the time dioxin was measured, serum triglycerides, and military occupation.
[e]Self-reported medical history; answer to question, Since your first day of service in Vietnam, have you been told by a doctor that you have diabetes?

In addition to this study, NIOSH conducted a cross-sectional study that included a comprehensive medical history, medical examination, and measurement of pulmonary function of workers employed in the manufacture of chemicals with TCDD contamination at chemical plants in Newark, New Jersey, from 1951 to 1969; and in Verona, Missouri, from 1968 to 1969 and from 1970 to 1972 (Sweeney et al., 1989, 1993; Calvert et al., 1991, 1992; Alderfer et al., 1992). The plant in New Jersey manufactured TCP and 2,4,5-T; the Missouri plant manufactured TCP, 2,4,5-T, and hexachlorophene.

Later studies involving this cohort included examinations of pulmonary function (Calvert et al., 1991), liver and gastrointestinal function (Calvert et al., 1992), mood (Alderfer et al., 1992), the peripheral nervous system (Sweeney et al., 1993), porphyria cutanea tarda (Calvert et al., 1994), and reproductive hormones (Egeland et al., 1994).

Halperin et al. (1995) examined cytochrome P-450 1A2 induction in the New Jersey and Missouri plant chemical workers originally examined by Sweeney et al. (1990). Sweeney et al. (1996, 1997) evaluated other noncancer end points for liver function, gastrointestinal disorders, chloracne, serum glucose, hormone and lipid levels, and diabetes in 281 of the 586 workers first identified by Calvert et al. (1991) in New Jersey and Missouri. In addition, 260 controls were examined. Appendix B reproduces the discussion of the Sweeney et al. papers in *Update 1998*.

New Studies Steenland and colleagues (1999) followed death status through 1993 of the TCDD-exposed industrial cohort (a total of 5,172 workers at 12 U.S. plants), using records of the Social Security Administration, National Death Index, and Internal Revenue Service. In this paper, they report positive findings for cancer and heart diseases and a significant "negative" (inverse) trend between diabetes mortality and cumulative TCDD exposure. After excluding individuals with inadequate exposure data, the authors looked at death certificate coding of diabetes (International Classification of Diseases, Ninth Edition [ICD·9] code 250) as the underlying cause of death and in any context, such as contributing or associated causes of death. Among the 5,132 individuals examined, the standardized mortality ratio (SMR) associated with diabetes as an underlying cause of death was 1.18 (95 percent confidence interval [95%] 0.77–1.73, based on 26 deaths). Expanding the SMR to include all individuals with any mention of diabetes on the death certificate, the SMR decreased slightly to 1.08 (0.87–1.33, 89 deaths). For the subcohort of 608 workers who had chloracne following exposure, the SMR for diabetes was 1.06 (0.29–2.71, 4 deaths). It is unclear whether this last figure includes any mention of diabetes or was for diabetes as an underlying cause only. None of these SMRs was statistically significant at the 95 percent level.

The authors also examined SMRs and risk ratios (using Cox regression) by exposure septile among the 3,538 workers with usable exposure quantification. The job exposure matrix included materials used, fraction of day worked, and qualitative contact level based on estimates of skin or inhalation contamination.

SMRs, from lowest- to highest-exposure septile, were 1.87, 2.17, 1.36, 0.92, 1.33, 1.10, and 0 for diabetes as the underlying cause of death. The trend for cumulative exposure, with $p = .10$, was not significant; the logarithm of cumulative exposure, $p = .09$. Risk ratios for any mention of diabetes on the death certificate were 1.00 (the referent), 1.27, 0.92, 0.81, 0.98, 0.72, and 0.54, respectively; this is a statistically significant negative trend with cumulative exposure, $p = .02$. The logarithm of cumulative exposure was not, however, significant ($p = .12$). The Cox regression model was controlled for year of birth (quartiles) and age (the time variable).

The consistency of results from the two sets of analyses—the underlying cause of death and any mention on the death certificate—could be the result of the low power and limitations common to analyses relying on death certificates for ascertaining a chronic condition such as diabetes. The exposure likelihood matrix assembled by the authors is a noteworthy attempt to rank-order people without the confounding of age and obesity. The caveats remain, though, that misclassification of exposure is likely and that there is potential for systematic underascertainment related to exposure level. The absence of weight data on death certificates also complicates the assessment of diabetes. Additionally, because the chloracne cohort had a markedly higher median cumulative exposure score (11,546) than workers without chloracne (77), the fact that there was no significant increase in the SMR for diabetes greatly dampens the hypothesized dioxin–diabetes association.

The SMR calculation made in this paper employs a methodology described in an earlier paper (Steenland et al., 1992) that presented the rationale for using multiple-cause-of-death data, especially when examining diseases and conditions that are often present at death, but are not the cause of death, yet are "serious enough to be noted by the physician on the death certificate," such as diabetes. The authors created a ratio of the number of deaths for which a cause is listed at all and the number of deaths for which that cause is listed as the underlying cause of death. At one extreme are the ratios for transportation accidents and lung cancer—1.02 and 1.09. The other extreme is made up of diseases that are less likely to be fatal but likely to be present and significant at death, such as arthritis and hypertension without heart disease—10.70 and 12.10. Diabetes lies near the center, with a ratio of 3.82, and is one of the examples the authors present to demonstrate the multiple-cause-of-death approach.

This 1992 paper—which was not previously reviewed in a *Veterans and Agent Orange* series report—uses data regarding deaths in a U.S. worker cohort exposed to dioxin during the manufacture of herbicides and other chemicals to demonstrate the utility of examining multiple-cause mortality information. The authors calculated SMRs for underlying cause of death and for any mention of diabetes. The more narrow underlying-cause-of-death categorization for diabetes yielded 16 deaths, while the broader multiple-cause-of-death categorization yielded 58. This validated the attempt to capture more diabetes-related cases but did not substantially change the SMR—1.07 (0.61–1.75) for underlying

cause versus 1.05 (0.80–1.36) for multiple cause—which remained not statistically significant.

Using information from interviews, including lifetime occupational histories, and medical examinations, Calvert and NIOSH colleagues (1996, 1999) compared serum lipid concentrations, serum glucose, and diabetes in a group of TCP production workers to neighborhood controls, matched on age, race, and gender. The workers were drawn from two U.S. plants and were exposed at least 15 years prior to the study.

In their 1996 paper,[4] the authors examined data regarding 281 workers and 260 referents; data from 273 workers and 259 referents were used in the analyses. Mean total cholesterol, mean high-density lipoprotein (HDL) cholesterol, and the ratio of mean total cholesterol to HDL were determined for the workers, divided into roughly equal-sized quartiles by whole-weight serum TCDD concentration (<158 fg/g serum,[5] 158–520, 521–1,515, and 1,516–19,717 fg/g serum), and controls. Measures were based on blood drawn after a 12-hour or longer fast. The authors used reference values described in the National Cholesterol Education Program to set thresholds for categorizing a value as abnormal. Cut points chosen were

- cholesterol ≥ 6.21 mmol/l (240 mg/dl),
- HDL cholesterol ≤ 0.91 mmol/l (35 mg/dl),
- triglyceride > 2.82 mmol/l (250 mg/dl), and
- total cholesterol/HDL ratio ≥ 5.

The highest serum TCDD concentration group had the highest rate of abnormal HDL cholesterol concentration (odds ratio [OR] = 2.2, 1.1–4.7), controlling for body weight index, use of beta blocker, and current diabetes. The trend for mean triglyceride concentration quartiles was borderline significant (p = .05), controlling for gender, plant location, body weight index, cumulative cigarette consumption, use of beta-blocker medication, race, and diabetes. None of the other relationships tested yielded statistically significant results. To explore whether the observed associations were influenced by total serum lipid variations, the authors added a total serum lipid term to the model—it did not, however, change the findings.

The authors concluded that the association of serum TCDD concentration with their lipid measures was small compared to the influence of other factors. They also observed that because TCDD is lipophilic and partitions into serum lipids, individuals with higher serum lipid concentrations would be expected to have higher serum TCDD concentrations, all else being equal.

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[4]This paper is also reviewed in *Update 1998* under the discussion of lipid and lipoprotein disorders.

[5]The unit femtograms per gram of serum is *not* directly comparable to the lipid-adjusted measures (picograms per gram of lipid and, equivalently, nanograms per kilogram of lipid) used in the other papers reviewed here.

In their 1999 paper, Calvert and colleagues examined diabetes, serum glucose, and thyroid function (as determined by interviews and physical examinations) in 279 workers and 258 neighborhood referents with no occupational dioxin exposure, again matched for age, race, and sex. Workers were divided into four roughly equal-sized categories based on their lipid-adjusted serum TCDD level (<20, 20 ≤ TCDD < 75, 75 ≤ TCDD < 238, and 238 ≤ TCDD < 3,400 pg/g lipid). The glucose regression model included age, race, sex, body mass index (BMI) (stratified), and current medications that can increase serum glucose. The diabetes regression model added history of diabetes among parents or siblings. Diabetes was defined as a fasting serum glucose concentration greater than or equal to 7.8 mmol/l (140 mg/dl) on two days or the participant's reporting a history of diabetes diagnosed by a physician. Medical records were not obtained to validate self-reported diabetes.

The authors used three exposure indices, each in a separate regression analysis: (1) a dichotomous comparison of workers and referents; (2) serum TCDD concentration at the 1986 or 1992 examination, adjusted for serum lipid concentration; and (3) calculated half-life extrapolated, lipid-adjusted serum TCDD concentration.[6] Using measures from the second index, the authors split the workers into four equal-sized groups before beginning analyses. In the statistical analysis, each of the four groups was compared with the unexposed referent group. As expected, the workers had significantly increased mean current serum lipid-adjusted TCDD concentration (220 versus 7 pg/g; $p < .001$) and increased mean half-life extrapolated lipid-adjusted serum TCDD concentrations compared to neighborhood referents.

The worker and referent groups did not differ on serum glucose overall; neither was there a dose–response trend. The authors note, however, that the workers with the highest half-life extrapolated serum TCDD concentrations had significantly increased adjusted mean serum glucose concentration compared to referents. Overall, 9.3 percent of workers (26 individuals) and 7.0 percent of the referent group (18) met one of the definitions for diabetes. This translated to an increased, but not statistically significant, odds ratio of 1.49 (0.77–2.91) for diabetes, adjusted for race, age, BMI, family history of Type 2 diabetes, and current use of medications that can increase serum glucose concentrations. No dose–response trend was observed with serum TCDD or half-life extrapolated lipid-adjusted serum TCDD concentration. However, of the 10 workers with the highest current serum TCDD concentrations (>1,500 pg/g lipid),[7] 6 (60 percent) had diabetes mellitus. The authors also reanalyzed their data using the newer American Diabetes Association (ADA, 1997) serum glucose concentration diagnostic

[6]It is widely recognized that current serum dioxin measures are merely estimates of original exposure levels.

[7]The units "picograms per gram lipid" used in this paper and "nanograms per kilogram lipid" used in other papers discussed in this report are equivalent. The reviews of the papers use the same units as the papers themselves for consistency.

criterion for diabetes—7.0 mmol/l (126 mg/dl) rather than 7.8 (140). They report that their findings were essentially unchanged.

The use of neighborhood controls in this study has several disadvantages relative to the use of an industrial worker control group. In addition to the explicit matching on race, age, and gender available for the neighborhood controls, using worker controls adjusts secondarily for unmeasured contributors to the healthy worker effect and other life-style choices and circumstances. It is also necessary to interpret the subgroup findings with caution, especially given their inconsistent pattern and the fact that the overall odds ratio was not statistically significant. It would have been helpful if demographic data for the approximately 260 referents used in this analysis had been provided to assess whether the reported comparability to the full 900-worker referent group was maintained for the subset analysis. If, for example, the referent group has a low (high) prevalence of diabetes, any relative risk for an exposed group would necessarily be inflated (reduced).

International Register of Workers Exposed to Phenoxy Herbicides

Background To avoid problems of small studies with insufficient power to detect increased cancer risks, the International Agency for Research on Cancer (IARC) created a multinational registry of workers exposed to phenoxy herbicides, chlorophenols, and their contaminants (Saracci et al., 1991). The IARC register included information on mortality and exposures of 18,390 workers—16,863 men and 1,527 women. *Update 1996* describes the individual national cohorts included in this multinational registry.

