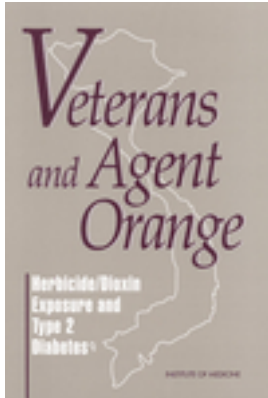


## Free Executive Summary



### **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

## 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<sup>1</sup> and exposure to dioxin<sup>2</sup> 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*:

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<sup>1</sup>Also referred to as Type II diabetes, diabetes mellitus, non-insulin-dependent diabetes mellitus, and adult-onset diabetes.

<sup>2</sup>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.<sup>3</sup>

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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<sup>3</sup>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-

# 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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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 Department of Veterans Affairs. The views presented in this report are those of the Institute of Medicine Committee to Review the Evidence Regarding the Link Between Exposure to Agent Orange and Diabetes and are not necessarily those of the funding agency.

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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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(IOM new snake -final black cop)  
Creator:  
Adobe Illustrator(TM) 7.0  
Preview:  
This EPS picture was not saved  
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## COMMITTEE TO REVIEW THE EVIDENCE REGARDING THE LINK BETWEEN EXPOSURE TO AGENT ORANGE AND DIABETES

- David Tollerud, MD, MPH** (*Chair*),<sup>1,2,3</sup> Professor of Public Health and Medicine and Director, Center for Environmental and Occupational Health, Drexel University School of Public Health
- Michael Aminoff, MD,**<sup>2,3</sup> Professor, Department of Neurology, University of California at San Francisco, School of Medicine
- Steven Goodman, MD, MHS, PhD,**<sup>3</sup> Associate Professor, Department of Oncology, Division of Biostatistics, Johns Hopkins University School of Medicine
- Robert Herrick, PhD, CIH,**<sup>3</sup> Lecturer on Industrial Hygiene, Department of Environmental Health, Harvard School of Public Health
- Irva Hertz-Picciotto, PhD,**<sup>3</sup> Associate Professor, Department of Epidemiology, University of North Carolina at Chapel Hill
- David Hoel, PhD,**<sup>3</sup> Distinguished University Professor, Medical University of South Carolina
- Andrew Olshan, PhD,**<sup>1,2,3</sup> Associate Professor, Department of Epidemiology, University of North Carolina at Chapel Hill
- Howard Ozer, MD, PhD,**<sup>3</sup> Eason Chair and Chief of the Hematology/Oncology Section, Director of the Cancer Center, and Professor of Medicine, University of Oklahoma
- Kenneth Ramos, PhD,**<sup>2,3</sup> Professor, Department of Physiology and Pharmacology, Texas A&M University College of Veterinary Medicine
- Noel Rose, MD, PhD,**<sup>2,3</sup> Professor, Department of Molecular Microbiology and Immunology, Johns Hopkins University School of Hygiene and Public Health
- Arthur Rubenstein, MBBCh,** Dean and Executive Vice President, Mount Sinai School of Medicine
- Michael Stern, MD,** Professor, Department of Medicine, and Chief, Division of Clinical Epidemiology, University of Texas Health Science Center at San Antonio
- Susan Woskie, PhD, CIH,**<sup>3</sup> Associate Professor, Department of Work Environment, University of Massachusetts at Lowell

### *Staff*

- David A. Butler,** Study Director
- James Bowers,** Research Assistant
- Jennifer A. Cohen,** Research Assistant
- Rose Marie Martinez,** Director, Division of Health Promotion and Disease Prevention

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<sup>1</sup>Member of the committee responsible for *Veterans and Agent Orange* (1994).

<sup>2</sup>Member of the committee responsible for *Veterans and Agent Orange: Update 1996*.

<sup>3</sup>Member of the committee responsible for *Veterans and Agent Orange: Update 1998*.

**Kathleen Stratton**, Acting Director (1997–1999), Division of Health Promotion  
and Disease Prevention

**Donna D. Thompson** and **Rita Gaskins**, Division Assistants

**Melissa Goodwin**, Financial Associate

*Staff Consultants*

**Susan Thaul**, Senior Project Officer, Institute of Medicine

**Florence Poillon**, Contract Editor

## 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 Melissa 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*

# Contents

<b>EXECUTIVE SUMMARY</b> .....	1
<b>INTRODUCTION</b> .....	4
Background, 4	
Organization and Framework, 5	
Methodologic Considerations in Evaluating the Evidence, 6	
Publication Bias, 9	
Exposure Assessment, 9	
Issues Related to the Epidemiologic Study of Exposure to Herbicides and Type 2 Diabetes, 10	
<b>SUMMARIES OF EPIDEMIOLOGIC EVIDENCE</b> .....	11
Occupational Cohorts, 11	
Vietnam Veteran Cohorts, 22	
Environmental Cohorts, 33	
<b>SYNTHESIS</b> .....	35
<b>CONCLUSIONS</b> .....	36
Strength of Evidence in Epidemiologic Studies, 36	
Increased Risk of Diabetes Among Vietnam Veterans, 37	
Biologic Plausibility, 38	
<b>REFERENCES</b> .....	38

**APPENDIXES**

- A** Summary of Workshops on the Evidence Regarding a Link Between Exposure to Agent Orange and Diabetes, 45
- B** Excerpts from the Discussion of Type 2 Diabetes in *Veterans and Agent Orange: Update 1998*, 47
- C** Committee and Staff Biographies, 61