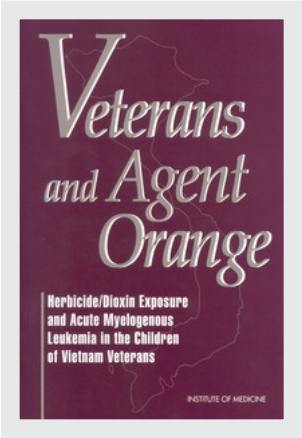

Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans

DETAILS

42 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-08338-6 | DOI 10.17226/10309

AUTHORS

Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third Biennial Update), Division of Health Promotion and Disease Prevention

Veterans and Agent Orange

Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans

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

Division of Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C.

NATIONAL ACADEMY PRESS • 2101 Constitution Avenue, N.W. • Washington, DC 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

Support for this project was provided by the U.S. Department of Veterans Affairs. The views presented in this report are those of the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third Biennial Update) and are not necessarily those of the funding agency.

International Standard Book No. 0-309-08338-9

Additional copies of this report are available for sale from the National Academy Press, 2101 Constitution Avenue, N.W., Box 285, Washington, DC 20055. Call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP's home page at **www.nap.edu.** The full text of this report is available at **www.nap.edu.**

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America.

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

INSTITUTE OF MEDICINE

Shaping the Future for Health

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Bruce M. Alberts is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Bruce M. Alberts and Dr. Wm. A. Wulf are chairman and vice chairman, respectively, of the National Research Council.

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

Irva Hertz-Picciotto, Ph.D. (Chair),[1,2] Professor, Department of Epidemiology, University of North Carolina at Chapel Hill
Margit L. Bleecker, M.D., Ph.D., Director, Center for Occupational and Environmental Neurology, Baltimore, Maryland
Thomas A. Gasiewicz, Ph.D., Professor of Environmental Medicine and Deputy Director of the Environmental Health Sciences Center, University of Rochester
Tee L. Guidotti, M.D., M.P.H., Professor and Chair of the Department of Environmental and Occupational Health, The George Washington University School of Public Health and Health Services
Robert Herrick, Sc.D., C.I.H.,[1,2] Senior Lecturer on Industrial Hygiene, Department of Environmental Health, Harvard School of Public Health
David G. Hoel, Ph.D.,[1,2] Distinguished University Professor, Medical University of South Carolina
Loren D. Koller, D.V.M., Ph.D., Professor, Oregon State University, College of Veterinary Medicine
Howard Ozer, M.D., Ph.D.,[1,2] Eason Chair and Chief of the Hematology/Oncology Section, Director of the Cancer Center, and Professor of Medicine, University of Oklahoma
John J. Stegeman, Ph.D., Senior Scientist and Chair of the Biology Department, Woods Hole Oceanographic Institution
David S. Strogatz, Ph.D., M.S.P.H., Associate Professor and Chair of Epidemiology, School of Public Health, State University of New York at Albany

Staff

David A. Butler, Study Director
Rose Marie Martinez, Director, Division of Health Promotion and Disease Prevention
Jennifer A. Cohen, Research Assistant
Anna Staton, Research Assistant

---

[1]Member of the committee responsible for *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes.*
[2]Member of the committee responsible for *Veterans and Agent Orange: Update 1998.*

Elizabeth Albrigo, Project Assistant
Rita Gaskins, Division Assistant
Melissa French, Financial Associate

Staff Consultants

Michelle Catlin, Program Officer

Acknowledgments

The committee 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 the following individuals, who gave presentations at the October 18, 2001, Workshop on the Review of Health Effects in Vietnam Veterans of Exposure to Herbicides:

Keith Horsley, M.D., Medical Services Adviser, Commonwealth Department of Veterans' Affairs, Australia

Paul Jelfs, Ph.D., Head, Population Health Unit, Australian Institute of Health and Welfare and epidemiological consultant for the Department of Veterans' Affairs

Xiao Ou Shu, M.D., Ph.D., Associate Professor of Medicine, Vanderbilt University School of Medicine, Center for Health Service Research, Nashville, Tennessee

Joachim Schüz, Ph.D., Institute for Medical Biometrics, Epidemiology and Informatics, University of Mainz, Germany

Reviewers

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 its 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 review of this report:

Linda S. Birnbaum, Ph.D., U.S. Environmental Protection Agency
Andrew F. Olshan, Ph.D., University of North Carolina
Gilbert S. Omenn, M.D., Ph.D., University of Michigan
Peter S. Spencer, Ph.D., F.R.C.Path., Oregon Health Sciences University

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

Contents

Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans

EXECUTIVE SUMMARY

In 2001, in response to a request by the U.S. 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 between exposure to dioxin[1] and other chemical compounds in herbicides used in Vietnam and acute myelogenous leukemia in the offspring of Vietnam veterans. 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 associated with exposure to herbicides during Vietnam service;
(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

[1] 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.

"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*; *Veterans and Agent Orange: Update 1998; Veterans and Agent Orange: Update 2000*—and information published or identified through October 18, 2001, the date the deliberations of the *Update 2000* committee were completed.

Strength of Evidence in Epidemiologic Studies

Based on the scientific evidence reviewed in this report, the committee finds **there is inadequate or insufficient evidence to determine if an association exists between exposure to the herbicides used in Vietnam or their contaminants and acute myelogenous leukemia (AML) in the children of Vietnam veterans**. This is a change in classification from the recent *Veterans and Agent Orange: Update 2000* report, which found limited/suggestive evidence for such an association.

The *Update 2000* report committee primarily based its findings on three studies. One—a report on AML incidence in the children of Australian veterans of Vietnam (AIHW, 2000)—was later found to have contained an error that led its authors to incorrectly conclude that these children faced a significantly greater risk of AML than the general population. The revised analysis found that while AML incidence was somewhat elevated, it was within the range that might be expected in the community (AIHW, 2001).

A second study of U.S. veterans found that paternal self-reported service in Vietnam or Cambodia was associated with an elevated risk of AML in offspring after adjusting for some potentially confounding lifestyle and sociodemographic factors (Wen et al., 2000). The third study found that occupational use of pesticides by either the mother or the father, as reported in detailed interviews, was associated with an elevated risk (Buckley et al., 1989). However, because of a high correlation among exposures in the three periods studied (before, during, and after pregnancy), it was not possible to determine whether exposure uniquely prior to the pregnancy was associated with increased risk of AML in the children. This is an important consideration because the wartime exposure of male veterans to herbicides would have occurred prior to conception. For female veterans, it could have occurred during early pregnancy.

Two other analyses not previously reviewed in a *Veterans and Agent Orange* series report were also evaluated by the committee: a paper on cancer morbidity in the children of agricultural workers in Norway (Kristensen et al., 1996) and an unpublished extension of an interview study of childhood cancers in Germany (Meinert et al., 2000) presented at an October 2001 IOM workshop by co-investigator Dr. Joachim Schüz. These provided the committee with little additional information due to the relatively small numbers of exposed cases and lack

of data on exposures to specific substances. The German study did have a general measure of paternal exposure prior to conception and found no association with AML in offspring.