Following earlier work covering 10 countries, Kogevinas et al. (1997) assembled national studies from 12 countries using the same core protocol jointly developed by study participants and coordinated by IARC. The expanded study consisted of 26,615 male and female workers engaged in the production or application of phenoxy herbicides and was composed of (1) the Saracci et al. (1991) cohort, (2) the German cohorts of Becher et al. (1996), and (3) the NIOSH cohorts of Fingerhut et al. (1991).

Of the total study population, 21,863 (20,851 men and 1,012 women) were classified as exposed to phenoxy herbicides or chlorophenols based on individual job records and company exposure questionnaires; 4,160 were unexposed; and 592 were classified as "unknown exposure." Most workers were classified as exposed if they had ever worked in the production or spraying of phenoxy herbicides or chlorophenols (for four cohorts, a minimum employment period of 1 to 12 months was specified). The period of follow-up also varied between cohorts; overall, it extended from 1939 to 1992 (488,482 person-years at report). A total of 4.4 percent (970 workers) were lost to follow-up. Exposure information varied between cohorts, but in general, exposures were reconstructed from job records. The exposed workers were aggregated into five groups: main production; maintenance; other exposed jobs; unspecified tasks; and sprayers. Based on these categories and information on production processes and the composition of

the materials used, the exposed workers were further classified into three categories: (1) exposed to TCDD or higher chlorinated dioxins (HCDs); (2) unexposed to the same; and (3) unknown exposure to the same. Analysis was performed by calculating SMRs and 95% CIs, using the World Health Organization (WHO) mortality data bank to calculate national mortality rates by sex, age (5-year intervals), and calendar period (5 years). Within-cohort analysis was also performed using Poisson regression adjusting for time since first exposure, duration of exposure, and employment status.

A number of these individual cohorts were evaluated apart from the IARC coordinated efforts. *VAO*, *Update 1996*, and *Update 1998* discuss the IARC and related cohort studies in more detail.

New Studies Vena and colleagues (1998) examined noncancer mortality, including diabetes, between 1939 and 1992 in the IARC cohort. Subjects represented 36 cohorts assembled in 12 countries and included workers who produced or sprayed phenoxy herbicides and chlorophenols. Three of the thirty-six included cohorts were sprayers; the remaining were production workers. The entire 26,976-member cohort yielded 21,863 exposed workers who met minimum employment period, exposure, and exposure rate information availability requirements and who were the subject of this paper. Exposure estimates for the subjects were reconstructed using job records, company exposure questionnaires, and in some cohorts, measures of TCDD and other congeners in serum or adipose tissue and in the workplace environment.

The authors calculated male- and female-specific SMRs for major cause-of-death categories, and also combined male and female data. Workers were further categorized into those with known TCDD/HCD exposure (N = 13,831) and known nonexposure (N = 7,553); 479 individuals with unknown amounts of TCDD/HCD exposure were excluded. Calculations were adjusted for country, age, gender, calendar period, and employment status. The SMRs for the category "diseases of the endocrine system and blood" (ICD·9 codes 240–289), which includes diabetes, were less than 1.0, not statistically significant, and lower than the all-cause SMRs.

The authors also carried out internal comparisons of the cohort, using the nonexposed workers as the referent. Poisson regression analyses were conducted for all circulatory disease, ischemic heart disease, cerebrovascular disease, and diabetes. Variables examined in the models were exposure, years since first exposure, duration of exposure, and year of first exposure. Relative risk (RR) values were adjusted for age, gender, country, calendar period, employment status, years since first exposure, and duration of exposure.

The dichotomous exposure model yielded an RR of 2.25 (0.53–9.50) for diabetes, based on 11 deaths in the referent group and 33 in the exposed group. Relative risks calculated for the other exposure variables ranged between 0.97 and 2.52; all were nonsignificant. No trend was noted for increasing risk with increased years since first exposure, increased duration of exposure, or calendar year of first exposure.

The authors state that the study's strengths are its large number of subjects, validated exposure assessment, and extended latency period. Among the weaknesses they identify are its lack of morbidity data, the crudeness and inaccuracy involved in death certificate data, the lack of specific quantitative measures of exposure, and possible confounding by factors known to influence diabetes incidence such as obesity and physical inactivity.

While the authors assert that their results reinforce the hypothesis that TCDD exposure increases the risk for diabetes, it must also be noted that the elevated RRs reported are point estimates with wide confidence intervals based on a small number of deaths. It is not possible to draw firm inferences from a model with 44 cases, seven predictor variables, and results that are not statistically significant. Further, the small number of deaths due to diabetes reported in this cohort seems anomalous and may reflect defects in the coding of death certificate data.

Vietnam Veteran Cohorts

Studies of Vietnam veterans who were potentially exposed to herbicides, including Agent Orange, have been conducted in the United States at the national and state levels, as well as in Australia. Exposure measures in these studies have been done on a variety of levels, and evaluations of health outcomes have been made using a variety of different comparison or control groups.

United States—Operation Ranch Hand

Background The men responsible for the majority of the aerial spraying of herbicides in Vietnam were volunteers from the Air Force who participated in Operation Ranch Hand. To determine whether there are adverse health effects associated with exposure to herbicides, including Agent Orange, the Air Force made a commitment to Congress and the White House in 1979 to conduct an epidemiologic study of Ranch Hand veterans (AFHS, 1982). *VAO*, *Update 1996*, and *Update 1998* discuss the cohort in more detail.

A retrospective matched cohort study design was implemented to examine morbidity. National Personnel Records Center and U.S. Air Force Human Resources Laboratory records were searched and cross-referenced to ascertain completely 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 but not occupationally exposed to herbicides (AFHS, 1983) was selected from the same data sources used to identify the Ranch Hand population. Controls were individually matched on age, type of job (using Air Force specialty code), and race (white or not white). The rationale for matching on these variables was to control for the aging process, educational and socioeconomic status, and potential differences by race in the development of chronic disease. Since Ranch Hand veterans and controls performed similar combat or combat-related

jobs (with the exception of handling herbicides), many possible confounders related to the physical and psychophysiologic effects of combat stress and the Southeast Asia environment were potentially controlled (AFHS, 1982).

Ten matches for each exposed subject formed a control set. For the mortality study, each exposed subject and a random sample of half of each subject's control set are being followed for 20 years, in a 1:5 matched design. The morbidity component of follow-up consists of a 1:1 matched design, using the first control randomized to the mortality ascertainment component of the study. If a control is noncompliant, another control from the matched "pool" is selected; controls who die are not replaced.

The baseline physical exam occurred in 1982, with subsequent exams in 1987, 1992, and 1997. One more exam is scheduled for 2002. Morbidity was ascertained through questionnaire and physical examination, which emphasize dermatologic, neuropsychiatric, hepatic, immunologic, reproductive, and neoplastic conditions. There were 1,208 Ranch Hand veterans and 1,668 comparison subjects eligible for baseline examination. Initial questionnaire response rates were 97 percent for the exposed cohort and 93 percent for the unexposed; baseline physical exam responses were 87 and 76 percent, respectively (Wolfe et al., 1990). For the 1987 examination and questionnaire (Wolfe et al., 1990), 84 percent of the Ranch Hand veterans (N = 955) and 75 percent of the comparison subjects (N = 1,299) were fully compliant and thus available for matching. Mortality outcome was obtained and reviewed by using U.S. Air Force Military Personnel Center records, the DVA's Death Beneficiary Identification and Record Location System (BIRLS), and the Internal Revenue Service's data base of active Social Security numbers. Death certificates were obtained from the appropriate health departments (Michalek et al., 1990). Eighty-four percent of the 1,148 eligible Ranch Hand veterans (N = 952), 76 percent of the original comparison group (N = 912), and 65 percent of the 567 replacement comparisons (N = 369) invited to the 1992 follow-up chose to participate in the examination and questionnaire (AFHS, 1995). The methods used to assess mortality and morbidity were identical to the methods described previously for the 1982 and 1987 examinations.

Ranch Hand veterans were divided into three categories on the basis of their potential exposures:

1. *Low potential:* This group included pilots, copilots, and navigators. Exposure was primarily through preflight checks and during actual spraying.
2. *Moderate potential:* This group included crew chiefs, aircraft mechanics, and support personnel. Exposure could occur by contact during dedrumming and aircraft loading operations, on-site repair of aircraft, and repair of spray equipment.
3. *High potential:* This group included spray console operators and flight engineers.

Results have been published for the baseline morbidity (AFHS, 1984a) and baseline mortality studies (AFHS, 1983). Follow-up examinations were administered in 1985, 1987, and 1992 (AFHS, 1987, 1990, 1995). Mortality updates have been published for 1984–1986, 1989, and 1991 (AFHS, 1984b, 1985, 1986, 1989, 1991a). Serum dioxin levels in Ranch Hands and the control population were measured in 1982 (Pirkle et al., 1989); 1987 (AFHS, 1991b); and 1992 (AFHS, 1995). Serum dioxin analysis of the 1987 follow-up examinations was published in 1991 (AFHS, 1991b). Continued follow-up and results will be forthcoming.

An interim technical report (AFHS, 1996) and subsequent paper (Michalek et al., 1998) updated the cause-specific mortality among 1,261 Ranch Hand personnel compared to 19,080 controls through the end of 1993. Study design followed that of the previous Ranch Hand mortality studies. The analysis found no significant differences between the observed and expected number of Ranch Hand deaths. No specific information on diabetes was reported. However, there was one death coded under "endocrine diseases" (ICD·9 codes 240–279) where 1.1 was expected.

Henriksen and colleagues (1997) analyzed the Ranch Hand data to address the relationship between wartime exposure to herbicides and Type 2 diabetes, glucose levels, and insulin levels. For this analysis, a total of 989 Ranch Hand veterans and 1,276 comparisons were clinically examined. Blood samples were collected and medical records were reviewed to determine diabetes status, severity, and time to onset of diabetes. Serum insulin and glucose levels were calculated from blood samples taken in 1992. Exposure to TCDD was classified on the basis of original exposure calculated from serum (lipid-adjusted) dioxin levels determined in 1987 or 1992. At follow-up (1992), the mean age of the comparison group was 53.5 years (±7.6), and the mean ages of the three exposed groups were 54.6 ± 7.2, 54.9 ± 7.6, and 50.9 ± 7.4 years, respectively, by increasing exposure category. This study was reviewed in detail in *Update 1998*; the material is duplicated in Appendix B of this report.

New Studies Michalek and colleagues (1999) explored the influence of dioxin levels on the relationship between sex hormone-binding globulin (SHBG) and insulin-related metabolism, using laboratory measurements of the Ranch Hand cohort and the established referent group of Air Force personnel who were in Southeast Asia during the same period and had no herbicide exposure. Individuals were excluded if they took hormone medications; had prostatic cancer, cancer of the testes or other genital organs, or surgery of the testes; or had a history of diabetes diagnosis before service in Southeast Asia.

Blood drawn in 1987 or 1992 was measured for serum dioxin, insulin, fasting glucose, and SHBG. Individuals were excluded if they were without a dioxin measurement or had a measurement that was below the limit of quantitation. Referents with a serum dioxin level greater than 10 ppt, which the authors considered to be background range, were also excluded. An individual was classified as having diabetes if there was a medical diagnosis or a 2-hour post-oral

glucose load of ≥200 mg/dl before July 1995.[8,9] The authors stratified the analysis of nondiabetic veterans by age and percentage of body fat. They note that the highly exposed individuals were more likely to be younger, enlisted personnel and to be heavier than both the background and the less exposed individuals. The analyses include 871 Ranch Hand veterans and 1,121 comparison subjects.

Two sets of analyses were conducted. The first compared the geometric mean of the veterans' insulin, fasting glucose, and SHBG levels by dioxin category and diabetes status. In nondiabetic veterans in the high-exposure category, the geometric mean of the serum insulin level was significantly increased relative to that in the comparison group (8.1 versus 67.7 μIU/ml; IU = International Unit) (p = .004). For diabetic veterans in the high category, fasting serum glucose level was significantly increased relative to that in the comparison group (156.1 versus 137.4 mg/dl) (p = .03). No other statistically significant differences were noted. Although not noted in the text, the Ranch Hand veterans overall did not have a statistically higher diabetes prevalence than the comparison group:

$$\text{Ranch Hand veterans: } \frac{111}{871} = 12.7\%, \text{ Comparison group: } \frac{125}{1{,}121} = 11.2\%,$$

$$\text{RR} = \frac{12.7}{11.2} = 1.1\ (0.9\text{–}1.5).$$

The authors state that their findings suggest a compensatory metabolic relationship between dioxin and insulin regulation. Specifically, in young, lean, nondiabetic veterans exposed to dioxin, the negative correlation between SHBG levels and insulin levels suggests that the transported sex hormones are downregulating insulin release. They speculate that factors like age, body fat, and diabetes may overwhelm and thus mask the observed effects in other subcohorts.