None of the other studies of childhood cancer outcomes reviewed in *Veterans and Agent Orange* reports provides explicit information specific to the evaluation of AML in the offspring of exposed individuals.

Considered together, the corrected data from the AIHW report, the other newly reviewed research results, and the information from previously reviewed studies no longer meet the definition for "limited/suggestive evidence"—evidence suggestive of an association but limited because chance, bias, and confounding could not be ruled out with confidence.

Risk of Acute Myelogenous Leukemia Among the Children of Vietnam Veterans

Presently available data allow for the possibility of an increased risk of AML in the children of Vietnam veterans. Studies of both U.S. and Australian veterans reported a slightly elevated incidence of the disease in offspring.[2] However, for the reasons detailed in this report, the committee believes that these studies and the other available information constitute inadequate/insufficient evidence to determine whether an association does or does not exist. As a consequence, there is also inadequate/insufficient information to assess the risk to veterans' children.

Biologic Plausibility

Studies reviewed in earlier *Veterans and Agent Orange* series reports suggest that the reproductive systems of adult male laboratory animals are relatively insensitive to TCDD. Effects on testes and accessory organ weights, testicular morphology, spermatogenesis, and fertility were observed in many species, including rats, mice, guinea pigs, marmosets, monkeys, and chickens, but generally occurred only at doses that caused overt toxicity. Animal studies reviewed in *Update 1998* did not observe paternally mediated developmental effects in the offspring of mice exposed to mixtures of the herbicides used in Vietnam, except at levels that also caused paternal toxicity. The committee is not aware of any information published since the release of *Update 2000* that bears on the issue of the biologic plausibility of an association between paternal exposure to the herbicides used in Vietnam (or dioxin) and AML in offspring.

[2]The report *Veterans and Agent Orange: Update 2000* indicated that there was insufficient or inadequate evidence to determine whether an association exists between exposure to the herbicides used in Vietnam and leukemia in adults. AML was not addressed as a separate disease outcome in this report, due to the lack of data on this outcome in exposed adults.

Given the present lack of information, the committee believes that further research aimed at evaluating long-term effects of herbicide exposures on male reproductive organs and on understanding the effects on sex ratio and functional developmental toxicities would be useful.

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, subsequently codified as 38 USC Sec. 1116. 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 referred to as *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* (hereafter, *Update 1996*) (IOM, 1996), *Veterans and Agent Orange: Update 1998* (hereafter, *Update 1998*) (IOM, 1999), *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (IOM, 2000), and *Veterans and Agent Orange: Update 2000* (hereafter, *Update 2000*) (IOM, 2001).

The committee responsible for *Update 2000* concluded that there was limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam and acute myelogenous leukemia (AML) in the children of veterans. This was a change in classification from previous *Veterans and Agent Orange* reports, which found inadequate/insufficient evidence to determine whether an association existed for AML and other cancers in the children of veterans. The finding was based in part on a 2000 study of the children of Australian Vietnam veterans by the Australian Institute of Health and Welfare (AIHW).

In May 2001, AIHW announced it had found an error in the way that it calculated the expected incidence of AML that led them to incorrectly conclude that the children of Australian veterans were at a significantly increased risk for the disease. In response to the announcement, the Department of Veterans Affairs

(DVA) requested that IOM convene a committee to revisit the issue of AML in the children of veterans and evaluate updated information from AIHW, other newly available or identified scientific studies, and information developed in previous reviews by IOM committees.

While limited to one health outcome, this report adheres to the format of other *Veterans and Agent Orange* reports. 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, Update 1998, Update 2000,* and information published or identified through October 18, 2001, when the committee completed its deliberations. This report is intended to supplement rather than replace the previous updates; therefore, not all of the information on studies reviewed in those reports has been repeated.

This 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, Update 1998,* and *Update 2000* and a more thorough discussion of the new information 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, Update 1998,* and *Update 2000,* as well as newly available or identified information, 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 acute myelogenous leukemia in the children of veterans, 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 that they do not show 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 acute myelogenous leukemia in the children of those who

served. 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 the disease associated with exposure 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 situation in which the disease is observed *more* frequently among persons who are exposed than among those who are not exposed—whereas values between 0 and 1 may indicate a negative or inverse association—that is, a situation in which the disease is observed *less* frequently among persons who are exposed than among those who are not exposed. 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 assessed them in the context of the strengths and weaknesses of the study that produced them, evaluating 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 might never be attained. As in science generally, studies of health outcomes following herbicide exposure are not capable of demonstrating that the purported association 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 an association between a health outcome and 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 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 8 of *Update 2000* 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 in biomedical research that studies with a statistically significant finding are more likely to be published than studies with nonsignificant results (see, for example, Song et al., 2000). 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, journal referees, and editors. 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 chemical type, amount, 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 Request 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.

Childhood Acute Myelogenous Leukemia

The American Cancer Society (ACS) estimates that approximately 8,600 children under the age of 15 will be diagnosed with cancers in the United States in 2001. Leukemias, which are cancers of the white blood cells, are the most common of these cancers. They account for about one-third of all childhood cases, with nearly 2,700 children projected to be diagnosed in 2001 (ACS, 2001). Of these, about 2,000 cases will be acute lymphocytic leukemia (ALL) and most of the rest will be acute myelogenous leukemia. Chronic leukemias are very rarely seen in children.

Acute myelogenous leukemia (AML)[3] is a cancer of the bone marrow cells that form two types of white blood cells called granulocytes and monocytes. There are several different forms of AML that are primarily distinguished by how the affected cells appear under the microscope. According to a recent review paper (Langmuir et al., 2001) AML is the seventh most common malignancy among children. The highest rates of incidence are found in those 2 years of age (12 cases per one million), but this rate decreases to 3.8 cases per one million by the age of 9. After this age the incidence rises again to 9 cases per one million at

[3]*Acute myelogenous leukemia* (ICD·9 205) is referred to by other names as well, including acute myeloid leukemia and acute nonlymphocytic leukemia. For consistency, this report uses "acute myelogenous leukemia," or the abbreviation AML, no matter how the disease or its subtypes are referred to in the work being reviewed.

the age of 16. Leukemias in younger children are believed to have a different etiology from those of older children because the genetic abnormalities underlying them are more likely to have been present at birth. Incidence rates through age 19 are similar in males and females, and in whites and African Americans (NCI, 2002).

Research has identified parental exposure to pesticides (Buckley et al., 1989), in utero exposure to ethanol (Severson et al., 1993) and dietary topoisomerase II inhibitors (Ross et al., 1996), and parental use of marijuana during pregnancy (Robison et al., 1989) as potential environmental risk factors for childhood AML. However these findings require replication in other populations. Many other studies of environmental risk factors have examined childhood leukemia as one entity, failing to separate out the histologic subtypes. Chemotherapy may also be responsible for secondary AML.

As in adults, the genetic disorders Down syndrome, Fanconi anemia, and Bloom syndrome are considered risk factors for the development of AML in children. Other illnesses associated with increased incidence include neurofibromatosis Type I, Kostmann's disease, Blackfin-Diamond anemia, paroxysmal nocturnal hemoglobinuria, Shwachman-Diamond syndrome, and thrombocytopenia-absent radii syndrome (Langmuir et al., 2001).

Chapter 7 of *Update 2000* contains additional information on leukemia as part of the discussion of adult cancer outcomes. Chapter 8 of that report covers childhood cancers in general as part of a review of the scientific literature regarding herbicide and dioxin exposure and reproductive effects.

SUMMARIES OF EPIDEMIOLOGIC EVIDENCE

In seeking evidence for associations between health outcomes and exposure to herbicides and dioxin, many different kinds of epidemiologic studies must be considered. Each study has various strengths and weaknesses and contributes evidence regarding 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.

Epidemiologic studies and reports evaluated by the committee are summarized below. Each subsection begins with a recapitulation of relevant reviews originally presented in *Update 2000*. Information reviewed by the committee since the release of the *Update 2000* report is then summarized under the heading *New Studies*. Table 1 lists the estimated risk, confidence interval, and number of observed cases for each of the epidemiologic studies considered by the committee, where these data are available.

Occupational Studies

In a case-control study, Buckley and colleagues examined possible relationships between parental occupational exposures and acute myelogenous leukemia[4] incidence in workers' children in a case-control study (1989). This study was assembled by the Children's Cancer Study Group and included cases diagnosed in North America from 1980 to 1984. Initial analyses focused on self-reported job titles, which were used as a proxy for exposures based on a previously developed job-exposure matrix (Hoar et al., 1980). One hundred seventy-eight case-control pairs provided information regarding paternal occupational pesticide exposures, including weed killers. Using the job-title linkage, pesticide exposures were associated with a 2.3-fold increased risk. Using self-reported information on workplace exposure to specific types of products and on duration of exposure, a 2.7-fold (1.0–7.0) increased risk of fathering a child who developed AML was found for men exposed more than 1,000 days. Results were comparable when interviews conducted with surrogates for the fathers were excluded from the analysis. An elevated risk was seen for exposure before, during, and after the pregnancy, but since these were highly correlated, it was not possible to determine if preconception exposure alone would lead to increased risk of a child developing AML. This is an important consideration because the wartime exposure of male veterans to herbicides would have occurred prior to conception. For female veterans, it could have occurred during early pregnancy.

A second study addressed childhood cancers in children born to male sawmill workers in British Columbia, Canada (Heacock et al., 2000). The primary exposures in these plants were to chlorophenate fungicides, which are contaminated with PCDDs and PCDFs formed during the production of these chemicals. Employees who worked at least 1 year at any of 11 such lumber mills in 1950–1985 formed the cohort of 23,829. Estimates of exposure were made from job title in each mill using information from mill records as well as interviews with persons knowledgeable about technology and formulation changes; a validation study that compared urinary chlorophenates with job-based estimates yielded a correlation of 0.49. The cohort was linked to birth files and also to marriage files that were linked to birth files (since the mother's name is on all birth certificates, whereas the father's name is not always), in order to identify the cohort of workers' children. The children's cohort was then linked to the British Columbia Cancer Registry to determine cancer diagnoses by age 20. Cancer cases in children born to sawmill plant workers from 1952 through 1988 and diagnosed in 1969–1993 were included. There were a total of 40 such cases, of which 22 were female and 18 male.

The initial analysis proceeded by calculation of a standardized incidence ratio (SIR), in which the cancer experience of these children was compared to

[4]Referred to as "acute nonlymphocytic leukemia" in the paper.

that of the general population of the province of British Columbia, adjusted for age and sex of the children and calendar year. Results showed no elevation of risk for all cancers (SIR = 1.0, 0.7–1.4) or for leukemia (SIR = 1.0, 0.5–1.8). An internal comparison was conducted using a nested case-control design. For each case, five controls were selected from within the cohort matched on sex and year of birth. These results compared risks for differing cumulative exposure groups within four time windows: (1) more than 90 days prior to conception; (2) from 90 days before conception to conception; (3) from conception to birth; and (4) after birth. The risk for all cancers combined was greater in the high-exposure groups than in the low-exposure groups for all windows except the first (more than 90 days before conception); however, all confidence intervals included values consistent with no effect or even a lowered risk in those with high exposures. The risk for leukemia was not elevated; no specific information on AML risk was provided. The main limitations of the study were the small number of cases and the lack of quantitative data on chlorophenate or TCDD exposure.

Environmental Studies

A large population-based case-control interview study of several childhood cancers was conducted in Germany by Meinert et al. (2000). Information on exposures was gathered from interviews of parents and questionnaire responses, based on the methodology used by the Children's Cancer Group. The children were diagnosed at less than 15 years of age, and there were 1,184 cases of leukemia. Parental occupational exposures to herbicides, insecticides, or fungicides were found to be related to childhood cancers regardless of the time period of exposure and the type of cancer (lymphoma or leukemia). Of particular note is the finding that there was a statistically significant association between paternal exposure in the year before pregnancy and leukemias (odds ratio [OR] = 1.5, 1.1–2.2, based on 62 cases). Statistically significant associations were also found between leukemias and paternal exposure during pregnancy (1.6, 1.1–2.3) and "ever" (1.6, 1.1–2.3). However the strongest associations were in relation to maternal exposures during pregnancy (e.g., leukemia OR = 3.6, 1.5–8.8). No analyses of the separate types of leukemia were reported.

The data provide some evidence of an increased leukemia risk for children exposed in utero to herbicides, insecticides, or fungicides, and also for children whose fathers were exposed prior to their conception. While this study may have been the largest ever to examine this hypothesis, the possibility of recall bias could not be ruled out, and there was some evidence suggesting that parents of cases consistently reported more occupational exposures than parents of controls. Neither study reported the effect of paternal preconception exposures independent of maternal exposures (or vice versa). The relevance of this study to exposures to the herbicides used in Vietnam and their contaminants is uncertain because the data did not permit analysis by specific chemicals.

New Studies

At the October 2001 workshop held by the committee (described in Appendix A), one of the authors of the Meinert et al. (2000) paper—Dr. Joachim Schüz—presented additional information on leukemia outcomes in the study cohort. This included the inclusion of additional observations and details on AML incidence. The committee took into consideration the fact that the data presented have not been subject to peer review.

All of the cases in the expanded cohort were identified by the German Childhood Cancer Registry, which is believed to be greater than 95% complete. They were matched 1:1 with controls on gender, date of birth (within one year) and community of residence. The analyses included adjustment for socioeconomic status and whether the community of residence was rural, urban, or mixed. A self-administered questionnaire with telephone follow-up was used to obtain information on parental occupational history, chemical exposures, and the timing of exposure (prior to conception, during gestation, or after birth).