This study does not address diabetes incidence per se, but notes associations among metabolic indices in the Ranch Hand cohort that are consistent with an association between dioxin body burden and Type 2 diabetes. It shares some characteristics with Henriksen et al. (1997) reported in *Update 1998* and reproduced in Appendix B. The analyses do not take advantage of the individual matching used to construct the comparison group, although there was statistical control for age and percentage body fat. However, an unpublished analysis of the Henriksen et al. (1997) data provided to the committee in response to a question raised at the June 2000 workshop (Michalek, 2000b) showed no material difference in the results when matching was performed, making it unlikely

[8]A 100-g glucose load was used for this test in order to make the results comparable to earlier AFHS studies. This load is expected to slightly inflate the positive rate for the test compared to the presently recommended 75-g load.

[9]The text of the paper states this is a postprandial value; however, Dr. Michalek indicates that a glucose load was used from 1985 onward (Michalek, 1999).

that such a change would substantially alter the results of this study. Another potential issue was that each exposure group was compared to the entire comparison group, which was chosen by an original matched design to be comparable to Ranch Hand veterans as a whole. The three exposure groups should ideally have been compared to appropriate subgroups of comparison subjects matched to the specific exposed group. If these subgroups differed on confounders other than age and body fat, this could impact the findings, although the Henricksen matched results suggest the impact would be minimal. Issues concerning diabetes case definition and adequacy of control for obesity and other confounders were outlined in *Update 1998*.

Longnecker and Michalek (2000), examined the association between serum dioxin levels and diabetes mellitus within the group of Air Force veterans chosen as the comparison cohort for the Ranch Hand veterans.[10] Seventy-three percent of the 1,762 individuals identified as part of this cohort were examined in 1992. Data included measurements taken in 1987 or 1992 of fasting serum glucose, serum glucose, and insulin 2 hours after oral administration of 100 g of glucose, as well as serum dioxin level. Diabetes diagnoses were acknowledged for 14.1 percent of those examined, based on individual-reported physician diagnosis that the authors subsequently verified by medical record or postchallenge glucose ≥200 mg/dl in 1992.

Of the 1,281 individuals participating in the 1992 examination, the authors excluded 84. Twenty-four were excluded because their serum dioxin levels were greater than 10 ng/kg lipid, which the authors considered to be above background range, and 60 because their serum dioxin, glucose, triglycerides, or waist measurements were missing. The analyses in this paper are based on 93 percent of individuals examined (1,197 out of 1,281 who participated in the 1992 examination) and 68 percent of the presumed eligible cohort (1,197 out of 1,762 invited to be examined in 1992). Although not indicated in the paper, the authors noted in a presentation before the committee that the detection limit for the analytic technique used to measure dioxin levels is ~1 ng/kg of serum lipid and that the test exhibited good repeatability at the low levels examined.

The study population was divided into quartiles according to serum dioxin levels, and the lowest quartile (<2.8 ng/kg) defined the referent group. Multivariate regression models were formulated, adjusting for the continuous variables: age, 1992 body mass index (BMI), BMI at time of dioxin blood drawing, and 1992 waist size, and for the categorical variables: race, military occupation, and family history of diabetes. These regressions indicated that age, BMI, waist size, family history, and enlisted military rank were associated with increased odds ratios of diabetes. The adjusted OR for Type 2 diabetes increased with serum dioxin level. Adding serum triglyceride level to the model attenuated the associations. Table 2 summarizes the results.

[10]The results of this study were presented at the 1999 workshop described in Appendix A; the study was subsequently published in the peer-reviewed journal *Epidemiology*.

TABLE 2 Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Diabetes in the Ranch Hand "Comparison Cohort," According to Serum Dioxin Concentration Quartile

Variable	Quartile 1, <2.8 ng/kg	Quartile 2, 2.8 to <4.0 ng/kg	Quartile 3, 4.0 to <5.2 ng/kg	Quartile 4, ≥5.2 ng/kg
No. of cases	26	25	57	61
No. of controls	272	280	238	238
Subjects with diabetes	8.7%	8.2%	19.3%	20.4%
Ors				
Crude	1	0.93	2.51	2.68
95% CI		0.53–1.66	1.53–4.11	1.64–4.38
Adjusted[a]	1	0.89	1.88	1.71
95% CI		0.48–1.63	1.11–3.19	1.00–2.91
Adjusted[b]	1	0.91	1.77	1.56
95% CI		0.50–1.68	1.04–3.02	0.91–2.67

[a]Adjusted for age, race, body mass index, waist size, family history of diabetes, body mass index at time dioxin was measured, and military occupation.
[b]In addition to the factors listed for the first adjusted model, ORs were also adjusted for serum triglycerides.

SOURCE: Adapted from Longnecker and Michalek, 2000, Table 2.

Analyses also identified an association between serum dioxin level and serum insulin level in both the crude model and the model adjusted for age, race, body mass index in 1992, waist size, family history of diabetes, BMI at the time dioxin was measured, and military occupation.

Some care must be exercised in interpreting the results of this study. There is a rather narrow spread of serum dioxin levels across quartiles, between 1 and 2 parts in 10^{12}. The characteristics and influence of the 84 excluded subjects are unknown, although they represent only 7 percent of the cohort. Finally, AFHS reports and papers that evaluate diabetes in the comparison cohort and Ranch Hands (Henriksen et al., 1997; Michalek et al., 1999; AFHS, 2000) find similar incidence rates in the two cohorts, which would not be expected in the presence of a strong dioxin–diabetes association. Notwithstanding these observations, the committee found this study to be interesting, provocative, and generally well analyzed.

The Air Force Health Study In February 2000, the Air Force Heath Study (AFHS) released a report based on data from the 1997 physical examination of Ranch Hand veterans and their comparison cohort (AFHS, 2000). The authors evaluated 266 health-related end points, including measures of Type 2 diabetes incidence, severity, time to onset, and associated laboratory values. These end

points were analyzed using four statistical models, each based on a different approach to exposure measurement.

Model 1 uses group (Ranch Hands, comparisons) and military occupation (officer, enlisted flyer, and enlisted ground crew) as proxies for exposure. As indicated above, prior AFHS analyses report that, on average, enlisted ground crew had the highest dioxin exposure, followed by enlisted flyers, then officers. This model does not include any direct dioxin measure.

Model 2 is applied only to Ranch Hands. The exposure estimate is an individual's serum dioxin level extrapolated to a time-of-exposure value (initial) adjusted for a 1987 body fat measure. Extrapolations were calculated based on a first-order elimination assumption of an exponential decrease in dioxin body burden with time; the half-life of 8.7 years is based on a sample of Ranch Hand participants with repeat dioxin measures over time. It is further limited to Ranch Hands with serum dioxin levels greater than 10 ppt measured at the 1987, 1992, or 1997 physical exams.

Model 3 divides the Ranch Hand veterans in Model 2 into two discrete dioxin categories—"low" and "high"—based on current serum dioxin levels extrapolated to initial values. This model also includes as a third category ("background") Ranch Hand veterans who had been excluded from Model 2 because current serum dioxin measures were less than 10 ppt, and as a fourth category all comparison subjects with serum levels less than 10 ppt. All exposure values are adjusted for 1987 body fat. The specific category definitions follow:

- *comparisons*: comparison subjects with up to 10 ppt lipid-adjusted serum dioxin level;
- *background:* Ranch Hand veterans with up to 10 ppt lipid-adjusted serum dioxin level;
- *low:* Ranch Hand veterans with more than 10 ppt lipid-adjusted serum dioxin *but at most* 94 ppt estimated initial serum dioxin level; and
- *high:* Ranch Hand veterans with more than 10 ppt lipid-adjusted serum dioxin *and more than* 94 ppt estimated initial serum dioxin level.

Model 4, restricted to the Ranch Hand cohort only, uses the serum dioxin level measured in 1987 (the year in which most Ranch Hand veterans were initially assayed) or a later measurement extrapolated to a 1987 value. All Ranch Hand veterans with available dioxin measurements were considered in Model 4 analyses, including those with levels less than 10 ppt who were excluded from Model 2 and treated as a separate category in Model 3.

Models 2, 3, and 4 all use the same 1987 serum dioxin measures (or later where a 1987 value was not available), and the authors note that the extrapolations in Model 2 and 3 assume that the dioxin elimination rate is constant across individuals. Models 2 and 3 use serum dioxin values adjusted for body fat at the time of the dioxin measure. All four models were run both "unadjusted" and "adjusted" for a set

of potential confounders: age, race, military occupation, personality type, body fat, and family history of diabetes.

The diabetes assessment included medical records, physical examination, and laboratory examination variables. The outcome measures—a composite diabetes indicator, diabetic severity, time to diabetes onset, fasting glucose (continuous and discrete), 2-hour postprandial[11] glucose (continuous and discrete), fasting urinary glucose, 2-hour postprandial urinary glucose, serum insulin (continuous and discrete), and α-1-C hemoglobin[12] (continuous and discrete)—provide dozens of association estimates. Longitudinal analyses were conducted on some of the outcome measures to examine possible differences in results over time. The report details these multiple analyses; the following text highlights some of the results.

AFHS researchers examined three medical outcomes related to diabetes: a composite diabetes indicator, diabetic severity, and time to diabetes onset. Individuals who were diagnosed with diabetes prior to their service in Southeast Asia were excluded from these analyses.

The composite diabetes indicator was coded "yes" if the participant had either a verified history of diabetes (a medical records measure) or a 2-hour postprandial glucose level of at least 200 mg/dl (a laboratory examination measure). Overall, approximately 17 percent of each cohort (16.9 percent of the Ranch Hands and 17.0 percent of the comparisons) were considered to be diabetic based on the indicator criteria. The unadjusted (RR = 0.99, 0.79–1.25) and adjusted (RR = 1.04, 0.81–1.33) comparisons of the groups did not yield statistically significant differences in the number of diabetic participants (Model 1). However, the percentage of Ranch Hands with diabetes varied in a dose–response fashion among the dioxin-categorized subgroups: 9.8 percent in the background category; 20.9 percent in the low category; and 23.8 percent in the high category. The adjusted forms of Models 2, 3, and 4 all yielded statistically significant associations between the exposure measure and the composite diabetes indicator. There was a significant positive association between initial serum dioxin level and the percentage of diabetic participants among Ranch Hands (Model 2: RR = 1.36, 1.09–1.69). Ranch Hands in the low (RR = 1.22, 0.83–1.79), high (RR = 1.47, 1.00–2.17), and combined low and high (RR = 1.34, 1.00–1.80) dioxin categories were more likely to be diabetic than were comparisons (Model 3). Finally, there was a significant positive association between 1987 serum dioxin levels and diabetes (RR = 1.47, 1.21–1.68) (Model 4). The unadjusted form of Models 4 also yielded a statistically significant positive relationship; the unadjusted forms of Models 2 and 3 did not.

A diabetic severity index was constructed from the responses of (Type 2) diabetic participants to 1997 questionnaire inquiries regarding the use of three

[11]The text of the report refers to "postprandial" values; however, a 100-g glucose load was used for nondiabetics. The load was not given to diabetics unless requested by the participant (AFHS, 2000).

[12]Some studies render this as "A1C" or "A(1c)" hemoglobin.

treatment regimes: diet, oral diabetes medication (oral hypoglycemics), and insulin. This self-reported information was verified by medical records review. In general, diet is used to treat the less severe forms of diabetes; [13] oral hypoglycemics are employed where diet is insufficient; and injected insulin is employed if oral agents do not adequately control blood glucose. Adjusted model analyses showed that

- diabetic Ranch Hand veterans were significantly more likely than diabetic comparison subjects to use insulin (Model 1: RR = 2.20, 1.15–4.20);
- the percentage of Ranch Hand veterans using insulin to control their diabetes increased with initial serum dioxin level (Model 2: RR = 2.47, 1.43–4.25);
- diabetic Ranch Hand veterans in the low (RR = 2.41, 1.00–5.82), high (RR = 3.46, 1.36–8.81), and combined low and high (RR = 2.90, 1.40–5.99) dioxin categories were significantly more likely than diabetic comparison subjects to use insulin (Model 3); and
- there was a statistically significant association between 1987 serum dioxin levels and diabetic Ranch Hand veterans' use of diet only (RR = 1.49, 1.00–2.20) and oral hypoglycemics (RR = 1.85, 1.37–2.49) (Model 4).