A total of 167 AML cases were available for analysis. Among the subset of cases where the father had a preconceptional occupational exposure to pesticides/herbicides, the adjusted OR for AML was 0.9 (0.3–2.4). Similar odds ratios were reported for paternal exposure during gestation (1.1, 0.4–3.1) and after birth (1.1, 0.4–3.1). The authors concluded that there was no evidence supporting an association between preconceptional exposure to pesticides/herbicides and AML in this cohort. They noted that the study had a low statistical power to detect such an association and that there were few data available on exposure to specific substances.

In a paper not previously reviewed in a *Veterans and Agent Orange* series report, Kristensen et al. (1996) analyzed cancer morbidity in children of agricultural workers in Norway. The cohort consisted of 323,359 offspring born between 1952 and 1991. Cancer diagnoses and outcome classifications were obtained from the Cancer Registry of Norway. Data from the Statistics Norway agricultural census closest to the year of birth were used to model parental exposure. Variables included type of agricultural activity, money spent on pesticides (including herbicides), and presence of spraying equipment. Reference rates were estimated using rural, non-farm Norwegian populations that were age- and gender-matched in 5-year strata.

A total of 1,275 cases of cancer were identified. Of these, 36 were AML, 92 were ALL, and 35 were acute leukemias not classified by type. Overall, the rate of leukemia in the children of farmers was indistinguishable from the reference population (SIR = 1.0, 0.8–1.2;[5] based on 113 cases). When the analysis was limited to the children of farming parents who had purchased pesticides, the rate ratio for AML, adjusted for year of birth and calendar year, was non-significantly

[5]These values are reported as SIR = 101; 95% CI 83–122 in the paper.

elevated: 1.4 (0.6–2.9). The adjusted relative risks (RRs) for ALL and other acute leukemias were close to unity. Restricting the calculations to cases in which the child most likely spent the first few years of life on a farm did not affect the results. The researchers concluded that the data did not support an association between exposure to pesticides and AML.

This study's primary strengths are the completeness of the birth data and its linkage to census and cancer registry databases. Several weaknesses, however, limit its informativeness: the crudeness of the pesticide exposure proxies, the lack of adjustment for confounders other than farm-related exposures, and the small number of AML cases, which resulted in low statistical power and low precision for the effect estimate.

Vietnam Veteran Studies

In a large case-control study, Wen et al. (2000) examined service in Vietnam or Cambodia as a risk factor for childhood leukemia. The study included 1,805 cases of ALL and 528 cases of AML, including cases diagnosed through 17 years of age. It combined data from three studies conducted by the Children's Cancer Group, which represents a consortium of hospitals and medical centers in the United States and Canada that pool their cases to enable large studies of childhood cancers and thereby achieve sufficient statistical power. The cases were matched to controls on year of birth, location of residence, sex, and race. Controls were found through random-digit dialing, and cases were restricted to those with a telephone in the home. The overall response rates were 89 percent for cases and 77 percent for controls, and they were slightly lower for paternal interviews (83 percent for cases, 70 percent for controls). Analyses were conducted using conditional logistic regression for all leukemias combined, for ALL and AML separately, and stratified by age at diagnosis. Regression models were adjusted for potential confounders, including education, race, family income, smoking, exposure to X-rays, and paternal marijuana use.

The results indicated no increased risk of either leukemia subtype associated with military service in general. However, for service in Vietnam or Cambodia, the risk of AML (OR = 1.7, 1.0–2.9), but not ALL (1.0, 0.8–1.4), was increased. Analyses examining tours in Vietnam and Cambodia were hampered by the small number of observations: the higher calculated risk was for offspring whose father served two or more tours there (OR = 5.0, 1.0–24.5; based on 8 cases). However, length of service produced a different pattern. For those serving one year or less in these countries, the OR was 2.4 (1.1–5.4; 21 cases), whereas the OR for those present more than one year was 1.5 (0.7–3.2; 16 cases). When stratified by years between service and conception of the child, the association was strongest in those who had served more than 15 years earlier; however, the numbers in this stratum were small. Self-reported exposure to Agent Orange showed no association. The strongest association was for cases diagnosed under the age of 2 years

(OR = 4.6, 1.3–16.1). It is believed that childhood cancers at very young ages are more likely to be etiologically related to preconception or in utero exposures than those diagnosed at later ages.

Limitations of the study include possible residual confounding from not having detailed exposure data on smoking and marijuana use; the unexplained stronger association with increasing interval between service and conception; and lack of adjustment for factors associated with service in Vietnam or Cambodia, including postwar exposures. The authors point out that the inconsistency in results for number of tours of duty versus number of years in Vietnam or Cambodia could have been related to exposures being correlated with movement in and out of these areas, rather than with duration, or to other exposures in Southeast Asian countries. Longer duration in Vietnam or Cambodia does not necessarily mean higher exposure to herbicides, since no information is available on the nature of these veterans' activities during their service.

In another study, close to 50,000 Australian Vietnam veterans were surveyed about their and their children's health; an 80 percent response rate was achieved (Commonwealth Department of Veterans' Affairs [CDVA], 1998). A follow-up validation study of selected conditions included children's cancers (AIHW, 1999); a later supplement (AIHW, 2000) had, as one of its aims, the collection and analysis of data on specific subtypes of leukemia among children of veterans. Validation sources included pathology reports, doctor certifications, or records from a disease or death registry. Australia has had a cancer registry since 1982. Nine AML cases in the children of veterans were confirmed through clinical records. The investigators used various assumptions to adjust for nonrespondents in the validation study and for circumstances in which it was not possible to validate a reported case (e.g., physician could not be located, medical records were incomplete, etc.). Depending on the specific assumptions, up to nine additional cases of AML were estimated for the full cohort (for a projected total of from 9 to 18 cases). The assumptions adopted by the study's authors estimated 4 additional cases, for a total of 13 validated cases.

The original (AIHW, 2000) report indicated that 3 *(range 0–6) cases of AML were expected in the cohort based on incident rates in the community. Given this estimate, the authors reported a statistically significant 4.3-fold increased risk of AML. All of the alternative analyses, including those with the most restrictive assumptions (i.e., assuming zero cases among nonrespondents and no valid AML diagnoses among reported cases for which validation was not possible), also yielded large, precise, and hence statistically significant excesses of AML.*

These analyses did not adjust for any sociodemographic or life-style factors associated with increased risk of AML, although adjustment for age and gender was achieved through the methods used to derive expected numbers of cases in Australia's community standard. No excess risk was observed for the other forms of childhood leukemia: ALL, chronic lymphocytic leukemia (CLL), or chronic myelogenous leukemia (CML).

New Studies

Subsequent to the release of the *Update 2000* report, AIHW announced that it had discovered an error in its derivation of the Australian community standard for AML in veterans' children. This affected the estimate of the expected number of cases and the associated confidence interval. Based on community rates, the previously reported expected number of cases (3 with a 95% confidence interval of 0–6) was corrected to 9 (95% CI 3–15 cases). The number of cases of AML among the offspring of Australian veterans who served in Vietnam and whose diagnoses were validated in the study was unchanged (n = 9). The predicted numbers of cases under various assumptions regarding non-respondents and cases not able to be validated changed slightly, yielding a total of 12 cases in veterans' children under the assumptions adopted by the authors. Two leukemia cases were also reclassified after further investigation: one case of CLL in veterans' children was reclassified to AML and one case of AML was reclassified to ALL. These changes had a small effect on the predicted number of cases.

A revised report correcting this error was published in October 2001 (AIHW, 2001). Under the assumptions favored by the study's authors[6] regarding cases they could not validate, the predicted number of cases (12) remained higher than the new expected number of cases (9) but the difference was not statistically significant (RR = 1.3; range = 0.8–4.0).

SYNTHESIS

In *Update 2000*, three studies were found to provide evidence regarding an association between exposure to the herbicides used in Vietnam and acute myelogenous leukemia in the children of veterans. The first was a case-control study of AML and parental occupational exposures conducted by the Children's Cancer Study Group (Buckley et al., 1989). Use of pesticides by either the mother or father, as reported in detailed interviews, was associated with an elevated risk. However, because of a high correlation among exposures in the three time periods studied (before, during, and after pregnancy), it was not possible to determine whether exposure uniquely prior to the pregnancy was associated with increased risk of AML in the children. The strongest associations were for children diagnosed before 5 years of age and for children with M4/M5[7] morphology.

In a second case-control study of AML conducted by the Children's Cancer

[6]One alternative calculation for the number of exposed cases—which factored the number of positively validated responses and prorated estimates of the number of cases that would have been found had all survey information been validated and complete information been available for all non-respondents—did yield a statistically significant excess of cases (18).

[7]M4/M5 are subtypes for a morphologic-histochemical classification system for AML developed by the French-American-British (FAB) Cooperative Group. M4 subtype is acute myelomonocytic leukemia (AMML) and M5 subtype is acute monocytic leukemia (AmoL).

TABLE 1 Selected Epidemiologic Studies—Childhood Leukemias

Reference	Study Population	Exposed Cases	RR, OR, or SIR (95% CI)
OCCUPATIONAL STUDIES			
Studies Reviewed in *Update 2000*			
Heacock et al., 2000	Cohort of sawmill workers' offspring; exposure via fungicides contaminated with PCDDs and PCDFs		
	Leukemia, children of all workers	11	SIR = 1.0 (0.5–1.8)
	Leukemia, children of workers with high chlorophenate exposure	5	OR = 0.8 (0.2–3.6)
Buckley et al., 1989	Children's Cancer Study Group—case-control study of children of parents exposed to pesticides or weed killers		
	AML in children with any paternal exposure	27	OR = 2.3 (p = .05)
	AML in children with paternal exposure >1,000 days	17	OR = 2.7 (1.0–7.0)
	AML in children with maternal exposure >1,000 days	7	OR undefined (no exposed controls)
ENVIRONMENTAL STUDIES			
New Studies			
Kristensen et al., 1996*	Children of agricultural workers in Norway		
	Children with AML whose parents purchased pesticides	12	1.4 adjusted (0.6–2.9)
Studies Reviewed in *Update 2000*			
Meinert et al., 2000	Population-based case-control study of childhood cancer		
	Leukemias, paternal exposure, year before pregnancy	62	1.5 (1.1–2.2)
	Leukemias, paternal exposure, during pregnancy	57	1.6 (1.1–2.3)
	Leukemias, maternal exposure, year before pregnancy	19	2.1 (1.1–4.2)
	Leukemias, maternal exposure, during pregnancy	15	3.6 (1.5–8.8)
Studies Reviewed in *Update 1996*			
Pesatori et al., 1993	Seveso residents aged 0–19 years—10-year follow-up, morbidity		
	All cancers	17	1.2 (0.7–2.1)
	Lymphatic leukemia	2	1.3 (0.3–6.2)
	Myeloid leukemia	3	2.7 (0.7–11.4)

TABLE 1 Continued

Reference	Study Population	Exposed Cases	RR, OR, or SIR (95% CI)
Bertazzi et al., 1992	Seveso residents aged 0–19 years—10-year follow-up, mortality—		
	All cancers	10	7.9 (3.8–13.6)
	Leukemias	5	3.9 (1.2–1.8)
	Lymphatic leukemia	2	1.6 (0.1–4.5)
	Myeloid leukemia	1	0.8 (0.0–3.1)
	Leukemia, others	2	1.6 (0.1–4.6)
VIETNAM VETERANS			
New Studies			
AIHW, 2001	Australian Vietnam veterans' children—**Revised** Validation Study		
	AML	12 estimated (9 observed; 3 additional)	1.3 (Range 0.8–4.0)
Studies Reviewed in *Update 2000*			
AIHW, 2000	*Australian Vietnam veterans' children—Validation Study*		
	AML	*This study, which incorrectly calculated the expected number of cases, is superceded by AIHW, 2001, above. See text for details.*	
Wen et al., 2000	Case-control study of children's leukemia (AML and ALL)		
	Father ever served in Vietnam or Cambodia	117	1.2 (0.9–1.6)
	<1 year in Vietnam or Cambodia	61	1.4 (0.9–2.0)
	>1 year in Vietnam or Cambodia	49	1.2 (0.8–1.7)
	AML only		
	Father ever served in Vietnam or Cambodia	40	1.7 (1.0–2.9)
	<1 year in Vietnam or Cambodia	13	2.4 (1.1–5.4)
	>1 year in Vietnam or Cambodia	16	1.5 (0.7–3.2)
Studies Reviewed in *VAO*			
CDC, 1989	Vietnam Experience Study		
	Cancer in children of veterans	25	1.5 (0.7–2.8)
	Leukemia in children of veterans	12	1.6 (0.6–4.0)
Field and Kerr, 1988	Cancer in children of Australian Vietnam veterans	4	—
Erikson et al., 1984	CDC Birth Defects Study		
	"Other" neoplasms — children of Vietnam veterans	87	1.8 (1.0–3.3)

*This study had not been reviewed in previous *Veterans and Agent Orange* series reports.

Group (Wen et al., 2000), self-reported service in Vietnam or Cambodia was associated with an elevated risk of AML (OR = 1.7, 1.0–2.9), after adjusting for potential confounders including education, race, income, smoking, X-ray exposure, and paternal marijuana use. Since service in Vietnam or Cambodia would be an extremely memorable event, under-reporting by controls or over-reporting by cases seems unlikely. Also arguing against recall bias was the lack of association with ALL in this study, as well as the lack of association of AML with general paternal military service. When stratified by time spent in Vietnam or Cambodia, those with one year or less of service there showed a stronger risk than those with more than one year; additionally, self-reported exposure to Agent Orange was not associated with AML. However, these results are not particularly convincing evidence against a causal association since neither length of service in Vietnam or Cambodia nor self-reported exposure are known to be strongly related to the actual level of herbicide exposure. Two or more tours of duty in Vietnam showed a stronger association than a single tour, although the number of cases and controls were small. This study showed the strongest association to be with childhood AML diagnosed before the age of two years (OR = 4.6, 1.3–16.1). One concern was the apparent lack of adjustment for maternal marijuana use, which has been shown to be related to AML (Robison et al., 1989). Additionally, the authors point out that an unexplained increase in risk with longer time since service in Vietnam or Cambodia might have been due to randomness in the data, but could also have been due to an unmeasured post-war exposure that was different from those who did not serve in the military, or who served elsewhere.