Unadjusted models generally showed positive, but not statistically significant, associations for these outcomes.

The date on which a participant was first diagnosed with diabetes was used to measure a time to diabetes onset by determining the number of years between the date of diagnosis and the end date of the last tour of duty in Southeast Asia. Models adjusted for known confounders showed that time to onset was significantly shorter for Ranch Hand veterans with higher initial (Model 2, $p = .013$) and 1987 serum dioxin levels (Model 4, $p < .001$), compared to other Ranch Hand veterans. However, diabetic Ranch Hand and comparison subjects did not differ significantly in time to onset (Model 1), and only Ranch Hand veterans with background levels of dioxin showed a significantly shorter time to onset than the comparison groups (Model 3).

Laboratory examinations of endocrine parameters associated with Type 2 diabetes yielded, for the most part, inconsistent and statistically nonsignificant results. However, it was noted that α-1-C hemoglobin increased in Ranch Hand veterans as initial serum dioxin (Model 2) and 1987 dioxin (Model 4) increased. Increased levels of α-1-C hemoglobin were also observed in Ranch Hand veterans with high dioxin levels (Model 3). High levels of α-1-C hemoglobin are a marker for poorly controlled diabetes. Analyses also showed that fasting glucose levels increased in Ranch Hand veterans as initial dioxin (Model 2) and 1987 dioxin (Model 4) increased.

[13] That is, controlling blood sugar through some combination of meal planning, weight control, and exercise.

AFHS researchers carried out extensive analyses of potential confounders in their efforts to identify alternative explanations for their observed association between dioxin and diabetes. Rejected hypotheses include the following: the "association between diabetes and dioxin represents an association between diabetes and dioxin elimination and is therefore artifactual," and "dioxin binds differentially to lipid fractions and therefore the relation between dioxin and diabetes interacts with lipid concentrations" (Michalek, 2000a).

Overall, the study authors assert that their results "indicate a consistent and potentially meaningful adverse relation between serum dioxin levels and diabetes," noting the findings of a significant dose–response relationship, and a dioxin-related increase in disease severity and decrease in the time from exposure to first diagnosis. The increase in fasting glucose and α-1-C hemoglobin levels in Ranch Hand veterans, they contend, support this finding.

The committee found the AFHS report's evaluations of diabetes and related outcomes and physical parameters to be generally strong. In particular, the committee noted the efforts made to control for known confounders. However, it reiterates the observation made in *Update 1998* that measures of central fat distribution, diabetogenic drug exposure,[14] and a measure of obesity at the time of Vietnam service would be helpful additions to the analyses.

In response to questions and comments offered by the committee, AFHS researchers conducted additional analyses (Michalek, 2000b). The analyses include additional assessments of the relationship between diabetes and dioxin elimination rate, evaluation of covariate interactions, a matched case-control analysis of diabetes and dioxin using all Ranch Hand veterans, and a series of area-under-the-curve (AUC) analyses. This unpublished work provided additional support for the assertion that diabetes prevalence increases and time to onset of diabetes decreases with dioxin exposure in Ranch Hand veterans. It did not provide support for the lipid binding hypothesis or for the hypothesis that diabetes prevalence or time to onset are related to the dioxin elimination rate. No significant interactions were found between diabetes, dioxin, and covariates. A linear effect of dioxin on diabetes incidence was observed in analyses in which the Ranch Hand and comparison groups were combined. This last finding is difficult to understand, however, given that the diabetes rates in comparison subjects were as high as in Ranch Hand veterans despite the much lower dioxin levels in the comparison group. The committee encourages the researchers to seek publication of these results in a peer-reviewed journal so that they can be fully evaluated.

Australia

Background The Australian government has also commissioned studies to investigate the health risks of Australian veterans. Studies of birth anomalies

[14]Some antihypertensive medications, for example, have been reported to increase the risk of Type 2 diabetes (Gress et al., 2000).

(Donovan et al., 1983, 1984; Evatt, 1985); mortality (Commonwealth Institute of Health, 1984a,b,c; Evatt, 1985; Fett et al., 1987a,b; Forcier et al., 1987); deaths from all causes (Fett et al., 1987b); and cause-specific mortality (Fett et al., 1987a) have been conducted. A series of papers by O'Toole and colleagues (1996a,b,c) describe the results of a simple random sample of Australian Army Vietnam veterans on self-reported health status.

More recently, the Australian Department of Veterans' Affairs conducted a mortality study of more than 59,000 male and 484 female Australian veterans who served in Vietnam (Crane et al., 1997). Based on data provided by the Australian Department of Defense and civilian agencies, researchers created a nominal list of all members of the Army, Navy, and Air Force and some civilian personnel who served on land or in Vietnamese waters for at least one day during the period of the Vietnam war—59,036 in all. Vital statistics, including cause of death, collected from Department of Defense records, Department of Veterans' Affairs records, the National Death Index, Electoral Commission rolls, and the Health Insurance Medicare data base were matched to the nominal list. There were no direct measures or indirect estimates of veterans' exposure to herbicides or other chemical agents, and the authors suggest that any variations in outcomes found in the study would "probably need to be attributed to service in Vietnam rather than exposure to particular agents."

New Studies The government of Australia conducted mail surveys of all individuals with Vietnam service that included, besides those involved in combat, entertainers, medical teams, war correspondents, and philanthropy workers (Commonwealth Department of Veterans' Affairs 1998a,b). The self-report data gathered were compared with age-matched Australian national data. Questionnaires were mailed to 49,944 male veterans (80 percent response rate) and 278 female veterans (81 percent response rate).

The authors found an excess of diabetes among male veterans and a deficit among female veterans when comparing the number of Vietnam veterans responding yes to the question: Since your first day of service in Vietnam, have you been told by a doctor that you have diabetes? to expected national rates. Six percent (2,391) of the male veterans responded yes compared to the expected 4.5 percent (1,780; range 1,558–2,003) (Commonwealth Department of Veterans' Affairs, 1998a). This translates to an observed/expected ratio of 1.34. Two percent of female veterans (5) responded yes, while 10 (9–11) were expected, for an observed/expected ratio of 0.50 (Commonwealth Department of Veterans' Affairs, 1998b). The reports acknowledge that the questionnaire did not define diabetes. Respondents whose doctors had informed them of a single high blood sugar measure, for example, may have interpreted that as "having diabetes."

Strengths of these surveys include their relatively high response rates. Weaknesses, however, include the aforementioned failure to define diabetes in the questionnaire, the use of self-reported cases, the inability to control for important confounders, and the use of general population prevalence data as the comparison. Results for females were based on a very small number of subjects.

Environmental Cohorts

Seveso

Background The occurrence of accidents and industrial disasters has offered opportunities to evaluate the long-term health effects of exposure to dioxin and other potentially hazardous chemicals. One of the largest industrial accidents involving environmental exposures to TCDD occurred in Seveso, Italy, in July 1976 as a result of an uncontrolled reaction during trichlorophenol production. A variety of indicators were used to estimate individual exposure; soil contamination by TCDD has been the most extensively used. On the basis of soil sampling, three areas were defined around the release point: zone A, the most heavily contaminated (mean soil levels of TCDD 15.5–580 $\mu g/m^2$), from which all residents were evacuated within 20 days; zone B, an area of lesser contamination (<50 $\mu g/m^2$) that children and pregnant women in their first trimester were urged to avoid during daytime; and zone R, a region with some contamination (<1.5 $\mu g/m^2$), in which consumption of local crops was prohibited (Bertazzi et al., 1989a,b). Subsequent analysis of chloracne prevalence, animal mortality, and available human serum dioxin levels all confirmed the validity of the zone designation as an exposure measure. Residents of the surrounding uncontaminated area were used as a referent population, which the authors determined—based on 1981 census data—to have characteristics similar to the exposed population.

Several cohort studies based on these exposure categories have been conducted. These studies are reviewed extensively in *VAO*, *Update 1996*, and *Update 1998*. Seveso residents have had long term follow-up of their health outcomes, particularly cancer. For example, Bertazzi et al. (1989a,b, 1992, 1997)) conducted 10- and 15-year mortality follow-up studies among adults and children age 1 to 19 at the time of the accident.

New Studies Since the publication of *Update 1998*, two papers on the Seveso cohort have become available from the Research Centre for Occupational, Clinical and Environmental Epidemiology at the University of Milan. Pesatori and colleagues (1998) report noncancer mortality for the 15-year period following exposure, comparing the three groups of exposed individuals— from zones A (N = 805), B (N = 5,943), and R (N = 38,625)—and the referent group (N = 232,747) residing in surrounding noncontaminated areas. Bertazzi and colleagues (1998) published an overview of the circumstances, exposure assessment, health measures, and observed health effects of the 1976 industrial accident that draws, in part, on the same data. The remainder of this section focuses on the results reported in the Pesatori et al. paper.

Among males, zones B and R had a slightly, but not statistically significant, higher risk of diabetes deaths than the reference population in the 15 years since the accident (1976–1991). Among females, RRs for each zone—A, B, and R—

were elevated, reaching statistical significance in zone B only. Results are detailed in Table 1.

The authors note that the zone B risk ratio for females is 3.1 (1.6–6.1) when limited to mortality in the second decade following the accident. They suggest that the higher relative risks seen among exposed women than among exposed men may be the result of a "complex, and not fully understood, interaction of dioxin with hormonal factors or systematically higher TCDD concentrations in females. . . . "

The authors acknowledge the study weaknesses to include low power, especially within zone A, the most highly contaminated area; imprecise exposure definition based solely on soil contamination measures; comparison of exposed and reference populations based on census data, not individual characteristics; and inability to separate the effects of chemical exposure from the psychosocial stressors associated with the community disaster. It must also be noted that zone A had too few deaths to adequately assess, so zone B would be the most relevant to analyze.

Vertac/Hercules

Cranmer and colleagues (2000) formulated a study to evaluate the relationship between TCDD exposure and hyperinsulinemia among nondiabetic persons. The study population included individuals living near the Vertac/Hercules Environmental Protection Agency (EPA) Superfund site in Jacksonville, Arkansas. The site includes a plant that manufactured pesticides from 1948 until 1986. The TCDD-contaminated pesticide 2,4,5-trichlorophenoxyacetic acid was manufactured in this plant until 1979. Area streams, parks, and nearby neighborhoods were contaminated with TCDD (Cranmer et al., 1994). An earlier exposure study had evaluated blood serum lipid levels of TCDD in 177 individuals including those who had lived near the site and others that had lived in a town 25 miles away. TCDD levels varied between persons (range = 2–95 ppt). Repeated TCDD measurements in the same persons in 1991, 1994, and 1995 showed relatively constant levels over this period, indicating continuing exposure (Cranmer et al., 2000).

Among the 177 individuals in the original study group, a total of 69 subjects with normal glucose metabolism and known TCDD levels were included in this analysis. Normal glucose metabolism was defined as a fasting glucose of less than 110 mg/dl and normal glucose levels after a 75-g glucose challenge (2 hours, <140 mg/dl). Excluded were individuals with a history of diabetes or past treatment with oral hypoglycemic drugs or insulin as well as individuals with subclinical hepatic, renal, thyroid, or other chronic diseases as determined by routine tests. Glucose tolerance was tested by a fasting 75-g glucose challenge with plasma glucose and insulin measurement at prechallenge and 30, 60, and 120 minutes postchallenge.