A third study was that of the Australian Vietnam veterans. Investigators surveyed veterans regarding their medical conditions and the health of their children (AIHW, 1998), with a follow-up validation of the self-reported conditions and a calculation of the expected number of cases based on Australian community standards (AIHW, 1999; AIHW, 2000). The results were adjusted for age and gender, but not for other potential confounding factors. Among respondents, 9 cases of AML were successfully validated. The expected number of cases had been originally reported in error as 3, with a range of 0–6. The corrected calculations indicate 9 expected cases, with a range of 3–15 (AIHW, 2001). Taking into account possible additional cases among non-respondents and cases that might have been validated had the information been obtainable, the authors estimated that there were 13 cases of AML among the children of the surveyed veterans, representing a 1.4-fold increased risk. Therefore, though elevated, the number of cases fell within the range that might be expected in the community. Sensitivity analyses were conducted using a variety of strategies for assignment of non-respondent cases. This finding was not outside the range of values consistent with random fluctuations.

There are two other analyses not previously reviewed by the *Update 2000* or previous committees that are pertinent to the issue of childhood AML and paternal preconceptional exposure to herbicides used in Vietnam or their contaminants.

They are Kristensen and colleagues' 1996 paper on cancer morbidity in the children of agricultural workers in Norway, and an unpublished extension of the Meinert et al. (2000) case-control interview study of childhood cancers in Germany presented to the committee at an October 2001 IOM workshop by co-investigator Dr. Joachim Schüz. These provide little additional information, however, because of the relatively small numbers of exposed cases (12 and 6, respectively) and lack of data on exposures to specific substances. Previous analyses of the German study found an association (OR = 1.5, 1.1–2.2) between preconceptional paternal exposure and all childhood leukemia combined. No association (OR = 0.9, 0.3–2.4) was observed when the analysis was restricted to AML alone.

Two studies reviewed in *Update 1996* of cancers among subjects aged 0–19 living in the area surrounding Seveso, Italy—site of a 1976 industrial accident that released dioxin into the environment—were also examined (Bertazzi et al., 1992; Pesatori et al., 1993). However, since all 3 AML cases in this cohort were in individuals born prior to the accident, these data were not relevant to the issue of paternal exposures prior to conception. While other studies reviewed in earlier *Veterans and Agent Orange* series reports address leukemia incidence in the children of individuals exposed to herbicides or dioxin, none provide specific information concerning AML.

CONCLUSIONS

The committee assessed the association between paternal herbicide or dioxin exposure and acute myelogenous leukemia in offspring. The assessment included studies reviewed in previous *Veterans and Agent Orange* reports and newly identified or published reports.

Strength of Evidence in Epidemiologic Studies

Based on the scientific evidence reviewed above, the committee finds **there is inadequate or insufficient evidence to determine if an association exists between exposure to the herbicides used in Vietnam or their contaminants and acute myelogenous leukemia (AML) in the children of Vietnam veterans**. This is a change in classification from the recent *Veterans and Agent Orange: Update 2000* report, which found limited/suggestive evidence for such an association.

The *Update 2000* committee had based its findings in part on a study of AML incidence in the children of Australian veterans of Vietnam (AIHW, 2000) that was later found to have contained an error. The error led the study's authors to incorrectly conclude that these children faced a significantly greater risk of AML than the general population. A revised analysis found that while AML incidence was somewhat elevated in the cohort, it was within the range that might be expected in the community (AIHW, 2001).

In reaching this finding, the committee took into account the other studies that had figured prominently in the previous decision. These included a case-control study of AML conducted by the Children's Cancer Group (Wen et al., 2000) in which self-reported service in Vietnam or Cambodia was associated with an elevated risk after adjusting for numerous potentially confounding life-style and sociodemographic factors; it also considered a study that had played a lesser role in the previous committee decision that showed an association of childhood AML with paternal occupational exposure to herbicides/pesticides before, during, or after gestation (Buckley et al., 1989). The committee also considered newly identified information on a cohort from Norway (Kristensen et al., 1996), and an unpublished extension of a study of childhood cancers in Germany (Meinert et al., 2000), presented at an October 2001 IOM workshop by co-investigator Dr. Joachim Schüz.

Taken together, these studies constitute inadequate or insufficient evidence to determine whether an association exists between childhood AML and the herbicides used in Vietnam or their contaminants; that is, they are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association.

Risk of Acute Myelogenous Leukemia Among the Children of Vietnam Veterans

Presently available data allow for the possibility of an increased risk of AML in the children of Vietnam veterans. Studies of both U.S. (Wen et al., 2000) and Australian (AIHW, 2001) veterans reported a slightly elevated risk of the disease in offspring. However, for the reasons detailed in this report, the committee believes that these studies and the other available information constitute inadequate/insufficient evidence to determine whether an association does or does not exist. There is thus also inadequate/insufficient information to assess the risk to veterans' children.

Biologic Plausibility

Toxicologic studies reviewed in earlier *Veterans and Agent Orange* series reports suggest that the reproductive systems of adult male laboratory animals are relatively insensitive to TCDD because high doses are required to elicit effects. *VAO* reported that effects on testes and accessory organ weights, testicular morphology, spermatogenesis, and fertility had been observed in many species, including rats, mice, guinea pigs, marmosets, monkeys, and chickens, but generally occurred only at doses that caused overt toxicity.

Two animal studies reviewed in *Update 1998* investigated developmental effects following paternal exposure to the chemicals of interest. No paternally mediated effects were observed in the offspring of mice exposed to a mixture of

2,4-D, 2,4,5-T, and dioxin (Lamb et al., 1980). The offspring of mice exposed to a mixture of 2,4-D and picloram showed some effects, but only at doses that also caused paternal toxicity (Blakley et al., 1989).

The mechanism by which herbicide or TCDD exposures could lead to childhood cancers in the offspring of persons exposed many years previously is unknown. One possible mechanism would involve germ cell mutations whereby damaged cells might later undergo spermatogenesis and result in fertilization, leading to the birth of a genetically susceptible child. However, assays do not indicate that the herbicides of interest or TCDD are genotoxic except at very high doses or concentrations. The link between Down syndrome and AML appears to imply some genetic origin of susceptibility for at least a portion of AML cases. Leukemias in younger children, the period during which childhood AML cases are more common, are believed to have a different etiology from those of older children because the genetic abnormalities underlying them are more likely to have been present at birth.

The Committee is not aware of any information published since the release of *Update 2000* that bears on the issue of the biologic plausibility of any association between paternal exposure to the herbicides used in Vietnam or dioxin and AML in offspring. Given the present lack of information, the committee believes that further research aimed at evaluating long-term effects of herbicide exposures on male reproductive organs and on understanding the effects on sex ratio and functional developmental toxicities would be useful.

REFERENCES

ACS (American Cancer Society). 2001. Cancer Reference Information. All About Leukemia—Children's. http://www.cancer.org/eprise/main/docroot/CRI/CRI_2x?sitearea=CRI&dt=24 (accessed November 26, 2001).

AIHW (Australian Institute of Health and Welfare). 1998. Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community: Volume 1, Male Vietnam Veterans Survey and Community Comparisons Outcomes. Canberra: AIHW.

AIHW. 1999. Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community: Volume 3, Validation Study. Canberra: AIHW.

AIHW. 2000. Morbidity of Vietnam veterans. Adrenal gland cancer, leukaemia and non-Hodgkin's lymphoma: Supplementary report no. 2. (AIHW cat. no. PHE 28). Canberra: AIHW.

AIHW. 2001. Morbidity of Vietnam veterans. Adrenal gland cancer, leukaemia and non-Hodgkin's lymphoma: Supplementary report no. 2. Revised edition (AIHW cat. no. PHE 34). Canberra: AIHW.

Bertazzi PA, Zocchetti C, Pesatori AC, Guercilena S, Consonni D, Tironi A, Landi MT. 1992. Mortality of a young population after accidental exposure to 2,3,7,8-tetrachlorodibenzodioxin. International Journal of Epidemiology 21(1):118–123.

Blakley PM, Kim ES, Firneisz GD. 1989. Effects of paternal subacute exposure to Tordon 202c on fetal growth and development in CD-1 mice. Teratology 39(3):237–241.

Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P, Nesbit ME, Odom L, Peters JM, Woods WG, Hammond GD. 1989. Occupational exposures of parents of children with acute nonlymphocytic leukemia: A report from the Childrens' Cancer Study Group. Cancer Research 49:4030–4037.

CDC. 1989. Health Status of Vietnam Veterans. Vietnam Experience Study, Vol. V, Reproductive Outcomes and Child Health. Atlanta: U.S. Department of Health and Human Services.

CDVA (Commonwealth Department of Veterans' Affairs). 1998. Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community. Vol. 1: Male Vietnam Veterans Survey and Community Comparison Outcomes. Canberra: Department of Veterans' Affairs.

Erickson JD, Mulinare J, McClain PW, Fitch TG, James LM, McClearn AB, Adams MJ. 1984. Vietnam veterans' risks for fathering babies with birth defects. Journal of the American Medical Association 252(7):903–912.

Field B, Kerr C. 1988. Reproductive behaviour and consistent patterns of abnormality in offspring of Vietnam veterans. Journal of Medical Genetics 25:819–826.

Heacock H, Hertzman C, Demers PA, Gallagher R, Hogg RS, Teschke K, Hershler R, Bajdik CD, Dimich-Ward H, Marion SA, Ostry A, Kelly S. 2000. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. Environmental Health Perspectives 108:499–503.

Hill AB. 1971. Principles of Medical Statistics, 9th Ed. New York: Oxford University Press.

Hoar SK, Morrison AS, Cole P, Silverman DT. 1980. An occupation and exposure linkage system for the study of occupational carcinogenesis. Journal of Occupational Medicine 22:722–726.

IOM (Institute of Medicine). 1994. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam. Washington, DC: National Academy Press.

IOM. 1996. Veterans and Agent Orange: Update 1996. Washington, DC: National Academy Press.

IOM. 1997. Characterizing Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam: Scientific Considerations Regarding a Request for Proposals for Research. Washington, DC: National Academy Press.

IOM. 1999. Veterans and Agent Orange: Update 1998. Washington, DC: National Academy Press.

IOM. 2000. Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes. Washington, DC: National Academy Press.

IOM. 2001. Veterans and Agent Orange: Update 2000. Washington, DC: National Academy Press.

Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. 1996. Cancer in offspring of parents engaged in agricultural activities in Norway: Incidence and risk factors in the farm environment. International Journal of Cancer 65(1):39–50.

Lamb JC, Moore JA, Marks TA. 1980. Evaluation of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxicity in C57BL/6 mice. Reproduction and Fertility in Treated Male Mice and Evaluation of Congenital Malformations in Their Offspring. National Toxicology Program.

Langmuir PB, Aplenc R, Lange BJ. 2001. Acute myeloid leukaemia in children. Best Practice & Research Clinical Haematology 14(1):77–93.

Meinert R, Schüz J, Kaletsch U, Kaatsch P, Michaelis J. 2000. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: Results of a register-based case-control study in Germany. American Journal of Epidemiology 151(7):639–646.

NCI (National Cancer Institute). 2002. Surveillance, Epidemiology, and End Results (SEER) Program, Cancer Query System 2.0. http://www.seer.cancer.gov/ScientificSystems/Canques (accessed February 13).

Pesatori AC, Consonni D, Tironi A, Zocchetti C, Fini A, Bertazzi PA. 1993. Cancer in a young population in a dioxin-contaminated area. International Journal of Epidemiology 22(6):1010–1013.

Robison LL, Buckley JD, Daigle AE, Wells R, Benjamin D, Arthur DC, Hammond GD. 1989. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). Cancer. 63(10):1904–1911.

Ross JA, Potter JD, Reaman GH, Pendergrass TW, Robison LL. 1996. Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Children's Cancer Group. Cancer Causes Control 7(6):581–590.

Severson RK, Buckley JD, Woods WG, Benjamin D, Robison LL. 1993. Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia: an analysis within morphological subgroups—a report from the Childrens Cancer Group. Cancer Epidemiology, Biomarkers and Prevention 2(5):433–439.

Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. 2000. Publication and related biases. Health Technology Assessment 4(10):1–115.

Wen WQ, Shu XO, Steinbuch M, Severson RK, Reaman GH, Buckley JD, Robison LL. 2000. Paternal military service and risk for childhood leukemia in offspring. American Journal of Epidemiology 151(3):231–240.

Appendix A
Workshop on the Review of Health Effects in Vietnam Veterans of Exposure to Herbicides (Third Biennial Update)

AML Review Session

PUBLIC WORKSHOP

October 18, 2001
Members Room, National Academy of Sciences
Washington, D.C.