None of the nine lowest deciles of TCDD had mean fasting insulin levels greater than 2.5 μIU/ml. The highest decile (TCDD >15 ppt) had a significantly

higher fasting insulin level ($p < .05$; mean = 7.0 μIU/ml). Subsequent analyses defined persons with TCDD levels below 15 ppt as "normal." Comparison of the normal and high (>15 ppt) groups with respect to gender, age, body mass index, or total lipids failed to find any significant differences. No differences were found for fasting glucose or for glucose levels after a 75-g glucose challenge. However, insulin levels were significantly higher in the group with TCDD greater than 15 ppt at 30, 60, and 120 minutes. The ORs for high insulin among individuals with high TCDD relative to those with levels less than 15 ppt were 8.5 (1.5–49.4) at fasting (high insulin, >4.5 μIU/ml); 12 (2.2–70.1) at 60 minutes postchallenge (high insulin, 228μIU/ml); and 56 (5.7–556) at 120 minutes (high insulin, 97.7 μIU/ml). The high insulin levels were determined using the ninetieth percentile at each time point. The authors concluded that the study provides evidence that TCDD may cause insulin resistance.

The study provides useful data from a group of nondiabetic healthy individuals sampled from a community with potential TCDD exposure. Insulin resistance was not measured directly, but the presence of hyperinsulinemia provides indirect supporting evidence for TCDD-induced effects on insulin regulation. The comparison groups appeared to be relatively similar on several characteristics that may be potential confounding factors. The study was limited by the sample size, with only 15 individuals in the "high" (>15 ppt) TCDD group.

SYNTHESIS

As anticipated, the methodologic challenges described in the "Issues Related to the Epidemiologic Study of Exposure to Herbicides and Type 2 Diabetes" section earlier in this report hampered clear assessment of the data relevant to a possible association between herbicide or dioxin exposure and the subsequent development of Type 2 diabetes. The committee identified several specific issues, some of which may be addressed through additional research. One concern is that the diabetes rates reported in some studies may be underestimated.[15] The committee strongly recommends that a rigorous and consistent case definition of diabetes be applied in all studies, which would allow comparison of findings across studies and comparisons with available population data. It specifically recommends use of the ADA criteria. The committee further recommends replication of the analyses described by Longnecker and Michalek (2000) of serum TCDD level, diabetes incidence, and serum insulin level, examining other populations with background levels of serum dioxin. It is noted that a recommendation made in *Update 1998* for a combined analysis of the data generated by the Ranch Hand and NIOSH studies is being pursued. The committee welcomes this effort to further examine the possibility that herbicide or dioxin exposure leads to an increased risk of diabetes.

[15]This is not an issue in the Ranch Hand cohort, in which ascertainment is unusually thorough for an epidemiologic study, and the use of a 100-g load increases the sensitivity of the oral glucose tolerance test.

CONCLUSIONS

The committee assessed the association between Type 2 diabetes and herbicide or dioxin exposure. The assessment included several papers and reports published after deliberations were completed for the last National Academies report that addressed this topic, *Veterans and Agent Orange: Update 1998*.

Strength of Evidence in Epidemiologic Studies

Based on material presented in the papers and reports reviewed here, as well as the cumulative findings of research reviewed in *Veterans and Agent Orange* (1994), *Veterans and Agent Orange: Update 1996*, and *Veterans and Agent Orange: Update 1998*, the committee finds that **there is limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and Type 2 diabetes.**

No one paper or study was determinative in reaching this decision. Instead, the committee found that the information accumulated over years of research now meets the definition established for limited/suggestive evidence—that is, *evidence is suggestive of an association between herbicides and the outcome, but limited because chance, bias, and confounding could not be ruled out with confidence*. In reaching this decision, the committee observed the following:

- **Positive associations are reported in many mortality studies, which may underestimate the incidence of diabetes.** Morbidity (the rate of incidence of a disease) is thought to be a more informative end point than mortality (the rate of death) when conducting epidemiologic studies of Type 2 diabetes because the disease is not typically fatal, its known complications may be more likely to be implicated as the underlying cause of death, and reporting of contributory causes of death on death certificates may be spotty. These reasons also lead epidemiologists to suspect that mortality studies may underestimate the incidence of diabetes, although, as Steenland and colleagues (1992) point out, such underreporting might be expected to equally affect the exposed and referent populations and thus wash out the effect. Four mortality studies were reviewed in this report. Individuals living near the site of a 1976 industrial accident involving dioxin were found to have a higher risk of diabetes death than a reference population in all exposure zones where diabetes deaths were recorded (Pesatori et al., 1998). Two studies of a TCDD-exposed cohort of workers at 12 U.S. plants (Steenland et al., 1992, 1999) found positive but non-statistically significant associations between measures of exposure and notations of diabetes on death certificates, although the later paper also found a significant negative trend between diabetes mortality and cumulative TCDD exposure. The fourth study, which examined workers in 12 countries who produced or sprayed phenoxy herbicides and chlorophenols (including some of those investigated by Steenland and colleagues), reported an elevated relative risk of mortality from diabetes in exposed workers versus non-exposed referents (Vena

et al., 1998). Earlier studies reviewed in *Update 1998*, *Update 1996*, and *VAO*—and cited in Appendix B—show an inconsistent but weakly positive association between exposure measures and Type 2 diabetes mortality.

- **Positive associations are reported in most of the morbidity studies identified by the committee.** Several studies that used Type 2 diabetes morbidity as an outcome measure have been published since the last *Veterans and Agent Orange* review: studies of male and female Vietnam veterans from Australia; a NIOSH study of U.S. chemical workers; the Air Force Health Study (Ranch Hand study); and a separate examination of the Ranch Hand comparison group. One of these studies did not show a positive association: the survey of female veterans from Australia indicated 5 self-reported cases of diabetes where 10 were expected (Commonwealth Department of Veterans' Affairs, 1998b). However, the survey of male Australian veterans of Vietnam (Commonwealth Department of Veterans' Affairs, 1998a) did find a statistically significant excess of self-reported diabetes—2,391 cases were reported when 1,780 were expected. The NIOSH (Calvert et al., 1999) and Ranch Hand comparison group (Longnecker and Michalek, 2000) studies both reported an elevated incidence of diabetes in individuals who had high levels of serum dioxin relative to others examined in that study. The primary analysis in the Air Force Health Study (AFHS, 2000) showed nearly identical diabetes incidence in Ranch Hand veterans and the matched comparison group. Despite this negative finding, the study is considered suggestive because dose–response relationships between dioxin levels and diabetes incidence were observed in several other analyses that controlled for confounding variables. In presently unpublished material provided by AFHS researchers, additional analyses were carried out that support the 2000 report findings (Michalek, 2000b). The committee encourages the researchers to seek publication of these results in a peer-reviewed journal so that they can be fully evaluated.

Although some of the risk estimates in the studies examined by the committee are not statistically significant and, individually, studies can be faulted for various methodological reasons, the accumulation of positive evidence is suggestive. The committee does not believe that publication bias plays a crucial role in this tendency in the data.

Increased Risk of Diabetes Among Vietnam Veterans

Presently available data allow for the possibility of an increased risk of Type 2 diabetes in Vietnam veterans. It must be noted, however, that these studies indicate that the increased risk, if any, from herbicide or dioxin exposure appears to be small. The known predictors of diabetes risk—family history, physical inactivity, and obesity—continue to greatly outweigh any suggested increased risk from wartime exposure to herbicides.

Biologic Plausibility

As discussed in *Update 1998,*[16] animal, laboratory, and human data provide reasonable evidence that TCDD exposure could affect Type 2 diabetes risk in humans. TCDD's association with triglyceride and high-density lipoprotein (HDL) concentrations suggests a general consistency because these are the hallmarks of altered lipid metabolism in diabetes, since fatty acid metabolism, insulin resistance, and glucose metabolism are closely linked. Other observed effects include alteration of glucose transport in a variety of cells, modulation of protein kinase C (PKC) activity, reduction in adipose tissue lipoprotein lipase in guinea pigs, hypertriglyceridemia in rabbits, and down-regulation of low-density lipoprotein (LDL) receptors on the plasma membrane in guinea pig hepatocytes.

Three recent studies of humans reviewed here add to that evidence by reporting a compensatory metabolic relation between dioxin and insulin regulation in Air Force Health Study participants (Michalek et al., 1999), an apparent association between serum dioxin levels and fasting glucose levels among nondiabetic AFHS comparison group members with less than 10 ppt serum dioxin (Longnecker and Michalek, 2000), and an elevated incidence of hyperinsulinemia among a cohort of nondiabetics with serum TCDD levels greater than 15 ppt (Cranmer et al., 2000). These studies, however, have methodologic limitations—primarily, inadequate measures of individual characteristics such as percentage of body fat at the time of exposure—that prevent more definitive conclusions from being drawn.

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[16]An overview of the biologic plausibility material addressed in *Update 1998* is given in the "Synthesis" section of its diabetes discussion, which is reproduced in Appendix B of this report.

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APPENDIX A
Summary of Workshops on the Evidence Regarding a Link Between Exposure to Agent Orange and Diabetes

PUBLIC WORKSHOP 1

July 23, 1999
Board Room, National Academy of Sciences Building,
Washington, D.C.

Workshop Presentations and Speakers

- **Cancer, Heart Disease, and Diabetes in Workers Exposed to 2,3,7,8-TCDD**

Marilyn A. Fingerhut, Ph.D., Chief of Staff, National Institute for Occupational Safety and Health, Washington, D.C.

- **Diabetes and TCDD in the Air Force Health Study**

Joel Michalek, Ph.D., Air Force Research Laboratory, Brooks Air Force Base, Texas

- **An Evolution of Diabetes Mellitus and Serum Glucose Among U.S. Workers Exposed to 2,3,7,8-TCDD**

Geoffrey M. Calvert, M.D., Medical Officer, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio

- **Dioxin and Diabetes in Subjects with Background-Level Exposure**

Matthew Longnecker, Ph.D., Medical Research Officer, National Institute for Environmental Safety and Health, Research Triangle Park, North Carolina

- **Potential Relationship Between TCDD and Diabetes**

Philip Kern, M.D., Associate Chief of Staff, Research, Central Arkansas Veterans Healthcare System, and Professor of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas

PUBLIC WORKSHOP 2

June 9, 2000
Room 180, National Academy of Sciences Building,
Washington, D.C.

Workshop Speaker

- **Dioxin and Diabetes in Ranch Hand Veterans**

Joel Michalek, Ph.D., Air Force Research Laboratory, Brooks Air Force Base, Texas

Discussants' Presentations

Philip Kern, M.D., Associate Chief of Staff, Research, Central Arkansas Veterans Healthcare System, and Professor of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Bonnie LaFleur, Ph.D., Associate Professor, Department of Epidemiology and Biostatistics, The George Washington University School of Public Health and Health Services, Washington, D.C.

Michael Stoto, Ph.D., Chair, Department of Epidemiology and Biostatistics, The George Washington University School of Public Health and Health Services, Washington, D.C.; and Member, Ranch Hand Advisory Board

APPENDIX B
Excerpts from the Discussion of Type 2 Diabetes in *Veterans and Agent Orange: Update 1998*

BACKGROUND

Primary diabetes (i.e., not secondary to another known disease or condition, such as pancreatitis or pancreatic surgery) is a heterogeneous metabolic disorder characterized by hyperglycemia and quantitative and/or qualitative deficiency of insulin action (Orchard et al., 1992). Two main types have been recognized based on the 1979 National Diabetes Data Group (NDDG) criteria and those of the World Health Organization (WHO, 1980, 1985): insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). In June 1997, the American Diabetes Association (ADA, 1997) suggested a revised classification, with IDDM being termed Type I and NIDDM, Type II. This new terminology is used in the remainder of this review, although the older diagnostic criteria are utilized as appropriate.

Type I diabetes is generally accepted to result from â-cell dysfunction, caused by a genetically based autoimmune destruction. It comprises approximately 10 percent of all cases of diabetes and characteristically has an abrupt onset in youth or young adulthood, although it may appear at any age. The usual autoimmune form results in complete â-cell destruction and complete insulinopenia, hence the "insulin dependency" of earlier classifications. The genetic basis of the autoimmune form is linked to the human lymphocyte antigen (HLA) system (class II antigens). A number of environmental triggers of the autoim-

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In this reproduction of the text, references to tables and chapters in *Veterans and Agent Orange: Update 1998* have been changed to reflect the numbering system used in this report and to clarify the location of sources of additional information. Typographic errors in the *Update 1998* text have also been corrected.

mune process and/or of symptomatic disease in genetically susceptible subjects have been proposed including viral infections.

Type II diabetes accounts for the majority (approximately 90 percent) of cases of primary diabetes. It is rare before age 30, but increases steadily with age thereafter. The age, sex, and ethnic prevalences are given in Table B-1. The etiology of Type II is unclear, but three cardinal components have been proposed: (1) peripheral insulin resistance (thought by many to be primary) in target tissues (e.g., muscle, adipose and liver); (2) â-cell insulin secretory defect; and (3) hepatic glucose overproduction. Although the relative contributions of these features are controversial, it is generally accepted that the main factors for increased risk of Type II diabetes include age (with older individuals at higher risk), obesity, central fat deposition, a history of gestational diabetes (if female), physical inactivity, ethnicity (prevalence is greater in African Americans and Hispanic Americans, for example), and perhaps most importantly, a positive family history of Type II (for example, more than 90 percent of monozygotic twins are concordant for diabetes compared to less than 50 percent for dizygotic twins). Defects at many intracellular sites could account for the impaired insulin action and secretion seen in Type II diabetes (Kruszynska and Olefsky, 1996). The insulin receptor itself, insulin receptor tyrosine kinase activity, insulin receptor substrate proteins, insulin-regulated glucose transporters, enhanced protein kinase C (PKC) activity, tumor necrosis factor-á, rad (ras associated with diabetes), and PC1 have all been proposed as potential mediators of insulin resistance; impaired insulin secretion has been linked to hyperglycemia itself, to abnormalities of glucokinase and hexokinase activity, and to abnormal fatty acid metabolism.

Finally, an increasing number of "other" types of diabetes have been described that are linked to specific genetic mutations, for example, maturity-onset diabetes of youth, which results from a variety of mutations of the â-cell glucokinase gene.

The diagnosis of diabetes is problematic and a major concern for clinicians and investigators. Whereas Type I is often clearly diagnosed at onset (a blood sugar >200 mg/dl plus symptoms), up to half of the Type II population goes

TABLE B-1 Three-Year Mean Prevalence of Diagnosed Diabetes (per 1,000 population) by Gender, Age, and Race, 1990–1992

Age	Total	Male	Female	White (men and women)	Black (men and women)
25–44	13.9	12.2	15.5	13.9	19.5
45–54	35.6	31.2	39.8	32.9	63.0
55–64	77.5	79.5	75.6	72.2	128.1
›65	101.1	101.4	100.8	93.5	178.6

SOURCE: Kenny et al., 1995, Appendix 4.5, Chapter 4 (1990–1992 National Health Interview Surveys).

TABLE B-2 Diagnostic Criteria for Diabetes (mg/dl plasma glucose)

	1979 NDDG/ 1980 WHO	1997 ADA
Fasting	≥140	≥126
2 hr[a]	≥200	≥200[b]
Random glucose[c]	≥200	≥200

[a]Post 75-g glucose load; midtest value also has to be >200 mg/dl for NDDG.
[b]Not recommended for routine use.
[c]In the presence of diabetes symptoms.

SOURCE: WHO, 1980; ADA, 1997.

undiagnosed. This occurs because the degree of metabolic disturbance needed to meet both the old and the recently revised criteria does not necessarily produce symptoms, but nonetheless is likely to lead to the late complications of diabetes (cardiovascular disease, nephropathy, retinopathy, and neuropathy). It is partly because of this large population of undiagnosed cases and the impracticability of the standard diagnostic test (oral glucose tolerance test) in busy clinical practice that a more simplified diagnostic approach has been recommended by the ADA based on the fasting plasma glucose. Table B-2 shows the earlier NDDG (WHO, 1980) and the current ADA (ADA, 1997) criteria. It should be noted that the vast majority of undiagnosed cases of diabetes under the 1979 criteria were diagnosable only by the 2-hour postglucose criterion (>200 mg/dl) and had fasting plasma glucose levels below the diagnostic level (140 mg/dl). This was one of the main reasons that current ADA recommendations have lowered the fasting criterion to 126 mg/dl (i.e., to capture those cases with the simpler [and more reproducible] fasting glucose test, as 126 mg/dl fasting approximates the 2-hour postchallenge diagnostic level).

Epidemiologic Concerns in the Study of Diabetes

As can be surmised from the above brief description, the epidemiologic study of diabetes is filled with problems. Pathogenetic diversity and diagnostic uncertainty are two of the more significant problems.

Pathogenetic Diversity

Given the multiple likely pathogenetic mechanisms leading to diabetes, which include diverse genetic susceptibilities (ranging from autoimmunity to obesity) and a variety of potential environmental and health behavior factors (e.g., viruses, nutrition, activity), it is probable that many agents or behaviors

contribute to diabetes risk, especially in genetically susceptible individuals. These multiple mechanisms may also lead to heterogeneous responses to various exposures.

Diagnostic Uncertainty

Because up to half the affected diabetic population is currently undiagnosed, the potential for ascertainment bias is high (i.e., more intensively followed groups or those with more frequent health care contact are more likely to be diagnosed), and the need for formal standardized testing (to detect undiagnosed cases) is great. Furthermore, the division of cases developing during young to middle age (i.e., 20–44 years) into Type I or Type II (which indicates the more likely pathogenetic mechanism) is very difficult. Indeed, it is now thought that as many as 10 percent of clinical "Type II" subjects may well have an incomplete form of "Type I" diabetes (Tuomi et al., 1993).

Epidemiologic Studies

Pazderova-Vejlupkova et al. (1981) reported on the 10-year follow-up of 55 workers who had become acutely ill while producing TCP and 2,4,5-T: 95 percent (52) developed chloracne and 8 percent (4) had diabetes at the onset of intoxication. Ten years later, one-fifth ($N = 11$) were reported to have a diabetic glucose tolerance test (diagnostic criteria are not stated, and the role of confounders is not addressed). In a survey of subjects up to 10 years after another industrial incident, May (1982) reported only two clinically recognized cases of diabetes in a total study group of 126 subjects including controls, with a mean age in the low forties. Reported diabetes did not increase in another study (after age adjustment) of 117 2,4,5-T production workers with chloracne compared to 109 without, 10–20+ years after mixed accidental and chronic TCDD exposure (Moses et al., 1984). Two mortality studies provide further negative data. Cook et al. (1987) examined mortality among 2,187 chemical workers and found a decreased SMR (0.7) for diabetes; Bertazzi et al. (1989) reported the 10-year mortality of those living in the area of Seveso, Italy, at the time of the incident in 1976. The relative risk of diabetes mortality was 1.3 (95% CI 0.7–2.3) for men and 1.5 (0.9–2.5) for women. It should be noted that vital statistics data are known to be unreliable in terms of complete ascertainment of diabetes-related mortality.

More recently, Ott et al. (1994), reporting on 138 BASF workers exposed to TCDD in a 1953 industrial incident, found borderline ($p = .06$) increased fasting glucose levels approximately 37 years later. Further analysis suggested that this association was limited to subjects without chloracne who happened to be more obese. The authors raise the possibility that the TCDD–glucose association may be secondary to the link between obesity and diabetes. In a morbidity follow-up of 158 TCDD-exposed BASF workers, significantly fewer (6.3 percent versus 14.3 percent) exposed subjects had medical insurance diagnoses of diabetes

(Zober et al., 1994). Interestingly, thyroid disease was increased ($p < .05$) in the exposed population. There is a considerable overlap between the subjects in this study and those in Ott et al. (1994). Reporting on a mortality study of 883 pulp and paper workers, Henneberger et al. (1989) did not find a statistically significant increase in diabetes (SMR 1.4, 95% CI 0.7–2.7). A German Cancer Research Center report (Von Benner et al., 1994) also found no TCDD effect on blood sugar levels in 153 TCDD-exposed workers from six chemical plants. Two recent mortality follow-up studies also found no increased diabetes (Ramlow et al., 1996) or endocrine mortality (Kogevinas et al., 1997) in chemical workers exposed to dioxins.

Early reports from the Air Force Health Study (the "Ranch Hand" study) of Vietnam veterans exposed to herbicide spraying and an unexposed comparison cohort suggested little relationship. At the first baseline exam in 1982, 10–20 years after exposure, no difference in the prevalence of an abnormal blood sugar (>120 mg/dl 2 hours after a standard carbohydrate load) was seen between the two groups (15 percent versus 17 percent) (AFHS, 1984). Reporting data using lipid-adjusted serum TCDD levels as a measure of exposure from the same cohort study, the Ranch Hand Study (AFHS, 1991) found a significant association between diabetic status on a 3-point scale—normal, impaired (2-hour postprandial glucose 140–200 mg/dl), and diabetic (verified past history or ≥200 mg/dl 2-hour postprandial glucose)—and TCDD level in both the Ranch Hands ($p = .001$) and the comparison group ($p = .028$). However, this correlation may be influenced by the strong correlation between obesity (percentage of body fat) and TCDD level in the same analysis ($r = 0.3$, $p < .001$ in Ranch Hands; $r = 0.15$, $p < .01$ in comparison). It should also be noted that the prevalence of an abnormal 2-hour blood glucose, either impaired or diabetic together (25 percent versus 22 percent Ranch Hands versus comparisons, respectively), or diabetic alone (10 percent versus 8 percent) is not markedly increased despite a nearly four-fold difference in mean dioxin levels between the Ranch Hand and comparison groups. The major impact of obesity in determining both diabetes risk and serum dioxin level has to be fully controlled for before firm conclusions can be drawn.

In view of the potential importance of the most recent report from this ongoing Ranch Hand study, it is reviewed here in more detail. Henriksen et al. (1997) compared 989 dioxin-exposed Operation Ranch Hand veterans (1962–1971) to 1,276 nonexposed veterans serving at the same time. Exposure was classified on the basis of original exposure calculated from serum (lipid-adjusted) dioxin levels determined in 1987 or 1992. At follow-up (1992), the mean age of the comparison group was 53.5 years (±7.6) and that of the exposed group was 54.6 ± 7.2, 54.9 ± 7.6, and 50.9 ± 7.4 years, according to increasing exposure category. The prevalence of diabetes mellitus by 1995 was 13.2 percent in the comparison group and increased from 9.5 percent to 17.2 percent

TABLE B-3 Selected Epidemiologic Studies—Diabetes

Reference	Study Population	Exposed Cases	Estimated Risk (95% CI)	*p* Value
OCCUPATIONAL				
New Studies				
Ramlow et al., 1996	Pentachlorophenol production workers	4	1.2 (0.3–3.0) [a]	
Studies reviewed in *Update 1996*				
Ott et al., 1994	Trichlorophenol production workers	134[g]		0.06[c]
Von Benner et al., 1994	West German chemical production workers	N/A	N/A	
Zober et al., 1994	BASF production workers	10	0.5 (0.2–1.0)	
Studies reviewed in *VAO*				
Sweeney et al., 1992	NIOSH production workers	26	1.6 (0.9–3.0)	
Henneberger et al., 1989	Paper and pulp workers	9	1.4 (0.7–2.7)	
Cook et al., 1987	Production workers	4	0.7 (0.2–1.9) [a]	
Moses et al., 1984	2,4,5-T and TCP production workers	22 (chloracne)	2.3 (1.1–4.8)	
May, 1982	TCP production workers	2	Not available	
Pazderova-Vejlupkova et al., 1981	2,4,5-T and TCP production workers	11	No referent group	
ENVIRONMENTAL				
Studies reviewed in *VAO*				
Bertazzi et al., 1989[b]	Seveso residents			
	Males	15	1.3 (0.7–2.3)	
	Females	19	1.5 (0.9–2.5)	
VIETNAM VETERANS				
New Studies				
Henriksen et al., 1997[c]	Ranch Hands			
	High-exposure category	57	1.5 (1.2–2.0)	
	All Ranch Hands	146	1.1 (0.9–1.4)	
O'Toole et al., 1996	Australian Vietnam veterans	12	1.6 (0.4–2.7)[c,d]	
Studies reviewed in *VAO*				
AFHS, 1991[b]	Ranch Hands	85		0.001,[e] 0.028[f]
AFHS, 1984[a]	Ranch Hands	158		0.234

[a]Standardized mortality ratio compared to U.S. population.
[b]Mortality compared to referent population.
[c]Comparison of fasting glucose values to referents.
[d]Compared to Australian population.
[e]Differences for mean dioxin level across three groups—normal, impaired, and diabetic glucose tolerance—of Ranch Hands.
[f]Differences for mean dioxin level across three groups—normal, impaired, and diabetic glucose tolerance—of comparisons.
[g]Total sample size listed.

to 20.1 percent across the three Ranch Hand exposure categories. There was a statistically significant increase of the prevalence of the highest-exposure category relative to the comparison group (RR 1.5, 95% CI 1.2–2.0). Of the diabetic veterans, 41 percent were not following any treatment regimen, 27 percent were treated with diet alone, 21 percent with oral medications, and 10 percent by insulin.

Two concerns about this potentially important and well-conducted study are case definition and the focus on subgroup analysis with only limited control of confounders. Two somewhat conflicting definitions are given of a case of diabetes: one implies that all cases were clinically verified in medical records; the other is a combination of history and glucose testing after a standard meal or 100-g oral glucose tolerance test (OGTT).

Generally, half of the cases of diabetes go undiagnosed, and, in most cases, those that are diagnosed are found only after formal OGTT testing; the total prevalence of diabetes is the sum of previously diagnosed and currently discovered cases. (Technically an abnormal OGTT has to be repeated before a clinical diagnosis is made, but in epidemiologic studies this is not often done.) Although OGTTs were performed in the current study (at least in the 1992 examination; earlier reports refer to postprandial values), a 100-g glucose load was used, which inflates the positive rate a little compared to the recommended 75-g load. Since the OGTT was given only to those without a diagnosis of diabetes, the prevalence of undiagnosed diabetes is approximated in Henriksen et al. (1997, Table 8) by the 2-hour "postprandial" glucose values that are labeled abnormal (>200 mg/dl). Compared to the rates for 50–59-year-old, non-Hispanic whites from a recent national study (National Health and Nutrition Examination Survey III [NHANES III] 1988–1994), only the high-exposure group has a marked increase in prevalence of known diabetes, whereas all exposure groups have lower rates of discovered diabetes than reported in NHANES. Total prevalences (known and discovered) are therefore similar or lower for the background (9.5 percent) or low-exposure group (17.2 percent) than in NHANES III (16.7 percent), with only the high-exposure group having an increased prevalence (20 percent). These results are consistent with the hypothesis that, generally, Ranch Hands have somewhat lower rates of diabetes (which might be expected for a healthy military population) and that relatively more of the diabetic veterans have been diagnosed (reflecting their more intensive medical follow-up).

A high proportion (41 percent) of all cases are not being treated (even with diet), particularly if the cases were verified in medical records and thus carried a clinical diagnosis. Although comparable data are difficult to find, the 1989 National Health Interview Survey (NHIS) suggests that 43.6 percent of NIDDM subjects age 55–64 years use insulin and 51.7 percent use oral agents. Even given some overlap of these groups (i.e., those who use both insulin and oral agents), it would seem that the proportion of Ranch Hands with diabetes, but not on treatment (diet, insulin, or oral agents), is two to four times higher than expected.

The analyses are problematic since they partially ignore the matched design employed in the study. In the report, each exposure group is compared to the entire comparison group (which was chosen by an original matched design to be

comparable to Ranch Hands as a whole). The three exposure groups should ideally be compared to appropriate subgroups of comparison subjects matched to the specific exposed group. Although the availability of serum dioxin levels enables a better measure of exposure and a focus on the risks of the low- and high-exposed groups is understandable, Ranch Hands as a group do not have an increased risk of diabetes:

Comparison group	13.2% (169/1,276)
Ranch Hands (all groups)	14.8% (146/989)
RR (95% CI)	1.1 (0.9–1.4)

The other major analytic concern involves the limited analyses concerning confounding. The authors note (Henriksen et al., 1997, Table 3) that the high-risk Ranch Hand group has both increased (body mass index [BMI]) and decreased (age) diabetes risk factors. Tables 4 and 5 in the paper list relative risks of diabetes based on the actual (or "raw") numbers of cases in each dioxin exposure category (Michalek and Ketchum, 1997). One analysis presented controls for obesity (Henriksen et al., 1997, Table 7) and appears to eliminate the significance of the negative coefficient of "time to onset of diabetes." A further matched analysis is described, including matching within 3 percent body fat, but relative risks (without confidence intervals) are given only for glucose and insulin values and not for diabetes risk or diabetes severity. In addition, the authors also reanalyzed the data using revised initial doses to take into account 1982 baseline body fat. The results are similar although the relative risk for the high-exposure category is now lower than the low-exposure group. No confidence intervals are given so it is difficult to more fully assess these data. A fully adjusted multivariate model is strongly recommended (e.g., Cox Proportional Hazard with time to diabetes as the outcome), fully controlling for baseline age and obesity (BMI) and, if possible, for family history of diabetes, central fat distribution, diabetogenic drug exposure, and a measure of obesity at the time of Vietnam service.

O'Toole et al. (1996), reporting on 641 Australian Vietnam veterans compared to the Australian population, found a response-adjusted RR of 1.6 (99% CI 0.4–2.7). There are a number of methodologic problems inherent in this study, including a lack of health outcome validation and the use of a control group that is not adequately representative of the cohort.

In a report of a NIOSH medical study of 281 dioxin-exposed workers from two chemical plants in New Jersey and Missouri, Sweeney et al. (1996, 1997) note a slight, statistically significant increase in the risk of diabetes (OR 1.1, $p <$ .003) and high (≥140 mg/dl) fasting serum glucose level ($p < .001$) with increasing serum concentrations of 2,3,7,8-TCDD. The authors suggest, without further documentation, that known diabetes risk factors (age, weight, family history of diabetes) appear more influential than TCDD exposure in explaining this result. An earlier report on this same cohort, published as a conference ab-

stract (Sweeney et al., 1992), finds increased diabetes prevalence (9.2 percent) in the exposed workers compared to 258 nonexposed workers (5.8 percent).

Although not reported, this difference is not significant. However, in a multiple logistic regression analysis, significant associations between serum TCDD level and diabetic status or (in those without diabetes) fasting blood sugar, were apparently noted that were independent of major confounders (age, body mass index, race, and family history of diabetes). Since an OGTT was not performed, many cases (in both groups) may not have been detected. It is recommended that this study be documented more completely and published in the peer-reviewed literature, so that these potentially important findings can be evaluated fully.

Synthesis

The evidence suggesting a connection between herbicide exposure and diabetes risk is equivocal. Consistency across studies is lacking in terms of early reports; however the two recent studies using serum TCDD levels appear to have some consistency (Henriksen et al., 1997; Sweeney et al., 1996, 1997). In many studies, no association is detected and even in NIOSH and Ranch Hand studies it is not significant in univariate analyses for exposed subjects overall. Thus, only a small fraction of cases to date could be linked to herbicide exposure. However the increased risk reported for the highest-exposure groups suggests dose responsiveness in both the Ranch Hand and the NIOSH studies. On the other hand, the much higher serum TCDD levels in the exposed groups in the NIOSH (Sweeney et al., 1996, 1997) and Ranch Hand study (Henriksen et al., 1997) compared to each study's control group do not lead to proportionately higher rates. Indeed in the 1991 Ranch Hand report (AFHS, 1991), the association with TCDD level was also seen in the comparison group. These observations raise the possibility of residual confounding by obesity. As obesity is a powerful determinant of both TCDD level and diabetes, it is very difficult to determine whether TCDD has an independent pathogenetic role. More rigorous statistical analyses are, as suggested, needed to address the issue of residual confounding. A different possibility, namely that obesity is a mediator of TCDD-enhanced diabetes risk, has not been formally addressed in the analyses to date. This possibility remains open but difficult to explore as obesity or percent body fat measures at the time of initial Vietnam service would be needed along with equally precise TCDD exposure measures. Animal data suggest that rather than being associated with obesity, TCDD exposure, if anything, leads to a wasting syndrome. Other possibilities, for example, that there is some interaction between TCDD and obesity, could be more fully explored with statistical analyses of existing data, and researchers with relevant data are encouraged to critically examine these possibilities.

Potential pathogenetic mechanisms add to the biologic plausibility of herbicide exposure increasing diabetes risk. Empirically, the TCDD association with triglyceride and high-density lipoprotein (HDL) concentrations suggests a general consistency because these are the hallmarks of altered lipid metabolism in

diabetes, since fatty acid metabolism, insulin resistance, and glucose metabolism are closely linked. The nature of the cases (i.e., few treated with insulin) does not suggest a Type I diabetes process with autoimmune â-cell destruction or chemical toxicity as seen with the rat poison Vacor (Drash et al., 1989). Nonetheless, measurement of glutamic acid decarboxylase (GAD) and insulin antibodies may be worthwhile given the uncertain nature of young adult-onset diabetes (Tuomi et al., 1993).

The well-established effect of TCDD on glucose transport in a variety of cells including human granulosa cells (by a cAMP [cyclic adenosine 5′-monophosphate] dependent protein kinase [Enan et al., 1996]), guinea pig adipose tissue (Enan and Matsumura, 1993), and mice and rats (by an Ah [aryl hydrocarbon] receptor-mediated mechanism [Enan and Matsumura, 1994]) provides some basis for biological plausibility. Furthermore, the association between TCDD and decreased PKC activity is of particular interest (Matsumura, 1995). TCDD may exert an influence on PKC activity which, in turn, may relate to insulin receptor kinase activity. Kruszynska and Olefsky report that increased PKC appears to inhibit insulin receptor kinase activity in humans (1996). Information about TCDD modulation of PKC is growing; for example, in vascular smooth muscle cells it appears to exhibit cell cycle dependence and isoform specificity (Weber et al., 1996) and is biphasic (Weber et al., 1994), while Bagchi et al. (1997) have shown that TCDD is a particularly strong stimulant of hepatic PKC in Sprague-Dawley rats. TCDD also has been reported to decrease glucose transporter 4 in adipose tissue and glucose transporter 1 in mice brains by the Ah receptor-dependent process operating at different levels (mRNA and protein, respectively) (Liu and Matsumura, 1995). Finally, since TCDD has been shown to affect hormone (including insulin) signaling, the likelihood that TCDD may be diabetogenic is further increased (Liu and Safe, 1996).

Thus, in summary, many animal studies provide potential biological mechanisms for an association between herbicide exposure and diabetes risk, and although the majority of earlier reports on humans suggest little association, the potentially more definitive 1997 report from the Ranch Hand study (Henriksen et al., 1997) raises the possibility that veterans in the highest herbicide exposure category may be at increased risk. Such a conclusion may be supported by a currently unpublished NIOSH study of workers exposed to TCDD. It is important to note that these studies used serum TCDD levels as the measure of exposure. At this time, questions concerning case definition and full control for obesity and other confounders (in the Ranch Hand study) preclude determining whether or not an association exists between herbicide exposure and diabetes in these studies.

The committee strongly urges that the NIOSH study be documented more completely and published in the peer-reviewed literature, so that its potentially important findings can be evaluated fully. It strongly recommends that the Ranch Hand study develop a fully adjusted multivariate model (e.g., Cox Proportional Hazard with time to diabetes as the outcome), fully controlling for baseline age and obesity (BMI) and, if possible, for family history of diabetes, central fat dis-

tribution, diabetogenic drug exposure, and a measure of obesity at the time of Vietnam service. The committee recommends that consideration be given to a combined analysis of the Ranch Hand and NIOSH studies to further examine the possibility that herbicide or dioxin exposure leads to an increased risk of diabetes. Using the new ADA definition of diabetes (i.e., fasting plasma glucose ≥ 126 mg/dl), outcome data from both studies could be made comparable.

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APPENDIX C

Committee and Staff Biographies

COMMITTEE BIOGRAPHIES

DAVID TOLLERUD, M.D., M.P.H. (*Chair*), is professor of medicine and director of the Center for Environmental and Occupational Health at MCP Hahnemann University School of Public Health. He received his M.D. from Mayo Medical School and his M.P.H. from the Harvard School of Public Health. He served as a medical staff fellow in the Environmental Epidemiology Branch, National Cancer Institute; pulmonary fellow at Brigham and Women's and Beth Israel Hospitals in Boston; assistant professor of medicine at the University of Cincinnati; and associate professor of environmental and occupational health at the University of Pittsburgh Graduate School of Public Health. He is a fellow of the American College of Occupational and Environmental Medicine and the American College of Chest Physicians, a member of numerous professional societies, including the American Thoracic Society, the American Association of Immunologists, the Clinical Immunology Society, the American Public Health Association, and the American Association for the Advancement of Science, and a member of the editorial review board of the *American Industrial Hygiene Association Journal*.

MICHAEL AMINOFF, M.D., is professor of neurology, director of the Clinical Neurophysiology Laboratories, and director of the Movement Disorders Clinic and the Epilepsy Program at the University of California Medical Center, San Francisco. He has published extensively on topics related to clinical neurol-

ogy and neurophysiology, has authored or edited 15 textbooks, is on the editorial board of several medical and scientific journals, and is editor of the journal *Muscle and Nerve*.

STEVEN GOODMAN, M.D., M.H.S., Ph.D., is an associate professor of oncology, pediatrics, epidemiology, and biostatistics at the Johns Hopkins School of Medicine. He trained in pediatrics at Washington University and received degrees in biostatistics and epidemiology in 1989 from Johns Hopkins University, where he is currently in the Oncology Center's Division of Biostatistics. As statistician for the Hopkins Oncology Center, General Clinical Research Center, and Pediatric Clinical Research Unit, he has participated in the design and analysis of a wide range of clinical and epidemiologic studies. He has served as statistical editor at the *Annals of Internal Medicine* since 1987 and has been on a variety of committees at the National Institutes of Health. His research interests include meta-analysis, statistical inference, the ethics of clinical trials, and the use of likelihood and bayesian methodology in clinical research.

ROBERT F. HERRICK, Sc.D., is a lecturer on industrial hygiene at the Harvard School of Public Health. His educational background includes a B.A. degree in chemistry from the College of Wooster, an M.S. in environmental health science from the University of Michigan, and a D.Sci. in industrial hygiene from the Harvard School of Public Health. He is certified in the comprehensive practice of industrial hygiene. His research interests are centered on the assessment of exposure as a cause of occupational and environmental disease. He has conducted research on the development of methods to measure the biologically active characteristics of reactive aerosols, and on studies of work processes in the construction and foundry industries to develop task-based models to identify and control the primary sources of worker exposures. Dr. Herrick is past chair of the American Conference of Governmental Industrial Hygienists, and past president of the International Occupational Hygiene Association. He is active in the association's mentor program, which facilitates training for occupational hygienists in industrializing countries. Prior to joining the faculty at the Harvard School of Public Health, Dr. Herrick spent 17 years at the National Institute for Occupational Safety and Health, where he conducted occupational health research.

IRVA HERTZ-PICCIOTTO, Ph.D., is associate professor in the Department of Epidemiology, School of Public Health, at the University of North Carolina at Chapel Hill. She received her Ph.D. in epidemiology from the University of California at Berkeley. She is a member of several professional societies, including the International Society for Environmental Epidemiology, for which she hosted the 1994 Annual Meeting and currently serves as president-elect. She also serves on the editorial boards of the *American Journal of Epidemiology*, *Epidemiology*, and *Human and Ecological Risk Assessment*. She has published extensively on

several topic areas, including risk assessment, occupationally related cancer, environmental exposures, reproductive outcomes, and methods for epidemiologic data analysis. Her primary research interests are in the area of environmental chemical exposures and their effects on pregnancy, young children, and other susceptible populations. She has also been involved in the development of risk assessments using epidemiologic data, comparisons of reproductive toxicity and carcinogenic potency between animals and humans, and methodologic issues such as dose–response analysis and techniques for standardization.

DAVID G. HOEL, Ph.D., received his Ph.D. from the University of North Carolina at Chapel Hill and has more than 25 years of experience as a biostatistician, toxicologist, and environmental health researcher. Dr. Hoel currently holds the position of Distinguished University Professor and associate director of the Hollings Oncology Center at the Medical University of South Carolina. Before joining the Medical University of South Carolina, he held administrative positions at the National Institute of Environmental Health Sciences, where he was most recently director of the Division of Biometry and Risk Assessment. Internationally, Dr. Hoel has been a member of the United States–Japan Cooperative Medical Science Program and also a member of numerous working groups of the International Agency for Research on Cancer of the World Health Organization.

ANDREW OLSHAN, Ph.D., is associate professor in the Department of Epidemiology, School of Public Health, at the University of North Carolina at Chapel Hill. He received his Ph.D. in epidemiology from the University of Washington. He was a postdoctoral fellow in medical genetics at the University of British Columbia from 1987 to 1989 and assistant professor in the Department of Clinical Epidemiology and Family Medicine, University of Pittsburgh, from 1989 to 1991. He is a member of several professional societies, including the Society for Epidemiologic Research, the American Society of Human Genetics, and the Teratology Society. His major areas of interest include cancer and perinatal health in relation to environmental, occupational, and genetic factors. He has a particular interest in male-mediated effects on abnormal reproduction and development.

HOWARD OZER, M.D., Ph.D., is Eason Chair and chief of the Hematology/Oncology Section, director of the Cancer Center, and professor of medicine at the University of Oklahoma. Dr. Ozer is a member of several professional societies and has served on the Board of the Society for Biologic Therapy and the Governor's Cancer Advisory Board for the State of Georgia. He serves on the editorial boards of the *Journal of Cancer Biotherapy*; *Cancer Research, Therapy and Control*; *Cancer Biotherapy and Radiopharmaceuticals*; and *Emedicine;* he is a reviewer for numerous journals including *Cancer Research, Journal of the National Cancer Institute,* and *New England Journal of Medicine*. Dr. Ozer has published extensively on the treatment of hematologic malignancies.

KENNETH S. RAMOS, Ph.D., is professor in the Department of Physiology and Pharmacology, College of Veterinary Medicine, and vice-chairman of the faculty of toxicology at Texas A&M University. He also holds joint appointments in the Department of Medical Physiology and the Department of Environmental and Occupational Health at the Texas A&M University Health Sciences Center. Dr. Ramos is a member of several professional societies including the Society of Toxicology, the Society for In Vitro Biology, the American Society for Cell Biology, and the American Society for Pharmacology and Experimental Therapeutics. He serves on the editorial boards of the *Journal of Biochemical Toxicology*, *Journal of Toxicology and Environmental Health*, *Annual Review of Pharmacology and Toxicology*, *Toxicology in Vitro, American Journal of Physiology, Toxicology and Applied Pharmacology*, *Chemico-Biological Interactions*, and *Cell Biology and Toxicology*. His primary research interests are in the area of cellular and molecular toxicology, with an emphasis on the study of chemically induced deregulation of gene expression, cell differentiation, and somatic growth control.

NOEL R. ROSE, M.D., Ph.D., is professor of pathology and of molecular microbiology and immunology at the Johns Hopkins University and holds joint appointments in the Departments of Medicine and of Environmental Health Sciences. He is also director of the World Health Organization Collaborating Center for Autoimmune Diseases and of the Johns Hopkins Reference Laboratory. Dr. Rose directs the university's training program in immunotoxicology and is active as a consultant in immunotoxicology. He has also served on panels of the National Institutes of Health, the Food and Drug Administration, the National Center for Toxicological Research, the National Research Council, and other governmental agencies. He is past-president of the Clinical Immunology Society and editor-in-chief of the journal *Clinical Immunology and Immunopathology*. Dr. Rose's main area of research is autoimmune disease.

ARTHUR RUBENSTEIN, M.B.B.Ch., is dean of the Mount Sinai School of Medicine and executive vice president of the Mount Sinai Center. Prior to this appointment, he was chair of the Department of Medicine at the University of Chicago Pritzker School of Medicine. He is an authority on diabetes, a widely sought counselor to academic health centers, and a frequent panelist at the annual meetings of the senior research societies in internal medicine. He was a member of the National Institutes of Health Advisory Board and the National Diabetes Board, and he is a member of the Institute of Medicine, the Academy of Arts and Sciences, and the Residency Review Committee in Internal Medicine. Dr. Rubenstein has authored more than 350 papers, and has been on the editorial boards of *Annals of Internal Medicine* and the *Journal of Diabetes and Its Complications, and Medicine*.

MICHAEL P. STERN, M.D., graduated Harvard College in 1959 and the University of Pennsylvania School of Medicine in 1963. After completing his internship at the Mount Sinai Hospital in New York, he completed his residency in internal medicine and a fellowship in endocrinology and metabolism at Stanford University School of Medicine. He was a member of the faculty of Stanford University School of Medicine in the Department of Medicine until 1976, when he joined the faculty of the University of Texas Health Science Center at San Antonio, also in the Department of Medicine. His current position at that institution is professor of medicine and head of the Division of Clinical Epidemiology. He has performed extensive research on the epidemiology and genetics of diabetes, obesity, and related conditions, particular in Mexican Americans.

SUSAN WOSKIE, Ph.D., C.I.H., is associate professor in the Department of Work Environment at the University of Massachusetts at Lowell. She holds a doctoral degree in biomedical science (industrial hygiene) from Clark University and a master's in environmental health from the Harvard School of Public Health. Her research has focused on assessing exposures for epidemiologic studies, including exposure assessments in the metalworking and semiconductor industries. She has also studied diesel exhaust exposures among railroad and construction workers, lead exposures in bridge painting, and silica exposures in construction. Dr. Woskie currently serves on the editorial review board of the *American Industrial Hygiene Association Journal* and is a scientific adviser on the NIOSH/NCI Lung Cancer Mortality Study of Diesel Exposure in Non-Metal Mines.

STAFF BIOGRAPHIES

ROSE MARIE MARTINEZ, Sc.D., is director of the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. Prior to joining IOM, she was a senior health researcher at Mathematica Policy Research, where she conducted research on the impact of health system change on the public health infrastructure, access to care for vulnerable populations, manage care, and the health care workforce. Dr. Martinez is a former assistant director for health financing and policy with the U.S. General Accounting Office, where she directed evaluations and policy analysis in the area of national and public health issues. Dr. Martinez received her doctorate from the Johns Hopkins School of Hygiene and Public Health.

KATHLEEN STRATTON, Ph.D., was acting director of the Division of Health Promotion and Disease Prevention of IOM from 1997 to 1999. She received a B.A. degree in natural sciences from Johns Hopkins University and a Ph.D. from the University of Maryland at Baltimore. After completing a postdoctoral fellowship in the neuropharmacology of phencyclidine compounds at the University of Maryland School of Medicine and in the neurophysiology of second-messenger

systems at the Johns Hopkins University School of Medicine, she joined the staff of the IOM in 1990. Dr. Stratton has worked on projects in environmental risk assessment, neurotoxicology, the organization of research and services in the Public Health Service, vaccine safety, fetal alcohol syndrome, and vaccine development. She has had primary responsibility for the reports *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality; DPT Vaccine and Chronic Nervous System Dysfunction; Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment;* and *Vaccines for the 21st Century: An Analytic Tool for Prioritization*.

DAVID A. BUTLER, Ph.D., is a senior project officer in the Division of Health Promotion and Disease Prevention. He received B.S. and M.S. degrees in engineering from the University of Rochester, and a Ph.D. in public policy analysis from Carnegie-Mellon University. Prior to joining IOM, Dr. Butler served as an analyst for the U.S. Congress Office of Technology Assessment and was a research associate in the Department of Environmental Health at the Harvard School of Public Health. He is on the editorial advisory board of the journal *Risk: Health, Safety and Environment.* His research interests include exposure assessment and risk analysis.

JAMES A. BOWERS is a research assistant in the Division of Health Promotion and Disease Prevention. He received his undergraduate degree in environmental studies from Binghamton University. He has also been involved with the IOM committees that produced *Characterizing Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam*, *Adequacy of the Comprehensive Clinical Evaluation Program: Nerve Agents,* and *Clearing the Air: Asthma and Indoor Air Exposures.*

JENNIFER A. COHEN is a research assistant in the Division of Health Promotion and Disease Prevention. She received her undergraduate degree in art history from the University of Maryland. She has also been involved with the IOM committees that produced O*rgan Procurement and Transplantation* and *Clearing the Air: Asthma and Indoor Air Exposures*.

SUSAN THAUL, Ph.D., is a senior program officer in the Medical Follow-up Agency of the Institute of Medicine. She received a Ph.D. in epidemiology from Columbia University and an M.S. in health policy and management from Harvard University. Dr. Thaul is the lead author of several IOM reports on veterans' health. She previously headed the health staff of the U.S. Senate Committee on Veterans' Affairs. Prior to coming to the Institute she worked at the Agency for Health Care Policy and Research, the Harlem Hospital Prevention of Prematurity Project, and the New York City Health and Hospitals Corporation.