Workshop Presentations and Speakers

- **Morbidity of Vietnam Veterans. Acute Myeloid Leukaemia (AML) in Vietnam Veterans' Children in Australia**

Keith Horsley, M.D., Medical Services Adviser, Commonwealth Department of Veterans' Affairs, Australia

Paul Jelfs, Ph.D., Head, Population Health Unit, Australian Institute of Health and Welfare and Epidemiological consultant for the Department of Veterans' Affairs

- **Paternal Military Service and Risk of Childhood Acute Leukemia**

Xiao Ou Shu, M.D., Ph.D., Associate Professor of Medicine, Vanderbilt University School of Medicine, Center for Health Service Research, Nashville, Tennessee

- **Pesticides and Childhood Acute Leukemia: Results from a German Case-Control Study**

Joachim Schüz, Ph.D., Institute for Medical Biometrics, Epidemiology and Informatics, University of Mainz, Germany

Appendix B

Committee and Staff Biographies

COMMITTEE BIOGRAPHIES

IRVA HERTZ-PICCIOTTO, Ph.D. *(Chair)*, is professor in the Department of Epidemiology, School of Public Health, at the University of North Carolina, Chapel Hill; director of the Reproductive Epidemiology Program; and a fellow at the Carolina Population Center. She has published extensively on risk assessment, occupationally related cancer, environmental exposures, reproductive outcomes, and methods for epidemiologic data analysis. Dr. Hertz-Picciotto serves on several editorial boards and is currently president of the International Society for Environmental Epidemiology.

MARGIT L. BLEECKER, M.D., Ph.D., is director of the Center for Occupational and Environmental Neurology in Baltimore. Her research interests are in the areas of clinical industrial neurotoxicology and occupational neurology. Dr. Bleecker recently served on the Institute of Medicine (IOM) Committee on the Safety of Silicone Breast Implants, and has served on the IOM Committee on the Evaluation of the Department of Defense Comprehensive Clinical Evaluation Protocol and the IOM Committee on the Persian Gulf Syndrome Comprehensive Clinical Evaluation Program.

THOMAS A. GASIEWICZ, Ph.D., is professor of Environmental Medicine and deputy director of the Environmental Health Sciences Center in the Department of Environmental Medicine at the University of Rochester School of Medicine. He serves on the editorial board of *Biochemical Pharmacology* and is the

associate editor of *Toxicology and Applied Pharmacology*. He also is a peer reviewer for several scientific journals including *Biochemical Pharmacology, Cancer Research*, *Fundamental and Applied Toxicology*, *Journal of Biological Chemistry*, *Science*, and *Toxicology and Applied Pharmacology*. Dr. Gasiewicz has published extensively on the toxicokinetics of dioxin, dioxin toxicity, and the role of the aryl hydrocarbon receptor in the molecular mechanism of dioxin toxicity.

TEE L. GUIDOTTI, M.D., M.P.H., holds the position of department chair, Department of Environmental and Occupational Health in the School of Public Health and Health Services of The George Washington University. He is also director of the Division of Occupational Medicine in the Department of Medicine of George Washington University School of Medicine and Health Science and is cross-appointed as professor of pulmonary medicine. Prior to accepting this position, he served as professor of occupational and environmental medicine and director of the Occupational Health Program in the Department of Public Health Sciences at the University of Alberta Faculty of Medicine, Edmonton. Dr. Guidotti is certified as a specialist in internal medicine, lung diseases, and occupational medicine. His primary research interests are air quality, inhalation toxicology, and occupational and environmental lung diseases. Dr. Guidotti is past president of the Association of Occupational and Environmental Clinics, and sits on the Board of Directors of the American College of Occupational and Environmental Medicine and of the International Commission on Occupational Health.

ROBERT F. HERRICK, Sc.D., is senior lecturer on industrial hygiene at the Harvard School of Public Health, where he earned a doctor of science in industrial hygiene. Dr. Herrick 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. Dr. Herrick is past chair of the American Conference of Governmental and Industrial Hygienists, and past president of the International Occupational Hygiene Association. Prior to joining the faculty at Harvard, Dr. Herrick spent 17 years at the National Institute for Occupational Safety and Health where he conducted occupational health research.

DAVID G. HOEL, Ph.D., holds the position of distinguished university professor and associate director of the Hollings Oncology Center at the Medical University of South Carolina. Prior to that he held the posts of director of the Division of Biometry and Risk Assessment and acting director of the National Institute of Environmental Health Sciences. Dr. Hoel has been a member of numerous working groups of the International Agency for Cancer Research of the World Health Organization. He also serves as chair of the IOM Committee on the Assessment of Wartime Exposure to Herbicides.

LOREN D. KOLLER, D.V.M., Ph.D., served in academia for nearly 30 years, the last 16 as professor, College of Veterinary Medicine, Oregon State University, Corvallis. For 10 of those years he served as Dean of the College. He presently operates a business in environmental health and toxicology. Dr. Koller pioneered the discipline now known as immunotoxicology with a research focus also in the areas of toxicology, pathology, carcinogensis and risk assessment. He is on the IOM Committee on the Assessment of Wartime Exposure to Herbicides and served for six years as a member of the National Research Council, Committee on Toxicology.

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.

JOHN J. STEGEMAN, Ph.D., is senior scientist and chair of the Department of Biology at the Redfield Lab of the Woods Hole Oceanographic Institution, in Woods Hole, Massachusetts. He received his Ph.D. in biochemistry, concentrating on enzymology, from Northwestern University, Evanston, Illinois. His research interests center on metabolism of foreign chemicals in animals and humans, and the structure, function, and regulation of the enzymes that accomplish this metabolism.

DAVID S. STROGATZ, Ph.D., M.S.P.H., is associate professor and chair, Department of Epidemiology at the University at Albany, State University of New York, and adjunct professor, Department of Epidemiology, University of North Carolina, Chapel Hill. He received his M.S.P.H and Ph.D. in epidemiology from the University of North Carolina, Chapel Hill. Dr. Strogatz's research examines the epidemiology of diseases, including diabetes and cardiovascular disease, and the impact of socioeconomic status and race on health.

STAFF BIOGRAPHIES

ROSE MARIE MARTINEZ, Sc.D., is director of the 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, managed care, and the health care work force. 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.

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 Research Associate in the Department of Environmental Health at the Harvard School of Public Health. He previously served as study director for the *Veterans and Agent Orange: Update 1996*, *…Update 1998*, and *…Update 2000* reports as well as other environmental health and risk assessment projects for the National Academies.

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 been involved with the IOM committees that produced O*rgan Procurement and Transplantation, Clearing the Air: Asthma and Indoor Air Exposures, Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*, and *Veterans and Agent Orange: Update 2000.*

ANNA B. STATON is a research assistant in the Division of Health Promotion and Disease Prevention. Ms. Staton joined the IOM in December 1999 and has also worked with the committees that produced *No Time to Lose: Getting More from HIV Prevention* and *Veterans and Agent Orange: Update 2000*. Prior to joining the IOM, she worked at the Baltimore Women's Health Study. Ms. Staton graduated from the University of Maryland Baltimore County with a bachelor of arts degree in visual arts (major) and women's studies (minor). She is currently working toward a master of public administration at The George Washington University School of Business and Public Management.

ELIZABETH J. ALBRIGO is a project assistant in the Division of Health Promotion and Disease Prevention of the Institute of Medicine. She received her undergraduate degree in psychology from the Virginia Polytechnic Institute and State University. In addition to her work on this study she is currently involved with the following IOM committees: the Committee on the Review of the USDA *E. coli* O157:H7 Draft Farm-to-Table Process Risk Assessment, and the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam.