Veterans and Agent Orange

Update 2006

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

Board on Population Health and Public Health Practices

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Goethe

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

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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:

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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 **Kristine M. Gebbie,** Columbia University School of Nursing, New York**.** Appointed by the Institute of Medicine, she 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.

Preface

In 1991, Congress passed Public Law 102-4, the Agent Orange Act of 1991, to address the uncertainty about the long-term health effects on Vietnam veterans who during their service in Vietnam were exposed to herbicides (mixtures of 2,4-dichlorophenoxyacetic acid [2,4-D], 2,4,5-trichlorophenoxyacetic acid [2,4,5-T], and its contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD], picloram, and cacodylic acid). That legislation directed the Secretary of Veterans Affairs to ask the National Academy of Sciences (NAS) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of those herbicides, including TCDD. The resulting committee report *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (*VAO*) was published by the NAS Institute of Medicine (IOM) in 1994. That report evaluated and integrated the scientific evidence regarding statistical associations between health outcomes and exposure to the herbicides and TCDD, based on published literature that had accumulated prior to 1994.

As required by Public Law 102-4, the Secretary also asked that NAS conduct updates at least every 2 years for 10 years from the date of the first report, to review newly available literature and draw conclusions from the overall evidence. The first of these updates, *Veterans and Agent Orange: Update 1996* (*Update 1996*) was published in March of that year. The second, *Veterans and Agent Orange: Update 1998* (*Update 1998*) was published in 1999. The third, *Veterans and Agent Orange: Update 2000* (*Update 2000*) was published in 2001. The fourth, *Veterans and Agent Orange: Update 2002* (*Update 2002*) was published in 2003, and the fifth, *Veterans and Agent Orange: Update 2004* (*Update 2004*) was published in 2005, concluding 10 years of updates.

PL 107-103, The Veterans Education and Benefits Expansion Act of 2001, extended the period for biennial updates until 2014. The present report is the first of this second 10-year period of evaluation.

The focus of this update is on the scientific studies published since the release of *Update 2004*. To accomplish the review, the IOM established a committee of 12 members representing a wide range of expertise to evaluate the newest scientific evidence and to consider this in light of the studies reviewed in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004*. Five of the members of the committee responsible for this report were recruited from the committee responsible for *Update 2004*, providing a link to the experience and expertise of the previous committees. All committee members were selected because they are experts in their fields, have no conflicts of interest with regard to the matter under study, and have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or TCDD exposure. Biographical sketches of committee members and staff appear in Appendix D.

Embarking on this second decade of evaluation, the committee approached a number of issues concerning the presentation of the information in the report, as well as seeking the most accurate information and advice from the widest possible range of knowledgeable sources for consideration. Consistent with NAS procedures, the committee met in a series of closed sessions in which members could freely examine, characterize, and weigh the strengths and limitations of the evidence. The committee also convened two open meetings in March and June, 2006, to provide the opportunity for veterans and veterans' service organizations, researchers, policymakers, and other interested parties to present their concerns, review their research, and exchange information directly with committee members. The oral presentations and written statements submitted to the committee are listed in Appendix A. The committee thanks the individuals who provided valuable insights into the health problems experienced by Vietnam veterans.

The committee is grateful to Mary Paxton, who skillfully served as study director for this project. The committee would also like to acknowledge the excellent work of IOM staff members Jennifer Cohen, Tia Carter, Sonia Cheruvillil, David Butler, and Rose Marie Martinez. Thanks are also extended to Christie Bell, who handled the finances for the project; Norman Grossblatt, who provided editorial skills; and William McLeod, who conducted database searches.

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. Dr. Maria Teresa Landi, an investigator at the National Cancer Institute, gave the committee a very informative presentation on her work on the Seveso Women's Health Study. Dr. Michael Alavanja, also of the National Cancer Institute, was very helpful in answering questions about the conduct of the Agricultural Health Study, as were Julienell Robinson and Billy Jackson of Brooks Air Force Base in addressing questions about the Air Force Health Study. Special thanks are extended to Dr. Han Kang, Director of the Department of Veterans Affairs' Environmental Epidemiology Service, for his prompt response in providing supplementary analyses on the data presented in his recent publication on Vietnam-era veterans who served in the Army Chemical Corps.

John Stegeman, Ph.D., *Chair*

Contents

Abbreviations and Acronyms

2,4-D	2,4-dichlorophenoxyacetic acid
2,4-DB	4-(2,4-dichlorophenoxy)butyric acid
2,4-DCP	2,4-dichlorophenol
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4,5-TCP	2,4,5-trichlorophenol
2,4,5-TP	2-(2,4,5-trichlorophenoxy) propionic acid or Silvex
4NQO	4-nitroquinolone 1-oxide
AFHS	Air Force Health Study on veterans who served in Vietnam in Operation Ranch (Ranch Hand subjects) who were compared to Vietnam-era Air Force veterans who were deployed to Southeast Asia (SEA comparisons)
AhR	aryl hydrocarbon receptor
AhRR	aryl hydrocarbon receptor repressor
ARNT	aryl hydrocarbon nuclear translocator
AHS	Agricultural Health Study of commercial and private herbicide applicators and the spouses of private applicators in Iowa and North Carolina
ALL	acute lymphocytic leukemia
AML	acute myelogenous leukemia
CADM	concentration- and age-dependent elimination model
CAS	Chemical Abstracts Service
CCR	California Cancer Registry
CDC	Centers for Disease Control and Prevention
CLL	chronic lymphocytic leukemia
CPUR	California Pesticide Use Reporting Database
DMA	dimethylarsinic acid (or cacodylic acid)
DoD	Department of Defense
EC_{50}	effective concentration for 50% of subjects treated
FSH	follicle-stimulating hormone
GCT	germ-cell tumor
GIS	geographic information system
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICD; ICD-#	International Classification of Diseases; specifies edition of ICD
IOM	Institute of Medicine
IUGR	intrauterine growth retardation
JEM	job–exposure matrix
LD_{50}	lethal dose to 50% of treated animals
LH	luteinizing hormone
M	molar
MCPA	2-methyl, 4-chlorophenoxyacetic acid
MCPP	2-(2-methyl-4-chlorophenoxy) propionic acid or Mecoprop™
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NAS	National Academy of Sciences
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
NOEL	no-observed-effect level

OHR	Operation Ranch Hand
OR	odds ratio
PBPK model	physiologically-based pharmacokinetic model
PCBs	polychlorinated biphenyls
PCDD/Fs	polychlorinated dibenzo-*p*-dioxins and dibenzofurans
PCT	porphyria cutanea tarda
PL	Public Law
ppb	parts per billion (10^9), equivalent to μg/kg or ng/g
ppm	parts per million (10^6), equivalent to mg/kg or μg/g
ppt	parts per trillion (10^{12}), equivalent to ng/kg or pg/g
PTD	preterm delivery
RA	rheumatoid arthritis
RBC	red blood cell
RR	relative risk
SEA	Southeast Asia
SEER	National Cancer Institute Surveillance Epidemiology and End Results
SIR	standardized incidence ratio
SMP	submitochondrial particle
SMR	standardized mortality ratio
SWHS	Seveso Women's Health Study
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCP	trichlorophenol (not specifically 2,4,5-TCP)
TEF	toxic equivalency factor, potency of a dioxin-like compound relative to TCDD
TEQ	total toxic equivalency, sum of TEQs for a mixture of PCDDs, PCDFs, and PCBs
TNFα	tumor necrosis factor-alpha
VA	Department of Veterans Affairs
VAO	*Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, (IOM,1994), first report in series
VAO	Veterans and Agent Orange, used to indicate this series of reports (*VAO* and updates) and the committees responsible for their preparation

Summary

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

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

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

This seventh *VAO* report is the first in a second decade of biennial updates, to continue through 2014, mandated by PL 107-103, the Veterans Education and Benefits Expansion Act of 2001. It presents the current committee's review of recent scientific publications concerning associations between health outcomes and exposure to TCDD and other chemicals in herbicides used in Vietnam and the committee's integration of this information with the previously established evidentiary database.

THE CHARGE TO THE COMMITTEE

In accordance with PL 102-4 and PL 107-103, the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Sixth Biennial Update) was asked to "determine (to the extent that available scientific data permit meaningful determinations)" the following regarding associations between specific health outcomes and exposure to TCDD and other chemicals in herbicides:

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

The committee notes that both its congressional mandate and its statement of task are phrased in such a way that the target of evaluation is "association," not "causality," between exposure and health outcomes. As used technically, the criteria for causation are somewhat more stringent than those for association. This target was not the choice of *VAO* committees but the consequence of congressional and judicial history. IOM has recently convened a separate committee to evaluate the methods of the Department of Veterans Affairs (VA) for determining whether medical conditions are service-related; that committee will address this and other issues.

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

In delivering the above charge to the current committee, VA specifically requested a focused review of the evidence related to whether the occurrence of acute myeloid leukemia, tonsil cancer, AL amyloidosis, and lupus may be associated with exposure to the components of herbicides used by the military in Vietnam and requested explicit indication of the appropriate category of association for all forms of cancer.

THE COMMITTEE'S APPROACH TO ITS CHARGE

Following the pattern established by prior *VAO* committees, the present committee concentrated its review on epidemiologic studies to fulfill its charge of assessing whether specific human health effects are associated with exposure to at least one of the herbicides sprayed in Vietnam or to TCDD. The committee also considered controlled laboratory investigations that

provide information on whether association of the compounds of interest to a given effect is biologically plausible.

The *VAO* committees began their evaluation presuming neither the presence nor the absence of association for any particular health outcome. Over the sequence of reviews, evidence of various degrees of association, lack of association, or persisting indeterminacy with respect to a wide array of disease states has accrued. For many conditions, however, particularly ones that are very uncommon, any association with the chemicals of interest has remained unaddressed in the medical research literature; for these, the committee remains neutral based on the understanding that "absence of evidence is not evidence of absence."

To obtain additional information potentially relevant to the evaluation of health effects related to herbicide exposure, in addition to that available in studies of Vietnam veterans, the committee reviewed studies of other groups potentially exposed to the constituents of the herbicide mixtures used in Vietnam (2,4-D, 2,4,5-T, TCDD, cacodylic acid, and picloram). In addition to retrieving articles identified on the basis of keywords specifying the compounds and chemical classes of interest, literature searches for the earliest reports in the *VAO* series had been structured to retrieve all studies on several occupational groups, including chemical, agricultural, pulp and paper, sawmill, and forestry workers. To the extent that studies on those workforces were recovered in new searches directed at particular agents of exposure, they were incorporated into the database. Some occupational and environmental cohorts that received exceptionally high exposures (such as the International Agency for Research on Cancer and Seveso cohorts discussed in this report) are now well characterized and producing a stream of informative results. A continuing prospective cohort study of agricultural populations with specific information on the chemicals of interest is also contributing a steady stream of the information in the database. Most importantly, the Vietnam veterans themselves are advancing in age and, when studied, capable of directly providing substantial information on chronic health conditions. As the information in the database on populations with established exposures to the chemicals of interest has grown, the committee has become less dependent on data from studies with nonspecific exposure information and has been able to focus more on findings from studies with refined exposure specificity.

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

The information that the present committee reviewed was identified through a comprehensive search of relevant databases, including databases covering biologic, medical, toxicologic, chemical, historical, and regulatory information. Literature identification continued through September 30, 2006. More than 5,000 potentially relevant studies were identified, about 1,200 were screened more closely, and about 350 ultimately contributed new information to this review. Additional information came from veterans and other interested persons who testified at public hearings and offered written submissions.

To determine whether there is an association between exposure and a health outcome, epidemiologists estimate the magnitude of an appropriate measure (such as the relative risk or the odds ratio) that describes the relationship between exposure and disease in a defined population or group. In evaluating the strength of the evidence linking herbicide exposure with a particular

outcome, the committee considered whether such estimates of risk might be incorrect (the result of confounding, chance, or bias related to errors in selection and measurement) or might accurately represent true associations. It has been the practice of all *VAO* committees to evaluate all studies according to the same criteria and then to weight findings of similar strength and validity equivalently, whether or not the study subjects are Vietnam veterans, when drawing conclusions. The committee recognizes that an absolute conclusion about the absence of association might never be attained, because, as is generally the case in science, studies of health outcomes after herbicide exposure cannot demonstrate that a purported effect is impossible, only that it is statistically improbable.

EVIDENCE REVIEWED BY THE COMMITTEE

The sections below summarize the new information that was evaluated in this update and integrated with that previously assembled. It is presented here for topics that correspond to chapters in the report.

Toxicology

Since *Update 2004*, several experimental studies have been published on the chemicals of interest. Some examine particular disease outcomes in animals after exposure to the compounds; others focus more on the mechanism or mode of action by which effects are elicited in cells, tissues, or whole animals. Despite extensive study, the exact mechanisms by which the compounds exert their effects are still unclear. Toxicologic information on disease outcomes in animals can, however, support an association seen in an epidemiologic study by providing evidence that an effect is biologically plausible.

Many health effects have been seen in animals after exposure to TCDD or to the herbicides used in Vietnam. Although animal experiments demonstrate that some of the compounds (alone or in conjunction with other treatments) can cause specific cancers, the compounds of interest generally have slight or no demonstrated ability to act by directly mutating DNA. TCDD is thought to be the most toxic of the compounds, and there continues to be a voluminous literature on the toxicology of this chemical. It has variable but typically long half-lives in animals and humans, and recent experimental research has shown a great deal about the cellular and molecular effects of TCDD that are associated with health outcomes in animal models. All the data are consistent with the hypothesis that those effects are mediated by the ability of TCDD to modulate cell-signaling pathways by binding a cellular protein, the aryl hydrocarbon receptor. However, the exact mechanisms by which those molecular events cause the various health outcomes seen in animals and in humans remain unknown.

Studies of effects of 2,4-D and 2,4,5-T published since *Update 2004* are consistent with the earlier conclusion that these chemicals are not acutely toxic and have only weak carcinogenic potential. Both chemicals have short half-lives in animals. There continue to be more studies on 2,4-D; studies in animals show effects on physiologic systems, but the effects typically occur only

at high doses. Like TCDD, 2,4-D has been shown to have effects on expression of many genes, but the mechanisms of toxic action are not understood.

Cacodylic acid is an organic arsenical that has variable biologic uptake into cells. Like the chlorophenoxy herbicides and TCDD, it has been implicated in oxidative stress in cells and animals. Studies of gene expression with newer approaches also are being applied to cacodylic acid. Forms of this chemical are being found to elicit changes in expression of many genes involved in cell signaling and stress response.

The literature on picloram toxicity is still sparse. Studies in humans and animals indicate that picloram is rapidly eliminated as parent compound. Studies in animals have indicated that it is sparingly toxic at very high doses. It is unlikely that human exposures to Agent White, which consisted of picloram and 2,4-D, were great enough to be comparable with exposures that animal data suggest are necessary to produce health effects.

Relevant effects observed in experimental animals treated with any of the chemicals of interest and their relevance to human health outcomes are discussed as part of the biologic-plausibility section for each outcome.

Exposure Assessment

Assessment of exposure to a toxic substance is an important element in determining whether specific health outcomes are linked to it. Under ideal circumstances, exposure assessment would measure the concentration of a substance at its site of action; that is rarely possible in human studies. Most exposure estimates, therefore, should be viewed as surrogates for actual internal doses.

Recent studies of Vietnam veterans, including those of the Air Force Health Study (Ranch Hand) and Army Chemical Corps cohorts, have used the measurement of serum TCDD as the best available estimator of historical exposures to Agent Orange. Serum concentrations of TCDD have also been used in studies of health effects in the Seveso population in Italy. Since *Update 2004*, the National Academies convened a committee to determine the future course of the Air Force Health Study. That committee has produced a report, *Disposition of the Air Force Health Study* (IOM 2006), in which it recommends that additional epidemiologic analyses be conducted on the vast amount of information accumulated on the study population, making full use of the high-quality exposure data developed.

A recent study comparing members of the US Army Chemical Corps (ACC) who did and did not served in Vietnam has provided important new information regarding exposure and health effects. The ACC performed chemical operations on the ground and by helicopter in Vietnam, so those who served there were potentially involved in the direct handling and distribution of herbicides. A health survey completed by almost 3,000 Vietnam-era ACC veterans was supplemented by assessment of exposure through analysis of TCDD concentrations in serum specimens from a subset of the study population. Veterans who reported spraying herbicides had significantly higher serum TCDD concentrations than did Vietnam veterans and other veterans who did not report herbicide spraying. The final analysis of the self-reported occurrence of health outcomes compared herbicide sprayers with non-sprayers among those ACC subjects who had served in Vietnam.

In 1997, IOM convened a committee on behalf of VA and requested research proposals designed to reconstruct herbicide and TCDD exposures of US veterans who served as ground troops in Vietnam. The request resulted in a project called Characterizing Exposure of Veterans to Agent Orange and Other Herbicides in Vietnam. The final report of the project included an "exposure-opportunity index" based on records of herbicide spraying and troop movements. IOM has convened a new committee to examine the feasibility of conducting epidemiologic studies of Vietnam veterans by incorporating the exposure-opportunity index.

Epidemiology

The health outcomes reviewed by the committee are categorized as cancer, reproductive and developmental effects, neurologic disorders, and other health effects. This section briefly summarizes the relevant epidemiologic studies published on those health outcomes since *Update 2004*. In the health-outcomes chapters, the new literature is evaluated and considered in the context of the previous reviews to derive comprehensive updated conclusions that integrate the entire body of information.

Cancer

Since *Update 2004*, several articles have reported results on multiple cancer types in occupational cohorts. An continuing prospective study on applicators of agricultural pesticides (including 2,4-D) in Iowa and North Carolina is generating a steady stream of papers on cancer incidence and mortality. A collaborative international study of pulp and paper workers reported findings on cancer mortality in relation to exposure to nonvolatile chlorinated hydrocarbons, which included dioxins and diverse other compounds. Studies of phenoxy herbicide producers and sprayers from New Zealand and of licensed Italian pesticide users presented supplementary information on a variety of cancer types.

For this update, a substantial amount of information on cohorts of Vietnam veterans became available. Mortality in the cohort of the Vietnam Experience Study was updated by the Centers for Disease Control and Prevention, but there were still too few cancer deaths to yield definitive results on individual cancer sites. Analytic approaches based on serum TCDD concentrations that had been applied to the Ranch Hand subjects were extended to cancer incidence in the comparison subjects, Vietnam-era veterans deployed elsewhere in Southeast Asia (SEA); the findings in the SEA group were consistent with results reported previously for respiratory and prostate cancers in the Ranch Hand subjects and appeared to fortify the evidence with respect to melanoma. A set of three reports on Australian Vietnam veterans provided findings on incidence and mortality related to a wide array of cancer types in comparison with those in the national population and addressed the possibility of a "healthy warrior" effect by comparing smaller samples of deployed and non-deployed drafted male Army subjects (National Service veterans) from the Vietnam era.

Many new case-control studies have investigated risk factors for various specific cancer types. The results of additional studies on non-Hodgkin's lymphoma and prostate cancer were consistent

with prior *VAO* findings of association with the components of the herbicides sprayed in Vietnam. The evidence in support of an association with breast cancer was strengthened by findings from case-control studies; others on brain, esophageal, and stomach cancers did not produce substantial evidence of a relationship.

Reproductive and Developmental Effects

Four new studies examined the association between exposures to the chemicals of interest and different aspects of menstrual function. In the Agricultural Health Study, no associations were found between menstrual cycles or the onset of menopause and herbicide exposure. In two reports of the Seveso cohort, no association was found between TCDD and age of menarche or of menopause. There have been only two new relevant reports on spontaneous abortion, stillbirths, neonatal or infant death, or birth weight or preterm status.

Given the age of the population of Vietnam veterans, it is unlikely that any sizable new studies of its reproductive function will be published. Controversy continues about whether there is an increased risk of birth defects and childhood cancers among the children, and now the grandchildren, of Vietnam veterans. The concern is fueled in part by persisting reports of congenital defects in the present Vietnamese population, whose mode of continuing exposure is quite different from that experienced by predominantly male US soldiers. The limited number of offspring among studied populations of US and allied Vietnam veterans has seriously constrained the ability to detect associations between herbicide exposures and specific birth defects, so meta-analyses of all the available data on such effects among the children of veterans would be valuable. A better understanding of the current Vietnamese experience, appropriately factored into the veterans' experience, would also be helpful.

Neurologic Disorders

Since *Update 2004*, one study of Vietnam veterans reported an association between deployment in Vietnam and both "mental disorders" and an increase in mortality from mental disorders. All the deaths, however, were due to conditions associated with alcohol or drug misuse. Therefore, the report did not inform the committee's conclusions regarding the possible association between neurobehavioral disorders and exposure to herbicides in Vietnam.

Also since *Update 2004*, several reports examined possible associations between herbicide-related exposures and movement disorders, including Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Several epidemiologic studies examined a variety of occupational exposures as potential risk factors for PD. The value of the data in those studies was lowered for the committee's purposes by persistent limitations in methodology and the lack of specificity for the compounds of interest.

ALS was first considered in *Update 2002*. Since *Update 2004*, a prospective cohort study identified an association between self-reported military service and mortality from ALS; risk estimates were similar for all branches of the military and for service in World War II, the Korean War, and the Vietnam War. The committee reviewed the findings carefully and determined that the conclusion is not directly relevant to its charge, because the evidence suggests an association

with military service itself rather than with exposure to the specific compounds of interest. Similarly, a study comparing Australian Vietnam veterans to non-deployed Vietnam-era veterans showed an association between deployment in Vietnam and ALS—a finding specific to Vietnam deployment rather than to military service itself or to the chemicals of interest in this review. A case-control study from Australia reported a possible association between ALS and exposures to various environmental toxicants, but the means of identifying subjects raised serious concerns about selection bias.

In *Update 2004*, peripheral neuropathies were distinguished as early-onset transient peripheral neuropathy and delayed or persistent peripheral neuropathy. Since *Update 2004*, there have not been any reports dealing with either early-onset or delayed peripheral neuropathy specifically as a diagnosis. A cohort report assessed neurologic symptoms, some of which could arise from peripheral neuropathy, but it is not clear how to interpret a study that reports on nonspecific clinical findings.

Other Health Effects

Several new studies have investigated the association of exposure to the chemicals of interest with other health effects, including chloracne, respiratory disorders, diabetes, gastrointestinal and digestive disease (including liver toxicity), circulatory diseases, endometriosis, and alterations in thyroid homeostasis. The previous conclusions related to chloracne, porphyria cutanea tarda (for which there was no new information), and type 2 diabetes have not changed. The new literature was deemed of sufficient quality and exposure specificity to revise the categorization of one circulatory disease, hypertension, and to raise the possibility of doing so for another, ischemic heart disease. In two new studies, Vietnam veterans with the highest exposure to herbicides exhibited distinct increases in the prevalence of hypertension; the prevalence of heart disease was also increased, with ischemic heart disease representing nearly 70% of cardiac conditions reported. Those studies have the strengths of controlling for the major circulatory-disease risk factors, confirming diagnoses by medical-record review, and relating the health outcome to the degree of herbicide or dioxin exposure. The results on circulatory-disease mortality were consistent with the findings from two additional new studies on Vietnam veterans and previous cohort studies, which all lacked the information on covariates needed for full control of known cardiovascular risk factors.

THE COMMITTEE'S CONCLUSIONS

Health Outcomes

The present committee weighed the strengths and limitations of the epidemiologic evidence reviewed in this report and in previous *Veterans and Agent Orange* reports. Although the studies published since *Update 2004* are the subject of detailed evaluation in this report, the committee drew its conclusions in the context of the entire body of literature. The contribution of recent publications to the evidentiary database was substantial, but the committee did not weigh them more heavily merely because they were new. Epidemiologic methods and analytic capabilities

have improved, but many of the recent studies were also particularly useful for this committee's purpose because they produced results in terms of serum TCDD concentrations or because their findings consisted of observations on the aging population of primary concern, Vietnam veterans.

The committee assigned each health outcome to one of four categories on the basis of the evidence. Table S-1 defines the categories and gives criteria for assigning a health outcome to each of them. On the basis of the committee's evaluation of occupational, environmental, and veterans studies, the table also lists the relative weight of evidence of associations between particular health outcomes and exposure to the herbicides that were used in Vietnam or to any of their components or contaminants (with no intention of specifying a particular chemical).

After careful consideration, the present committee changed the categorizations of several health outcomes in this report from what they had been in *Update 2004*. AL amyloidosis was deemed to satisfy the criteria for "limited or suggestive evidence of association," primarily on the basis of its close biologic relationship with multiple myeloma. One cardiovascular condition, hypertension, was also found to have "limited or suggestive evidence of an association," primarily on the basis of data gathered directly from Vietnam veterans.

This committee also moved several cancers (of the brain, stomach, colon, rectum, and pancreas) from the category of "limited or suggestive evidence of *no* association" back into the default category of "inadequate or insufficient evidence to determine association" because accumulating evidence is no longer as uniformly neutral as it had been when the original review was conducted in 1994 and because this committee had concerns about the lack of information on all the five chemicals of concern and each of these cancers. The only health outcome remaining in the "*no* association" category is spontaneous abortion only for paternal exposure specifically to TCDD.

For the first time, a *VAO* committee found itself deadlocked with respect to classifying the evidence for several health outcomes. The committee could not reach consensus about the strength of the evidence concerning association of herbicide exposure with three health outcomes: two cancers, breast cancer and melanoma, and the specific cardiovascular condition, ischemic heart disease. In each case, the debate was whether there was now enough evidence to move the condition from "inadequate or insufficient evidence to determine association" to "limited or suggestive evidence of association."

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

TABLE S-1 Summary of Findings in Occupational, Environmental, and Veterans Studies Regarding the Association Between Specific Health Outcomes and Exposure to Herbicides[a]

Sufficient Evidence of Association

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

Soft-tissue sarcoma (including heart)
Non-Hodgkin's lymphoma
Chronic lymphocytic leukemia (CLL)
Hodgkin's disease
Chloracne

Limited or Suggestive Evidence of Association

Evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Laryngeal cancer
Cancer of the lung, bronchus, or trachea
Prostate cancer
Multiple myeloma
AL amyloidosis (category change from *Update 2004*)
Early-onset transient peripheral neuropathy
Porphyria cutanea tarda
Hypertension (category change from *Update 2004*)
Type 2 diabetes (mellitus)
Spina bifida in offspring of exposed people

Inadequate or Insufficient Evidence to Determine Association

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, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes *that were explicitly reviewed*:

Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)
Cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs
Esophageal cancer (category change from *Update 2004*)
Stomach cancer (category change from *Update 2004*)
Colorectal cancer (including small intestine and anus) (category change from *Update 2004*)
Hepatobiliary cancers (liver, gallbladder, and bile ducts)
Pancreatic cancer (category change from *Update 2004*)
Bone and joint cancer
* Melanoma
Non-melanoma skin cancer (basal cell and squamous cell)
* Breast cancer
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
Urinary bladder cancer
Renal cancer

Cancers of brain and nervous system (including eye) (category change from *Update 2004*)
Endocrine cancers (thyroid, thymus, and other endocrine)
Leukemia (other than CLL)
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than for paternal exposure to TCDD, which appears *not* to be associated) [b]
Neonatal or infant death and stillbirth in offspring of exposed people
Low birth weight in offspring of exposed people
Birth defects (other than spina bifida) in offspring of exposed people
Childhood cancer (including acute myelogenous leukemia) in offspring of exposed people
Neurobehavioral disorders (cognitive and neuropsychiatric)
Movement disorders, including Parkinson's disease and amyotrophic lateral sclerosis (ALS)
Chronic peripheral nervous system disorders
Respiratory disorders
Gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities, and ulcers)
Immune system disorders (immune suppression, allergy, and autoimmunity)
* Ischemic heart disease
Circulatory disorders (other than hypertension and perhaps ischemic heart disease)
Endometriosis
Effects on thyroid homeostasis

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

Limited or Suggestive Evidence of *No* Association

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

Spontaneous abortion and paternal exposure to TCDD [b]

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

[b] This conclusion appropriately constrained by specific chemical and exposed parent was drawn in *Update 2002*, but was not carried into the summary table,

***** The committee was unable to reach consensus as to whether these endpoints had **Limited or Suggestive Evidence of Association** or had **Inadequate or Insufficient Evidence to Determine Association**, and so were left in the lower category**.**

Risk in Vietnam Veterans

There have been numerous health studies of Vietnam veterans, but most have been hampered by relatively poor measures of exposure to herbicides or TCDD and by other methodologic problems. In light of those problems, many conclusions regarding associations between exposure

to the chemicals of interest and disease have been based on studies of people exposed in various occupational and environmental settings rather than on studies of Vietnam veterans, although studies of health consequences in the maturing veterans themselves have now begun to generate more informative findings. The committee believes that there is sufficient evidence to reach general or qualitative conclusions about associations between herbicide exposure and health outcomes, but the lack of adequate exposure data on Vietnam veterans themselves makes it difficult to estimate the degree of increased risk of disease in Vietnam veterans, as a group or individually. Without information on the extent of herbicide exposure among Vietnam veterans and quantitative information about the dose–time–response relationship for each health outcome in humans, estimation of the risks experienced by veterans exposed to the compounds of interest during the Vietnam War is not possible.

Because of those limitations, only general assertions can be made about risks to Vietnam veterans, depending on which category of association has been attributed to a given health outcome. If there were "limited or suggestive evidence of *no* association" between herbicide exposure and a health outcome, the evidence would suggest no increased risk of the outcome among Vietnam veterans attributable to exposure to the compounds of interest (at least for the conditions, exposures, and lengths of observation covered by the studies reviewed). The only health outcome remaining in this category is spontaneous abortion with respect to paternal exposure specifically to TCDD. Even qualitative estimates are not possible when there is "inadequate or insufficient" evidence of an association. For outcomes categorized as having "sufficient" or "limited or suggestive" evidence of an association with herbicide exposure, the lack of exposure information on Vietnam veterans prevents calculation of precise risk estimates.

The requisite information to assign risk estimates continues to be absent despite concerted efforts to model the exposure of the troops in Vietnam, to measure the serum TCDD concentrations of individual veterans, and to model the dynamics of retention and clearance of TCDD in the human body. Accordingly, this committee has deleted the repetitious statements about the inability to calculate risk for Vietnam veterans that had appeared with each health outcome in prior updates. In place of those repeated statements, the committee states a general conclusion that, at least for the present, it is not possible to derive quantitative estimates of any increased risks of various adverse health effects that Vietnam veterans may have experienced in association with exposure to the herbicides sprayed in Vietnam.

RESEARCH RECOMMENDATIONS

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

This committee recommends the pursuit of additional research in toxicology, exposure assessment, and epidemiology. The development of animal models of various chronic health conditions and their progression would be useful for understanding the possible contributions of the chemicals of interest to compromised health in aging Vietnam veterans. Several specific

endpoints, such as metabolic syndrome and male-mediated effects in offspring, merit laboratory investigation and study of human populations. Meta-analyses of the available data on effects among the children of veterans are recommended. In addition, as the offspring of Vietnam veterans grow older, the possibility of a paternal effect on adult cancers, cognitive problems, and other diseases of maturity will be of increasing interest**.** This committee notes that the earlier investment in studying several exposed populations is now producing useful findings; the National Institute for Occupational Safety and Health, Seveso, Air Force Health Study, and Army Chemical Corps cohorts all merit continuing follow-up or more comprehensive analysis. It is especially important that longitudinal analyses be conducted on cancer and reproductive endpoints from the complete database assembled in the course of the Air Force Health Study. Consideration should also be given to restarting the National Vietnam Veterans Longitudinal Study. New epidemiologic studies, such as a case-control study of tonsil cancer developed from VA's existing files or a study of reproductive effects in the Vietnamese population, could enable the recovery of valuable information.

1

Introduction

The Agent Orange Act of 1991 (Public Law [PL] 102-4, enacted February 6, 1991, and codified as 38 USC Sec. 1116) directed the Secretary of Veterans Affairs to ask the National Academy of Sciences (NAS) to conduct an independent comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to herbicides used during military operations in Vietnam. The herbicides picloram and cacodylic acid were to be addressed, as were chemicals in various formulations containing the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The most well-known of the formulations, Agent Orange, was a 50:50 mixture of the herbicides 2,4-D and 2,4,5-T, which contained the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD); thus, it should be noted that TCDD and Agent Orange are not synonymous. NAS also was asked to recommend, as appropriate, additional studies to resolve continuing scientific uncertainties and to comment on particular programs mandated in the law. In addition, the legislation called for biennial reviews of newly available information for a period of 10 years; the period was extended to 2014 by the Veterans Education and Benefits Expansion Act of 2001 (PL 107-103).

In response to the request from the Department of Veterans Affairs (VA), the Institute of Medicine (IOM) of NAS convened the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. The results of the original committee's work were published in 1994 as *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam,* hereafter referred to as *VAO* (IOM, 1994). Successor committees formed to fulfill the requirement for updated reviews produced *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), and *Update 2004* (IOM, 2005). In 1999, VA asked IOM to convene a committee to conduct an interim review of type 2 diabetes; that effort resulted in the report *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes,* hereafter referred to as *Type 2 Diabetes* (IOM, 2000). In 2001, VA asked IOM to convene a committee to conduct an interim review of childhood acute myelogenous leukemia (AML) associated with parental exposure; its review of the literature, including literature available since the review for *Update 2000,* was published in *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans,* hereafter referred to as *Acute Myelogenous Leukemia* (IOM, 2002). Also in 2001, Congress (PL 107-103) directed the Secretary of Veterans Affairs to ask NAS to review "available scientific literature on the effects of exposure to an herbicide agent containing dioxin on the development of respiratory cancers in humans" and to address "whether it is possible to identify a period of time after exposure to herbicides after which a presumption of service-connection" of the disease would not be warranted; the result of that effort was *Veterans and*

Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer, hereafter referred to as *Respiratory Cancer* (IOM, 2004).

In conducting their work, the committees responsible for those reports operated independently of VA and other government agencies. They were not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. The reports were intended to provide scientific information for the Secretary of Veterans Affairs to consider as VA exercises its responsibilities to Vietnam veterans.

CHARGE TO THE COMMITTEE

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

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

The committee notes that both its congressional mandate and the statement of task are phrased with the target of evaluation being "association," not "causality," between exposure and health outcomes. As used technically, the criteria for causation are somewhat more stringent than those for association. The standard of association was not the choice of *VAO* committees, but the consequence of congressional and judicial history. IOM has recently convened a separate committee to evaluate VA's methods of determining whether medical conditions are service-related; that committee will address this and other issues.

In delivering the above charge to the current committee, the VA project officer made two additional specific requests. First, he asked the committee to examine the evidence related to whether the occurrence of AML, tonsil cancer, AL amyloidosis, and lupus may be associated with exposure to the components of herbicides used by the military in Vietnam. Second, he made the more general request that the appropriate category of association be explicitly indicated for all forms of cancer, leaving no gaps in the exhaustive range of codes for malignant neoplasms (ICD-9 140-208, according to the *International Classification of Diseases, Ninth Edition*).

Details of the committee's approach to its charge and the methods it used in reaching conclusions are provided in Chapter 2 and elaborated on in the health-outcome chapters, particularly Chapter 6, on evidence concerning specific cancers.

CONCLUSIONS OF PREVIOUS *VETERANS AND AGENT ORANGE* REPORTS

Health Outcomes

VAO, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Type 2 Diabetes*, *Acute Myelogenous Leukemia*, and *Respiratory Cancer* provide detailed reviews of the scientific studies evaluated by the committees and their implications for cancer, reproductive and developmental effects, neurobehavioral disorders, and other health effects.

The original committee addressed the statutory mandate to determine whether there is a statistical association between a given health effect and herbicide exposure by assigning each of the health outcomes under study to one of four categories on the basis of the epidemiologic evidence reviewed. Those categories were adapted from the ones used by the International Agency for Research on Cancer (IARC) in evaluating evidence of the carcinogenicity of various substances (IARC, 1977). Successor committees adopted the same categories.

The establishment of categories regarding the evidence for "statistical association," rather than "causality," has been controversial. It should be noted, however, that this principle was established in legal proceedings that predate passage of the legislation mandating the *VAO* series of reviews. *Nehmer vs United States Veterans Administration* (712 F. Supp. 1404, 1989) found that:

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

The categories, the criteria for assigning a particular health outcome to a category, and the health outcomes that have been assigned to the categories in past updates are discussed below. Table 1-1 summarizes the conclusions of *Update 2004* (IOM, 2005) regarding associations between health outcomes and exposure to the herbicides used in Vietnam or to any of their components or contaminants. This integration of the literature to 2004 served as the starting point for the current committee's deliberations. It should be noted that the categories of association concern the occurrence of health outcomes *in human populations* in relation to chemical exposures; they do not address the likelihood that *any individual's* health problem is associated with or caused by the chemicals in question.

TABLE 1-1 Summary of Conclusions from *Update 2004* on Specific Health Outcomes and Exposure to Herbicides[a]

Sufficient Evidence of Association

- Chronic lymphocytic leukemia (CLL)
- Soft-tissue sarcoma
- Non-Hodgkin's lymphoma
- Hodgkin's disease
- Chloracne

Limited or Suggestive Evidence of Association

- Cancer of the lung, bronchus, or trachea
- Cancer of the larynx
- Prostate cancer
- Multiple myeloma
- Early-onset transient peripheral neuropathy
- Porphyria cutanea tarda
- Type 2 diabetes (mellitus)
- Spina bifida in offspring of exposed people

Inadequate or Insufficient Evidence to Determine Association

- Hepatobiliary cancers
- Oral, nasal, and pharyngeal cancer
- Bone and joint cancer
- Skin cancers (melanoma, basal cell, and squamous cell)
- Breast cancer
- Female reproductive cancer (cervix, uterus, and ovary)
- Testicular cancer
- Urinary bladder cancer
- Renal cancer
- Leukemia (other than CLL)
- Abnormal sperm characteristics and infertility
- Spontaneous abortion (other than for paternal exposure to TCDD, which appears *not* to be associated) [b]
- Neonatal or infant death and stillbirth in offspring of exposed people
- Low birth weight in offspring of exposed people
- Birth defects (other than spina bifida) in offspring of exposed people
- Childhood cancer (including acute myelogenous leukemia) in offspring of exposed people
- Neurobehavioral disorders (cognitive and neuropsychiatric)
- Movement disorders, including Parkinson's disease and amyotrophic lateral sclerosis (ALS)
- Chronic peripheral nervous system disorders
- Respiratory disorders
- Gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities, and ulcers)
- Immune system disorders (immune suppression and autoimmunity)
- Circulatory disorders
- AL amyloidosis
- Endometriosis
- Effects on thyroid homeostasis

Limited or Suggestive Evidence of *No* Association

- Gastrointestinal tumors (stomach, pancreas, colon, and rectum)
- Brain tumors
- Spontaneous abortion and paternal exposure to TCDD [b]

[a] *Herbicides* indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from occupational, environmental, and veteran studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.
[b] New finding from *Update 2002*, which had not been listed in previous summary tables.

Health Outcomes with Sufficient Evidence of an Association

In this category, a positive association between herbicides and the outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regarded evidence from several small studies that have satisfactorily addressed bias and confounding and that show an association that is consistent in magnitude and direction as sufficient evidence of an association.

The original committee found sufficient evidence of an association between exposure to herbicides and three cancers—soft-tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease—and two other health outcomes, chloracne and porphyria cutanea tarda (PCT) (IOM, 1994). After reviewing all the literature available in 1995, the committee responsible for *Update 1996* concluded that the statistical evidence still supported that classification for the three cancers and chloracne but that the evidence of an association with PCT warranted its being placed in the category of limited or suggestive evidence of an association with exposure; Chapter 11 of *Update 1996* details the decision. No changes were made in this category in *Update 1998* or *Update 2000*.

As the committee responsible for *Update 2002* began its work, VA requested that it evaluate whether chronic lymphocytic leukemia (CLL) should be considered separately from other leukemias. The committee concluded that CLL could be considered separately and, on the basis of the given epidemiologic literature and the etiology of the disease, placed CLL in the "sufficient" category.

Health Outcomes with Limited or Suggestive Evidence of an Association

In this category, the evidence must suggest an association between exposure to herbicides and the outcome considered, but the evidence can be limited by the inability to rule out chance, bias, or confounding confidently. The wording "For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent" has appeared in prior *VAO* reports. The present committee interpreted that statement as an example of one particular situation. The coherence of the full body of epidemiologic information, in light of biologic plausibility, is considered when the committee reaches a judgment about association for a given endpoint. Because the *VAO* series has four herbicides and TCDD as agents of concern whose profiles of toxicity are not expected to be uniform, apparent inconsistencies can be expected among study populations that have experienced different exposures. Even for a single exposure, a spectrum of results would be expected, depending on the power of the studies and other design factors. If the committee encountered a high-quality study showing an association for a given health outcome in a body of evidence that also contained a high-quality study showing strong

negative findings on exposure to the same agent, it would not automatically adopt a classification of limited or suggestive evidence of an association.

The committee responsible for *VAO* found limited or suggestive evidence of an association between exposure to herbicides and three categories of cancer: respiratory cancer (after individual evaluations of laryngeal cancer and of cancers of the trachea, lung, or bronchus), prostate cancer, and multiple myeloma. The *Update 1996* committee added three health outcomes to the list: PCT, acute and subacute transient peripheral neuropathy (hereafter called early-onset transient peripheral neuropathy), and spina bifida in children of veterans. Transient peripheral neuropathies had not been addressed in *VAO*, because they are not amenable to epidemiologic study. In response to a VA request, however, the *Update 1996* committee reviewed those neuropathies and based its determination on case histories (*Update 1996*, Chapter 10). A 1995 analysis of birth defects among the offspring of veterans who served in Operation Ranch Hand, combined with earlier studies of neural-tube defects in the children of Vietnam veterans (published by the Centers for Disease Control and Prevention), led the *Update 1996* committee to distinguish spina bifida from other reproductive outcomes and to classify it in the "limited or suggestive evidence" category (*Update 1996*, Chapter 9). No changes were made in this category in *Update 1998*.

After the publication of *Update 1998* and on the basis of its evaluation of newly available scientific evidence and the cumulative findings of research reviewed in previous *VAO* reports, the committee responsible for *Type 2 Diabetes* concluded that there was limited or suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant TCDD and type 2 diabetes (mellitus). The evidence reviewed in *Update 2000* supported that finding.

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

Health Outcomes with Inadequate or Insufficient Evidence to Determine an Association

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

The cancers and other health effects so categorized in *Update 2004* are listed in Table 1-1, but several health effects have been moved into or out of this category since the original *VAO* committee reviewed the evidence then available. Skin cancer was moved into this category in *Update 1996* when inclusion of new evidence no longer supported its classification as a condition

with limited or suggestive evidence of *no* association. Similarly, the *Update 1998* committee moved urinary bladder cancer from the category of limited or suggestive evidence of *no* association to this category; although there was no evidence that exposure to herbicides or TCDD is related to urinary bladder cancer, newly available evidence weakened the evidence of *no* association. The committee for *Update 2000* had partitioned AML in the offspring of Vietnam veterans from other childhood cancers and put it into the category of suggestive evidence; but a separate review, as reported in *Acute Myelogenous Leukemia* (IOM, 2002), found errors in the published information and returned it to the category of inadequate or insufficient evidence with other childhood cancers. In *Update 2002,* CLL was moved from this category to join Hodgkin's and non-Hodgkin's lymphomas in the category of sufficient evidence of an association.

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

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

The original *VAO* committee found a sufficient number and variety of well-designed studies to conclude that there is limited or suggestive evidence of *no* association between the exposures of interest and a small group of cancers: gastrointestinal tumors (colon, rectum, stomach, and pancreas), skin cancers, brain tumors, and urinary bladder cancer. The *Update 1996* committee removed skin cancers and the *Update 1998* committee removed urinary bladder cancer from this category because the evidence no longer supported a conclusion of no association. The *Update 2002* committee concluded that there was adequate evidence to determine that spontaneous abortion is not associated with paternal exposure specifically to TCDD; the evidence for this endpoint was deemed inadequate for drawing a conclusion about association for maternal exposure overall or for paternal exposure to any other of the chemicals of interest. No changes in this category were made in *Update 2000*, or *Update 2004.* As will be discussed in greater detail in this volume, the current committee was concerned that the overall paucity of information on picloram and cacodylic acid make this assertion questionable for the endpoints (brain cancer and several digestive cancers) remaining in this category.

Determining Increased Risk in Vietnam Veterans

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

The evidence of herbicide exposure among various groups studied suggests that most Vietnam veterans (except those with documented high exposures, such as participants in Operation Ranch Hand or the Army Chemical Corps) had lower exposures to herbicides and TCDD than did the subjects of many occupational and environmental studies. Individual veterans who had very high exposures to herbicides, however, could have risks approaching those described in the occupational and environmental studies.

Estimating the magnitude of risk of each particular health outcome among herbicide-exposed Vietnam veterans requires quantitative information about the dose–time–response relationship for the health outcome in humans, information on the extent of herbicide exposure among Vietnam veterans, and estimates of individual exposure. Previous committees have concluded that in general it is impossible to quantify the degree of risk likely to be experienced by veterans because of their exposure to herbicides in Vietnam. Overall statements to that effect were made in *VAO* (IOM, 1994) and in every update, but uniformity in the set explanations about the unavailability of the necessary information for performance of quantitative risk assessment for Vietnam veterans in the concluding section for each health outcome or in chapter summaries became somewhat idiosyncratic over the course of the updates. In an effort to streamline the presentation for the individual health outcomes, the point will no longer be reiterated in each instance. The present committee has chosen to eliminate the repetitive restatements in favor of the following general conclusion: At least for the present, it is not possible to derive quantitative estimates of the increase in risk of various adverse health effects that Vietnam veterans may have experienced in association with exposure to the herbicides sprayed in Vietnam.

After decades of research, the challenge of estimating the magnitude of potential risk posed by exposure to the compounds of interest remains intractable. The requisite information is still absent despite concerted efforts to reconstruct likely exposure by modeling based on records of troop movements and spraying missions (Stellman et al., 2003a,b; Stellman and Stellman, 2003, 2004), to measure serum TCDD in individual veterans (Kang et al., 2006; Michalek et al., 1995), and to model the pharmacokinetics of TCDD clearance (Aylward et al., 2005a,b; Emond et al., 2004, 2005, 2006; Cheng et al., 2006). Uncertainty remains about the specific agent that may be responsible for a particular health effect. Even if one accepts an individual veteran's serum TCDD level as the optimal surrogate for his overall exposure to Agent Orange and the other herbicide mixtures sprayed in Vietnam, not only is the measurement nontrivial but the hurdle of accounting for biologic clearance and extrapolating to the proper timeframe remains. The committee

therefore believes that it cannot accurately estimate the risk to Vietnam veterans that is attributable to exposure to the compounds associated with herbicide spraying in Vietnam.

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

Toxicologic data form the basis of the committee's response to the third part of its charge—to determine whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and a health effect. That information is summarized in general terms in separate toxicology chapters in previous reports: Chapter 4 of *VAO* and Chapter 3 of *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004*. An analogous chapter in this update summarizes recent toxicologic findings on the chemicals of concern, and specific findings on each health outcome are also given in the chapters that review the epidemiologic literature.

In previous updates, this topic has been discussed in the conclusions section for each health outcome after a statement of the committee's judgment about the adequacy of the epidemiologic evidence of an association of that outcome with exposure to the chemicals of interest. In fact, the degree of biologic plausibility itself influences whether the committee perceives positive findings to be indicative of a pattern or the product of statistical fluctuations. To provide the reader with a more logical sequence, biologic-plausibility sections have been placed between the presentation of new epidemiologic evidence and the synthesis of all the evidence, which in turn leads to the ultimate statement of the committee's conclusion.

ORGANIZATION OF THIS REPORT

The remainder of this report is organized in nine chapters. Chapter 2 briefly describes the considerations that guided the committee's review and evaluation of the scientific evidence. Chapter 3 updates the toxicology data on the effects of 2,4-D, 2,4,5-T and its contaminant TCDD, cacodylic acid, and picloram; those data contribute to the biologic plausibility of health effects in human populations. Chapter 4 provides an overview of populations repeatedly studied in the course of investigating the toxic potential of the chemicals of interest in this report; it also gives design information on the epidemiologic studies new in this update that investigated those populations or that report multiple health outcomes. Chapter 5 addresses exposure-assessment issues and the exposure assessments conducted in the studies of the major cohorts. The committee's evaluation of the epidemiologic literature and its conclusions regarding associations between the exposures of interest and cancer, reproductive and developmental effects, neurobehavioral disorders, and other health effects are discussed in Chapters 6, 7, 8, and 9, respectively. The committee's research recommendations are presented in Chapter 10.

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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2

Evaluating the Evidence

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

CHOICE OF HEALTH OUTCOMES

As discussed in Chapter 1, the committee was charged with summarizing the strength of the scientific evidence of an association between herbicide exposure during service in the Vietnam War and individual diseases or health outcomes. Public Law 102-4, which mandated the committee's work, however, did not specify particular health outcomes of interest. *VAO* listed health outcomes addressed in the scientific literature, and the list has been amended in the VAO updates in response to new publications, to requests from the Department of Veterans Affairs (VA) and various veterans' service organizations, and to concerns of Vietnam veterans and their families. Comments received at public hearings and in written submissions from veterans and other interested persons have been valuable in identifying issues to be pursued in greater depth in the scientific literature.

IDENTIFICATION OF RELEVANT LITERATURE

Mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid made up the bulk of the herbicides sprayed in Vietnam. At the time of the spraying, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, one form of dioxin) was an unintended contaminant from the production of 2,4,5-T and was present in Agent Orange and some other herbicide formulations sprayed in Vietnam; thus, it should be noted that TCDD and Agent Orange are not synonymous. Therefore, databases have been searched for the names of those compounds, their synonyms and abbreviations, and their Chemical Abstracts Service (CAS) numbers. The evidence indicates that a tissue protein, the aryl hydrocarbon receptor (AhR), mediates most of the toxicity of TCDD, so "AhR" also was used as a keyword, as were "dioxin," "Agent Orange," and "Vietnam veteran."

As discussed in Chapter 3, one of the herbicides used in Vietnam, cacodylic acid, is dimethylarsinic acid (DMA), an organic form of arsenic. In addition to being synthesized as an

herbicide, DMA is a metabolite of inorganic arsenic in humans. DMA was long thought to be a biologically inactive metabolite of inorganic arsenic, but recent evidence suggests that one form —DMA^{III}—might be responsible for some of the adverse effects of inorganic arsenic. That evidence, however, is not sufficient to support a conclusion that exposure to cacodylic acid results in the same adverse health effects as would exposure to toxic concentrations of inorganic arsenic. Therefore, the literature on the health effects of inorganic arsenic was not considered in this report. Further details on the effects of inorganic arsenic can be found in *Arsenic in Drinking Water* (NRC, 1999) and *Arsenic in Drinking Water: 2001 Update* (NRC, 2001). For cacodylic acid and picloram, the search terms were the chemical names, synonyms, and CAS numbers of the herbicides.

This report concentrates on the evidence published after the completion of work on *Veterans and Agent Orange: Update 2004* (IOM, 2005). Relevant new contributions to the literature made during the period June 1, 2004 through September 30, 2006, were sought. The information the committee used was compiled from a comprehensive electronic search of public and commercial databases—biologic, medical, toxicologic, chemical, historical, and regulatory—that provide citations from the scientific literature. In addition, the reference lists of some review and research articles, books, and reports were examined for potentially relevant articles. As noted above, the terms used in the search strategy included the chemical names, synonyms, and CAS numbers of the specific chemicals of interest (2,4-D, 2,4,5-T, TCDD, cacocylic acid, and picloram—see Figure 2-1 for chemical structures and CAS numbers), and the more generic terms involved with this project ("Vietnam veteran," "Agent Orange," "AhR," "dioxin," "herbicide," "phenoxy"). By analogy, results on other specific phenoxy herbicides are also of interest: 2-methyl, 4-chlorophenoxyacetic acid (MCPA) and 2-(2-methyl-4-chlorophenoxy) propionic acid (MCPP or Mecoprop™) for 2,4-D; 2-(2,4,5-trichlorophenoxy) propionic acid (2,4,5-TP or Silvex™) for 2,4,5-T (see Figure 2-1 for chemical structures and CAS numbers). Findings only related to exposure to the diverse chemical families of pesticides were considered too nonspecific for inclusion in the evidentiary database for drawing conclusions about association. However, "pesticide" was included among the search terms to ensure that all possible articles on herbicides (for which our specific targets were only the phenoxy herbicides, cacodylic acid, and picloram) would be identified and subjected to the next phase of screening.

Because they are the target population of the VAO charge, studies of Vietnam veterans (American or otherwise) have always been accorded considerable weight in the committees' deliberations, whether or not estimation of exposure to herbicide-related substances has been attempted. Characterization of exposure in studies of the veterans was extremely uncommon at the time of the original *VAO*, and the Vietnam veterans' own ages were still below the ages at which many chronic illnesses are manifested. Consequently, the original committee made extensive efforts to consider several groups known or thought to have potentially higher and better-characterized exposure to TCDD or phenoxy herbicides than Vietnam veterans themselves—both occupational exposure (as of chemical production, paper and pulp, sawmill, tannery, waste-incinerator, railroad, agricultural, and forestry workers) and environmental exposure (as of residents of Seveso, Times Beach, Quail Run, and Vietnam). Successive committees have chosen to concentrate more on studies that explicitly addressed the exposures specified in the charge. In light of knowledge of which highly exposed occupational and environmental cohorts under continuing study to monitor, the intention of improving scientific reliability by focusing on better-characterized information, and more available results on the

maturing cohort of Vietnam veterans, global searches have no longer been conducted for possibly highly exposed occupational and environmental study populations. Searches based solely on job titles, occupations, or industries assumed to be related to one of the substances of interest were not done, because they are more likely to retrieve citations with information about a health outcome at the expense of considerable uncertainty about exposure. In general, an article did not merit review in VAO updates if its own authors had not thought that exposure to one of the substances of concern was prominent enough to mention it as a keyword that would be picked up by searches based on chemical names, synonyms, or CAS numbers.

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

The search strategy was devised to ensure that abstracts of all potentially relevant articles were subjected to closer screening, but it also resulted in the identification of a large number of non-relevant studies. The searches produced 5,800 "hits," including some studies that were identified more than once. For the most of the citations, it was evident from the abstract that the articles did not address health effects in association with exposure to the chemicals of interest; for example, many of the identified citations investigated the efficacy of herbicides in killing weeds and searching for "AhR" systematically also retrieved numerous investigations of "airway hyper-responsiveness." All studies that discussed health effects were considered if the search-related information (title, abstract, and keywords) indicated that any of the herbicides of interest (or any of their components) may have been investigated. For the more than 1,200 potentially relevant citations thus identified, a copy of the entire article was obtained online or retrieved from library sources and reviewed more thoroughly by the committee for inclusion in the report.

In large part, included reports are peer-reviewed journal articles, but generally available and formally published government studies (particularly those investigating health effects in Vietnam veterans) are also included under the presumption that they have been carefully reviewed. In practice, the articles are generally in English, but the committee would obtain translations for crucial studies, as was done for a study of Korean veterans of the Vietnam War (Kim HA et al. 2003; Kim JS et al., 2003) when *Update 2004* was produced.

TCDD, the 2,3,7,8-chlorinated congener of dioxin, is the most potent of the polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls (PCBs), so it is presumed to be most problematic. However, our concern is not limited to this single congener. In non-laboratory settings—that is, epidemiologic studies—exposures occur not only to TCDD, but to mixtures of dioxins, dibenzofurans, and PCBs, which vary in their degree of chlorination. Toxic equivalency factors, which express the toxicity of an individual congener relative to the toxicity of TCDD, are available and often used to estimate the cumulative toxic potency of such mixtures in terms of an

equivalent concentration of TCDD. That approach is often taken in epidemiologic studies focusing on PCBs. Many epidemiologic studies of PCB were recovered in the literature search, although they were not specifically sought. Because dioxin-like and non-dioxin-like PCB congeners are found together in environmental mixtures and are known to mediate toxicity by unique mechanisms, the relative contribution of dioxin-like PCBs to an individual health outcome can be difficult to determine. Thus, epidemiologic studies that included analyses of PCBs were retained only if they reported data on the contribution of polychlorinated dioxins to the health outcome of interest.

Roughly 350 citations contributed new information to this update. For each health outcome, new evidence was reviewed in detail. The conclusions, however, are based on the accumulated evidence, not just on recently published studies. If statistics have been generated on the same study population over time (as noted in Chapter 4), multiple entries correspond to successive updates in the summary tables of Chapters 6-9, but only the most comprehensive version of the information on a given population is factored into the committee's conclusion on any health outcome. Primary findings are the components of the evidence the committee endeavors to integrate; reanalyses, pooled analyses, reviews, and so on, may be discussed in conjunction with primary results or in synthesis sections for a given health outcome, but they are not themselves part of the evidentiary data set.

COMMITTEE'S APPROACH

The committee's general approach to the evaluation of scientific evidence is presented here. It corresponds very closely with the approached developed by the original committee, as delineated in detailed in Chapter 5 of *VAO* (IOM, 1994). The committee had three specific tasks: to determine whether there is a statistical association between exposure to the herbicides used in Vietnam and health outcomes, to determine the degree of increased risk of effects among Vietnam veterans, and to determine whether plausible biologic mechanisms provide support for a causal relationship with a given health outcome. This section discusses the committee's approach to each task.

Statistical Association

The issues in determining whether a statistical association exists are detailed in Chapter 5 of *VAO*. The committee found that the most relevant evidence came from epidemiologic studies—investigations in which large groups of people are studied to identify an association between exposure to a chemical of interest and the occurrence of particular health outcomes. Epidemiologists estimate associations between exposure and outcome in a specific population or group by using such measures as relative risk, standardized mortality ratio, and odds ratio. Those measures indicate the magnitude of a difference in the rate of an outcome between two populations. For example, if the rate in an exposed population is twice the rate in a non-exposed population, the relative risk, or rate ratio, is 2. Similarly, if the odds of a health outcome are 1:20 in an exposed population but 1:100 in a non-exposed population, the odds ratio is 5. In this report *relative risk* refers to the results of cohort studies; *odds ratio* (an estimate of relative risk) usually

refers to the results of case–control studies. (The results of cohort studies sometimes are reported with odds ratios, again to estimate relative risk.) An estimated relative risk greater than 1 indicates a positive association (that is, it is more likely that the outcome will be seen with exposure than with non-exposure), whereas a relative risk between zero and 1 indicates a negative or inverse association (that is, the outcome is less likely with exposure). A ratio of 1 suggests the absence of association. A statistically significant association is one that would be unlikely to occur by chance if there were truly no association (that is, if the null hypothesis is true).

Determining whether an estimated association between an exposure and an outcome represents a real relationship requires careful scrutiny because there can be more than one explanation for the estimate. *Bias* is a distortion of the measure of association that results from flawed selection in the assembly of the study population or from error in measurement of the characteristics studied. *Confounding* is the distortion of the measure of association that results from the failure to recognize or account for some other factor related both to exposure and to outcome. *Chance* is the degree to which the estimated association might vary randomly among different samples of the population studied. The width of the confidence interval is used to quantify the likely variability of the exposure-disease association. Even when a relative risk or standardized mortality ratio exceeds 1, a conclusion regarding increased risk must be qualified when the confidence interval is broad. In drawing its conclusions, the committee examined the quantitative estimates of association and evaluated the potential influences of bias, confounding, and chance. When integrating the findings from various studies, the committee considered the degree of statistical significance associated with every estimated risk (a reflection of the magnitude of the observed effect and the power of the study designs), rather than simply tallying the "significant" and "non-significant" outcomes as dichotomous items of evidence.

In pursuing the question of statistical association, the committee recognized that an absolute conclusion about the absence of association is unattainable. As in science generally, studies of health effects associated with herbicide exposure cannot demonstrate that a purported effect is impossible or could never occur. Any instrument of observation, even the most excellent epidemiologic study, is limited in its resolving power. In a strict technical sense, therefore, the committee could not prove the absence of an association between a health outcome and exposure to any of the compounds of interest. That contributed to the current committee's decision to re-evaluate findings on the health endpoints classified in *Update 2004* as having "suggestive evidence of *no* association."

Such factors as consistency of evidence, biologic plausibility, temporality, dose-response relationships, and strength of association may be considered when deciding whether an observed statistical association is causal. The committee's charge, however, did not extend to making determinations of causality, so it drew no conclusions regarding cause-and-effect relationships.

Interaction or synergism among the chemicals of interest, or with other agents, is another theoretical concern. The committee was not charged with attributing effects to specific chemicals of interest; joint effects among them should be adequately identified by the committee's approach. The number of combinations of these chemicals with other agents that might be problematic is virtually infinite. Real-life experience, as investigated with epidemiologic studies, effectively integrates any results of exposure to a target substance over all other possibly detrimental or mitigating exposures that a population might have. It may not be possible quantitatively to partition contributions of the chemicals of interest from those of all other factors, but, to the

extent that the possibility of confounding influences can be appraised, the committee will have achieved its objective.

Increased Risk in Vietnam Veterans

When all the available epidemiologic evidence has been evaluated, it is presumed that Vietnam veterans are at increased risk for a specific health outcome if there is evidence of a positive association between one or more of the chemicals of interest and the outcome. The best measure of potency for the quantification of risk to veterans would be the rate of the outcome in exposed Vietnam veterans compared with the rate in non-exposed veterans, adjusted for the degree to which any other factors that differ between exposed and non-exposed veterans might influence those rates. A dose-response relationship established in another human population suitably adjusted for such factors would be similarly suitable.

It is difficult, however, to quantify risk when exposures in a population have not been measured accurately. Fairly accurate exposure data for Vietnam veterans in terms of recent serum TCDD concentrations are available only for subgroups enrolled in the Air Force Health Study (the Ranch Hand and comparison subjects) and in VA's study for deployed and non-deployed members of the Army Chemical Corps. Therefore, the absence of reliable measures of exposure to the chemicals of interest among Vietnam veterans limits the committee's ability to quantify risk of specific diseases in this population.

As explained in Chapter 1, the committee has decided to make a general statement about its continuing inability to address this aspect of its charge quantitatively rather than reiterate a disclaimer in the concluding section for every health outcome.

Plausible Biologic Mechanisms

Chapter 3 details the experimental basis for assessment of *biologic plausibility* or the extent to which an observed statistical association in epidemiologic studies is consistent with other biologic or medical knowledge. In other words, would causation of the particular health effect observed make sense based on what is known about how the chemicals in question act at the tissue, cellular, or molecular level? The relationship between a particular exposure and a specific human health outcome is addressed in the context of research on the effects of the chemicals on biologic systems and of evidence from animal studies. In this report, the committee reviews toxicology studies that were published after *Update 2004* (IOM, 2005) and considers them in combination with earlier studies in commenting on the biologic plausibility of individual health outcomes.

A positive statistical association between an exposure and an outcome does not necessarily mean that the exposure is the cause of the outcome. Data from toxicology studies may support or refute a hypothesis that a specific compound can cause a particular disease. Many toxicology studies are conducted with laboratory animals so that variables, including the amount and duration of exposure, can be controlled precisely. Studies that use isolated cells in culture also can elucidate how a compound alters cellular processes. The objectives of those toxicology studies are to determine what toxic effects are observed at different exposure concentrations and to identify

the mechanisms by which the effects are produced. Ultimately, the results of the toxicology studies should be consistent with what is known about the human disease process to support a conclusion that the development of the disease was caused by exposure.

That approach is not without shortcomings; for example, the dose of a chemical required to produce an effect in experimental animals is often many times higher than human exposures. (For TCDD, however, effects have been observed in animals whose body burdens are no more than 10 than those at the high end of the general population in the industrialized world.) Furthermore, animal and cell-culture models do not always accurately mimic human responses. When the epidemiologic evidence is strong, the absence of evidence for biologic plausibility from toxicology studies does not rule out the possibility that a causal relationship exists. In fact, such cases often drive new toxicology research.

As noted in *VAO* (IOM, 1994), not only is information on biologic plausibility one of the primary elements in the widely accepted Bradford Hill (1965) criteria for causality, but insights about biologic processes also provide information as to whether an observed pattern of statistical association ought to be questioned as being attributable to error, bias, confounding, or chance, as is the task of this committee. The committee used toxicologic information in this fashion and believes that placing this information before its conclusion presents readers of its report with a more coherent argument for its ultimate conclusion about the adequacy of the available evidence to support the existence of a particular association; therefore, this section has been moved from the final section for each health outcome to precede the synthesis section.

EVALUATION OF THE EVIDENCE

Associations between exposures to the chemicals of interest and specific health outcomes are determined through an analysis of available epidemiologic studies that is informed by an understanding of the toxicology of the chemicals and their exposure pathways. In reaching conclusions, VAO committees consider the nature of the exposures, the nature of the health outcomes, the populations exposed, and the quality of the evidence examined. Some specific issues that this and prior committees have considered are addressed below.

Human Studies

The committee reviewed studies of Vietnam veterans and of other populations that might have been exposed to the chemicals of interest. Those studies included cohorts of workers in chemical production and agriculture, populations that reside near sites of environmental contamination, and residents of Vietnam. The committee believes that studies of such non-veteran subjects can help in the assessment of whether the chemicals of interest are associated with particular health outcomes, although (as mentioned above in describing the literature search) these studies were identified on the basis of the agents considered by the original researchers to be possible toxic exposures rather than by occupational definitions. Some of the studies, especially those of workers in chemical-production plants, provide stronger evidence about health outcomes than do studies of veterans, because the industrial exposures were measured sooner after occurrence and were more thoroughly characterized than has been the case in most studies of Vietnam veterans.

Furthermore, in the studies of workers at chemical-production plants, the magnitude and duration of exposure to the chemicals were generally greater, increasing the likelihood that any possible health consequence would be manifested. The studies were often large enough to examine health risks among groups of people with different levels of exposure, so dose-response relationships could be investigated. The general practice of VAO committees has been to evaluate all studies, whether or not their subjects are Vietnam veterans, according to the same criteria when determining the strength and validity of the findings. Because the subjects of studies of Vietnam veterans are the concern of the legislation that mandated this review, however, demonstrations of increased incidence of particular health outcomes among them are of unquestionable pertinence when drawing conclusions.

The committee has concluded that it would be inappropriate to use quantitative techniques, such as meta-analysis, to combine individual study results into a single summary measure of statistical association. The committee reached that conclusion because of the many differences among studies in definitions of exposure, health outcomes considered, criteria for defining study populations, correction for confounding factors, and degree of detail in reporting results. The appropriate use of meta-analysis requires more methodologic consistency across studies, especially in the definition of exposure, than is present in the literature reviewed by the committee (Egger et al., 2002; Petitti, 2000). It is more informative to include a detailed discussion of the results from individual studies in appropriate categories (occupational, environmental, and Vietnam veterans) with a thorough examination of each study's strengths and weaknesses.

In general, the committee did not consider case reports, case series, or other published studies that lacked control or comparison groups. An exception was made, however, for early-onset transient peripheral neuropathy. Individual case reports were reviewed because the rapid appearance and transient nature of that condition imposes methodologic constraints that might have precluded the application of standard epidemiologic techniques.

Because any effect of Agent Orange in individuals or groups of veterans is evaluated in terms of disease or medical outcome, attention to disease classification was important to the committee in assembling pertinent data related to a particular endpoint from various investigations before integrating the information. The researchers conducting the studies reviewed by the committee faced the same challenge in interpreting the available documentation when assigning a diagnostic label to a given subject and then grouping the labels for analysis.

Pathologists, clinicians, and epidemiologists use several classification systems, including the International Classification of Diseases (ICD), the International Classification of Diseases—Clinical Modification (ICD-CM), and the International Classification of Diseases for Oncology (ICD-O). The International Classification of Diseases, 10th Edition (ICD-10) is currently used to classify mortality information. Most of subjects investigated in the studies cited in this update were diagnosed under earlier systems and most of the articles report results in accordance with the ICD-9, if they use ICD codes at all, so the committee has also employed ICD-9. ICD codes are a hierarchic system for indicating type of disease and site (for example, ICD-9 162 specifies cancers of the lung, trachea, or bronchus; 162.2 specifies cancer of the main bronchus; 162.3, cancer of the upper lobe of the lung; and 162.4, cancer of the middle lobe of the lung).

For a patient to be correctly diagnosed, careful staging of the extent of disease is necessary and a biopsy of the tissue must be analyzed by microscopy, often with special immunohistochemical stains, to confirm a clinical impression. Many of the epidemiologic studies reviewed by this committee did not use the ICD approach to classification of disease and relied

instead on clinical impression alone. Death-certificate diagnoses are notoriously inaccurate if the certificates are completed by medical officers who are not familiar with the decedents' medical history (Smith Sehdev and Hutchins, 2001). Self-reported diagnoses, which are obtained from survey questionnaires, often are partially or completely inaccurate; for instance, a patient may state that he was treated for stomach cancer when the correct diagnosis was gastric adenocarcinoma, gastric lymphoma, pancreatic cancer, large bowel cancer, or peritoneal cancer.

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

The committee recognizes that outcome misclassification is a possibility when recording of a diagnosis with a specific ICD code is used as the means to enter an observation into an analysis, but this system has been refined over many decades and is virtually universally used and understood, in addition to being exhaustive and explicit. Therefore, this and previous VAO committees have opted to use the ICD system as an organizing tool. Although the groupings of cancer sites for which conclusions about association have been presented may correspond more closely to National Institute for Occupational Safety and Health (NIOSH) or National Cancer Institute Surveillance Epidemiology and End Results (SEER) categories (see Appendix B), the underlying ICD codes provide the most exactitude. In this report, ICD codes appear almost exclusively in the introductory sections of health-outcome discussions (particularly for cancers) to specify precisely what endpoint the committee is addressing and, when available, on the results table to indicate exactly what the primary researchers believed they were investigating. (See Appendix B for cancer groupings with corresponding ICD-9 and ICD-10 codes.)

For *Update 2006*, VA requested two refinements in the system used in previous VAO reports for presenting conclusions about the adequacy of evidence concerning associations between cancer types and exposure to the herbicides sprayed in Vietnam. First, conclusions should be provided for the full range of cancer types; that is, the cancer groupings for which conclusions are drawn should be exhaustive. Second, it should be apparent into which of these groupings any specific cancer diagnosis falls. Table B-1 in Appendix B delineates the groups used in reporting conclusions through *Update 2004* and points out the ICD-9 codes that had not been expressly addressed and so could be considered "gaps." The opening section of Chapter 6 explains how this committee addressed each of those gaps with prescriptions for how they ought to be handled in future updates.

Rare diseases are difficult to study because it is hard to accumulate enough cases to permit analysis. Often, the result is that whatever cases are observed are included in a broader, less specific category. Thus, epidemiologic data may not be available for assessing whether a particular rare disease is associated with Agent Orange exposure. In some instances, as for chronic lymphocytic leukemia, VAO committees have reached conclusions on the basis of the data available and the etiology of the disease. Through more systematic application of the

hierarchic nature of the ICD coding system, this and future VAO committees will offer an explicit conclusion about the adequacy of available evidence to support an association. For nonmalignant conditions, however, the diversity of disease processes involved makes the use of broad ICD ranges less meaningful, but, because VAO committees could not possibly address every rare nonmalignant disease, no explicit conclusion is drawn about a disease that has not been discussed. Thus, the category of "inadequate or insufficient evidence to determine an association" is the default or starting point for any health outcome; if a condition or outcome is not addressed specifically, it will be in this category.

The committee is aware of the concerns of some veterans about the role of herbicide exposure in the occurrence of multiple health outcomes, such as multiple cancers, in a given person. Little research has been done to address whether the rate of concurrence is greater than would be expected by chance. Simultaneous analysis of multiple health outcomes could potentially provide more insight into the effect of the chemicals of interest in causing multiple health effects, competing risks between various health outcomes, and the interactive effects of some health endpoints on others, but addressing health conditions individually has remained challenging.

For this and future updates, the committee wanted to be more transparent about indicating what evidence is factored into its conclusions. The ongoing practice in this series has been to augment the results table for a given health outcome with any additional publications considered in the current update in the categories of occupational, environmental, or Vietnam-veteran studies; the inclusion of sequential sets of results from follow-ups of a study population has the potential to create the appearance of a greater weight of evidence than exists. The cumulative set of reports noted for each endpoint was reviewed to identify the ones that represent multiple longitudinal reports derived from a given study population. In this update, tables have been revised to indicate a report that has been superseded by italicizing its citation.

Another issue related to evidence evaluation that was of concern for this update was the evidence category of *no* association. It is the current committee's judgment that a conclusion of *no* association would require substantive evidence of such a lack of effect for *each* of the chemicals of interest. Given the paucity of information that has ever been found on cacodylic acid and picloram, that conclusion would seem suspect even if substantial evidence uniformly supported a finding of *no* association both with exposure to the phenoxy herbicides and with exposure to TCDD. Accordingly, the entire evidentiary sets for brain and gastrointestinal cancers, which had been classified as showing "*no* association," were reviewed in this respect.

Exposure Assessment

Much of the evidence that VAO committees have considered is drawn from studies of populations that were not in Vietnam during the period when Agent Orange and other herbicides were used as defoliants. The most informative studies have been well-documented investigations of occupational exposures to TCDD or specific herbicides, such as 2,4-D or 2,4,5-T. In many studies, TCDD exposure is combined with exposures to an array of "dioxin-like" compounds, and the herbicides are often analyzed as members of a functional class; this is less informative for the committee's purpose than individual results for each specific compound. In the real-world situations investigated in epidemiology studies, exposure to multiple possibly toxic chemicals is the rule rather than the exception; for example, farmers or other agricultural populations are likely

to be exposed to insecticides and fungicides as well as to herbicides. In such studies, the committee looked for evidence of health effects that are associated with the specific compounds in the defoliants used in Vietnam and also sought consideration of and adjustment for other possibly confounding exposures.

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

Exposure or dose reconstruction is a particularly challenging aspect of exposure assessment for a population, such as Vietnam veterans, in which few measurements were made during the period of exposure. Much work has relied on records of herbicide production and use and on military records of troop locations. A recent effort overseen by the Institute of Medicine developed a new algorithm for application to Vietnam veterans (the "Stellman model") by using records of herbicide applications in Vietnam and revised data on troop movements (IOM, 2003). The new information holds promise for use in the estimation of what is called ***exposure opportunity*** for individual veterans, that is, estimates of the amount of herbicides (with characteristic TCDD contamination) applied at particular places over particular periods. Recent studies of veterans known to have been exposed to herbicides in Vietnam have included collection of blood samples and analysis of TCDD in them. The readings from those contemporary samples have been used to identify groups of Vietnam veterans with relatively high exposures and to validate estimates from the Stellman model extrapolated to the present. Although such analysis clearly is valuable, it must be viewed with caution. In most cases, the measurement of compounds in blood has taken place many years after exposure. The recognized difficulty of extrapolating back from contemporaneous tissue TCDD concentrations to estimate TCDD (and indirectly herbicide) doses at the time of first exposure or to estimate maximal exposure was highlighted in this update by recent work supporting biphasic, rather than single-compartment elimination. Previous uncertainty about back-extrapolated estimates arising from questions about the appropriate value for the biologic half-life of TCDD in humans is augmented by those modeling insights.

Chapter 5 of this update addresses issues of exposure estimation in more detail and discusses

the presumed hierarchy in quality for various types of exposure information. The agent of interest may be assessed with various degrees of specificity. For instance, TCDD concentrations may be estimated exactly as the most potent congener, 2,3,7,8-TCDD; as dioxin; as dioxin-like toxic equivalents in a mixture of dioxins, furans, and PCBs; or, more vaguely, as nonvolatile chlorinated hydrocarbons. Any of the four herbicides in question could be individually measured and phenoxy herbicides would be a meaningful broader category for 2,4,5-T and 2,4-D; but a report of findings in terms simply of "herbicides" is on the margin of being informative, whereas results stated in terms of "pesticides" are too vague to be useful. For a given chemical of interest, the measure of exposure may be increasingly imprecise—for example, concentrations in target tissue, serum concentrations, cumulative exposure, possible exposure, and so on down to merely a report of service in a job or industry category. Those approaches can address complexities in specificity, duration, and intensity of exposure with various degrees of success. All may provide some information about association with a chemical of interest, but this committee has determined that investigation of associations between most health outcomes and the exposures of concern has advanced to the stage where some characterizations of exposure are too nonspecific to advance insight. For health outcomes with very little evidence, a somewhat looser criterion would apply so that no possible signal of an association would be overlooked.

Animal and Mechanistic Studies

Animal models used as surrogates for the study of a human disease must reproduce, with some degree of fidelity, the manifestations of the disease in humans. However, a given effect of herbicide exposure in an animal species cannot always be used to establish its occurrence in humans. In addition to possible species differences, many factors affect the ability to extrapolate from results of animal studies to health effects in humans. Animals used in experimental studies are most often exposed to purified chemicals, not to mixtures. Even if herbicide formulations or mixtures are used, the conditions of exposure might not realistically reproduce exposures that occur in the field. Furthermore, Vietnam veterans were probably exposed to other agents—such as tobacco smoke, therapeutics, drugs, diesel fumes, and alcohol—that may increase or decrease the ability of chemicals in herbicides to produce a particular adverse health outcome. Few, if any, studies either in humans or in experimental animals have examined those interactions.

As discussed in Chapter 3, TCDD, a contaminant of 2,4,5-T, is thought to be responsible for many of the toxic effects of the herbicides used in Vietnam. Attempts to establish correlations in the effects of TCDD between experimental systems and humans are particularly problematic because of known species-, sex-, and endpoint-specific differences in susceptibility to TCDD toxicity. Some data indicate that humans might be more resistant than are other species to TCDD's toxic effects (Ema et al., 1994; Moriguchi et al., 2003); other data suggest that, for some endpoints, human sensitivity could be the same as or greater than that of some experimental animals (DeVito et al., 1995). Differences in susceptibility may also be affected by variations in the rate at which TCDD is eliminated from the body (see Chapter 3 for details on the toxicokinetics of TCDD).

It also is important to account for TCDD's mode of action when considering species and strain differences. There is a consensus that most of or all the toxic effects of TCDD involve interaction with the AhR, a protein that binds TCDD and other aromatic hydrocarbons with high affinity.

Formation of an active complex involving the intracellular receptor, the ligand (the TCDD molecule), and other proteins is followed by interaction of the activated complex with specific sites on DNA. That interaction can alter the expression of genes involved in the regulation of cellular processes. The development of mice that lack the AhR has helped to establish a definitive association between the AhR and TCDD-mediated toxicity. The affinity of TCDD for the AhR is species- and strain-specific, and responses to binding of the receptor vary among cell types and developmental stages. In addition, genetic differences in the properties of the AhR are known in human populations, as they are in laboratory animals, so some people are at intrinsically greater or less risk for the toxic effects of TCDD.

Although studying AhR biology in transformed human cell lines minimizes the inherent error associated with species extrapolations, caution must be exercised because it is still not clear to what extent toxicity is affected by the transformation itself or by the conditions under which cell lines are cultured in vitro.

Publication Bias

Some studies are more likely to be published than others. That is the concept of publication bias, which has been documented in biomedical research (Song et al., 2000; Stern and Simes, 1997). Most commonly, bias can be introduced when studies whose hypotheses are supported by statistically significant results or that are otherwise deemed favorable by their authors are selectively submitted for publication. Conversely, "negative" studies, in which the hypotheses being tested are not supported by the study findings, often go unpublished. Therefore, conclusions about associations between exposure and outcome that are based solely on published results could be subject to bias. Despite that, the committee does not believe that its conclusions have been unduly affected by publication bias, for two reasons: the extensive publicity surrounding the possibility of health effects associated with the herbicides used in Vietnam has created considerable pressure to publish all findings on the subject, and the many published studies assembled and reviewed contain among their results the full range of possible statistical associations, from convincingly negative through indeterminate to strongly positive.

Role of Judgment

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

The realized approach, as described here, has been determined to a large extent by the nature of the exposures, of the health outcomes, and of the resulting evidence available for examination; therefore, it has evolved in the course of the work of this and previous VAO committees. The

quantitative and qualitative procedures underlying this review have been made as explicit as possible, but ultimately the conclusions about association expressed in this report are based on the committee's collective judgment. The committee has endeavored to express its judgments as clearly and precisely as the data allowed.

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

3

Toxicology

The purpose of this chapter is to summarize recent experimental data that provide the scientific basis of assessment of the biologic plausibility of the effects of herbicide exposure as reported in epidemiologic studies. Establishment of biologic plausibility through laboratory studies strengthens the evidence of the effects of herbicide exposure that are believed to occur in humans. Toxic effects are influenced by dosage (magnitude and frequency of administration); by exposure to other substances, including compounds other than herbicides; by pre-existing health status; and by genetic factors. Those variables are difficult to control in epidemiologic studies of humans exposed to herbicides. Experimental studies using laboratory animals or cultured cells allow observation of effects of herbicide exposure under conditions that control for such variables.

The routes and rates of uptake, tissue distribution, metabolism, and elimination of a toxic substance collectively are termed toxicokinetics (also pharmacokinetics). Those processes determine the amount and persistence of a particular chemical or metabolite that reaches specific organs or cells in the body. Understanding the toxicokinetics of a compound is important for valid reconstruction of exposure in humans and for assessing the risk of effects of a particular toxicant. The principles involved in toxicokinetics are similar among chemicals, although the degree to which different processes may influence the distribution depends on the structure and other inherent properties of the chemicals. Thus, properties such as the lipophilicity or hydrophobicity of a chemical influence the pathways by which it is metabolized (structurally transformed) and whether it persists in the body or is excreted. Chemical structure and pathways of metabolism also determine the reactivity and toxic potential of a chemical. Those properties differ among the chemicals of concern in this report and may differ among species as well. Attempts to extrapolate from experimental studies to human exposure must therefore consider them carefully.

Many chemical compounds were used by the US armed forces in Vietnam. The nature of the substances themselves is discussed in more detail in Chapter 6 of *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam,* hereafter referred to as *VAO* (IOM, 1994). Four herbicides documented in military records were of particular concern and are examined here: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 4-amino-3,5,6-trichloropicolinic acid (picloram), and cacodylic acid (dimethylarsinic acid, DMA). This chapter also focuses on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or dioxin), a contaminant of 2,4,5-T, because its potential toxicity is of concern; considerably more information is available on TCDD than on the herbicides. Other contaminants present in 2,4-D and 2,4,5-T are of less concern. Except as noted, the laboratory studies of the chemicals of concern were done with pure compounds or formulations; t the epidemiologic studies discussed in later chapters often track exposures to mixtures.

This chapter begins with a discussion of major conclusions presented in reports by

predecessors of the current committee: *VAO* (IOM, 1994); *Veterans and Agent Orange: Update 1996,* hereafter referred to as *Update 1996* (IOM, 1996,); *Veterans and Agent Orange: Update 1998,* or *Update 1998* (IOM, 1999); *Veterans and Agent Orange: Update 2000,* or *Update 2000* (IOM, 2001); *Veterans and Agent Orange: Update 2002,* or *Update 2002* (IOM, 2003); and *Veterans and Agent Orange: Update 2004,* or *Update 2004* (IOM, 2005). The rest of the chapter consists mostly of overviews and discussions of the relevant experimental studies that have been published since *Update 2004* (IOM, 2005) on 2,4-D, 2,4,5-T, picloram, cacodylic acid, and TCDD. The update for each substance includes a review of the toxicokinetic investigations and a summary of the toxic endpoints and their underlying mechanisms of action.

HIGHLIGHTS OF PREVIOUS REPORTS

Prior reports have reviewed the results of animal and in vitro studies published through 2004 that investigated the toxicokinetics, mechanisms of action, and disease outcomes of exposure to the herbicides used in Vietnam and TCDD, the contaminant of Agent Orange. The herbicides have not been studied extensively, but in general none of them is considered highly toxic. High concentrations usually are required to alter cellular and biochemical processes. In contrast, experimental data reviewed in previous reports led to the conclusion that TCDD elicits a spectrum of toxic effects that vary with exposure level and the age, sex, and species of the animals studied. Carcinogenicity, immunotoxicity, reproductive and developmental toxicity, hepatotoxicity, and neurotoxicity have been observed in several species. The scientific consensus is that TCDD is not directly genotoxic and that its ability to influence the carcinogenic process is mediated by epigenetic events, such as enzyme induction, cell proliferation, apoptosis, and intracellular communication. Most, if not all, of the biochemical and toxic effects of TCDD are mediated by the aryl hydrocarbon receptor (AhR), a cellular protein that functions as a regulator of gene transcription. Studies to understand the role of AhR in normal physiology are important for understanding the risks associated with human exposure to TCDD.

UPDATED TOXICITY PROFILE OF 2,4-D

The herbicide 2,4-D is a synthetic chemical that mimics specific plant-growth regulators, the auxins, and interferes with their function. According to previous reports, 2,4-D is considered moderately toxic, eliciting a number of adverse effects in animal studies, including carcinogenesis, immunotoxicity, teratogenesis, endocrine disruption, renal toxicity, and hepatotoxicity. The studies reported in the last 2 years continue to indicate that the toxicity of 2,4-D can involve effects on several processes. Thus, studies reviewed in *Update 2006* and previous updates indicate that 2,4-D's effects include membrane disruption, uncoupling of oxidative phosphorylation, lipid peroxidation, altered redox status, and chromosomal abnormalities. 2,4-D can be a peroxisome proliferator and can induce cytotoxic effects, including apoptosis. Those effects occur at very high doses, and the mechanisms of 2,4-D action are not understood. 2,4-D does cause changes in gene expression, so newer studies that identify pathway changes by using gene-expression profiling may provide insights into the mechanisms of 2,4-D toxicity.

Toxicokinetics

2,4-D is moderately hydrophobic and is rapidly excreted as the unchanged parent compound. The half-life in animals varies from hours to weeks and in humans from less than a day to several days, depending on the route of exposure. After oral administration, most of the dose typically will be excreted within 48 hours.

Since the publication of *Update 2004*, several studies have examined the toxicocokinetics and metabolism of 2,4-D in animals and humans. Their results support the previous conclusions that metabolism of 2,4-D to its primary metabolite, 2,4-dichlorophenol (2,4-DCP), is rapid and that the elimination of 2,4-D and 2,4-DCP is relatively rapid, thus limiting the amount that is taken up into tissues.

In a study in rats, Aydin et al. (2005) examined the accumulation of 2,4-D in kidney; the kidney is a target organ in subchronic studies of 2,4-D toxicity in rodents. Male and female rats were given different doses of 2,4-D in drinking water and food for 30 days, and kidney tissue was analyzed for residues of 2,4-D and 2,4-DCP. Both compounds were found in kidney with all dose regimens, and the amounts of metabolite exceeded the parent compound at all doses. Also in rodents, Sturtz et al. (2006) examined the distribution of 2,4-D to milk of dams after parturition. The rats were fed diets supplemented with 2,4-D at doses equivalent to 15, 25, 50, and 70 mg/kg per day for 16 days. There was a dose-dependent increase in 2,4-D content in the dams' serum and milk and in serum collected from the pups. Analysis of the lipid composition of the milk found a dose-dependent reduction in polyunsaturated fatty acids.

Two papers documented the effects of sunscreen ingredients on dermal uptake of 2,4-D, which is of concern because sunscreens may be used in agricultural or other occupational settings where exposure to herbicides might occur. The first study (Pont et al., 2003) used hairless mouse skin explants as the model. Six combinations of sunscreen active ingredients were applied and then 2,4-D, and material that passed the dermal barrier was collected and measured at various times over 24 hours. All six formulations enhanced the penetration of 2,4-D in through the skin. Among the active ingredients, *N*,*N*-diethyl-*m*-toluamide (DEET) was most effective in enhancing penetration; octocrylene was the only ingredient found to antagonize 2,4-D uptake. In a related study using the same mouse skin model, the same group (Brand et al., 2003) examined the effects of the physical blockers titanium oxide (TiO_2) and zinc oxide (ZnO), which are UVA absorbers, on the uptake of 2,4-D in the presence of commercially formulated sunscreens or in an alternative carrier, phenyl trimethicone. Five of nine sunscreens tested alone increased the transdermal absorption of 2,4-D. However, ZnO impeded uptake of 2,4-D, and TiO_2 had no effect when phenyl trimethicone was the solvent. Thus, inert ingredients can modify the enhancing effect of active sunscreen agents. The study also included washing the skin as a variable; washing between applications resulted in the same penetration effect of a second application, and repeating the application without washing resulted in greater penetration of the second dose.

Underlying Mechanisms of Toxic Action

Studies of effects of 2,4-D published since *Update 2004* are consistent with the earlier

conclusion that 2,4-D is not acutely toxic and has only weak carcinogenic potential. Recent animal studies of disease outcomes after 2,4-D exposure and possible mechanisms are discussed below.

Genotoxic Effects and Mechanisms Related to Carcinogenicity

Carcinogenicity may occur as a result of mutations (genotoxicity) or epigenetic effects involving promotion of tumor-cell proliferation and tumor growth.

Studies reviewed in previous updates indicated that 2,4-D has weak genotoxic potential. A recent report supports the suggestion of a weak but positive association between 2,4-D exposure and genotoxic potential. Gonzalez et al. (2005) examined DNA damage and cytogenetic endpoints in Chinese hamster ovary (CHO) cells exposed to 2,4-D and to a formulation containing 2,4-D dimethylamine salt (2,4-DMA), a derivative that is used in Argentina. The chemicals were applied to cells in culture at 0, 2, 6, or 10 µg/mL of media. DNA strand breaks increased in a dose-dependent manner with a doubling at the highest dose. Mitotic indexes were decreased only at the higher doses. Comet assay showed damage by both 2,4-D and 2,4-DMA. The mechanism of the effects is not known, but it is speculated that the chemicals stimulate production of reactive oxygen species. Overall, the studies suggest only weak genotoxicity of 2,4-D.

In a study of 2,4-D effects on human prostatic-cancer cells, Kim et al. (2005) examined the androgenic action of 2,4-D and of 2,4-DCP as synergists of dihydrotestosterone (DHT) on activation of the androgen receptor (AR). Two human prostatic-cancer cell lines were exposed to the chemicals at various doses with or without the AR agonist DHT. Among endpoints examined was induction of an AR-dependent reporter gene (luciferase). Neither 2,4-D nor 2,4-DCP alone increased reporter-gene expression, but they both enhanced the agonist-mediated activation of the reporter gene by DHT. Further analysis suggested that the effect might involve facilitation of translocation of the DHT-bound AR to the nucleus.

Neurotoxicity

Update 2004 cited case reports of acute poisonings of humans exposed to large amounts of 2,4-D formulations, indicating neurologic manifestations of drowsiness, coma, hyperreflectivity, hypertonia, and cerebral edema (Brahmi et al., 2003). No relevant studies involving neurotoxicity in adult humans have been published since *Update 2004*. However, a variety of studies address neurologic systems in animal models, and several studies support effects of 2,4-D on the developing brain in animal models. Studies concerning neurologic effects during development are detailed in the section on developmental toxicity below.

Some studies have suggested that 2,4-D has effects on brain processes (dopamine metabolism and action) and structures (such as the nigrostriatus) implicated in movement disorders, such as Parkinson's disease. A study by Thiffault et al. (2001) addressed the hypothesis that 2,4-D causes damage to dopaminergic terminals and contributes to nigrostriatal degeneration. Male C57BL/6 mice 7-8 weeks old were given a single subcutaneous injection of 100 or 200 mg/kg 2,4-D methyl ester. After 7 days, dopamine and dopamine metabolites (3,4-dihydroxyphenylacetic acid and homovanillic acid) were measured in the striatum. Neither dose

produced any change in the concentrations of dopamine. The only statistically significant change was a slight (about 15%) decrease in 3,4-dihydroxyphenylacetic acid at the highest dose. Challenge with 2,4-D 7 days after a 15-mg/kg dose of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a known dopaminergic toxicant, did not potentiate the effects of MPTP. The results do not support a link between acute exposure to 2,4-D and nigrostriatal injury in the mouse model.

Zafeiridou et al. (2006) used nerve preparations from a nonmammalian vertebrate model, the frog *Rana ridibunda*, to address effects of 2,4-D on peripheral nerve function. The study involved isolated sciatic nerves exposed to 2,4-D in a specialized chamber that allowed the action potential to be measured as an indication of proper physiologic functioning of the nerves. The effective concentration 50% (EC_{50}) of 2,4-D for neurotoxicity in this preparation was determined to be 3.8 mM. Inasmuch as 2,4-D is a weak acid, pH is thought to affect its toxicity. Changing the pH in the nerve media from a physiologic pH of 7.2 to 3.3 enhanced the toxicity and reduced the EC_{50} to 0.24 mM. The results suggest an effect of 2,4-D on the peripheral nervous system, but the mechanisms are unknown, and the significance of the nonphysiologic-pH result is not clear.

Reproductive and Developmental Toxicity

Previous studies have indicated that 2,4-D is embryotoxic in vivo and that the fetus may be more sensitive than adults to its toxic effects. Since *Update 2004*, studies continue to indicate that 2,4-D has effects in developing animals, including multiple effects on the developing central nervous system.

Sameshima et al. (2004) examined the effects of 2,4-D on rat embryos maintained in culture to determine whether toxicity involved direct effects on the embryo. Embryos of Wistar rats were isolated on day 9.5 of gestation and were exposed to 2,4-D in culture media at 50, 100, 200, or 500 µg/mL. Several indexes of growth (number of somites, crown-rump length, head length, and yolk sac diameter) and structure (such as eye development, ear development, neural tube defects, and forelimb development) were examined. Growth retardation and morphologic defects were progressively more severe at higher doses, and all endpoints were significantly affected at the highest dose. The results indicate that 2,4-D can directly affect the embryo in vitro, but the mechanisms for the effects are not apparent.

Bortolozzi et al. (2004) examined the effects of 2,4-D on the ontogeny of dopaminergic D2 receptors in rat pups that had been exposed to 2,4-D in utero, during lactation, and after weaning. Eight female Wistar rats were exposed to 2,4-D in the diet at 70 mg/kg per day from gestation day 16 to postpartum day 23, while four control females were fed vehicle in the diet. After weaning, half the litters in the 2,4-D group were fed the control diet until day 90, and the others were fed the 2,4-D diet. A specific binding assay for D2 receptors was used to measure D2 receptor concentrations in striatum, prefrontal cortex, hippocampus, and cerebellum at various times up to postnatal day 90. There were modest statistically significant increases in D2 receptors in all four regions of brains of pups that had been fed the 2,4-D diet after weaning. However, the effect was not evident in pups that were exposed in utero and then fed a control diet after weaning. The results suggest that the effect induced in utero or during lactation was reversible on cessation of exposure.

A study by the same group (Garcia et al., 2004) examined the effects of 2,4-D on tyrosine

hydroxylase activity in midbrain areas (the substantia nigra and the ventral tegmental area) in neonatal rats exposed to 2,4-D only through lactation. After birth of litters, female mice were treated with 2,4-D by intraperitoneal injection at 70 or 100 mg/kg per day for 16 days; control females received injections of carrier. Pups were nursed in one of the three groups. On postnatal day 25, cellular expression of tyrosine hydroxylase (TH) and serotonin transporters (5-HTT) was determined with immunohistochemical staining and image analysis. In both brain regions, there were reductions in TH and 5-HTT in substantia nigra of both dose groups. In the ventral tegmental area, there were reductions in both in the high-dose group and of 5-HTT in the low-dose group.

In a similar study Garcia et al. (2006), examined concentrations of dopamine ß-hydroxylase, the enzyme that synthesizes noradrenaline from dopamine, in the *locus coeruleus* of neonatal rats that had been exposed to 2,4-D by lactation. As in the previous study, 9-day old primaparous female Wistar rats were exposed by intraperitoneal injection to 2,4-D at 70 or 100 mg/kg per day for 14 days (postnatal days 9–22), and control females received carrier. On day 22, brains were examined for dopamine hydroxylase with immunohistochemistry. Pups exposed to either dose of 2,4-D showed a pronounced and significant ($p < 0.001$) reduction (of 73–75%) in dopamine hydroxylase staining in the locus coeruleus. Taken together the Garcia studies indicate that the neonatal rat brain can be influenced by lactational exposure to 2,4-D.

Chemicals that interact with estrogen receptors may cause reproductive problems or could affect estrogen-dependent cancers, including breast cancer. Lemaire et al. (2006) addressed possible interaction of 2,4-D with human estrogen receptors ERα and ERß. Cell lines stably transfected with human ERα or ERß, with a luciferase reporter construct, were used to assess the interactions of 49 chemicals, including 2,4-D. 2,4-D showed no agonist activity and no antagonist activity with either ERα or ERß.

Immunotoxicity

Previous updates concluded that 2,4-D has at most a weak effect on the immune system. Recent publications are consistent with that conclusion.

The ability of 2,4-D to cause thymic involution was studied in C57BL/6 mice exposed to 2,4-D and another herbicide, propanil, or to mixtures of the two (de la Rosa et al., 2005). Mice 6-8 weeks old were treated by injection of either propanil or 2,4-D at 50, 100, 150, or 200 mg/kg of body weight or with 1:1 combinations of the stated doses of each chemical. Two days after treatment, thymus weight was measured, and CD4 CD8 thymocyte populations were measured by flow cytometry. Thymic atrophy was observed only in the highest-dose groups, that is, with the combination of chemicals both at 150 mg/kg and with each chemical alone at 200 mg/kg. A decrease in $CD4^+$ $CD8^+$ and $CD4^-$ $CD8^+$ cells occurred at the next-lower dose. A role for glucocorticoids was assessed by determining whether thymic effects could be reversed by treatment with a glucocorticoid receptor antagonist (RU486) 2 hours before and 12 hours after dosing. The effects of the herbicide on the thymus appeared at least partly to require the glucocorticoid receptor.

A study of 2,4-D effects on antibody responses was carried out with a design similar to that used above by the same group (Salazar et al., 2005). C57BL/6 mice were exposed to 2,4-D at 150 mg/kg, to propanil, or to mixtures of the two by intraperitoneal injection within an hour of receiving an injection of heat-killed *Streptococcus pneumoniae*. Responses to two specific

antigens were determined: a T-cell-independent type 2 antigen (phosphorylcholine) and a T-cell-dependent antigen (pneumococcal surface protein). At 3, 5, 7, 10, and 14 days after treatment, spleen and bone marrow cells were obtained, cell populations were analyzed with flow cytometry, and antibody-secreting cells and antibody production were determined with immunoassay. The number of phosphorylcholine antigen-specific bone marrow antibody-secreting B cells was decreased by 2,4-D. However, the number of antibody-secreting B cells in spleen was not changed. The response to pneumococcal surface-protein antigen A was not affected. The results suggest a modest inhibitory effect of 2,4-D on the ability to mount a humoral immune response.

Mechanisms Related to Effects on Energy Metabolism or Mitochondrial Function

Several reports cited in previous updates suggested that the toxicity of relatively high concentrations of 2,4-D might be related, at least in part, to its effect on calcium homeostasis and energy metabolism. Those effects might be mediated by a direct action on mitochondria. It is generally recognized that the toxicity of 2,4-D is not understood at the molecular level. There may be multiple avenues of toxicity, and uncovering the pathways that are affected by 2,4-D could lead to hypotheses about the mechanisms.

A study by Argese et al. (2005) examined 15 phenolic and phenoxy herbicides, including 2,4-D, for toxic effects on mitochondrial function and the dependence of EC50 on structural and physicochemical properties of the chemicals. The assay used submitochondrial particles (SMPs) prepared from beef-heart mitochondria, and effects on NADH generation by the particles in vitro were assessed. An EC_{50} for the effect was determined as the concentration of herbicide that gave 50% inhibition of NADH generation. The EC_{50} for 2,4-D was 32 µM. The investigators concluded that the compounds were acting by a nonspecific mode of action at the membrane.

Effects of 2,4-D on metabolic enzymes of the glycolytic, citric acid, and pentose phosphate pathways involved in generating NADH and NADPH were examined by Yilmaz and Yuksel (2005). Enzyme activities were measured in liver of offspring of females that had received injections of 2,4-D at 3.38 mg/kg of body weight (0.01 of the LD_{30}), or ethanol or saline. The study was repeated in three generations of mice and the offspring were exposed only in utero and through lactation. Increases in malate dehydrogenase were noted, but the effects were modest and highly variable. The authors also examined chromosomal structure in bone marrow cells; no abnormalities were observed.

Mechanism Related to Effects on Thyroid Hormones

Effects of 2,4-D on serum concentrations of thyroid hormones, particularly decreases in thyroxine, were noted in previous updates. No new studies related to possible involvement of the thyroid were identified.

Mechanisms Related to Effects of Cell Stress Responses

Several investigations examined the ability of 2,4-D to promote or inhibit oxidative damage

to cell membranes. Together, they suggest that at high concentrations 2,4-D is incorporated into cellular membranes and modifies membrane structure and integrity. A number of prior studies implicated oxidative stress in the mechanisms of 2,4-D toxicity.

Oxidative stress was addressed further by Celik et al. (2006) in a study of serum enzymes, antioxidant defenses, and lipid peroxidation in various tissues of rats exposed to 2,4-D. Male (Sprague-Dawley) rats 4 months old (weight, 150–200 g) were given 2,4-D (of unspecified source) in drinking water ad libitum for 25 days. The doses amounted to an intake of about 1.5 or 3 mg/kg per day. After 25 days, serum, red blood cells, and other tissues were obtained for assay. Serum alanine aminotransferase, lactate dehydrogenase, and creatine phosphokinase were significantly increased by both doses of 2,4,D, but aspartate aminotransferase was not affected. The lipid peroxidation end product malondialdehyde was significantly increased in liver, kidney, and heart but not in red cells or brain. Glutathione was significantly depleted in kidney and brain at both doses, and other organs variably. Other antioxidant enzymes showed varied responses in the different organs. Together, the data implicate oxidative stress as a factor in the toxicity of 2,4-D.

Gene-expression profiling

The first expression-profiling study of 2,4-D effects was that of Bharadwaj et al. (2005), who examined global gene expression in human hepatoma cells (HepG2 cells) exposed to 2,4-D at low concentrations. HepG2 cells (at four to 10 passages) were continuously cultured in a commercial formulation of 2,4-D at concentrations 0.1 nM to 4 mM, a range spanning the full spectrum of toxic and environmental concentrations. RNA isolated from control and treated cells was prepared and hybridized to Human 1.7k-Expressed Sequence Tag microarrays. At least 87 genes showed significant changes (two-fold threshold), which were evenly divided between those showing up-regulation and those showing down-regulation. Changes began to appear at a 2,4-D concentration of 1.0 nM. The affected genes included genes involved in cell-cycle control, stress response, immune function, and DNA repair. Bharadwaj et al. (2005) concluded that “the cellular response to 2,4-D is complex” and ostensibly associated with altered expression of many genes.

UPDATED TOXICITY PROFILE OF 2,4,5-T

Commercial production of 2,4,5-T resulted in the formation of TCDD as a contaminant. This section summarizes the toxicity of 2,4,5-T itself. TCDD toxicity is summarized later in this chapter.

The herbicide 2,4,5-T is an auxin mimic. It is similar to 2,4-D in its mode of action. *VAO* and the updates concur that 2,4,5-T is only weakly toxic or carcinogenic. Updates have indicated that 2,4,5-T has only weak mutagenic potential but that it might alter the profile of enzymes involved in the metabolism of procarcinogens. Earlier reports indicated that 2,4,5-T could interfere with the formation of the neurotransmitter acetylcholine, which could be involved in effects on growth and the nervous system. Earlier studies also indicated membrane disruption and possibly oxidative stress as effects of 2,4,5-T. A few studies relevant to mechanisms of toxicity of 2,4,5-T

have been published since *Update 2004;* most of them included assessment of 2,4-D as well as 2,4,5-T, and those studies are discussed in the sections on each of these herbicides.

Toxicokinetics

2,4,5-T is moderately hydrophobic and, like 2,4-D, is generally rapidly excreted, largely as the unchanged parent compound although some is conjugated to amino acids. The half-life in animals varies from hours to weeks and in humans from less than a day to several days, depending on the route of exposure.

No relevant studies on the toxicokinetics of 2,4,5-T in experimental animals or humans after exposure to 2,4,5-T were identified in the search for *Update 2006.*

Mechanisms of Toxic Action

Neurotoxicity

The study by Zafeiridou et al. (2006), described in the section on 2,4-D toxicity, also addressed the effects of 2,4,5-T on peripheral nerve function. Isolated sciatic nerve preparations from a frog model (*Rana ridibunda*) were exposed to 2,4,5-T in a specialized chamber that allowed the action potential to be measured as an indication of nerve vitality. Adding 2,4,5-T to this preparation at various concentrations resulted in a dose-dependent decrease in the time to reduce the amplitude of the action potential relative to saline. An EC_{50} of 0.9 mM was determined for 2,4,5-T. Because 2,4,5-T also is a weak acid, changing the pH in the nerve media from physiologic (7.2) to 3.3 reduced the EC_{50} to 0.2 mM. The results suggest an effect of 2,4,5-T on the peripheral nervous system, but the mechanisms of the effect are unknown.

Cell Stress Responses

One report describing cellular effects of 2,4,5-T and its metabolite 2,4,5-trichlorophenol (2,4,5-TCP) on human erythrocytes has been published (Bukowska, 2004a). The study examined the effects of 2,4,5-T and 2,4,5-TCP on indexes of oxidative stress in human red blood cells (RBCs). Exposure of RBCs to the chemicals was in buffered saline, in which RBCs constituted 5% of the volume. Superoxide dismutase, catalase, reduced and total glutathione, glutathione reductase, and adenylate energy charge were measured in the RBCs. Modest decreases in superoxide dismutase and catalase were observed in cells exposed to 2,4,5-TCP at 250 ppm but not in those exposed to 2,4,5-T. The decrease in catalase activity was pronounced at a dose of 1,000 ppm. (In comparison, at that dose, 2,4-D and its metabolite 2,4-DCP did not affect RBC catalase activity.) Both 2,4,5-T and 2,4,5-TCP elicited modest decreases in the content of reduced glutathione but did not affect total glutathione. The two compounds also caused changes in RBC structure that suggested effects on membrane integrity.

Energy Metabolism or Mitochondrial Function

Argese et al. (2005) used SMPs prepared from beef heart to assay effects of 2,4,5-T on NADH generation as a measure of toxicity. Effects on mitochondrial respiratory functions were considered in relation to structural and physicochemical properties of 2,4,5-T and other chemicals in the study. The EC_{50} of 2,4,5-T for inhibition of NADH generation determined with this assay was 21 µM. Comparing effects of a number of chemicals in relation to their chemical properties, the investigators concluded that 2,4,5-T had a nonspecific mode of action at the membrane.

Reproductive and Developmental Toxicity

Chemicals that interact with estrogen receptors can impair reproduction. Lemaire et al. (2006) addressed possible interaction of 2,4,5-T with estrogen receptors. Cell lines stably transfected with human ERα or ERß, with a luciferase reporter construct, were used to assess the interaction of 49 chemicals, including 2,4,5-T, with the receptors. 2,4,5-T did not show any agonist activity with either ERα or ERß. However, 2,4,5-T showed antiestrogenic activity in the ERα cells. A 2,4,5-T concentration of 10 µM inhibited the response induced by E2, an ovarian steroid hormone, by 20%. Whole-cell competition binding assays showed that 2,4,5-T could inhibit the binding of E2 to the ERα.

UPDATED TOXICITY PROFILE OF CACODYLIC ACID

Cacodylic acid, or dimethylarsinic acid (DMA), and its sodium salt constituted about 30% of Agent Blue, one of the mixtures used for defoliation in Vietnam. DMA is a metabolic product of exposure to inorganic arsenic. Methylation of inorganic arsenic generally has been considered a detoxification process, producing less acutely toxic methylated species—monomethyl arsonic acid and DMA—and increasing excretion. More recently, however, some of the methylated metabolic intermediates have been thought to be more toxic than the parent compound. The methylation pathway of inorganic arsenic results in the formation of pentavalent DMA (DMA^V) and trivalent DMA (DMA^{III}) (IOM, 2005). The committee considered the relevance of data on inorganic arsenic to DMA. Although inorganic arsenic is a human carcinogen, there is no evidence that direct exposure to DMA produces cancer in humans. DMA also is not demethylated to inorganic arsenic. It has not been established, nor can it be inferred, that the observed effects of exposure to inorganic arsenic are also caused by exposure to DMA. Therefore, the literature on inorganic arsenic is not considered in this report. The reader is referred to *Arsenic in Drinking Water* (NRC, 1999a) and *Arsenic in Drinking Water: 2001 Update* (NRC, 2001).

Toxicokinetics

DMA^V appears to be less toxic than DMA^{III}, perhaps in part because of its rapid excretion (IOM, 2005). Recent studies confirm that DMA^V administered intravenously to rats is excreted

unchanged and rapidly in the urine with none detected in the bile and less than 4% distributing into tissues after 12 hours (Cui et al., 2004; Suzuki et al., 2004). However, about 10% binds to hemoglobin in RBCs (Suzuki et al., 2004), and rat hemoglobin exhibits a binding affinity to DMA^V 10 times higher than human hemoglobin; this which may account for its accumulation in rat blood (Lu et al., 2004). Chronic exposure of normal rat hepatocytes to DMA^V resulted in reduced uptake over time and in acquired cytotoxic tolerance (Kojima et al., 2006); the tolerance was mediated by induction of glutathione-*S*-transferase activity and of multiple-drug-resistant protein expression.

Endpoints and Underlying Mechanisms of Toxic Action

Neurotoxicity

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

Immunotoxicity

In a preliminary study, a low concentration of DMA^V (10^{-7} M) increased proliferation of human peripheral blood monocytes after their stimulation with phytohemoagglutinin, whereas only a high concentration (10^{-4} M) inhibited release of interferon-γ; this suggested that immune modulatory effects of DMA^V are concentration-specific (Di Giampaolo et al., 2004).

Genotoxicity and Carcinogenicity

Since *Update 2004*, most of the new literature concerning the toxic activity of DMA has addressed genotoxicity, a major mechanism of carcinogenesis. Cancer has been induced in the urinary bladder, kidneys, liver, thyroid glands, and lungs of laboratory animals exposed to high concentrations of DMA (IOM, 2003; 2005). DMA might act through induction of oxidative damage or damage to DNA, and exposure results in necrosis of the urinary bladder epithelium followed by regenerative hyperplasia (IOM, 2005).

In a new study, DMA^{III} was considerably more potent than DMA^V in inducing DNA damage in Chinese hamster ovary cells (Dopp et al., 2004), and this was associated with a 10% uptake of DMA^{III} into the cells compared with 0.03% for DMA^V. Additional study showed that DMA^V is poorly membrane-permeable, but when forced into cells by electroporation it can induce DNA damage (Dopp et al., 2005). Furthermore, DMA^V induced protein-DNA adducts in lung fibroblast cells (MRC-5) (Mouron et al., 2005) and transformation loci in 3T3 fibroblasts after post-treatment with the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (Tsuchiya T et al., 2005). However, DMA^V was devoid of promotion activity in 3T3 fibroblasts when cells were pretreated with either 3-methylcholanthrene or sodium arsenite.

DMA^V, but not inorganic arsenic species, exhibited genotoxicity in *Drosophila* as assessed by the somatic mutation and recombination test (Rizki et al., 2006). *Drosophila* lacks the ability to methylate arsenic, so these data suggest that arsenic biomethylation is a key determinant of arsenic genotoxicity.

Both DMA^{III} and DMA^V have been shown to induce DNA damage by increasing oxidative stress. Chronic exposure of ddY mice to DMA^V at 400 ppm in drinking water increased staining for 4-hydroxy-2-nonenal adducts, which are indicative of oxidative stress, and for 8-oxo-2′-deoxyguanosine (8-oxodG), reactive oxygen species-induced DNA damage, in Clara cells of the lung (An et al., 2005). Gomez et al. (2005) demonstrated that DMA^{III} induced a dose-related increase in DNA damage and oxidative stress in Jurkat cells.

Two separate studies investigated the degree to which oxidative stress may mediate DMA^V cytotoxicity. In one study, an antioxidant (*N*-acetylcysteine, vitamin C, or melatonin) and DMA at 100 ppm DMA^V were coadministered to F344 rats for 10 weeks (Wei et al., 2005). *N*-Acetylcysteine inhibited DMA^V-induced proliferation of the urinary bladder epithelium, whereas neither vitamin C nor melatonin had an effect; this suggested that oxidative stress may mediate the cytotoxic process in the urothelium. In a second study, metallothionein wildtype and null mice were exposed to a single oral dose of DMA^V at 0, 188, 375, or 750 mg/kg (Jia et al., 2004). DMA^V induced a dose-dependent increase in metallothionein in the liver of wildtype mice but metallothionein was undetectable and uninducible in the null mice. At 24 hours after exposure, DMA^V induced dose-dependent DNA adducts, DNA strand breaks, and pulmonary and bladder apoptosis in both genotypes, but the incidence of damage was significantly higher in the null mice. Those results suggest that metallothionein may play a protective role against DMA^V-induced DNA damage.

In a recent study, gene-expression profiling of bladder urothelium after chronic exposure to DMA^V in the drinking water showed significant increases in genes that regulate apoptosis, the cell cycle, and oxidative stress (Sen et al., 2005). Furthermore, doses that were nontoxic, according to a lack of histologic and ultrastructural changes, could be distinguished from toxic doses on the basis of the expression of a subset of gene involved in control of cell signaling and the stress response, such as thioredoxin, E-cadherin, and heat shock 70 kDa.

Since *Update 2004*, further studies have investigated the carcinogenicity of DMA. Xie et al. (2004) administered DMA^V at 1,000 ppm in drinking water to v-Ha-*ras* transgenic mice for 17 weeks and after 4 weeks of treatment applied TPA to the skin twice a week. The results were an initial 10% body-weight loss, a cumulative mortality of 20%, hepatic arsenic accumulation, hepatocellular degeneration and foci of inflammation without evidence of liver tumors, and hepatic DNA hypomethylation. Hepatic gene-expression profiling showed that DMA^V exposure induced changes consistent with oxidative stress, including induction of heme oxygenase, NAD(P)H:quinone oxidoreductase, and glutathione-*S*-transferase.

Mizoi et al. (2005) found that chronic administration of DMA^V at 400 ppm to mice after their initiation with 4-nitroquinolone 1-oxide (4NQO) significantly increased the number of lung tumors and the percentage of mice with lung tumors. DMA^V also significantly increased pulmonary 8-oxodG adducts regardless of whether the mice had been treated with 4NQO. Hairless mice treated with DMA^{III} on the skin after initiation with dimethylbenz[*a*]anthracene exhibited a significant increase in epidermal 8-oxodG adducts and skin tumors.

In a 2-year bioassay, F344 rats were exposed to DMA^V at 0, 2, 10, 40, or 100 ppm in drinking water, and C57BL/6 mice were exposed at 0, 8, 40, 200, or 500 ppm (Arnold et al., 2006). The rats developed epithelial carcinomas and papillomas in the urinary bladder and

nonneoplastic changes in the kidney. In contrast, the mice failed to develop any tumors but exhibited glomerular nephropathy, nephrocalcinosis, and vacuolation of the urinary epithelium. The murine no-observed-effect level (NOEL) based on nonneoplastic changes was 40 ppm in males and 8 ppm in females; the rat NOEL based on neoplastic and nonneoplastic changes was 10 ppm in both sexes.

UPDATED TOXICITY PROFILE OF PICLORAM

Picloram (4-amino-3,5,6-trichloropyridine-2-carboxylic acid or 4-amino-3,5,6-trichloropicolinic acid) was used with 2,4-D in the herbicide formulation Agent White, which was sprayed in Vietnam. Picloram also is commonly used in Australia in a formulation under the trade name Tordon 75D®. Tordon 75D contains several chemicals, including 2,4-D, picloram, a surfactant diethyleneglycolmonoethyl ether, and a silicone defoamer. A number of studies on picloram actually used such mixtures as Tordon or other mixtures of 2,4-D and picloram that are similar to Agent White.

The initial VAO committee reviewed studies on the toxicokinetics, carcinogenicity, genotoxicity, acute toxicity, chronic systemic toxicity, reproductive and developmental toxicity, and immunotoxicity of picloram. Studies in animals showed rapid absorption through the gastrointestinal tract and rapid elimination of picloram in urine as the unaltered parent compound. Previously reviewed carcinogenicity assays reported finding thyroid or liver tumors in rodents treated with picloram, but the results were largely negative. An Environmental Protection Agency review panel concluded that the one report of a significant increase in liver tumors was attributable to hexachlorobenzene contaminant of the picloram test agent. Some cellular abnormalities in liver and inconsistent developmental effects were reviewed in *VAO* and updates. *Update 2002* assessed possible effects of picloram in male Sprague-Dawley rats exposed to commercial-grade Tordon 75D. Effects included atrophy and histologic changes in testes (Oakes et al., 2002). The animals had been exposed to various doses, some very high, over various periods. The authors did not determine which of the chemicals in the Tordon 75D formulation caused the testicular damage but cited other studies that suggested that picloram was not responsible; in the long-term carcinogenesis studies in Fischer 344 rats conducted by Stott et al. (1990), administration of daily doses of picloram up to 200 mg/kg for 2 years resulted in no evidence of testicular atrophy. Oakes and Pollack (1999) also examined effects of Tordon 75D on mitochondrial function and reported that effects probably could be attributed to the surfactant in the formulation rather than to picloram.

Update of the Scientific Literature

No relevant studies of picloram have been published since the preparation of *Update 2004*. Two earlier studies that were not reviewed, however, do merit mention.

Nolan et al. (1984) examined the toxicokinetics of picloram in six healthy male human volunteers, who were given single oral doses of 0.5 or 5.0 mg/kg and a dermal dose of 2.0 mg/kg. Picloram was rapidly absorbed in the gavage study and rapidly excreted as unchanged compound in the urine. More than 75% of the dose was excreted within 6 hours, and the remainder was excreted with an average half-life of 27 hours. On the basis of the quantity of picloram excreted in urine in the skin study, the authors noted that only 0.2% of the picloram

applied to the skin was absorbed. Thus, because of its rapid excretion, picloram has a low potential to accumulate in humans.

The other study reported on effects of picloram on induction of drug-metabolizing enzymes in the liver (Reidy et al., 1987). Male and female Sprague-Dawley rats were treated with a variety of doses up to 200 mg/kg for 7 or 14 days. Modest increases (a factor of 5-8) in activity of microsomal ethoxyresorufin-*O*-deethylase activity (which is associated with the cytochrome P450 enzymes that are under control of the aryl hydrocarbon receptor) were observed but only at the highest doses of picloram. In contrast, 3-methylcholanthrene, a known inducer of CYP1A, induced the activity by a factor of 150.

In general, then, the literature on picloram toxicity continues to be sparse. Studies in humans and animals indicate that picloram is rapidly eliminated as the parent compound. Studies in animals have indicated that picloram is sparingly toxic at very high doses.

UPDATED TOXICITY PROFILE OF TCDD

Toxicokinetics

Unlike the herbicides described earlier in this chapter, which tend to be rapidly excreted from the body and do not accumulate to any substantial degree in tissues, TCDD is poorly metabolized and highly lipid-soluble, so it can accumulate in the body and distribute among tissues. The toxicokinetics of TCDD are therefore important in predicting the amounts that will reach specific target organs or cells and thereby contribute to toxicity in thems. The more complex models, known as *p*hysiologically *b*ased *p*harmaco*k*inetic (PBPK) models, are powerful tools that divide the body into compartments that represent organs and integrate the exposure dose with organ mass, blood flow, metabolism, and lipid content to predict the movement of toxicants into and out of each organ.

The distribution of TCDD and other chlorodibenzo-*p*-dioxin congeners has been examined extensively in experimental-animal toxicokinetic models over the last 25 years. In animal models, it is possible to control exposure and thus to test the validity of PBPK or other models. In humans, the utility of such models is determined by examining TCDD tissue and blood concentrations in relation to occupational or environmental exposure. The models show that TCDD is distributed to all compartments of the body although the amounts differ from organ to organ, and lipid content has a substantial effect on the net accumulation of TCDD in different organs and in the body as a whole. Whole-blood or serum concentrations of TCDD can also fluctuate with differences in physiologic states and metabolic processes, which can affect the mobilization of lipids and possibly of compounds stored in them. Moreover, processes in one organ can influence distribution to others. For example, binding proteins in the liver, such as hepatic cytochrome P450 1A2 (CYP1A2) in liver, can influence accumulation in other organs.

Modeling the toxicokinetics of TCDD has several objectives: to estimate organ distribution on the basis of concentrations measured in surrogate tissue, such as blood; to determine organism concentrations from diet or other external sources of exposure; and to back-extrapolate from current tissue concentrations to those at the time of original exposure. The most recent animal and human studies modeling the toxicokentics of TCDD are reviewed below.

Animal Studies

Several additions to the literature since the last report (IOM, 2005) detail the processes that affect distribution of TCDD. TCDD is known to distribute to and accumulate in adipose. Irigaray et al. (2005) compared the kinetics of uptake and release of TCDD in isolated porcine adipocytes with those of the free fatty acid palmitic acid. Their study revealed that under conditions of lipogenesis the uptake kinetics of palmitic acid and TCDD were similar; however, under conditions of lipolysis, palmitic acid was released significantly faster than TCDD. Thus, they concluded that the storage rate of TCDD in adipose is greater than the release rate and results in net accumulation at steady state and that increases in serum TCDD could be likely in the presence of radical weight loss.

In addition to the distribution to adipose, studies continue to investigate the distribution of TCDD to the liver and the role of hepatic sequestration by CYP1A2 in TCDD pharmacokinetics and toxicity. Iwata et al. (2004) showed a preferential deposition of TCDD-like dioxins and biphenyls into the liver, rather than adipose, of Baikal seals as exposure increased; this showed that concentration-dependent hepatic sequestration of these congeners is common in mammals. The hepatic sequestration is believed to result from direct binding of TCDD to TCDD-induced CYP1A2 (Poland et al., 1989). Dragin et al. (2006) demonstrated that distribution of TCDD is highest in adipose, mammary gland, and serum of pregnant mice lacking CYP1A2 expression compared with wildtype mice that show the highest TCDD concentrations in liver. Furthermore, fetuses from CYP1A2 null dams exhibit higher sensitivity to teratogenicity and lethality than fetuses of wildtype dams at the same maternal TCDD dose. Notably, knock-in of human CYP1A1 and 1A2 genes into the CYP1A2 null mouse reduces the TCDD teratogenic sensitivity of the fetuses back to the wildtype levels. Thus, the study revealed that maternal hepatic CYP1A2 sequesters TCDD and protects against fetal teratogenicity, and human CYP1A2 provides the same degree of protection.

Previous data from experimental animal models show that as TCDD exposure increases, its apparent half-life decreases; this suggests dose-dependent elimination (Diliberto et al., 2001; Michalek et al., 2002). In a recent study, Emond et al. (2006) investigated the influence of cytochrome P450 1A2 induction and adipose tissue mass on the dose-dependent elimination of TCDD by using a rat PBPK model. When an inducible-elimination component was included in the PBPK model on the basis of dose-dependent induction of hepatic CYP1A2, the TCDD half-life of elimination varied significantly with dose, with high doses resulting in much faster elimination. In addition, Emond et al. (2006) found that increasing adipose tissue mass slows the elimination of TCDD at low doses, but the relationship between adipose tissue mass and TCDD elimination reachs a maximal level at higher doses as CYP1A2 is induced. Thus, the authors suggest that at low TCDD exposures the diffusion from adipose is the rate-limiting step in TCDD elimination, whereas at higher TCDD exposures metabolic elimination is the rate-limiting step.

Human Studies

Efforts have continued to identify dietary or other approaches that can enhance the elimination of dioxins, decreasing their uptake and half-life, and previous studies over the last several years have attempted to enhance elimination of TCDD, for example, with activated charcoal, crude dietary fiber, Olestra, and seaweed (reviewed in previous updates). TCDD

residues are generally eliminated in the feces, which can include ingested matter that is not absorbed, and in residues excreted from the body in bile. In a pilot study with nine subjects, Sakurai et al. (2004) showed that treatment of hyperlipoproteinemia patients with the anion-exchange resin colestimide for 6 months decreases blood TCDD by 20% without significantly reducing any of the lipid fractions. Clearly, randomized placebo-controlled studies are needed to confirm those results.

Since *Update 2004*, two new human PBPK models have been developed in an effort to incorporate the increasing evidence that TCDD elimination is dose-dependent. The models challenge the current dogma of using a first-order elimination model and assuming an 8.7-year half-life for TCDD to back-extrapolate peak human exposures from current serum concentrations. In humans, when initial exposure is very high (over 1,000 ppt), TCDD-inducible elimination results in estimated elimination half-life of 1–3.6 years. Thus, the new human PBPK models incorporate a concentration-dependent TCDD-elimination component, which is assumed to be a function of hepatic CYP1A2 induction in one model (Emond et al., 2005) and of hepatic TCDD concentration in the other (Aylward et al., 2005a,b).

Aylward et al. (2005a) modified a previously published toxicokinetic model (Carrier et al., 1995a,b) to include a concentration-dependent distribution of TCDD to liver and adipose and tissue-specific rates of elimination from these two compartments. To optimize the model, serial measurements of serum TCDD concentrations from 39 people were used with initial serum lipid TCDD concentrations of 130-144,000 ppt, including 36 adults exposed during the Seveso accident and three poisoned in Vienna, Austria. The model predicts that the apparent half-life of TCDD is less than 3 years when serum TCDD concentrations are greater than 10,000 ppt and over 10 years when serum TCDD concentrations are less than 50 ppt. The model results also indicate that men eliminate TCDD faster than women and young people faster than older people.

Application of the model to serum sampling data from the National Institute for Occupational Safety and Health (NIOSH) cohort indicates that previous estimates of peak serum TCDD concentrations, based on first-order elimination, have been underestimated and the underestimation may be by as much as a factor of 10 for the most highly exposed subcohorts. Aylward and colleagues (2005b) then compared a concentration- and age-dependent elimination model (CADM) with a first-order elimination model with an 8.7-year half-life to predict the cumulative serum TCDD concentration. The CADM resulted in a significantly better fit to the measured serum lipid data than the first-order elimination model. Furthermore, use of the CADM to back-extrapolate cumulative serum TCDD exposure predicts significantly higher cumulative-exposure estimates than the first-order elimination model. Thus, Aylward et al. (2005b) conclude that the underestimation of occupational exposures by use of a first-order elimination model may result in an overestimation of TCDD's carcinogenic potency.

Cheng et al. (2006) applied the same CADM to estimate the cancer risk associated with occupational TCDD exposure in the NIOSH cohort. They found that the model predicted cumulative serum TCDD concentrations 4–5 times higher than those obtained with the first-order elimination model and an 8.7-year fixed-half-life model. Further use of the PBPK model failed to find a significant relation between untransformed TCDD exposure and cancer response using any lag period, but did identify a positive association between logarithmically transformed TCDD exposure and cancer mortality when a lag period of 1–15 years was applied and when the individuals with the most extreme exposures (i.e., highest 5%) were excluded from the analysis. Several explanations could account for the strengthened association between cancer risk and TCDD exposure for a sustained period, including the experimental evidence that TCDD acts as a

potent tumor promoter, which requires a sustained period to accelerate tumor growth.

Using a similar approach, Emond et al. (2005) extrapolated a previously published rodent pharmacokinetic model of TCDD (Emond et al., 2004), which incorporates dose-dependent elimination as a function of hepatic CYP1A2 induction, to human exposures. The model was optimized by using serial serum TCDD concentrations from 20 Ranch Hand veterans, data from a single human volunteer exposed to a high dose of TCDD (Poiger and Schlatter, 1986), and data from two women poisoned with TCDD (Geusau et al., 2002). The model shows good correlations with measured serum TCDD concentrations for both the Ranch Hand cohort and the two highly exposed women. Application of the model to serum sampling data from another group of Ranch Hand veterans to back-extrapolate peak serum TCDD concentrations at the time of military discharge indicates that previous estimates, based on first-order elimination, are much too low and may result in exposure misclassification of people in epidemiology studies. It should be noted that there was substantial inter-individual variability in the TCDD kinetics of the data sets used to estimate the parameters in the PBPK models developed by Aylward et al. (2005) and Emond et al. (2005). This inter-individual variability will add to the uncertainty in quantitative dose-response assessment for cohorts relying on back-extrapolated exposures.

In summary, the new concentration-dependent PBPK models, which predict that TCDD elimination is considerably faster after high exposure, suggest that (1) previous back-extrapolation of peak serum TCDD concentrations may be significantly underestimated and result in a potential for exposure misclassifications and (2) peak human exposures may be more similar to doses used in animal toxicity studies than previously estimated.

Metabolism and Half-Life Studies

It is generally agreed that the toxicity of TCDD is related in part to its persistence in the body; however, a wide range of elimination half-life estimates in humans have been reported (Table 3-1). Recent studies suggest that TCDD half-life in humans is concentration-dependent—that rapid elimination follows hepatic sequestration at high doses and much slower elimination follows redistribution of TCDD to adipose at lower body burdens. Thus, the half-life of TCDD in humans varies with body-mass index (BMI), age, sex, and TCDD concentration (reviewed in IOM, 2005). The relevant papers were reviewed in *Update 2004* and are discussed above in the context of new PBPK models, and they will not be reviewed again here. Rather, papers that have been published since *Update 2004* will be discussed.

Table 3-1 Estimates of TCDD Half-Life in Humans and Animals

Reference	Half-Life[a]	Confidence Interval	Comment
Human Studies			
Leung et al., 2006	0.4 years		Breast-fed infants, 0–1 year PE
Kumagai and Koda, 2005	1.1–2.3 years		Adult males, Incinerator workers, 0–1.3 years PE
Aylward et al., 2005a	<3 years		Calculated for exposures >10, 000 pg/g serum lipid
	>10 years		Calculated for exposures <50 pg/g serum lipid
Flesch-Janys et al., 1996	7.2 years		Adult males, Boehringer cohort
Geusau et al., 2002	1.5 years[b]		Adult female, severe exposure 0–3 years PE
	2.9 years[b]		Adult female, severe exposure 0–3 years PE
Michalek et al., 2002	0.34 years[b]		Adult males, Seveso cohort, 0–3 months PE
	6.9 years		Adult males, Seveso cohort, 3–16 years PE

	9.8 years		Adult females, Seveso cohort, 3–16 years PE
	7.5 years		Adult males, Ranch Hands 9–33 years PE
Needham et al., 1994	7.8 years	7.2–9.7 years	Adults, Seveso cohort
Pirkle et al., 1989	7.1 years	5.8–9.6 years	Adult males, Ranch Hands 9–23 years PE
Animal Studies			
Neubert et al., 1990	73.7 days	60.9–93.8 days	Monkeys, Marmoset, single injection
DeVito and Birnbaum, 1995	15 days		Mice, female B6C3F1
Gasiewicz et al., 1983	11.0 days[c]		Mice, C5BL/6J
	24.4 days[c]		Mice, DBA/2J
	12.6 days[c]		Mice, B6D2F1/J
Koshakji et al., 1984	20 days		Mice, male ICR/Ha Swiss
Hurst et al., 1998	8 days		Rats, Long-Evans, excretion from liver
Pohjanvirta et al., 1990	21.9 days		Rats, male Han/Wistar resistant strain
Viluksela et al., 1996	20.2 days		Rats, Long-Evans TurkuAB strain
	28.9 days[d]		Rats, Long-Evans Charles River strain
Weber et al., 1993	16.3 ± 3.0 days		Rats, male Sprague-Dawley

[a] Half-lives of TCDD in humans based on measurement of TCDD in serum samples.
[b] Shorter half-lives measured in humans during first months after exposure or in severely contaminated persons consistent with nonlinear elimination predicted by PBPK modeling (e.g., by Carrier et al., 1995). Greater half-life in females attributed to greater body mass index.
[c] Total cumulative excretion of ^{3}H-TCDD-derived radioactivity.
[d] Attributed to differences in dilution due to different growth rates.
ABBREVIATION: PE, postexposure.

One and 16 months after occupational exposure of incinerator workers in Japan to TCDD-like polychlorinated dibenzodioxins and polychlorinated dibenzofurans, Kumagai and Koda (2005) measured blood lipid concentrations. Blood samples were also collected from unexposed control subjects. The mean TCDD-equivalent concentration was 49.1 and 29.4 ppt on a lipid basis 1 and 16 months, respectively, after exposure, whereas control subjects averaged 18 ppt. With a one-compartment model, the half-life estimates of those TCDD-like chemicals were 1.1–2.3 years.

Leung et al. (2006) measured TCDD intake and blood lipid concentrations in two infants exposed via breast milk and then estimated their TCDD-elimination half-life. Blood lipid concentrations of TCDD increased by factors of 1.7 and 1.9 in the two infants from birth to about 1 year of age. The average elimination half-life estimate of TCDD from the infants was 0.4 year, considerably lower than the roughly 7.6 years in adult humans.

Summary

Studies that model the disposition and effects of TCDD in rodents continue to be refined and to support the development and use of PBPK models to estimate congener-specific concentrations in human tissues. It will be important to continue to refine PBPK models for evaluating tissue distribution in humans.

The information on TCDD toxicokinetics is expanding, and new studies are beginning to challege the previous paradigm of a one-compartment, first-order elimination model to back-extrapolate to earlier exposure estimates. The data show that BMI and body fat content are important determinants of TCDD half-life, particularly after low exposure. However, persons who accumulate high concentrations of TCDD show an initial phase of elimination that is rapid with half-lives that are much shorter than average. The mechanism underlying the rapid phase of

elimination is not known but appears to be related to hepatic CYP1A2 induction that sequesters TCDD in liver and prevents it from distributing; prevention of distribution results in rapid elimination from the liver into the bile. Thus, biphasic elimination continues to confound back-extrapolation to initial exposure in persons who might have experienced high exposures years before blood or other tissue samples were obtained for analysis. Estimates from biphasic elimination models suggest that significant individual variation in elimination can occur and that the use of the first-order models may lead to misclassification of people into the wrong exposure groups on the basis of back-extrapolation to earlier exposure concentrations. The implications for exposure misclassification are discussed in more detail in Chapter 5.

Evidence presented in the new studies suggests that a multicompartment model is appropropriate. However, it remains unclear which type of model should be used for dose reconstruction. As the biphasic models are validated and optimized further, continued assessment of the potential for misclassification with the first-order elimination models is highly warranted for epidemiologic studies that rely on back-extrapolated estimates of initial exposure concentrations.

Efforts to enhance the rate of absorption of dietary TCDD and to enhance elimination by inclusion of fiber or other dietary supplements continue to show promise.

Underlying Mechanisms of Toxic Action

Studies published since *Update 2004* are consistent with the hypothesis that TCDD produces its biologic and toxic effects by binding to a gene regulatory protein, the aryl hydrocarbon receptor, which can modulate gene expression through several mechanisms that will be discussed in greater detail in the following sections. The hypothesis that TCDD toxicity requires the AhR is supported by numerous studies that have evaluated structure–activity relationships of various compounds that bind to the AhR, the genetics of mutant genes that express the AhR, AhR-deficient mice, and the molecular events that contribute to and regulate AhR expression and its activity.

As our understanding of the mechanisms involved in TCDD-induced toxicity and carcinogenicity unfolds, it is clear that our attention must also include an appreciation of the physiologic role of the AhR. The AhR signaling pathway may be viewed as regulating multiple physiologic processes that may not be mutually exclusive, including the adaptive pathway that mediates the metabolism of xenobiotics, such as the polycyclic aromatic hydrocarbons; a toxic pathway that mediates the deleterious effects of xenobiotic exposure; and pathways that regulate developmental and adult cardiovascular homeostasis and adult fertility.

The finding that many AhR-regulated genes are modulated in a species-, cell-, and developmental-stage-specific pattern suggests that the molecular and cellular pathways that lead to a particular toxic event are complex. Many of the data are consistent with the notion that the cellular processes most sensitive to TCDD-induced modulation as mediated by the AhR are those involving growth, maturation, and differentiation. The findings in animals indicate that the reproductive, developmental, and oncogenic endpoints are sensitive to TCDD. The data support the biologic plausibility of similar endpoints in exposed humans. Many of the responses, however, are tissue- and species-specific. Hence, the appearance of some toxic endpoint in one or even several animal species exposed to TCDD does not necessarily indicate that the same endpoint will occur in exposed humans, or vice versa. The mechanisms responsible for the

differences are not known exactly but will be considered in greater detail in the sections below.

The conclusions indicated above are similar to those in *Update 2004*. Since those updates, many cellular and molecular interactions of the AhR have been reported. However, in many cases, it is not clear how they might be related to a particular toxic endpoint. Therefore, although the text below cites related work published since *Update 2004* that was identified by the committee, closer attention is given only to studies that add substantial information, particularly as it might be relevant to the exposure of Vietnam veterans. As discussed in *Update 2004*, it is important to consider exposure and species sensitivity in discussing animal data and their relevance to humans. Likewise, it is important to note that many of the effects that are reported in animals are seen at dose levels of greater than 1 to 10 ug/kg, far higher than current measured and most back-extrapolated estimates of veterans' exposure levels.

TCDD-Mediated Alterations of Gene Expression

Much of our current understanding of the mechanism of TCDD action is based on analysis of the induction of particular genes and analysis of altered intracellular signaling pathways. The genes modulated by TCDD exposure are involved in numerous biologic processes, as described in *Update 2004*. As shown in Tables 3-2 and 3-3, a number of recently reported genomic and proteomic studies lend insight into the gene pathways that are altered by TCDD in many cell types and tissues. Examples of pathways or processes (with some specific genes involved indicated in square brackets) that are altered by TCDD exposure are: metabolism of xenobiotics, carbohydrates, glucose, fatty acids, and cholesterol and transport of small molecules (Yueh et al., 2005); cell-cycle control [cyclin E1, cyclin G2]; oncogenesis and proliferation [myc] (Yang X et al., 2005); EGFR ligands (Martinez et al., 2004); apoptosis or programmed cell death [Bax]; matrix remodeling [matrix metalloproteinase-1 and -9, plasminogen-activator inhibitor-2]; inflammation [interleukin 1β, TNFα]; angiogenesis [VEGF, endothelin]; and altered immune function [TNFα-induced protein 2). It is presumably through alterations of those basic processes that TCDD exerts its carcinogenic and toxic effects.

Table 3-2 Overview of TCDD-induced changes in gene expression as identified by microarray analysis.

MODEL	CONDITIONS	BIOLOGICAL OUTCOMES	MAJOR PATHWAYS AFFECTED	EXAMPLE	REF
Three day old zebrafish	0.5 or 5 nM TCDD, expression in heart analyzed after 24 hr.	TCDD-induced pericardial edema/circulatory impairment	**Metabolic Processes** Xenobiotic metabolism Fatty acid metabolism Steroid synthesis **Sarcomeric components** **Mitochondrial energy transfer** **Ribosomal Machinery**	CYP1A1↑ Acyl-coenzyme A dehydrogenase↑ Myosin heavy chain ↑ NADH dehydrogenase↑ Mitochondrial 12S rRNA ↑	Handley-Goldstone et al., 2005
C57BL/6	1.5, 3 and 6	TCDD-induced	**Metabolic Processes**		Thackaberry

N pregnant mice, GD 12.5	µg/kg TCDD, expression in hearts at GD 17.5.	cardiac tetratogenicity, impaired cardioproliferation	Xenobiotic metabolism Carbohydrate metabolism Organic transporters **Cell cycle (G1/S)** **Extracellular matrix**	CYP1A1↑ Fbp1 ↑ Abcc3 ↓ Cyclin E1↓ MMP13 ↑	et al., 2005
C57BL/6 pregnant mice, ED 7	20 µg/kg TCDD, expression in brain at ED 12.	TCDD-induced decrease in neocortical neurogenesis (Mitsuhashi et al 2003).	**Metabolic Processes** Xenobiotic metabolism **Organogenesis**	CYP1A1↑ Mab21L2↓	Fujita et al., 2006
6-8 wk female C57BL/6J mice OR Vascular smooth muscle cells	150 and 1500 ng/kg TCDD, expression in aorta after 40 weeks 5 nM TCDD, expression after 8 hr	Gene expression consistently altered in both systems by TCDD was emphasized.	**Metabolic Processes** Xenobiotic metabolism Glycolysis Insulin signaling **Cell cycle** **Signal Transduction/ Mitogenesis** **Membrane Channels** **Growth Arrest/DNA damage** **Transcription factors** **Immune function** **Platelet function**	CYP1B1↑ Glyoxalase ↑ Igfbp2 ↑ Cyclin G2 ↑ Slp65 ↓ Scn5a ↓ GADD45g ↓ Jmy ↓ Ly4911 ↑ Clec2 ↑	Puga et al., 2004
10 wk female C57BL/6J ovariecto mized	1 and 10 µg/kg TCDD +/- E2, expression in uterus after 6 hr		**Metabolic Processes** Xenobiotic Fatty acid metabolism **Cell Structure** **Proliferation** **Immune function**	CYP1A1↑ Fabp1 ↑ Connexin 26 ↑ PCNA ↑ Immunoglobulin heavy chains ↓	Watanabe et al., 2005
28 PND female C57BL/6 mice, ovari-ectomized	30 µg/kg TCDD +/- E2 (100 µg/kg), expression in uterus after 2-72 hr.	No TCDD-induced effect on E2 induced uterine wet weight, luminal epithelial cell height or stromal thickness.	**<u>TCDD Only</u>** **Metabolic Processes** Xenobiotic metabolism Protein/small molecular transport Amino acid metabolism Fatty acid transport/metabolism **<u>EE + TCDD</u>** **Metabolic processes** Amino acid metabolism Small molecule transport **Proliferation**	CYP1A1↑ Kpna6↑ Asns ↑ Lrp2 ↑ Asns ↑ Slc 25a5 ↑ PCNA ↑	Boverhof et al., 2006

			Signal Transduction **Protease function** **Microtubule structure** **Transcription factors**	Inpp5a ↑ Serpinh1 ↑ Dctn2 ↑ Rcor3 ↓	
Rat ovarian granuloa cells	100 pM TCDD, expression after 24 hrs.	FSH induced differentiation	**Metabolic Processes** Xenobiotic metabolism **Cell Cycle** **Cell Structure Proteins** **Cell Adhesion** **Ovarian differentiation** **Steroidogenesis**	 CYP1B1 ↑ Cyclin G↑ α-actin ↓ Filamin A ↓ LH receptor ↓ P450 scc ↓	Miyamato, 2004
C3H 10 T1/2 cells (mouse embry-onic fibro-blasts)	10 nM TCDD treatment during adipogenesis, expression after 24 hr.	IDMB-induced differentiation into adipocytes, cooperative enhancement with the addition of EGF	**<u>IDMB induced change inhibited by TCDD</u>** **Metabolic Processes** Oxidation-linked Metabolism Triglyceride synthesis Cholesterol regulation **Cell Structure** Extracellular matrix Proteoglycans Protease function **Secreted Proteins** **Transcription Factors** **Plasma Membrane Receptors** **Signal Transduction** **Cytokines**	 Cytosolic epoxide hydrolase ↓ ADRP↓ Phospholipid transferase protein ↑ Procollagen VI ↓ Osteoglycin ↑ Plasminogen activator inhibitor 1↓ Adiponectin ↓ C/EBPα ↓ Anion carrier protein 4 ↓ ERK3 ↓ Clustein ↑	Hanlon et al., 2005
C3H 10 T1/2 cells (mouse embryoni c fibroblast s)	10 nM TCDD treatment 48 hr prior to 24 hr treatment with EGF and IDMB		**<u>TCDD-regulated genes under four conditions (quiescent, EGF, IDMB, EGF+IDMBinduced changes in genes not altered by IDMB alone</u>** **Metabolic Processes** Xenobiotic metabolism	 CYP1B1 ↑ Phosphoglycerate	Trasande et al., 2006

			Glucose-linked energy metabolism Iron metabolism **Cytokines** **Oxidative Stress Response** **Growth factor signaling**	kinase 1 Coproporphyrin-ogen oxidase↓ Interleukin receptor type 1 Superoxidase dismutase 3 ↑ Glypican 1 ↑	
HPL1A lung airway epithelial cells	0.1-10 nM TCDD, expression after 24 hrs		**Metabolic Processes** Xenobiotic metabolism Fatty acid β-oxidation **Retinoic acid transport** **Differentiation**	CYP1A1 ↑ Human peroxisomal acyl-CoA oxidase ↑ Cellular retinoic acid binding protein 1 ↓ Retinoic acid receptor β ↑	Toyoshiba et al., 2004
30 PND female C57BL/6 mice, ovariecto mized	30 ug/kg TCDD, expression in liver afeter 2-168 hrs or 0.001-300 μg/kg TCDD, expression in liver after 24 hrs	↑ liver weight at 24, 72 and 168 hrs., apoptosis, immune cell accumulation at 168 hrs. ↑liver weight at 100 and 300 μg/kg, mild to moderate cytoplasmic vacuolization (0.001-.1 μg/kg)(lipid accumulation) ↑alanine aminotransferase at 24 and 168 hrs ↓serum cholesterol (72 and 168 hrs) ↑FFA at 24, 72 and 168 hrs ↑Triglycerides at 24, 72 and 168 hrs	**Metabolic Processes** Xenobiotic metabolism Fatty acid uptake/Metabolism Glucogenogenesis **Oncogenesis** **Apoptosis** **Immune function**	CYP1A1 ↑ Apolipoprotein A-1↓ Gpd2 ↓ Myc ↑ Hip1 ↑ Cd44 ↑	Boverhof et al., 2005
250-300 g Male Sprague-Dawley outbred CD rats	0.4 or 40 μg/kg TCDD, expression in liver after 6 hr, 24 hr and 7 days	↓ body weight (40 μg/kg, 7 day) ↑serum cholesterol (24 h and 7 day) serum triglycerides ↑ (40 μg/kg, 24 hr ↓ 40 μg/kg, 7 day) ↑serum glucose (40 μg/kg, 7 day)	**Metabolic Processes** Xenobiotic metabolism Lipid metabolism Carbohydrate metabolism Insulin signaling Nitrogen metabolism Retinoid metabolism	CYP1A1↑ Acaa1 ↑ Mel ↑ Igfbp1↑ Glu ↓ CES3 ↓	Fletcher et al., 2005

		↑ total protein, globulin (40 µg/kg, 7 day) ↑Hemoglobin (40 µg/kg, 6hr, 24 hr and 7 day) ↓Alanine aminotransferase (0.4 and 40 µg/kg, 7 day) 24 hr and 7 d, evidence of centrilobular hypertrophy (40 µg/kg)	Steroid metabolism Protein/small molecule transport **Cell Cycle** **Cell Signaling** **Immune Response** **Cell Structure**	Srd5a1↓ Slc17a1↑ Ccnd1↓ Tgfb1i4↓ Fkb4↓ MPL3↑	
Female Harlan SD rats	1-100 ng/kg/day TCDD, expression in liver after 13 weeks.	Liver hypertrophy, multinucleated hepatocytes and diffuse fatty change in 100 ng dose(NTP 2004a)	**Metabolic Processes** Xenobiotic metabolism **Oxidative Stress** **Cell Adhesion** **Protease Function** **Immune response** **Cell Structure** **Signal transduction** **Cell signaling**	 CYP1A1 ↑ Cytochrome c oxidase subunit VIII-H ↑ C-Cam 4 ↑ Serpin 7A ↓ Ig non-productively rearranged lamda-chain CAP2 ↑ iNO synthatase ↑ EGF ↓	Vezina et al., 2004
10 wk Male Ahr -/- or wild-type Ahr +/+ C57BL/6J mice	1000 µg/kg TCDD, expression in liver afeter 19 hr.		**<u>AHR effects independent of TCDD</u>** **Metabolic Processes** Xenobiotic metabolism Steroid metabolism Glucose metabolism Protein/small molecule transport **Protease function** **Retinoic acid signaling** **Cell Structure** **<u>AHR-Dependent effects of TCDD</u>** **Metabolic Processes** Xenobiotic metabolism	 CYP1A2 ↑ CYP17a1 ↓ Pck1 ↓ Slc16a5 ↑ Serpina 12 ↑ Retinal binding protein 1 ↓ Tuba 8 ↓ CYP1A1 ↑ TNF 19 ↑ Ti-PARP ↑ Serpina 7 ↓	Tijet et al., 2006

			Immune response **Apoptosis** **Protease Function** **Cell Structure**	Tuba 8 ↑	
30 PND female C57BL/6 mice, ovariectomized	30 ug/kg TCDD, expression in liver afeter 2-168 hrs or 0.001-300 μg/kg TCDD, expression in liver after 24 hrs	Same as those in #11622	**<u>TCDD induced both in vivo and in vitro</u>** **Metabolic Processes** Xenobiotic metabolism Fatty acid synthesis Small molecule transport **Growth Arrest/DNA damage** **Cell cycle** **Mitochondrial function** **Development** **Immune response** **Cell Structure** **<u>TCDD repressed both in vivo and in vitro</u>** **Metabolic Processes** **DNA modification** **Proliferation** **<u>TCDD induced in vivo and repressed in vitro</u>** **CO_2 hydration** **Fatty acid signaling** **Growth arrest/DNA damage** **Oncogenesis** **<u>TCDD repressed in vivo and induced in vitro</u>** **Small molecule transport** **Immune function**	 CYP1A1 ↑ Ptgs 1 ↑ Slc20a1 ↑ GADD45b ↑ Cda5 ↑ Mrp137 ↑ Cfdp 1 ↑ Irf1 ↑, Tnfaip2 ↑ Col1a1 ↑ Gyk ↓ Dnmt 1 ↓ Tk1 ↓ Carbonic anhydrase 2 Fabp5 GADD45gip1 Myc	Dere et al., 2006

			TCDD-elicited gene expression responses unique to C57BL/6 hepatic tissue **Metabolic Processes** Xenobiotic metabolism Fatty acid metabolism Glucose metabolism CO_2 hydration **Growth Arrest** **Development** **Immune response**	Slco Ib2 Btg2 Gsta2 Elovl5↑ Gpd2 ↓ Car3↓ Gas1 ↓ Notch1 ↑ Cd3d↓	
Mouse hepatoma cells (Hepa1c1c7 wild-type and c4 ARNT-deficient)	10 nM TCDD, expression after 1-48 hrs or 0.001 nM-100 nM, expression after 168 hrs.				
Mouse hepatoma cells, Hepa1c1c7 (c1, CYP1A1 deficient; c4, ARNT deficient; c12, AHR deficient	Basal conditions	Differences in morphology and proliferation (c1<WT<c4,c12	**Relative to wild-type** **Cell structure/cytoskeleton** C1 C4 C12 **Bioenergetics** C1 C4 C12	 Anxa7↑ Dncl2a↑ Mapt↓ Kif20a↑ Vim↑ Epb4.115↓ Vcl ↑ Nadufv ↑ Cox6b ↑ Ndufs2 ↑ Cox8a ↑	Fong et al., 2005

			Proliferation C1 C4 C12	 Banf1 ↓ Lyar ↑ tgfb1i4 ↑ Degs ↑ Oaz1 ↑ Ranbp1 ↑ Cdkn1a ↑ Arg2 ↓	
Human hepatoma cell lines, Hep3B and HepG2	50 nM TCDD, expression after 1-4 hr		**Metabolic Processes** **Proliferation** **Signal Transduction** **Development**	CYP1A1 ↑ JUN ↑ SOS1 ↑ TBX3 ↑	Kim et al., 2006
Long-Evans and Sprague Dawley rats	100 µg/kg TCDD, expression in liver after 3 and 19 hr.		**<u>TCDD modulated AHRE-II genes</u>** **Metabolic Processes** Xenobiotic metabolism **Cell Signaling** **Proteosome function** **Circadian Rhythm** **Ribosomal proteins**	 CYP2b19 ↓ Tgfβ3 ↓ Proteasome type5 ↓ Period 2 ↑ Rib L 29 ↓	

Table 3-3 Overview of TCDD-induced changes in gene expression as identified by proteomics.

MODEL	CONDITIONS	PROTEINS DIFFERENTIALLY EXPRESSED BY TCDD EXPOSURE	REF
5 wk, male Sprague-Dawley rats	1–50 µg/kg TCDD, expression in liver after 7 days. or 0.01–2.5 µg/kg TCDD, expression in liver after 4 weeks.	Apoliprotein A-IV ↑ A-1-Macroglobulin ↑ Acidic ribosomal protein P0 ↑ Bal-647 ↑ Endoplasmic reticulum protein 29 ↑ Proteasome subunit β type 3 ↑ A-1-macroglobulin ↑ Ba1-647-newly expressed MAWD binding protein-newly expressed δ-Aminolevulinate dehydratase ↑ MAWD binding protein ↑ Phosphatidylethanolamine binding proteins; hippocampal cholinergic neurostimulating peptide ↑ Transthyretin precursor;prealbumin ↑ Histidine triad nucleotide binding protein ↑ Phosphoglycerate mutase type B subunit ↑	Jiang et al., 2005
10 wk, male Long-	100 µg/kg TCDD, expression in	**<u>Protein and mRNA expression altered by</u>**	Pastorelli et

Evans and Hans /Wistar rats	liver after 5 days.	**TCDD in sensitive (Long-Evans) rats** Aldehyde dehydrogenase family 3, member A1 ↑ Apolipoprotein A-1 ↑ Programmed cell death protein 8 ↓ Argininosuccinate synthetase ↓ Carbonic anhydrase 3 ↓ MAWD-binding protein ↑ Paraoxonase 3 ↑ Selenium binding protein 2 ↑ Sulfotransferase family 1A, member 1 ↓ Transferrin ↑	al., 2006
G. *gallus* eggs (ED0)	20 ng TCDD/egg, expression in liver and ovary in one-day old chicks.	**Liver ($p < 0.05$)** Fibrinogen gamma chain precursor ↑ Hypothetical protein;high homology with NADH ubituinone oxidoreductase, 42 kDa subunit. **Ovary ($p < 0.05$)** 60 kDa heat shock protein ↑ Regucalcin ↓	Bruggeman et al., 2006
59 wk (± 12 wk) marmosets	100 ng/kg TCDD, expression in liver and thymus after 4 weeks.	**Liver** Voltage-dependent anion channel protein 1 ↑ Transferrin ↑ Lamin A ↑ Heat shock 70 kDa protein 1, Chain A ↑ Hemoglobin beta chain ↓ Eukaryotic translation initiation factor 4H ↓ Thymidine phosphorylase precursor ↓ Delta 3,5-delta2,4-dienoyl-CoA isomerase ↓ Fructose-bisphosphate aldolase B ↓ Dihydrolipoamide succinyltransferase ↓ **Thymus** NADH-ubiquinone oxidoreductase 51 kDa subunit ↑ 60 kDa heat shock protein ↑ Isocitrate dehydrogenase subunit alpha ↑ Glycerol-3-phosphoate dehydrogenase ↑ Dihydrolipoamide dehydrogenase ↑ Isocitrate dehydrogenase subunit alpha ↑ Citrate synthase ↑ Mitochondrial innter membrane protein ↑	Oberemm et al., 2005

		Adseverin ↑ Pyruvate dehydrogenase subunit beta ↑ Mitochondrial aldehyde dehydrogenase ↑ Motor protein ↑ Heat shock cognate 71 kDa protein ↑ Protein disulfide isomerase A3 ↓ Cytoplasmic actin 1 ↓ Thiopurine S-methyltransferase ↓ Ca-dependent protease ↓ Vimentin ↓	
Rat 5L hepatoma cells	1 nM TCDD, expression after 8 hr.	**Histones** Histone H1 strongly ↑ **Structural proteins** Vimentin ↓ **Molecular chaperones** GRP78 ↓ **Oxidant defense** Superoxide dismutase [Mn], mitochondrial precursor ↑ **Ribosomal proteins** 60 S ribosomal protein L7a ↓ **Elongation factors** Eukaryotic translation initiation factor 4B ↓ **Nucleolus biogenesis** Nucleophosmin **(B23)** ↓ **Glycolysis** Mitochondrial hexokinase I ↓ **Xenobiotic metabolism** Aldehyde dehydrogenase ↑	Sarioglu et al., 2006

Like many ligand-activated transcription factors, the AhR alters gene expression via mechanisms that can be classified as genomic mechanisms that require direct binding of the AhR/ARNT heterodimer to DNA ("genomic/direct DNA binding"), genomic mechanisms that do not require direct DNA binding ("genomic/non-DNA binding"), or nongenomic mechanisms that occur at the post-transcriptional level and include modification of translation and signal transduction. A large body of literature indicates that the binding of TCDD to the AhR, the dimerization of the AhR with a nuclear protein (AhR nuclear-transport protein, or ARNT), and the interaction of that complex with specific DNA sequences (often called Ah-responsive elements, or AhREs; dioxin-responsive elements, or DREs; or xenobiotic-responsive elements, or XREs) present in the 5′-promoter regions of particular genes lead to the inappropriate modulation of gene expression. Genes that are directly regulated by binding of the AhR/ARNT heterodimer to DREs (the "genomic/direct DNA binding mechanism") include CYP1A1, CYP1A2, and CYP1B1, which are upregulated after TCDD exposure, as described in *Update 2004*. The recent finding that the AhR/ARNT heterodimer upregulates NF-E2 p45-related factor (NRF2; Miao et al., 2005), which is an important regulator of phase II metabolizing enzymes, presents an additional means by which TCDD can alter xenobiotic metabolism via the "genomic/direct DNA binding mechanism." Also included in the mechanism are genes that are

downregulated by TCDD, such as pS2 (Gillesby et al., 1997). Given that the mechanism requires the appropriate recruitment of coactivators (Hankinson, 2005) and possibly corepressors, the relative cellular concentration of the coregulators may strongly influence TCDD's actions on gene expression and may be an underlying contributor to at least some of TCDD's tissue- and cell-specific effects.

In the "genomic/non-DNA binding" mechanism of TCDD's actions, gene transcription would be altered in a manner that does not require direct binding of the AhR/ARNT heterodimer to DNA. This mechanism includes the TCDD modulation of interactions between the AhR and other nuclear transcription factors, such as the estrogen receptor (ER)-alpha (Beishlag and Perdew, 2005; Mathews et al., 2005), NKκβ (Tian et al., 2002), and Rb (Puga et al., 2002). Recent investigations into the toxicologic significance of the interaction between the AhR and Rb have revealed that the corepression elicited by it facilitates the TCDD-induced growth-arrest response (Huang and Elferink, 2005; Marlowe et al., 2004). When AhR is activated by TCDD, it binds to ARNT; this could decrease the ARNT available for complexing with other PAS proteins (e.g., hypoxia-inducible factors such as HIF1α) that employ ARNT as a dimer partner and could likewise affect formation of ARNT/ARNT homodimers, thereby affecting the regulation of additional genes.

As noted in *Update 2004*, the AhR cross-talks with the ER signaling pathway via a number of mechanisms that include its direct interaction with ERα. Recent data have expanded our understanding of this mechanism by revealing that both the AhR and ERα are recruited to the CYP1A1 promoter (Beischlag and Perdew, 2005; Matthews et al., 2005), and this indicates that ERα is a coregulator of the AhR. It is not clear whether ERα may act as a coactivator or a corepressor. Furthermore, recruitment of the liganded AhR to the breast-cancer gene BRCA-1 appears to be important in the ability of estrogen to upregulate BRCA-1 transcription (Hockings et al., 2006). Although the relevance of those events to human health is unclear, they may prove important in sex- or age-dependent (premenopausal vs postmenopausal) effects of TCDD.

Additional transcription factors that have been recently reported to interact with the AhR include SMRT (Widerak et al., 2006) and C/EBP (Liu and Matsumura, 2006), which may play a role in TCDD's ability to interfere with retinoic acid receptor α signaling and glucose transport, respectively. An additional "genomic/non-DNA binding mechanism" would include TCDD's alteration in the methylation status of genes that is thought to result in gene silencing. Recent studies have shown that in some experimental conditions TCDD suppresses the expression $p16^{Ink4a}$ and p53, tumor-suppressor genes that regulate the onset of cellular senescence, via a mechanism that appears to involve DNA methylation (Ray and Swanson, 2004). Similarly, when an approach that involved exposure of mouse embryos to TCDD before exposure was used, it was reported that TCDD increased methylation of two growth-related imprinted genes, H19 and Igf2, in the developing fetus (Wu et al., 2004).

Progress in understanding the "nongenomic mechanisms" by which TCDD exerts its biologic effects has been restricted largely to its effect on signal transduction. TCDD has been reported to activate the p38-mitogen-activated protein kinase (MAPK) (Park SJ et al., 2005; Weiss et al., 2005) and c-Src kinase (Mazina et al., 2004) pathways. TCDD's activation of at least MAPK appears to occur in an AhR-dependent manner (Weiss et al., 2005).

Factors That May Contribute to the Tissue-, Species-, and Developmental-Stage-Specific Actions of TCDD

As indicated in previous updates, factors that underlie the tissue-, species-, and developmental-stage-specific actions of TCDD include its variations in expression levels of the AhR expression, variations in the expression levels of proteins that regulate its activity, and variations in AhR amino acid composition, phosphorylation status, and cellular localization. High expression of the AhR is presumed to correspond to higher responsiveness to the effects of TCDD, but this has not been conclusively demonstrated. As described in *Update 2004*, expression of the AhR represents a balance between synthesis (regulated at the transcriptional and translational levels) and degradation (mediated by agonist-dependent and agonist-independent mechanisms).

Recent progress in our understanding of the factors involved in regulation of AhR synthesis includes the discovery that IL-4 can induce AhR synthesis at the transcriptional level in B cells (Takana et al., 2005). Additional progress in understanding regulation of AhR expression has come from studies in which the investigators questioned whether the expression of the AhR varies during the progression of diseases and between specific cell types.

With respect to disease state, that best examined is the progression of cancer. For example, as mentioned previously, the expression of either the AhR or its target genes, CYP1B1 and CYP2S1, is upregulated in tumor tissues isolated from human pancreatic, lung, prostatic, ovarian, and colon cancers compared with that detected in normal tissues (Abdelrahim et al., 2003; Downie et al., 2005; Koliopanos et al., 2002; Kumarakulasingham et al., 2005; Tokizane et al., 2005). More recently, it has been shown that expression of the AhR is lower in endometrial cancer than in the normal endometrium (Michalak et al., 2005) and in hematologic malignancies, such as acute lymphoblastic leukemia due to hypermethylation of the AhR promoter (Mulero-Navarro et al., 2006). Expression of both the AhR and its dimerization partner, ARNT, has been reported to be lower in pancreatic islets isolated from subjects with type 2 diabetes than in patients without this disease (Gunton et al., 2005).

The observations that in some cases the expression of the AhR is cell-type-specific imply that a specific population of cells in an organ may elicit the primary effects of TCDD. In the lung, AhR expression has recently been shown to be higher in bronchiolar Clara cells than in the progenitor human small-airway epithelial cells (Chang et al., 2006). In the liver, the hepatocytes appear to be the "primary responder" to the toxic effects of TCDD (Walisser et al., 2005). And the finding that both the cerebral endothelial cells and astrocytes express a functional AhR signaling pathway implies that components of the blood-brain barrier are also targets of TCDD toxicity (Filbrandt et al., 2004).

Also, agonist-induced degradation of the AhR is thought to play a major role in limiting its signaling capacity. Recent progress reveals that agonist-induced degradation of the AhR involves multiple mechanisms and appears to depend on the absence or presence of a functional transcriptional activation domain and binding of the AhR to DNA (Pollenz et al., 2005).

Influence of Other Proteins on the Ability of TCDD to Activate the AhR

As mentioned in *Update 2004*, the ability of TCDD to activate the AhR is influenced by a number of interacting proteins that have various functions. XAP2 mediates cellular localization and stability of the AhR and appears to be capable of inducing a conformational change in the AhR that excludes p23 from the AhR complex, retains the AhR in the cytoplasm, and hence

represses AhR transcriptional activity (Hollingshead et al., 2004). An additional chaperone protein, CyP40, has recently been found to assist in formation of the AhR/ARNT heterodimer (Shetty et al., 2004). The AhR repressor (AhRR) associates with the AhR and negatively regulates its function. Although high expression levels of AhRR have been shown in cultured cells to inhibit AhR signaling (Nishihashi et al., 2006), an expected negative correlation between its tissue-dependent expression and AhR agonist activity was not observed, so expression of the AhRR may not dictate a tissue's responsiveness to TCDD (Bernshausen et al., 2006). Additional proteins that are critical for appropriate AhR function are transcriptional coactivators. Recently discovered AhR transcriptional coactivators of the AhR are coiled-coil coactivator (Kim and Stallcup, 2004), GRIP1-associated coactivator 63 (Chen et al., 2006), the Epstein-barr virus-encoded EBNA-3 protein (Kashuba et al., 2006), and thyroid-hormone receptor/retinoblastoma-interacting protein 230 (Beishlag et al., 2004).

Effect of Phosphorylation on AhR Activity

In addition to variations in protein expression, phosphorylation status can dictate a cell's responsiveness to the effects of TCDD. Recent progress has shown that the AhR-signaling pathway is regulated by c-scr (Backlund and Ingelman-Sundberg, 2005), the mitogen-activated protein kinases (Chen et al., 2005; Shibazaki et al., 2004; Tan et al., 2004), and protein kinase C (Kawajiri and Ikuto, 2004; Kayano et al., 2004; Machemer and Tukey, 2005; Minsavage et al., 2004). Those kinases not only regulate transcriptional activity of the AhR but participate in targeting the AhR for degradation. The phosphorylation status of the AhR chaperone HSP90 also plays a role in the ability of the AhR to form a cytosolic complex capable of binding TCDD (Ogiso et al., 2004).

Effect of Pharmacologic Agents, Dietary Factors, and Environmental Exposures on the AhR and TCDD's Adverse Effects

It is predicted that coexposure to agents that act as AhR agonists or AhR antagonists that may be encountered pharmacologically, via the diet, and in the environment may modulate a person's response to TCDD. For example, although omeprazole, an antiulcer drug, is an AhR agonist, its metabolite that is generated by CYP3A4 acts as a potent AhR antagonist (Gerbal-Chaloin et al., 2006). New data indicate that activators of PPARα (for example WY-146430) may modulate the ability of the AhR to upregulate its target genes, albeit via mechanisms that do not require their direct binding to the AhR (Fallone et al., 2005; Shaban et al., 2005).

As discussed in *Update 2004*, a number of dietary agents may act as AhR agonists or antagonists. Several investigators have proposed that diets rich in particular micronutrients can play an important role in protecting people from the adverse effects of xenobiotics, such as TCDD. Of particular interest are the flavonoids, catechins, and theaflavins found in fruits, vegetables, and black and green tea (Chen et al., 2004; Kim et al., 2004; Fukuda et al., 2004a,b, 2005; Ramadass et al., 2003). The observations that those compounds at relatively low concentrations act as AhR antagonists, which inhibit the ability of TCDD to induce formation of the AhR/ARNT complex and thus induction of CYP1A1, indicate that their ingestion via dietary means may be sufficient to confer a protective effect.

A number of environmental agents have also been found to alter the ability of TCDD to activate AhR signaling. For example, the heavy metals Hg^{2+}, Pb^{2+}, and Cu^{2+} have been shown to decrease TCDD-mediated induction of CYP1A1 activity via a mechanism that appears to involve enhanced heme degradation (Korashy and El-Kadi, 2004, 2005). Furthermore, the heavy metals As^{3+}, Cd^{2+}, and Cr^{6+} have been reported to mediate oxidative stress, down-regulate CYP1A1 at posttranscriptional levels, and potentiate Nqo1 and GstYa at the transcriptional level (Elbekai and El-Kadi, 2005). Examination of the effects of other halogenatated aromatic compounds on the ability of TCDD to induce the AhR-signaling pathway revealed that the coplanar PCBs77 and 126 that act as AhR agonists exhibit additive behavior with TCDD (Chen and Bunce, 2004). The nonplanar PCB 153, in contrast, exhibits antagonist activity and competitively inhibits the actions of TCDD. The environmental estrogen bisphenol A was reported to inhibit the expression of the AhR.

It has also been postulated that TCDD exerts its toxicity by mimicking an endogenous ligand for the AhR and activating the receptor at inappropriate times or for inappropriately long periods. The physiologic ligand for the AhR has not yet been identified, but endogenous AhR agonists reported thus far and described in Update 2004 include 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester, metabolites of tryptophan, and lipoxin A4. Recently, it has been shown that although 1′*H*-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester can act as a potent AhR agonist both in vitro and in vitro, it failed to incur adverse effects typically associated with TCDD exposure, that is, cleft-palate formation, hydronephrosis, and thymic atrophy (Henry et al., 2006). Simiarly, studies performed in vivo support the idea that lipoxin A4 that mediates a number of inflammatory events is an AhR agonist (Machado et al., 2006).

Impact of Genetic Polymorphisms on Responses to TCDD

As noted in *Update 2004*, the species-specific effects observed with respect to TCDD's toxic responses appear to be due largely to differences in the amino acid composition of the AhR. As recently reviewed by Conner and Aylward (2006), the data have consistently demonstrated that humans have lower responsiveness than many laboratory animals. Results of a recent study (Ramadoss and Perdew, 2004) that examined the ligand-binding capabilities of the human AhR compared with that obtained from the $mAhR^{d}$ and $mAhR^{b-1}$ are consistent with that statement and show that the $mAhR^{d}$ and $mAhR^{b-1}$ have 2 and 10 times the relative binding affinity of the human AhR, respectively. That the species-specific effects of TCDD toxicity are due largely to differences in amino acid composition was also recently confirmed in a study of avian species, which display one of the most dramatic differences in sensitivity to TCDD (Karchner et al., 2006). It was reported that the tern AhR has lower activity than the chicken AhR because of two amino acids, Val325 and Ala 381. An additional approach is being used to understand the genetic basis of susceptibility to TCDD's toxic effects in a study of a population of killifish that are dioxin-resistant; recently, it was reported that although two alleles were identified (AHR1*1 and AHR1*3), they did not contribute to functional differences in AhR action (Hahn et al., 2004).

Given that polymorphisms of the AhR have been found in rats, mice, and birds that significantly alter the ability of TCDD to activate the AhR-signaling pathway, it has been proposed that similar differences may exist in the human population. Only eight polymorphisms have been identified in the human population (Harper et al., 2002). Most human AhR

polymorphisms are restricted to exon 10, which encodes the C-terminal region of the AhR known as the transcriptional activation domain, in particular, at codons 517, 554, and 570. However, the polymorphisms that have been discovered thus far in the human AhR have not yet been shown to change their ability to confer responsiveness to TCDD substantially (Okey et al., 2005). And although differences in the composition of the C-terminal region of the AhR had previously been thought to result in only subtle differences in AhR function, this idea is now challenged by a recent report that the C-terminal region of the AhR plays a role in determining its cellular localization and hence its ability to respond to the presence of TCDD (Ramadoss and Perdew, 2005).

Several human population studies designed to identify an association between the AhR, ARNT, or AhRR and human disease states have recently been reported. Study of cleft-palate formation resulted in the association of nonsyndromic oral clefts and a polymorphic form of ARNT (IVS12-19T/G) (Kayano et al., 2004). With respect to reproduction, it has been found that micropenis and male infertility are associated with the Pro185Ala polymorphism of AhRR (Soneda et al., 2005; Watanabe et al., 2004). The same polymorphism has been found to be associated with susceptibility to and severity of endometriosis (Tsuchiya M et al., 2005). Finally, a recent report (Long et al., 2006) indicates that the AhR polymorphism Lys554Arg may confer increased susceptibility to breast cancer.

Effects Related to Particular Toxic Endpoints and Health Outcomes

Accumulated studies in experimental animals indicate that TCDD affects a variety of tissues, and the types of effect observed are often tissue-specific. Effects are most often dose-dependent; that is, some toxic endpoints appear to be more sensitive to low exposures, and others occur only at high concentrations. Toxic effects also have been found to depend on the species examined and often on the age and sex of the animal. There is no reason to suspect that humans would be different in that respect. Findings in animals suggest that reproductive, developmental, and oncogenic endpoints are the most sensitive to TCDD, and this is consistent with the notion that growth, maturation, and differentiation are the most sensitive cellular processes. The data support the biologic plausibility of similar toxic endpoints in humans. Although the exact biologic mechanisms of those endpoints and the observed differences are not yet understood, recent data show the possibility that at least some of the effects are mediated by TCDD's ability, through the AhR, to modulate cell-cycle control, signaling pathways that lead to cell death or inappropriate cell activation, hormones and growth factors and the responses to them, or the biochemical pathways that lead to oxidative stress. Those mechanisms are implicated in many of the toxic endpoints discussed below.

Lethality and Wasting Syndrome

As indicated above and in *Update 2004*, there is some variation among species in susceptibility to the lethal effects of TCDD that is attributable in part to differences in primary amino acid sequences and expression of the AhR protein. Exposure of most animal species to relatively high doses of TCDD elicits a wasting syndrome characterized by decreased food consumption and loss of body weight. The biochemical pathways affected by TCDD that lead to

the wasting syndrome have not been identified. Several groups posit that TCDD, via the AhR, alters a body-weight set point. The hypothalamus contains neuroendocrine cells that regulate several physiologic processes, including energy balance. Recent research that has focused on the ability of TCDD to perturb hypothalamic function has found that the effects of TCDD differed from those of leptin and indicated that TCDD affected primarily orexigenic factors (Linden et al., 2005).

Several studies focused on the ability of different agents to block the TCDD-induced wasting syndrome. Treatment with curcumin (Ishida et al., 2004) protected against the loss of body-weight gain but failed to alter a classic AhR-mediated event, induction of hepatic ethoxyresorufin-*O*-deethylase activity; TCDD's effect on body-weight gain might not require activation of the AhR. Cotreatment with the antioxidants vitamins A and E protected against TCDD's effect on body weight—an indication that TCDD may induce the wasting syndrome by increasing oxidative stress (Alsharif and Hassoun, 2004).

Effects on Skin and Adipose Tissue

Skin lesions, including chloracne, are often reported in animals and humans after exposure to TCDD and related compounds. Chloracne is characterized by altered proliferation and differentiation of epidermal cells. TCDD affects the temporal expression of protein markers of keratinocyte terminal differentiation during murine skin morphogenesis (Loertscher et al., 2002). Henley et al. (2004a) reported that TCDD exposure induced increased expression of IL-1β in human keratinocytes by a posttranscriptional mechanism; the investigators also reported that ERK and JNK MAP kinase pathways are necessary for this to occur (Henley et al., 2004b).

As indicated in previous updates, TCDD inhibits the differentiation of some preadipocyte cell lines to adipocytes (fat cells); the process is AhR-dependent. Several groups have examined the mechanism because it could help to explain how TCDD acts in various tissues. Fibroblasts stimulated by a hormone mixture undergo a cascade of molecular events to initiate adipocyte differentiation, including regulation of c-myc, fos, and jun and then upregulation of CCAAT-enhancer-binding proteins and of the peroxisome proliferators-activated receptor (PPAR) γ. A recent microarray analysis has revealed that the ability of TCDD to inhibit adipocyte differentiation appears to involve a synergistic interaction between the AhR and the growth factors EGF and FGF that results in changes in cell adhesion (Hanlon et al., 2005). Several investigations cited in previous updates noted that TCDD exposure alters plasma and tissue lipid content in animals. A microarray study performed with liver mRNA isolated from male rats treated with a relatively high dose of TCDD supports the idea that TCDD alters cell adhesion and demonstrated that in the liver TCDD exposure results in major deregulation of cholesterol metabolism and bile acid synthesis and transport (Fletcher et al., 2005a).

Effects on Bone and Teeth

Previous studies have suggested that defects in children's tooth development may be associated with environmental exposure to dioxins and dioxin-like chemicals (Alusuusua et al., 2002; Funatsu et al., 1971; Lind et al., 1999, 2000a,b; Rogan et al., 1988). In a recent follow-up study of dental aberrations in subjects exposed to dioxin in Seveso, Italy (Alaluusua et al., 2004), developmental enamel defects were not significantly increased in individuals that had serum

TCDD less than 226 ng/kg at the time of accident, compared to unexposed individuals. However, the percentage of individuals with developmental enamel defects was significantly increased for those that had serum TCDD between 238-592 ng/kg (45%) or 700-26,000 ng/kg (60%) at the time of the accident, compared to unexposed individuals (26%). Furthermore, 93% of the subjects with developmental enamel defects had been under 5 years old at the time of the Seveso accident.

A number of recent animal studies confirm the effects of developmental TCDD exposure on tooth development. Offspring of female mink exposed in utero and via lactation to dioxin, dioxin-like chemicals, and non-dioxin like chemicals (including non-dioxin like PCBs and polybrominated diphenyl ethers) exhibited mandibular and maxillary squamous epithelial cell proliferation, which could contribute to tooth loss (Bursian et al., 2006). The incidence of tooth abnormalities was significantly increased in surviving offspring of rhesus monkeys exposed in utero and via lactation to TCDD (Yasuda et al., 2005); the abnormalities occurred at maternal body burdens maintained at 300 µg/kg and included precocious eruption, dysplasia, incomplete calcification, and missing teeth; no effects were observed at maternal body burdens of 30 µg/kg. When rat offspring exposed in utero and via lactation to a single maternal TCDD dose of 0.03, 0.1, 0.3, or 1.0 µg/kg were challenged with a sugar-rich diet and exposure to *Streptococcus mutans* at the age of 11 weeks (Miettinen et al., 2006), TCDD exposure increased the number of caries lesions in the enamel at the lowest maternal dose and in the dentin at the two highest maternal doses; changes in mineral composition were not related to the increased caries incidence.

TCDD also can interfere with enamel maturation when exposure occurs only postnatally. A single oral dose of TCDD at 50 or 1,000 µg/kg given to lactating Han/Wistar dams 1 day after delivery induced retention of enamel matrix and retarded dentin mineralization in pups on postnatal day 22 (Gao et al., 2004). The changes were associated with decreased AhR and CP1A1 immunoreactivity in ameloblasts and odontoblasts.

Only two relevant studies of TCDD's effects on bone have been published since *Update 2004*. Ilvesaro et al. (2005) found that rat bone cell cultures expressed mRNA for both the AhR and ARNT and that osteoclasts expressed much higher levels of the AhR than osteoblastic mononuclear cells. However, treatment of rat osteoclasts with 10 nM TCDD failed to alter osteoclast activity. In the second study, three strains of rats, which varied in their sensitivity to TCDD because of a mutated AhR, were exposed to TCDD at 0, 0.1, 0.3 or 1.0 µg/kg at different times during gestation or lactation, and offspring were analyzed 5–6 or 52 weeks after birth for bone mineral density and geometry (Miettinen et al., 2005). Only the most sensitive line of rats exhibited significant decreases in tibial and femoral mineral density and breaking force and decreases in femoral cross-sectional area, length, and endosteal and periosteal circumference. Earlier exposure induced more severe defects, but gestational exposure alone was not sufficient. Notably, most of the bone defects returned to normal limits 52 weeks after birth.

Cardiovascular Toxicity

It is well established that TCDD can affect the developing cardiovascular system, and there is growing evidence from a variety of experimental models that the cardiovascular system may also be a target of TCDD toxicity in adult animals. The evidence is derived from studies of the AhR-null mice, of constitutively active-AhR mice, of TCDD's effects on vascular smooth muscle and

endothelial cell cultures, and of chronic TCDD exposure of rodents.

A role of the AhR in cardiovascular homeostasis in adults has been demonstrated by a number of previously published studies. Briefly, the studies showed that AhR-null mice develop age-progressive cardiac hypertrophy and fibrosis (Fernandez-Salguero et al., 1997; Thackaberry et al., 2003; Vasquez et al., 2003), which was preceded by increases in blood pressure, plasma angiotensin II, and plasma endothelin-1 (Lund et al., 2003). Blockade of angiotensin II synthesis ameliorated the hypertension and cardiac hypertrophy (Lund et al., 2003), but more recent studies demonstrated that blockade of endothelin-1 signaling was significantly more effective, normalizing blood pressure and cardiac hypertrophy to AhR-wildtype values (Lund et al., 2006). In a recent study, Lund et al. (2005) showed that high endothelin-1 mediated increases in reactive oxygen species (ROSs) that were associated with cardiac hypertrophy via increased NAD(P)H oxidase activity and superoxide anion generation. Those studies suggest that the AhR may play a protective role in the adult cardiovascular system and that genetic deletion abolishes that benefit. Constitutive activation of the AhR also results in disruption of cardiovascular homeostasis. Brunnberg et al. (2006) have shown that male mice expressing a constitutively active AhR develop an age-progressive cardiac hypertrophy associated with greater expression of CYP1A1 in coronary capillary endothelial cells than in AhR-wildtype mice.

Three recent cell-culture studies demonstrate that sustained activation of the AhR by TCDD or the AhR agonist 3-methylcholanthrene disrupts vascular-cell gene expression, proliferation, and function. Exposure of human umbilical vein endothelial cells (HUVECs) to either 3-methylcholanthrene or TCDD inhibited basal proliferation, and exposure to TCDD also inhibited proliferation stimulated by vascular endothelial growth factor (Juan et al., 2006; Ivnitski-Steele and Walker, 2003). Both AhR agonists also inhibited angiogenesis as assessed in vitro. In a third study, global gene-expression profiling after TCDD exposure of mouse aorta in vivo or cultured vascular smooth muscle cells in vitro showed that more than 4,500 genes differed in expression between the two models but that a subset of 35 genes showed similar responses to dioxin exposure (Puga et al., 2004). Commonly responding genes included phase I and phase II metabolic enzymes, signal-transduction kinases and phosphatases, and regulators of DNA repair and the cell cycle.

Pulmonary Toxicity

This and previous updates report evidence suggestive of an association between herbicide exposure in Vietnam and respiratory cancer (see “Carcinogenesis”, below). Several published reports have suggested an association between TCDD exposure and chronic obstructive pulmonary disease, but the present committee found insufficient evidence to support a relationship between herbicide exposure and respiratory disorders that are not considered cancer, noting the lack of toxicity to the pulmonary system in laboratory animals exposed acutely to low doses (1–10 µg/kg) of TCDD that result in toxicity to other organ systems.

Recent studies have shown that when mice exposed to TCDD are challenged with a respiratory virus (influenza), they experience a higher mortality. The increase in mortality did not reflect TCDD suppression of the antiviral adaptive immune response, as initially suspected, but was associated with an enhanced influx of neutrophils into the lung (IOM, 2005). Neutrophils produce several toxic substances (for the purpose of killing pathogens), so it is possible that excess neutrophils in the lung produce excess collateral damage and pathologic

changes that result in increased mortality. Later studies to test that hypothesis showed that prevention of the neutrophilia (by using an antineutrophil antibody) provided partial protection of TCDD-treated mice from influenza-induced death (Teske et al., 2005). Furthermore, the increased mortality and neutrophilia were AhR-dependent and not observed in TCDD-treated AhR-knockout mice (Teske et al., 2005). However, TCDD exposure did not alter the concentrations of common lung neutrophil chemoattractants—macrophage inflammatory protein 1α (MIP)-1α, MIP-2, keratinocyte chemoattractant, lipopolysaccharide-induced CXC chemokine, interleukin 6, and complement split product C5a—the expression of adhesion molecules by neutrophils (CD11a, CD11b, CD49d, CD31, CD38), or the normal neutrophil apoptotic process. Likewise, concentrations of ROSs and myeloperoxidase activity were normal in neutrophils from TCDD-treated mice (ibid). In the absence of evidence of TCDD effects at the level of neutrophil recruitment or function, several indicators of lung damage were assessed (Bohn et al., 2005). However, TCDD exposure did not alter the concentrations of lactate dehydrogenase (a marker of lung cell damage) or enhance edema (measured by proteins in bronchoalveolar-lavage fluid and wet-to-dry weight ratios). Lung concentrations of Clara cell secretory protein (CSSP), an inflammatory mediator produced by lung-associated Clara cells, were also not altered by TCDD. Despite the absence of functional changes, TCDD induced CYP1A1 expression in the Clara cells of the lung and in lung endothelial cells and Type II pneumocytes, indicating the ability of TCDD to affect the lung directly via AhR activation **(ibid)**. CYP1A1 and CYP1B1 were also induced in the lungs of rats given a single high dose (5 µg/kg) of TCDD 4 hours before termination (Harrigan et al., 2006), and treatment of human broncoalveolar H358 cells with 10 nM TCDD in vitro induced the expression of enzymes as well (Jiang et al., 2005).

In a unique design, Esser et al. (2005) investigated the possible long-term effects of TCDD on the health of aged mice that had been given a single dose of TCDD (2.5 or 25 µg/kg) when they were young. Histologic examination of several tissues revealed no differences except in the lungs, where TCDD was associated with an increased incidence of activated bronchus-associated lymphoid tissue; the significance of this finding remains to be determined.

In terms of chronic-exposure studies, treatment of rats with low doses of TCDD for 2 years, but not 1 year, resulted in increased lung weight and bronchiolar metaplasia of the alveolar epithelium in female rats (Update 2002; 2004). Recent studies show that CYP1A1 and CYP1B1 are strongly induced in Clara cells after treatment of rat lung slices in vitro with TCDD (Chang et al., 2006). In human lung tissue, AhR and CYP1A1 are expressed mainly in bronchiolar epithelial cells (Lin et al., 2003). Using primary cultures of human small-airway epithelial (SAE) cells that differentiate into Clara cells in vitro, Chang et al. (2006) showed mRNA and protein levels of CYP1A1, CYP1B1, and the AhR are increased in SAE cells cultured with TCDD. The authors suggest that Clara cells may be the most sensitive lung-cell type responsive to TCDD.

Previous toxicogenomic studies identified EGR1 as a potential novel target for TCDD and other AhR agonists in human lung epithelial cells (IOM, 2005). Follow-up studies have now shown that TCDD (via the AhR) does not act as a transcriptional promoter but rather appears to increase the half-life of the mRNA via a post-transcriptional mechanism that leads to higher EGR1 protein concentrations in treated cells (Martinez et al., 2004). EGR1 is of interest because it functions as a transcription factor to regulate the expression of several genes involved in cell growth, apoptosis, and differentiation and may play a role in tumor development.

Hepatotoxicity

Several studies addressed mechanisms of TCDD-induced hepatotoxicity. Chang H et al (2005) examined AhR expression, AhR activation (CYP 1A2 induction), and hepatocellular pathology together, in young male mice, and correlated these factors in the same animal and in the same cells in centrilobular location, providing direct evidence on the relationship between AhR activation and hepatic toxicity.

Boverhof et al. (2005) sought to further characterize TCDD toxicity by comprehensive analysis of temporal and dose-response changes in hepatic tissues, using a microarray approach. Liver from immature ovariectomized C57BL/6 mice that had been treated with 30 microg/kg of TCDD or vehicle were sacrificed after times up to 168 hour or were exposed by gavage to doses up to 300 microg/kg of TCDD and sacrificed after 24 h. There were 443 and 315 features that exhibited a significant change at one or more doses or time points, respectively. Gene expression changes were associated with physiological processes such as oxidative stress and metabolism, differentiation, apoptosis, gluconeogenesis, and fatty acid uptake and metabolism. Histopathology and clinical chemistry showed phenotypes supporting a mechanism for TCDD-mediated fatty liver, one that would involve mobilization of peripheral fat and inappropriate increases in hepatic uptake of fatty acids.

Vezina et al. (2004) employed DNA microarrays to seek unique gene expression patterns in liver, associated with sub-chronic exposure to TCDD and related chemicals. Female Harlan Sprague-Dawley rats were exposed to toxicologically equivalent doses of four different compounds, based on the TEFs of each chemical: TCDD (100 ng/kg/day), 2,3,4,7,8-pentachlorodibenzofuran (PeCDF; 200 ng/kg/day), 3,3',4,4',5-pentachlorobiphenyl (PCB126; 1,000 ng/kg/day), or 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153; 1,000 microg/kg/day). Global gene expression profiles assessed with Affymetrix GeneChips were compared by principal components analysis. TCDD, PeCDF, and PCB126 produced very similar expression profiles that were distinct from the PCB153. Such findings may help to uncover some fundamental features of dioxin toxicity.

An expression profiling study to identify further genes involved in hepatotoxicity and hepatocarcinogenesis by TCDD was carried out using C57BL/6 (AhR+/+, wild type) and B6.129-J (AhR-/-, knock out) mice (Yoon et al, 2006). Mice were injected i.p. with TCDD at 100 µg/kg. Relative liver weight was significantly increased after 72 hr after TCDD in AhR+/+ mice, but without apparent histopathological change. The liver was analyzed for gene expression profiles 72 hr later. As compared with AhR-/- mice, the expression of 51 genes (>3-fold) was changed in AhR+/+ mice; 28 genes were induced, while 23 genes were repressed. Most of the genes were associated with chemotaxis, inflammation, carcinogenesis, acute-phase response, immune responses, cell metabolism, cell proliferation, signal transduction, and tumor suppression. The study suggests that the analysis of genes in liver of AhR+/+ and AhR-/- mice may help clarify the mechanisms of AhR-mediated hepatotoxicity and hepatocarcinogenesis by TCDD.

Oxidative stress is induced by TCDD, but the mechanism is not understood. Shen et al. (2005) examined oxidative stress in mouse liver after one dose of TCDD (5 µ/kg body weight). Mitochondrial succinate-dependent production of superoxide and H2O2 in doubled at 7-28 days, then subsided by day 56, at the time that levels of cytosolic and mitochondrial GSH and GSSG increased. Comparing Ahr(-/-) knock-out and wild-type mice, showed that TCDD-induced thiol changes in both cytosol and mitochondria were dependent on the AhR. The TCDD-stimulated

increase in production of reactive oxygen paralleled a four-fold increase in formamidopyrimidine DNA N-glycosylase (FPG)-sensitive cleavage sites in mitochondrial DNA, compared with nuclear DNA. TCDD-dependent oxidative stress in mitochondria and mitochondrial DNA damage appear to involve the mitochondrial thiol reduction state.

A couple of studies assessed TCDD effects on retinoid metabolism. Fletcher et al. (2005b) examined the effects of long-term low-dose 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure on retinoid, thyroid hormone, and vitamin D homeostasis in Long-Evans and Han/Wistar rats, given a tumor initiation regimen. These results showed that TCDD disrupts both retinoid storage and metabolism of retinoic acid and retinoic acid metabolites in liver, kidney, and plasma from doses as low as 1 ng/kg bw/day. Furthermore, 9-cis-4-oxo-13,14-dihydro-RA was identified as a novel and sensitive indicator of TCDD exposure, in a resistant and sensitive rat strain, thereby extending the database of low-dose TCDD effects. Fletcher et al. (2005a) in a separate study, sought to identify novel genes and pathways possibly associated with TCDD-induced hepatotoxicity. Male Sprague-Dawley rats were given single low or high doses of TCDD and gene expression analyzed by microarray. In addition to altering expression of phase I and phase II metabolizing enzymes, 0.4 microg/kg bw TCDD also altered the expression of Gadd45a and Cyclin D1, genes indicative of cellular stress or DNA damage and associated with cell cycle control. At the high-dose, widespread changes occurred with genes encoding cellular signaling proteins, cellular adhesion, cytoskeletal and membrane transport proteins as well as transcripts coding for lipid, carbohydrate and nitrogen metabolism and some genes involved in cholesterol metabolism.

Yang Y-M et al. (2005a) investigated the effects of vitamin A on TCDD effects on liver of mice. Mice were given a single oral dose of 40 µg TCDD/kg body weight with or without the continuous administration of vitamin A (2500 IU /kg body weight/day) or were given daily an oral dose of 0.1 mug TCDD /kg body weight with or without vitamin A. Mice were sampled at various days. TCDD caused liver damage and increased liver weights, and the liver damage was less severe in mice receiving TCDD + vitamin A. EROD activities, CYP1A1 expression, and AhR mRNA expression in vitamin A + TCDD-treated mice were lower than those in TCDD-treated mice; supplementation of vitamin might attenuate the liver damage caused by TCDD. In a companion study, Yang Y-M et al. (2005b) found that TCDD affected the metabolism of vitamin A as well. TCDD significantly decreased the hepatic all-trans-retinol level and increased the hepatic all-trans-retinoic acid (RA) content, increased the mRNA and enzymatic activities of retinal oxidase.

Pancreatic and Gastrointestinal Tract Effects

Novelli et al (2005) examined TCDD effects on secretory function of isolated pancreatic islets from rat. At 24 hr after TCDD (1 µ/kg b.w., i.p.), rats showed no significant differences in levels of plasma glucose, insulin, triglycerides and leptin, but plasma-free fatty acids increased significantly increased compared to untreated rats. In isolated islets, Insulin content of islets isolated from TCDD-treated rats was significantly decreased although DNA and protein content were unchanged. Incubation of islets with varied concentrations of glucose resulted in significant impairment of glucose-stimulated insulin secretion in islets isolated from TCDD-treated rats. A significant reduction of [3H]-2-deoxy-glucose uptake was seen in pancreatic tissue of TCDD-treated rats, while no significant reduction in GLUT-2 protein levels was detected in islets from

TCDD-treated rats. The results suggest that low-dose TCDD could rapidly induce significant alterations of the pancreatic endocrine function in the rat.

Previous 2-year studies of TCDD on female Harlan Sprague-Dawley rats revealed acinar-cell vacuolation, atrophy, inflammation, and arteritis, as well as a rare occurrence of pancreatic acinar-cell adenomas and carcinomas. Yoshizawa et al. (2005a) sought to identify mechanisms involved in early stages of acinar-cell lesions. Pancreas from Animals treated for 14 and 31 weeks with 100 ng TCDD/kg body weight or corn oil vehicle were examined for acinar-cell kinetics and proliferating cell nuclear antigen, CYP1A1, AhR cholecystokinin-A receptor (CCK-A receptor; CCKAR), duodenal cholecystokinin 8 (CCK), and amylase localization. Increased apoptotic activity in acinar cells occurred in 14- and 31-week-treated animals, with an increase in proliferative activity in the latter. Also in the latter, in the vacuolated acinar cells, CYP1A1 was overexpressed, and statistically significant decreases in expressions of AhR, CCKAR, and amylase occurred. Changes in the expression of the various genes may be related to acinar-cell lesions.

TCDD effect on the intestine is not well understood. Ishida et al. (2005) examined the effect of dioxin on the pathology and function of the intestine in AhR-sensitive and -less-sensitive mice, after oral administration of TCDD (100 µg/kg). C57BL/6J mice showed changes in villous structure and nuclear/cytoplasm ratio in the epithelial cells of the intestine. In an oral glucose tolerance test, the serum glucose level was significantly increased in the C57BL/6J mouse but not in the DBA/2J mouse. The expression of intestinal mRNAs coding sodium-glucose co-transporter 1 (SGLT1) and glucose transporter type 2 were increased only in C57BL/6J mice. The intestinal activity of sucrase and lactase also was significantly increased in C57BL/6J mice by TCDD.

Neurotoxicity

Several of the studies referred to in the preceding section concerning developmental effects if TCDD in fact deal with effects in developing brain (e.g., Chang SF et al., 2005; Mitsui et al., 2006) A number of other papers concern possible mechanisms by which chemicals including chemicals of interest might cause effects on neurological and cognitive function. For example, Parkinson's disease (PD) is characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra and movement defects. Oxidative stress has been implicated in the pathogenesis of Parkinson disease based on its role in the cascade of biochemical changes that lead to dopaminergic neuronal death. Thiruchelvam et al. (2005) analyzed the role of oxidative stress as a mechanism of the dopaminergic neurotoxicity in mice, showing possible protection by over-expression of superoxide dismutase or glutathione peroxidase. Choi et al (2006) also showed that defense against reactive oxygen can protect against dopaminergic neuron damage in a mouse model. Although not concerning the chemicals of interest, such studies continue to support suggestions that the level of reactive oxygen species could alter the functions of specific signaling cascades and may be involved in neurodegeneration. This is potentially relevant to chemicals of concern, as TCDD has been reported to elicit oxidative stress in some organs (e.g., Shen et al., 2005).

TCDD is thought to produce neurobehavioral abnormalities associated with both cognitive and locomotor systems, yet the regional and cellular targets involved in developmental neurotoxicity are largely unknown. Williamson et al. (2005) assessed whether developing

cerebellar granule neuroblasts may be direct targets for TCDD. AhR and Arnt proteins were present in mouse cerebellum from birth throughout postnatal development. AhR protein levels peaked between postnatal days 3–10, critical period for neuroblast growth and maturation. Both AhR and Arnt were expressed in cerebellar granule neuroblast cultures, and TCCD elicited time-dependent and concentration-dependent increases in CYP1A1 and 1B1 expression. TCDD treatment also reduced thymidine incorporation and granule neuroblast survival in a concentration-dependent manner. The study suggests that granule neuroblasts are direct targets for developmental AhR-mediated TCDD neurotoxicity and that TCDD exposure may disrupt granule cell neurogenesis.

Kim and Yang (2005) also addressed possible molecular mechanism and intracellular targets by which TCDD could lead to neurodevelopmental and neurobehavioral deficit. They analyzed TCDD-induced neurotoxic effects in the granule cells from the cerebellum, where certain cognitive abilities and motor function command are executed. TCDD induced a dose-dependent increase of total protein kinase C activity and this AhR-dependent and N-methyl-D-aspartate receptor (NMDAR) independent, and was an PKC isozyme-specific pattern of the induction. Increase of the ROS formation was also observed in the cells treated with TCDD in a dose-dependent and an AhR-dependent manner. TCDD also increased [Ca2+]i, which is associated with ROS formation and PKC activation in the cerebellar granule cells. It is suggested that TCDD activates the NMDA receptor, which may induce a sustained increase of [Ca2+]i in neurons followed by the ROS formation.

In an effort to develop other model systems, Ton et al. (2006) examined several parameters of neurotoxicity during development in zebrafish exposed to 7 well-characterized compounds. Embryos were exposed by immersion from 6 hrs postfertilization (hpf). Dying cells in the brain were assessed by acridine orange staining (likely to be apoptotic). Motor neurons were assessed by antiacetylated tubulin staining and catecholaminergic neurons were visualized by antityrosine hydroxylase staining. TCDD was primarily teratogenic and not specifically neurotoxic, while 2,4-D showed neurotoxicity. The results showed a correlation with mammalian data and suggest that zebrafish is a predictive animal model for neurotoxicity screening.

Lensu et al. (2006) explored possible brain areas that could be involved in mechanisms by which TCDD causes wasting syndrome (a dramatic loss of body weight over 2–5 weeks). The studies used Long-Evans (Turku/AB); (L-E) and Han/Wistar (Kuopio) rats, which show 1000-fold differences in TCDD sensitivity. Rats were examined for brain areas that might be activated by a single dose of TCDD (50 µg/kg) given 24 hr prior to sampling. Leptin (1.3 mg/kg, IP) was used as a reference compound, as its neural pathway for decreasing food intake is fairly well known. Serial sections of brain were stained with antibody against c-Fos, and selected areas in the hypothalamus were examined. TCDD alone did not elicit any major alterations in c-Fos protein levels in the hypothalamic nuclei at 24 hr after administration, in either rat strain, while leptin increased the number of c-Fos-immunopositive cells in the hypothalamic ventromedial and arcuate nuclei. The findings are not suggestive of a primary role for the hypothalamus in the wasting syndrome, however in a related study (Lindén et al., 2005), TCDD mainly affected expression of orexigenic but not anorexigenic factor mRNAs, and there were temporal differences in response found between the rat strains.

Immunotoxicity

The immune system has been recognized as a sensitive target for the toxicity of TCDD for many years (see previous updates). Immunotoxicity is manifested as increased susceptibility to infectious disease and increased tumor development in laboratory animal studies. Many cell types make up the immune system, and most of the cells have been shown to express the AhR, which is required for initiating the toxicity of TCDD. Identifying the specific cells that are altered by TCDD and how they contribute to TCDD-induced alterations in immune function is of great interest to the research community. Understanding how TCDD affects the immune system in rodents increases the ability to extrapolate experimental results to assessment of human risks. Since *Update 2004*, several papers have addressed the mechanisms of TCDD's effects on the immune system.

A hallmark of TCDD's immunotoxicity is involution of the thymus, the gland that serves as the site of T-cell development. The mechanism of action of TCDD on the thymus includes both direct AhR-mediated changes in developing thymocytes and indirect effects on thymocytes via the AhR-expressing thymic epithelial and dendritic cells. Studies published since *Update 2004* have investigated the effects of TCDD exposure on the thymus. Nottebrock et al. (2006) studied the mechanisms underlying thymic involution in marmosets treated with a low dose of TCDD. They reported a dose-dependent increase in expression of several extracellular matrix proteins, TGF-β1, and integrins CD49d and CD29. Camacho et al. (2005) reported that activation of the AhR by TCDD in murine thymic stromal cells induced the expression of Fas ligand (FasL), a death-receptor ligand that induces apoptosis when it binds to cells that express Fas. The increase in FasL expression occurred through AhR-dependent activation of the transcriptional regulator NFkB. When TCDD-treated thymic stromal cells were incubated with thymic T cells, the T cells underwent apoptosis, which is consistent with the process of thymic atrophy seen in TCDD-treated mice. In other studies, Ji et al. (2005) reported that down-modulation of the fas gene by an herbal extract of *Artemisia iwayomogii* protected thymocytes from TCDD-induced apoptosis in vitro.

The main function of the thymus is T-cell selection, a two-step process that has the overarching goal of allowing T cells that recognize foreign material to survive while T cells that react to self-antigens are deleted through apoptosis. Self-reactive T cells that escape thymic selection have the potential to trigger autoimmune responses that lead to autoimmune disease. Using an HY-T cell receptor transgenic mouse model and an acute dose of TCDD (50 μg/kg), Fisher et al. (2005a) reported that exposure of mice to TCDD altered the process of T-cell selection in the thymus and produced an increase in self-reactive T cells in the periphery of male mice. The findings contrast with the lack of effect of TCDD on T-cell selection in a different model system (de Heer et al., 1995). Other studies reported that exposure to TCDD promoted the premature emigration of double-negative thymocytes from the thymus to the peripheral lymphoid tissues (Temchura et al., 2005). The effect was associated with increased expression of calgranulin B, a calcium-binding protein involved in cell migration. Premature emigration of the double-negative precursor population could contribute to TCDD-induced thymic atrophy.

The ability of mature lymphocytes in the secondary lymphoid organs to respond to antigenic challenge is also affected by TCDD. Many prior studies showed profound and dose-dependent suppression of primary immune responses in TCDD-treated animals. Recent studies show that suppression of the antibody response by TCDD in mice is related to suppression of IL-5 production by T helper cells (Inouye et al., 2005). TCDD was also shown to alter the expression

of several genes in $CD4^+$ T cells and B cells after immunization of mice with OVA (Nagai et al., 2005). Down-regulation of genes involved in GTP-binding protein-linked signaling was most notable in $CD4^+$ T cells. Funatake et al. (2004) used OVA-specific transgenic T cells to track the effects of TCDD on the early response of $CD4^+$ T cells to antigen stimulation. As in previous studies, the early proliferative response of the T cells to antigen stimulation was not altered by TCDD, but their numbers declined significantly on day 4. The decline was preceded by a decreased expression of CD62L and CD11a but no change in CD49d. By day 4, proliferation of the cells had ceased in TCDD-treated mice, and by day 5, the frequency of apoptotic cells was increased. Fas-FasL signaling was excluded as the mechanism of increased T-cell death. However, the expression of several other genes associated with cell survival or death was increased in the T cells by TCDD exposure. Many of the upregulated genes belong to the TNF/TNFR superfamilies, including 4-1BB, CD30, trance, and trail. P53 was also increased in T cells exposed to TCDD. The results suggest that a complex interplay of survival and death signals exists in the T cells and that AhR activation by TCDD alters the delicate balance and leads to changes in T-cell survival. A novel explanation of altered T-cell numbers in TCDD-treated mice is the induction of T regulatory cells. Funatake et al. (2005) showed that treatment of mice with TCDD during T-cell activation generated a population of T cells that expressed high levels of CD25 and suppressed the proliferation of naïve T cells in vitro. Those changes depended on AhR expression in the T cells.

There is extensive evidence that suppression of immune function by TCDD depends on signaling through the AhR. Recently, mice expressing a constitutively active AhR in T cells were genetically engineered (Nohara et al., 2005). They showed CYP1A1 expression in the thymus and spleen, thymic atrophy, and suppressed T-cell and B-cell numbers in the spleen after immunization. The effects were similar in scope but not in magnitude to those seen after AhR activation by TCDD. In similar studies, Ito et al. (2004) used transient transfection to study the effects of a constitutively active AhR in human Jurkat T cells in vitro. Their results suggest that AhR activation causes apoptosis and cell-cycle arrest through changes in AhR-regulated gene expression. In addition, Ndebele et al. (2004) showed that treatment with TCDD suppressed the production of IL-2 by Jurkat cells; suppression was associated with decreased NFkB. NFkB signaling in B cells is also affected by TCDD exposure. Recent studies indicate that the dioxin-response element overlaps with an NFkB-response element in the enhancer region of the gene for immunoglobulin heavy chain. Interference with enhancer activity may explain the suppression of antibody production in TCDD-treated B cells. Suppression of B-cell responses by TCDD may also be induced by AhR-dependent induction of the gene for suppressor of cytokine signaling 2 in B cells treated with TCDD (Boverhof et al., 2004).

The AhR is expressed in a variety of cells in most species, including humans. However, the ability of the AhR to bind TCDD and activate gene expression can vary with the species. The human AhR has been considered to have less affinity for binding TCDD than the AhR in many other species. This has been interpreted to mean that humans are among those species having lower sensitivity to toxic effects of TCDD. Nohara et al. (2006) recently reported results of a study comparing TCDD induction of lymphocytes from humans with the responses in lymphocytes from two species with high affinity AhR (SD rats and C57BL/6 mice) and a species with a low affinity AhR (DBA/2 mice). The EC_{50} for induction of CYP1A1 mRNA (at the time of peak response) in human lymphocytes was similar to that in the DBA/2 mice and about 10-fold lower than in lymphocytes from the SD rats or the C57BL/6 mice. However, the levels of CYP1A1 mRNA induced at maximally effective doses were greater in the human lymphocytes

than in the other species. The authors suggest that some unknown mechanisms modulate the extent of CYP1A1 gene expression in lymphocytes.

Inflammation

Cells of the immune system contribute to inflammation. That is advantageous in fighting infections. However, if inflammation is inappropriately enhanced or prolonged, tissue damage can result. In several human diseases (such as rheumatoid arthritis and coronary arterial disease), prolonged inflammatory responses appear to contribute to tissue damage and disease severity. Past studies have shown that TCDD can act on macrophages and increase inflammatory mediator production. Park S-J et al. (2005) now show that TCDD activates ERK and p38 mitogen-activated protein kinases in a macrophage cell line (RAW 264.7 cells). Using a different macrophage cell line (U937), Vogel et al. (2005) showed that TCDD increases the expression of a number of genes related to inflammation, including cyclo-oxygenase-2, TNFα, IL-8, and C-reactive protein. Those effects could underlie the enhanced inflammatory response reported in several early studies of TCDD toxicity.

Carcinogenecity and Contributing Molecular Mechanisms

TCDD has been demonstrated to be a carcinogenic agent and potent tumor promoter in several model systems. As mentioned in ***Update 2004***, the carcinogenic actions of TCDD have been revealed in a 2-year bioassay in female rats. It was reported that TCDD treatment increased the incidence of cholangiocarcinoma and hepatocellular adenoma of the liver, cystic keratinizing epithelioma of the lung, and gingival squamous cell carcinoma of the oral mucosa (NTP, 2004). Observations reported in a follow-up study support the idea that formation of gingival squamous cell carcinoma induced by TCDD is preceded by gingival squamous hyperplasia that is associated with dysplasia (Yoshizawa et al., 2005b). Further evidence that TCDD exposure may contribute to the formation of squamous cell carcinoma is provided by a study performed by Wyde et al. (2004), who used a genetically initiated mouse tumorigenesis model (TgAC transgenic mice). They reported that exposure to TCDD via either gavage or dermal administration significantly increased formation of papillomas and squamous cell carcinomas in the skin.

With respect to the role that TCDD may play in hepatocarcinogenesis in mice, a follow-up of the NTP study (NTP, 2004) revealed that during the course of TCDD treatment, proliferation of the hepatocytes, biliary epithelium, and oval cells was increased in a time- and dose-dependent manner (Hailey et al., 2005). In considering the mechanisms by which TCDD may exert these effects, the authors concluded that the evidence was not sufficient to support the idea that the TCDD-induced response was regenerative in the liver and suggested that at this stage the response should be classified as a "proliferative response". A role of the AhR in eliciting TCDD's tumor-promoting effects in the liver is supported by the recent finding that in mice bearing the constitutively active form of the AhR, tumor formation initiated by the hepatocarcinogen *N*-nitrosodiethylamine was significantly greater than that in wild-type mice (Moennikes et al., 2004). Histopathologic examination of the spontaneous stomach tumors formed in the mice that express the constitutively active form of the AhR revealed that although

the tumors penetrated into the layers of the muscle and exhibited metaplasia, they did not metastasize and were not dysplastic (Andersson et al., 2005).

Hahn and Weinberg (2002) have proposed that the development of human cancers requires only six changes: resistance to growth inhibition, evasion of apoptosis, immortalization, independence from mitogenic stiumulation, angiogenesis, and metastasis and invasion. Those changes are thought to be due to inherited and acquired alterations in DNA that include such genetic events as DNA mutations and chromosomal aberrations, such epigenetic events as DNA methylation that silences gene expression, and DNA damage that follows exposure to such agents as ROSs. Although it is apparent that TCDD can participate in genotoxic events by inducing such enzymes as CYP1A1, CYP1A2, and CYP1B1—which are responsible for the metabolic activation of many promutagens, increasing oxidative stress and increasing DNA methylation of tumor-suppressor genes (Ray and Swanson, 2004; Wu et al., 2004)—a large body of evidence indicates that TCDD's carcinogenic actions occur primarily by nongenotoxic means that would facilitate a damaged cell's progression through Weinberg's six requisite changes (Table 3-4**)**.

Table 3-4 Impact of TCDD on the six requisite changes proposed by Hahn and Weinnberg[1] to be required for the development of human cancers.

Proposed Set of Acquired Capabilities	**Actions of TCDD**	**TCDD-regulated gene products that may mediate its actions.**
Resistance to Growth Inhibition	Increases Decreases	↑$p27^{Kip1}$, E2F ↓ER, AR
Evasion of apoptosis	Increases Decreases	
Immortalization	Increases	↓$p16^{Ink4a}$, p53 ↑Telomerase activity
Independence from Mitogenic stimulation	Increases	↑EGFR ligands ↑Kinases
Angiogenesis	Inhibits	↓HIF, VEGF
Metastasis Invasion	? Increases	TGFβ, ↑MMPs

[1]Adapted from Hahn and Weinberg (2002).

TCDD Exposure and DNA Damage At the mechanistic level, TCDD is considered to be a tumor promoter that lacks genotoxic actions, that is, direct interaction with DNA. However, some evidence supports the idea that TCDD may participate in genotoxic effects through its induction of cytochrome P450s that increase formation of ROSs, increase oxidative DNA damage, and increase the frequency of chromosomal abnormalities. For example, in mice given a single dose of TCDD by injection, increases in superoxide and H_2O_2 and a decrease in GSH relative to GSSG (classic indicators of an oxidative-stress response) were observed in the liver (Shen et al., 2005). Given that the changes in thiol concentrations were observed in the wild-type mice, but not in mice that lack the AhR, the TCDD response appears to be AhR-dependent. Furthermore, the TCDD-inducible oxidative stress response appears to involve localization of CYPs normally present in the endoplasmic reticulum of the mitochondria (Genter et al., 2004).

Similar increases in ROSs and oxidative DNA damage have been reported when primary rat hepatocytes were used (Knerr et al., 2006). Changes in lipid peroxidation, haemoglobin oxidation, and catalase and glutathione peroxidase activity (measures of oxidative stress) in human RBCs are also consistent with the idea that TCDD induces oxidative stress (Bukowska et al., 2004b). In fact, it has been proposed that the TCDD-induced increase in intracellular oxygen-species formation may underlie its ability to increase the cytotoxic actions of mitomycin C used in chemotherapeutic treatment for solid tumors (Collier et al., 2006). In contrast, it has been reported that in a Chinese hamster ovary cell line, TCDD failed to increase oxidative stress (Chan et al., 2004a) but increased the frequency of DNA double-strand break repair (Chan et al., 2004b) and homologous recombination (Chan et al., 2004a).

In vivo evidence that TCDD exposure may lead to chromosomal abnormalities was found in studies of sheep flocks that reside in the provinces of Naples and Caserta, Italy (Perucatti et al., 2006). Animals with high levels of dioxins exhibited a higher rate of chromosomal abnormalities (aneuploidy, gaps, chromatid breaks, chromosomal breaks, and fragments) than control sheep raised away from the control area. A follow-up study of two flocks that had higher concentrations of dioxin (milk mass of human World Health Organization TCDD equivalent, 50.65 and 39.51 pg/g of fat in the two exposed herds) similarly reported higher rates of increases in chromosomal abnormalities and sister-chromatid exchange in the exposed group than in the control animals (Perucatti et al., 2006).

Finally, in a study of two human patients inadvertently exposed to TCDD (TCDD blood concentrations, 85,600 and 17,700 pg/g of blood lipids 4 months after intoxication was diagnosed), the presence of genotoxic events was evaluated by measuring micronuclei, sister-chromatid exchange, and DNA strand breaks (comet assay tail factor) (Valic et al., 2004). High concentrations of micronuclei (16.0 and 21.8 per 500 binucleated cells compared with the laboratory baseline of 3.7 $\pm$ 0.6 per 500) and comet assay tail factor (33.5 and 4.6% compared with the laboratory baseline of 3.6% + 0.5%) were observed, but sister-chromatid exhange values remained within the normal range. The values of micronuclei and comet assay tail factor were transient and after 13 months were reported to be nearly normal.

Resistance to Growth Inhibition As discussed in *Update 2004*, TCDD has been found to alter cell-cycle progression. In most cases, activation of the AhR by TCDD results in antiproliferative effects that are thought to be mediated by an induction of cell-cycle arrest (Huang and Elferink, 2005), or by inhibition of either insulin-induced (Park et al., 2004), estrogen-induced (Oenga et al., 2004), or androgen-induced (Barnes-Ellerbe et al., 2004) proliferation. However, the effect of TCDD on cell proliferation may be cell-dependent or dose-dependent inasmuch as TCDD has also been reported to increase proliferation of nontumorigenic human breast luminal epithelial cells (Ahn et al., 2005). Alternatively, the effect of TCDD on cell proliferation may depend on the stage of their confluence in the culture dish. For example, recent data (Vondráček et al., 2005) are consistent with those reported previously (Hoelper et al., 2004; Milstone and Lavigne, 1984; Ray and Swanson, 2003) in demonstrating that TCDD induces proliferation in contact-inhibited cells.

Effect of TCDD on Apoptosis As reported in *Update 2004* (IOM, 2005), TCDD has been shown to exert anti-apoptotic effects. The effect of TCDD on apoptosis appears to depend on

whether apoptosis is induced by the intrinsic or extrinsic pathways. For example, although TCDD has been shown to inhibit apoptosis induced by either the genotoxin diethylnitrosoamine (Paajarvi et al., 2005) or ultraviolet radiation (Park and Matsumura, 2006)—the instrinsic apoptotic pathway—the presence of a functional AhR promotes apoptosis stimulated by FasL—the extrinsic pathway (Park KT et al., 2005).

Effect of TCDD on Immortalization The immortalization process involves primarily inactivation of the Rb/$p16^{Ink4a}$ pathway, inactivation of the p53 pathway, and activation of telomerase. As reported in *Update 2004* (IOM, 2005), TCDD has been shown to extend the life span of normal human keratinocytes by a mechanism that appears to involve inhibition of senescence and silencing of p53 and $p16^{Ink4a}$ (Ray and Swanson, 2003). A recent report indicates that TCDD may also affect the immortalization process favorably by inducing telomerase activity (Sarkar et al., 2006).

Effect of TCDD on Promoting Independence from Mitogenic Stimulation Mitogens, such as ligands of the epidermal growth factor, exert their growth-stimulating effects by initiating signal-transduction cascades that ultimately result in activation of the immediate early gene family. As mentioned previously, TCDD has been shown to increase the activity of a number of kinases: c-scr (Backlund and Ingelman-Sundberg, 2005), the mitogen-activated protein kinases (Chen et al., 2005; Shibazaki et al., 2004; Tan et al., 2004), and protein kinase C (Kayano et al., 2004; Machemer and Tukey, 2005; Minsavage et al., 2004; Puebla-Osorio et al., 2004). Additional means by which TCDD can contribute to activation of this pathway include upregulation of the expression of the mitogen epiregulin (Patel et al., 2006) and the transcription factor EGR1 (Martinez et al., 2004).

Effect of TCDD on Angiogenesis TCDD has been shown to inhibit angiogenesis in diverse models, such as during fin regeneration in the zebrafish (Zodrow and Tanguay, 2003; Zodrow et al., 2004) and during embryonic development in the chick embryo (Ivnitksi-Steele and Walker, 2003), and this inhibition is associated with downregulation of vascular endothelial growth factor (VEGF) and other genes involved in vascularization. The degree to which CYP1A1 induction or oxidative stress in the vascular endothelium contributes to inhibition of angiogenesis remains unclear. Recent studies further demonstrate that TCDD or other AhR agonists disrupt neovascularization in various models, including suppression of vascular remodeling in the placenta during late gestation (Ishimura et al., 2006), reduction of responsiveness of endothelial cells to angiogenic stimuli in the chick embryo (Ivnitski-Steele et al., 2005), and inhibition of endothelial cell proliferation and tube formation in vitro after VEGF stimulation (Juan et al., 2006; Ivnitski-Steele and Walker, 2005). The degree to which TCDD inhibition of angiogenesis affects its carcinogenic potential remains to be elucidated.

Effect of TCDD on Tumor Invasion and Metastasis The final stage of the cancer process requires alterations in cell-cell contact and cell-matrix adhesion (a transition from the epithelial to mesenchymal cellular structure), an increase in cell migration, and invasion into neighboring

tissue and metastasis (Christofori, 2006). Gene pathways that play important roles include those of transforming growth factor β (TGFβ), matrix metalloproteinases, and osteopontin. A role of the AhR in regulating the migration process is supported by recent findings that lack of the AhR leads to impaired migration of xenotransplanted tumors (Mulero-Navarro et al., 2005). Lack of the AhR also results in overexpression of a negative regulator of TGFβ, latent TGFβ binding protein-1 (Corchero et al., 2004), and a decrease in TGFβ activity (Gomez-Duran et al., 2006). Furthermore, TCDD has been shown to increase the invasiveness of cultured melanoma cells (Villano et al., 2006) and the expression of matrix metalloproteinases (Haque et al., 2005; Murphy et al., 2004; Villano et al., 2006) in several cultured cell lines. Finally, in mice that express a constitutively active form of the AhR, downregulation of osteopontin that correlated with the development of stomach tumors was observed (Kuznetsov et al., 2005). Taken together, those findings indicate that activation of the AhR by TCDD can facilitate five of the six steps required for the development of human cancers.

Effects on the Male Reproductive Organs

Effects on the Testis Many effects of TCDD in male rodents have been reported previously, including decreases in the size of the accessory sex organs and daily sperm production. Both the AhR and Arnt are expressed in rat and human testis, and studies suggest that TCDD causes tissue damage by induction of oxidative stress (IOM, 2005). In a recent study, Khorram et al. (2004) demonstrated that human sperm express abundant AhR and Arnt mRNA; other studies have identified gene targets of TCDD in the testis that may mediate toxicity. Yamano et al. (2005) identified the novel spermatogenesis-related factor-2, which is expressed primarily in the spermatocyte and which was significantly decreased in the rat testis after TCDD exposure of neonatal rat pups. Kuroda et al. (2005) found that the mouse homologue of the *Drosophila wapl* (wings apart-like) gene was expressed exclusively in murine testis and that its expression was suppressed by TCDD exposure.

Lai et al. (2005a) showed that exposure of primary Sertoli cells in culture to TCDD significantly induced P450 aromatase and sertolin mRNA, increased estradiol secretion, and suppressed Müllerian-inhibiting substance and testin mRNA expression, although these changes required TCDD doses 100-1,000 times those needed to induce CYP1A1. Lai et al. (2005b) also showed that exposure of primary Sertoli cells to TCDD significantly reduced P450 side-chain cleavage expression, progesterone secretion, and hCG-stimulated testosterone secretion.

TCDD exposure of the medaka demonstrated significant histologic changes in the testis, including disorganized spermatogenesis, Leydig cell swelling, and Sertoli cell vacuolation (Volz et al., 2005). Those changes were not associated with CYP1A1 induction but were associated with significant changes in gene ontology pathways, including proteolysis, signal transduction, metabolism, cell proliferation, and cell motility.

Two studies investigated the effects of TCDD on spermatogenesis and erectile function in vivo. Simanainen et al. (2004a) exposed three rat lines, which vary in their sensitivity to TCDD, to a single dose of TCDD at 0, 30, 300, or 3,000 µg/kg and analyzed effects on male reproductive organs 17 days later. The highest dose of TCDD reduced serum testosterone equally in all three rat lines, but the reduction in spermatogenesis was smaller in two more resistant lines. In a second study, TCDD also inhibited spermatogenesis in rabbits treated with 1.0 µg/kg, and this was associated with reduced contractile and relaxation responses in smooth muscle isolated

from erectile tissue (Moon et al., 2004).

One study also demonstrated that TCDD-induced effects on sperm require the AhR and are mediated by ROSs (Fisher et al., 2005b). Exposure of C57BL/6 male mice to TCDD at 0, 0.1, 1.0, 10, or 50 µg/kg induced a dose-dependent loss of mitochondrial membrane potential in AhR-wildtype mice but not in AhR-null mice. TCDD increased sperm concentrations of ROSs, and treatment with an antioxidant prevented the increase in ROSs and the loss of mitochondrial membrane potential.

Effects on the Prostate Prostate cells and prostatic-cancer cell lines are responsive to TCDD in induction of various genes, including those involved in drug metabolism. Simanainen et al. (2004b) used different rat lines (TCDD-resistant Hans/Wistar and TCDD-sensitive Long Evans) and showed that TCDD treatment resulted in a significant decrease in the weight of prostate lobes; however, the effect did not appear to be line-specific. In contrast, the TCDD reduction in sperm does appear to be line-specific and not fully related to the effects of TCDD on serum testosterone (Simanainen et al., 2004a). TCDD effects appear to occur through actions on the urogenital sinus (Lin et al., 2004). In utero and lactational exposure to TCDD appears to retard the aging process in the prostate (Fritz et al., 2005).

As mentioned in Update *2004*, exposure of human prostatic-cancer cell line 9LnCaP to TCDD inhibits androgen-dependent growth. Further probing of the mechanisms that underlie that effect indicate that TCDD alters cell-cycle regulatory proteins by blocking androgen-induced hyperphosphorylation of retinoblastoma protein, reducing cyclin D, and inducing p21 expression (Barnes-Ellerbe et al., 2004).

Effects on the Female Reproductive Organs

The ovaries of experimental animals provide targets for the action of TCDD. The ovary expresses both the AhR and Arnt and is responsive to TCDD-inducible CYP1A1 and 1B1 expression, which depends on the phase of the estrous cycle (IOM, 2005). Earlier studies have established that TCDD alters ovarian steroidogenesis, reducing ovarian expression of luteinizing and follicle-stimulating hormone receptors, reducing circulating progesterone and estradiol, and decreasing fertility (IOM, 2005).

Bussman and Barañao (2006) characterized the regulation of AhR expression in rat granulosa cells by the endogenous hormones follicle-stimulating hormone and estradiol and by the exogenous AhR ligand β-naphthaflavone. Both follicle-stimulating hormone and estradiol reduced AhR protein and mRNA expression in a time-dependent manner, and β-naphthaflavone induced a rapid decrease in AhR protein via proteasomal degradation but also induced a delayed increase in AhR mRNA after prolonged exposure.

Two new studies further elucidate TCDD-induced changes in gene expression and function in the ovary. Exposure of rat granulosa cells to 100 pM TCDD for 24 hours significantly suppressed expression of genes that are essential to ovarian function, including luteinizing-hormone receptor and P450 side-chain cleavage, the latter required for ovarian steroidogenesis (Miyamoto, 2004). Hombach-Klonisch et al. (2006) determined that exposure of oviduct epithelial cells to 0, 0.1, 1.0, or 10 nM TCDD downregulated the amount of estrogen receptor in the nucleus and suppressed estrogen receptor-dependent signaling in a dose-dependent manner.

Three recent studies have shown that TCDD reduces fertility and reproductive success. Chronic dietary exposure of female zebrafish to TCDD for 20 days decreased serum estradiol and serum vitellogenin, and these changes were associated with a decreased number of follicles and increased number of atretic follicles, which probably accounted for more than a 50% decrease in egg production (Heiden et al., 2006). Li et al. (2006) showed that TCDD accumulated in the uterus of pregnant mice to the same degree as in the liver, and this exposure during early pregnancy reduced circulating progesterone and the numbers of implanted embryos and implantation sites. Franczak et al. (2006) reported that a single TCDD exposure of female rats before puberty delayed the onset of puberty and induced premature reproductive senescence; life-long TCDD exposure resulted in a loss of cyclicity and accelerated the transition to reproductive senescence.

Previous studies had shown that TCDD-induced placental dysfunction, including placental hypoxia, contributes to reduction in reproductive success (Ishimura et al., 2002). A recent study expands on that observation. TCDD-induced fetal death was associated with delayed disappearance of glycogen cells and the presence of cysts at the placental junctional zone when pregnant rats were exposed on gestation day (GD) 15 (Kawakami et al., 2006). Pregnant Holtzman rats were significantly more susceptible to those effects than Sprague-Dawley rats, but the sensitivity was not a result of sequence differences in the AhR or of inducibility of placental CYP1A1.

Ishimura et al. (2006) showed that a single TCDD dose to pregnant Holtzman rats on GD15 suppressed vascular remodeling in the labyrinth zone of the placenta during late gestation, which was associated with decreased expression of Tie2, a gene associated with vascular remodeling. The lack of remodeling resulted in constriction of fetal capillaries in the placenta. Global gene-expression profiling of the placentas of TCDD-exposed pregnant Holtzman rats demonstrated that TCDD strongly induced glucose transporters, interferon-inducible genes, and anti-angiogenic cytokines (Mizutani et al., 2004).

Effects on the Uterus *Update 2004* (IOM, 2005) reported that TCDD decreased uterine weight, altered endometrial structure, and blocked estrogen-mediated endometrial proliferation and hypertrophy via an AhR-dependent mechanism in rodents and increased the incidence of endometriosis in rhesus monkeys. There have been some additional studies regarding TCDD's effects on the uterus and the development of endometriosis. Mueller et al. (2005) showed that glycodelin, a glycoprotein with contraceptive and immunosuppressive effects, was a direct AhR-mediated target of TCDD in human endometrial endothelial cells and that TCDD exposure significantly increased gene transcription and protein secretion. In another study, uterine gene expression was examined in ovariectomized C57BL/6 mice that were treated with TCDD, ethynylestradiol (EE), or both (Boverhof et al., 2006). Of the 281 genes regulated by TCDD, 228 were also regulated by EE, but TCDD-mediated responses temporally lagged behind EE responses. An estrogen-receptor antagonist blocked the estrogen-like gene expression induced by TCDD, and this suggested that the responses are estrogen-receptor-mediated. Kitajima et al. (2004) demonstrated that TCDD blocked an estrogen-induced increase in proliferation of a pre-existing endometriotic lesion and significantly increased the expression of both the estrogen receptor and the AhR in mice.

In an earlier review of the literature on endometriosis in humans and nonhuman primates, Guo (2004) concluded that there was insufficient evidence to support the hypothesis that dioxin

exposure leads to the development of endometriosis. One recent study provides some new correlative evidence of a link between TCDD and endometriosis. Igarashi et al. (2005) showed that TCDD exposure of normal human endometrial stromal cells significantly reduced the ratio of the expression of progesterone receptor B (PR-B) to that of progesterone receptor A (PR-A). TCDD also blocked the ability of progesterone to suppress matrix metalloproteinase (MMP) expression, specifically MMP-3 and MMP-7. Both the reduced PR-B:PR-A ratio and the resistance to progesterone-mediated MMP suppression are observed in endometrial tissue from women who have endometriosis.

Effects on the Mammary Gland As discussed in *Update 2004*, TCDD exposure disrupts mammary gland differentiation and lactation, reduces formation of primary and lateral branches of the mammary glands, decreases epithelial elongation, and decreases the number of alveolar buds. The mechanism of those effects has not been determined. However, because the effects preceded hormone-induced events, it has been proposed that altered hormone concentrations were unlikely to have been a mechanism of impaired mammary development. More recent investigations into the mechanisms that regulate branching morphogenesis have revealed that expression of the AhR, ARNT, and CYP1A1 and CYP1B1 is associated with the extracellular matrix interactions that promote cell-cell and cell-extracellular matrix adhesion (Larsen et al., 2004).

Human breast-cancer cells have been useful in investigations of the mechanisms of AhR signaling and of the effects of TCDD on hormone-induced responses, especially responses to estrogen. Previous updates reported that TCDD blocks many estrogen-induced responses in human breast-cancer cells. Recent data have demonstrated that TCDD-activated AhR inhibits the ability of the estrogen receptor to upregulate the trifunctional carbamoylphosphate synthetase/aspartate transcarbamylatransferase/dihydroorotase (CAD) gene that mediates some of the effects of estrogen on cell-cycle progression (Khan et al., 2006). Additional work has shown that estrogen receptor α and the TCDD-activated AhR directly interact and thereby modulate the ability of the AhR to upregulate CYP1A1 (Beishlag and Perdew, 2005; Matthews et al., 2005). TCDD-activated AhR was also shown to inhibit the ability of estrogen to upregulate estrogen receptors α and β (Kietz et al., 2004). Finally, TCDD-activated AhR was shown to inhibit the ability of estrogen to upregulate tumor-suppressor gene BRACA-1 (Hockings et al., 2006).

TCDD has previously been shown to alter growth, differentiation, and apoptosis of cultured breast epithelial cells. Along those lines, Park et al. (2004) have shown that the ability of TCDD to inhibit growth and differentiation of MCF10A (mammary epithelial) cells appears to involve TCDD inhibition of insulin signaling and c-Src kinase and ERK activation (Park et al., 2004). With respect to TCDD effects on apoptosis in those cells, more recent data have shown that the anti-apoptotic actions of TCDD also involve c-Src/ERK signaling (Park and Matsumura, 2006). Most previous studies have reported that TCDD exerts anti-proliferative effects on breast epithelial cells, but it has been by using cells with stem-cell and luminal characteristics that the effects of TCDD followed a U-shaped curve: with 1 nM TCDD, cell proliferation increased, but cell proliferation decreased at higher concentrations of TCDD. TCDD was also shown to increase the ability of the cells to grow in soft agar—an indicator of anchorage-independent growth (Ahn et al., 2005). Kanno et al. (2006) have shown that overexpression of the AhR target gene, AhR repressor (AhRR), inhibits the growth of breast-cancer cells; this may be an

additional mechanism by which TCDD activation of the AhR inhibits proliferation of breast-cancer cells (Kanno et al., 2006).

Finally, the AhR target genes CYP1A1 and CYP1B1 can metabolize β-estradiol to metabolites, some of which can act as tumor initiators. Recent data indicate that those reactions may be important in increasing formation of ROSs and oxidative damage in breast-cancer cells (Chen et al., 2004).

Endocrine and Other Effects

TCDD and related compounds affect the thyroid and thyroid hormones in several animal species (IOM, 2003, 2005) and affect other endocrine organs, such as the pituitary and adrenal gland (IOM, 2005). Previously proposed mechanisms of altering thyroid hormone function include the displacement of hormones from serum transport proteins, the alteration of deiodinase activity, and an increase in thyroid hormone catabolism via glucuronidation (IOM, 2005). A recent study showed that TCDD significantly alters expression of enzymes necessary for thyroid hormone biosynthesis and release (Pocar et al., 2006). TCDD exposure of primary porcine thymocytes significantly down-regulated mRNA expression of the sodium iodide symporter, which is required for accumulation of iodide in the thyroid, and cathepsin B, which is required for proteolysis of thyroglobulin and release of thyroid hormones from the thyroid gland.

Nishimura et al. (2005a) demonstrated that lactational but not in utero exposure was responsible for a TCDD-induced decrease in serum thyroxin and increase in thyroid-stimulating hormone in offspring. That disruption of thyroid hormone homeostasis required expression of the AhR; TCDD exposure of AhR-null pups had no effect on thyroid hormone levels (Nichimura et al., 2005b).

Elango et al. (2006) showed that TCDD exerted estrogenic effects on the rainbow trout pituitary by stimulating a concentration-dependent increase in growth hormone and prolactin mRNA expression.

Developmental Toxicity

Extensive data from studies in animal experiments suggest that developing tissues are highly sensitive to the toxic effects of TCDD, as mediated by the AhR, and that tissue growth and differentiation processes are affected. Recent publications are consistent with that. All the following are studies in which effects of TCDD on the developing embryo or fetus were investigated after maternal exposure to TCDD; they include an array of animal models and a variety of experimental endpoints. Since *Update 2004*, no studies in which the effect of TCDD on the fetus was investigated after paternal exposure have been published.

Elimination of TCDD from the Embryo It is notable that previous studies have shown that several frog species are relatively insensitive to the developmental toxicity of TCDD (Jung and Walker, 1997). Philips et al. (2006) investigated whether the insensitivity might result from rapid elimination of the toxicant. They found that although 1-month-old tadpoles exhibited fast elimination of TCDD, frog embryos exhibited very little elimination of TCDD; mechanisms

other than TCDD elimination might account for the insensitivity of frog species to TCDD-induced developmental toxicity.

Effects on Cardiovascular Structure, Function, and Gene Expression Since *Update 2004*, several reports have detailed the role of AhR signaling and the effects of TCDD on the developing cardiovascular system. Developmentally, the AhR plays a normal role in vascular remodeling and, in particular, is required for normal closure of the hepatic ductus venosus (Lahvis et al., 2000). A recent study in which the AhR was genetically deleted only from hepatocytes or only from endothelial cells demonstrated that AhR expression in endothelial cells was necessary for developmental closure of the ductus venosus (Walisser et al 2005). That study illustrates the requirement for endothelial-cell AhR signaling during development. Not surprisingly, the vascular endothelium of the developing embryo also has been identified as a primary target of TCDD toxicity, and studies cited in *Update 2002* and *Update 2004* (IOM, 2003, 2005) conclude that circulatory failure, oxidative stress in vascular endothelial cells, and abnormal angiogenesis are primary events that mediate the toxicity. Further study has shown that reduced angiogenesis in the chick embryo after TCDD exposure is associated with reduced secretion of vascular endothelial growth factor and reduced responsiveness of endothelial cells to angiogenic stimuli (Ivnitski-Stele et al., 2005).

Garrick et al. (2005) showed that endothelial cells isolated from different microvascular beds of the eel exhibited significantly different sensitivity to TCDD-induced cytochrome P450 1A activity. Cardiac endothelial cells exhibited the highest induction response, renal endothelium was significantly lower, and rete mirabile endothelium was virtually unresponsive.

A number of new studies have investigated the effects of TCDD exposure on the morphogenetic development of the heart. Exposure of zebrafish embryos to TCDD immediately after fertilization reduced heart size and cardiac myocyte cell number and induced cardiac structural malformations and abnormal looping (Antkiewicz et al., 2005). The structural changes were associated with reduced ventricular contraction that progressed to ventricular standstill. The observed cardiotoxicity occurred within 72 hours of fertilization and before circulatory failure, suggesting that the heart is a direct target of TCDD. Similar effects were described in zebrafish larvae exposed to TCDD 3 days after fertilization (Carney et al., 2006); this exposure regimen decreased perfusion of intersegmental vessels, cardiac stroke volume and output, and cardiac ejection fraction within 8–12 hours of exposure. The changes were later associated with pericardial edema, altered cardiac looping, and decreased myocyte number by 24 hours after exposure.

Two additional studies using antisense morpholinos showed that zebrafish ARNT1 is required for the developmental cardiovascular toxicity of TCDD (Prasch et al., 2006) but that induction of CYP1A is not required (Carney et al., 2004). The latter finding contrasts with an earlier study by Teraoka et al. (2003) that showed that knocking down CYP1A expression by antisense morpholinos protected against TCDD-induced developmental toxicity. The reasons for the discrepancy between the two studies remain to be elucidated but may be related to differences in the timing of assessment of the specific toxic endpoints.

Developmental exposure of chick embryos and murine fetuses to TCDD has shown effects on cardiac chronotropic responses. Electrocardiographic (ECG) recordings in chick embryos in ovo after TCDD exposure showed an increased incidence of arrhythmias, normal basal heart rate, and decreased responsiveness to β-adrenergic-stimulated tachycardia (Sommer et al., 2005).

Additional data suggest that those changes resulted from alterations in signal transduction upstream of adenylyl cyclase. In contrast, ECGs of mouse pups after in utero and lactational TCDD exposure demonstrated significant reductions in basal heart rate but normal chronotropic responses to β-adrenergic stimulation (Thackaberry et al., 2005a).

Three studies have conducted global gene-expression profiling of the developing heart after TCDD exposure in an attempt to identify changes that mediate cardiotoxicity. In 3-day-old zebrafish larvae, significant alterations in expression of cardiac sarcomere and mitochondrial energy-transfer components after embryonic exposure to TCDD were identified, including induction of cardiomyosin light chains 1 and 2, myosin heavy chain, and cytochromes b and c (Handley-Goldstone et al., 2005). Those changes are consistent with the dilated cardiomyopathy phenotype observed in piscine and avian embryos. A similar study exposed 3-day-old zebrafish larvae to TCDD for 1 hour and found significant induction of xenobiotic metabolism genes within 1 hour and significant repression of genes that regulate cell division and proliferation after 12 hour, corresponding to the onset of TCDD-induced cardiac toxicity (Carney et al., 2006). In murine fetuses on GD 17.5, 3 days after TCDD exposure, significant alterations were identified in expression of cell-cycle and extracellular-matrix genes, including induction of two matrix metalloproteinases and downregulation of cyclins associated with the progression from G1 to S phase (Thackaberry et al., 2005b). Those changes are consistent with reduced myocyte proliferation, thinner ventricle walls, and low heart size observed in piscine, avian, and murine fetuses (Antkiewicz et al., 2005; Ivnitski et al., 2001; Walker and Catron, 2000; Thackaberry et al., 2005a)

Effects on Male Reproductive Structure, Function, and Gene Expression Previous updates cited several reports that indicated that development of the male reproductive system is exceptionally sensitive to in utero and lactational TCDD exposure. Those effects have included impaired development of the prostate that is lobe-specific, with the ventral prostate exhibiting absence of branching morphogenesis and the dorsal, lateral, and anterior prostate exhibiting inhibition of duct formation (IOM, 2005). More recent work has shown that TCDD inhibition of murine ventral prostate development after in utero and lactational exposure persisted into senescence as determined at the ages of 100 and 510 days (Fritz et al., 2005). Castration of TCDD-exposed mice at senescence resulted in a more significant reduction in prostate weight and androgen-dependent gene expression than castration of control mice; TCDD inhibits the normal aging of the prostate when the organ becomes increasingly androgen-independent with age.

In another study, in utero and lactational TCDD exposure of rats reduced ventral prostate weight without affecting the weight of other male reproductive organs or reducing sperm number. However, when the TCDD-exposed male offspring were mated to unexposed females, the percentage of male pups in F2 generation (38/100, 38%) was significantly lower than female pups (62/100, 62%; $p < 0.05$), compared the sex ratio produced from unexposed males (male pups, 83/159, 52%; female pups, 76/159, 48%) (Ikeda et al., 2005a). Yonemoto et al. (2005) related the maternal dose that significantly reduces ventral prostate weight postnatally to the maternal body burden and fetal concentration of TCDD 1 day after dosing; they found that a maternal dose of 800 ng/kg on GD15 resulted in a maternal body burden of 290 pg/g and a fetal concentration of 52 pg/g on GD16.

Lin et al. (2004) demonstrated that the urogenital sinus (UGS), from which the prostatic

epithelial bud is derived, is a direct target of TCDD requiring the AhR. TCDD exposure of the UGS in organ culture prevented prostatic epithelial buds from forming in the UGS isolated from AhR-wildtype mice but not in the UGS from AhR-null mice.

Effects on Fetal and Postnatal Steroidogenesis The developmental toxicity of TCDD also includes alterations in fetal and postnatal steroidogenesis. Pregnant Wistar rats were administered a single oral dose at 0, 0.01, 0.1, or 1.0 µg/kg TCDD on GD15, and expression of steroidogenetic enzymes and steroid receptors was analyzed in the fetal testis on GD20 (Mutoh et al., 2006). Only the highest dose of TCDD reduced mRNA expression of steroid acute regulatory protein (StAR); 3β-hydroxysteroid dehydrogenase; estrogen receptor α; androgen receptor; cytochromes P450 CYP11A1, CYP17, and CYP11B1; and SF-1, a transcription factor that positively regulates StAR, while there was no effect of the lower doses. In addition, expression of circulating luteinizing hormone (LH) was reduced in the fetal serum following exposure of pregnant dams to 1.0 µg/kg TCDD. Administration of chorionic gonadotropin on GD17 prevented the reduction in fetal testis StAR mRNA induced by maternal exposure to 1.0 µg/kg TCDD, while 100 nM TCDD had no effect on StAR mRNA expression when the fetal testis was exposed in organ culture. These data suggest that TCDD may impair fetal steroidogenesis by targeting pituitary gonadotropins.

In another study, pregnant Sprague-Dawley rats were given a single oral dose of 0, 0.04, 0.2, or 1.0 µg/kg TCDD on GD13, and steroidogenic outcomes were evaluated in male and female pups postnatally (Haavisto et al., 2006; Myllymaki et al., 2005). In male offspring, plasma testosterone was increased on postnatal day (PND) 10 at the highest TCDD dose, but unchanged on PND14 at all TCDD doses. Additionally, neither LH nor follicle-stimulating hormone concentrations were affected in male offspring at any dose of TCDD. In contrast, a maternal dose of 1.0 µg/kg TCDD reduced plasma estradiol in female pups on PND14 and PND16, but increased plasma LH and follicle-stimulating hormone at PND14 without affecting plasma progesterone . Ovarian expression of StAR and cytochrome P450 aromatase mRNA was reduced on PND14, but only by the 0.2 µg/kg TCDD, while P450 aromatase activity was reduced in isolated ovarian follicles at the 1.0 µg/kg TCDD dose.

Effects on Avian Reproductive Development TCDD affects the reproductive systems of birds after in-ovo exposure. Bruggeman et al. (2006) showed that exposure of fertile chicken eggs to 20 ng of TCDD before incubation significantly increased expression of 60-kDa heat-shock protein and decreased expression of regucalcin in the hatchling ovary. That exposure also reduced hatchability and body-weight gain of hatchlings and resulted in the retention of the right oviduct in laying hens, which usually regresses during late embryonic development (Bruggemen et al., 2005). However, there were no effects on circulating steroid hormones or laying performance.

Effects on Brain Sexual Differentiation, Structure, and Gene Expression and on Neurobehavior Several reports of studies in animals and exposed humans suggest that perinatal exposure to TCDD or to dioxin-like compounds can impair brain development and induce neurobehavioral deficits. *Update 2004* (IOM, 2005) reported that perinatal TCDD

exposure decreased neuron number and reduced or reversed sexual dimorphic brain development, and these changes were associated with altered sexual behavior and learning. Recent studies confirm and extend those observations. Nayyar et al. (2003) found that offspring of F-344 rats that were exposed to TCDD at 0 or 700 ng/kg on GD15 exhibited a significant decrease in the hippocampal expression of the *N*-methyl-D-aspartate receptor subtype 1 mRNA and protein. Chang SF et al. (2005) exposed pregnant Sprague-Dawley rats to a single dose of TCDD at 0 or 2 µg/kg on GD15 and analyzed expression of Bcl-2 gene family members in the brain of offspring on PND 0 and and at the age of 4 months. On PND 0, expression of the anti-apoptotic gene Bcl-$_{xL}$ was increased in the cerebral cortex and decreased in the cerebellum of males; this pattern was reversed in females. At 4 months, expression of the anti-apoptotic gene Bcl-2 was increased in the cerebellum of both males and females but was increased in the cerebral cortex only of females. The variable patterns of expression of these genes indicate that early exposure of dioxin could effect the development of certain brain regions with gender differences.

Hojo et al. (2006) administered TCDD to pregnant Sprague-Dawley rats at 0 or 180 ng/kg on GD 8 and found that it altered cortical-cell size distribution only in males, increasing the number of small cells and decreasing the number of large cells. The perinatal exposure also induced a reversal of hemisphere lateralization in cell number in both males and females.

Altered sexual differentiation of the brain was also described in offspring of pregnant Holtzman rats given TCDD at 0, 200, or 800 ng/kg on GD15 (Ikeda et al., 2005b). The sex ratio of brain aromatase activity (male:female) was significantly decreased on PND 2, and the volume of the sexual dimorphic nucleus was significantly reduced in males on PND 98. Those changes were associated with demasculinized behavior in males as reflected in increased consumption of a saccharin solution.

Altered brain development after perinatal TCDD exposure was associated with other behavioral changes later in life. Rainbow trout swim-up fry that had been exposed to TCDD as newly fertilized eggs exhibited decreased densities of retinal ganglion and corresponding deficits in visual and motor function that resulted in decreased prey-capture rate (Carvalho and Tillitt, 2004). Exposure of pregnant Wistar rats to TCDD at 0 or 1 µg/kg on GD 15 altered response to contextual fear conditioning in adult male offspring (Mitsui et al., 2006); this response was associated with a decreased percentage of neurons in the hippocampus that express phosphorylated cyclic AMP response-element-binding protein, a transcription factor associated with learning and memory.

Negishi et al. (2006) evaluated the social behavior of surviving offspring of rhesus monkeys that had been exposed in utero and via lactation to TCDD at such a dosage that maternal body burdens were maintained at 300 µg/kg. Perinatal TCDD exposure had no effect on learning or interest in or hostility to an observer but significantly increased visual exploration and mutual proximity during a first-encounter test.

To begin to elucidate changes in fetal gene expression that may account for alterations in fetal brain development, Fujita et al. (2006) exposed pregnant C57BL/6 mice to TCDD at 20 µg/kg on GD 7 and analyzed global gene expression in the fetal brains on GD 12. TCDD exposure significantly altered the expression of 40 genes, including induction of xenobiotic metabolizing enzymes CYP1A1 and 1B1 and suppression of transcription factors associated with human morphogenetic malformations.

Effects on Craniofacial Development A number of studies have reported detailed morphology and mechanisms of TCDD-induced jaw, palatal, and submandibular gland defects. Yamada et al. (2006) treated pregnant A/J, C57BL/6, and ICR mice with a single dose of TCDD at 0, 10, 20, or 40 µg/kg and assessed the timing and incidence of cleft palate and lip. The potency of TCDD-induced cleft palate was similar in C57BL/6 and ICR mice and occurred at a high incidence in the absence of fetal mortality. In contrast, the dose-response relationships for cleft-palate incidence and fetal mortality were similar in A/J mice. TCDD induced the highest incidence of cleft palate when administered in the period GD 11.5-12.5 but failed to induce cleft lip.

Branching morphogenesis and cleft formation of the salivary gland was significantly impaired in cultured murine GD 13 submandibular gland exposed to 0.1, 1.0, or 2 µM TCDD (Kiukkonen et al., 2006). Neither epidermal growth factor nor fibronectin could rescue this abnormal morphogenesis.

Teraoka et al. (2006) found that zebrafish embryos exposed to TCDD at 0, 0.3, 0.5, or 1.0 ppb 24 hours after fertilization exhibited reduced expression of sonic hedgehog a and b mRNA in the upper and lower jaw; expression was rescued by antisense morpholinos against AhR2. Cell proliferation in the developing jaw was also significantly reduced by TCDD.

Cleft palate induced by TCDD in fetal C57BL/6 mice in utero or in palatal shelves in organ culture was characterized by a reduced number of filopodial extensions and increased cellularity at the medial epithelial edge resembling the phenotype observed in transforming growth factorβ3-null (Tgfβ3-null) mice (Thomae et al., 2005). Addition of Tgfβ3 to a palate culture prevented the TCDD-induced reduction in filopodial outgrowth, the increased cellularity, and the palatal clefting; thus, the Tgfβ3 pathway may be involved in TCDD-induced teratogenesis. Thomae et al. (2006) demonstrated that the sensitivity to TCDD-induced cleft palate in mice was significantly influenced by a locus on chromosome 3 and modestly influenced by a locus on chromosome 12.

Effects on Thymus Differentiation and Function The effects of perinatal TCDD exposure on the differentiation of the thymus and postnatal function of the immune system have been reported in two recent studies. Besteman et al. (2005) reported that when pregnant C57BL/6 mice were exposed to TCDD at 0, 5, or 10 µg/kg on GD 14 or 16, the fetal thymuses on GD 18 exhibited loss of distinction between the cortical and medullary regions, decreased thymocyte viability, and a dose-related increase in thymocyte early apoptosis. Vorderstrasse et al. (2006) studied the effects of perinatal TCDD exposure of C57BL/6 mice on immune responses to influenza virus in the adult offspring. Only females exhibited suppressed cell-mediated and antibody responses to influenza virus, whereas both male and female offspring exhibited enhanced innate immune responses.

Effects on Fetal Growth and Gene Imprinting Wu et al. (2004) exposed preimplantation murine embryos from the one-cell stage to the blastocyst stage to 10 nM TCDD and then implanted them into unexposed recipients. TCDD significantly reduced fetal growth and tended to decrease the expression of two imprinted genes: *H19* and *Igf2* (insulin-like growth factor 2). The decrease in expression was associated with increased promoter methylation and methyltransferase activity.

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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4

Epidemiologic Studies – New Citations for *Update 2006* and Background on Repeatedly Studied Populations

The continuing effort to evaluate and integrate all results from human studies pertinent to possible health effects of exposure to any of the chemicals of interest (2,4-dichlorophenoxyacetic acid [2,4-D]; 2,4,5-trichlorophenoxyacetic acid [2,4,5-T] and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD]; 4-amino-3,5,6-trichloropicolinic acid [picloram]; and cacodylic acid [dimethylarsinic acid or DMA]) has involved the consideration of thousands of citations over the successive updates. Results on a single population may be reported concerning a multiplicity of health outcomes and in more than one publication, particularly when a study is of the cohort design with repeated follow-ups.

The major purpose of the chapters on "epidemiology" or "epidemiologic studies" in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (*VAO*) and its updates has always been to reduce repetition of design information in the health outcomes chapters from endpoint to endpoint and from update to update. Deviating somewhat from the format of previous VAO reports, this chapter first provides tables listing the epidemiologic citations new to this update, which represent a compendium of the sources of new information on health outcomes in humans considered by this committee. The citations correspond to publications that appeared from June 1, 2004 (the closing date for inclusion in the previous update) through September 30, 2006.

Earlier reports in the VAO series used an organizational framework for this chapter, for discussions of health outcomes, and for results tables, which categorized each publication containing primary epidemiologic findings as an occupational study, an environmental study, or a study of Vietnam veterans. These categories were not intended to imply that any of these populations is intrinsically more valuable for the committee's purpose. Various study designs (most importantly cohort, case-control, and cross-sectional) have strengths and weaknesses (see Chapter 2) that influence their potential to contribute evidence of an association with the health outcomes considered in Chapters 6–9 of this report. *Update 2006* has retained the categorization scheme; cycling through these categories, the second part of this chapter discusses the design details of new reports on populations already under study and of studies on new populations reporting multiple endpoints. The occupational section covers studies of production workers, agriculture and forestry workers (including herbicide and pesticide applicators), and paper and pulp workers. The environmental section covers studies of populations unintentionally exposed to unusually high concentrations of herbicides or dioxins as a result of where they lived, such as

Seveso, Italy; Times Beach, Missouri; and the southern portion of Vietnam. The section on Vietnam veterans covers studies of US veterans conducted by the Air Force, the Centers for Disease Control and Prevention (CDC), the Department of Veterans Affairs (VA), the American Legion, and individual states; it also discusses studies of veterans from other nations (e.g., Australia and Korea) that fought in Vietnam.

In addition to reviewing studies involving exposures to the chemicals of interest (2,4-D; 2,4,5-T and its contaminant TCDD; cacodylic acid; and picloram), this and earlier VAO committees have examined any available studies that address compounds chemically related to the herbicides used in Vietnam, such as 2-(2-methyl-4-chlorophenoxy) propionic acid (MCPP), hexachlorophene, and chlorophenols, particularly 2,4,5-trichlorophenol. Some study investigators do not indicate in their published reports the specific herbicides to which study participants were exposed or the magnitude of exposure; those complicating factors were considered when the committee weighed the relevance of a study, as detailed in Chapter 2 of this report. Available details of exposure assessment and use of the resulting data in analyses are discussed in Chapter 5, which follows the same sequence to categorize study populations.

NEW CITATIONS REVIEWED IN *UPDATE 2006*

To elucidate further the new epidemiologic data reviewed by the committee for *Update 2006*, three tables have been added to this chapter that list new citations. Tables 4-1 and 4-2 both list citations for studies of populations that have not been reviewed in previous updates*;* studies listed in Table 4-1 address single health outcomes, and studies in Table 4-2 address multiple health outcomes. Studies listed in Table 4-1 are discussed and critiqued in the health-outcome section for the outcome investigated. To reduce repetition in the report, studies in Table 4-2 are described in detail in this chapter and only briefly in the health-outcome sections; this avoids recapitulation of the information every time a new health outcome from the same study is discussed. Finally, new studies that report on populations that have been discussed in previous updates are listed in Table 4-3; these are described in detail in this chapter in the context of associated studies reviewed by earlier VAO committees and are addressed briefly thereafter in the relevant health-outcome sections.

Citations Reporting on a Single Endpoint in New Populations

New studies reporting on only a single health outcome in previously unstudied populations are listed in Table 4-1 with an indication of the outcome. A description and critique of each study will appear only in the section of the report where the results on health outcomes are discussed.

Table 4-1 Citations on Study Populations New in *Update 2006* with Results on a Single Health Outcome.

Author	Year	Study Design	Exposure(s) Having Results	Health Outcome Reported	Study Population
Occupational Studies					
Fritschi et al.	2005	Case-control	Phenoxy herbicides	NHL (B-cell, diffuse large B-cell, follicular)	Cases diagnosed 2000–2001 in New South Wales
Hallquist et al.	1993	Case-control	Phenoxy herbicides; chlorophenols	Thyroid cancer	Cases from Swedish Cancer Registry
Hardell and Eriksson.	1999	Case-control	Phenoxy herbicides, MCPA	NHL	Population from northern and middle Sweden
Merletti et al.	2006	Case-control	Pesticides (collinear results for herbicides, insecticides, and fungicides)	Bone sarcomas	Studies of rare cancers in seven European countries
Morahan and Pamphlett	2006	Case-control	Herbicides/ pesticides	ALS	Contributors to Australian Motor Neuron Disease DNA Bank
Nordby et al.	2004	Record linkage	Purchase proxies for general pesticide use	Lip cancer	Norwegian farmers
Nordstrom et al.	1998	Case-control	Herbicides	Hairy-cell leukemia	Population-based study of patients
Environmental Studies					
Ascherio et al.	2006	Prospective cohort	Pesticides/herbicides	Parkinson's disease	Cancer Prevention Study II Nutrition Cohort
Bloom et al.	2006	Cross-sectional	Serum dioxins, serum TEQs	Thyroid function	New York State Angler Cohort Study
Cohen et al.	2004	Case histories	No specific exposures	AL amyloidosis	Six case histories of people with AL amyloidosis and NHL
Foster et al.	2005	Cross-sectional	2nd trimester serum dioxin TEQ (CALUX)	Thyroid function (TSH and thyroxine) in mother	Pregnancies at McMaster University (2002–2003)
Heiler et al.	2005	Case-control	Dioxin TEQs in blood	Endometriosis	Belgian surgical patients vs healthy gynecologic patients
Kato et al.	2004	Case-control	"Herbicides/lawn pesticides"	NHL	Women diagnosed 10/1995–9/1998 in upstate New York
Lee C et al.	2006	Cross-sectional	Serum TEQ PCDD/Fs	Liver disease (fatty liver, hepatic function)	Residents around incinerators in Taiwan
Lin et al.	2006	Ecologic cross-sectional	Residence in areas defined by ambient TEQ levels after incinerator operation	Reproduction (gestational age, birth weight, and sex ratio)	Births before and after incinerator in operation for three residential cohorts
Matsuura et al.	2001	Prospective cohort	PCDDs; PCDFs; PCBs	Thyroid function	Breast-fed vs bottle-fed infants

Author	Year	Study Design	Exposure(s) Having Results	Health Outcome Reported	Study Population
Mills and Yang	2006	Cross-sectional	Organochlorines and triazine herbicides	Breast cancer	Latina women in California
Nagayama et al.	2001	Cross-sectional	Serum TEQs	Thyroid hormone levels	Yusho patients
Porpora et al.	2006	Case-control	Blood levels of PCBs (dioxin-like compounds)	Endometriosis	Italian women undergoing laparoscopy
Reynolds et al.	2004	Cohort	Residential distance from application of "probable human carcinogens" (including cacodylic acid), "endocrine disruptors" (including 2,4-D; cacodylic acid)	Breast cancer	California Teachers Study cohort
Reynolds et al.	2005a	Case-control	Tissue levels (TCDD, TEQs) in breast biopsies	Breast cancer	Patients with breast cancer or benign breast condition
Reynolds et al	2005b	Case-control	Gestational proximity to use of pesticides listed as "probable human carcinogen" (including cacodylic acid)	Childhood cancers (all, leukemias, CNS)	California Childhood Cancer Study
Sterling and Hanke	2005	Case reports	Dioxin	Chloracne	Individual poisonings
Wang et al.	2005	Cross-sectional	PCDD, PCDF, and PCB congeners	Thyroid function and growth hormone status	Measurements from cord blood, one minute after delivery
Studies of Vietnam Veterans					
Leavy et al.	2006	Case-control	Service in Vietnam	Prostate cancer	Cancer registry of Western Australia

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; ALS, amyotrophic lateral sclerosis; CALUX, Chemically Activated Luciferase Gene Expression; DNA, deoxyribonucleic acid; MCPA, 2-methyl, 4-chlorophenoxyacetic acid; NHL, non-Hodgkin's lymphoma; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, total toxicity equivalency; TSH, thyroid-stimulating hormone.

Citations Reporting on Multiple Endpoints in New Populations

Newly accessed citations reporting on multiple health outcomes in populations that have not been studied before are listed in Table 4-2, which indicates which endpoints were investigated. A single comprehensive discussion of each study is presented in this chapter, organized according to the type of study population. The results, with comments related to their reliability or

limitations, appear in the appropriate outcome-specific sections. Their design information is presented in the cumulative tables in Appendix C.

Table 4-2 Citations on Study Populations New in *Update 2006* with Results on Multiple Health Outcomes.

Author	Year	Study Design	Exposure(s) Having Results	Health Outcome(s) Reported	Study Population
Occupational Studies					
Carreon et al.	2005	Case-control	Arsenicals, phenoxy herbicides; 2,4-D	Gliomas in women	Upper Midwest Health Study
Chen Z et al.	2005	Case-control	Parental occupational exposures to pesticides and chemicals	Childhood cancers	Children's Oncology Group, US study of germ-cell carcinomas
Chen Z et al.	2006	Case-control	Maternal exposure to herbicides	Childhood cancers	Children's Oncology Group, US study of germ-cell carcinomas
Chiu et al.	2004	Pooled analysis	Occupational exposure to herbicides	NHL	Upper Midwest Health Study
Chiu et al.	2006	Case-control	Occupational exposure to herbicides	NHL	Upper Midwest Health Study
Lee WJ et al.	2004a	Case-control	2,4,5-T; 2,4-D	Cancer (esophageal, stomach)	Residents of eastern Nebraska
Lee WJ et al.	2004b	Pooled analysis	Occupational exposure to herbicides	NHL	Upper Midwest Health Study
Lee WJ et al.	2005	Case-control	2,4,5-T; 2,4-D	Brain cancer	Residents of eastern Nebraska
Magnani et al.	1987	Case-control	Herbicides, chlororphenol	Cancers of brain, kidney, esophagus, pancreas, and melanoma	Male residents of 3 English counties
McLean et al.	2006	Cohort	Nonvolatile organochlorine compounds	Cancer mortality by type	International collaborative study of pulp and paper industry
Mills and Yang	2005	Nested case-control	2,4-D	Breast cancer	United Farm Workers members (1987–2001)
Mills et al.	2005	Nested case-control	2,4-D	Leukemias, NHL	United Farm Workers members (1987–2001)
Oh et al.	2005	Cross-sectional	Dioxin	Immunotoxicity, effects on sperm	Waste incerator workers
Park et al.	2005	Cross-sectional	"Pesticides" in farming (based on usual occupation on death certificate)	Neuro-degenerative diseases: PD, presenile dementia, Alzheimers, motor neuron disease	All deaths in 22 states from 1992–1998

Author	Year	Study Design	Exposure(s) Having Results	Health Outcome(s) Reported	Study Population
Reif et al.	1989	Mixed	Forestry worker	Cancer incidence	Men entered in New Zealand Cancer Registry from 1980-1984
Ruder et al.	2004	Case-control	Arsenicals, phenoxy herbicides, 2,4-D	Gliomas in men	Upper Midwest Health Study
Torchio et al.	1994	Cohort	Farm work	Cancer mortality	Men licensed to use agricultural pesticides in Peidmont area of Italy
Environmental Studies					
Chen H-L et al.	2006	Cross-sectional	PCDD/Fs	Hypertension, diabetes, glucose modulation, liver function	Tiawanese residents living near and incinerator
Colt et al.	2005	Repeat	2,4-D in carpet dust	NHL	Same study as Hartge et al., 2005 and Lee WJ et al., 2006
De Roos et al.	2005a	Case-control	Dioxin, PCBs, furans, TEQs in plasma	NHL	NCI SEER Case-control of NHL
Hartge et al.	2005	Case-control	2,4-D in carpet dust	NHL	NCI SEER Case-control of NHL (same study as Colt et al., 2005 and Lee WJ et al., 2006)
Lee WJ et al.	2006	Repeat	2,4-D in carpet dust	NHL	Same study as Colt et al., 2005 and Hartge et al., 2005
Tango	2004	Environ-mental	Dioxin	Spontaneous abortion or infant death (with or without congenital malformations), low birth weight	Residential proximity to incinerators

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CNS, central nervous system; HD, Hodgkin's disease; NCI, National Cancer Institute; NHL, non-Hodgkin's lymphoma; NIOSH, National Institute of Occupational Safety and Health; PCB, polychlorinated biphenyls; SEER, Surveillance Epidemiology and End Results; TEQ, total toxicity equivalency.

New Citations on Previously Studied Populations

A number of long-term studies of populations exposed to the herbicides sprayed in Vietnam or to their components are of particular importance to the VAO project. It is essential that laboriously amassed information on a single population be recognized as such. Placing each new publication in historical context helps the committee to avoid factoring what is actually a single

observation into its deliberations repeatedly. Such clusters of studies are useful in describing the timecourse of a population's response to an exposure, and joint consideration of an entire body of research on a population may permit more insightful evaluation of relationships with potential confounding factors. Many of the cohorts that have contributed to the cumulative findings of the VAO committees have become dormant; the cohorts' histories are briefly recapitulated in the body of this report, and the design properties of publications on them are tabled in Appendix C. Additional background information can be found in earlier reports in this series.

Many cohorts potentially exposed to any of the chemicals of interest are monitored periodically, including the cohorts of the National Institute for Occupational Safety and Health (NIOSH), the International Agency for Research on Cancer (IARC), and the National Cancer Institute (NCI); residents of Seveso; and Ranch Hand personnel. For the sake of thoroughness, the discussions of specific health outcomes and the associated cumulative-results tables in Chapters 6–9 include references to studies discussed in previous VAO reports and to new studies. However, in drawing its conclusions, the committee focused on the most recent update when multiple reports on the same cohorts and endpoints were available. Individual researchers who are a part of research consortia evaluating cohorts in large multicenter studies (such as the IARC and NCI cohort studies) sometimes publish reports based solely on the subset of subjects they themselves are monitoring. All the studies are noted in the present report, but when drawing its conclusions, the committee focused on the studies of the larger, multicenter cohorts.

The new citations on previously studied populations are listed in Table 4-3. For citations listed in this table, the current study is discussed in the context of the entire history of publications on the population with an explanation of how the new work meshes with earlier efforts. The associated cumulative tables in Appendix C include the basic type of study design; a brief description of sample selection, exposure determination, and endpoints assessed; and the sizes of subject and comparison populations.

Table 4-3 Citations on Previously Studied Populations.

Author	Year	Study Design	Exposure(s) Having Results	Health Outcome(s) Reported	Study Population
Occupational Studies					
Alavanja et al.	2004	Cohort	Farmers, spouses of farmers, commercial applicators	Lung cancer incidence	AHS
Alavanja et al.	2005	Cohort	Farmers, spouses of farmers, commercial applicators	Cancer incidence (full spectrum) (1993–2002)	AHS
Blair et al.	2005a	Cohort	Farmers (years used pesticides ≤10 or >10), spouses of farmers	Mortality (cancers—all and specific, diabetes, COPD, cardiovascular, renal)	AHS
De Roos et al.	2005b	Nested case-control	"Herbicides", 2,4-D	Rheumatoid arthritis	Women in AHS
Engel et al.	2005	Cohort	Ever/never use of phenoxy herbicides; 2,4-D; 2,4,5-T; 2,4,5-TP	Breast cancer incidence	AHS

Author	Year	Study Design	Exposure(s) Having Results	Health Outcome(s) Reported	Study Population
Farr et al.	2004	Cohort	VAO chemicals not specifically addressed	Reproduction–fertility (timing of menstrual cycle)	AHS
Farr et al.	2006	Cohort	VAO chemicals not specifically addressed	Reproduction–fertility (timing of menopause)	AHS
Hoppin et al.	2006	Cohort	Commercial pesticide applicators; 2,4-D	Respiratory effects (wheeze)	AHS
Kamel et al.	2005	Cohort	Days exposed to herbicides	Neurologic symptoms	AHS
Lawson et al.	2004	Cross-sectional	Paternal serum lipid TCDD levels at conception based on PBPK exposure reconstruction	Reproduction–birth weight, preterm delivery, birth defects	NIOSH cohort
’t Mannetje et al.	2005	Cohort	Phenoxy herbicide production worker or sprayer (also exposed to TCDD)	Cancer mortality (full spectrum)	Subcohort of IARC cohort (New Zealand)
Environmental Studies					
Baccarelli et al.	2005b	Cohort	Serum TCDD	Health status (GI disease, endocrine, respiratory, allergy, infectious disease, misc), current dioxin levels	Chloracne cases vs unexposed & exposed controls from Seveso
Eskenazi et al.	2005	Cross-sectional	Serum TCDD	Age at menopause	Seveso Women’s Health Study
McDuffie et al.	2005	Case-control	Any phenoxy herbicide, 2,4-D	NHL	Cross-Canada Study of Pesticides and Health
Pahwa et al.	2006	Case-control	Any phenoxy herbicide, 2,4-D	HD, multiple myeloma, STS	Cross-Canada Study of Pesticides and Health
Warner et al.	2004	Cross-sectional	Serum TCDD	Age at menarche	Seveso Women’s Health Study
Studies of Vietnam Veterans					
AFHS	2005	Cross-sectional	Ranch Hand vs Comparison subjects, serum TCDD	Lipid levels, liver enzymes, cardiovascular findings	AFHS subjects participating in 2002 exam cycle
ADVA	2005a	Cohort	Deployed veterans vs. Australian population	Cancer incidence (full spectrum) (1982–2000)	Male Australian Vietnam veterans (all, Army, Navy, Air Force)
ADVA	2005b	Cohort	Deployed veterans vs. Australian population	Mortality through 2001 (endocrine, nervous, circulatory, respiratory, digestive, external causes, cancer)	Male Australian Vietnam veterans

Author	Year	Study Design	Exposure(s) Having Results	Health Outcome(s) Reported	Study Population
ADVA	2005c	Cohort	Deployed vs. non-deployed National Service veterans	Mortality, cancer incidence (as in ADVA, 2005a,b)	Australian male Army National Service Vietnam veterans
Boehmer et al.	2004	Cohort	Deployed vs. non-deployed men	Mortality through 2000 (endocrine, metabolic, immune; nervous system; respiratory; circulatory; and digestive diseases; cancer)	CDC's Vietnam Experience Study
Kang et al.	2006	Cross-sectional	Serum TCDD, deployed {sprayers vs non-sprayers} vs non-deployed	Diabetes, GI/digestive disease (liver disorders = hepatitis), circulatory disorders (heart conditions, hypertension), respiratory disorders, all cancer	Army Chemical Corps Vietnam-era veterans
Kern et al.	2004	Cohort	Serum TCDD	Diabetes (insulin sensitivity)	AFHS
Ketchum and Michalek	2005	Cohort	Cohort grouping	Mortality (cancer, endocrine, nervous system, circulatory, respiratory, or digestive diseases)	AFHS
Pavuk et al.	2005	Cohort	Serum TCDD level (4 groups), years in SEA	Cancer (melanoma, other skin, prostate)	AFHS (Comparison subjects only)
Pavuk et al.	2006	Cohort	Serum TCDD level (low or high group)	Prostate cancer	AFHS

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2 (2,4,5-trichlorophenoxy) propionic acid; ADVA, Australian Department of Veterans Affairs; AFHS, Air Force Health Study; AHS, Agricultural Health Study; ALL, acute lymphocytic leukemia; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HD, Hodgkin's disease; IARC, International Agency for Research on Cancer; NCI, National Cancer Institute; NHL, non-Hodgkin's lymphoma; NIOSH, National Institute for Occupational Safety and Health; PBPK, physiologically-based pharmacokinetic; PCB, polychlorinated biphenyls; SEA, Southeast Asia; SEER, Surveillance Epidemiology and End Results; STS, soft-tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VAO, Veterans and Agent Orange.

RELEVANT POPULATIONS: NEW REPORTS WITH MULTIPLE ENDPOINTS OR RESULTS ON PREVIOUSLY STUDIED GROUPS

The rest of this chapter and Appendix C do not cover one-time reports on a given study population that addressed only a single health outcome.

Of particular importance to the VAO project are a number of continuing studies of populations that have been exposed to the herbicides sprayed in Vietnam or to their components. Properly integrating new information into the existing database can enhance the usefulness of the entire compendium. On the one hand, if new results are in fact an update on or concern a subset

of previously considered study populations, "double-counting" resulting from ignoring this can bias overall findings. On the other hand, separately reported information can impart new relevance to other data on a study population; for instance, the documentation in Blair et al. (2005a) that 2,4-D was the most commonly used herbicide in the Agricultural Health Study (AHS) population lends relevance to results regarding health outcomes among the members of this study population who were characterized only as applicators in separate publications.

To avoid repetition in the health-outcome chapters, this section and Appendix C also summarize the design characteristics of studies reporting on multiple endpoints, even when the study populations have not been addressed in other publications. Appendix C is organized into three tables—Table C-1 on occupational studies, Table C-2 on environmental studies, and Table C-3 studies of Vietnam veterans. Detailed descriptions of many of the study populations can be found in Chapter 2 of the original report (hereafter referred to as *VAO*), and the criteria for inclusion in the review were discussed in Appendix A of that report. Available details of exposure assessment and use of exposure data are discussed in Chapter 5 of the present report.

The occupational section covers studies of production workers, agriculture and forestry workers (including herbicide and pesticide applicators), and paper and pulp workers. Case-control studies are primarily of interest for their evaluation of occupational exposures, so those that address multiple endpoints or that are represented by several citations considered in VAO reports are presented at the end of the section on occupational studies and at the end of Table C-1. The environmental section covers studies of populations unintentionally exposed to unusually high concentrations of herbicides or dioxins as a result of where they lived, such as Seveso, Italy; Times Beach, Missouri; and the southern portion of Vietnam. The section on Vietnam veterans covers studies conducted in the United States by the Air Force, CDC, VA, the American Legion, and the state of Michigan; it also discusses studies of Australian and South Korean Vietnam veterans.

OCCUPATIONAL STUDIES

Several occupational groups in the United States and elsewhere have been exposed to the compounds of interest. Exposure characterization varies widely in the metric used, the extent of detail, confounding by other exposures, and whether individual, surrogate, or group (ecologic) measures are used. Some studies use job titles as broad surrogates of exposure, others rely on disease-registry data. Occupational groups include workers in chemical production plants; agriculture and forestry workers, including farmers and herbicide appliers; and workers in paper and pulp manufacturing.

Production Workers

National Institute for Occupational Safety and Health

Starting in 1978, NIOSH began a study to identify all US workers who might have been exposed to TCDD between 1942 and 1984 (Fingerhut et al., 1991). The personnel and payroll records of a total of 12 companies were used to identify 5,132 workers as having been involved in production or maintenance processes associated with TCDD contamination. Their possible exposure resulted from working with substances for which TCDD was a contaminant: 2,4,5-trichlorophenol (2,4,5-TCP), 2,4,5-T Silvex® (2,4,5-TP), Erbon® (2-(2,4,5-trichlorophenoxy) ethyl 2,2-dichloropropionate), Ronnel® (*o*,*o*-dimethyl *o*-(2,4,5-trichlorophenoxy) phosphoro thioate), and hexachlorophene. Another 172 workers identified previously by their employers as being exposed to TCDD were also included in the study cohort. The 12 plants involved were large manufacturing sites of major chemical companies, so many of the subjects were potentially exposed to many other compounds, some of which could be toxic and carcinogenic. The NIOSH cohort was added to the IARC cohort as of the 1987 publication by Kogenvinas et al.

Before the publication of the first study of the main cohort, NIOSH conducted a cross-sectional study that included a comprehensive medical history, medical examination, and measurement of pulmonary function of workers employed in chemical manufacturing at a plant in Newark, New Jersey, during 1951–1969, and at a plant in Verona, Missouri, during 1968–1969 and 1970–1972. Control subjects were recruited from surrounding neighborhoods (Alderfer et al., 1992; Calvert et al., 1991, 1992; Sweeney et al., 1989, 1993). The New Jersey plant manufactured 2,4,5-TCP and 2,4,5-T; the Missouri plant manufactured 2,4,5-TCP, 2,4,5-T, and hexachlorophene.

Later studies examined specific health outcomes among the cohort members, including porphyria cutanea tarda (Calvert et al., 1994) and effects on pulmonary function (Calvert et al., 1991), liver and gastrointestinal function (Calvert et al., 1992), mood (Alderfer et al., 1992), the peripheral nervous system (Sweeney et al., 1993), and reproductive hormones (Egeland et al., 1994). Sweeney et al. (1996, 1997/1998) evaluated non-cancer endpoints, including liver function, gastrointestinal disorders, chloracne, serum glucose concentration, hormone and lipid concentrations, and diabetes in a subgroup of the original cohort studied by Calvert et al. (1991). More recent studies of the main cohort examined cardiovascular effects (Calvert et al., 1998); diabetes mellitus, thyroid function, and endocrine function (Calvert et al., 1999); immune characteristics (Halperin et al., 1998); and cancer incidence (Kayajanian, 2002). Cross-sectional medical surveys reported serum TCDD concentrations and surrogates of cytochrome P450 induction (Halperin et al., 1995) in that cohort. A follow-up study (Steenland et al., 1999) examined the association between TCDD exposure and cause of death; it examined specific health outcomes, including cancer (all and site-specific), respiratory disease, cardiovascular disease, and diabetes. Steenland et al. (2001) published a paper that reanalyzed data from two studies on TCDD and diabetes mellitus: one in the US workers of the NIOSH cohort (Calvert et al., 1999) and one in veterans of Operation Ranch Hand in which the herbicides were sprayed from planes in Vietnam (Henriksen et al., 1997). Bodner et al. (2003) compared mortality in Dow Chemical Company workers with mortality in the NIOSH and IARC cohorts; study details are in the Dow Chemical Company section of this chapter.

VAO, Update 1996 (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), and *Update 2004* (IOM, 2005) describe the details of those studies.

Since *Update 2004*, Lawson et al. (2004) published a follow-on study of the children of men in the NIOSH cohort—part of a cross-sectional investigation of workers exposed to TCDD during production of 2,4,5-TCP or its derivatives. Of 400 living and located NIOSH workers, 281 participated (70%). They were matched by age (± 5 years) and race to a pool of 938 eligible

neighborhood referent subjects with self-reports of no occupational exposure to TCDD, which was drawn upon until 260 referents were recruited. The living current and former wives of these subjects were sought for interviews, and 245 worker wives (77.5%) and 221 referent wives (73.9%) participated. Reproductive history was obtained through responses to a detailed questionnaire and through retrieval of birth certificates, neonatal death certificates, and, when applicable, medical records. Of the interviewed wives, 176 of the worker wives (71.8%) and 217 of the referent wives (98.2%) had at least one singleton live birth; no comment was made about this disparity). The analysis of birth weight considered 1,117 singleton, full-term births (at least 37 weeks gestation) to 217 referent wives (604 referent births) and to 176 worker wives (513 births). The work histories of the NIOSH subjects were used to partition their pregenancies into 221 pre-exposure births for which conception occurred before exposure began and 292 exposed births conceived after exposure had begun. In order to consider the possibility that the mothers might have experienced direct exposure from materials carried home by the fathers when they were engaged in their NIOSH employment during a pregnancy, another analysis was restricted to those pregnancies for the cohort members (98 exposed births) and pregnancies occurring while the NIOSH plants were in operation for the referents (334 referent births). Similarly, the analysis of preterm delivery was based on a total of 1,153 live births: 618 referent, 238 pre-exposure, and 297 exposed births, and the analysis of birth defects was performed on 1,166 live-born or stillborn infants. Referent and pre-exposed pregnancies were compared in a qualitative fashion to those exposed. Confirmation from vital and medical records was attempted, but was successful for only about 50% of the reported birth defects. Serum TCDD concentrations were available for the NIOSH subjects, and serum TCDD measurements were made on a random sample of 79 referent subjects for the background unexposed levels. The median value for the sampled referents (6 pg/g) was assigned to all the referent and pre-exposure pregnancies. For exposed pregnancies, workers' serum TCDD concentrations at the time of conception were estimated using a pharmacokinetic model. The logarithms of the TCDD estimates at the time of conception were used in continuous-variable analyses; for categorical analyses, the groups were: referent, <20 pg/g (20% of exposed pregenancies), 20–<255 pg/g (30% of exposed pregnancies), and ≥255 pg/g (50% of exposed pregnancies). It is worth noting that the TCDD concentrations in the NIOSH worker population (estimated serum TCDD concentrations greater than 1,120 pg/g for 20% of the exposed pregnancies) were much higher than in other studied populations.

Monsanto

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

Dow Chemical Company

Several studies of Dow Chemical Company production workers are summarized in *VAO*, *Update 1996*, *Update 1998*, *Update 2002*, and *Update 2004*. The populations of many of those studies were included in the NIOSH cohort (Fingerhut et al., 1991). Originally, Dow conducted a study of workers engaged in the production of 2,4,5-T (Ott et al., 1980) and one on TCP-manufacturing workers with chloracne (Cook et al., 1980). Extension and follow-up studies compared potential exposure to TCDD with morbidity (Bond et al., 1983) and potential paternal TCDD exposure with reproductive outcomes (Townsend et al., 1982). Those Dow employees diagnosed with chloracne or classified as having chloracne on the basis of clinical description were followed prospectively for mortality (Bond et al., 1987). Large-scale cohort mortality studies of workers exposed to herbicides in several of its plants (Bloemen et al., 1993; Bond et al., 1988; Burns et al., 2001; Ramlow et al., 1996) also were conducted.

Dow assembled a large cohort at the Midland, Michigan, plant (Bond et al., 1989a; Cook et al., 1986, 1987). Exposure to TCDD was characterized in the cohort on the basis of chloracne diagnosis (Bond et al., 1989b). Within the cohort, a cohort study of women (Ott et al., 1987) and a case–control study of soft-tissue sarcoma (STS) (Sobel et al., 1987) were conducted. In 2003, Bodner et al. (2003) published a 10-year follow-up of the work of Cook et al. (1986), comparing the mortality experience of 2,187 male Dow workers potentially heavily exposed to dioxin before 1983 with that of the NIOSH and IARC cohorts.

No new studies specifically on the Dow subjects have been published since *Update 2004*. The Dow cohorts have been followed as part of the NIOSH and IARC cohorts since 1991 and 1997, respectively.

BASF

An accident on November 17, 1953, during the manufacture of TCP at BASF plant in Aktiengesellschaft, Germany, resulted in extreme exposure of some workers to TCDD. *VAO*, *Update 1996*, *Update 1998*, and *Update 2000* summarized studies on those workers, including a mortality study of persons initially exposed or later involved in cleanup (Thiess et al., 1982), an update and expansion of that study (Zober et al., 1990), and a morbidity follow-up (Zober et al., 1994). In addition, Ott and Zober (1996, 1997) examined cancer incidence and mortality of workers exposed to TCDD after the accident, during reactor cleanup, maintenance, or demolition.

No new studies have been published on those cohorts since *Update 2000*.

International Agency for Research on Cancer (IARC)

To overcome problems of small studies with insufficient power to detect increased cancer risks, IARC created a multinational registry of workers exposed to phenoxy herbicides, chlorophenols, and their contaminants (Saracci et al., 1991). The registry includes information on

exposures and deaths of 18,390 workers—16,863 men and 1,527 women. *Update 1996* described the individual national cohorts included in the registry.

One study evaluated cancer mortality from STS and malignant lymphoma among people from 10 countries (Kogevinas et al., 1992). Two nested case–control studies were undertaken using the IARC cohort to evaluate the relationship between STS and non-Hodgkin's lymphoma (NHL) (Kogevinas et al., 1995). In an update and expansion including cohorts from the United States and Germany, Kogevinas et al. (1997) assembled national studies from 12 countries that used the same protocol (jointly developed by study participants and coordinated by IARC) to study cancer mortality. Vena et al. (1998) studied non-neoplastic mortality in the IARC cohorts. A cohort study of cancer incidence and mortality was conducted among 701 women from seven countries who were occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins (Kogevinas et al., 1993). *VAO*, *Update 1996*, *Update 1998*, and *Update 2000* highlight those studies.

In addition to the NIOSH cohort and its component subcohorts (discussed above), several of the other subcohorts that make up the IARC cohort have been evaluated apart from the IARC-coordinated efforts. They include Danish production workers (Lynge, 1985, 1993), British production workers (Coggon et al., 1986, 1991), Dutch production workers (Bueno de Mesquita et al., 1993; Hooiveld et al., 1998), German production workers (Becher et al., 1996; Flesch-Janys, 1997; Flesch-Janys et al., 1995; Manz et al., 1991), and Austrian production workers (Jäger et al., 1998; Neuberger et al., 1998, 1999). *VAO*, *Update 1996*, *Update 1998*, and *Update 2000* discuss those studies in more detail.

Since *Update 2004*, 't Mannetje et al. (2005) conducted a follow-up cancer mortality study on New Zealand production workers and herbicide sprayers who were part of the original IARC cohort. They were previously studied for reproductive outcomes (Smith et al., 1981,1982) and were included in the IARC cohort (Kogevinas et al., 1992, 1993, 1997), but cancer findings on them had not been published individually before. The 813 production workers in the study worked for at least one month between January 1969 and December 1984 in a plant that produced phenoxy herbicides and chlorophenols. The 699 herbicide sprayers were registered chemical applicators who had sprayed 2,4,5-T and other phenoxy herbicides from backpacks or from vehicles between January 1973 and December 1984, primarily for agricultural purposes. No direct data on levels of exposure were available for either of these worker groups. Exposure categories for production workers were based on job codes, whereas estimates for sprayers were based on exposure history questionnaires.

Other Chemical Plants

Studies have reviewed health outcomes among UK chemical workers exposed to TCDD as a result of an industrial accident in 1968 (Jennings et al., 1988; May, 1982, 1983), 2,4-D production workers in the former Soviet Union (Bashirov, 1969), factory workers in Prague who exhibited symptoms of TCDD toxicity 10 years after occupational exposure to 2,4,5-T (Pazderova-Vejlupkova et al., 1981), 2,4-D and 2,4,5-T production workers in the United States (Poland et al., 1971), white men employed at a US chemical plant manufacturing flavors and fragrances (Thomas, 1987), and US chemical workers engaged in the production of pentachlorophenol, lower-chlorinated phenols, and esters of chlorophenoxy acids (Hryhorczuk et

al., 1998). The long-term immune-system effects of TCDD were examined in 11 industrial workers involved in production and maintenance operations at a German chemical factory producing 2,4,5-T (Tonn et al., 1996), and immune effects were studied in a cohort of workers formerly employed at a German pesticide-producing plant (Jung et al., 1998). *VAO, Update 1998,* and *Update 2000* detailed those studies.

No new studies have been published on cohorts from other chemical plants since *Update 2000.*

Agriculture Workers

VAO and subsequent updates have reviewed cohort studies that examined various health outcomes in people involved in agriculture, which cluster into several sets investigating different study populations.

Agricultural Health Study (AHS)

The US Agricultural Health Study (AHS) is a prospective investigation of cohorts of private pesticide applicators (farmers), their spouses, and commercial pesticide applicators, for a total of almost 90,000 individuals. It is being sponsored by the National Cancer Institute and the National Institute of Environmental Health Sciences of National Institutes of Health and by the Environmental Protection Agency. Enrollment in the study was offered to applicants for applicator certification in Iowa and North Carolina. The project's Web site (www.aghealth.org) provides many details about conduct of the study, including specification of which pesticides had information gathered from the enrollment forms and mailed questionnaires. In Phase I (1993–1997), the enrollment form for both commercial and private (largely farmers) applicators asked for the details of use for 22 pesticides (10 herbicides, including 2,4-D; nine insecticides; two fungicides; one fumigant) and yes/no responses as to whether 28 other pesticides (8 herbicides, including 2,4,5-T and Silvex [2,4,5-TP]; 13 insecticides; four fungicides; three fumigants) had ever been used. A subset of 24,034 applicators also completed a take-home questionnaire. The mailed questionnaire for this phase asked for details about use of the 28 "yes-no" pesticides and yes-no as to whether 108 other pesticides (34 herbicides, including organic arsenic which would cover cacodylic acid; 36 insecticides; 29 fungicides; nine fumigants) had ever been "frequently" used.

In Phase II (a 5-year follow-up of farmers, 1999–2003), computer-assisted telephone interviews specified "pesticides" in general to include herbicides. It asked about specific pesticides on individual crops; for several crops, only if atrazine or 2,4-D were specified, the subject was asked whether it had been used alone or as part of manufacturer's mix. A full "pesticide list" was not posted on the Web site with this follow-up questionnaire.

Several reports from the AHS effort have been considered in earlier updates of the VAO series. They have addressed a variety of health endpoints: doctor visits resulting from pesticide exposure (Alavanja et al., 1998), chemical predictors of wheeze (Hoppin et al., 2002), prostate-cancer incidence (Alavanja et al., 2003), and cancer risk in the 21,375 children of pesticide appliers born in 1975 or later (Flower et al., 2004). Since *Update 2004*, the AHS has begun to publish a stream of articles, several of which were considered relevant for the present update. Many of them report results only in terms of the three subcohorts (private applicators, spouses of

private applicators, and commercial applicators), but published information on reported pesticide use (Blair et al., 2005a) stating that 2,4-D was the most commonly used pesticide establishes that the AHS cohort is relevant to the committee's charge.

Alavanja et al. (2004, 2005) investigated health outcomes in the AHS cohort consisting of 4,916 commercial applicators, 52,395 private pesticide applicators (farmers or nursery workers), and 32,347 spouses of private applicators (a mixture of men and women) by using enrollment and self-administered questionaires. In an analysis of lung-cancer incidence, Alavanja et al. (2004) examined questionnaire data that included detailed exposure information (lifetime days), medical histories, and demographic information. Standardized incidence ratios (SIR) for licensed private applicators and their spouses were computed relative to the general population of the two states (Iowa and North Carolina), controlling for age, sex, and race. Detailed results were provided on only three herbicides and four insecticides; for chemicals of interest to this report (2,4-D, 2,4,5-T, 2,4,5-TP, and organic arsenic), there were no suggestions of dose-response relationships, but the authors did not present detailed results. A second study by Alavanja et al. (2005) analyzed cancer incidence in the same cohort. In addition to SIRs for licensed private applicators and their spouses relative to the general population of the two states, SIRs for commercial applicators were computed relative to the general population of Iowa. Of the spouses of private applicators(farmers), 99% were female and about 58% had applied pesticides at least 1 year. Because this study presents the exposure information at an ecologic level, it is impossible to determine about how specific chemicals (2,4-D, for example) may have influenced the cancer experience of the study participants.

Blair et al. (2005a) studied overall mortality in the AHS cohort of private pesticide applicators and spouses in North Carolina and Iowa; commercial applicators were excluded from this analysis. Death among the private pesticide applicators and spouses was identified by using the National Death Index and state mortality databases for the two states from the start of study enrollment (1994) through 2000. Cause of death for selected cancers and several other major illnesses was categorized according to International Classification of Diseases, 9th edition (ICD-9) codes. Standardized mortality ratios (SMRs) were calculated by comparing mortality in the AHS cohort to mortality in the general population in North Carolina and Iowa. Another study by Blair et al. (2005b) examined morbidity (cancer incidence, respiratory disease, retinal degeneration, injuries, and accidents) in the AHS cohort and used the study design described previously. Neither of the studies by Blair et al. (2005a,b) included specific exposure data on study participants, however, according to the questionnaire results from Blair et al. (2005a), 2,4-D was the most commonly used pesticide in Iowa; 69% of farmers and 14% of spouses reported 2,4-D exposures.

A study by De Roos et al. (2005b) reported on rheumatoid arthritis (RA) cases in the AHS cohort. Researchers identified 136 physician-validated cases of RA among 594 self-reports from all women (both applicators and spouses) and matched each of 135 cases (excluding one case diagnosed in infancy) to five controls (n = 675). Controls were female AHS participants with no prior RA diagnosis who were matched to cases according to birth date within 1 year. The study included data on "herbicides" (including 2,4-D, 2,4,5-T, and MCPA) and on 2,4-D, one of 21 pesticides with case exposure frequency over 1%.

Engel et al. (2005), looked at breast cancer incidence among private pesticide applicators' wives who were diagnosed with breast cancer between 1993 and 2000 (n = 309). SIRs for breast cancer were caluculated for study participants based on prior pesticide use and all analyses were adjusted for age, race, and state of residence. Exposure data was based on self-administered

questionnaire data pertaining to ever/never having used pesticides. Additional analyses were done for women who identified themselves as having applied pesticides for more than 10 years or at least 40 days cumulatively. The analysis included 18 herbicides, including several chemicals of interest to this committee (2,4-D, 2,4,5-T, and 2,4,5-TP).

Two studies looked at reproductive effects among women in the AHS cohort. Farr et al. (2004) studied menstrual cycle characteristics in 3,103 premenstrual women in the AHS aged 21–40; women who were pregnant, nursing, taking oral contraceptives, had extreme BMIs, or had missing values were excluded. Study participants completed a female health and family health questionnaire. The researchers examined the association between pesticide mixing or applying and menstrual characteristics of short cycles, long cycles, irregular cycles, missed periods, and bleeding or spotting between periods in the last 12 months. Women who had never mixed or applied pesticides were considered the control group. Physical activity was measured by days during the last growing season working in the fields. Although using hormonally active pesticides was found to be associated with increased cycle length and frequency of missed cycles, the pesticides with this observed association did not include any of the chemicals of interest to this review committee. This study used self-reported information on menstrual cycle that may be unreliable, and no hormonal confirmation of menstrual dysfunction was available.

A subsequent study by Farr et al. (2006) concerned age at menopause for 8,038 women aged 35–55 at the time of their enrollment in the AHS study. Study participants were classified according to their self-reported pesticide exposure. Data on herbicides and phenoxy herbicides exposures were included in the analysis of information pertaining to women who ever mixed or applied pesticides.

Kamel et al. (2005) conducted a cross sectional analysis of 18,782 white male licensed private pesticide applicators to study the neurotoxicity of chronic exposure to modest amounts of pesticides. Study participants, enrolled in the AHS between 1993–1997, provided information on lifetime exposures to pesticides and provided self-reports of 23 neurologic symptoms. This study provides information on "herbicides", but the chemicals of interest to this committee are not individually mentioned.

In a new report from the Agricultural Health Study, Hoppin et al. (2006) used a cross-sectional design to investigate the prevalence of wheeze among 2,375 commercial pesticide applicators. The authors defined wheeze as a positive response to the question, "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?" Exposure to pesticides—including herbicides and 2,4-D—was defined as the period one year before administration of the baseline questionnaire.

California United Farm Workers Study

Two new studies, Mills et al. (2005) and Mills and Yang (2005), analyzed lymphohematopoietic and breast cancer, respectively, in nested case-control studies among Hispanic workers drawn from a larger cohort of 139,000 California United Farm Workers (UFW). The exposed populations were defined as those who had ever been a UFW member. Exposure estimates to specific pesticides, including 2,4-D, were developed through linkage of job histories with the California Pesticide Use Reporting database. Vital status and cancer incidence was ascertained through a probabilistic record linkage to the California Cancer Registry for the period 1988–2001. Exposure to pesticides and herbicides was obtained by

linking job titles of subjects recorded by the Union, to the California Department of Pesticide Regulation which has records of all agricultural applications of pesticides in the state since 1970. Individual-level data on established breast cancer risk factors were not available in the study by Mills and Yang (2005); county-level data on fertility and socioeconomic status were used as surrogates in adjusted analyses. This is a significant limitation in a breast cancer study, because misclassification of established risk factors as covariates can introduce substantial bias.

Upper Midwest Health Study

Chiu et al. (2004) and Lee et al. (2004b) conducted a pooled (combined) analysis of two case-control studies that were carried out in three midwestern American states (Iowa and Minnesota (Cantor et al., 1992) and Nebraska (Zahm et al., 1990). In the Iowa/Minnesota component of the study, 530 white, male cases age 30 years and over were identified between 1980 and 1983, and in the Nebraska component 346 male and female cases 21 years of age and older were identified between 1983 and 1986. Control subjects were frequency-matched to case subjects by age, sex, and race. Two sampling frames were used to select control subjects: for cases between 20 and 64 years of age, random digit dialing was used and, for older subjects, files from the Health Care Financing Administration were used (2,357 controls). Response rates for cases were in the order of 90% and for controls it ranged from 78% (Iowa/Minnesota) to 85% in Nebraska. In-depth interviews provided information on self-reported use of pesticides and herbicides. The study by Chiu et al. (2004) examined the association between agricultural pesticide use and familial cancer with the risk of non-Hodgkin's lymphoma while the study by Lee et al. (2004b) looked at non-Hodgkin's lymphoma among asthmatics who reported previous pesticide exposure.

A recent analysis of the data from the Nebraska data (Chiu et al., 2006, based on Zahm et al., 1990, 1993) was used to identify whether there were sub-types of NHL that expressed a higher risk. Specifically, tissue samples were analysed according to the presence of a specific chromosomal translocation (t[14;18][q32;q21]); only 172 of 385 cases were included.

Researchers evaluated farm pesticide exposure in men (Ruder et al., 2004) and women (Carreon et al., 2005) from Iowa, Michigan, Minnesota, and Wisconsin in relation to gliomas, as part of the Upper Midwest Health Study. Self-reported lifetime agricultural pesticide exposures were collected by telephone interview from cases previously identified through participating medical facilities and neurophysician's offices. As part of the interview, cases, or proxies for cases who were too ill to participate or were deceased, answered specific questions about exposure phenoxy herbicides and 2,4-D. Controls were matched by gender and age within ten years .

Lee WJ et al. (2004a, 2005) published two new studies examining pesticide use and selected cancers. Cases were white Nebraska residents over the age of 21 who were identified from the Nebraska cancer registry and matched to controls drawn from an earlier study by Zahm et al. (1990). A structured questionnaire was administered via phone interviews between 1992 and 1994. Along with demographic information and medical histories, participants were asked about their exposure to occupational and residential exposures to pesticides including phenoxy herbicides (2,4,5-T and 2,4-D). Specifically, the two studies focus on pesticide use and adenocarcinomas of the stomach and oesophagus (Lee WJ et al., 2004a) and risk of gliomas (Lee WJ et al., 2005). The strengths of the studies were case ascertainment and diagnostic certainty.

The need to rely on proxy responses for most subjects was a limitation arising out of interviewing being conducted during 1992–1994, while the cases were diagnosed from 1988–1993. The pronounced and systematic discrepancy between the results for subject-reported exposures (reduced odds ratios) and proxy-reported exposures (significantly increased odds ratios), however, underscores concern about recall bias and casts doubt on any interpretations.

Ontario Farmers

Reproductive endpoints were addressed in a series of studies of couples living on family farms in Ontario, Canada. Arbuckle et al. (1999, 2001) studied the frequency of spontaneous abortion., Curtis et al. (1999) investigated time-to-pregnancy, while Savitz et al. (1997) reported on the pregnancy outcomes of stillbirth, gestational age, and birth weight.

Mortality Study of Canadian Male Farm Operators

The Mortality Study of Canadian Male Farm Operators evaluated the risk to farmers of death and specific health outcomes: NHL (Morrison et al., 1994; Wigle et al., 1990), prostatic cancer (Morrison et al., 1992), brain cancer (Morrison et al., 1993), multiple myeloma (Semenciw et al., 1993), leukemia (Semenciw et al., 1994), and asthma (Senthilselvan et al., 1992).

Swedish Cancer Environment Register

The Swedish Cancer Environment Register linked the cancer cases entered in the Swedish Cancer Registry with the records of individuals responding to the 1960 and 1970 national censuses, which provide data on current occupation. The resulting database has been used in cohort studies that evaluated cancer mortality and farm work (Wiklund, 1983); STS and malignant lymphoma among agricultural and forestry workers (Wiklund and Holm, 1986; Wiklund et al., 1988a); and the risk of NHL, Hodgkin's disease (HD); and multiple myeloma in relation to occupational activities (Eriksson et al., 1992).

Farmers of Italian Piedmont

VAO reviewed a study of cancer incidence among farmers licensed to spray pesticides in Italy's southern Piedmont (Corrao et al., 1989).

The current update considered an older agricultural study, which continued the investigation of Carrao et al. (1989). Torchio et al. (1994) reported on the mortality experience of a cohort of 23,401 male farmers from the Piedmont area of Italy from the time they registered to use agricultural pesticides (1970–1974) through 1986. These provinces are characterized by higher used of herbicides, particularly 2,4-D and MCPA, than the rest of the country. The cohort was partitioned into individuals who resided near arable land, those who lived near woodlands, and those who resided near mixed use land; separate results were reported for the first two groups.

Other Studies of Agricultural Workers

Studies of proportionate mortality were conducted among Iowa farmers (Burmeister, 1981) and among male and female farmers in 23 states (Blair et al., 1993). Cancer mortality was investigated among a cohort of rice growers in the Novara Province of northern Italy (Gambini et al., 1997), and cancer incidence was studied among Danish gardeners (Hansen et al., 1992). Lerda and Rizzi (1991) studied the incidence of sperm abnormalities among Argentinian farmers. Kristensen et al. (1997) tested whether either cancers or birth defects were elevated among the offspring of Norwegian farmers. Faustini et al. (1996) evaluated the immune, neurobehavioral, and lung function of residents from an agricultural area of Saskatchewan, Canada, and focused upon immunologic changes in 10 farmers who mixed and applied commercial formulations that contained the chlorophenoxy herbicides. Brain, lymphatic, and hematopoietic cancers in Irish agricultural workers also have been studied (Dean, 1994).

In this update's retrospective screening for information on uncommon cancers, the study of Ronco et al. (1992) was the source of information on mortality among Danish farmers and incidence among Italian farmers for very specific types of cancers. The informativeness of these findings was very limited, however, because they are the largely unanalyzed product of linking each country's cancer registry with census records to garner information on recent occupation.

Forestry Workers

Studies have been conducted among forestry workers potentially exposed to the types of herbicides used in Vietnam. A cohort mortality study examined men employed at a Canadian public utility (Green, 1987, 1991), a Dutch study of forestry workers exposed to 2,4,5-T investigated the prevalence of acne and liver dysfunction (van Houdt et al., 1983), and a study examined mortality and cancer incidence in a cohort of Swedish lumberjacks (Thörn et al., 2000).

Previous VAO updates had not considered the publication by Reif et al. (1989), which consisted of a series of case-control analyses. The researchers addressed the sample of 19,904 individuals with a specified occupation among the 24,762 male cases 20 years of age or older entered from 1980–1984 into the the New Zealand Cancer Registry. The focus of this article was on the 134 registrants for whom forestry worker was the most recent occupation listed. For each type of cancer, the subjects with any other type of cancer were used as controls and the odds of having the specified occupation of forestry worker were calculated.

Other Herbicide and Pesticide Applicators

In addition to cohorts such as IARC and AHS that included agricultural herbicide sprayers (as discussed above), additional cohorts of herbicide and pesticide applicators have been assessed health outcomes: cancer mortality among Swedish railroad workers (Axelson and Sundell, 1974; Axelson et al., 1980), mortality among pesticide applicators in Florida (Blair et al., 1983), and general and cancer mortality and morbidity measured prospectively among Finnish male 2,4-D and 2,4,5-T applicators (Asp et al., 1994; Riihimaki et al., 1982, 1983). Other studies examined the risk of cancer—including STS, HD, NHL, and prostate cancer—among

pesticide and herbicide applicators in Sweden (Dich and Wiklund, 1998; Wiklund et al., 1987, 1988b, 1989a,b), general and cancer mortality among Dutch male herbicide applicators (Swaen et al., 1992, 2004), cancer mortality among Minnesota highway-maintenance workers (Bender et al., 1989) and Minnesota pesticide applicators (Garry et al., 1994, 1996a,b), lung-cancer morbidity in male agricultural plant-protection workers in the former German Democratic Republic who spent a portion of their work year applying pesticides (Barthel, 1981), British Columbia sawmill workers potentially exposed to chlorophenate wood preservatives used as a fungicide during spraying and dipping of sawed logs and planed boards (Dimich-Ward et al., 1996; Heacock et al., 1998; Hertzman et al., 1997), and cancer risk among pesticide users in Iceland (Zhong and Rafnsson, 1996). Details of the studies' designs and results are included in *VAO*, *Update 1996, Update 1998, Update 2000, Update 2002,* and *Update 2004.*

Paper and Pulp Workers

Workers in the paper and pulp industry can be exposed to TCDD and other dioxins that can be generated by the bleaching process during the production and treatment of paper and paper products. *VAO* describes studies of pulp and paper mill workers potentially exposed to TCDD and various health outcomes, including general mortality in workers at five mills in Washington, Oregon, and California (Robinson et al., 1986); cancer incidence among male paper mill workers in Finland (Jappinen and Pukkala, 1991); respiratory health in a New Hampshire mill (Henneberger et al., 1989); and cause-specific mortality among white men employed in plants identified by the United Paperworkers International Union (Solet et al., 1989). *Update 2000* described studies of cancer risk among workers in the Danish paper industry (Rix et al., 1998) and oral cancer risk among occupationally exposed workers in Sweden (Schildt et al., 1999).

McLean et al. (2006) is the first new study of paper and pulp workers to have been reviewed by a VAO committee since *Update 2000*. IARC coordinated this collaborative study of a cohort of 60,468 pulp and paper industry workers employed for at least a year during 1920–1996 in 11 countries. A panel of industrial hygienists developed a job-exposure-matrix on a department-level basis for 27 agents over that time period. This was applied to work histories to estimate individual cumulative exposure to these agents. These estimates were integrated for reporting in terms of ever or never having had dermal or inhalation exposure to nonvolatile organochlorine compounds (which would include TCDD) for 58,162 of these workers; the full cohort was also classified for having had inhalation exposure to volatile organochlorine compounds (primarily organic solvents). The procedures used to follow mortality varied by country, but mortality was followed for between 12 and 50 years. Causes of death were coded (ICD-9) from death certificates or cancer registries.

Studies of Other Occupational Groups

Since *Update 2004*, a South Korean study evaluated immunologic and reproductive toxicities (DNA damage and sperm quality) in 31 waste incinerator workers in comparison to 84 controls subjects (Oh et al., 2005). Rather than measuring serum dioxin levels, both studies inferred dioxin exposure levels for individual workers on the basis of dioxin air concentrations and also

estimated exposures to polycyclic aromatic hydrocarbons through analysis of two urinary metabolites: 1-hydroxypyrene and 2-napthol.

Case-Control Studies

Several case–control studies have been reviewed in previous updates. In 1977, case-series reports in Sweden (Hardell, 1977, 1979) of a potential connection between STS and exposure to phenoxyacetic acids prompted several case–control investigations of a possible association (Eriksson et al., 1979, 1981, 1990; Hardell and Eriksson, 1988; Hardell and Sandstrom, 1979; Wingren et al., 1990). After the initial STS reports (Hardell, 1977, 1979), case–control studies of other cancer outcomes including HD, NHL, and other lymphomas were conducted in Sweden (Hardell et al., 1980, 1981; Hardell and Bengtsson, 1983). Also studied were HD and NHL (Persson et al., 1989, 1993); NHL (Hardell and Eriksson, 1999; Olsson and Brandt, 1988); nasal and nasopharyngeal carcinomas (Hardell et al., 1982); gastric cancer (Ekström et al., 1999); and primary or unspecified liver cancer (Hardell et al., 1984). To address criticism regarding potential observer bias in some of the case–control series, Hardell (1981) conducted another case–control study on colon cancer. Hardell et al. (1994) also examined the relationship between occupational exposure to phenoxyacetic acids and chlorophenols and various characteristics related to NHL—including histopathologic measures, stage, and anatomic location—on the basis of the NHL cases from a previous study (Hardell et al., 1981).

Prompted by the Swedish studies (Hardell, 1977, 1979), a set of case–control studies in New Zealand evaluated the association between phenoxy herbicide and chlorophenol exposure and STS incidence and mortality (Smith and Pearce, 1986; Smith et al., 1983, 1984). Additional case–control studies and an expanded case series were conducted on phenoxy herbicide and chlorophenol exposure and the risks of malignant lymphoma, NHL, and multiple myeloma (Pearce et al., 1985, 1986a,b, 1987).

Geographic patterns of increased leukemia mortality in white men in the central part of the United States prompted a study of the leukemia mortality in Nebraska farmers (Blair and Thomas, 1979). Additional case–control studies were later conducted on leukemia in Nebraska (Blair and White, 1985), in Iowa (Burmeister et al., 1982) on the basis of the cohort study of Burmeister (1981), in Iowa and Minnesota (Brown et al., 1990), and on leukemia associated with NHL in eastern Nebraska (Zahm et al., 1990).

Case–control studies have been conducted in various US populations for other cancers, including NHL (Cantor, 1982; Cantor et al., 1992; Tatham et al., 1997; Zahm et al., 1993); multiple myeloma (Boffetta et al., 1989; Brown et al., 1993; Morris et al., 1986); cancers of the stomach, prostate, NHL, and multiple myeloma (Burmeister et al., 1983); STS, HD, and NHL (Hoar et al., 1986); NHL and HD (Dubrow et al., 1988); and STS and NHL (Woods and Polissar, 1989; Woods et al., 1987).

Other studies outside the United States have examined ovarian cancer in the Piedmont region of Italy (Donna et al., 1984); brain gliomas in two hospitals in Milan, Italy (Musicco et al., 1988); STS and other cancers in the 15 regional cancer registries that constitute the National Cancer Register in England (Balarajan and Acheson, 1984); STS and malignant lymphomas in the Victorian Cancer Registry of Australia (Smith and Christophers, 1992); lymphoid cancer in Milan, Italy (LaVecchia et al., 1989); STS among rice weeders in northern Italy (Vineis et al.,

1986); primary lung cancer among pesticide users in Saskatchewan (McDuffie et al., 1990); and renal-cell carcinoma in the Denmark Cancer Registry (Mellemgaard et al., 1994). Nanni et al. (1996) conducted a population-based case–control study, based on the work of Amadori et al. (1995), of occupational and chemical risk factors for lymphocytic leukemia and NHL in northeastern Italy.

Non-cancer endpoints also have been investigated in case–control studies: spontaneous abortion (Carmelli et al., 1981); congenital malformations (García et al., 1998); immunosuppression and subsequent decreased host resistance to infection among AIDS patients with Kaposi's sarcoma (Hardell et al., 1987); mortality in US Department of Agriculture extension agents (Alavanja et al., 1988, 1989); spina bifida in offspring associated with paternal occupation (Blatter et al., 1997); mortality from neurodegenerative diseases associated with occupational risk factors (Schulte et al., 1996); Parkinson's disease (PD) associated with occupational and environmental risk factors (Liou et al., 1997); PD associated with various rural factors, including exposure to herbicides and wood preservatives (Seidler et al., 1996); PD associated with occupational risk factors (Semchuk et al., 1993); and birth defects in offspring of agriculture workers (Nurminen et al., 1994). Those studies are discussed in detail in previous Updates.

Since *Update 2004*, a case-control study of multiple cancer outcomes was identified that had not been reviewed by earlier committees. Magnani et al. (1987) conducted a case-control mortality study that examined five cancers—oesophageal, pancreatic, cutaneous melanoma, kidney, and brain. Both cases and controls were deceased male residents between the ages of 18–54 who had resided in one of three English counties where chemical manufacturing had occurred. Controls, chosen based on place of residence and cause of death other than the 5 selected cancers, were matched according to sex, county of residence, and age at death. A job-exposure matrix (JEM) was used to predict exposures to various chemical agents on the basis of job title as indicated on the death certificates. Associations between each of the five selected cancers and occupational exposures, including chlorophenols and herbicides, were included in the analyses.

A pair of new case–control studies from the US Children's Oncology Group (Chen Z et al., 2005, 2006) reported on exposures to pesticides (including "herbicides") and the risk of childhood germ-cell tumors (GCTs). One focused on parental occupational exposures (Chen Z et al., 2005) and the other on residential pesticides and chemicals (Chen Z et al., 2006), but they are based on the same overall case-control study. Since GCTs are very rare childhood cancers, national recruitment of cases under the age of 15 newly diagnosed from 1993–2001 was undertaken. Controls were selected by random-digit dialing and frequency-matched on sex, year of birth, and state; to increase power, matching was 1:2 for the rarer male cases. Study participants provided data—demographic information, medical histories, and work histories — via two questionnaires (telephone and self-administered). Residential pesticide exposures were obtained by asking the mothers whether there had been contact with specific products 6 months prior to conception, during pregnancy, or while they were breastfeeding; the fathers were apparently asked about the same time periods of exposure, although the biologic relevance of the lasat two are questionable. A job-exposure matrix approach was used to estimate of occupational exposures to herbicides, insecticides, and fungicides for the same time periods relative to the pregnancy. Telephone interviews were completed with mothers of 278 of the 344 eligible cases (80.8%) and 423 mothers of 634 potential controls (66.7%), and fathers were interviewed as available. The occupational study (Chen Z et al, 2005) reported on 647 mothers (of 253 cases

and 394 controls) and 492 fathers (of 215 cases and 277 controls), while in the residential study (Chen Z et al, 2006) the necessary information was available on 690 mothers (of 272 cases and 418 controls) and 508 fathers (of 223 cases and 285 controls). Both studies are limited by the questionable reliability of the self-reported exposures, reporting of the results only for full the preconception through postnatal period, the small numbers of subjects, and the failure to consider residential and occupational herbicide exposures simultaneously.

Park et al. (2005) investigated the association between occupational factors and mortality from neurodegenerative diseases, including Alzheimer disease and presenile dementia, PD, and motor neuron disease. The authors examined data from 1992–1998 death certificates in 22 states comprising over 2.6 million deaths. Mortality odds ratios based on subjects' "usual occupation" as well as for a subgroup of "pesticide exposed" occupations were provided. However, the exposure assessment did not provide specific data pertaining to the chemicals of interest in this update.

ENVIRONMENTAL STUDIES

The occurrence of industrial accidents has led to the evaluation of the long-term health outcomes of exposure to the compounds of interest.

Seveso, Italy

Among the largest industrial accidents resulting in environmental exposures to TCDD was one in Seveso, Italy, in July 1976 that resulted from an uncontrolled reaction during trichlorophenol production. TCDD contamination of soil has been the most extensively used of the indicators for estimating individual exposure. Three areas were defined on the basis of soil sampling: zone A, the most heavily contaminated, from which all residents were evacuated within 20 days; zone B, an area of lower contamination that all children and women in the first trimester were urged to avoid during daytime; and zone R, a region with some contamination in which consumption of local crops was prohibited (Bertazzi et al., 1989a,b). Several cohort studies were conducted on the basis of those exposure categories. The studies are reviewed extensively in *VAO*, *Update 1996, Update 1998, Update 2000*, *Update 2002,* and *Update 2004* and are summarized here.

Caramaschi et al. (1981) presented the distribution of chloracne among Seveso children, and Mocarelli et al. (1986) measured several compounds in the blood and urine of children who had chloracne. In a follow-up study, dermatologic and laboratory tests were conducted among a group of the children with chloracne and compared with results for a group of controls (Assennato et al., 1989a).

In addition to a 2-year prospective controlled study that was conducted of workers potentially exposed to TCDD during cleanup of the most highly contaminated areas after the accident (Assennato et al., 1989b), other studies examined specific health effects associated with TCDD exposure among Seveso residents: chloracne, birth defects, spontaneous abortion, and crude birth and death rates (Bisanti et al., 1980); chloracne and peripheral nervous system conditions (Barbieri et al., 1988); hepatic-enzyme-associated conditions (Ideo et al., 1982, 1985); abnormal birth outcomes (Mastroiacovo et al., 1988); cytogenetic abnormalities in maternal and fetal

tissues (Tenchini et al., 1983); neurologic disorders (Boeri et al., 1978; Filippini et al., 1981); cancer incidence (Bertazzi et al., 1993; Pesatori et al., 1992, 1993); sex ratio of offspring who were born in zone A (Mocarelli et al., 1996); breast cancer (Warner et al., 2002); immunologic effects (Baccarelli et al., 2002); aryl-hydrocarbon receptor-dependent pathway and toxic effects of TCDD in humans (Baccarelli et al., 2002); and the effect of TCDD-mediated alterations in the AhR-dependent pathway in residents living in zones A and B in Seveso (Landi et al., 2003).

Seveso residents have had long-term follow-up of their health outcomes, especially cancer. Bertazzi and colleagues conducted 10-year mortality follow-up studies among adults and children who were 1–19 years old at the time of the accident (Bertazzi et al., 1989a,b, 1992), 15-year follow-up studies (Bertazzi et al., 1997, 1998), and a 20-year follow-up study (Bertazzi et al., 2001). Pesatori et al. (1998) also conducted a 15-year follow-up study to update non-cancer mortality.

Since *Update 2004*, Baccarelli et al. (2005b) conducted a case-control study of chloracne in individuals from the population of Seveso, Italy. There were 101 cases of chloracne diagnosed following the accident and 211 controls in two subsets. 101 controls were matched to the individual cases by sex, age, and zone of residence at the time of the Seveso accident. The remaining 110 controls were a random sample of non-cases recruited previously by Landi et al. (1997, 1998) from the populations residing in contaminated and non-contaminated areas. The second control group was much older (median age = 31 years versus 8 years for the cases and the matched control group). Serum TCDD levels had been measured in the mid-1990s.

Seveso Women's Health Study (SWHS) To date, several studies have been published using data from the SWHS to evaluate the association between individual serum TCDD and reproductive effects in women who resided in Seveso at the time of the accident in 1976. The study group consisted of 981 volunteers who were between infancy and age 40 at the time of the accident, who had resided in zones A or B, and for whom there was adequate stored serum collected shortly after the explosion for TCDD measurements. Previously reviewed studies have examined associations between serum TCDD and menstrual cycle Eskenazi et al. (2002a), endometriosis (Eskenazi et al., 2002b), birth outcome (Eskenazi et al., 2003), and age at exposure of female Seveso residents (Eskenazi et al., 2004).

The committee reviewed two studies published since *Update 2004* that focused on age of menarche and age of menopause in the Seveso population exposed to high levels of TCDD as the result of an industrial explosion in 1976. Eskenazi et al. (2005) conducted a study on serum dioxin concentrations and age of menopause. The 616 women included in the study were premenopausal at the time of the explosion, older than 35 years of age at the time of the interview, and had archived blood samples taken after the Seveso accident. Of the SWHS women who participated in this study, 564 had sera collected between 1976 and 1977, 28 had sera collected between 1978 and 1982, and 24 had sera collected a second time between 1996 and 1997 because there was too little sera from the initial sample to use for analyses. Samples taken after 1977 that had detectable TCDD measurements had the TCDD exposure level back-extrapolated to 1976. Further analyses were conducted to determine correlations between individual serum TCDD levels and age of menopause for the study participants. Using a similar methodology, Warner et al. (2004) examined the age of menarche in 282 SWHS women who were premenarcheal at the time of the Seveso explosion. TCDD was measured in archived blood samples. Subjects had a mean age of 6.9 years at the time of the explosion. Analyses were

conducted to determine how serum TCDD level correlated with age of menarche for the study participants. A major limitation of this study was that age of menarche was based on recall and the time between onset of menarche and study interview ranged from 5 to 19 years.

Times Beach and Quail Run Cohorts

During early 1971, byproducts of a hexachlorophene and 2,4,5-T production facility in Verona, Missouri, were mixed with waste oils and sprayed on various sites around the state, including the Times Beach and Quail Run areas, for dust control. TCDD was a contaminant of the mixtures sprayed, and the contamination was reported by the Environmental Protection Agency. Several studies evaluated health effects attributable to potential exposure (Evans et al., 1988; Hoffman et al., 1986; Stehr et al., 1986; Stehr-Green et al., 1987; Stockbauer et al., 1988; Webb et al., 1987). *VAO* discussed those studies; no further work has been published.

Vietnam

Researchers in Vietnam have studied the native population exposed to the spraying that occurred during the Vietnam conflict. In a review paper, Constable and Hatch (1985) summarized the unpublished results of those studies. That article also examined nine reports that focus primarily on reproductive outcomes (Can et al., 1983a,b; Huong and Phuong, 1983; Khoa, 1983; Lang et al., 1983a,b; Nguyen, 1983; Phuong and Huong, 1983; Trung and Chien, 1983). Vietnamese researchers later published results of four additional studies, two on reproductive abnormalities (Phuong et al., 1989a,b), one on mortality (Dai et al., 1990), and one on hepatocellular carcinoma (Cordier et al., 1993). *VAO* and *Update 1996* discuss those studies. No studies have been published since *Update 1996*.

Other Environmental Studies

VAO, Update 1996, and *Update 1998* reported on numerous studies of reproductive outcomes attendant to environmental exposure in Oregon (US EPA, 1979); Arkansas (Nelson et al., 1979); Iowa and Michigan (Gordon and Shy, 1981); New Brunswick, Canada (White et al., 1988); Skaraborg, Sweden (Jansson and Voog, 1989); and Northland, New Zealand (Hanify et al., 1981).

Other studies reviewed in previous updates have focused on different outcomes of environmental exposure: STS and connective-tissue cancers in Midland County, Michigan (Michigan Department of Public Health, 1983); NHL in Yorkshire, England (Cartwright et al., 1988); cancer in Finland (Lampi et al., 1992); lymphomas and STS in Italy (Vineis et al., 1991); neuropsychological effects in Germany (Peper et al., 1993); early-onset PD in Oregon and Washington (Butterfield et al., 1993); adverse health effects after an electric transformer fire in Binghamton, New York (Fitzgerald et al., 1989); skin cancer in Alberta, Canada (Gallagher et al., 1996); NHL, HD, and chronic lymphocytic leukemia in a rural Michigan community (Waterhouse et al., 1996); cancer mortality in four northern wheat-producing states

(Schreinemachers, 2000); HD, NHL, multiple myeloma, and acute myeloid leukemia in various regions of Italy (Masala et al., 1996); effects of inhalation exposure to TCDD and related compounds in wood preservatives on cell-mediated immunity in German day-care center employees (Wolf and Karmaus, 1995); mortality and cancer incidence in two cohorts of Swedish fishermen whose primary exposure route was assumed to be diet (Svensson et al., 1995); immune effects in hobby fishermen in the Frierfjord in southeastern Norway (Lovik et al., 1996); immunologic effects of prenatal and postnatal exposure to PCB or TCDD in Dutch infants from birth to 18 months of age (Weisglas-Kuperus et al., 1995); public health and cytogenetic effects in residents of Chapaevsk, Russia (Revazova et al., 2001; Revich et al., 2001); diabetes and endometriosis and serum dioxin concentration in Belgian towns (Fierens et al., 2003); and mortality and incinerator dioxin emissions in municipalities in Japan (Fukuda et al., 2003).

Since *Update 2004*, a population-based case-control study of NHL by Hartge et al. (2005) identifyed cases from four SEER registries (Iowa, Los Angeles County, Detroit, Seattle) during the period 1998–2000. (These data were also addressed in Colt et al. [2005] and the study was also reanalyzed by Lee WJ et al. [2006].) Control subjects were frequency-matched to case subjects by age, sex, race, and SEER centre. Two sampling frames were used to select control subjects: for cases between 20 and 64 years random digit dialing was used and for older subjects Medicare files were used. The authors investigated residential exposures to pesticides and herbicides through detailed in-person interviews. In addition, analyses of pesticides in carpet dust were also conducted. Response rates for cases were 59% and for controls 59%, resulting in data for 1,321 cases and 1,057 controls. In a subset of 100 cases of NHL and 100 control subjects for whom serum levels had been determined, De Roos et al. (2005a) studied associations for TEQs overall from PCBs, furans, and dioxins, but not from dioxins alone.

Chen H-L et al. (2006) investigated the prevalence of hypertension in Taiwanese residents living near municipal waste incinerators for at least 5 years. Health information was obtained from an interviewer-administered questionnaire where individuals were asked about their medical histories, including physician-diagnosed high blood pressure, and serum samples were collected for analysis of PCDD/PCDFs.

Tango et al. (2004) conducted a large study of multiple pregnancy outcomes based on maternal residence at the time of birth. In 1997, the Japanese government had reported that 72 of 1,150 areas surrounding municipal solid-waste incinerators had emissions of dioxin exceeding the action level of 80 ng TEQ/m^3. Of the 72 high-emission incinerators, 9 did not have available addresses; radii of 10 km around the remaining 63 incinerators defined the investigation's "study area." The wider "study region" was defined by the 451 municipalities within or overlapping the "study area." Records on the 489,154 live births, 7,242 fetal deaths (non-induced abortions after 12 weeks of gestation), and 1,796 infant deaths occurring from 1997-1998 in the municipal regions were gathered. The mother's residence at the time of birth could be geocoded for 92% of the assembled records. This study presented results on birth weight and on sex ratio, in addition to findings on fetal loss (after 12 weeks gestation) and infant deaths (within 1 week, 1 month, or 1 year of birth) both with and without congenital malformations. Associations were evaluated between the pregenancy outcome and proximity of the mother's residence to an incinerator (defined in terms of 1-km bands around it). Previous soil sampling had demonstrated that the areas with the highest soil concentrations of dioxin were about 2 km from the incinerators, so analyses were also conducted using a "peak-decline" approach, in which "peak" areas were limited to less than 1 km, 1–2 km, and 2–3 km.

Cross-Canada Study of Pesticides and Health In a nation-wide case-control study of men, 19 years of age and older in 1991–1994, living in six Canadian provinces, Pahwa et al. (2006) investigated whether exposure to phenoxy herbicides and other pesticides was associated with incidence of Hodgkin's Disease (HD), multiple myeloma (MM), or soft tissue sarcomas (STS). (The results of this study in terms of farm work or residence were also reported in Pahwa et al. (2003)—not previously included, but the current citation more specifically addresses the VAO charge). Case subjects newly diagnosed from September 1991–1994 were identified from selected provincial cancer registries and through active ascertainment. Control subjects were frequency-matched to cases by age and, depending on the province, were selected from universal medicare provincial plans (four provinces), telephone lists (one province), and voter's lists (one province). Response rates were in the order of 67% for cases and 48% for controls. Participating subjects completed self-administered postal questionnaires; those subjects who reported more than 10 hours per year of pesticide exposure, structured in-depth telephone interviews were conducted. Questionnaires adapted from the US National Cancer Institute's studies in Kansas and Nebraska were used to obtain further details of exposure. Interviews were completed with 316 HD cases, 342 MM cases, 357 STS cases, and 1,506 control subjects. McDuffie et al. (2001, 2005) followed an analogous protocol in conducting a case-control study on 513 male cases of non-Hodgkin's lymphoma compared to 1,056 controls. The current articles (McDuffie et al., 2005; Pahwa et al., 2006) considered the possible interaction of exposure to insect repellants (DEET in particular) and phenoxy herbicides in the genius of the malignancies in question.

VIETNAM-VETERAN STUDIES

Studies of Vietnam veterans who might have been exposed to herbicides, including Agent Orange, have been conducted in the United States at the national and state levels and in Australia, Korea, and Vietnam. Exposures in those studies have been estimated by various means, and health outcomes have been evaluated with reference to various comparison or control groups. This section is organized primarily by research sponsor because it is more conducive to a methodologic presentation of the articles. Exposure measures fall on a crude scale from individual exposures of Ranch Hand personnel, as reflected in serum TCDD measurements, to some statewide studies' use of service in Vietnam as a surrogate for TCDD exposure.

Several comparison groups have been used for veteran cohort studies: Vietnam veterans who were stationed in areas essentially not exposed to active herbicide missions and were unlikely to have been in areas sprayed with herbicides; Vietnam-era veterans who were in the military at the time of the conflict but did not serve in Vietnam; non-Vietnam veterans who served in other wars or conflicts such as the Korean War or World War II; and various US male populations (either state or national).

For all studies of Vietnam veterans (whether or not the subjects are American), the study subjects are in fact the target population of our charge and they are assumed to have had an elevated probability of having received the exposure(s) of concern than individuals who did not serve in Vietnam, whether or not their individual exposures are not further characterized than that they were deployed.

United States

Operation Ranch Hand

Serum TCDD was measured in 1982 (36 Ranch Hands; Pirkle et al., 1989), 1987 (866 Ranch Hands; AFHS, 1991b), 1992 (455 Ranch Hands; AFHS, 1995), and 1997 (443 Ranch Hands; AFHS, 2000). Serum TCDD analysis of the 1987 follow-up examinations was published in 1991 (AFHS, 1991b).

Results have been published for baseline morbidity (AFHS, 1984a) and baseline mortality studies (AFHS, 1983); the first (1984), second (1987), third (1992), and fourth (1997) follow-up examinations (AFHS, 1987, 1990, 1995, 2000); and for the reproductive-outcomes study (AFHS, 1992; Michalek et al., 1998d; Wolfe et al., 1995). Mortality updates have been published for 1984–1986, 1989, and 1991 (AFHS, 1984b, 1985, 1986, 1989, 1991a). An interim technical report updated the cause-specific mortality among Ranch Hands through 1993 (AFHS, 1996), and Michalek et al. (1998b) reported on a 15-year follow-up of postservice mortality in veterans of Operation Ranch Hand, updating their cause-specific mortality study (1990).

Other Ranch Hand publications have addressed the relationship between serum TCDD and reproductive hormones (Henriksen et al., 1996); diabetes mellitus, glucose, and insulin (Henriksen et al., 1997); skin disorders (Burton et al., 1998); infant death (Michalek et al., 1998a); sex ratios (Michalek et al., 1998c); skin cancer (Ketchum et al., 1999); insulin, fasting glucose, and sex-hormone-binding globulin (Michalek et al., 1999a); immunologic responses (Michalek et al., 1999b); diabetes mellitus (Longnecker and Michalek, 2000; Steenland et al., 2001); cognitive function (Barrett et al., 2001); hepatic abnormalities (Michalek et al., 2001a); peripheral neuropathy (Michalek et al., 2001b); hematologic results (Michalek et al., 2001c); psychological functioning (Barrett et al., 2003); corrolations between diabetes and TCDD elimination (Michalek et al., 2003); thyroid function (Pavuk et al., 2003); and cancer incidence (Akhtar et al., 2004).

Since *Update 2004*, the Air Force Health Study (AFHS, 2005) completed the official report on their scheduled 2002 follow-up examination of their participants. This examination included questionnaires, physical examinations, and clinical assessments for all Ranch Hand veterans and controls who attended the 2002 physical examination. The new AFHS official report does not attempt to interpret or synthesis the new results with previous examination results, rather it provides an accounting of the new findings without analysis or elucidation. The AFHS (2005) examination results are not peer reviewed and the report does not include any information about Ranch Hand veterans or controls who did not attend the follow-up examination or account for former study participants who may have died or were otherwise too ill to attend the 2002 examination.

In addition to the 2002 physical examination results, several new studies have been published since *Update 2004* that provide additional information about the health status of the AFHS cohort. A study by Kern et al. (2004) report result on insulin sensitivity from a substudy two subsets of AFHS participants: one subset from those who participated in the 1997 AFHS physical exam and the other from those who participated in the 2002 AFHS physical exam. Insulin sensitivity was measured from serum samples using two different methods, S_1 and QUICKI. Each of the two subsets consisted of selected Ranch Hand veterans who were then 1:1

matched (on age, BMI, black/non-black race, and first-order family history of diabetes) to a veteran from the AFHS comparison-group. A total of 29 matched pairs were studied from the 1997 exam and 71 matched pairs were studied from the 2002 exam.

Ketchum and Michalek (2005) published findings from 20 years of follow-up for mortality in the US Air Force study comparing Ranch Hands (n = 1,262) to referent subjects (n = 19,078). Controls were Air Force veterans who flew or serviced C-130 cargo aircraft in Southeast Asia during the same time periods that the Ranch Hand units were operating primarily in Vietnam (1962–1971). Because risk factor data was available for only a subgroup of this cohort, the researchers were unable to adjust for confounders such as smoking or drinking for all study participants. For the subgroup of 1,016 RH veterans and 1,436 Vietnam-era comparison veterans for whom serum dioxin measurements were available—those who had attended at least one physical exam between 1982 and 1997—analyses were conducted comparing mortality of the exposed and unexposed veterans on the basis of their serum dioxin measurements. For this subgroup only, potential risk factors were assessed, including smoking, alcohol consumption, and family history of heart disease. All of the mortality analyses presented in this study focus on broad cause of death categories—cancer, endocrine, nervous system, circulatory, respiratory, digestive diseases, accident, suicide, homicide—rather than focusing on specific endpoints.

Pavuk et al. (2005) analyzed the cancer incidence among 1,482 Air Force veterans who were referent controls to the Ranch Hand subjects in the Air Force Health Study. These veterans had served in SEA, primarily conducting transport missions while stationed in Taiwan, Philippines, Guam, Japan, or Thailand and spent little of their SEA tour in Vietnam (~23%). Referent controls were required to have attended an AFHS physical examination or in-person interview between 1982 and 2002. Serum TCDD was measured from blood collected from veterans who attended the AFHS physical exam in 1987; additional serum was collected from some participants who attended the 1992 or 1997 physical exams. Cancer incidence, confirmed from medical records or death certificates were analyzed along with TCDD measurements, divided into four quartiles, and length of time served in SEA.

Another publication from Pavuk et al. (2006) focuses solely on prostate cancer in contrast to earlier analyses (Akhtar et al., 2004; Pavuk et al., 2005), using information on serum TCDD and years of service in Southeast Asia (SEA) in both the Ranch Hand and comparison subcohorts to look for potential associations. From a total of 2,516 veterans who participated in at least one physical exam and had stored serum TCDD measurements (1,019 Ranch Hands and 1,497 Comparisons), 59 Ranch Hands and 81 Comparisons were diagnosed with prostate cancer between Jaunuary 1982 and December 2003. Analyses were adjusted for age and BMI at time of SEA service, occupation (officer, enlisted flyer, or enlisted ground personnel), and smoking.

In trying to harvest evidence from a fairly broad spectrum of populations targeted in epidemiologic studies, *VAO* factored in results from Vietnam veterans in general as being representative of subjects with the possibility of elevated exposure to herbicide components (as surrogates for VA's clientele). With respect the "Blue Water Navy" issue, the AFHS data document that herbicide spraying did not occur solely in Vietnam and did not impact those deployed to Vietnam exclusively. AFHS's serum TCDD results have demonstrated that the Ranch Handers in general were, indeed, more highly exposed than the SEA vets; the SEA vets, however, do have serum TCDD levels that tend to exceed background levels for the US population.

The Air Force Health Study (AFHS) is perceived by many to be the central piece of research for decision-making for the series of VAO reports, but it represents an unwieldy body of

information that was gathered in (evolving) accord with a protocol intended to address certain questions, but which in practice has generated data that have proved more challenging to interpret. It took the committee that produced *Disposition of the Air Force Health Study* (IOM, 2006) much effort to sort out what data were sought and actually assembled in the course of this 20+ year enterprise. Here are the IOM report's conclusions (pp. 80–81) about the AFHS study's limitations:

Limitations Related to the Design and Execution of the Study

The AFHS—like all epidemiologic studies—suffers from limitations related to factors intrinsic to its design and resulting from implementation decisions made by the investigators. Many of these are specific to the study of the health effects of wartime exposure to herbicides and would carry into future research on this topic, although some of the limitations can be addressed by making different assumptions in analyses. However, the limitations would not necessarily extend to more general studies using the data assets.

Study limitations were a central topic of the 1999 GAO report on the AFHS (GAO, 1999). The GAO study director, Kwai-Cheung Chan (2000), summarized that report's findings as follows:

> The [AFHS] has two major limitations: it has difficulty in detecting low to moderate increases in risks of rare diseases because of the relatively small size of the Ranch Hand population, and its findings cannot be generalized to all Vietnam veterans because Ranch Hands and ground troops were exposed to different levels of herbicides in different ways. Blood measurements of dioxin . . . suggest that the Ranch Hands' exposure levels were significantly higher than those of many ground troops. But ground troops may have been exposed in ways (such as through contaminated food and water) that Ranch Hands were not, and little is known about the potential effects of such differences.

GAO asserted that "the Air Force has not clearly or effectively communicated these limitations to the public" (GAO, 1999) and suggested that lack of knowledge of these issues was leading to misunderstanding of the study's results.

In congressional testimony concerning the GAO report in 2000, Dr. Linda Spoonster Schwartz—a Yale University researcher and retired Major USAF nurse—offered additional observations (Schwartz, 2000). Among her comments were that the AFHS protocol (AFHS, 1982) stated that data collected from active duty personnel[17] were not confidential because information that indicated a risk to "public safety or national defense" would be made known to the USAF. The fact that a subject's information could affect his career could, she said, have had an influence on the subject's responses and willingness to submit to certain tests. Dr. Schwartz also indicated that, since all of the AFHS participants were in Vietnam at one time, it could not be assumed that the comparison subjects had no significant exposure to herbicides,[18] and that this called into question the validity of the comparison group for studies of the health effects of herbicides.

Dr. Joel Michalek, then principal investigator of the AFHS, spoke in a January 2005 presentation before the committee about how the study had dealt with obstacles (Michalek, 2005). He noted four limitations of the study related to herbicide health effects research: the inherently small size of the cohort; lack of any biomarkers of herbicide exposure other than dioxin; little information on participants' locations in the theater of operations; and unavailability of a detailed exposure history. Michalek also indicated that AFHS investigators had confronted several exposure-related design and analysis issues. Lack of a good herbicide exposure metric led to concerns over exposure misclassification and bias that were recognized in the study's original protocol (AFHS, 1982).[19] After CDC developed an assay for measuring serum TCDD levels in the late 1980s that AFHS adopted as a proxy, more issues arose. One of these was the effect of measurement error in the estimation of TCDD half-life, an issue because this value was used to estimate a common baseline serum dioxin level for each study participant. Papers by Caudill et al. (1992) and Michalek et al. (1992) discuss this in greater detail. Later papers addressed the validity of dioxin body burden as an exposure index (Michalek et al., 1995), reliability of the dioxin assay

(Michalek et al., 1996), and the correction of bias in half-life calculations (Michalek et al., 1998b). The AFHS web site notes a weakness specific to the examination of questions outside of the study's stated mission to evaluate the health effects of wartime exposure to herbicides: "[b]ecause all of our study subjects served in Vietnam or Southeast Asia, contrasting Ranch Hands with comparisons may not fully reveal health differences associated with service in Vietnam" (AFHS, 2005a).

An additional obstacle identified by this committee is related to study design. As described above, the design allowed the addition of replacement comparisons at each cycle. The integration of replacements in statistical analyses cannot be handled using standard statistical techniques.

Subjects who were found to have been misclassified (designated as a comparison subject when in fact they were a Ranch Hand subject and vice versa) were in turn reassigned to the other group and followed under this new group assignment. Such a design, coupled with the usual issues of missing data and losses to followup, complicates the reanalysis of results presented in AFHS reports and papers.

[17]At the time of the Cycle 1 exam,185 Ranch Hands and 184 comparison subjects were on active duty; in addition, 210 Ranch Hand subjects and 234 comparison subjects held current military or civilian flying certificates, which have rigorous physical and mental fitness requirements (AFHS, 1984a).
[18]Serum dioxin levels in study subjects are not a reliable proxy for exposure because these levels decrease over time in the absence of exposure, blood draws were not taken until several years after the end of US military involvement in Vietnam, and not all herbicides were contaminated with dioxin.
[19]The protocol also addresses a number of other recognized study difficulties and planned correction measures.

In the Preface of the report on the 2002 physical examinations (AFHS, 2005, page ii of front matter), the AFHS researchers themselves warn against considering the contents (and those of the five earlier sets of examinations) as the most definitive presentations of the assembled information on the Ranch Hand subjects and the Comparison veterans:

> This report is comprehensive and detailed, but limited in that (a) it included only those veterans who attended the final physical examination, (b) it addressed only those risk factors that were thought to be important when the study was designed, and (c) it did not account for potentially important risk factors that were discovered after the analytical plan was set. In addition to these six reports, study results have been summarized in articles published in peer-reviewed scientific journals. Such articles differ from the reports in that they (a) incorporate all participants who attended at least one physical examination, (b) use different methods of analysis, (c) focus on particular health endpoints, and (d) include recently discovered risk factors. The results in the journal articles are often consistent, but sometimes lead to conclusions that differ from the six reports. For example, published articles on diabetes in Ranch Hand veterans revealed an association with dioxin exposure consistent with the current report. Published articles on peripheral neuropathy, memory loss, and cancer, however, revealed associations not discussed in this report.

As the Preface notes, the conclusions of the examination reports and of the journal articles are not always in obvious accord.

The methods sections of AFHS (2005; e.g., p. 10–7 for neoplasia) state that cumulative individual histories were compiled on those individuals who participated in the 2002 cycle (giving something akin to cumulative prevalence for 1987–2002 among participating survivors) for the neoplasia, neurological, pychological, gastrointestinal, dermatological, cardiovascular, renal, endocrinological, and pulmonary variables. For general health, hematological, and immunological variables, however, the analyses in the 2002 exam report were apparently just for information gathered in that cycle.

The multiple analysis models, changing inclusion criteria, different exposure groupings, etc., applied to the evolving data set make it challenging to track the findings for an outcome through the course of the study. For example, noting the number of various types of cancer cases reported to have been analyzed in various documents produced during the final stages of the AFHS gives a confusing picture (see Table 4-4).

Table 4-4 Number of Ranch Hand and SEA Comparison Subjects with Particular Types of Cancer Included in Various Analyses Bases on AFHS Data.

	Number of Cases among Ranch Handers			**Number of Cases among SEA Comparisons**			
Tumor type	**AFHS (2005)**	**Akhtar et al. (2004) Table 4 (Table 7)**	**Pavuk et al. (2006) Table 1**	**AFHS (2005)**	**Akhtar et al. (2004) Table 4 (Table 7)**	**Pavuk et al. (2005) Table 4**	**Pavuk et al. (2006) Table 1**
Digestive system (SEER?)		16 (6 dead)			31 (14 dead)	24	
Respiratory system (SEER?)	13	33 (21 dead)		7	48 (38 dead)	36	
Melanoma	19	17 (<4 dead)		31	15 (<2 dead)	25	
Basal or squamous cell	175	?		213	?	253	
Basal	154			183			
Squamous	45			61			
Prostate	53	36 (2 dead)	62 total 59 TCDD	67	54 (3 dead)	83	89 total 81 TCDD

The case counts from AFHS (2005) are cumulative for cases diagnosed from the end of service in SEA through 2003 for those who participated in the 2002 exam cycle (i.e, deceased excluded). An individual was counted only once for having any tumor in a given analysis.The analyses for melanoma and non-melanoma skin cancers only excluded just black veterans.
The case counts from Akhtar et al. (2004) are cumulative for whites from the end of service in SEA through 1999, so did not include any cancers found in the 2002 exam cycle. The analyses for all sites excluded veterans whose race was black or other.
The case counts from Pavuk et al. (2005) are cumulative for first cancers diagnosed from 1982-2003 for those SEA comparison subjects with TCDD readings. The analyses for melanoma and non-melanoma skin cancers only excluded just black veterans.
The case counts from Pavuk et al. (2006) are cumulative for first prostate cancers diagnosed from 1982-2003 for those with TCDD readings.

The discrepancies in the table are large enough to require explanation.

- the paucity of prostate cancer cases among the Ranch Hand subjects as analyzed in Akhtar et al. (2004) compared to the number in Pavuk et al. (2006).
- The 15 melanoma cases and 54 prostate cancer cased in the comparison group (Akhtar et al., 2004) are much lower than the respective numbers who had ever been diagnosed prior to the 2002 exams.

It is unclear whether the large difference in the number of melanoma and prostate cancer cases analyzed for the Comparison subjects between Akhtar et al. (2004) and Pavuk et al. (2005, 2006) is entirely accounted for by the fact that the Akhtar dataset did not include subjects diagnosed

during the 2002 exam cycle (melanoma and prostate cancer are among those cancers likely to be detected during a thorough physical). If so, especially given the asymetrical nature of the changes for the Ranch Hand and and Comparison subjects, would this imply that the results reported by Akhtar et al. could not be considered representative of the final AFHS sample? The AFHS researchers themselves remark in the preface to the final report on the final physical exam cycle:

> ... the lack of a particular finding does not prove that no association exists and should not lead the reader to conclude that there is no association between herbicide exposure and adverse health. In particular, a recently published analysis showed an increase in cancer risk with increased dioxin body burden in Ranch Hand veterans who spent less than 2 years in Southeast Asia; a stratified analysis was performed because years of service in Southeast Asia was identified as a risk factor for cancer in Comparison veterans. These patterns require that more sophisticated statistical models be used to study cancer in Ranch Hand veterans. Consistent with the protocol, study investigators continue to question the underlying assumptions of all analyses, explore new ways to analyze data, and collaborate with specialists to determine whether exposure to Agent Orange adversely affected the health of Ranch Hand veterans.

Not only have the "exposed" subjects (Ranch Hand [RH] veterans) been compared to the "comparison" (southeast Asia [SEA] veterans) subjects; both groups have been contrasted to non-veteran US men, and analyses of various subsets (some seemingly arcane) of the entire sample have been made on the basis of serum TCDD levels. For purposes of the VAO project, all this actually represents a unitary observation on each of a multitude of health endpoints, which it would desirable to distill as concisely as possible. In seeking a consistent approach to incorporating the AFHS data into this VAO report for a variety of outcomes, the committee decided the following:

- The limitations of the AFHS are such that it was under-powered for detecting actual effects, so indications of positivity, especially if they are repeated over exam cycles, are likely to be a real signal. The findings in the cycle reports are more of a large data dump with analyses dictated by the original protocol; they have not really been scientifically processed and interpreted.
- The exam cycle reports are not useful for cancer endpoints (they are only "sort of cumulative" for incidence; people who have died are excluded from the cycle sample); we will work from the more fully cumulative and thoughtfully analyzed findings from the published peer-reviewed articles.
- For some of the non-cancer endpoints, the findings do seem to be useful, but they would need to be combined with other findings to carry a conclusion other than "inadequate."

The men responsible for most of the aerial spraying of herbicides in Vietnam were Air Force volunteers who participated in Operation Ranch Hand. To determine whether exposure to herbicides, including Agent Orange, had adverse human health effects, the Air Force made a commitment to Congress and the White House in 1979 to conduct an epidemiologic study of Ranch Hands (AFHS, 1982). *VAO, Update 1996*, *Update 1998*, *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (hereafter referred to as *Type 2 Diabetes*)

(IOM, 2000), *Update 2000*, *Update 2002*, *Veterans and Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer* (IOM, 2004), and *Update 2004* (IOM, 2005) have discussed reports and papers addressing the cohort in more detail.

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

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

The baseline physical examination occurred in 1982; subsequent exams took place in 1985, 1987, 1992, 1997, and 2002. Morbidity was ascertained through questionnaire and physical examination, which emphasized dermatologic, neurobehavioral, hepatic, immunologic, reproductive, and neoplastic conditions. Some 1,208 Ranch Hands and 1,668 comparison subjects were eligible for baseline examination. Initial questionnaire response rates were 97% for the exposed cohort and 93% for the non-exposed; baseline physical examination responses were 87% and 76%, respectively (Wolfe et al., 1990). Mortality outcome was obtained and reviewed by using US Air Force Military Personnel Center records, the VA's Death Beneficiary Identification and Record Location System (BIRLS), and the Internal Revenue Service database of active social security numbers. Death certificates were obtained from the appropriate health departments (Michalek et al., 1990).

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

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

Ostensibly the AFHS was designed to answer exactly the question the VAO project is asking, but the realized nature of the "exposed" (RH vets) and "comparison" (SEA vets) groups and the practice of VAO committees while endeavoring to realize the intention of its Congressional mandate make interpretation less straightforward.

Centers for Disease Control and Prevention

CDC has undertaken a series of studies to examine various health outcomes of Vietnam veterans, as directed by Congress (Veterans' Health Programs Extension and Improvement Act of 1979, Public Law 96-151; and Veterans' Health Care, Training, and Small Business Loan Act of 1981, Public Law 97-72). *VAO* and *Update 1996* describe those studies in detail. The first was a case–control interview study of birth defects among offspring of men who served in Vietnam (Erickson et al., 1984a,b).

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

To examine concerns about Agent Orange more directly, CDC conducted the Agent Orange Validation Study to evaluate TCDD in US Army veterans compared with exposure estimates based on military records and TCDD in veterans who did not serve in Vietnam (CDC, 1989a).

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

Since *Update 2004*, the first new CDC study since 1990 has been published. In a follow-up on CDC's VES Cohort, Boehmer et al. (2004) reported findings on mortality from 1965–2000. When the first findings of the VES were considered in *VAO* (Boyle et al., 1987), fewer than 250 deaths had occurred and the results were too limited to support any conclusions; now, however, more than 1,500 deaths have occurred. Crude Rate Ratios (CRRs) between the two groups were determined for mortality overall (CRR = 1.07, 95% CI 0.97–1.18) and deaths attributable to specific cancers or diseases of the circulatory system were analyzed.

Department of Veterans Affairs

Numerous cohort and case–control studies are discussed in detail in *VAO, Update 1996, Update 1998, Update 2000*, and *Update 2002*. Among the earliest was a proportionate-mortality study (Breslin et al., 1988). The subjects were ground troops who served in the US Army or

Marine Corps at any time from July 4, 1965, through March 1, 1973. A list of 186,000 Vietnam-era veterans who served in the Army or Marine Corps and were reported deceased as of July 1, 1982, was assembled from VA's BIRLS. A random sample of 75,617 names was selected from the list. Cause of death was ascertained for 51,421 men, including 24,235 who served in Vietnam. On the basis of the proportionate-mortality study (Breslin et al., 1988), Burt et al. (1987) conducted a nested case–control study of NHL with controls selected from among the cardiovascular-disease deaths. Later, Bullman et al. (1990) examined whether Army I Corps Vietnam veterans had cancer mortality similar to that of other Army Vietnam-era veterans, using the study design of Breslin et al. (1988). Watanabe et al. (1991) compared the Vietnam-veteran mortality experience of Breslin et al. (1988) with three referent groups and with additional follow-up through 1984. A third follow-up proportionate-mortality study using the veterans from Breslin et al. (1988) and Watanabe et al. (1991) also was conducted (Watanabe and Kang, 1996).

VA also examined the morbidity and mortality experience of a subgroup of Vietnam veterans from some US Army Chemical Corps units who might have been exposed to high concentrations of herbicides (Thomas and Kang, 1990). In an extension, Dalager and Kang (1997) compared mortality among veterans of the Chemical Corps specialties, including Vietnam veterans and non-Vietnam veterans. Watanabe and Kang (1995) examined postservice mortality among Marine Vietnam veterans compared with Vietnam-era marines who did not serve in Vietnam. Mortality among female Vietnam veterans was assessed by Thomas et al. (1991) and updated in Dalager et al. (1995a).

VA has evaluated specific disease and health outcomes—including case–control studies of STS (Kang et al., 1986, 1987), NHL (Dalager et al., 1991), testicular cancer (Bullman et al., 1994), HD (Dalager et al., 1995b), lung cancer (Mahan et al., 1997), and pregnancy outcomes and gynecologic cancers in female veterans (Kang et al., 2000a,b). It also has conducted a co-twin study of self-reported physical health (Eisen et al., 1991) and PTSD (Goldberg et al., 1990) among monozygotic twins who served during the Vietnam era. A preliminary long-term health study of US Army Chemical Corps Vietnam veterans began in 2001 (Kang et al., 2001).

VA has examined other outcomes—PTSD (Bullman et al., 1991; True et al., 1988), suicide and motor-vehicle crashes (Farberow et al., 1990), and tobacco use (McKinney et al., 1997)—among Vietnam veterans and has studied cause-specific mortality among veterans with non-lethal (combat and non-combat) wounds sustained during the Vietnam War (Bullman and Kang, 1996). *VAO* and *Update 1998* discuss those studies in detail. Most of those publications do not discuss exposure to Agent Orange; exposure to "combat" is evaluated as the risk factor of interest.

The first new VA study published since *Update 2002* is Kang et al. (2006), a long-awaited report on deployed and non-deployed veterans of the US Army Chemical Corps during the Vietnam era. Investigation of this highly exposed population of veterans was recommended by the original VAO committee.

In the cohort study of US Army Chemical Corps personnel, Kang et al. (2006) conducted a cross-sectional survey among 2,247 Vietnam veterans and 2,242 non-Vietnam veterans. The Vietnam veterans served at least one tour of duty between 1965 and 1973 and were likely to have been involved in chemical operations. The survey was conducted by the Veteran's Health Administration in 1999–2000 and 1,499 (66.7%) Vietnam veterans and 1,428 comparison subjects participated (63.7%). Self-reported data were collected from the participants via telephone interview and medical and hospital records were sought to document reported cases of

diabetes. Serum dioxin levels measured in a subgroup of 897 of the participants confirmed the reliability of self-reports of herbicide spraying as a surrogate for TCDD exposure. Analyses in the study were adjusted for age, race, BMI, rank, and smoking.

American Legion

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

State Studies

Several states have conducted studies of Vietnam veterans, most of them unpublished in the scientific literature. *VAO* and *Update 1996* reviewed studies from Hawaii (Rellahan, 1985), Iowa (Wendt, 1985), Maine (Deprez et al., 1991), Massachusetts (Clapp, 1997; Clapp et al., 1991; Kogan and Clapp, 1985, 1988; Levy, 1988), Michigan (Visintainer et al., 1995), New Jersey (Fiedler and Gochfeld, 1992, Kahn et al., 1992a,b,c, 1998), New Mexico (Pollei et al., 1986), New York (Greenwald et al., 1984; Lawrence et al., 1985), Pennsylvania (Goun and Kuller, 1986), Texas (Newell, 1984), West Virginia (Holmes et al., 1986), and Wisconsin (Anderson et al., 1986a,b).

Other US Vietnam-Veteran Studies

Additional studies have examined health outcomes including spontaneous abortion (Aschengrau and Monson, 1989) and late adverse pregnancy outcomes in spouses of Vietnam veterans (Aschengrau and Monson, 1990). After a published study indicated a potential association for testicular cancer in dogs that served in Vietnam (Hayes et al., 1990), Tarone et al. (1991) conducted a case–control study of testicular cancer in male veterans. *VAO* summarizes those studies, and no new studies have been published.

Australia

The Australian government has commissioned studies to investigate health risks to Australian veterans: birth anomalies (Donovan et al., 1983, 1984; Evatt, 1985), mortality (Crane et al., 1997a,b; Commonwealth Institute of Health, 1984a,b,c; Evatt, 1985; Fett et al., 1987a,b; Forcier et al., 1987), deaths from all causes (Fett et al., 1987b), cause-specific mortality (Fett et

al., 1987a), and morbidity (AIHW, 1999, 2000; CDVA 1998a,b). A revised morbidity study has been published (AIHW, 2001). An independent study in Tasmania evaluated reproductive and childhood-health problems for associations with paternal service in Vietnam (Field and Kerr, 1988). O'Toole et al. (1996a,b,c) described self-reported health status in a random sample of Australian Army Vietnam veterans. *VAO*, *Update 1998*, *Update 2000*, and the acute myelogenous leukemia report (IOM, 2001) describe the studies.

Three of the four recent reports updating the health experience of Australian Vietnam veterans contain findings relevant to the investigations of this committee, while the fourth (which concerns the response of Army personnel to treatment with the anti-malarial drug Dapsone) is not regarded as pertinent to the committee's charge. Although the recent Australian reports did not characterize the exposure of these veterans to the herbicides sprayed in Vietnam, it is the convention of this committee to regard Vietnam veterans in general as being more likely to have received higher exposures to the chemicals of concern than the general public.

The term "Australian Vietnam veterans" corresponds with the cohort defined by the "Nominal Roll of Vietnam Veterans" listing Australians who served on land or in Vietnamese waters from May 23, 1962, to July 1, 1973, including military and some non-military personnel of both sexes. Individuals were considered who served in all branches of service in the "defence forces" and "Citizen Military Forces" (e.g., diplomatic, medical, entertainment personnel). The cohort studied in the first and second reports in the current series, however, is limited to male members of the military and most of the analyses focus on men in the "defence forces," Army (n = 41,084), Navy (n = 13,538), and Air Force (n = 4,570).

The first of these reports, *Cancer Incidence in Australian Vietnam Veteran Study 2005* (ADVA, 2005a), sought associations in cancer incidence by comparing diagnoses from 1982–2000 among male Vietnam veterans to those in the general population of Australia. The results in this report supersede those in the reports of the Australian DVA (CVDA 1998a,b) for men and women respectively.

The Third Australian Vietnam Veterans Mortality Study (ADVA, 2005b) considered the causes of death for men from all branches of service: number of deaths Army (n = 4,045), Navy (n = 1,435), and Air Force (n = 686). The mortality experience of these military personnel serving in Vietnam was compared to that of the general population of Australia. Findings were reported by branch of service for both incidence and mortality; the results for the Navy are relevant to the eligibility issue concerning having set foot on Vietnam's soil. The findings of this study supersede those in Crane et al. (1997a) for mortality from 1980 to 1994.

In third report, *Australian National Service Vietnam Veterans: Mortality and Cancer Incidence 2005* (ADVA, 2005c), a subset of the veterans considered in the first two reports (19,240 conscripted male Army veterans deployed to Vietnam or "National Service" veterans), were compared to their 24,729 non-deployed counterparts ("National Service non-veterans"). This comparison between contemporaries who had been sufficiently healthy to enter the service provided a mean of adjusting for a possible "healthy warrior" effect. The results of this study supersede those of the Commonwealth Institute of Health (1984a; Fett et al., 1984) and of Crane et al. (1997b).

The Australian Veterans Health (AVH) Study (CIW, 1984a,b,c; Fett et al. 1984, 1987a,b) was also an internal comparison study of deployed and non-deployed Vietnam War era National Service veterans; results in this report (ADVA, 2005c) supersede those in CDVA (1997b , referred to as Crane et al. in earlier updates).

In addition, Leavy et al. (2006) reported the results of a case-control study including 606 prostate cancer cases and 471 controls in Western Australia. Cases were men between the ages of 40–75 who were identified from the Cancer Registry of Western Australia. Controls were randomly selected men with no history of prostate cancer who were matched to cases by age within 5 years. Study participants provided demographic information, cancer and occupational histories, and history of military service history via a self-administered questionnaire.

Other Vietnam-Veteran Studies

Studies have also been published examining health effects in Vietnam-veterans from countries other than the United States and Austrialia who were also believed to be exposed to dioxin. The studies reviewed in earlier Updates examined antinuclear and sperm autoantibodies in Vietnamese veterans (Chinh et al., 1996) and evaluated health (Kim J-S et al., 2003), immunotoxicologic effects (Kim H-A et al., 2003), and skin and general disease patterns (Mo et al., 2002) in Korean Vietnam veterans who were exposed to Agent Orange during the Vietnam conflict. No new studies of other Vietnam veteran groups were identified by the current committee.

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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5

Exposure Assessment

Assessment of human exposure to specific herbicides and the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is a key element in determining whether specific health outcomes are linked to these chemicals. In this chapter we review information on occupational and environmental exposures to these herbicides and TCDD, including exposure of Vietnam veterans. We discuss exposure assessments from selected epidemiologic studies introduced in Chapter 4 and provide background information for the health-outcome chapters that follow; health outcomes are not discussed here. Further discussion of exposure assessment and a detailed review of the US military's wartime use of herbicides in Vietnam can be found in Chapters 3 and 6 of *Veterans and Agent Orange* (*VAO*; IOM, 1994); additional information is in Chapter 5 of *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003a), and *Update 2004* (IOM, 2005). Reviews of the most recent studies of the absorption, distribution, metabolism, and excretion of herbicides and TCDD can be found in the discussion of toxicokinetics in Chapter 3 of this report.

EXPOSURE ASSESSMENT IN EPIDEMIOLOGIC STUDIES

An ideal exposure assessment would provide quantification of the concentration of a chemical at the site of toxic action in the tissue of an organism. In studies of human populations, however, it rarely is possible to measure those concentrations. Instead, exposure assessments are based on questionnaires and interviews, measurements in environmental media, or measurements in biologic specimens. Table 5-1 provides a guide to exposure monitoring and assessment methods used in selected epidemiologic studies of the health effects of herbicides applied in Vietnam by US military forces and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

Exposure assessments based on measurements of environmental contaminants provide estimates of the amount of the contaminant that contacts a body barrier over a defined period. Exposure can occur through inhalation, skin contact, and ingestion. Exposure also can be assessed by measuring the compounds of interest—or their metabolites—in human tissues. Such biologic markers of exposure integrate absorption from all routes, and their interpretation is usually complex. Knowledge of pharmacokinetics is essential to the linkage of measurements at the time of sampling with past exposures.

Quantitative assessments based on environmental or biologic samples are not always available for epidemiologic studies, so investigators often rely on a mixture of qualitative and quantitative information to derive estimates (Armstrong et al., 1994; Checkoway et al., 2004). The most basic approach compares members of a presumably exposed group with the general population or with a non-exposed group. This method of classification offers simplicity and ease of interpretation.

Table 5-1 Exposure monitoring and assessment methods used in selected epidemiologic studies of the health effects of herbicides applied in Viet Nam by U.S. military forces and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

Exposure Method	NIOSH Cohort Study	Dow Cohort Study	Ontario Farm Health Study	U.S. Ag Health Study	New Zealand Herbicide Sprayers	Seveso Area Study	Seveso Women's Health Study	Air Force Health Study	Army Chemical Corps Study	Australian Veteran study
Job title	x	x	x	x	x			x	x	x
Self-reported chemical use			x	x	x				x	
Exposure duration	x	x	x	x		x		x	x	
Exposure categories	x	x	x	x				x	x	
Review of records	x			x				x		
Job-exposure matrix	x	x								
Proximity to source						x	x			x
Soil sampling						x				
Air sampling		x								
2,4-D concentration in urine			x							
TCCD concentration in serum	x					x	x	x	x	

A more refined method assigns each study subject to an exposure category, such as high, medium, and low exposure. Disease risk for each group is calculated separately and compared with a reference or non-exposed group. This method can identify the presence or absence of a dose–response trend. In some cases, more detailed information is available for quantitative exposure estimates, and these can be used to construct what are sometimes called exposure metrics. These metrics integrate quantitative estimates of exposure intensity (such as chemical concentration in air or extent of skin contact) with exposure duration to produce an estimate of cumulative exposure.

The temporal relationship between exposure and disease is complex and often difficult to define in epidemiologic investigations. Many diseases do not appear immediately following exposure. In the case of cancer, for example, the disease may not appear for many years after the exposure. The time between a defined exposure period and the occurrence of disease is often referred to as a latency period (IOM, 2004). Exposures can be brief (sometimes referred to as acute exposures) or protracted (sometimes referred to as chronic exposures). At one extreme the exposure can be the result of a single insult, as in an accidental poisoning. At the other extreme, an individual exposed to a chemical that is stored in the body may continue to experience "internal exposure" for years, even if exposure from the environment has ceased. The definition of the proper time frame for duration of exposure represents a challenge to the assessment of exposure in epidemiologic studies.

Occupational-exposure studies use work histories, job titles, and workplace measurements of contaminant concentration; this information is often combined to create a job–exposure matrix (JEM) wherein a quantitative exposure estimate is assigned to each job or task, and the time spent on each job or task is calculated. This approach may also incorporate exposure mitigation factors, such as process changes, engineering controls, or the use of protective clothing. The production-worker cohort analysis conducted by the US National Institute for Occupational Safety and Health (NIOSH) included these methods (Table 5-1).

Many environmental-exposure studies use proximity to the source of a contaminant to classify exposure (Table 5-1). If an industrial facility emits a contaminant, investigators might identify geographic zones around the facility and assign exposure categories to people on the basis of residence. That approach was used to analyze data from the industrial accident in Seveso, Italy, that contaminated nearby areas with TCDD; the zones established were calibrated by the collection of soil samples. In general it is difficult to use this type of information to classify the exposures of individuals with confidence. Such assessments can be refined to include analyses of exposure pathways (how chemicals move from the source through the environment) and personal behaviors (how individuals interact with their environment).

Biologic markers of exposure can provide important information for use in occupational and environmental studies, permitting assignment of a quantitative exposure estimate to each person in a study group. The most important marker in the context of Vietnam veterans' exposure to Agent Orange is the measurement of TCDD in serum, although it should be noted that TCDD and Agent Orange are not synonymous. Studies of the absorption, distribution, and metabolism of TCDD have been conducted over the past 20 years. In the late 1980s, the Centers for Disease Control and Prevention (CDC) developed a highly sensitive assay to detect TCDD in serum and demonstrated a high correlation between serum TCDD and TCDD in adipose tissue (Patterson et al., 1986, 1987). The serum TCDD assay is now used extensively to evaluate exposure in Vietnam veterans and other people (Table 5-1).

Studies of the patterns of individual chlorinated hydrocarbons observed in the tissues of people exposed to specific sources (Pless-Mulloli et al., 2005) suggest that the profiles are not

sufficiently distinct to permit discrimination from general urban background exposure.

Exposure Misclassification

Exposure misclassification in epidemiologic studies can affect estimates of risk. A typical situation is in a case-control study where the reported measurement of exposure can be misclassified for either or both groups. The simplest situation to consider is where the exposure is classified into just two levels, for example ever vs. never exposed. If the probability of exposure misclassification is the same (i.e., non-differential) between cases and controls, then it can be shown that the estimated association between disease and exposure is biased towards the null value. So in other words, one would expect the true association to be stronger than the association actually observed. However, if the probability of misclassification is different for cases and controls, then bias in the estimated association can occur in either direction. In this case, the true association might be stronger or weaker than the association actually observed.

The situation when exposure is classified into more than two levels is somewhat more complicated. Dosemeci et al. (1990) have demonstrated that for this situation, the slope of a dose-response trend is not necessarily attenuated towards the null value, even if the probability of misclassification is the same for the two groups of subjects being compared. So in other words, the observed trend in disease risk across the several levels of exposure may be either an over-estimate or an under-estimate of the true trend in risk.

The probabilities of misclassification will typically be unknown at the start of the study. Even if one had perfect knowledge of the misclassification probabilities, statistical adjustment will not necessarily lead to a result that is more significant than the unadjusted analysis, even if the misclassification probabilities are non-differential between the comparison groups. So, analyses where adjustments have been made for exposure misclassification should not be assumed to increase the certainty that an association is truly present. The situation is even more complicated when one has to estimate the probabilities of misclassification from the study data themselves.

Finally, it is important to consider the effect of exposure misclassification on the statistical significance of the result. Greenland and Gustafson (2006) have shown that if one adjusts for exposure misclassification when the exposure is represented as binary (e.g. ever/never exposed), the resulting association is not necessarily more significant than in the unadjusted estimate. This result remains true even though the observed magnitude of the association (for example the relative risk) might be increased, as indicated previously.

Exposure to Dioxin-like Compounds

A major focus of the work of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Sixth Biennial Update) has been the analysis of studies concerning exposure to a single compound: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, commonly referred to as TCDD. TCDD is one of a number of tetrachlorodibenzo dioxins. The committee recognizes that under real-world conditions exposure to TCDD virtually never occurs in isolation and that there are hundreds of similar compounds to which humans might be exposed, among them other polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs). Exposure to TCDD is almost always accompanied by exposure to one or more of these other compounds. The

literature on these other compounds, particularly PCBs and PAHs, was not reviewed systematically by the committee, unless TCDD was identified as an important component of the exposure. We took this approach for two reasons. First, exposure of Vietnam veterans to significant amounts of these other compounds, as compared to exposure to TCDD, has not been documented. Second, the most important mechanism for TCDD toxicity involves its ability to bind to and activate the aryl hydrocarbon receptor (AhR). Many of these other compounds act by different or multiple mechanisms, so it is difficult to attribute toxic effects from such exposures to TCDD.

Exposure to mixtures of dioxin-like compounds presents a particularly difficult challenge for toxicology and risk assessment. The total toxic equivalency (TEQ) method uses the sum of the relative toxicities of dioxin-like compounds in a mixture to express the overall toxicity of the mixture as a single TCDD-toxic equivalent value. This approach has come into common use by regulatory agencies around the world, and most agencies in the United States, including the Environmental Protection Agency, support its use as providing a reasonable estimate of toxicity for complex mixtures. World Health Organization values (Van den Berg et al., 2006) are most often cited and generally accepted.

Calculation of a TEQ value for a mixture of dioxin-like compounds requires that each specific dioxin-like compound in the mixture be assigned a toxicity equivalency factor (TEF) relative to the toxicity of TCDD. This determination is based on an evaluation of existing biologic and biochemical data. These data are of variable quality, and their evaluation includes scientific judgment and expert opinion, so the resulting TEFs are by no means precise. Furthermore, the TEQ method is based on the premise that the toxic and biologic responses of dioxin-like compounds are mediated through the AhR mechanism. Available data support this premise, but data on some compounds are incomplete. The TEQ method also has several important limitations. It is not able to account for possible synergistic or antagonistic interactions among compounds, possible actions or interactions of compounds that are not mediated by the AhR mechanism, and exposures to dietary flavonoids and other phytochemicals that bind the AhR (Ashida et al., 2000; Ciolino et al., 1999; Quadri et al., 2000). For some mixtures the risk posed by non-dioxin-like compounds that can act as AhR antagonists (e.g., non-coplanar PCBs) is not assessed (Safe, 1997–1998). It should also be noted that the kinetics and metabolism of each dioxin-like compound might differ considerably from the others, and complete data on tissue concentrations often are unavailable. Finally, extrapolation of TEF values derived from blood or adipose tissue samples to a meaningful target dose can carry considerable uncertainty. Considering the many difficulties of interpreting exposures to chemical mixtures relative to the exposure of veterans to Agent Orange and other herbicides in Vietnam, the committee's analyses have focused primarily on TCDD exposures.

Background levels of TEQ overall are thought to have declined along with a decline in PCB levels in the environment (e.g., Schneider et al., 2001). There have also been apparent declines in the background levels of TCDD itself (Alyward and Hays, 2002). However, such declines may be influenced by local differences in specific sources.

Exposure Specificity for the Herbicides Used in Vietnam

Only a limited number of herbicidal compounds were used as defoliants during the American-Vietnamese conflict: esters and salts of 2,4-D and 2,4,5-T, cacodylic acid, and picloram, as combined in various formulations. Many scientific studies reviewed by the committee have

reported exposures to broad categories of chemicals rather than to these specific compounds. These categories are presented in Table 5-2, along with their relevance to the committee's charge. The information in Table 5-2 represents the current committee's thinking, and has helped to guide our evaluation of studies. Previous committees did not necessarily address the issue of exposure specificity in this manner.

Table 5-2 Current committee guidance for the classification of exposure information in epidemiologic studies that focus on the use of pesticides or herbicides, and relevance of the information to the committee's charge to evaluate exposures to 2,4-D, 2,4,5-T (phenoxy herbicides), cacodylic acid, and picloram.*

Specificity of exposure reported in study	Additional Information	Relevance to committee's charge
Pesticides	Chemicals of interest were not used or no additional information	Not relevant
	Chemicals of interest were used	Relevant
Herbicides	Chemicals of interest were not used	Not Relevant
	No additional information	Limited relevance
	Chemicals of interest were used	Relevant
Phenoxy herbicides		Highly relevant
2,4-D or 2,4,5-T		Highly relevant

* None of the epidemiologic studies reviewed by the committee to date have specified exposure to cacodylic acid or picloram.

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

Among the various chemical classes of herbicides that have been identified in published studies reviewed by the committee, only phenoxy herbicides, and particularly 2,4-D and 2,4,5-T, are directly relevant to the exposures experienced by US military forces in Vietnam. The committee has decided to retain many studies that report on unspecified pesticides or herbicides for this report, so such studies are discussed in the health effects sections, and their results have been entered in the health outcome-specific tables. However, these studies tend to contribute little to the evidence considered by the committee. The many studies that provide chemical-specific exposure information are considered far more informative for the committee's purposes.

OCCUPATIONAL EXPOSURE TO HERBICIDES AND TCDD

The committee reviewed many epidemiologic studies of occupationally exposed groups for evidence of an association between health risks and exposure to TCDD or to the herbicides used in Vietnam, primarily the phenoxy herbicides 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). TCDD is an unwanted byproduct of 2,4,5-T production, but not of 2,4-D. Other contaminants including other dioxins (e.g., 1,3,6,8-tetrachlorodibenzo-*p*-dioxin) have been reported at low levels in 2,4-D, however those identified do not possess the toxicity of TCDD (ATSDR, 1998; Huston, 1972; Norström et al., 1979). In reviewing these studies, the committee separated consideration of two types of exposure: exposure to 2,4-D or 2,4,5-T and exposure to TCDD from 2,4,5-T or other sources. This separation was necessary because of the possibility that some health effects could be associated with exposure to 2,4-D or 2,4,5-T in the absence of significant TCDD exposure.

This distinction is particularly important for workers in agriculture and forestry, where exposure is primarily the result of mixing, loading, and applying herbicides. In addition to these occupational groups the committee considered studies of occupational exposure to dioxins, focusing primarily on workers in chemical plants that produced phenoxy herbicides or chlorophenols, which tend to be contaminated with PCDDs. Waste incineration workers were also included in the production work category, since they can contact dioxin-like compounds while handling byproducts of production and incineration. Other occupationally exposed groups include pulp-and-paper workers exposed to dioxins through bleaching processes that use chlorinated compounds, and saw mill workers exposed to chlorinated dioxins that can be contaminants of chlorophenates used as wood preservatives.

Production Work

US National Institute for Occupational Safety and Health Cohort Study

One extensive set of data on chemical production workers potentially contaminated with TCDD has been compiled by NIOSH. More than 5,000 TCDD-exposed workers in 12 companies were identified from personnel and payroll records. Exposure status was determined initially through a review of process operating conditions; employee duties; and analytical records of TCDD in industrial-hygiene samples, process streams, products, and waste (Fingerhut et al., 1991). Occupational exposure to TCDD-contaminated processes was confirmed by measuring serum TCDD in 253 cohort members. Duration of exposure was defined as the number of years worked in processes contaminated with TCDD and was used as the primary exposure metric in the study. The use of duration of exposure as a surrogate for cumulative exposure was based on a correlation (Pearson correlation efficient = 0.72) between log-transformed serum TCDD and years worked in TCDD-contaminated processes. Duration of exposure for individual workers was calculated from work records, and exposure duration categories were created: <1 year, 1 to <5 years, 5 to <15 years, and 15+ years. In some cases, information was not available for duration of exposure, so a separate metric, called duration of employment, was defined as the total time each worker was employed at the study plant.

The NIOSH cohort study was updated in 1999 (Steenland et al., 1999), and a more refined

exposure assessment was conducted. Workers whose records were inadequate to determine duration of exposure were excluded. The final analysis was restricted to 8 plants because 4 plants (with 591 workers) had no records on the degree of TCDD contamination of work processes or lacked the detailed work histories required to estimate TCDD exposure by job. Another 38 workers at the remaining 8 plants were eliminated because they worked in processes in which TCDD contamination could not be estimated. Finally, 727 workers with exposure to both pentachlorophenol (PCP) and TCDD were eliminated to avoid possible confounding of any TCDD effects by PCP effects. Those restrictions led to a subcohort of 3,538 workers (69% of the overall cohort).

The exposure assessment for the subcohort was based on a job–exposure matrix (Piacitelli and Marlow, 1997) that assigned each worker a quantitative exposure score for each year of work. The score was based on three factors: concentration of TCDD in micrograms per gram of process materials, fraction of the day when the worker worked in the specific process, and a qualitative contact value (0.01–1.5) based on the estimated TCDD contamination reaching exposed skin or the potential for inhalation of TCDD-contaminated dust. The scores for each year of work were combined to yield a cumulative exposure score for each worker. The new exposure analysis presumably reduced misclassification (through exclusion of non-exposed workers) and uncertainty (through exclusion of workers with incomplete information) and improved accuracy (through more detailed information on daily exposure).

Steenland et al. (2001) conducted a detailed exposure–response analysis from data on workers at one of the original 12 companies in the cohort study. A group of 170 workers was identified with serum TCDD greater than 10 ppt (parts per trillion), as measured in 1988. The investigators conducted a regression analysis by using the following information: the work history of each worker, the exposure scores for each job held by each worker over time, a simple pharmacokinetic model for the storage and excretion of TCDD, and an estimated TCDD half-life of 8.7 years. That pharmacokinetic model allowed calculation of the estimated serum TCDD concentration at the time of last exposure for each worker. Results of the analysis were used to estimate serum TCDD concentration over time that was attributable to occupational exposure for all 3,538 workers in the subcohort defined in 1999.

Crump et al. (2003) conducted a meta-analysis of dioxin dose–response studies for three occupational cohorts: the NIOSH cohort (Fingerhut et al., 1991); the Hamburg cohort (Flesch-Janys et al., 1998); and the BASF cohort (Ott and Zober, 1996). That analysis incorporated recent exposure data for the NIOSH cohort generated by Steenland et al. (2001).

Aylward et al. (2005a) applied a concentration- and age-dependent elimination model to the NIOSH cohort data to determine its impact on estimates of serum TCDD concentrations. The authors found that their model produced a better fit to serum sampling data compared to first-order models. Dose rates varied by a factor of 50 among different combinations of input parameters, elimination models, and regression models. The authors concluded that earlier dose reconstruction efforts may have under-estimated peak exposure levels in these populations. Aylward et al. (2005b) also applied this model to serial measurements of serum lipid TCDD concentrations from 36 adults from Seveso, Italy, and 3 adults from Vienna, Austria. They concluded that a large degree of uncertainty is characteristic of back-calculated dose estimates of peak TCDD exposure, and recommended that further analyses explicitly recognize this uncertainty.

Lawson et al. (2004) continued the NIOSH cross-sectional medical study reported by Sweeney et al. (1989, 1993). They compared serum lipid TCDD concentrations from the NIOSH cohort with those in a reference population, and examined three birth outcomes of offspring: birth

weight, preterm delivery, and birth defects. TCDD exposures at conception were estimated using PBPK modeling approaches (Dankovic et al., 1995; Thomaseth and Salvan, 1998). No other reports on the cohort have been published since *Update 2004*.

International Agency for Research on Cancer Cohort Studies

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

Questionnaires were constructed for workers manufacturing chlorophenoxy herbicides or chlorinated phenols and for herbicide sprayers, and were completed with the assistance of industrial hygienists. Information from production records and job histories were examined when available. Workers were classified as exposed, probably exposed, exposure unknown, or non-exposed. The exposed-workers group (n = 13,482) consisted of all individuals known to have sprayed chlorophenoxy herbicides and all who worked in particular aspects of chemical production. Two cohorts (n = 416) had no job titles available, but worked in chemical production facilities that were likely to produce TCDD exposure, so they were deemed probably exposed. Workers with no exposure information (n = 541) were classified as "exposure unknown." Non-exposed workers (n = 3,951) were those who had never been employed in parts of factories that produced chlorophenoxy herbicides or chlorinated phenols and those who had never sprayed chlorophenoxy herbicides.

An expanded and updated analysis of the IARC cohort was published in 1997 (Kogevinas et al., 1997). The researchers added herbicide production workers from 12 plants in the United States (the NIOSH cohort) and from four plants in Germany. The 21,863 workers exposed to phenoxy herbicides or chlorophenols were classified in three categories of exposure to TCDD or higher-chlorinated dioxins: those exposed (n = 13,831), those not exposed (n = 7,553), and those with unknown exposure (n = 479). Several exposure metrics were constructed for the cohort—years since first exposure, duration of exposure (in years), year of first exposure, and job title—but detailed methods were not described. No new studies of the full cohort have been reported since *Update 2000*.

Researchers have studied various subgroups of the IARC cohort. Flesch-Janys et al. (1995) updated the cohort and added a quantitative exposure assessment based on blood or adipose measurements of polychlorinated dibenzo-*p*-dioxin and furan (PCDD/F). The authors estimated maximum PCDD/F exposure for 190 workers using a first-order kinetics model, half-lives from an elimination study in 48 workers from this cohort, and background concentrations for the German population. The authors then regressed the estimated maximum PCDD/F exposures of the workers against the length of time they worked in each production department in the plant. The working-time weights were then used with work histories for the remainder of the cohort to estimate PCDD/F exposure for each member at the end of that person's exposure. These values were then used to estimate TCDD doses in the population.

Becher et al. (1996) conducted an analysis of several German cohorts, including the Boehringer–Ingelheim cohort described above (Kogevinas et al., 1997), a cohort from the BASF

Ludwigshafen plant that did not include those involved in a 1953 accident, and a cohort from a Bayer plant in Uerdingen and a Bayer plant in Dormagen. All of the plants were involved in production of phenoxy herbicides or chlorophenols. Exposure assessment involved estimates of duration of employment from the start of work in a department where exposure was possible until the end of employment at the plant. Analysis was based on time since first exposure.

Hooiveld et al. (1998) reported on an update of a mortality study of production workers who had known exposure to dioxins, workers in herbicide production, non-exposed production workers, and workers known to be exposed as a result of an accident that occurred in 1963, drawn from two chemical factories in the Netherlands. Assuming first-order TCDD elimination with an estimated half-life of 7.1 years, measured TCDD levels were extrapolated to the time of maximum TCDD exposure for a group of 47 workers. A regression model then estimated the effect on estimated maximum TCDD exposure for each cohort member attributable to exposure as a result of the accident, duration of employment in the main production department, and time of first exposure before (or after) 1970.

No new reports for components of the IARC cohort have been published since *Update 2004*.

Dow Cohort Studies

Workers at Dow Chemical Company facilities where 2,4-D was manufactured, formulated, or packaged have been the focus of a cohort analysis since the 1980s (Bond et al., 1988). Industrial hygienists developed a job–exposure matrix that ranked employee exposures as low, moderate, or high on the basis of available air-monitoring data and professional judgment. That matrix was merged with employee work histories to assign an estimate of exposure to each job assignment. A cumulative dose was then developed for each of the 878 employees by multiplying the representative eight-hour time-weighted average (TWA) exposure value for each job assignment by the number of years in the job and then adding those products for all jobs. The 2,4-D TWA of 0.05 mg/m^3 was used for low, 0.5 mg/m^3 for moderate, and 5 mg/m^3 for high exposure. The role of dermal exposure in the facilities does not appear to have been considered in the exposure estimates. It is not clear to what extent the use of air measurements alone can provide accurate classification of workers into low-, moderate-, and high-exposure groups. Biologic monitoring of 2,4-D apparently was not included in this study. Follow-up reports were published in 1993 (Bloemen et al., 1993) and most recently in 2001 (Burns et al., 2001); neither of those studies modified the exposure assessment procedures of the original study. Bodner et al. (2003) reported new risk estimates for cancer, using the same assessments.

Dow also has conducted a cohort study of its manufacturing workers exposed to PCP (Ramlow et al., 1996). Assessment of exposure for this cohort was based on consideration of the available industrial hygiene and process data, including process and job description information obtained from employees, process and engineering controls change information, industrial-hygiene surface-wipe sample data, area exposure monitoring, and personal breathing-zone data. Jobs with higher estimated potential exposure involved primarily dermal exposure to airborne PCP in the flaking–prilling–packaging area; the industrial hygiene data suggested about a 3-fold difference between the areas of highest to lowest potential exposure. All jobs were therefore assigned an estimated exposure intensity score on a scale of 1–3 (from lowest to highest potential exposure intensity). Reliable information concerning the use of personal protective equipment was not available. Cumulative PCP and TCDD exposure indices were calculated for each subject by multiplying the duration of each exposed job by its estimated exposure intensity and then summing

across all exposed jobs.

Since *Update 2004*, Dow researchers have published a study of serum dioxin levels measured in 2002 in former chlorophenol workers (Collins et al., 2006). Most of the workers in this study were included in the NIOSH and IARC cohorts. The authors used these data to estimate worker exposures at the time of exposure termination using several different pharmacokinetic models. They concluded that their findings were consistent with other studies reporting high serum dioxin levels among chlorophenol workers after occupational exposures.

Waste Incineration Worker Studies

Four studies of waste incineration workers have been published recently. A study of infectious waste incineration plant workers in Japan used serum dioxin levels to document elevated exposures in workers when compared to controls (Kumagai and Koda, 2005). A second study in Japan examined the association between serum dioxin levels and oxidative DNA damage markers in municipal waste incineration workers (Yoshida et al., 2006).

Researchers in South Korea compared plasma protein levels for 31 waste incineration workers with those of 33 unexposed subjects (Kang et al., 2005). A second Korean study evaluated immunologic and reproductive toxicities in 31 waste incinerator workers in comparison to 84 controls subjects (Oh et al., 2005). Rather than measuring serum dioxin levels, both studies inferred dioxin exposure levels for individual workers on the basis of dioxin air concentrations and also estimated exposures to polycyclic aromatic hydrocarbons through analysis of two urinary metabolites: 1-hydroxypyrene and 2-napthol.

Other Production Worker Studies

Several other studies of chemical production workers have relied on job titles as recorded on individual work histories and company personnel records to classify exposure to TCDD (Coggon et al., 1986, 1991; Cook et al., 1986; Ott et al., 1980; Zack and Gaffey, 1983; Zober et al., 1990). Similarly, TCDD exposure of chemical plant workers has been characterized by worker involvement in various production processes, such as synthesis, packaging, waste removal, shipping, and plant supervision (Bueno de Mesquita et al., 1993; Garaj-Vrhovac and Zeljezic, 2002; Manz et al., 1991).

Since *Update 2004*, a follow-up cancer mortality study on New Zealand production workers and herbicide sprayers has been published (’t Mannetje et al., 2005). No direct data on levels of exposure were available for either of these worker groups. Exposure categories for production workers were based on job codes, while estimates for sprayers were based on exposure history questionnaires.

Agriculture, Forestry, and Other Outdoor Work

In occupational studies of agricultural workers various methods have been used to estimate exposure to herbicides or TCDD. The simplest method derives data from death certificates, cancer registries, or hospital records (Burmeister, 1981). Although such information is relatively easy to obtain, it cannot be used to estimate duration or intensity of exposure or to determine

whether a worker was exposed to a specific agent. In some studies of agricultural workers differences in occupational practices have been examined, allowing identification of subsets of workers who were likely to have had higher exposures (Hansen et al., 1992; Musicco et al., 1988; Ronco et al., 1992; Vineis et al., 1986; Wiklund and Holm, 1986; Wilklund et al., 1988a). In other studies county of residence was used as a surrogate for exposure, relying on agricultural censuses of farm production and chemical use to characterize exposure in individual countries (Blair and White, 1985; Cantor, 1982; Gordon and Shy, 1981). In other studies exposure was estimated according to the number of years employed in a specific occupation as a surrogate for exposure duration, using supplier records of pesticide sales to estimate exposure or estimating acreage sprayed to determine the amount used (Morrison et al., 1992; Wigle et al., 1990). Other studies used self-reported information on exposure that recounted direct handling of a herbicide, whether it was applied by tractor or hand-held sprayer, and what type of protective equipment or safety precautions were used (Hoar et al., 1986; Zahm et al., 1990). Another set of studies have validated self-reported information through written records, signed statements, or telephone interviews with co-workers or former employers (Carmelli et al., 1981; Woods and Polissar, 1989).

Forestry and other outdoor workers, such as highway maintenance workers, are likely to have been exposed to herbicides and other compounds (see Table A-1 in Appendix A for a summary of studies). Exposure for those groups has been classified by approaches similar to those noted above for agricultural workers, for example, by the number of years employed, job category, and occupational title.

Ontario Farm Family Health Study

The Ontario Farm Family Health Study has produced several reports that are relevant to phenoxyacetic acid herbicide exposures, including 2,4-D. A study of male pesticide exposure and pregnancy outcome (Savitz et al., 1997) developed an exposure metric based on self-reports of mixing or application of crop herbicides, crop insecticides, and fungicides; livestock chemicals; yard herbicides; and building pesticides. Subjects were asked whether they participated in those activities during each month, and their exposure classifications were based on activities in 3-month segments of time. The exposure classification was refined through answers to questions regarding use of protective equipment and specificity of pesticide use.

A related study included analysis of 2,4-D residues in semen as a biologic marker of exposure (Arbuckle et al., 1999a). The study began with 773 potential participants, but only 215 eventually consented to the study. Of the 215, 97 provided semen and urine samples for 2,4-D analysis.

The Ontario Farm Family Health Study also examined the effect of pesticide exposure, including 2,4-D, on time to pregnancy (Curtis et al., 1999) and the risk of spontaneous abortion (Arbuckle et al., 1999b, 2001). About 2,000 farm couples participated in the study. Exposure information was pooled from interviews with husbands and wives to construct a history of monthly agricultural and residential pesticide use. Exposure classification was based on a yes–no response for each month. Data on such variables as acreage sprayed and use of protective equipment were collected but were not available in all cases. More recent studies have used herbicide biomonitoring in a subset of the population to evaluate the validity of self-reported predictors of exposure (Arbuckle et al., 2002). Assuming that the presence of 2,4-D in urine was an accurate measure of exposure and that the results of the questionnaire indicating 2,4-D use were more likely to be subject to exposure classification error (that is, the questionnaire results

were less accurate than was the urine analysis), the questionnaire's prediction of exposure, when compared with the urine 2,4-D concentrations, had a sensitivity of 57% and a specificity of 86%. In multivariate models, the variables for pesticide formulation, protective clothing and gear, application equipment, handling practice, and personal-hygiene practice were significant as predictors of urinary herbicide concentrations in the first 24-hours after application was initiated.

Since *Update 2004*, three additional publications have reported results from the Ontario Farm Family Health Study. Urinary concentrations of 2,4-D and MCPA were measured in samples from farm applicators (Arbuckle et al., 2005) and for women living on Ontario farms (Arbuckle and Ritter, 2005). Indirect sources of herbicide exposure for farm families were evaluated through wipe sampling of surfaces and drinking water samples (Arbuckle et al., 2006).

The Agricultural Health Study

The Agricultural Health Study in the United States enrolled approximately 58,000 commercial and private pesticide applicators in two states (Iowa and North Carolina) between 1993 and 1997 (Alavanja et al., 1994). Exposure assessment in this study has been based primarily on questionnaire data collected at the time of enrollment and in periodic follow-ups. Dosemeci et al. (2002) published an algorithm designed to better characterize personal exposures for that population. Weighting factors for key exposure variables were developed from the literature on pesticide exposure. This quantitative approach has potential to improve the accuracy of exposure classification for the cohort, but has not yet been used in published epidemiologic studies.

Since *Update 2004*, eight epidemiologic studies have been published on the AHS cohort. All have developed pesticide exposure estimates or exposure categories from self-administered questionnaires (Alavanja et al., 2004, 2005; Blair et al., 2005, De Roos et al., 2005; Engel et al., 2005; Farr et al., 2004, 2006; Kirrane et al., 2005). Three additional publications discuss pesticide use patterns in this population (Hoppin, 2005; Kirrane et al., 2004; Samanic et al., 2005). The Agricultural Health study questionnaire collected detailed information regarding herbicide use, with 2,4-D being the most commonly reported herbicide.

United Farmworker (UFW) Population Studies

California researchers evaluated breast cancer risk (Mills and Yang, 2005) and lymphohematpoietic cancer risk (Mills et al., 2005) in members of the United Farmworkers of America (UFW). The exposed populations were defined as those who had ever been a UFW member. Exposure estimates to specific pesticides, including 2,4-D, were developed through linkage of job histories with the California Pesticide Use Reporting database.

Other Agricultural Worker Studies

A study of Canadian farmers examined pesticide exposures of men (McDuffie et al., 2001). Data were collected by questionnaires that included information on specific chemicals (including 2,4-D), frequency of application, and duration of exposure. A small validation study (n = 27) was performed to test the self-reported pesticide use data against records of purchases. Investigators reported an "excellent concordance" between the two sources, but they did not provide a

statistical analysis.

Ruder et al. (2004) and Carreon et al. (2005) evaluated farm pesticide exposure in men and women, respectively, in relation to gilomas as part of the Upper Midwest Health Study. Self-reported lifetime agricultural pesticide exposures were collected by telephone interview, including specific questions on phenoxy herbicides and 2,4-D.

Mandel et al. (2005) reported urinary biomonitoring results for farm families in Minnesota and South Carolina as a part of the CropLife America's Farm Family Pesticide Exposure Study. The peak geometric mean concentration for 2,4-D was 64 parts per billion.

Lee et al. (2004) used a telephone interview of cases and control or their next-of-kin in a Nebraska study to determine the extent of agricultural pesticide use, including use of 2,4,5-T and 2,4-D. Fritschi et al. (2005) used a computer-assisted telephone interview and occupational histories reviewed by an industrial hygienist to estimate exposures to phenoxy herbicides in an Australian study. Curwin et al. (2005) measured 2,4-D concentrations in urine and hand wipe samples to characterize exposures among farmers and nonfarmers in Iowa.

Other studies of the agricultural use of pesticides do not provide specific information on exposure to 2,4-D, TCDD, or other compounds relevant to Vietnam veterans' exposure (Bell et al., 2001a,b; Chiu et al., 2004; Duell et al., 2001; Garry et al., 2003; Gorell et al., 2004; Hanke et al., 2003; Van Wijngaarden et al., 2003).

A series of papers from a recent workshop focused on pesticide exposure methods for farmworker populations (Arcury et al., 2006; Barr et al., 2006a,b; Hoppin et al., 2006; Quandt et al., 2006). These publications provide a helpful review of current methodological issues in exposure science for these populations, but do not address directly the *VAO* compounds of interest.

Commercial Herbicide Sprayers

Studies of commercial herbicide applicators are relevant because they can be presumed to have had more sustained exposure to herbicides. However, because they also are likely to be exposed to a variety of compounds, assessment of individual or group exposure to specific phenoxy herbicides or TCDD is complicated. Some studies have attempted to measure applicators' exposure on the basis of information from work records on acreage sprayed or on the number of days of spraying. Employment records also can be used to extract information on which compounds are sprayed.

One surrogate indicator of herbicide exposure is the receipt of a license to spray. Several studies have specifically identified licensed or registered pesticide and herbicide applicators (Blair et al., 1983; Smith et al., 1981, 1982; Swaen et al., 1992; Wiklund et al., 1988b, 1989). Individual estimates of the intensity and frequency of exposure were rarely quantified in the studies that the committee examined, however, and many applicators were known to have applied many kinds of herbicides, pesticides, and other substances. In addition, herbicide spraying is generally a seasonal occupation, and information is not always available on possible exposure-related activities during the rest of the year.

Only one study has provided information on serum TCDD concentrations in herbicide applicators. Smith et al. (1992) analyzed blood from nine professional spray applicators in New Zealand who first sprayed before 1960 and were also spraying in 1984. The duration of actual spray work varied from 80 to 370 months. Serum TCDD was 3–131 ppt on a lipid basis (mean = 53 ppt). The corresponding values for age-matched controls were 2–11 ppt (mean = 6 ppt).

Serum TCDD was positively correlated with the number of months of professional spray application.

Several studies have evaluated various herbicide exposures: type of exposure, routes of entry, and routes of excretion (Ferry et al., 1982; Frank et al., 1985; Kolmodin-Hedman and Erne, 1980; Kolmodin-Hedman et al., 1983; Lavy et al., 1980a,b; Libich et al., 1984). Those studies appear to show that the major route of exposure is dermal absorption, with 2–4% of the chemical that contacts the skin being absorbed into the body during a normal workday. Air concentrations of the herbicides were usually less than 0.2 mg/m^3. Absorbed phenoxy acid herbicides are virtually cleared within 1 day, primarily through urinary excretion. Typical measured excretion in ground crews was 0.1–5 mg/day, for air crews the value was lower.

A study of 98 professional turf sprayers in Canada developed new models to predict 2,4-D dose (Harris et al., 2001). Exposure information was gathered from self-administered questionnaires. Urine samples were collected throughout the spraying season (24-h samples on 2 consecutive days). Estimated 2,4-D doses were developed from the data and used to evaluate the effect of protective clothing and other exposure variables.

Since *Update 2004*, one study of New Zealand herbicide sprayers has been published (’t Mannetje et al., 2005). This study, which included both herbicide production workers and sprayers, was discussed in the earlier section on production workers.

Pulp, Paper, and Saw Mill Work

Pulp, paper, and saw mill workers are likely to be exposed to TCDD and chlorinated phenols. Depending on the type of paper mill or pulping operation and the product manufactured, pulp and paper production workers also are likely to be exposed to toxic compounds in addition to those of concern encountered during the bleaching process (Henneberger et al., 1989; Jappinen and Pukkala, 1991; Robinson et al., 1986; Solet et al., 1989). One study of a cohort of Danish paper mill workers (Rix et al., 1998) presented no direct measures of occupational exposure, and the qualitative assessment of compounds used by each department did not include chlorinated organic compounds, although chlorine, chlorine dioxide, and hypochlorite were used.

In the past, workers in sawmills might have been exposed to pentachlorophenates, which are contaminated with higher-chlorinated PCDDs (Cl_6–Cl_8), or to tetrachlorophenates, which are less contaminated with higher-chlorinated PCDDs. Wood is dipped in those chemical preservatives and then cut and planed in the mills. Most exposure is dermal, although some exposure can occur by inhalation (Hertzmann et al., 1997; Teschke et al., 1994). No new studies in those populations have been reported since *Update 2000*.

ENVIRONMENTAL EXPOSURES TO HERBICIDES AND TCDD

The committee reviewed several new studies of TCDD-exposed populations associated with industrial facilities, including recent investigations at Seveso, Italy. The committee also reviewed exposure studies related to Agent Orange use in Vietnam.

Industrial Sources

Seveso, Italy

A large industrial accident involving environmental exposure to TCDD occurred in Seveso in July 1976 as the result of an uncontrolled reaction during trichlorophenol production. Various indicators, including TCDD measurements in soil, have been used as indicators of individual exposure. Three areas were defined around the release point on the basis of soil sampling for TCDD (Bertazzi et al., 1989). Zone A was the most heavily contaminated; all residents were evacuated within 20 days. Zone B was less contaminated; women in the first trimester and all children were urged to avoid it during daytime. Zone R had some contamination; consumption of crops grown there was prohibited.

Data on serum TCDD concentrations in Zone A residents have been presented by Mocarelli et al. (1990, 1991) and by CDC (1988a). In those with severe chloracne (n = 10), TCDD was 828–56,000 ppt of lipid weight. Those without chloracne (n = 10) had TCDD 1,770–10,400 ppt. TCDD was undetectable in all control subjects but one. The highest of those concentrations exceeded any that had been estimated at the time for TCDD-exposed workers on the basis of backward extrapolation and a half-life of 7 years. Data on nearby soil concentrations, number of days a person stayed in Zone A, and whether local food was consumed were considered in evaluating TCDD. That none of those data correlated with serum TCDD suggested strongly that the exposure of importance was from fallout on the day of the accident. The presence and degree of chloracne did correlate with TCDD. Adults seem much less likely than children to develop chloracne after acute exposure, but surveillance bias could have affected that finding. Recent updates (Bertazzi et al., 1998, 2001) have not changed the exposure assessment approach.

As part of the Seveso Women's Health Study (SWHS), Eskenazi et al. (2001) tested the validity of exposure classification by zone. Investigators measured serum TCDD in samples collected between 1976 and 1980 from 601 residents (97 from Zone A; 504 from Zone B). A questionnaire the women completed between 1996 and 1998 included age, chloracne history, animal mortality, consumption of homegrown food, and location at the time of the explosion. Participants did not know their TCDD concentrations at the time of the interview, although most knew their zone of residence. Interviewers and TCDD analysts were blinded to participants' zone of residence. Zone of residence explained 24% of the variability in serum TCDD. Addition of the questionnaire data improved the regression model, explaining 42% of the variance. Those findings demonstrate a significant association between zone of residence and serum TCDD, but much of the variability in TCDD concentrations is still unexplained by the models.

A number of studies of the Seveso population have been published using lipid-adjusted serum TCDD concentrations as the primary exposure metric (Baccarelli et al., 2002; Eskenazi et al., 2002a,b, 2003, 2004; Landi et al., 2003). Fattore et al. (2003) measured current air concentrations of PCDDs in zones A and B, and compared them with measurements from a control area near Milan. The authors concluded that release from PCDD-contaminated soil does not add appreciably to air concentrations in the Seveso study zone. Finally, Weiss et al. (2003) collected breast milk from 12 mothers in Seveso to compare TCDD concentrations with those from a control population near Milan. The investigators reported that the TCDD concentrations in human milk from mothers in Seveso were two times higher than were those in controls. The authors concluded that breastfed children in the Seveso area are likely to have higher body burdens of TCDD than are children from other areas.

Since *Update 2004*, five reports have been published on dioxin exposure in the Seveso

population. Baccarelli et al. (2005a) used serum TCDD concentrations to evaluate chloracne cases. Bacarelli et al. (2005b) reviewed statistical strategies for handing non-detectable values in dioxin measurement datasets. They recommended that a distribution-based multiple imputation method be used to analyze environmental data when substantial proportions of observations are non-detectable. In the SWHS subgroup, Warner et al. (2004) used serum dioxin concentrations to evaluate effects on age at menarche, while Eskanazi et al. (2005) used serum dioxin concentrations to evaluate effects on age at the onset of menopause. Warner et al. (2005) compared a chemical-activated luciferase gene expression bioassay to an isotope dilution high-resolution gas chromatography/high-resolution mass spectrometry assay to measure dioxin-like toxicity equivalents for samples 78 women residing near Seveso, and found similar results from the two methods.

Chapaevsk, Russia

Researchers in the Samara region of Russia have identified a chemical plant in Chapaevsk as a major source of TCDD pollution (Revich et al., 2001). From 1967 to 1987 the plant produced hexachlorocyclohexane (lindane) and its derivatives. Since then, the plant has produced various crop protection products. Dioxins have been detected in air, soil, drinking-water, and cows' milk. However, the researchers do not describe air-, soil-, or water-sampling methods. The number of samples analyzed was small for some media (2 drinking-water samples, 7 breast-milk samples pooled from 40 women, and 14 blood samples) and unreported for others (air, soil, and vegetables). Results from the samples suggested elevated concentrations of dioxin around the center of Chapaevsk compared with those from outlying areas. That conclusion was based primarily on concentrations measured in soil: 141 ng TEQ/kg soil less than 2 km from the plant, compared with 37 ng TEQ/kg soil 2–7 km from the plant, and 4 ng TEQ/kg soil 7–10 km from the plant. Concentrations outside the city (10–15 km from the plant) were approximately 1 ng TEQ/kg soil. The authors also compared measurements from Chapaevsk with those from other Russian cities with industrial facilities. The data presented do not allow direct comparison of dioxin concentrations in soil as a function of distance from the industrial facilities. However, the highest TCDD concentrations in the Chapaevsk study (those nearest the plant) were higher than were the maximum concentrations reported by four other studies referenced in the article. Residence in the city of Chapaevsk was used as a surrogate for exposure in the epidemiologic analyses presented in the report. No attempt was made to create exposure categories based on residential location within the city or with occupational or lifestyle factors that might have influenced TCDD exposure.

Akhmedkhanov et al. (2002) sampled 24 volunteers from this same population for lipid-adjusted serum dioxin concentrations. Residents living near the plant (<5 km) had higher concentrations than did those who lived farther from the plant. It was not clear whether the analysis included adjustments for age, body mass index, or education, all of which are significant predictors of dioxin concentrations. No new studies have been published since *Update 2004.*

Other Studies

Several reports have provided information on environmental exposure to TCDD in the Times Beach area of Missouri (Andrews et al., 1989; Patterson et al., 1986). In 1971, TCDD-

contaminated sludge from a hexachlorophene production facility was mixed with waste oil and sprayed in various community areas for dust control. Soil contamination in some samples exceeded 100 ppb. Among the Missouri sites with the highest TCDD soil concentrations was the Quail Run mobile-home park. Residents were considered exposed if they had lived in the park for at least 6 months during the time that contamination occurred (Hoffman et al., 1986). Other investigations of Times Beach have estimated exposure risk on the basis of residents' reported occupational and recreational activities in the sprayed area. Exposure has been estimated from duration of residence and TCDD soil concentrations.

Andrews et al. (1989) provided the most extensive data on human adipose tissue TCDD in 128 non-exposed control subjects with comparison concentrations from 51 exposed persons who had ridden or cared for horses at arenas sprayed with TCDD-contaminated oil; who lived in areas where the oil had been sprayed; who were involved in trichlorophenol (TCP) production; or who were involved in TCP non-production activities, such as laboratory or maintenance work. Persons were considered exposed if they lived near, worked with, or had other contact for at least 2 years with soil contaminated with TCDD at 20–100 parts per billion (ppb) or for 6 months or more with soil contaminated with TCDD above 100 ppb. Of the exposed-population samples, 87% had adipose tissue TCDD concentrations below 200 ppt; however, TCDD concentrations in 7 of the 51 exposed persons were 250–750 ppt. In non-exposed persons, adipose tissue TCDD ranged from undetectable to 20 ppt, with a median of 6 ppt. On the basis of a 7-year half-life, it is calculated that 2 study participants would have had adipose tissue TCDD near 3,000 ppt at the time of the last date of exposure.

Several epidemiologic studies have been conducted in association with industrial-facility emissions, or in regions with documented differences in dioxin exposures. Viel et al. (2000) reported on an investigation of apparent clusters of cases of soft-tissue sarcoma and non-Hodgkin's lymphoma in the vicinity of a municipal solid-waste incinerator in Doubs, France. The presumptive source of TCDD in the region is a municipal solid-waste incinerator in the Besançon electoral ward in western Doubs. Dioxin emissions from the incinerator were measured in international toxicity equivalent (I-TEQ) units at 16.3 nanograms (ng) I-TEQ per cubic meter (m^3), far in excess of the European Union (EU) standard of 0.1 ng I-TEQ/m^3. TCDD concentrations in cows' milk measured at three farms near the incinerator were well below the EU guideline of 6 ng I-TEQ/kg of fat, but the concentrations were highest at the farm closest to the incinerator.

Combustion records for the Zeeburg area of Amsterdam in the Netherlands were used as a surrogate for exposure to dioxins in a study of orofacial clefts (ten Tusscher et al., 2000). Location downwind or upwind of an incineration source was used to define exposed and reference groups for the study. A study of soft-tissue sarcomas in the general population was conducted in northern Italy around the city of Mantua (Costani et al., 2000). Several industrial facilities are in Mantua, and residential proximity to them was presumed to result in increased TCDD exposure, but TCDD was not measured in the environment or in human tissues.

A study of dioxin exposure pathways in Belgium focused on long-time residents in the vicinity of two municipal-waste incinerators (Fierens et al., 2003a). Residents near a rural incinerator had significantly higher serum dioxin concentrations than did a control group (38 vs. 24 picograms (pg) TEQ/g fat). Concentrations in residents living near the incinerators increased proportionately with intake of local-animal fat. A second study (Fierens et al., 2003b) measured dioxin body burden in 257 people who had been environmentally exposed, with the object of determining whether dioxin and PCB exposures were associated with type 2 diabetes and endometriosis. No difference in body burden was found between women with endometriosis and women in a control

group, but the risk of type 2 diabetes was significantly higher for those with higher body burdens of dioxin-like compounds and PCBs. Another study of the correlation between dioxin-like compounds in Italian and Belgian women and the risk of endometriosis used measurements of TCDD and other dioxins in blood (De Felip et al., 2004). There was no difference in body burden among women with endometriosis and a control group, but dioxin concentrations were substantially higher in the control groups of women from Belgium than in a similar group from Italy (45 vs. 18 pg TEQ/g, lipid-adjusted, respectively).

Since *Update 2004*, Bloom et al. (2006) measured serum dioxin levels in New York sports fishermen as part of a study of thyroid function. Also, a methodological study by Petreas et al. (2004) found generally quite high correlations between breast and abdominal fat within the same woman for dioxins and related compounds, suggesting that they could be used interchangeably in epidemiological studies. The same study, however, also found that adjusting concentrations for actual lipid content rather than weight of the fat sample is important due to the presence of non-lipid components in these samples.

Studies in Vietnam

Studies of exposure to herbicides among the residents of South Vietnam have compared unexposed residents of the South with residents of the North (Constable and Hatch, 1985). Other studies have attempted to identify wives from veterans of North Vietnam who served in South Vietnam. Records of herbicide sprays have been used to refine exposure measurements, comparing individuals who lived in sprayed villages in the South with those living in unsprayed villages. In some studies, village residents were considered exposed if a herbicide mission had passed within 10 km of the village center (Dai et al., 1990). Other criteria for classifying exposure included length of residence in a sprayed area and the number of times the area reportedly had been sprayed.

A small number of studies provide information on TCDD concentrations in Vietnamese civilians exposed during the war. Schecter et al. (1986) detected TCDD in 12 of 15 samples of adipose tissue taken during surgery or autopsy in South Vietnam during 1984. The concentrations in the positive samples were 3–103 ppt. TCDD was not detected in 9 samples from residents of North Vietnam who had never been to South Vietnam; detection sensitivity was 2–3 ppt. Analysis of 3 breast-milk samples collected in 1973 from Vietnamese women thought to have been exposed to Agent Orange yielded TCDD concentrations of 77–230 ppt on a lipid basis.

Blood samples from 43 residents of Bien Hoa City were analyzed for TCDD analysis (Schecter et al., 2002). Bien Hoa City is in the southern part of South Vietnam, and the surrounding area was treated heavily with Agent Orange. The median lipid-normalized TCDD concentration was 67 ppt in those residents, compared with an average of 2 ppt in residents of Hanoi. The study also indicated that TCDD exposure of the population was continuing, presumably through consumption of fish and other foods. Schechter et al. (2006) recently reported additional sampling of residents in areas believed to have ongoing TCDD contamination. Blood samples from residents at eight sites were analyzed for TCDD and related compounds. Elevated TCDD concentrations were found in residents from one of these sites; data from a second site were suggestive of elevated exposures; results from the other six sites were similar to those found in the general population in the south of Vietnam.

Dwernychuk et al. (2002) collected environmental and food samples, human blood, and breast milk from residents of the Aluoi Valley of central Vietnam. The investigators identified locations

where relatively high dioxin concentrations remain in soil or water systems. Dioxin soil concentrations were particularly high around former air fields and military bases where herbicides were handled. Fish harvested from ponds in these areas were found to contain elevated dioxin concentrations. More recently Dwernychuk (2005) elaborated on the importance of "hot spots" as important locations for future studies and argued that herbicide use at former U.S. military installations was the most likely cause of these hot spots. These studies are not directly relevant to this IOM committee's task, but they may prove useful in future epidemiologic studies of the Vietnamese population and in the development of risk mitigation policies.

MILITARY USE OF HERBICIDES IN VIETNAM

Military use of herbicides in Vietnam began in 1962, expanded in 1965 and 1966, and reached a peak between 1967 and 1969. The herbicides were used primarily to defoliate inland hardwood forests, coastal mangrove forests, cultivated land, and zones around military bases. In 1974, a National Academy of Sciences committee estimated the amount of herbicides sprayed from helicopters and other aircraft using records gathered from August 1965 to February 1971 (NAS, 1974). The committee calculated that about 17.6 million gallons (~66.5 million liters [L]) of herbicide were sprayed over about 3.6 million acres (~1.5 million hectares) in Vietnam in that time period. The amounts of herbicides sprayed on the ground to defoliate the perimeters of base camps and fire bases, and amounts sprayed by Navy boats along river banks were more difficult to quantify.

In 1997, a committee convened by IOM issued a request for proposals (RFP) seeking individuals and organizations to develop historical exposure reconstruction approaches suitable for epidemiologic studies of herbicide exposure among US veterans during the Vietnam War (IOM, 1997). The RFP resulted in the project, Characterizing Exposure of Veterans to Agent Orange and Other Herbicides in Vietnam, carried out under contract by a team of researchers from Columbia University's Mailman School of Public Health.

This work yielded new estimates of the use of military herbicides in Vietnam from 1961 to 1971 (IOM, 2003b,c; Stellman et al., 2003a). Investigators reviewed the original data used in the 1970s to make estimates and identified inconsistencies, data gaps, and typographical errors. They determined the amounts of herbicide applied but not recorded on the data tapes (the so-called HERBS tapes) compiled in the 1970s and clarified data on missions that presumably "dumped" herbicide loads over very short periods before returning to base. The new analyses led to a revision in estimates of the amounts of the agents applied, as indicated in Table 5-3. Previous *VAO* reports estimated that a total of 67.8 million liters of military herbicides were applied from 1961 to 1971. The new research effort estimated that ~77 million liters was applied; a difference of more than 9 million liters.

TABLE 5-3. Military Use of Herbicides in Vietnam (1961–1971)

Code Name	Chemical Constituents[a]	Concentration of Active Ingredient[a]	Years Used[a]	Amount Sprayed	
				VAO Estimate[b]	Revised Estimate[a]
Pink	60%–40% *n*-butyl, isobutyl ester of 2,4,5-T	961–1,081 g/L acid equivalent	1961, 1965	464,817 L (122,792 gal)	50,312 L sprayed; 413,852 L additional on procurement records

Green	*n*-butyl ester 2,4,5-T	—	—	31,071 L (8,208 gal)	31,026 L shown on procurement records
Purple	50% *n*-butyl ester 2,4-D, 30% *n*-butyl ester 2,4,5-T, 20% isobutyl ester 2,4,5-T	1,033 g/L acid equivalent	1962–1965	548,883 L (145,000 gal)	1,892,733 L
Orange	50% *n*-butyl ester 2,4-D, 50% *n*-butyl ester 2,4,5-T	1,033 g/L acid equivalent	1965–1970	42,629,013 L (11,261,429 gal)	45,677,937 L (could include Agent Orange II)
Orange II	50% *n*-butyl ester 2,4-D, 50% isooctyl ester 2,4,5-T	910 g/L acid equivalent	Post–1968 (?)	—	Unknown, but at least 3,591,000 L shipped
White	Acid weight basis: 21.2% triisopropanolamine salts of 2,4-D and 5.7% picloram	By acid weight: 240 g/L 2,4-D and 65 g/L picloram	1966–1971	19,860,108 L (5,246,502 gal)	20,556,525 L
Blue powder	Cacodylic acid (dimethylarsinic acid) and sodium cacodylate	Acid: 65% active ingredient; salt: 70% active ingredient	1962–1964	—	25,650 L
Blue Aqueous Solution	21% Sodium cacodylate + cacodylic acid to yield at least 26% total acid equivalent by weight	Acid weight: 360 g/L	1964–1971	4,255,952 L (1,124,307 gal)	4,715,731 L
Total, all formulations				67,789,844 L (17,908,238 gal)	76,954,766 L (including procured)

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

Four compounds were used in the herbicide formulations: 2,4-D, 2,4,5-T, picloram, and cacodylic acid. The chlorinated phenoxy acids (2,4-D and 2,4,5-T) persist in soil only for a few weeks (Buckingham, 1982). Picloram is more mobile than 2,4-D and 2,4,5-T and is extremely persistent in soils. Cacodylic acid, or dimethylarsinic acid, is an organic form of arsenic.

Herbicides were identified by the color of a band on 55-gal containers and called Agents Pink, Green, Purple, Orange, White, and Blue (Table 5-3). Agent Green and Agent Pink were used in 1961 and 1965; Agent Purple was used from 1962 through 1965. Agent Orange was used from 1965 through 1970, and a slightly different formulation (Agent Orange II) probably was used after 1968. Agent White was used from 1966 through 1971. Agent Blue was used in powder form from 1962 through 1964 and as a liquid from 1964 through 1971. Agents Pink, Green, Purple, Orange, and Orange II all contained 2,4,5-T, and were contaminated to some extent with TCDD. Agent White contained 2,4-D and picloram. Agent Blue (powder and liquid) contained cacodylic acid. More details on the herbicides used are presented in the earlier reports (IOM, 1994, 1996, 1999, 2001, 2003a).

In addition to the four major compounds, Dinoxol, Trinoxol, and diquat were applied to native grasses and bamboo (Brown, 1962). Soil-applied herbicides also were reportedly used around base camp perimeters, minefields, ammunition storage areas, and other sites where it was necessary to control grasses and woody vegetation (Darrow et al., 1969). Other accounts discuss the use of other herbicides, fungicides, insecticides, insect repellents, wetting agents, and wood preservatives (Gonzales, 1992). There are no data on the number of military personnel potentially

exposed to those substances.

TCDD in Herbicides Used in Vietnam

TCDD was formed as an unwanted by-product of 2,4,5-T production, but was not formed during 2,4-D production. The concentration of TCDD in any given lot of 2,4,5-T depended on the manufacturing process (Young et al., 1976), and different manufacturers produced 2,4,5-T with different concentrations of TCDD.

Of all the herbicides used in South Vietnam, only Agent Orange was formulated differently from the materials for commercial application that were readily available in the United States (Young et al., 1978). TCDD concentrations in individual shipments were not recorded, and they varied in sampled inventories of herbicides containing 2,4,5-T. Analysis of the TCDD concentration in stocks of Agent Orange remaining after the conflict, which either had been returned from South Vietnam or had been procured but not shipped, ranged from less than 0.05 ppm to almost 50 ppm and averaged 1.98 and 2.99 ppm in two sets of samples (NAS, 1974; Young et al., 1978). Comparable manufacturing standards for the domestic use of 2,4,5-T in 1974 required that TCDD be present at less than 0.05 ppm (NAS, 1974).

Until recently, data from Young and Gough have been used to estimate the amount of TCDD in the various herbicide formulations (Gough, 1986; Young, 1992; Young et al., 1978). Young et al. (1978) estimated that Agents Green, Pink, and Purple used early in the program (through 1965) contained 16 times the mean TCDD content of formulations used between 1965 and 1970. Analysis of archive samples of Agent Purple reported TCDD as high as 45 ppm (Young, 1992). The mean concentration of TCDD in Agent Purple was estimated at 32.8 ppm. In Agents Pink and Green, it was estimated at 65.6 ppm (Young et al., 1978). Gough (1986) estimated that ~167 kg of TCDD was sprayed in Vietnam over a 6-year period.

New analyses produced by the Columbia University team have proposed 366 kg of TCDD as a plausible estimate of the total amount of TCDD applied in Vietnam between 1961 and 1971, and the authors argue that the true amount may be higher (Stellman et al., 2003a).

EXPOSURE ASSESSMENT IN STUDIES OF VIETNAM VETERANS

Different approaches have been used to estimate the exposure of Vietnam veterans, including self-reports, record-based exposure estimates, and assessments of biologic markers of TCDD exposure. Each approach has a limited ability to ascribe individual exposure. Some studies rely on such gross markers as service in Vietnam—perhaps enhanced by branch of service, military region, military specialty, or combat experience—as a proxy for exposure to herbicides. Studies of that type include the CDC Vietnam Experience Study and Selected Cancers Study, Department of Veterans Affairs mortality studies, and most studies of veterans conducted by the states. This approach has the potential to miss associations between exposures and health effects, if they exist, since many members of these cohorts presumed to have been exposed to herbicides might, in reality, not have been.

The number of US military personnel who directly handled (mixed, loaded, or applied) herbicides is impossible to determine precisely, but two groups have been identified as high risk subpopulations among veterans: Air Force personnel involved in fixed-wing aircraft spraying activities known commonly as Operation Ranch Hand, and Army personnel who served in the US

Army Chemical Corps, who used hand-operated equipment and helicopters to conduct smaller (but potentially high exposure) operations, including defoliation around special forces camps, clearing the perimeters of airfields, depots, and other bases, and small-scale crop destruction (Thomas and Kang, 1990; Warren, 1968).

Units and individuals other than members of the Air Force Ranch Hand and Army Chemical Corps also were likely to have handled or sprayed herbicides around bases or lines of communication. Navy river patrols were reported to have used herbicides to clear inland waterways, and engineering personnel used herbicides to remove underbrush and dense growth in constructing fire support bases.

Because the herbicides were not considered to present a health hazard, few precautions were taken to prevent troop exposure. The precautions that were prescribed were consistent with those applied in the domestic use of herbicides before the Vietnam conflict (US GAO, 1979).

Air Force Health Study

Major defoliation activities in Vietnam were conducted by Air Force personnel as part of Operation Ranch Hand. These veterans became the first subpopulation with Vietnam veterans to receive special attention in regard to Agent Orange, and have become known as the Ranch Hand cohort within the Air Force Health Study (AFHS) The AFHS was initiated in 1979 by the US Air Force (IOM, 2006). Biologic marker studies of Ranch Hand personnel have shown consistency with their exposure to TCDD as a group. When the Ranch Hand cohort was further classified by military occupation, a general increase in serum TCDD was detected for jobs that involved more-frequent handling of herbicides (AFHS, 1991).

The exposure index initially proposed in the AFHS relied on military records of TCDD-containing herbicides (Agents Orange, Purple, Pink, Green) sprayed as reported in the HERBS tapes for the period starting July 1965 and on military procurement records and dissemination information for the period before July 1965. In 1991, the exposure index was compared with the results of the Ranch Hand serum TCDD analysis. The exposure index and the TCDD body burden correlated weakly.

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

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

Most recent AFHS studies have relied on serum dioxin concentration as the primary exposure metric for epidemiologic classification (Akhtar et al., 2004; Barrett et al., 2001, 2003; Michalek et al., 2001a,b,c, 2003; Pavuk et al., 2003). Since *Update 2004*, four additional publications employing serum dioxin concentrations have examined insulin sensitivity (Kern et al., 2004), post-service mortality (Ketchum and Michalek, 2005), risk of prostate cancer (Pavuk et al., 2006), and cancer risk in Air Force personnel who did not spray Agent Orange (Pavuk et al., 2005).

The National Academy of Sciences recently issued a comprehensive review of the AFHS, together with recommendations for the use of the extensive data collected through this project (IOM, 2006).

Army Chemical Corps Studies

Members of the US Army Chemical Corps performed ground and helicopter chemical operations and were thereby involved in the direct handling and distribution of herbicides in Vietnam. This population has only recently been identified for detailed study of health effects related to herbicide exposure (Thomas and Kang, 1990). Results of an initial feasibility study were reported by Kang et al. (2001). That study recruited 565 veterans: 284 Vietnam veterans and 281 non-Vietnam-veteran control subjects. Blood samples were collected in 1996 from 50 Vietnam veterans and 50 control veterans, and 95 of the samples met CDC standards for quality assurance and quality. Comparison of the entire Vietnam cohort with the entire non-Vietnam cohort showed that the geometric mean TCDD concentrations did not differ significantly ($p = 0.6$). Of the 50 Vietnam veterans sampled, analysis of questionnaire responses indicated that those who reported spraying herbicides had higher TCDD concentrations than did those who reported no spraying activities. The authors concluded that Agent Orange exposure was a likely contributor to TCDD concentrations in Vietnam veterans who had a history of spraying herbicides. The main study of 5,000 Vietnam veterans, including analysis of an additional 900 blood specimens, continues.

Since *Update 2004*, Kang et al. (2006) reported on the health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam. A health survey was conducted among 1,499 Vietnam veterans and 1,428 non-Vietnam veterans. Exposure to herbicides was assessed by analyzing serum specimens from a sample of 897 veterans for dioxin. Those veterans who reported spraying herbicides had significantly higher TCDD serum levels than did Vietnam veterans and other veterans who did not report herbicide spraying. The final analysis compared Vietnam veteran sprayers with Vietnam veteran non-sprayers from the entire study population.

Korean Vietnam Veterans

Military personnel from the Republic of Korea served in Vietnam between 1964 and 1973. Kim et al. (2001) evaluated the validity of an exposure index by comparing group exposure estimates with pooled serum dioxin concentrations. The study involved 720 veterans who served in Vietnam, and 25 veterans who did not serve in Vietnam. The exposure index was based on Agent Orange spray patterns across military regions in which Korean personnel served, time–location data for the military units stationed in Vietnam, and an exposure score derived from self-reported activities during service. A total of 13 blood samples were submitted to CDC for serum dioxin analysis. One sample was prepared from the 25 veterans who did not serve in Vietnam; the remaining 12 blood samples were created by pooling blood samples from 60 veterans into 12

exposure categories. The 12 categories ultimately were reduced to 4 exposure groups, each group containing 3 exposure categories and representing quartiles of veterans with Vietnam service.

The paper by Kim et al. (2001) reported highly significant Pearson correlation coefficients and multiple regression analysis results. The statistical analyses apparently were based on the assignment of the pooled-serum-dioxin value to each individual in the exposure group, thereby inflating the true sample size. The multiple regression analysis evaluated such variables as age, body-mass index, and consumption of tobacco or alcohol. In a subsequent report for the same exposure groups and serum dioxin data, the authors corrected their analysis (Kim et al., 2003). A correlation was observed between serum dioxin concentrations and ordinal exposure categories, but the correlation was not statistically significant. The authors attributed the lack of statistical significance to the small sample size, and they noted that the data exhibited a distinct monotone upward trend (average serum dioxin concentrations of 0.3, 0.6, 0.62, 0.78, and 0.87 pg/g (lipid adjusted) for exposure categories 0–4, respectively). The decision to pool blood samples from a large number of persons within each exposure set (Kim et al., 2001) greatly reduced the power of the validation study. Instead of 180 samples for each of the final exposure categories, the pooled analysis produced only 3 samples for each category. The lipid-adjusted serum TCDD concentrations from the 12 pooled samples for Vietnam veterans ranged from 0.25 to 1.2 pg/g, whereas the single sample from the non-Vietnam veterans contained 0.3 pg/g. The narrow range of results puts into question the biologic relevance of any differences.

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

No additional reports on this population have been published since *Update 2004*.

Other Vietnam Veterans

Surveys of Vietnam veterans who were not part of the Ranch Hand or Army Chemical Corps groups indicate that 25–55% believe they were exposed to herbicides (CDC, 1989; Erickson et al., 1984a,b; Stellman and Stellman, 1986). Several attempts have been made to estimate exposure of Vietnam veterans who were not part of the Ranch Hand or Army Chemical Corps groups. In 1983, the US government asked the Centers for Disease Control and Prevention (CDC) to conduct a study of the possible long-term health effects of Vietnam veterans' exposures to Agent Orange. The CDC Agent Orange study (CDC, 1985) attempted to classify veterans' service-related exposures to herbicides. That involved determining the proximity of troops to Agent Orange spraying by using military records to track troop movement and the HERBS tapes to locate herbicide-spraying patterns. The CDC Birth Defects Study developed an exposure opportunity index to score Agent Orange exposure (Erickson et al., 1984a,b).

In 1987, CDC conducted the Agent Orange Validation Study to test the validity of the various

indirect methods used to estimate exposure of ground troops to Agent Orange in Vietnam. The study measured serum TCDD in a non-random sample of Vietnam veterans and in Vietnam-era veterans who did not serve in Vietnam (CDC, 1988b). Vietnam veterans were selected for further study on the basis of the estimated number of Agent Orange hits, derived from the number of days on which at least one company location was within 2 km and 6 days of a recorded Agent Orange spray. The "low" exposure group consisted of 298 veterans, the "medium" exposure group had 157 veterans, and the "high" exposure group had 191 veterans. Blood samples were obtained from 66% of Vietnam veterans (n = 646) and from 49% of the eligible comparison group of veterans (n = 97). More than 94% of those whose serum was obtained had served in one of five battalions.

The median serum TCDD in Vietnam veterans in 1987 was 4 ppt, with a range of <1–45 ppt; 2 veterans had concentrations above 20 ppt. The distribution of TCDD measurements was nearly identical for the control group of 97 non-Vietnam veterans. The CDC validation study concluded that study subjects could not be distinguished from controls on the basis of serum TCDD. In addition, neither record-derived estimates of exposure, nor self-reported exposure to herbicides were able to identify Vietnam veterans with currently high serum TCDD (CDC, 1988b). The report concluded that it was unlikely that military records alone could be used to identify a large number of US Army veterans who might have been heavily exposed to TCDD in Vietnam.

The serum TCDD measurements for Vietnam veterans also suggested that exposure to TCDD in Vietnam was substantially less, *on the average*, than was that of persons exposed as a result of the industrial explosion in Seveso or that of the heavily exposed occupational workers who are the focus of many of the studies evaluated by the committee. This assessment of *average* exposure does not preclude the possibility of heavily exposed subgroups of Vietnam veterans.

The aforementioned 1997 IOM request for proposals for historical exposure reconstruction has led to the development of new methods for estimating Vietnam veterans' exposures to Agent Orange. The Columbia University project integrated various sources of information concerning spray activities to generate individualized estimates of the exposure potential of troops serving in Vietnam (Stellman and Stellman, 2003). Location data for military units assigned to Vietnam were compiled into a database developed from five primary and secondary sources: the Unit Identification Code list (a reference list of units serving in Vietnam created and used by the Army); a command post list (data on division level of the command locations for army personnel); Army Post Office lists (compilations of locations down to and including battalion size and other selected units that were updated on a monthly basis); troop strength reports (data assembled by the US Military Assistance Command on troop allocations, updated on a monthly basis and generally collected on the battalion level); and order of battle information (data on command post, arrival and departure dates, and authorized strength of many but not all units). For units that served in the III Corps Tactical Zone between 1966 and 1969, battalion-tracking data were also available. These are data on the grid coordinate locations of battalion-sized units derived from Daily Journals, which recorded the company locations over 24-hour periods.

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

All of these data were combined into a geographic information system (GIS) for Vietnam with

a grid resolution of 0.01° latitude and 0.01° longitude. Herbicide-spraying records were integrated into the GIS and linked with data on military unit locations to permit estimation of exposure opportunity scores for individuals. The results are the subject of reports by the contractor (Stellman and Stellman, 2003) and the committee (IOM, 2003b,c). A summary of the findings regarding the extent and pattern of herbicide spraying (Stellman et al., 2003a), a description of the GIS for characterizing exposure to Agent Orange and other herbicides in Vietnam (Stellman et al., 2003b) and an explanation of the exposure opportunity models based on that work (Stellman and Stellman, 2004) have been published in peer-reviewed journals. Those publications have argued that it is now feasible to conduct epidemiologic investigations of veterans who served as ground troops during the Vietnam War.

A different perspective has been put forth by Young and colleagues in a series of papers (Young and Newton, 2004; Young et al., 2004a,b). They have argued that ground troops had little direct contact with herbicide sprays, and that TCDD residues in Vietnam had low bioavailability. These conclusions were based on analyses of previously unpublished military records and environmental fate studies. They have also argued that ground troop exposures were relatively low because herbicide spray missions were carefully planned, and spraying only occurred when friendly forces were not located in the target area. Finally, they have noted that the GIS-based exposure opportunity model has not yet been validated through measurement of serum dioxin levels in veterans (Young, 2004).

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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6

Cancer

Cancer is the second-leading cause of death in the United States. Among men 50–64 years old, the group that includes most Vietnam veterans (see Table 6-1), the risk of dying from cancer nearly equals the risk of dying from heart disease, the main cause of death in the United States (US Census, 1999). About 564,830 Americans of all ages were expected to die from cancer in 2006—more than 1,500 per day. In the United States, one-fourth of all deaths are from cancer (Jemal et al., 2006).

TABLE 6-1 Age Distribution of Vietnam Era and Vietnam Theater Male Veterans 2004–2005 (numbers in thousands)

Ages Group (Years)	Vietnam Era N	(%)	Vietnam Theater N	(%)
All ages	7,934		3,853	
≤49	133	(1.6)	32	(0.1)
50–54	1,109	(13.8)	369	(9.4)
55–59	3,031	(37.6)	1,676	(43.1)
60–64	2,301	(28.5)	1,090	(28.0)
65–69	675	(8.4)	280	(7.2)
70–79	511	(6.3)	322	(8.3)
≥80	178	(2.2)	83	(2.1)

SOURCE: Table 3-3 (IOM, 1994), updated by 15 years.

This chapter summarizes and presents conclusions about the strength of the evidence from epidemiologic studies regarding associations between exposure to the compounds of interest—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid—and various types of cancer. If a new study reports on only a single type of cancer and does not revisit a previously studied population, its design information is summarized here with its results; design information on all other new studies can be found in Chapter 4; Appendix C contains cumulative tables that summarize studies that looked at multiple end points or involved repeatedly investigated populations that have contributed evidence to this series of reports.

In an evaluation of a possible connection between herbicide exposure and risk of cancer, how exposures of study subjects were assessed is of critical importance in determining the overall relevance and usefulness of findings. As noted in Chapter 5, there is a great variety in detail and accuracy of exposure assessment among studies. A few studies used biologic markers of

exposure, such as the presence of a compound in serum or tissues; some developed an index of exposure from employment or activity records; and others used surrogate measures of exposure, such as presence in a geographic locale when herbicides were used. As noted in Chapter 2, inaccurate assessment of exposure can obscure the relationship between exposure and disease.

Each section on a type of cancer opens with background information, including data on its incidence in the general US population and known or suspected risk factors. Cancer-incidence data on the general US population are included in the background material to provide a context for consideration of cancer risk in Vietnam veterans; the figures presented are estimates for the entire US population, however, not predictions for the Vietnam-veteran cohort. The incidence figures in this update are adapted to the demographic patterns defined by the 2000 US census data. The data reported are for 1998–2002, the most recent dataset available (NCI, 2006). Incidence data are given for all races combined and separately for blacks and whites. The age range of 50–64 years now includes about 80% of Vietnam-era veterans, so incidences are presented for three 5-year age groups: 50–54 years, 55–59 years, and 60–64 years. The data were collected for the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute of the National Institutes of Health and are categorized by sex, age, and race, all of which can have profound effects on risk. For example, the incidence of prostatic cancer is about 4.3 times as high as men who are 60–64 years old than in men 50–54 years old; it is about twice as high in blacks 50–64 years old as in whites in the same age group (NCI, 2006). Many factors can influence incidence, including behavior (such as tobacco and alcohol use and diet), genetic predisposition, and medical history. Those factors can make someone more or less likely than the average to contract a given kind of cancer; they also need to be taken into account in epidemiologic studies of the possible contributions of the compounds of interest.

The body of each section on a specific type of cancer includes a summary of the findings described in the previous Agent Orange reports: *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994); *Veterans and Agent Orange: Update 1996,* referred to as *Update 1996* (IOM, 1996); *Update 1998* (IOM, 1999); *Update 2000* (IOM, 2001); *Update 2002* (IOM, 2003); and *Update 2004* (IOM, 2005). That is followed by a discussion of the most recent scientific literature, a discussion of biologic plausibility, and a synthesis of the material reviewed. Where appropriate, the literature is discussed by exposure type (occupational, environmental, or service in Vietnam). Each section ends with the committee's conclusion regarding the strength of the evidence from epidemiologic studies. The categories of association and the committee's approach to categorizing the health outcomes are discussed in Chapters 1 and 2. As explained in the following paragraphs, this committee has slightly modified the format in which it has satisfied the other two aspects of its charge.

Biologic plausibility corresponds to the third element of the committee's congressionally mandated statement of task. In previous updates, it had been discussed in the conclusion section for each health outcome after a statement of the committee's judgment about the adequacy of the epidemiologic evidence of an association between exposure to the compounds of interest and the outcome. In fact, the degree of biologic plausibility itself influences whether the committee perceives positive findings to be indicative of a pattern of association or the product of statistical fluctuations. To provide the reader with a more logical sequence, in this update sections on biologic plausibility have been placed between the presentation of epidemiologic evidence and the synthesis of the evidence, which leads to the committee's conclusion about the adequacy of the evidence to support an association.

Information on biologic mechanisms that could contribute to the generic (rather than tissue- or organ-specific) carcinogenic potential of the compoundsof interest is summarized in the section on biologic plausibility that precedes the synopsis of conclusions for the entire chapter. It distills toxicologic information concerning the mechanisms by which the compounds of interest affect carcinogenesis, as presented in more detail in Chapter 3; such information, of course, applies to all the cancer sites discussed individually in this chapter. When biologic plausibility is discussed in the chapter's sections on particular cancer types, the generic information is implicit, and only toxicologic information peculiar to carcinogenesis at the site in question is been presented.

Considerable uncertainty remains about the magnitude of potential risk posed by exposure to the compounds of interest. Many of the occupational, environmental, and veterans studies reviewed by the committee did not control fully for important confounders. There is not enough information about individual Vietnam veterans to compare with exposures presented in scientific research studies. The committee therefore cannot accurately estimate the risk to Vietnam veterans that is attributable to exposure to the compounds of interest. Previous reports in the *VAO* series have had a rather formulaic statement to that effect as the third entry in the conclusion section for each cancer type, corresponding to the second element in the committee's statement of task as dictated by the congressional mandate. The (at least currently) insurmountable problems of deriving meaningful estimates of the risks of various health outcomes to Vietnam veterans are explained in Chapter 1 and the summary of this report, but the point is no longer reiterated for every health outcome addressed.

AN EXHAUSTIVE AND UNAMBIGUOUS SYSTEM FOR ADDRESSING CANCER TYPES

The Department of Veterans Affairs (VA) requested that the present committee ensure that evaluations of the possibility of associations between exposures to the compounds of interest and various types of cancer be framed in such a fashion that a corresponding conclusion would be available for any type of cancer that might be diagnosed in a veteran and that it would be clear which conclusion would be applicable when a veteran filed a claim.

VA also expressed concern that the episodic nature of the *VAO* series may have interfered with recognition and evaluation of cumulatively usable amounts of epidemiologic information on some uncommon cancers; in particular, VA asked for a focused examination of available information on cancer of the tonsil and acute myelogenous leukemia (AML). The committee therefore screened the studies that contributed results on the cancer types discussed in prior updates for results on tonsil cancer, AML, and other uncommon sites while gaining an overview of how cancer sites are typically grouped to report findings.

VA had indicated that a grouping system for reporting the committee's conclusions based on the *International Classification of Diseases* (ICD) codes would be appropriate to match the diagnostic information presented in veterans' claims. ICD is used to code and classify mortality data from death certificates. ICD CM (clinical modification) is used to code and classify morbidity data from medical records, hospital records, and surveillance surveys. The 10th edition (ICD-10) came into use in 1999 and constitutes a marked change from the previous four versions that evolved into the ninth edition (ICD-9). ICD-9 was in effect from 1979 to 1998; because ICD-9 is

the version most prominent in the research reviewed in this series, it has been used when codes are given for a specific health outcome.

The first modification made in this update toward addressing VA's request was to change the order in which cancer types are discussed, which had evolved from the original *VAO* report. The more systematic order of major and minor categories of cause of death for cancer sites established by the National Institute for Occupational Safety and Health (NIOSH) is now followed with minor exceptions. The NIOSH groups map the full range of ICD-9 codes for malignant neoplasms (140–208), and this somewhat coarser gradient has been adopted as an exhaustive organizing principle for the present chapter. Appendix B discusses the issue in more detail and delineates the correspondence between the NIOSH cause-of-death groupings and ICD-9 codes (Table B-1); the groupings for mortality are largely congruent with those of the SEER program for cancer incidence (see Table B-2, which presents equivalences between the ICD-9 and ICD-10 systems). The groups provide a comprehensive framework for software routinely used by epidemiologists to generate expected values based on the demographics of the cohort being studied and have well-documented correspondence with the more detailed ICD coding system in its successive iterations (Robinson et al., 2006). When conditions reported on in epidemiologic research are specified in ICD ranges, the specificity may not be as refined as might be desired for some purposes, and errors of misclassification in the research process cannot be excluded, but the grouping intended is unambiguous.

This rearrangement following a largely anatomic sequence should make locating a particular cancer easier for readers and facilitated the committee's identification of ICD codes for malignancies that had not been explicitly addressed in previous updates (as noted in italics in Table B-1). *VAO* reports' default category for any health outcome for which no epidemiologic research findings have been recovered has always been "inadequate evidence" of association, which in principle is applicable to specific cancers. In this update, it still is the case that failure to review a specific cancer or other condition separately reflects the paucity of information, so there is indeed inadequate or insufficient information to categorize such a disease outcome. However, in response to VA's request and in light of our review of how "rare cancers" are grouped or presented when they do have reported results, we state here how each of these previously overlooked ICD codes will be treated in this and future updates:

- ICD-9 149, other buccal cavity and pharynx—routinely included in full buccal cavity and pharynx range, 140–149.
- ICD-9 152, small intestine—rarely reported individually; to be encompassed in conclusions for colorectal cancers.
- ICD-9 156, gallbladder and extrahepatic bile ducts—to be tracked under hepatobiliary cancers.
- ICD-9 158–159, retroperitoneum and other and unspecified digestive cancers—rarely reported individually; to be encompassed in conclusions for colorectal cancers.
- ICD-9 162.0, trachea—intended grouping with lung and bronchus has not always been explicitly stated.
- ICD-9 163, pleura—rarely reported individually and not as yet seen for the chemicals on interest; would be considered with mediastinum and other and unspecified respiratory cancers.
- ICD-9 164.0, thymus—to be considered with thyroid and other endocrine cancers.

- ICD-9 164.2–164.9, mediastinum—rarely reported individually and not as yet seen for the chemicals on interest; would be considered with pleura and other and unspecified respiratory cancers.
- ICD-9 165, other and unspecified respiratory cancers—rarely reported individually and not as yet seen for the chemicals on interest; would be considered with pleura and mediastinum as other respiratory cancers.
- ICD-9 179, unspecified parts of uterus—to be considered with female reproductive system.
- ICD-9 181, placenta—to be considered with female reproductive system.
- ICD-9 183.2–183.9, fallopian tube and other uterine adnexa—to be considered with female reproductive system.
- ICD-9 184, other female genital organs—to be considered with female reproductive system.
- ICD-9 187, penis and other male genital organs—to be considered with testis as other male reproductive organs (excluding prostate).
- ICD-9 189.3–189.9, urethra, paraurethral glands, and other and unspecified urinary—rarely reported individually and not as yet seen for the chemicals on interest; would be considered with bladder cancer.
- ICD-9 190, eye—to be considered with brain and other parts of nervous system.
- ICD-9 193, thyroid—to be considered with thymus and other endocrine cancers.
- ICD-9 194, other endocrine cancers—to be considered with thyroid and thymus as endocrine cancers.
- ICD-9 195, other and ill-defined sites—rarely reported individually and not as yet seen for the chemicals on interest; would be considered with other and unspecified cancers.
- ICD-9, 196–198, stated or presumed to be secondary of specified sites—rarely reported individually and not as yet seen for the chemicals on interest; would be considered with other and unspecified cancers.
- ICD-9, 199, site unspecified—rarely reported individually and not as yet seen for the chemicals on interest; would be considered with other and unspecified cancers.

This committee's search of previously reviewed studies for results on tonsil cancer and AML also identified sets of previously considered papers with reported findings specifically on lip cancer (ICD-9 140) and on tongue cancer (ICD-9 141), which both fall within the range for cancers of the oral (buccal) cavity. The current update includes separate sections discussing the site-specific results. In future updates, however, findings for these sites will be tracked on the results tables for the broader grouping that contains them: buccal cavity, nose, and pharynx (ICD-9 140–149, 160) for tonsil, tongue, and lip, and leukemias (ICD-9 204–208) for AML. For the digestive cancers, in future updates esophageal, stomach, colorectal, hepatobiliary, and pancreatic cancers will be broken out into sections with individual conclusions. Care will be taken to specify as precisely as possible in results tables when findings are being reported for a subsite of a particular grouping.

ORAL, NASAL, AND PHARYNGEAL CANCER

Oral, nasal, and pharyngeal cancers (ICD-9 140–149, 160) are found in many anatomic subsites, including the structures of the mouth (inside lining of the lips, cheeks, gums, tongue, and hard and soft palate) (ICD-9 140–145), oropharynx (ICD-9 146), nasopharynx (ICD-9 147), hypopharynx (ICD-9 148), other buccal cavity and pharynx (ICD-9 149), and nasal cavity and paranasal sinuses (ICD-9 160). Although those sites are anatomically diverse, cancers that occur in the nasal cavity, oral cavity, and pharynx are for the most part similar in descriptive epidemiology and risk factors. The exception is cancer of the nasopharynx, which has a different epidemiologic profile.

The American Cancer Society (ACS) estimated that about 30,990 men and women would receive a diagnosis of oral, nasal, or pharyngeal cancer in the United States in 2006 and 7,430 men and women would die from these diseases (Jemal et al., 2006). Almost 91% of those cancers originate in the oral cavity or oropharynx. Most oral, nasal, and pharyngeal cancers are squamous-cell carcinomas. Nasopharyngeal carcinoma (NPC) is the most common malignant tumor of the nasopharynx; it is relatively rare in the United States, where it accounts for about 0.25% of all cancers. There are three types of NPC: keratinizing squamous-cell carcinoma, nonkeratinizing carcinoma, and undifferentiated carcinoma.

The average annual incidences reported in Table 6-2 show that men are at greater risk than women for those cancers and that the incidences increase with age, although there are few cases, and care should be exercised in interpreting the numbers. Tobacco and alcohol use are established risk factors for oral and pharyngeal cancers. Reported risk factors for nasal cancer include occupational exposure to nickel and chromium compounds (Hayes, 1997), wood dust (Demers et al., 1995), and formaldehyde (Blair and Kazerouni, 1997).

TABLE 6-2 Average Annual Incidence (per 100,000) of Nasal, Nasopharyngeal, Oral Cavity and Pharynx, and Oropharynx Cancers in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Nose, Nasal Cavity, and Middle Ear:									
Males	1.2	1.1	1.2	1.6	1.5	1.8	2.0	2.0	3.0
Females	0.6	0.6	0.4	1.0	1.1	0.3	1.1	1.1	1.6
Nasopharynx:									
Males	1.8	1.0	1.7	2.3	1.5	1.8	3.1	1.6	4.5
Females	0.7	0.3	0.8	0.6	0.3	0.3	1.2	0.6	0.4
Oral Cavity and Pharynx:									
Males	28.4	27.6	42.0	37.2	36.4	53.1	47.9	47.3	66.1
Females	9.2	8.7	11.6	12.6	12.7	15.5	17.3	17.5	19.0
Oropharynx:									
Males	1.0	0.8	3.1	1.1	1.0	3.2	2.2	2.0	6.5
Females	0.1	0.1	0.2	0.6	0.5	1.8	0.2	0.2	0.0

[a] SEER(Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and oral, nasal, and pharyngeal cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Studies evaluated previously and in this report are summarized in Table 6-3.

TABLE 6-3 Selected Epidemiologic Studies—Oral, Nasal, and Pharyngeal Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds (oral cavity and pharynx)		
	Never	33	0.9 (0.6–1.3)
	Ever	15	0.5 (0.3–0.9)
Alavanja et al., 2005	US Agriculture Health Study—incidence (buccal cavity)		
	Private applicators (men and women)	66	0.7 (0.5–0.8)
	Lip	25	1.4 (0.9-2.1)
	Spouses of private applicators (>99% women)	14	0.7 (0.4–1.2)
	Lip	2	1.4 (0.2–5.1)
	Commercial applicators (men and women)	5	0.9 (0.3–2.2)
	Lip	3	2.7 (0.6–8.0)
Blair et al., 2005a	US Agriculture Health Study (buccal cavity and pharynx)		
	Private applicators (men and women)	5	0.3 (0.1–0.7)
	Spouses of private applicators (>99% women)	0	0.0 (0–25.4)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women) (ICD-9 140–149)	2	2.8 (0.3–9.9)
	Lip (ICD-9 140)	0	*
	Mouth (ICD-9 141–145)	2	5.4 (0.7–20)
	Oropharynx (ICD-9 146)	0	*
	Nasopharynx (ICD-9 147)	0	0.0 (0.0–42)
	Hypopharynx and other (ICD-9 148–149)	0	*
	Phenoxy herbicide sprayers (>99% men) (ICD-9 140–149)	1	1.0 (0.0–5.7)
	Lip (ICD-9 140)	0	*
	Mouth (ICD-9 141–145)	0	0.0 (0.0–7.5)
	Oropharynx (ICD-9 146)	0	*
	Nasopharynx (ICD-9 147)	1	8.3 (0.2–46)
	Hypopharynx and other (ICD-9 148–149)	0	*
Torchio et al., 1994	Italian licensed pesticide users		
	Buccal cavity and pharynx	18	0.3 (0.2–0.5)
Reif et al., 1989	New Zealand forestry workers—incidence		
	Buccal cavity	3	0.7 (0.2–2.2)
	Nasopharyngeal	2	5.6 (1.6–19.5)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators		
	Nose	0	—
	Mouth and pharynx	0	—
Nordby et al., 2004	Norwegian farmers born 1925–1971—incidence, lip		
	Reported pesticide use	*	0.7 (0.4–1.0)
Studies Reviewed in *Update 2000*			
Caplan et al., 2000	Case–control study of US males born 1929–1953, all 70 nasal cancers (carcinomas, plus 11 lymphomas and 5 sarcomas) from CDC (1990a) study population		
	Selected landscaping and forestry occupations	26	1.8 (1.1–3.1)
	Living or working on farm	23	0.5 (0.3–0.8)
	Herbicides or pesticides	19	0.7 (0.4–1.3)
	Phenoxy herbicides	5	1.2 (0.4–3.3)
Studies Reviewed in *Update 1998*			
Hooiveld et al., 1998	Workers at Dutch chemical factory (lip, oral cavity, pharynx)		
	All working any time 1955–1985	1	2.3 (0.1–12.4)
	Cleaned up 1963 explosion	1	7.1 (0.2–39.6)
Rix et al., 1998	Danish men and women paper mill workers		
	Buccal cavity (ICD-7 140–144)		
	Men	24	1.0 (0.7–1.5)
	Women	4	1.5 (0.4–3.8)
	Pharynx (ICD-7 145–149)		
	Men	15	2.0 (1.1–3.3)
	Women	2	2.1 (0.2–7.6)
	Tonsil cancers among pharyngeal cancers	11	
Kogevinas et al., 1997	IARC cohort (males and females)—Workers exposed to any phenoxy herbicide or chlorophenol		
	Oral cavity and pharynx cancer (ICD-9 140–149)	26	1.1 (0.7–1.6)
	Exposed to TCDD	22	1.3 (0.8–2.0)
	Not exposed to TCDD	3	0.5 (0.1–1.3)
	Nose and nasal sinuses cancer (ICD-9 160)	3	1.6 (0.3–4.7)
	Exposed to TCDD	0	0.0 (0.0–3.5)
	Not exposed to TCDD	3	3.8 (0.8–11.1)
Studies Reviewed in *Update 1996*			
Becher et al., 1996	German phenoxy herbicide production workers (Included in the IARC cohort)		
	Buccal cavity, pharynx (ICD-9 140–149)	9	3.0 (1.4–5.6)
	Tongue	3	*
	Floor of mouth	2	*
	Tonsil	2	*
	Pharynx	2	*
Asp et al., 1994	Finnish herbicide applicators		
	Buccal and pharynx (ICD-8 140–149)		
	Incidence	5	1.0 (0.3–2.3)
	Mortality	0	0.0 (0.0–3.0)
	"Other Respiratory" (ICD-8 160, 161, 163)—Nose, larynx, pleura		

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Incidence	4	1.1 (0.3–2.7)
	Mortality	1	0.5 (0.0–2.9)
Studies Reviewed in *VAO*			
Blair et al., 1993	White male farmers from 23 state—deaths 1984–1988		
	Lip	21	2.3 (1.4–3.5)
Ronco et al., 1992	Italian farmers (lip, tongue, salivary glands, mouth, pharynx)—mortality		
	Self-employed	13	0.9 (*)
	Employees	4	0.5 (*)
	Danish self-employed farmers—incidence		
	Lip	182	1.8 ($p < 0.05$)
	Tongue	9	0.6 (*)
	Salivary glands	13	0.9 (*)
	Mouth	14	0.5 ($p < 0.05$)
	Pharynx	13	0.3 ($p < 0.05$)
	Nasal cavities and sinuses	11	0.6 (*)
	Danish farming employees—incidence		
	Lip	43	2.1 ($p < 0.05$)
	Tongue	2	0.6 (*)
	Salivary glands	0	0.0 (*)
	Mouth	0	0.0 ($p < 0.05$)
	Pharynx	9	1.1 (*)
	Nasal cavities and sinuses	5	1.3 (*)
Saracci et al., 1991	IARC cohort—exposed subcohort (males and females)		
	Buccal cavity and pharynx (ICD-8 140–149)	11	1.2 (0.6–2.1)
	Nose and nasal cavities (ICD-8 160)	3	2.9 (0.6–8.5)
Zober et al., 1990	BASF Aktiengesellschaft accident cohort—33 cancers among 247 workers at 34-yr follow-up		
	Squamous-cell carcinoma of tonsil	1	*
Wiklund et al., 1989a	Licensed Swedish pesticide applicators—incidence		
	Lip	14	1.8 (1.0–2.9)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)		
	Lip (ICD-9 140)	0	*
	Tongue (ICD-9 141)	1	1.1 (0.0–6.2)
	Pharynx (ICD-9 146–149)	1	0.5 (0.0–3.0)
	Nose (ICD-9 160)	3	4.9 (1.0–14.4)
Robinson et al., 1986	Northwestern US Paper and pulp workers		
	Buccal cavity and pharynx (ICD-7 140–148)	1	0.1 (0.0–0.7)
	Nasal (ICD-7 160)	0	—*
Wiklund, 1983	Swedish men and women agricultural workers—incidence		
	Lip	508	1.8 (1.6–2.1)
	Tongue	32	0.4 (0.2–0.6)
	Salivary glands	68	1.0 (0.7–1.4)
	Mouth	70	0.6 (0.5–0.8)
	Throat	84	0.5 (0.4–0.7)
	Nose and nasal sinuses	64	0.8 (0.6–1.2)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Hardell et al., 1982	Residents of northern Sweden (44 nasal and 27 naso-pharyngeal cancers)		
	Phenoxy acid exposure	8	2.1 (0.9–4.7)
	Chlorophenol exposure	9	6.7 (2.8–16.2)
Burmeister et al., 1981	Iowa farmers—deaths 1971–1978		
	Lip	20	2.1 ($p < 0.01$)
ENVIRONMENTAL			
Studies Reviewed in *VAO*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Buccal cavity (ICD-9 140–149)		
	Zone B—Men	6	1.7 (0.8–3.9)
	Women	0	—*
	Zone R—Men	28	1.2 (0.8–1.7)
	Women	0	—*
	Nose and nasal cavity (ICD-9 160)		
	Zone R—Men	0	—*
	Women	2	2.6 (0.5–13.3)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence		
	Head and neck	247	1.5 (1.3–1.6)
	Navy	56	1.6 (1.1–2.0)
	Army	174	1.6 (1.3–1.8)
	Air Force	17	0.9 (0.5–1.5)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—Mortality		
	Head and neck	101	1.4 (1.2–1.7)
	Navy	22	1.5 (0.9–2.1)
	Army	69	1.5 (1.1–1.8)
	Air Force	9	1.1 (0.5–2.0)
	Nasal	3	0.8 (0.2–2.2)
ADVA, 2005c	Australian conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Head and neck		
	Incidence	44	2.0 (1.2–3.4)
	Mortality	16	1.8 (0.8–4.3)
	Nasal		
	Mortality	0	0.0 (0.0–48.2)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (ICD-9 140–149)	6	*
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	White AFHS subjects vs national rates (buccal cavity)		
	Ranch Hand veterans		
	Mortality—All	0	0.0 *
	Incidence—All	6	0.9 (0.4–1.9)
	With tours between 1966–1970	6	1.1 (0.5–2.3)
	Comparison veterans		

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Mortality—All	1	0.5 *
	Incidence—All	5	0.6 (0.2–1.2)
	With tours between 1966–1970	4	0.6 (0.2–1.4)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force veterans participating in 1997 exam cycle, Ranch Hands vs Comparisons		
	Oral cavity, pharynx, and larynx	4	0.6 (0.2–2.4)
Studies Reviewed in Update 1998			
CDVA, 1997a	Australian Vietnam veterans vs Australian population —incidence		
	Lip (ICD-9 140)	0	*
	Nasopharyngeal cancer (ICD-9 147)	2	0.5 (0.1–1.7)
	Nasal cavities (ICD-9 160)	2	1.2 (0.1–4.1)
CDVA, 1997b	Australian conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		
	Nasopharyngeal cancer	1	1.3 (0.0– >10)
	Nasal cavities	0	0 (0.0– >10)
Vistainer et al., 1995	Michigan Vietnam veterans (lip, oral cavity, pharynx)		
	Non-blacks	11	1.1 (0.5–1.9)
Studies Reviewed in *VAO*			
CDC, 1990a	Case-control study of US males born 1929–1953		
	89 nasopharyngeal carcinomas		
	Vietnam service	3	0.5 (0.2–1.8)
	62 nasal carcinomas		
	Vietnam service	2	0.7 (0.2–2.9)

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational International Agency for Research on Cancer (IARC) cohort of 60,468 pulp and paper industry workers. A job–exposure matrix (JEM) was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Deaths from cancers of the oral cavity and pharynx were significantly fewer among those who had been exposed to nonvolatile organochlorine compounds (n = 15; standardized mortality ratio [SMR] = 0.51, 95% confidence interval [CI] 0.29–0.85) but not among those who had never been exposed (n = 33; SMR = 0.92, 95% CI 0.63–1.29).

Alavanja et al. (2005) reported that among the private pesticide applicators in the Agricultural Health Study (AHS), there were 66 cases of buccal-cavity cancer, which represented a significant deficit compared with the general population (standardized incidence ratio [SIR], 0.66, 95% CI 0.51–0.83). The corresponding results for commercial pesticide applicators were based on much smaller numbers of cases, so the confidence interval on the SIR was wide. Among the spouses of

private applicators, the SIR for buccal cavity cancer was 0.73 (95% CI 0.40–1.22) on the basis of 14 cases. Nasal and pharyngeal cancers were not explicitly reported in the study, but the portion of them that were specifically lip cancers was analyzed (see below).

Using death as the outcome among participants in the AHS, Blair et al. (2005a) reported five deaths from buccal-cavity and pharyngeal cancers combined in the private applicators, indicating a significant reduction in mortality (SMR = 0.3, 95% CI 0.1–0.7). There were no deaths from these cancers among spouses of applicators.

't Mannetje et al. (2005) reported results for lip, oral cavity, and pharynx combined (ICD-9 140–149), which represented two deaths from cancer of unspecified parts of the mouth (ICD-9 141–145) observed among the production workers and one from nasopharyngeal cancer (ICD-9 147) observed among the sprayers.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users from the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and (4-chloro-2-methylphenoxy) acetic acid (MCPA). The risk estimate for cancer of the buccal cavity and pharynx was significantly reduced (18 cases; SMR = 0.34, 95% CI 0.2–0.5). The authors suggested that the healthy-worker effect contributed to the observation of reduced mortality.

Reif et al. (1989) performed a series of case–control analyses on a sample of 19,904 men entered into the New Zealand Cancer Registry from 1980–1984 with an occupation specified. They focused on the 134 registrants for whom forestry worker (presumed to be exposed to phenoxyherbicides and chlorophenols) was the most recent occupation. The three forestry workers among the 649 cases with cancer of the buccal cavity did not constitute an excess (odds ratio [OR] = 0.71, 95% CI 0.23–2.19). However, two forestry workers among the 49 cases of nasopharyngeal cancer (OR = 5.56, 95% CI 1.59–19.48) did represent a significantly increased risk.

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and oral, nasal, or pharyngeal cancers were published since *Update 2004*.

Vietnam-Veteran Studies

The report titled *Cancer Incidence in Australian Vietnam Veterans Study 2005* (ADVA, 2005a) noted 247 head and neck cancers, including cancers of the tongue, gum, mouth, palate, salivary glands, tonsil, oropharynx, and nasopharynx. There was a significant increase in the incidence of head and neck cancers (SIR = 1.48, 95% CI 1.29–1.66). The results were equivalent in Navy veterans (SIR = 1.55, 95% CI 1.14–1.95) and Army veterans (SIR = 1.55, 95% CI 1.32–1.78), but the association was considerably weaker in Air Force veterans (SIR = 0.93, 95% CI 0.54–1.49).

On the basis of 101 observed deaths from head and neck cancer, *The Third Australian Vietnam Veterans Mortality Study 2005* (ADVA, 2005b) reported a significant increase in the Vietnam-veteran cohort (SMR = 1.44, 95% CI 1.16–1.73). There were 69 cases of head and neck

cancer in the Army veterans (SMR = 1.49, 95% CI 1.14–1.84), 22 cases in the Navy veterans (SMR = 1.49, 95% CI 0.87–2.10), and nine in the Air Force veterans (SMR = 1.09, 95% CI 0.49–2.03). Those cancers were previously found to be somewhat increased in an earlier mortality study of the same cohort; CDVA (1997a) reported an SMR of 1.2 (95% CI 0.2–4.4) for nasal cancers.

In commenting on the statistically significant roughly 50% increase in both incidence and mortality from head and neck cancers among the Australian Vietnam veterans, the authors noted that these cancers are associated with cigarette-smoking and alcohol use, but neither of these risk factors was measured or adjusted for in the reports. They commented that alcohol consumption is higher among servicemen than in the general population and that if cigarette-smoking were increased in this cohort, it also could explain some of the observed increase in head and neck cancers relative to the incidence in the general population.

Another Australian study (ADVA, 2005c), which compared deployed male Army National Service veterans with their non-deployed Vietnam-era counterparts, also reported on head and neck cancers. There were 44 cases among the deployed and 28 cases among the non-deployed, for an increased relative risk (RR) of 2.02 (95% CI 1.23–3.37) in this design aimed at accounting for factors in which the military subjects differed from the general Australian populace. With 16 deaths among the deployed and 11 among the non-deployed, the findings on mortality from head and neck cancers were more equivocal (RR = 1.82, 95% CI 0.79–4.33).

Mortality due to nasal cancer was also listed in the Australian reports, but the numbers observed were too small for estimation of any stable statistics: three cases in all the Australian Vietnam veterans (ADVA, 2005b) and no deaths from nasal cancer in the deployed and one in the non-deployed (ADVA, 2005c).

In the mortality update through 2000 on the Centers for Disease Control and Prevention (CDC) Vietnam Experience Study (VES) comparing deployed and non-deployed Vietnam-era veterans, Boehmer et al. (2004) reported six cases of lip, oral-cavity, or pharynx cancer (ICD-9 140–149) in the deployed and three in the non-deployed, for a crude RR of 2.0. The researchers did not consider the data sufficient for the calculation of risk statistics unless there were at least 10 deaths from cancer of a given type.

Biologic Plausibility

A recent National Toxicology Program (NTP) study (Yoshizawa et al., 2005a) reported an increase in the incidence of gingival squamous-cell carcinoma in female rats treated orally (by gavage) with TCDD at 100 ng/kg 5 days/week for 104 weeks. Incidences of gingival squamous-cell hyperplasia were significantly increased in all groups treated at 3–46 ng/kg. In addition, squamous-cell carcinoma in the oral mucosa of the palate was increased. Increased neoplasms of the oral mucosa were previously observed and described as carcinomas of the hard palate and nasal turbinates (Kociba et al., 1978). Kociba et al. (1978) also reported a small increase in the incidence of tongue squamous-cell carcinoma. A similar 2-year study performed in female rats failed to reveal a pathologic effect of TCDD on nasal tissues (Nyska et al., 2005). The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

The new occupational studies of cancers of the oral and nasal cavities or pharynx were generally small and so yielded unstable estimates of risk. Integration of the evidence on this set of cancers is challenging because different studies groupes cases differently. The significant results found in the AHS population of pesticide applicators (the incidence of buccal-cavity cancers in private applicators in the Alavanja study and mortality from buccal-cavity and pharyngeal cancers in the Blair study) were in the direction of deficits rather than excess risk associated with exposure. Studies on Australian Vietnam veterans showed some increases in risk, but the results were not adjusted for cigarette-smoking or alcohol use, both of which are known risk ractors.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and oral, nasal, or pharyngeal cancers.

At the request of VA, the committee attempted to ensure that the conditions making up the full array of relevant cancer types had been reviewed and reported on with the greatest appropriate degree of specificity. The results suggested that some of the head and neck cancers that have been considered together in this section starting with the original *VAO* report might merit more individualized consideration. Such a review is complicated, however, by the fact that a specific cancer type may have been implicitly subsumed in broader groupings, particularly when no cases of the specific type were observed in a given study. The following subsections, therefore, address the cumulative evidence that lip cancer, tongue cancer, or tonsil cancer might individually be associated with exposure to the herbicides used in Vietnam.

Lip Cancer

In the committee's review, at VA's request, for cancers may have been overlooked, a number of reported results were found specifically on lip cancer (ICD-9 140). They are evaluated as a group in this section, and information peculiar to lip cancer has been incorporated into Table 6-3, which presents the overall epidemiologic findings on oral, nasal, and pharyngeal cancers.

In addition to the risk factors for oral and pharyngeal cancers discussed above, exposure to sunlight is a risk factor for lip cancer.

Conclusions from VAO and Updates

This update considers lip cancer independently for the first time. Prior updates considered lip cancer only as a possible component of the various types of cancer grouped as oral, nasal, and

pharyngeal cancers, the evidence on which has been judged to be inadequate to support an association with exposure to the herbicides used in Vietnam.

Summary of the Epidemiologic Literature

Occupational Studies Burmeister (1981) reported cancer mortality from 1971 to 1978 in Iowa male farmers and non-farmer. Farming was defined according to the usual occupation as indicated on the death certificates. Both SMRs and proportional mortality ratios (PMRs) were computed. The SMR for lip cancer was 2.06 ($p < 0.01$); the PMR for white male farmers less than 65 years old was 4.65 (not significant), and the PMR for white male farmers 65 years old and older was 1.51 ($p < 0.05$). The combined PMR over all ages was 1.62 ($p < 0.01$). There were 20 lip-cancer deaths in farmers and 11 in non-farmer. There was no specific exposure information on the participants in the study, beyond that inferred from the indication of usual occupation on the death certificates.

Wiklund (1983) linked Sweden's National Cancer Registry with information from the 1960 census. The census categorization of occupation was determined for tumors diagnosed in the period 1961–1973. Some 19,490 persons were registered as having agriculture as their economic activity although no direct pesticide or herbicide exposure is necessarily inferred. The results showed 508 cases of lip cancer, leading to an SIR of l.83 (95% CI 1.62–2.05); similarly, for males alone the SIR was 1.82.

Wiklund et al. (1989a) studied 20,245 licensed Swedish pesticide applicators whose licenses were issued in 1965–1976. The vast majority of cohort members were male. Overall, the cohort had a significantly decreased SIR for all cancers combined and for several specific cancers. There were no statistically significant increases in risk for any cancers or any time trends. For lip cancer, there were 14 observed cases (SIR = 1.75, 95% CI 0.96–2.94).

Blair et al. (1993) analyzed deaths occurring in 23 states in 1984–1988. PMRs were calculated by sex and race for farmers, who were people whose death certificates indicated farming as their usual occupation and agricultural crop products or livestock as their industry. White men had a PMR of 2.31 (95% CI 1.43–3.53) on the basis of 21 lip-cancer cases. The findings for other race–sex groups were not significant and consisted of only one case. The authors noted that their mortality risk estimates in general were more likely to be underestimated than overestimated because of misclassification of disease and occupation. Those effects are thought to be more severe than any increase in risk associated with the use of proportional rather than absolute mortality analyses. It should be noted that this study has no specific data on pesticide or herbicide exposures beyond an indirect inference associated with the death-certificate occupation.

Nordby et al. (2004) reported on a cohort study of lip cancer in farmers in Norway born in 1925–1971. They were followed until 1999 to identify incident cases of lip cancer by using the national cancer registry in Norway. Exposure of cohort members was assessed through proxy measures, such as farm production, weather and fungal forecasts, and pesticide use (not peculiar to any particular agent). The results showed a statistically significantly reduced risk of lip cancer associated with exposure to pesticides. The lip-cancer rate among those not reporting pesticide use was 4.9 per 100,000 person-years, and the corresponding figure for pesticide users was 3.7. A multivariate model was fitted to examine the effects of pesticide use and other factors, including

grain farming, fungal forecasts, horses on the farm, and engagement of the farmer in the construction industry. The RR associated with pesticide use in this model was 0.7 (95% CI 0.4–1.0). The authors speculate that the reduction in risk might be associated with exposure to immunosuppressive mycotoxins, in which case pesticides would reduce the farmers' burden of exposure by reducing mold growth. There may also be effects of sun exposure in this occupational group.

Among the private pesticide applicators in the AHS, Alavanja et al. (2005) report 25 cases of lip cancer (SIR = 1.43, 95% CI 0.93–2.11). There were two lip-cancer cases in the spouses of private applicators and three in commercial applicators; the SIRS were modestly increased with very wide confidence intervals. Mortality from lip cancer was not reported in the companion AHS study (Blair et al., 2005b).

Environmental Studies No new environmental studies concerning exposure to the compounds of interest and lip cancer were published since *Update 2004*.

Vietnam-Veteran Studies The Australian veterans cohort study (CDVA, 1997a) reported that no deaths from lip cancer were observed. The updated study of mortality in Australian Vietnam veterans (ADVA, 2005b) does not mention lip cancer.

Synthesis

The studies reporting on lip cancer that were identified by the committee's retrospective screen for results on rare cancers in the publications considered previously in the *VAO* series generally had very low specificity with respect to exposure to the compounds of interest. Exposure status was defined almost exclusively in terms of occupation, and even the determination of occupation usually could not be regarded as rigorous. In most instances, occupation was not stringently defined and was ascertained at only one time (for example, in a census or on a death certificate).

Studies that use computer techniques to link records in comprehensive databases, such as those matching entries in tumor registries with compendiums of national censuses, amass large samples that may have the effect of inflating power. Such investigations are useful for generating hypotheses, but suggestive findings must be replicated by studies with more refined designs that are capable of gathering more extensive information about the subjects to use in adjusting for confounders.

The certainty of the diagnostic categories may also be dubious when information is culled directly from death certificates or other databases. For lip cancer, in particular, it is unclear to what extent this diagnostic category would overlap with non-melanoma skin cancers in the sources from which the information was gathered for the studies discussed here.

For lip cancer, it would be important to adjust for smoking and sunlight exposure before inferring that agricultural chemicals (perhaps in the family of phenoxy herbicides) played a role in any observed association in an occupational group. Such adjustment was not part of the analyses

conducted in the studies discussed here that reported increased risks of lip cancer in occupational groups that had theoretical exposure to the compounds of interest.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and lip cancer.

Tongue Cancer

In the committee's review, at VA's request, for cancers that may have been overlooked, a number of reported results were found specifically on tongue cancer (ICD-9 141). They are evaluated as a group in this section, and information peculiar to tongue cancer has been incorporated into Table 6-3, which presents the overall epidemiologic findings on oral, nasal, and pharyngeal cancers.

Conclusions from VAO and Updates

This update considers tongue cancer independently for the first time. Prior updates considered tongue cancer only as a possible component of the various types of cancer grouped as oral, nasal, and pharyngeal cancers, the evidence on which has been judged to be inadequate to support an association with exposure to the herbicides used in Vietnam.

Summary of the Epidemiologic Literature

Occupational Studies Among the 331,767 Swedish people who received a diagnosis of a malignant tumor in 1961–1973, Wiklund (1983) found 19,490 with agriculture indicated as their economic activity on the Swedish census. Direct pesticide or herbicide exposure cannot necessarily be inferred. The 32 cases of tongue cancer yielded a risk significantly below the null ratio of 1 (SIR = 0.40, 95% CI 0.24–0.61). The SIR for males alone was 0.35.

Coggon et al. (1986) described the mortality and cancer experience of workers at a factory that manufactured, formulated, and sprayed MCPA and other phenoxy acid herbicides. Overall mortality in 5,784 men employed in the company during 1947–1975 was traced until the end of 1983 and was shown to be lower than that in the national population; the picture was similar for cancer mortality. The single observed death due to tongue cancer—very close to the expected number—led to an SMR of 0.96 with a very wide CI. An adjustment for the overall difference between urban and rural mortality led to similar results.

Green (1991) conducted a cohort mortality study of forestry workers at a public electric utility in Ontario; cohort members had worked for more than 6 months during 1950–1982 and were routinely exposed to herbicides. The general population was used as a comparison. There was no

overall excess mortality compared with that in the reference population. Only a single death from tongue cancer was observed; no site-specific SMR was computed. The authors noted that members of the cohort were generally still young, and at the end of the study follow-up period most participants had not reached ages at which the incidence of cancer would usually increase. Consequently, this study may have had relatively low power. The specific pattern of herbicide use by Ontario Hydro (the study employer) was described in some detail, but there are no direct linkages of exposure to individual study participants.

Ronco et al. (1992) reported nine cases of tongue cancer among men self-employed as farmers in Denmark with an SIR of 0.58 and two cases among male farm employees with an SIR of 0.63; neither result is statistically significant. There were no incident cases of tongue cancer among Danish women.

Environmental Studies No new environmental studies concerning exposure to the compounds of interest and tongue cancer were published since *Update 2004*.

Vietnam-Veteran Studies The Australian Veteran Cohort Study (CDVA, 1997a) investigated mortality in Australian veterans who had served in Vietnam. There were 17 deaths from tongue cancer, with a calculated SMR of 2.53. The standardized relative mortality ratio (SRMR), the SMR for a specific cancer site divided by the SMR for all other causes of death combined, was 2.34 (95% CI 1.46–3.84) and suggested a risk increase relative to the risk of other causes of death.

Synthesis

Interpretation of the evidence on tongue cancer is constrained by the grouping of data on them with data on other oral cancers. Most of the studies with information on this specific tumor site observed only a small number of cases and therefore had unstable estimates of risk.

Conclusion

On the basis of its evaluation of the epidemiologic evidence reviewed retrospectively here on tongue cancer alone, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and tongue cancer.

Tonsil Cancer

VA asked that the committee undertake a focused examination of what information might be available on cancer of the tonsil (ICD-9 146.0–146.2), which constitutes a portion of the oropharynx (ICD-9 140). Tonsil cancer may also arise in proximal areas of the oral and throat

region, including the soft palate (ICD-9 145.3), the adenoid and the pharyngeal tonsil in the posterior pharyngeal wall (ICD-9 147.1), the base of the tongue (ICD-9 141.0), and the lingual tonsil (ICD-9 141.6). Tonsil cancers are usually classified as squamous-cell carcinomas, but the cell types found in biopsy tissue occasionally lead oral pathologists to classify some as sarcomas or lymphomas (Mayo Clinic, 2007). Tonsil cancer is somewhat more common in men than inwomen, and smoking and alcohol may increase the risk.

The committee screened the studies that contributed results on the cancer types discussed in prior updates for results on tonsil cancer. The committee's findings are discussed below, and information peculiar to tonsil cancers has been incorporated into Table 6-3, which presents the overall epidemiologic findings on oral, nasal, and pharyngeal cancers.

Conclusions from VAO and Updates

This update considers tonsil cancer independently for the first time. Prior updates considered tonsil cancer only as a possible component of the various types of cancer grouped as oral, nasal, and pharyngeal cancers, the evidence on which has been judged to be inadequate to support an association with exposure to the herbicides used in Vietnam.

Summary of the Epidemiologic Literature

Zober et al. (1990) noted that a squamous-cell carcinoma of the tonsil was among the 33 cancers diagnosed in 247 workers exposed during an accident at the BASF plant in Aktiengesellschaft 34 years earlier.

Becher et al. (1996) conducted an occupational cohort study of 2,479 workers in four industrial plants in Germany, which did not include the factory reported on by Zober et al. (1990). The factories produced various herbicides, including those known to have been contaminated with TCDD. High dioxin and furan exposures have been documented by blood fat measurements in two of the four plants. In one of the factories where TCDD contamination was so documented, one case of tonsil cancer was observed in a group of buccal-cavity and pharyngeal cancers (ICD-9 140–149), which as a group had a non-significantly increased SMR of 1.78.

Rix et al. (1998) studied a cohort of 14,362 workers at Danish paper mills employed during 1943–1990. There were 17 cases of pharyngeal cancer (ICD-7 145–148) in the cohort: 15 in men (SIR = 1.99, 95% CI 1.11–3.29) and two in women. The authors report that 11 of the 17 were in the tonsils, so the RR of tonsil cancers in particular would be about twice the corresponding RR for pharyngeal cancers as a whole.

No new environmental or Vietnam-veteran studies concerning exposure to the compounds of interest and tonsil cancer were published since *Update 2004*.

Synthesis

Among all the cohort studies of populations potentially exposed to the compounds of interest reviewed by *VAO* committees, only Rix et al. (1998), Becher et al. (1996), and Zober et al. (1990)

specifically stated an exact number of tonsil-cancer cases observed, as opposed to grouping them with the more general classification of oral, nasal, or pharyngeal cancers. The paucity of findings specifically related to tonsil cancer is a consequence of the extreme rarity of this type of cancer and its occurrence in an anatomic region whose cancers are generally grouped fairly idiosyncratically. That the tissue type developing into a neoplasm at this location might generate a carcinoma, a lymphoma, or a sarcoma has further constrained the committee's ability to assemble a meaningful body of evidence addressing risk factors for this unusual type of cancer. A case–control protocol would probably be more effective in determining whether tonsil cancer is associated with exposure to the herbicides used in Vietnam, but we have been unable to locate any publications reporting studies of this design. Anecdotal reports from veterans to VA suggest that the tonsil might be responsive to their exposure experience in Vietnam, but the likelihood of evaluating such an association convincingly is small unless primary research is conducted to address it specifically.

Conclusion

The committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and tonsil cancer.

CANCERS OF THE DIGESTIVE ORGANS

Until this update, *VAO* committees have reviewed "gastrointestinal tract tumors" as a group consisting of stomach, colorectal, and pancreatic cancers, with esophageal cancer being formally factored in only by *Update 2004*. These cancers are often subsumed under "cancers of the digestive organs", a classification that traditionally includes "hepatobiliary cancers", which have been considered separately by previous *VAO* committees. With evidence from occupational studies now available, this update and future updates will address cancers of the digestive organs individually. This section presents findings from reports since the last review that have considered cancers of the digestive organs as a group (ICD-9 150–159), which is in practice too broad for etiologic analyses; it then presents updated and integrated information on individual types of digestive cancer.

Esophageal cancer (ICD-9 150), stomach cancer (ICD-9 151), colon cancer (ICD-9 153), rectal cancer (ICD-9 154), and pancreatic cancer (ICD-9 157) are among the most common cancers. ACS estimated that about 219,170 people would receive diagnoses of those cancers in the United States in 2006, and 112,670 people would die from them (Jemal et al., 2006). When other digestive cancers (for example, small intestine, anal, and hepatobiliary) were included, the 2006 estimates for the United States were about 263,060 new diagnoses and 136,180 deaths (Jemal et al., 2006). Collectively, tumors of the digestive organs were expected to account for 19% of new diagnoses and 24% of cancer deaths in 2006. The average annual incidences of gastrointestinal cancers are presented in Table 6-4.

TABLE 6-4 Average Annual Incidence (per 100,000) of Selected Gastrointestinal Cancers in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Stomach:									
Males	9.2	8.0	15.9	15. 6	14.0	20.9	25.6	22.8	42.5
Females	4.7	3.6	9.2	6.9	5.7	11.3	10.5	8.5	18.6
Esophagus:									
Males	9.5	9.5	13.7	16.6	16.2	30.1	23.8	23.9	33.0
Females	1.8	1.3	6.3	3.3	2.8	9.5	5.3	5.0	11.7
Colon (excluding the rectum):									
Males	35.3	33.7	52.1	59.7	57.5	88.8	99.9	96.3	154.6
Females	27.6	25.3	43.4	43.9	40.7	74.3	71.9	69.3	112.2
Rectum and rectosigmoid junction:									
Males	24.4	23.6	26.8	35.5	35.2	32.9	52.3	51.8	48.5
Females	14.7	13.8	18.9	22.1	21.7	29.7	28.1	27.8	35.9
Liver and Intrahepatic Bile Duct:									
Males	16.4	12.6	33.8	18.4	13.7	38.2	23.2	17.0	30.5
Females	2.9	2.2	4.9	4.7	3.6	9.2	7.9	5.6	8.9
Pancreas:									
Males	12.5	12.2	20.3	21.4	20.4	34.7	33.8	33.5	45.5
Females	7.8	7.4	11.4	13.8	13.0	18.1	23.7	22.5	37.6
Small Intestine:									
Males	3.1	3.0	5.1	5.0	4.7	10.6	5.3	5.2	5.5
Females	1.9	1.7	4.9	2.8	2.9	3.3	4.4	4.2	7.3
Anus, Anal Canal and Anorectum:									
Males	2.1	2.0	4.1	2.3	2.5	2.1	3.4	3.5	5.0
Females	2.9	3.2	3.3	3.1	3.2	4.8	3.8	4.2	3.6
Other Digestive Organs:									
Males	0.6	0.4	0.7	0.8	0.9	0.7	1.1	1.1	1.5
Females	0.6	0.6	0.4	0.9	0.9	1.2	0.9	1.0	0.8
Gallbladder:									
Males	0.4	0.4	0.5	0.9	0.7	0.7	1.6	1.7	1.5
Females	1.2	1.1	1.6	1.8	1.8	0.9	3.2	3.2	2.8
Other Biliary:									
Males	1.2	1.0	1.9	2.6	2.5	3.5	4.0	4.0	2.5
Females	1.0	1.0	0.8	1.5	1.4	1.2	3.2	3.4	2.0

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

The incidences of stomach, colon, rectal, and pancreatic cancers increase with age. In general, incidence is higher in men than in women and higher in blacks than in whites. Other risk factors for the cancers vary but always include family history of the same form of cancer, some diseases of the affected organ, and diet. Tobacco use is a risk factor for pancreatic cancer and possibly stomach cancer (Miller et al., 1996). Infection with the bacterium *Helicobacter pylori* increases the risk of stomach cancer. Type 2 diabetes is associated with an increased risk of cancers of the colon and pancreas (ACS, 2006).

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the compounds of interest and gastrointestinal tract tumors (stomach, colon, rectal, and pancreatic tumors; esophageal tumors are included later). The evidence associated with hepatobiliary cancers was judged inadequate to support an association with exposure to the compounds of interest. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change those conclusions.

Update of the Epidemiologic Literature on All Cancers of the Digestive Organs

Occupational Studies

Since the last update, three occupational studies have reported data on all gastrointestinal and hepatic sites analyzed collectively. 't Mannetje et al. (2005) completed a mortality study in New Zealand of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers whose vital status was followed to 2000 from 1969 and 1973, respectively. Among producers and sprayers, rates of digestive cancers overall (including hepatic tumors, ICD-9 150–159) were not higher than expected (for producers: SMR = 1.38, 95% CI 0.77–2.28; for sprayers: SMR = 1.15, 95% CI 0.66–1.87). Reported results on specific tumor sites are discussed in subsections below.

Alavanja et al. (2005) reported cancer incidence in a prospective cohort study of private pesticide applicators, commercial applicators, and spouses of farmer applicators followed for an average of 7.2 years. Cancer cases were identified through cancer registry files in North Carolina and Iowa. The incidence of digestive system cancers (including liver and gallbladder cancers) was significantly lower than expected in private applicators (SIR = 0.83, 95% CI 0.76–0.91) and their spouses (SIR = 0.85, 95% CI 0.72–0.99). The incidence in commercial applicators was close to the expected (SIR = 0.97, 95% CI 0.62–1.44).

Blair et al. (2005a) reported cancer mortality in the same prospective cohort study of pesticide applicators and spouses in North Carolina and Iowa. After an average of only 5.3 years of follow-up, a reduction in the overall risk of digestive cancers was reported in the private applicators (SMR = 0.7, 95% CI 0.6–0.8) and a more modest reduction in their spouses (SMR = 0.9, 95% CI 0.7–1.2).

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and digestive system cancers were published since *Update 2004*.

Vietnam-Veteran Studies

In a set of three reports updating the health status of Australian Vietnam veterans, results concerning possible associations between Vietnam service and gastrointestinal cancers were reported; colorectal and stomach cancers were combined, and hepatobiliary cancers were reported separately. The SIR for gastrointestinal cancers was 1.05 (95% CI 0.97–1.12) when veterans were compared with the general population of Australia (ADVA, 2005a). Mortality from gastrointestinal cancers was unaffected (SMR = 0.96, 95% CI 0.86–1.06) when veterans were compared with the general population (ADVA, 2005b). A separate report compared the rates of gastrointestinal cancer in deployed and non-deployed National Service Vietnam veterans (ADVA, 2005c); the increase in incidence in the deployed did not reach significance (RR = 1.06, 95% CI 0.82–1.36), and the RR of death from gastrointestinal cancer was not increased (RR = 0.81, 95% CI 0.52–1.24).

Pavuk et al. (2005) analyzed the cancer incidence in 1,482 US Air Force veterans who were referent controls for the Ranch Hand subjects in the Air Force Health Study. The veterans had served in Southeast Asia, primarily conducting transport missions while stationed in Taiwan, the Philippines, Guam, Japan, or Thailand. The 24 cases of digestive system cancer (not explicitly defined) yielded an RR of 1.8 (95% CI 0.8–3.9) on the basis of serum TCDD concentrations (the natural logarithm was used in a Cox model). The highest quartile of TCDD (5.2–54.8 pg/g of lipid) was associated with an RR of digestive system cancer of 3.3 (95% CI 0.9–12.5). In contrast, on the basis of the number of years served in Southeast Asia, the overall RR of digestive system cancer was somewhat more convincingly increased (RR = 1.2, 95% CI 1.0–1.4), but the highest quartile for this measure of exposure (3.7–16.4 years) was associated with an RR of 2.1 (95% CI 0.6–7.3). In analyses of Ranch Hand subjects themselves (Akhtar et al., 2004) discussed in *Update 2004*, there was no suggestion of an association between herbicide exposure in Vietnam and digestive system cancers.

Esophageal Cancer

Epithelial tumors of the esophagus (squamous-cell carcinomas and adenocarcinomas) are responsible for more than 95% of all esophageal cancers (ICD-9 150); 14,550 newly diagnosed cases and 13,770 deaths were estimated for 2006 (Jemal et al., 2006). The considerable geographic variation in the incidence of esophageal tumors suggests that multifactorial etiology is responsible. Rates of esophageal cancer have been increasing in the last 2 decades. Adenocarcinoma of the esophagus has slowly replaced squamous-cell carcinoma as the most common type of esophageal malignancy in the United States and western Europe (Blot and McLaughlin, 1999). Squamous-cell esophageal carcinoma is seen more commonly in blacks than in whites and in men than in women. Smoking and alcohol ingestion are also associated with the development of squamous-cell carcinoma. Smoking and alcohol are less well linked to the development of esophageal adenocarcinoma. The rapid increase in obesity in the United States has been linked to increasing rates of gastroesophageal reflux disease (GERD), and the rise in chronic inflammation has been linked to the observed increase in esophageal adenocarcinoma.

Conclusions from VAO and Updates

This update considers esophageal cancer independently for the first time. Prior updates developed a table of results for esophageal cancer, but conclusions about the adequacy of the evidence of its association with herbicide exposure were reached in the context of gastrointestinal tract cancers. Table 6-5 summarizes the results of the relevant studies concerning esophageal cancer.

TABLE 6-5 Selected Epidemiologic Studies—Esophageal Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	27	0.7 (0.4–1.0)
	Ever	26	0.8 (0.5–1.2)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	2	2.0 (0.2–7.0)
	Phenoxy herbicide sprayers (>99% men)	1	0.7 (0.0–4.0)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	16	0.5 (0.3–0.9)
	Spouses of private applicators (>99% women)	1	0.3 (0.1–1.9)
Lee et al., 2004a	Population-based case–control—agricultural pesticide use and adenocarcinoma of the esophagus	137	
	Insecticides		0.7 (0.4–1.1)
	Herbicides		0.7 (0.4–1.2)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence) correspondence	4	1.8 (0.7–4.8)
Magnani et al., 1987	UK case–control		
	Herbicides	*	1.6 (0.7–3.6)
	Chlorophenols	*	1.2 (0.7–2.2)
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	28	1.0 (0.7–1.4)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	20	1.3 (0.8–1.9)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	6	0.5 (0.2–1.1)
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators—incidence	3	1.6 (0.3–4.6)
	Finnish herbicide applicators—mortality	2	1.3 (0.2–4.7)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish farm workers—incidence		
	Male—Self-employed	32	0.4 ($p < 0.05$)
	Employee	13	0.9 (*)
	Female—Self-employed	1	1.4 (*)
	Family worker	2	0.4 (*)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	8	0.6 (0.3–1.2)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	8	0.9 (0.4–1.9)
Wiklund, 1983	Swedish men and women agricultural workers—incidence	169	0.6 (0.5–0.7)
ENVIRONMENTAL			
None			
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	70	1.2 (0.9–1.5)
	Navy	19	1.6 (0.9–2.4)
	Army	40	1.1 (0.7–1.4)
	Air Force	11	1.5 (0.8–2.8)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—Mortality	67	1.1 (0.8–1.3)
	Navy	13	1.0 (0.5–1.7)
	Army	42	1.0 (0.7–1.3)
	Air Force	12	1.5 (0.8–2.6)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	9	1.9 (0.6–6.6)
	Mortality	10	1.3 (0.5–3.6)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	6	1.2 (0.4–4.0)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	23	1.2 (0.7–1.7)
CDVA, 1997b	Australian national service Vietnam veterans	1	1.3 (0.0– >10)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
Studies in *italics* have been superseded by newer studies of the same cohort.
ABBREVIATION: ADVA, Australian Department of Veteran Affairs; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer; ICD-9, *International Classification of Diseases*, Ninth Edition; MCPA, methyl-4- chlorophenoxyacetic acid

Update of the Epidemiologic Literature

Occupational Studies McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Death from esophageal cancer was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds (n = 26; SMR = 0.78, 95% CI 0.51–1.15) than with having never been exposed (n = 27; SMR = 0.71, 95% CI 0.41–1.03).

In the mortality study of phenoxy herbicide producers and sprayers in New Zealand (’t Mannetje et al., 2005), the numbers of observed and expected deaths from esophageal cancer were so small that the estimated risks in the producer group (SMR = 1.94, 95% CI 0.24–7.02) and in the sprayer group (SMR = 0.72, 95% CI 0.0–3.99) were in effect indeterminate.

In their study of cancer incidence in private and commercial pesticide applicators and in the spouses of the private applicators in the AHS, Alavanja et al. (2005) did not report results separately for esophageal cancer. Reporting on cancer mortality in the same prospective cohort study, Blair et al. (2005a) found death from esophageal cancer to be less frequent than expected in the private applicators (SMR = 0.5, 95% CI 0.3–0.9); only one case was observed in their spouses.

Lee WJ et al. (2004a) conducted a population-based case–control study of 170 cases of adenocarcinoma of the stomach and 137 cases of adenocarcinoma of the esophagus during 1988–1993. Controls were randomly selected from the same geographic area. Living on a farm, duration of farming, and having ever used herbicides were not associated with an increased risk of either type of cancer. No indication of increased risk of esophageal cancer was observed in connection with self-reported use of phenoxy herbicides, 2,4,5-T, or 2,4-D.

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 385 cases of esophageal cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with esophageal cancer (4 cases; OR = 1.77, 95% CI 0.66–4.75) was not significantly elevated.

Magnani et al. (1987) reported a case–control mortality study of 244 cases of esophageal cancer and 935 controls in the UK. A JEM was used to predict exposures to various chemical agents on the basis of job title as indicated on death certificates. Estimates of risk of esophageal cancer associated with exposure to herbicides (RR = 1.6, 95% CI 0.7–3.6) and chlorophenols (RR = 1.2, 95% CI 0.7–2.2) were not significantly increased.

Environmental Studies No new environmental studies concerning exposure to the compounds of interest and esophageal cancer were published since *Update 2004*.

Vietnam-Veteran Studies In reports updating the health status of Australian Vietnam veterans, 70 cases of esophageal cancer were diagnosed (SIR = 1.22, 95% CI 0.94–1.51) (ADVA, 2005a), and there were 67 deaths from esophageal cancer (SMR = 1.06, 95% CI 0.81–1.32) (ADVA, 2005b). In a separate study of diagnoses and deaths in deployed and non-deployed National Service veterans, the trend toward an increased rate of esophageal cancer remained with an RR of 1.93 (95% CI 0.61–6.59) for incidence and an RR of 1.33 (95% CI 0.50–3.55) for mortality based on nine observed cases (ADVA, 2005c).

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported six esophageal-cancer deaths in the deployed and five in the non-deployed (crude rate ratio [CRR], 1.2, 95% CI 0.4–4.0).

Biologic Plausibility

The committee did not find any new studies that supported the biologic plausibility of an association of exposure to the compounds of interest and esophageal cancer. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Previous updates did not review the risk of esophageal cancer separately. Reviewing the epidemiologic studies of esophageal cancer to date yielded no evidence of suggest an increased risk associated with the compounds of interest. The recent updates of the health status of the Australian Vietnam veterans present an interesting but non-significant pattern of increased risk of esophageal cancer. No toxicologic studies provide evidence of biologic plausibility of an association between the compounds of interest and tumors of the esophagus.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and esophageal cancer.

Stomach Cancer

The incidence of stomach cancer (ICD-9 151) increases in people 50–64 years old. ACS estimated that in 2006 13,400 men and 8,880 women would develop new cases of stomach cancer and 6,690 men and 4,740 women would die from it (Jemal et al., 2006). In general, the incidence is higher in men than in women and higher in blacks than in whites. Other risk factors include family history of this cancer, some diseases of the stomach, and diet. Infection with the bacterium *Helicobacter pylori* increases the risk of stomach cancer. Tobacco use, consumption of salt-preserved food, and a high salt intake may also increase the risk of stomach cancer (Key et al., 2004; Miller et al., 1996).

Conclusions from VAO and Updates

This update considers stomach cancer independently for the first time. Prior updates developed a table of results for stomach cancer, but conclusions about the adequacy of the evidence of its association with herbicide exposure have been reached in the context of

gastrointestinal tract cancers. Table 6-6 summarizes the results of the relevant studies concerning stomach cancer.

TABLE 6-6 Selected Epidemiologic Studies—Stomach Cancer

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	146	0.9 (0.8–1.1)
	Ever	98	0.9 (0.7–1.1)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	2	1.1 (0.1–4.0)
	Phenoxy herbicide sprayers (>99% men)	3	1.4 (0.3–4.0)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	462	0.8 (0.8–0.9)
	Spouses of private applicators (>99% women)	161	0.9 (0.7–1.0)
	Commercial applicators (men and women)	24	1.0 (0.6–1.4)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	10	0.5 (0.2–1.0)
	Spouses of private applicators (>99% women)	4	1.1 (0.3–2.8)
Lee et al., 2004	Population-based case-control—agricultural pesticide use and adenocarcinoma of the stomach	170	
	Insecticides		0.9 (0.6–1.4)
	Herbicides		0.9 (0.5–1.4)
Torchio et al., 1994	Italian licensed pesticide users	126	0.7 (0.6–0.9)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	13	2.2 (1.3–3.9)
Studies Reviewed in *Update 2004*			
Bodner et al., 2003	Dow production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	—	1.5 (0.7–2.7)
Swaen et al., 2004	Dutch licensed herbicide applicators	3	0.4 (0.1–1.3) [d]
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	Digestive organs and peritoneum	16	0.7 (0.4–1.2)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	13	1.0 (0.6–1.8)
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)	3	1.0 (0.2–2.9)
Rix et al., 1998	Danish paper mill workers—incidence		
	Men	48	1.1 (0.8–1.4)
	Women	7	1.0 (0.4–2.1)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	39	1.0 (0.7–1.3)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	72	0.9 (0.7–1.1)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	42	0.9 (0.7–1.2)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	30	0.9 (0.6–1.3)
Becher et al., 1996	German production workers (Included in the IARC cohort)		
	Plant I	12	1.3 (0.7–2.2)
	Plant II	0	—
	Plant III	0	—
	Plant IV	2	0.6 (0.1–2.3)
Ott and Zober, 1996	BASF employees—incidence	3	1.0 (0.2–2.9)
	TCDD <0.1 µg/kg of body weight	0	0.0 (0.0–3.4)
	TCDD 0.1–0.99 µg/kg of body weight	1	1.3 (0.0–7.0)
	TCDD >1 µg/kg of body weight	2	1.7 (0.2–6.2)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	4	1.7 (0.5–4.3)
	15-year latency	3	1.8 (0.4–5.2)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White males	657	1.0 (1.0–1.1)
	White females	12	1.2 (0.6–2.0)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort)	2	0.7 (0.1–2.7)
Collins et al., 1993	Monsanto Company workers (Included in NIOSH cohort)	0	0.0 (0.0–1.1)
Kogevinas et al., 1993	IARC cohort—females	1	1.4 *
Studies Reviewed in VAO			
Ronco et al., 1992	Danish farm workers—incidence		
	Men	286	0.9 *
	Women	5	1.0 *
Swaen et al., 1992	Dutch licensed herbicide applicators	1	0.5 (0.0–2.7) [d]
Fingerhut et al., 1991	NIOSH—entire cohort	10	1.0 (0.5–1.9)
	≥1-year exposure; ≥20-year latency	4	1.4 (0.4–3.5)
Manz et al., 1991	German production workers—men and women (Included in the IARC cohort)		
	Men	12	1.2 (0.6–2.1)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	40	0.9 (0.6–1.2)
Wigle et al., 1990	Canadian farmers	246	0.9 (0.8–1.0)
Zober et al., 1990	BASF employees—basic cohort	3	3.0 (0.8–7.7) [e]
Alavanja et al., 1989	USDA forest or soil conservationists	9	0.7 (0.3–1.3)
Henneberger et al., 1989	New Hampshire pulp and paper workers	5	1.2 (0.4–2.8)
Solet et al., 1989	US Paper and pulp workers	1	0.5 (0.1–3.0)
Alavanja et al., 1988	USDA agricultural extension agents	10	0.7 (0.4–1.4)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	— (0.0–3.7)
Thomas, 1987	US flavor and fragrance chemical plant workers	6	4.2 Expected
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	26	0.9 (0.6–1.3)
Robinson et al., 1986	Northwestern US paper and pulp workers	17	1.2 (0.8–1.9) [e]

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)		
	Males	12	1.3 *
	Females	1	0.7 *
Blair et al., 1983	Florida pesticide applicators	4	3.3 Expected
Burmeister et al., 1983	Iowa residents—farming exposures	1,812	1.3 ($p < 0.05$)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	2,599	1.1 (1.0–1.2)[f]
Burmeister, 1981	Iowa farmers	338	1.1 ($p < 0.01$)
Axelson et al., 1980	Swedish railroad workers—total exposure	3	2.2 *
ENVIRONMENTAL			
Studies Reviewed in *Update 2004*			
Fukuda et al., 2003	Residents of municipalities in Japan with or without waste incineration plants		
	Age-adjusted mortality (100,000) in men		38.2 ± 7.8 vs 39.0 ± 8.8 ($p = 0.29$)
	Age-adjusted mortality (100,000) in women		20.7 ± 5.0 vs 20.7 ± 5.8 ($p = 0.92$)
Studies Reviewed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Men	59	1.7 (1.3–2.2)
	Women	45	0.7 (0.5–0.9)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—men	16	0.9 (0.5–1.5)
	women	11	1.0 (0.6–1.9)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone A—women	1	0.9 (0.0–5.3)
	Zone B—men	10	0.8 (0.4–1.5)
	women	7	1.0 (0.4–2.1)
	Zone R—men	76	0.9 (0.7–1.1)
	women	58	1.0 (0.8–1.3)
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		
	East coast	17	1.4 (0.8–2.2)
	West coast	63	0.9 (0.7–1.2)
	Swedish fishermen—incidence (men and women)		
	East coast	24	1.6 (1.0–2.4)
	West coast	71	0.9 (0.7–1.2)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men	7	1.0 (0.5–2.1)
	women	2	0.6 (0.2–2.5)
	Zone R—men	45	0.9 (0.7–1.2)
	women	25	1.0 (0.6–1.5)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	7	0.9 (0.4–1.8)
	women	3	0.8 (0.3–2.5)
Bertazzi et al., 1989a	Seveso residents—10-year follow-up		

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
	Zones A, B, R—men	40	0.8 (0.6–1.2)
	women	22	1.0 (0.6–1.5)
Bertazzi et al., 1989b	Seveso residents—10-year follow-up		
	Zone B—men	7	1.2 (0.6–2.6)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—Incidence	104	0.9 (0.7–1.1)
	Navy	28	1.1 (0.7–1.6)
	Army	66	0.9 (0.7–1.1)
	Air Force	10	0.7 (0.3–1.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—Mortality	76	0.9 (0.7–1.2)
	Navy	22	1.3 (0.8–1.8)
	Army	50	0.9 (0. 7–1.2)
	Air Force	4	0.4 (0.1–1.0)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	11	0.6 (0.2–1.2)
	Mortality	7	0.7 (0.2–2.0)
Pavuk et al., 2005	White Air Force comparison subjects only (digestive system)—incidence		
	Serum TCDD levels (pg/g), based on model with exposure variable $\log_e$(TCDD) [f]		
	Per unit increase of -$\log_e$(TCDD) in pg/g	24	1.8 (0.8–3.9)
	Quartiles (pg/g)		
	0.4–2.6	4	—*
	2.6–3.8	3	1 (0.2–4.8)
	3.8–5.2	7	2 (0.5–8.2)
	>5.2	10	3.3 (0.9–12.5)
	Number of years served in southeast Asia (SEA)		
	Per year of service	24	1.2 (1–1.4)
	Quartiles (years in SEA)		
	0.8–1.3	4	
	1.3–2.1	4	1 (0.2–3.8)
	2.1–3.7	5	1.1 (0.3–4.2)
	3.7–16.4	11	2.1 (0.6–7.3)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (stomach)	5	—*
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	Air Force Ranch Hand veterans—cancer of the digestive system		
	All Ranch Hand veterans		
	Incidence (SIR)	16	0.6 (0.4–1.0)
	Mortality (SMR)	6	0.4 (0.2–0.9)
	Veterans, tours 1966–1970—incidence	14	0.6 (0.4–1.1)
	White Air Force comparison veterans—cancer of the digestive system		
	All comparison veterans		
	Incidence (SIR)	31	0.9 (0.6–1.2)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
	Mortality (SMR)	14	0.7 (0.4–1.1)
	Veterans, tours 1966–1970—incidence	24	0.9 (0.6–1.3)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	32	1.1 (0.7–1.4)
CDVA, 1997b	Australian national service Vietnam veterans	4	1.7 (0.3– >10)
Studies Reviewed in *VAO*			
Breslin et al., 1988	Army Vietnam veterans	88	1.1 (0.9–1.5)
	Marine Vietnam veterans	17	0.8 (0.4–1.6)
Anderson et al., 1986	Wisconsin Vietnam veterans	1	—*

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] Risk estimate is for stomach and small intestine.
[e] 90% CI
[f] 99% CI.
[g] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
* Information not provided by study authors.
— Denoted by a dash in the original study.
Studies in *italics* have been superseded by newer studies of the same cohort.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs ; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; MCPA, 2 methyl-4-chlorophenoxyacetic acid; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Death from stomach cancer was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds (n = 98; SMR = 0.89, 95% CI 0.72–1.08) than with having never been exposed (n = 146; SMR = 0.93, 95% CI 0.79–1.10).

In the mortality study of phenoxy herbicide producers and sprayers in New Zealand ('t Mannetje et al., 2005), the numbers of observed and expected deaths from stomach cancer among producers (n = 2) and sprayers (n = 3) were so small that the estimated risks were in effect indeterminate.

In their study of cancer incidence in private and commercial pesticide applicators and the spouses of the private applicators in the AHS, Alavanja et al. (2005) did not report results separately for stomach cancer. Reporting on cancer mortality in the same prospective cohort study, Blair et al. (2005a) found death from stomach cancer to be reduced in the private applicators (SMR = 0.5, 95% CI 0.2–1.0) and as expected in their spouses (SMR = 1.1, 95% CI 0.3–2.8).

Lee WJ et al. (2004a) conducted a population-based case–control study of 170 cases of adenocarcinoma of the stomach and 137 cases of adenocarcinoma of the esophagus in 1988–1993. Controls were randomly selected from the same geographic area. Living on a farm, duration

of farming, and having ever used herbicides were not associated with an increased risk of either type of cancer. No indication of an increased risk of stomach cancer was observed in association with self-reported use of phenoxy herbicides (OR = 0.8, 95% CI 0.5–1.5), 2,4,5-T (OR = 0.7, 95% CI 0.3–1.7), or 2,4-D (OR = 0.8, 95% CI 0.4–1.3).

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of dying from stomach cancer was significantly reduced among the licensed pesticide users (126 cases; SMR = 0.72, 95% CI 0.6–0.86) when compared with regional and provincial populations. The authors suggested that the relatively short duration of follow-up and the healthy-worker effect contributed to the observation of a reduction in mortality.

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 1,014 cases of stomach cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with stomach cancer (13 cases; OR = 2.22, 95% CI 1.26–3.91) was significantly elevated.

Environmental Studies No new environmental studies concerning exposure to the compounds of interest and stomach cancer were published since *Update 2004*.

Vietnam-Veteran Studies In the three reports updating the health status of Australian Vietnam veterans, 104 diagnoses of stomach cancer (SIR = 0.89, 95% CI 0.72–1.07) and 76 deaths (SMR = 0.94, 95% CI 0.73–1.15) were reported (ADVA, 2005a,b). No increase was reported in the National Service veteran study that examined the healthy-warrior effect (ADVA, 2005b).

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported five stomach-cancer deaths in the deployed and three in the non-deployed. The researchers did not consider the data sufficient for the calculation of risk statistics unless there were at least 10 deaths from a type of cancer.

Biologic Plausibility

No animal studies have reported an increased incidence of gastrointestinal cancer after exposure to the compounds of interest. However, treatment with TCDD in some animal models (female hairless mice) has been reported to result in hyperplasia of mucous cells in the fundic region of the stomach (Hebert et al., 1990). In addition, a transgenic mouse bearing a constitutively active form of the aryl hydrocarbon receptor (AhR) has been shown to develop stomach tumors (Andersson et al., 2002a). The tumors are neither dysplastic nor metaplastic but are indicative of both squamous and intestinal type metaplasia (Andersson et al., 2005). The validity of the transgenic animal model is indicated by the similarities in the phenotype of the transgenic animal (increased relative weight of the liver and heart, decreased weight of the

thymus, and increased expression of the AHR target gene CYP1A1) and animals treated with TCDD (Brunnberg et al., 2006).

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

The risk of stomach cancers has not been reviewed separately in previous updates. Among the newly reviewed studies, only Reif et al. (1989) reported a significant relationship, which was between stomach cancer and the rather non-specific exposure of being a forestry worker. There is some evidence of biologic plausibility in animal models, but the epidemiologic studies to date do not support an association between exposure to the compounds of interest and stomach cancer.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and stomach cancer.

Colorectal Cancer

Colorectal cancers include malignancies of the colon (ICD-9 153) and of the rectum and anus (ICD-9 154); less prevalent tumors of the small intestine (ICD-9 152) are frequently included in this grouping. Should any findings on cancers of the retroperitoneum and other and unspecified digestive organs (ICD-9 159) be found, they will be considered in this category. Colorectal cancers account for about 55% of digestive tumors; ACS estimated that in 2006 148,610 people would develop new cases and 55,170 would die from the cancers in the United States (ACS, 2006a). Excluding basal-cell and squamous-cell skin cancers, colorectal cancer is the third-most common form of cancer both in men and in women.

The incidence of colorectal cancer increases with age; it is higher in men than in women and in blacks than in whites. Because it is recommended that all persons over 50 years old receive colon-cancer screening, screening can affect incidence rates. Other risk factors include family history of this form of cancer, some diseases of the intestines, and diet. Type 2 diabetes is associated with an increased risk of cancer of the colon (ACS, 2004a).

Conclusions from VAO and Updates

This update considers colorectal cancer independently for the first time. Prior updates developed tables of results for colon and rectal cancer, but conclusions about the adequacy of the evidence of their association with herbicide exposure have been reached only in the context of

gastrointestinal tract cancers. Tables 6-7 and 6-8 summarize the results of the relevant studies concerning colon and rectal cancers, respectively.

TABLE 6-7 Selected Epidemiologic Studies—Colon Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	106	1.0 (0.9–1.3)
	Ever	62	0.7 (0.6–1.0)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	2	0.6 (0.0–2.3)
	Phenoxy herbicide sprayers (>99% men)	8	1.9 (0.8–3.8)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	208	0.9 (0.8–1.0)
	Spouses of private applicators (>99% women)	12	1.2 (0.6–2.1)
	Commercial applicators (men and women)	87	0.9 (0.7–1.1)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	56	0.7 (0.6–1.0)
	Spouses of private applicators (>99% women)	31	1.2 (0.8–1.6)
Torchio et al., 1994	Italian licensed pesticide users		
	Large intestine	84	0.6 (0.5–0.7)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	7	0.5 (0.2–1.1)
	Small intestine	2	5.2 (1.4–18.9)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	34	1.2 (0.8–1.6)[d]
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)	3	1.4 (0.3–4.0)
Rix et al., 1998	Danish paper mill workers—incidence		
	Men	58	1.0 (0.7–1.2)
	Women	23	1.1 (0.7–1.7)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	27	1.1 (0.7–1.6)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	86	1.1 (0.9–1.3)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	52	1.0 (0.8–1.3)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	33	1.2 (0.8–1.6)
Becher et al., 1996	German production workers—(Included in the IARC cohort)		
	Plant I	2	0.4 (0.1–1.4)
	Plant II	0	—
	Plant III	1	2.2 (0.1–12.2)
	Plant IV	0	—
Ott and Zober, 1996[e]	BASF employees—incidence	5	1.0 (0.3–2.3)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	TCDD <0.1 µg/kg of body weight	2	1.1 (0.1–3.9)
	TCDD 0.1–0.99 µg/kg of body weight	2	1.4 (0.2–5.1)
	TCDD >1 µg/kg of body weight	1	0.5 (0.0–3.0)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	4	0.8 (0.2–2.1)
	15-year latency	4	1.0 (0.3–2.6)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White men	2,291	1.0 (0.9–1.0)
	White women	59	1.0 (0.8–1.3)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers—(Included in the IARC cohort)	3	1.8 (0.4–5.4)
Collins et al., 1993	Monsanto Company workers—(Included in the NIOSH cohort)	3	0.5 (0.1–1.3)
Studies Reviewed in *VAO*			
Swaen et al., 1992	Dutch licensed herbicide applicators	4	2.6 (0.7–6.5)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	277	0.7 ($p < 0.05$)
	employee	45	0.6 ($p < 0.05$)
	Women—self-employed	14	0.9 (*)
	employee	112	0.9 (*)
	family worker	2	0.2 ($p < 0.05$)
Fingerhut et al., 1991	NIOSH—entire cohort	25	1.2 (0.8–1.8) [d]
	≥1-year exposure; ≥20-year latency	13	1.8 (1.0–3.0) [d]
Manz et al., 1991	German production workers (Included in the IARC cohort)	8	0.9 (0.4–1.8)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	41	1.1 (0.8–1.5)
Zober et al., 1990[be]	BASF employees—basic cohort	2	2.5 (0.4–7.8)[f]
Alavanja et al., 1989	USDA forest or soil conservationists	~~44~~[g]	1.5(1.1–2.0)
Henneberger et al., 1989	New Hampshire pulp and paper workers	9	1.0 (0.5–2.0)
Solet et al., 1989	US pulp and paper workers	7	1.5 (0.6–3.0)
Alavanja et al., 1988	USDA agricultural extension agents	41	1.0 (0.7–1.5)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	4	2.1 (0.6–5.4)
Thomas, 1987	US flavor and fragrance chemical plant workers	4	0.6 *
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	19	1.0 (0.6–1.6)
Robinson et al., 1986	Northwestern US pulp and paper workers	7	0.4 (0.2–0.7) [f]
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)		
	Men	10	1.0 *
	Women	1	0.3 *
Blair et al., 1983	Florida pesticide applicators	5	0.8 *
Wiklund, 1983	Swedish male and female agricultural workers—incidence	1,332	0.8 (0.7–0.8) [h]
Thiess et al., 1982	BASF production workers	1	0.4 *
Burmeister, 1981	Iowa farmers	1,064	1.0 (NS)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Hardell, 1981	Swedish residents		
	Exposed to phenoxy acids	11	1.3 (0.6–2.8)
	Exposed to chlorophenols	6	1.8 (0.6–5.3)
ENVIRONMENTAL			
Studies Reviewed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Men	17	1.3 (0.8–2.2)
	Women	24	1.0 (0.7–1.5)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—men	10	1.0 (0.5–1.9)
	women	5	0.6 (0.2–1.4)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone A—women	2	2.6 (0.3–9.4)
	Zone B—men	5	0.8 (0.3–2.0)
	women	3	0.6 (0.1–1.8)
	Zone R—men	34	0.8 (0.6–1.1)
	women	33	0.8 (0.6–1.1)
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		
	East coast	1	0.1 (0.0–0.7)
	West coast	58	1.0 (0.8–1.3)
	Swedish fishermen—incidence (men and women)		
	East coast	5	0.4 (0.1–0.9)
	West coast	82	1.0 (0.8–1.2)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—morbidity		
	Zone B men	2	0.5 (0.1–2.0)
	Zone B women	2	0.6 (0.1–2.3)
	Zone R men	32	1.1 (0.8–1.6)
	Zone R women	23	0.8 (0.5–1.3)
Studies Reviewed in *VAO*			
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination (men and women)	9	1.1 (0.7–1.8)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B men	3	0.6 (0.2–1.9)
	Zones A, B women	3	0.7 (0.2–2.2)
Bertazzi et al., 1989a	Seveso residents—10-year follow-up		
	Zones A, B, R men	20	1.0 (0.6–1.5)
	Zones A, B, R women	12	0.7 (0.4–1.2)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—Incidence	376	1.1 (1.0–1.2)
	Navy	91	1.3 (1.0–1.5)
	Army	239	1.1 (0.9–1.2)
	Air Force	47	1.1 (0.8–1.5)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—Mortality	176	1.0 (0.8–1.1)
	Navy	49	1.3 (0.9–1.6)
	Army	107	0.9 (0.7–1.0)
	Air Force	21	0.9 (0.5–1.3)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	54	0.9 (0.7–1.4)
	Mortality	29	0.8 (0.5–1.3)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (colon, rectum, anus)	9	1.0 (0.4–2.6)
Studies Reviewed in *Update 2000*			
AFHS, 2000[e]	Air Force Ranch Hand veterans	7	1.5 (0.4–5.5)
AIHW, 1999[e]	Australian Vietnam veterans—men	188	221 expected (191–251)
CDVA, 1998a	Australian Vietnam veterans—men	405[j]	117 expected (96–138)
CDVA, 1998b	Australian Vietnam veterans—women	1[j]	1 expected (0–5)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	78	1.2 (0.9–1.5)
CDVA, 1997b	Australian national service Vietnam veterans	6	0.6 (0.2–1.5)
Studies Reviewed in *Update 1996*			
Dalager et al., 1995	US Vietnam veterans—women	4	0.4 (0.1–1.2)
	Vietnam veteran nurses	4	0.5 (0.2–1.7)
Studies Reviewed in *VAO*			
Breslin et al., 1988[k]	Army Vietnam veterans	209	1.0 (0.7–1.3)
	Marine Vietnam veterans	33	1.3 (0.7–2.2)
Anderson et al., 1986	Wisconsin Vietnam veterans	6	1.0 (0.4–2.2)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] Colon and small intestine combines.
[e] Colon and rectal cancer results combined.
[f] 90% CI.
[g] P< 0.01.
[h] 99% CI.
[i] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[j] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have cancer of the colon?"
[k] Intestinal and other GI cancer results are combined in this study.
* Information not provided by study authors.
—Denoted by a dash in the original study.
Studies in *italics* have been superseded by newer studies of the same cohort.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture.

TABLE 6-8 Selected Epidemiologic Studies—Rectal Cancer

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	60	0.9 (0.7–1.1)
	Ever	51	1.0 (0.7–1.3)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	5	2.5 (0.8–5.7)
	Phenoxy herbicide sprayers (>99% men)	4	1.5 (0.4–3.8)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	94	0.8 (0.7–1.0)
	Spouses of private applicators (>99% women)	23	0.6 (0.4–0.9)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	*	*
	Spouses of private applicators (>99% women)	*	*
Torchio et al., 1994	Italian licensed pesticide users	*	*
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	10	1.2 (0.6–2.3)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators	5	2.1 (0.7–4.8)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	6	0.9 (0.3–1.9)
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC Cohort)	1	1.0 (0.0–5.6)
Rix et al., 1998	Danish paper mill workers—incidence		
	Men	43	0.9 (0.6–1.2)
	Women	15	1.5 (0.8–2.4)
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	44	1.1 (0.8–1.4)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	29	1.3 (0.9–1.9)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	14	0.7 (0.4–1.2)
Becher et al., 1996	German production workers (Included in the IARC Cohort)		
	Plant I	6	1.9 (0.7–4.0)
	Plant II	0	—
	Plant III	0	—
	Plant IV	1	0.9 (0.0–4.9)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	0	—
	15-year latency	0	—

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White men	367	1.0 (0.9–1.1)
	White women	4	0.5 (0.1–1.3)
Bueno de Mesquita et al., 1993	Dutch Phenoxy herbicide workers (Included in the IARC Cohort)	0	0 (0.0–4.3)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish workers—incidence		
	Male—self-employed	309	0.8 ($p < 0.05$)
	employee	55	0.8 (*)
	Female—self-employed	5	0.6 (*)
	employee	55	0.8 (*)
	family worker	2	0.4 (*)
Fingerhut et al., 1991	NIOSH—entire cohort	5	0.9 (0.3–2.1)
	≥1-year exposure; ≥20-year latency	2	1.2 (0.4–4.2)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	24	1.1 (0.7–1.6)
Alavanja et al., 1989	USDA forest or soil conservationists	9	1.0 (0.5–1.9)
Henneberger et al., 1989	New Hampshire pulp and paper workers	1	0.4 (0.0–2.1)
Alavanja et al., 1988	USDA agricultural extension agents	5	0.6 (0.2–1.3)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	1.7 (0.0–9.3)
Thomas, 1987	US flavor and fragrance chemical plant workers	6	2.5 *
Coggon et al., 1986	British MCPA chemical workers (Included in the IARC cohort)	8	0.6 (0.3–1.2)
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)		
	Men	14	1.5 *
	Women	2	1.0 *
Blair et al., 1983	Florida pesticide applicators	2	1.0 *
Wiklund, 1983	Swedish male and female agricultural workers—incidence	1,083	0.9 (0.9–1.0) [d]
ENVIRONMENTAL			
Studies Reviewed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Men	21	1.5 (1.0–2.4)
	Women	24	0.9 (0.6–1.4)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—men	9	2.4 (1.2–4.6)
	women	3	1.1 (0.4–3.5)
Studies Reviewed in *Update 1998*			
Bertazzi et al. 1997	Seveso residents—15-year follow-up		
	Zone B—men	7	2.9 (1.2–5.9)
	women	2	1.3 (0.1–4.5)
	Zone R—men	19	1.1 (0.7–1.8)
	women	12	0.9 (0.5–1.6)
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		
	East coast	4	0.7 (0.2–1.9)
	West coast	31	1.0 (0.7–1.5)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
	Swedish fishermen—incidence (men and women)		
	East coast	9	0.9 (0.4–1.6)
	West coast	59	1.1 (0.8–1.4)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men	3	1.4 (0.4–4.4)
	women	2	1.3 (0.3–5.4)
	Zone R—men	17	1.1 (0.7–1.9)
	women	7	0.6 (0.3–1.3)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	3	1.2 (0.4–3.8)
	women	2	1.2 (0.3–4.7)
Bertazzi et al., 1989a	Seveso residents—10-year follow-up		
	Zones A, B, R—men	10	1.0 (0.5–2.0)
	women	7	1.2 (0.5–2.7)
Bertazzi et al., 1989b	Seveso residents—10-year follow-up		
	Zone B—men	2	1.7 (0.4–7.0)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—Incidence	234	1.0 (0.91.1)
	Navy	54	1.1 (0.8–1.4)
	Army	152	1.0 (0.8–1.1)
	Air Force	28	1.0 (0.6–1.4)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—Mortality	69	0.9 (0.7–1.1)
	Navy	13	0.8 (0.4–1.4)
	Army	44	0.9 (0.6–1.1)
	Air Force	12	1.3 (0.6–2.2)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	46	1.4 (0.9–2.2)
	Mortality	10	1.8 (0.6–5.6)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (colon, rectum, anus)	9	1.0 (0.4–2.6)
Studies Reviewed in *Update 2000*			
AFHS, 2000[f]	Air Force Ranch Hand veterans	7	1.5 (0.4–5.5)
AIHW, 1999[f]	Male Australian Vietnam veterans	188	221 expected (191–251)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	16	0.6 (0.4–1.0)
CDVA, 1997b	Australian national service Vietnam veterans	3	0.7 (0.2–9.5)
Studies Reviewed in *VAO*			
Anderson et al., 1986	Wisconsin Vietnam veterans	1	—

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 99% CI.

[e] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[f] Colon and rectal cancer results combined.
* Information not provided by study authors.
— enoted by a dash in the original study.
Studies in *italics* have been superseded by newer studies of the same cohort.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Death from colon cancer was significantly decreased among those who had been exposed to nonvolatile organochlorine compounds (*n* = 62; SMR = 0.74, 95% CI 0.57–0.95) but not among those who had never been exposed (*n* = 106; SMR = 1.04, 95% CI 0.85–1.25). Death from rectal cancer, however, was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds (*n* = 51; SMR = 0.96, 95% CI 0.71–1.26) than with having never been exposed (*n* = 60; SMR = 0.87, 95% CI 0.66–1.12).

In their prospective cohort study of cancer incidence in private commercial pesticide applicators, Alavanja et al. (2005) found the incidence of rectal cancer significantly lower than expected (SIR = 0.81, 95% CI 0.65–0.99) and the incidence of colon cancer similar to that predicted in the general population (SIR = 0.88, 95% CI 0.76–1.01). In commercial applicators, the incidence of colon cancer (SIR = 1.20, 95% CI 0.62–2.10) and of rectal cancer (SIR = 1.25, 95% CI 0.50–2.58) remained insignificant.

In the same cohort, Blair et al. (2005a) found the rate of colon-cancer death reduced in the private applicators (SMR = 0.7, 95% CI 0.6–1.0) but slightly increased in their spouses (SMR = 1.2, 95% CI 0.8–1.6). Mortality from rectal cancer was not reported separately.

In the mortality study of phenoxy herbicide producers and sprayers in New Zealand (’t Mannetje et al., 2005), the data on colon-cancer death (SMR = 0.62, 95% CI 0.08–2.25) and rectal-cancer death (SMR = 2.45, 95% CI 0.79–5.73) among producers were indeterminate. In the sprayer group, there were non-significant excesses of cancer deaths from both colon cancer (SMR = 1.94, 95% CI 0.84–3.83) and rectal cancer (SMR = 1.47, 95% CI 0.40–3.76).

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of cancer of the large intestine was reduced (84 cases; SMR = 0.57, 95% CI 0.45–0.71).

Reif et al. (1989) performed a series of case–control analyses on a sample of 19,904 men entered into the New Zealand Cancer Registry from 1980–1984 with an occupation specified. They focused on the 134 registrants for whom forestry worker (presumed to be exposed to phenoxyherbicides and chlorophenols) was the most recent occupation. Two forestry workers among 63 cases of cancer of the small intestine (OR = 5.22, 95% CI 1.44–18.88) represented a significantly increased risk. The seven forestry workers among the 2,043 cases of colon cancer

(OR = 0.51, 95% CI 0.24–1.09) and the 10 forestry workers among the 1,376 rectal cancer cases (OR = 1.22, 95% CI 0.64–2.34) did not constitute excesses.

Environmental Studies No new environmental studies concerning exposure to the compounds of interest and colorectal cancer were published since *Update 2004*.

Vietnam-Veteran Studies The 2005 report updating the cancer incidence of Australian Vietnam veterans (ADVA, 2005a) noted a slight increase in the incidence of colon cancer (SIR = 1.13, 95% CI 1.01–1.24), but no excess of deaths from colon cancer was observed (SMR =0.98, 95% CI 0.83–1.12). The report did not include specific information on the incidence of rectal cancers, but a slight increase in deaths from colorectal cancer was observed (SMR = 0.96, 95% CI 0.86–1.06). The incidence of colorectal cancers among deployed National Service veterans (RR = 1.13, 95% CI 0.86–1.46) was not increased when compared with that in non-deployed troops, and no excess colorectal deaths were observed (RR = 0.80, 95% CI 0.48–1.30) (ADVA, 2005c).

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported nine deaths from cancer of the colon, rectum, or anus (ICD-9 153–154) in the deployed and eight in the non-deployed (CRR = 1.02, 95% CI 0.39–2.64).

Biologic Plausibility

No animal studies have reported an increased incidence of colorectal cancer after exposure to the compounds of interest. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Previous updates have not reviewed the risk of colorectal cancers separately. There has been no evidence to suggest an association between the compounds of interest and colorectal cancer in the epidemiologic studies reviewed to date. The only significant increase in intestinal cancers noted in this update was the reported result concerning cancer of the small intestine that was based on cases in two exposed people (Reif et al., 1989); this is a very uncommon tumor type that is reported here for completeness of coverage with the more common cancers of the large intestine and rectum. There is no evidence of biologic plausibility of an association between exposure to any of the compounds of interest and the development of tumors of the colon or rectum. Overall, the available evidence does not support an association between the compounds of interest and colorectal cancer.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and colorectal cancer.

Hepatobiliary Cancers

Hepatobiliary cancers include cancers of the liver (ICD-9 155.0, 155.2) and the intrahepatic bile duct (ICD-9 155.1). ACS estimated that in 2006 12,600 men and 5,910 women would receive diagnoses of liver or intrahepatic bile duct cancer in the United States and 10,840 men and 5,360 women would die from those cancers (ACS, 2006a). Gallbladder cancer and extrahepatic bile duct cancer (ICD-9 156) are fairly uncommon, but they are often grouped with liver cancers when they are addressed.

In the United States, liver cancers account for about 1.3% of new cancer cases and 1.2% of cancer deaths. Misclassification of metastatic cancers as primary liver cancer can lead to overestimation of the number of deaths attributable to liver cancer (Percy et al., 1990). In developing countries, especially those in sub-Saharan Africa and Southeast Asia, liver cancers are common and are among the leading causes of death. The known risk factors for liver cancer include chronic infection with hepatitis B or C virus and exposure to the carcinogens aflatoxin and vinyl chloride. Alcohol cirrhosis and obesity-associated metabolic syndrome may also contribute to the risk of liver cancer. In the general population, the incidence of liver and intrahepatic bile duct cancer increases slightly with age; at the ages of 50–64 years, it is greater in men than in women and greater in blacks than in whites. The average annual incidence of hepatobiliary cancers is shown in Table 6-4.

Conclusions from VAO and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and hepatobiliary cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-9 summarizes the results of the relevant studies.

TABLE 6-9 Selected Epidemiologic Studies—Hepatobiliary Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	27	0.9 (0.6–1.3)
	Ever	16	0.7 (0.4–1.1)
’ Mannetje et al., 2005	New Zealand phenoxy herbicide workers (ICD-9 155)		

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Producers (men and women)	1	1.6 (0.0–8.8)
	Sprayers (>99% men)	0	0.0 (0.0–4.2)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Liver		
	Private applicators (men and women)	35	1.0 (0.7–1.4)
	Spouses of private applicators (>99%women)	3	0.9 (0.2–2.5)
	Commercial applicators (men and women)	—	0.0 (0.0–4.2)
	Gall bladder		
	Private applicators (men and women)	8	2.3 (1.0–4.5)
	Spouses of private applicators (>99% women)	3	0.9 (0.2–2.5)
	Commercial applicators (men and women)	—	0.0 (0.0–35.8)
Blair et al., 2005a	US Agriculture Health Study		
	Liver		
	Private applicators (men and women)	8	0.6 (0.2–1.1)
	Spouses of private applicators (>99% women)	4	1.7 (0.4–4.3)
	Gall bladder		
	Private applicators (men and women)	3	2.0 (0.4–5.7)
	Spouses of private applicators (>99% women)	2	1.3 (0.1–4.6)
Torchio et al., 1994	Italian licensed pesticide users		
	Liver	15	0.6 (0.3–0.9)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)		
	Liver	1	0.8 (0.1–5.8)
	Gall Bladder	3	4.1 (1.4–12.0)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators	0	—
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	7	0.9 (0.4–1.6)
Rix et al., 1998	Danish paper mill workers—incidence		
	Liver—men	10	1.1 (0.5–2.0)
	women	1	0.6 (0.0–3.2)
	Gall bladder—men	9	1.6 (0.7–3.0)
	women	4	1.4 (0.4–3.7)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	7	1.3 (0.5–2.6)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	15	0.7 (0.4–1.2)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	12	0.9 (0.5–1.5)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	3	0.4 (0.1–1.2)
Becher et al., 1996	German production workers (Included in the IARC cohort)	1	1.2 (0.0–6.9)
Ott and Zober, 1996	BASF employees—incidence	2	2.1 (0.3–7.5)
	TCDD <0.1 µg/kg of body weight	1	2.8 (0.1–15.5)
	TCDD 0.1–0.99 µg/kg of body weight	0	0.0 (0.0–15.4)
	TCDD >1 µg/kg of body weight	1	2.8 (0.1–15.5)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	0	—*
	15-year latency	0	—*
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators—incidence	3	0.9 (0.2–2.6)
	Finnish herbicide applicators—mortality	2	0.6 (0.1–2.2)
Blair et al., 1993	US farmers in 23 states		
	White men	326	1.0 (0.9–1.1)
	White women	6	0.7 (0.3–1.6)
Collins et al., 1993	Monsanto Company 2,4-D production workers (Included in NIOSH cohort)	2	1.4 (0.2–5.2)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish farm workers—incidence		
	Liver		
	Men—self-employed	23	0.4 ($p < 0.05$)
	employee	9	0.8 (*)
	Female—family worker	5	0.5 (*)
	Gall bladder		
	Male—self-employed	35	0.8 (*)
	employee	7	0.8 (*)
	Female—self-employed	7	2.7 ($p < 0.05$)
	employee	1	0.7 (*)
	family worker	17	1.0 (*)
Fingerhut et al., 1991	NIOSH—entire cohort (liver and biliary)	6	1.2 (0.4–2.5)
	≥1-year exposure; ≥20-year latency	1	0.6 (0.0–3.3)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	4	0.4 (0.1–1.1)
Solet et al., 1989	US pulp and paper workers	2	2.0 (0.2–7.3)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	1.2 (*)
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)		
	Men	3	1.0 (*)
	Women	0	—
Hardell et al., 1984	Swedish residents—incidence and mortality combined	102	1.8 (0.9–4.0)
Wiklund, 1983	Swedish male and female agricultural workers—incidence		
	Liver (primary)	103	0.3 (0.3–0.4)[d]
	Biliary passages	169	0.6 (0.5–0.7)
	Liver (unspecified)	67	0.9 (0.7–1.3)
Zack and Suskind, 1980	Monsanto Company production workers (Included in NIOSH cohort)	0	—*
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—men (liver, gall bladder)	6	0.5 (0.2–1.0)
	(liver)	6	0.5 (0.2–1.1)
	women (liver, gall bladder)	7	1.0 (0.5–2.2)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	(liver)	6	1.3 (0.6–2.9)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B—men (liver, gall bladder)	4	0.6 (0.2–1.4)
	(liver)	4	0.6 (0.2–1.6)
	women (liver, gall bladder)	4	1.1 (0.3–2.9)
	(liver)	3	1.3 (0.3–3.8)
	Zone R—men (liver, gall bladder)	35	0.7 (0.5–1.0)
	(liver)	31	0.7 (0.5–1.0)
	women (liver, gall bladder)	25	0.8 (0.5–1.3)
	(liver)	12	0.6 (0.3–1.1)
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		
	East coast	1	0.5 (0.0–2.7)
	West coast (liver and bile ducts)	9	0.9 (0.4–1.7)
	Swedish fishermen—incidence (men and women)		
	East coast	6	1.3 (0.5–2.9)
	West coast (liver and bile ducts)	24	1.0 (0.6–1.5)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men (liver)	4	2.1 (0.8–5.8)
	(gall bladder)	1	2.3 (0.3–17.6)
	women (gall bladder)	4	4.9 (1.8–13.6)
	Zone R—men (liver)	3	0.2 (0.1–0.7)
	(gall bladder)	3	1.0 (0.3–3.4)
	women (liver)	2	0.5 (0.1–2.1)
	(gall bladder)	7	1.0 (0.5–2.3)
Cordier et al., 1993	Military service in South Vietnam for $\geq$10 years after 1960	11	8.8 (1.9–41.0)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zone A, B—men (liver)	4	1.5 (0.5–4.0)
	(gall bladder)	1	2.1 (0.3–15.6)
	women (liver)	1	1.2 (0.2–9.1)
	(gall bladder)	5	5.2 (2.1–13.2)
	Zone R—men (liver)	8	0.5 (0.2–0.9)
	(gall bladder)	3	1.0 (0.3–3.4)
	women (liver)	5	0.8 (0.3–2.1)
	(gall bladder)	7	1.0 (0.5–2.3)
Bertazzi et al., 1989b	Seveso residents—10-year follow-up		
	Zone A—women (gall bladder)	1	12.1 (1.6–88.7)
	Zone B—men (liver)	3	1.2 (0.4–3.8)
	women (gall bladder)	2	3.9 (0.9–16.2)
	Zone R—men (liver)	7	0.4 (0.2–0.8)
	women (liver)	3	0.4 (0.1–1.4)
	(gall bladder)	5	1.2 (0.5–3.1)
Hoffman et al., 1986	Residents of Quail Run Mobile Home Park (men and women)	0	*

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
VIETNAM VETERANS			
New Studies			
ADVA 2005a	Australian male Vietnam veterans vs Australian population—incidence	27	0.7 (0.4–1.0)
	Navy	8	1.0 (0.4–1.9)
	Army	18	0.7 (0.4–1.1)
	Air Force	1	0.2 (0.0–1.2)
ADVA 2005b	Australian male Vietnam veterans vs Australian population—mortality (liver and gallbladder)	48	0.9 (0.6–1.1)
	Navy	11	1.0 (0.5–1.7)
	Army	33	0.9 (0.6–1.2)
	Air Force	4	0.6 (0.2–1.5)
ADVA 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	2	2.5 (0.1–147.2)
	Mortality (liver and gallbladder)	4	2.5 (0.4–27.1)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (liver)	5	—*
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	2	1.6 (0.2–11.4)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans		
	Liver	8	0.6 (0.2–1.1)
	Gall bladder	5	1.3 (0.4–2.8)
CDVA, 1997b	Australian national service Vietnam veterans	1	—*
Studies Reviewed in *VAO*			
CDC, 1990a	US men born 1921–1953	8	1.2 (0.5–2.7)
Breslin et al., 1988	Army Vietnam veterans (liver and bile duct)	34	1.0 (0.8–1.4)
	Marine Vietnam veterans (liver and bile duct)	6	1.2 (0.5–2.8)
Anderson et al., 1986	Wisconsin Vietnam veterans	0	—*

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 99% CI.
[e] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
* Information not provided by study authors.
— Denoted by a dash in the original study.
Studies in *italics* have been superseded by newer studies of the same cohort.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; CDC, Centers for Disease Control and Prevention; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health, TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Update of the Epidemiologic Literature

Occupational Studies McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. The SMR for liver cancer was not associated with a JEM-based estimate of exposure to nonvolatile organochlorine compounds (never exposed: 27 cases; SMR = 0.87, 95% CI 0.57–1.27; ever exposed: 16 cases; SMR = 0.69, 95% CI 0.40–1.13).

Alavanja et al. (2005) reported cancer incidence in a prospective cohort study of private pesticide applicators, commercial applicators, and spouses of the private applicators. The risk of liver cancer was effectively unity for the private applicators (SIR = 0.98, 95% CI 0.68–1.37) and for their spouses (SIR = 0.86, 95% CI 0.17–2.51), as was the risk of gallbladder cancer in the spouses (SIR = 0.85, 95% CI 0.17–2.48). An excess of gallbladder cancers (*n* = 8) in the applicators approached significance (SIR = 2.26, 95% CI 0.87–4.45).

Blair et al. (2005a) reported cancer mortality in the same prospective cohort of pesticide applicators and spouses in North Carolina and Iowa. In the applicators, mortality from liver cancer was reduced (SMR = 0.6, 95% CI 0.2–1.1), but three cases of gallbladder cancer generated an increased risk estimate (SMR = 2.0, 95% CI 0.4–5.7). In their spouses, the risks of death from liver cancer (SMR = 1.7, 95% CI 0.4–4.3) and gallbladder cancer (SMR = 1.3, 95% CI 0.1–4.6) were not increased.

In New Zealand, 't Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers from 1969 and 1973, respectively, through 2000. The data on the risk of death from hepatic cancer (ICD-9 155) were uninformative; one death occurred in the producer group and none in the sprayer group.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of death from liver cancer was significantly reduced in this cohort (15 cases; SMR = 0.56, 95% CI 0.31–0.92) when compared with the expected mortality for the regional and provinicial population. The authors suggested that the relatively short duration of follow-up and the healthy-worker effect contributed to the observation of reduced mortality.

Reif et al. (1989) performed a series of case–control analyses on a sample of 19,904 men entered into the New Zealand Cancer Registry from 1980–1984 with an occupation specified. They focused on the 134 registrants for whom forestry worker (presumed to be exposed to phenoxyherbicides and chlorophenols) was the most recent occupation. A single forestry worker among the 184 cases with cancer of the liver did not constitute an excess (OR = 0.81, 95% CI 0.11–5.8). However, three forestry workers among the 120 cases of gallbladder cancer (OR = 4.13, 95% CI 1.42–12.04) in the cohort.

Environmental Studies No new environmental studies concerning exposure to the compounds of interest and hepatobiliary cancer were published since *Update 2004*.

Vietnam-Veteran Studies In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported five deaths from cancer of the liver or intrahepatic bile ducts (ICD-9 155) in the deployed and three in the non-deployed. The researchers did not consider the data sufficient for the calculation of risk statistics unless there were at least 10 deaths from a type of cancer.

A set of three reports updating the health status of Australian Vietnam veterans noted results concerning possible associations between Vietnam service and the incidence of liver cancer and mortality from liver and gallbladder cancer. The incidence of liver cancer was lower in Vietnam veterans than in the general population (SIR = 0.70, 95% CI 0.44–0.97) (ADVA, 2005a), and there was no increase in the risk of death from liver or gallbladder cancer (SMR = 0.88, 95% CI

0.63–1.13) (ADVA, 2005b). In a third report on the potential for a healthy-warrior effect, there were too few incident cases of liver cancer (*n* = 2) to calculate stable estimates (RR = 2.50, 95% CI 0.13–147); that was also the case for mortality from liver or gallbladder cancer (*n* = 4; RR = 2.45, 95% CI 0.35–27.06) (ADVA, 2005c).

Biologic Plausibility

A recent study used a mouse model bearing a constitutively active form of the AhR to examine the role of the AhR in promotion of hepatocarcinogenesis; treatment with the tumor initiator *N*-nitrosodiethylamine resulted in an increase in hepatic tumors that was significantly greater than that observed in the wild-type mice (Moennikes et al., 2004).

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

In this update, no new reports of a definitive link between exposure to the compounds of interest and hepatobiliary tumors were found. One study suggested a reduced risk of hepatic cancers in veteran populations, and one suggested an increased risk of cancer of the gallbladder among forestry workers. However, given the relatively low incidence of hepatobiliary cancers in Western populations, the evidence from epidemiologic studies remains inadequate to link the compounds of interest with hepatobiliary cancer.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and hepatobiliary cancer. The evidence regarding association is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components. Although several of those studies involved sizable cohorts, hepatobiliary cancers are rare, and the power of the studies to detect an increase in incidence is low.

Pancreatic Cancer

The incidence of pancreatic cancer (ICD-9 157) increases with age. ACS estimated that 17,150 men and 16,580 women would develop pancreatic cancer in the United States in 2006 and that 16,090 men and 16,210 women would die from it (Jemal et al., 2006). The incidence is higher in men than in women and higher in blacks than in whites. Other risk factors include family history, diet, and tobacco use; the incidence is about twice as high in smokers as in nonsmokers

(Miller et al., 1996). Chronic pancreatitis, obesity, and type 2 diabetes are also associated with an increased risk of pancreatic cancer (ACS, 2006a).

Conclusions from VAO and Updates

This update considers pancreatic cancer independently for the first time. Prior updates developed tables of results for pancreatic cancer, but conclusions about the adequacy of the evidence of its association with herbicide exposure have been reached in the context of gastrointestinal tract cancers. Table 6-10 summarizes the results of the relevant studies concerning pancreatic cancer.

TABLE 6-10 Selected Epidemiologic Studies—Pancreatic Cancer

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	67	0.8 (0.7–1.1)
	Ever	69	1.1 (0.9–1.4)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	3	2.1 (0.4–6.1)
	Phenoxy herbicide sprayers (>99% men)	0	0.0 (0.0–2.1)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	46	0.7 (0.5–1.0)
	Spouses of private applicators (>99%women)	20	0.9 (0.6–1.4)
	Commercial applicators (men and women)	3	1.1 (0.2–3.2)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	29	0.6 (0.4–0.9)
	Spouses of private applicators (>99% female)	10	0.7 (0.3–1.2)
Torchio et al., 1994	Italian licensed pesticide users	32	0.7 (0.5–1.0)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	6	1.8 (0.8–4.1)
Magnani et al., 1987	UK case–control		
	Herbicides	*	0.7 (0.3–1.5)
	Chlorophenols	*	0.8 (0.5–1.4)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators	5	1.2 (0.4–2.7)
Studies Reviewed in *Update 2000*			
Ojajärvi et al., 2000	Meta-analysis of 161 populations	127	MRR 1.0 (0.8–1.3)
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	16	1.0 (0.6–1.6)
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)	4	2.5 (0.7–6.3)
Rix et al., 1998	Danish paper mill workers—incidence		
	Men	30	1.2 (0.8–1.7)
	Women	2	0.3 (0.0–1.1)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	7	0.9 (0.4–1.9)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	47	0.9 (0.7–1.3)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	30	1.0 (0.7–1.4)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	16	0.9 (0.5–1.4)
Becher et al., 1996	German production workers (Included in the IARC cohort)		
	Plant I	2	0.6 (0.1–2.3)
	Plant II	0	—
	Plant III	0	—
	Plant IV	2	1.7 (0.2–6.1)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	2	0.7 (0.1–2.7)
	15-year latency	2	0.9 (0.1–3.3)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White men	1,133	1.1 (1.1–1.2)
	White women	23	1.0 (0.6–1.5)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort)	3	2.2 (0.5–6.3)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish farm workers—incidence		
	Men—self-employed	137	0.6 ($p < 0.05$)
	employee	23	0.6 ($p < 0.05$)
	Women—self-employed	7	1.2 (*)
	employee	4	1.3 (*)
	family worker	27	0.7 ($p < 0.05$)
Swaen et al., 1992	Dutch licensed herbicide applicators	3	2.2 (0.4–6.4)
Fingerhut et al., 1991	NIOSH—entire cohort	10	0.8 (0.4–1.6)
	≥1-year exposure; ≥20-year latency	4	1.0 (0.3–2.5)
Saracci et al., 1991	IARC cohort—exposed subcohort (males and females)	26	1.1 (0.7–1.6)
Alavanja et al., 1989	USDA forest or soil conservationists	22	1.5 (0.9–2.3)
Henneberger et al., 1989	New Hampshire paper and pulp workers	9	1.9 (0.9–3.6)
Solet et al., 1989	US Pulp and paper workers	1	0.4 (0.0–2.1)
Alavanja et al., 1988	USDA agricultural extension agents	21	1.3 (0.8–1.9)
Thomas, 1987	US flavor and fragrance chemical plant workers	6	1.4 *
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	9	0.7 (0.3–1.4)
Robinson et al., 1986	Northwestern US paper and pulp workers	4	0.3 (0.1–0.8)[d]
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)		
	Men	3	0.6 *
	Women	0	—
Blair et al., 1983	Florida pesticide applicators	4	4.0 Expected *

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Wiklund, 1983	Swedish male and female agricultural workers—incidence	777	0.8 (0.8–0.9)[e]
Burmeister, 1981	Iowa farmers	416	1.1 *
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—men	4	0.7 (0.3–1.9)
	women	1	0.3 (0.0–2.0)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone A—men	1	1.9 (0.0–10.5)
	Zone B—men	2	0.6 (0.1–2.0)
	women	1	0.5 (0.0–3.1)
	Zone R—men	20	0.8 (0.5–1.2)
	women	11	0.7 (0.4–1.3)
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		
	East coast	5	0.7 (0.2–1.6)
	West coast	33	0.8 (0.6–1.2)
	Swedish fishermen—incidence (men and women)		
	East coast	4	0.6 (0.2–1.6)
	West coast	37	1.0 (0.7–1.4)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	2	1.0 (0.3–4.2)
	women	1	1.6 (0.2–12.0)
Bertazzi et al., 1989a	Seveso residents—10-year follow-up		
	Zones A, B, R—men	9	0.6 (0.3–1.2)
	women	4	1.0 (0.3–2.7)
Bertazzi et al., 1989b	Seveso residents—10-year follow-up		
	Zone B—men	2	1.1 (0.3–4.5)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	86	1.2 (0.9–1.4)
	Navy	14	0.9 (0.5–1.5)
	Army	60	1.2 (0.9–1.5)
	Air Force	12	1.3 (0.7–2.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	101	1.2 (1.0–1.5)
	Navy	18	1.0 (0.6–1.6)
	Army	71	1.3 (1.0–1.6)
	Air Force	11	1.1 (0.5–1.8)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	17	2.5 (1.0–6.3)
	Mortality	19	3.1 (1.3–8.3)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	5	1.0 (0.3–3.5)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	38	1.4 (0.9–1.8)
CDVA, 1997b	Australian national service Vietnam veterans	6	1.5
Studies Reviewed in *Update 1996*			
Dalager et al., 1995	US Vietnam veterans—women	7	2.8 (0.8–10.2)
	Vietnam veteran nurses	7	5.7 (1.2–27.0)
Visintainer et al., 1995	Michigan Vietnam veterans	14	1.0 (0.6–1.7)
Studies Reviewed in *VAO*			
Thomas et al., 1991	US Vietnam veterans—women	5	2.7 (0.9–6.2)
Breslin et al., 1988	Army Vietnam veterans	82	0.9 (0.6–1.2)
	Marine Vietnam veterans	18	1.6 (0.5–5.8)
Anderson et al., 1986	Wisconsin Vietnam veterans	4	—

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 90% CI.
[e] 99% CI.
* Information not provided by study authors.
— Denoted by a dash in the original study.
Studies in *italics* have been superseded by newer studies of the same cohort.
ABBREVIATIONS: ADVA, Australian Department of Veteran Affairs; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC; International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. The SMR for pancreatic cancer was not associated with a JEM-based estimate of exposure to nonvolatile organochlorine compounds (never exposed: 67 cases; SMR = 0.84, 95% CI 0.65–1.06; ever exposed: 69 cases; SMR =1.12, 95% CI 0.87–1.42).

In the AHS study of cancer incidence, Alavanja et al. (2005) reported a slight decrease in the incidence of pancreatic cancer in private applicators (SIR = 0.73, 95% CI 0.53–0.97) and no increase in their spouses (SIR = 0.92, 95% CI 0.56–1.42). In the commercial applicators, the findings on pancreatic cancer were indeterminate; there were only three cases.

In investigating cancer mortality in the same prospective cohort study of private pesticide applicators and their spouses, Blair et al. (2005a) found that the rates of pancreatic cancer were reduced in both the applicators (SMR = 0.6, 95% CI 0.4–0.9) and their spouses (SMR = 0.7, 95% CI 0.3–1.2). The similarity to the results reported by Alavanja et al. (2005) is not unexpected, because median survival of pancreatic cancer is only about 3–6 months.

In the mortality study of phenoxy herbicide producers and sprayers in New Zealand ('t Mannetje et al., 2005), only three cases of pancreatic cancer were observed in the producer group and none in the sprayer group.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of pancreatic cancer was significantly reduced (32 cases; SMR = 0.7, 95% CI 0.48–0.99). The authors suggested that the relatively short duration of follow-up and the healthy-worker effect contributed to the observation of reduced mortality.

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 571 cases of pancreatic cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with pancreatic cancer was not significantly elevated (6 cases; OR = 1.79, 95% CI 0.79–4.05).

Magnani et al. (1987) reported a case–control mortality study of 343 pancreatic-cancer cases and 1,315 controls in the UK. A JEM was used to predict exposures to various chemical agents on the basis of job title as indicated on the death certificates. Estimated risks of pancreatic cancer associated with exposure to herbicides (RR = 0.7, 95% CI 0.3–1.5) and chlorophenols (RR = 0.8, 95% CI 0.5–1.4) were not significantly increased.

Environmental Studies No new environmental studies concerning exposure to the compounds of interest and pancreatic cancer were published since Update 2004.

Vietnam-Veteran Studies In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported five pancreatic-cancer deaths in the deployed and five in the non-deployed (CRR = 1.02, 95% CI 0.29–3.53).

A set of three reports updating the health status of Australian Vietnam veterans noted 86 cases of pancreatic cancer (SIR = 1.15, 95% CI 0.91–1.40) (ADVA, 2005a) and 101 deaths (SMR = 1.21, 95% CI 0.97–1.45) (ADVA, 2005b). However, in the report on the health of National Service veterans and non-deployed troops, the incidence of pancreatic cancer was much higher in deployed National Service veterans than in non-deployed veterans (RR = 2.46, 95% CI 1.04–6.27), and mortality from pancreatic cancer was also higher (RR = 3.13, 95% CI 1.31–8.26) (ADVA, 2005c). Information on the smoking status of neither National Service veterans nor non-deployed troops was available, but the investigators postulate that given the increased rates of lung, head, and neck cancers in the National Service veterans, those veterans might have higher rates of smoking than the non-deployed controls (ADVA, 2005c).

Biologic Plausibility

A 2-year study of female rats has reported increased incidences of pancreatic adenomas and carcinomas after treatment at the highest dose of TCDD (100 ng/kg per day) (Nyska et al., 2004). Chronic active inflammation, acinar-cell vacuolation, and an increase in proliferation of the acinar cells surrounding the vacuolated cells have been observed (Yoshizawa et al., 2005b).

Synthesis

The increased rates of pancreatic cancer among Australian Vietnam National Service veterans could be associated with increased rates of smoking and cannot be attributed to exposure to the compounds of interest. All other reports have been largely negative except the report of seven cases of pancreatic cancer (RR = 5.7, 95% CI 1.2–27) in US Vietnam female nurse veterans (Dalager et al., 1995).

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and pancreatic cancer.

Conclusions on All Cancers of the Digestive Organs

The original *VAO* report (IOM, 1994) considered "gastrointestinal tract tumors" as a group—which explicitly included stomach, colon, rectal, and pancreatic cancers—and concluded that there was suggestive evidence of *no* association with herbicide exposure. Cumulative results tables have been maintained for these four cancer sites, and another was added for esophageal cancer in *Update 2004*, but until now a global conclusion has been reached on gastrointestinal cancers overall while cancers associated with the liver have been considered separately. The committee decided to appraise the evidence separately for esophageal, stomach, colorectal, pancreatic, and hepatobiliary cancer to address VA's concern that all types of cancer be reported on with the greatest degree of specificity possible and to implement its own conviction that the tissues along the span of the digestive tract are likely to vary in their risk factors and responses to carcinogens. Drawing discrete conclusions is somewhat complicated because reported results on those sites are grouped in a variety of ways that may be influenced by the nature of the observed results in a given study.

For each of the cancer types previously grouped as "gastrointestinal tract tumors" with a categorization of limited or suggestive evidence of *no* association with exposure to the compounds of interest, this committee does conclude, however, that there is inadequate or insufficient evidence to support an association. There is not enough evidence to support an assertion about association, either positive or negative, with phenoxy herbicides or dioxin; and virtually no data are available on human response to cacodylic acid or picloram, so an assertion of *no* association with these two substances is not sustainable either.

LARYNGEAL CANCER

ACS estimated that 7,700 men and 1,810 women would receive diagnoses of cancer of the larynx (ICD-9 161) in the United States in 2006 and 2,950 men and 790 women would die from it

(Jemal et al., 2006). Those numbers constitute a little more than 0.7% of new cancer diagnoses and deaths. The incidence of cancer of the larynx increases with age, and it is more common in men than in women, with a sex ratio in the United States of about 4:1 among persons 50–64 years old. The average annual incidence of laryngeal cancer is shown in Table 6-11.

TABLE 6-11 Average Annual Cancer Incidence (per 100,000) of Laryngeal Cancer in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	10.4	9.7	21.9	15.8	15.4	28.3	24.1	24.4	38.0
Females	2.2	2.2	4.1	3.5	3.4	6.8	5.1	5.1	10.1

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Established risk factors for laryngeal cancer are tobacco and alcohol use, which are independent and act synergistically. Occupational exposures—long and intense exposures to wood dust, paint fumes, and some compounds used in the metalworking, petroleum, plastics, and textile industries—also could increase risk (ACS, 2004b). An IOM committee (2006) recently concluded that asbestos is a causal factor in laryngeal cancer (IOM, 2006), infection with human papilloma virus (HPV) might also raise the risk of laryngeal cancer (Hobbs and Burchall, 2004).

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and laryngeal cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-12 summarizes the results of the relevant studies.

TABLE 6-12 Selected Epidemiologic Studies—Laryngeal Cancer

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	18	0.9 (0.5–1.5)
	Ever	20	1.2 (0.8–1.9)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	*
	Phenoxy herbicide sprayers (>99% men)	0	*
Torchio et al., 1994	Italian farmers licensed to use pesticides	25	0.5 (0.3–0.7)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	2	1.1 (0.3–4.7)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators	1	1.0 (0.0–5.1)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Studies Reviewed in *Update 2002*			
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides		
	Foremen—incidence	0	*
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	7	0.9 (0.4–1.9)
Kogevinas et al., 1997	IARC cohort (men and women)	21	1.6 (1.0–2.5)
	Workers exposed to any phenoxy herbicide or chlorophenol	21	1.6 (1.0–2.5)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	15	1.7 (1.0–2.8)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	5	1.2 (0.4–2.9)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	2	2.9 (0.3–10.3)
	0-year latency	2	2.9 (0.4–10.3)
	15-year latency	1	—
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White men	162	0.7 (0.6–0.8)
	White women	0	— (0.0–3.3)
Studies Reviewed in *VAO*			
Fingerhut et al., 1991	NIOSH—entire cohort	7	2.1 (0.8–4.3)
	≥1-year exposure, ≥20-year latency	3	2.7 (0.6–7.8)
Manz et al., 1991	German production workers—men and women (Included in the IARC cohort)	2	2.0 (0.2–7.1)
Saracci et al., 1991	IARC cohort—exposed subcohort-(men and women)	8	1.5 (0.6–2.9)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	3.0 (0.0–16.8)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	4	2.3 (0.5–4.5)
ENVIRONMENTAL			
Studies Reviewed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Men	13	2.3 (1.2–3.8)
	Women	1	0.1 (0.0–0.6)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001[e]	Seveso residents—20-year follow-up		
	Zone A, B—men	64	1.3 (1.0–1.6)
	women	5	0.7 (0.3–1.7)
Bertazzi et al., 1998[e]	Seveso residents—15-year follow-up		
	Zone B—men	40	1.2 (0.9–1.7)
	women	2	0.5 (0.1–2.0)
	Zone R—males	208	0.9 (0.8–1.1)
	women	35	1.1 (0.8–1.5)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence	97	1.5 (1.2–1.8)
	Navy	21	1.5 (0.9–2.1)
	Army	69	1.6 (1.2–1.9)
	Air Force	7	0.8 (0.3–1.7)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—mortality	28	1.1 (0.7–1.5)
	Navy	6	1.1 (0.4–2.4)
	Army	19	1.1 (0.7–1.7)
	Air Force	3	0.8 (0.2–2.5)
ADVA, 2005c	Australian men conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	8	0.7 (0.2–1.6)
	Mortality	2	0.4 (0.0–2.4)
Boehmer et al., 2004	CDC Vietnam Experience Cohort	0	0 (*)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans		
	Oral cavity, pharynx, and larynx	4	0.6 (0.2–2.4)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	12	1.3 (0.7–2.2)
CDVA, 1997b	Australian national service Vietnam veterans	0	0 (0–>10)
Watanabe and Kang, 1996	Army Vietnam veterans compared with US men	50	1.3 *
	Marine Vietnam veterans	4	0.7 *
	Army Vietnam veterans	50	1.4 [f]

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[e] Report did not separate laryngeal from lung and other respiratory cancers.
[f] Statistically significant with the 95% CI not including 1.0.
* Information not provided by study authors.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. The SMR for cancer of the larynx was not associated with a JEM-based estimate of exposure to nonvolatile organochlorine compounds (never exposed: 18 cases; SMR = 0.92, 95% CI 0.54–1.45; ever exposed: 20 cases; SMR = 1.23, 95% CI 0.75–1.90).

In New Zealand, 't Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers from 1969 and 1973, respectively, through 2000. Laryngeal cancers were grouped with respiratory cancers (ICD-9 160–165; *n* = 13); from the results for the subcategories, "trachea, bronchus, lung" (ICD-9 162; *n* = 12) and "other" (ICD-9 163–165; *n* = 1), it is evident that no laryngeal cancer deaths (ICD-9 161) were observed in either the producer or the sprayer group.

Torchio et al. (1994) reported on the mortality experience of a cohort of 23,401 male farmers in the Piedmont area of Italy from the time they registered to use agricultural pesticides (1970–1974) through 1986. Those provinces are characterized by higher use of herbicides, particularly 2,4-D and MCPA, than the rest of the country. Mortality from laryngeal cancer was significantly lower in the farmers than in the regional population (SMR = 0.46, 95% CI 0.30–0.67).

Reif et al. (1989) performed a series of case–control analyses on the sample of 19,904 people with specified occupations among the 24,762 males 20 years old or older entered from 1980 to 1984 into the the New Zealand Cancer Registry. The focus of their study was on the 134 for whom forestry work was the most recent occupation listed. For each type of cancer, those with any other type of cancer were used as controls. Of 303 people with laryngeal cancer, two had most recently been forestry workers (OR = 1.14, 95% CI 0.28–4.65).

Environmental Studies

No relevant environmental studies concerning exposure to the compounds of interest and laryngeal cancer were published since *Update 2004*.

Vietnam-Veteran Studies

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported no deaths from laryngeal cancer in the deployed and two in the non-deployed. (The researchers estimated rate ratios only for sites of cancer with 10 or more deaths.)

A series of reports providing updates on the health status of Australian Vietnam veterans found a significant association with the incidence of laryngeal cancer (SIR = 1.46, 95% CI 1.17–1.75) (ADVA, 2005a) but not with mortality from laryngeal cancer (SMR = 1.09, 95% CI 0.69–1.49) (ADVA, 2005b) when comparing veterans with the general population. When Australian veterans deployed to Vietnam were compared with those not deployed there, however, both laryngeal-cancer incidence and mortality were non-significantly reduced (RR = 0.65, 95% CI 0.24–1.60 and RR = 0.42, 95% CI 0.04–2.37, respectively [ADVA, 2005c]).

Biologic Plausibility

No animal studies have identified an association between exposure to the compounds of interest and an increased incidence of laryngeal cancer. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Only three reports (all on Australian Vietnam veterans) published since *Update 2004* provided any useful data regarding the association between exposure to the compounds of interest and laryngeal cancer. Only in the study of cancer incidence compared with the general population was the rate of laryngeal cancer convincingly increased (ADVA, 2005a), but the study that included a reference group for comparing Vietnam-era veterans did not support the hypothesis that the increase was associated with having been in Vietnam (ADVA, 2005a). The conclusion that there is limited or suggestive evidence of an association between exposure to the compounds of interest and laryngeal cancer is not affected by the results of the new studies.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one compound of interest and laryngeal cancer.

LUNG CANCER

Lung cancer (carcinomas of the lung and bronchus, ICD-9 162.2–162.9) is the leading cause of cancer death in the United States. ACS estimated that 92,700 men and 81,770 women would receive diagnoses of lung cancer in the United States in 2006 and about 90,330 men and 72,130 women would die from it (Jemal et al., 2006). Those numbers represent roughly 12.5% of new cancer diagnoses and 29% of cancer deaths in 2006. The principal types of lung neoplasms are identified collectively as bronchogenic carcinoma (the bronchi are the two main branches of the trachea) and carcinoma of the lung. The trachea (ICD-9 162.0) is frequently grouped with the lung and bronchus under ICD-9 162. The lung is also a common site of the development of metastatic tumors.

In men and women, the incidence of lung cancer increases greatly beginning at about the age of 40 years. The incidence in people 50–54 years old is double that in people 45–49 years old, and it doubles again in those 55–59 years old. The incidence is consistently higher in black men than in women or white men. The average annual incidence of lung cancer in the United States is shown in Table 6-13.

ACS estimates that more than 90% of lung cancers in males are attributable to tobacco use (ACS, 1998). Smoking increases the risk of all histologic types of lung cancer, although the associations with squamous-cell and small-cell carcinomas are strongest. Other risk factors include exposure to asbestos, uranium, vinyl chloride, nickel chromates, coal products, mustard gas, chloromethyl ethers, gasoline, diesel exhaust, and inorganic arsenic (this does not imply that cacodylic acid, which is a metabolite of inorganic arsenic, can also be assumed to be a risk factor). Important environmental risk factors include exposure to tobacco smoke and radon (ACS, 2004c).

TABLE 6-13 Average Annual Incidence (per 100,000) of Lung and Bronchial Cancer in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	58.9	54.0	123.2	123.1	114.2	244.5	230.6	224.9	362.8
Females	46.7	47.0	67.0	96.0	98.2	125.5	159.3	168.3	177.6

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to at least one compound of interest and lung cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-14 summarizes the results of the relevant studies.

TABLE 6-14 Selected Epidemiologic Studies—Lung and Bronchus Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers—exposure to nonvolatile organochlorine compounds		
	Lung (ICD-9 162)		
	Never	356	1.0 (0.9–1.1)
	Ever	314	1.0 (0.9–1.2)
	Pleura (ICD-9 163)		
	Never	17	2.8 (1.6–4.5)
	Ever	4	0.8 (0.2–2.0)
	Other Respiratory (ICD-9 164–165)		
	Never	8	2.1 (0.9–4.2)
	Ever	2	0.7 (0.1–2.4)
Alavanja et al., 2005	US Agriculture Health Study - incidence (lung)		
	Private applicators (men and women)	266	0.5 (0.4–0.5)
	Spouses of private applicators (>99%women)	68	0.4 (0.3–0.5)
	Commercial applicators (men and women)	12	0.6 (0.3–1.0)
Blair et al., 2005a	US Agriculture Health Study (lung)		
	Private applicators (men and women)	129	0.4 (0.3–0.4)
	Years handled pesticides		
	≤10 years	25	0.4 * ($p < 0.05$)
	>10 years	80	0.3 * ($p < 0.05$)
	Spouses of private applicators (>99%women)	29	0.3 (0.2–0.5)
’t Mannetje et al., 2005	New Zealand phenoxy herbicide workers (trachea, bronchus, lung)		
	Producers (men and women)	12	1.4 (0.7–2.4)
	Sprayers (>99% men)	5	0.5 (0.2–1.1)
Torchio et al., 1994	Italian licensed pesticide users	155	0.5(0.4–0.5)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	30	1.3 (0.8–1.9)
Studies Reviewed in *Update 2004*			
Bodner et al., 2003	Dow chemical production workers— lung (Included in the IARC cohort and the NIOSH Dioxin Registry)	54	0.8 (0.6–1.1)
Swaen et al., 2004	Dutch licensed herbicide applicators (trachea and lung)	27	0.7 (0.5–1.0)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4–D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	Respiratory system	31	0.9 (0.6–1.3)
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxy herbicides		
	Foremen—incidence (bronchus and lung)	1	4.2 (0.1–23.2)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers—lung (Included in the IARC cohort and the NIOSH Dioxin Registry)	125	1.1 (0.9–1.3)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers (lung)	45	0.8 (0.6–1.1)
Kogevinas et al., 1997	IARC cohort (men and women, lung)		
	Workers exposed to any phenoxy herbicide or chlorophenol	380	1.1 (1.0–1.2)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	225	1.1 (1.0–1.3)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	148	1.0 (0.9–1.2)
Becher et al., 1996	German production workers (Included in the IARC cohort) (lung)	47	1.4 (1.1–1.9)
Ott and Zober, 1996	BASF employees—incidence		
	(respiratory system)	13	1.2 (0.6–2.0)
	TCDD 0.1–0.99 µg/kg of body weight	2	0.7 (0.1–2.5)
	TCDD >1 µg/kg of body weight	8	2.0 (0.9–3.9)
	(lung or bronchus)	11	1.1 (0.6–2.0)
	TCDD 0.1–0.99 µg/kg of body weight	2	0.8 (0.1–2.8)
	TCDD >1 µg/kg of body weight	8	2.2 (1.0–4.3)
Ramlow et al., 1996	Dow pentachlorophenol production workers—respiratory system (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	18	1.0 (0.6–1.5)
	15-year latency	17	1.1 (0.6–1.8)
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators 1972–1989 (trachea, bronchus, lung)		
	Incidence	39	0.9 (0.7–1.3)
	Mortality	37	1.0 (0.7–1.4)
Blair et al., 1993	US farmers from 23 states (lung)		
	White men	6,473	0.9 (0.9–0.9)
	White women	57	0.8 (0.6–1.1)
Bloemen et al., 1993	Dow 2,4-D production workers—respiratory system (Included in the IARC cohort and the NIOSH Dioxin Registry)	9	0.8 (0.4–1.5)
Kogevinas et al., 1993	IARC cohort, women (lung)—incidence	2	1.4 (0.2–4.9)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Lynge, 1993	Danish production workers, men (lung)—incidence (Included in the IARC cohort)	13	1.6 (0.9–2.8)
Studies Reviewed in *VAO*			
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort) (trachea, bronchus, lung)	9	0.8 (0.4–1.5)
Swaen et al., 1992	Dutch herbicide applicators (trachea and lung)	12	1.1 (0.6–1.9)
Coggon et al., 1991	British phenoxy herbicide workers (lung) (Included in the IARC cohort)	19	1.3 (0.8–2.1)
	Workers with exposure above background levels	14	1.2 (0.7–2.1)
Fingerhut et al., 1991	NIOSH—entire cohort (trachea, bronchus, lung)	89	1.1 (0.9–1.4)
	≥1-year exposure; ≥20-year latency	40	1.4 (1.0–1.9)
Green, 1991	Herbicide sprayers in Ontario (lung)	5	*
Manz et al., 1991	German production workers, men (lung) (Included in the IARC cohort)	26	1.7 (1.1–2.4)
Saracci et al., 1991	IARC cohort, men and women (trachea, bronchus, lung)	173	1.0 (0.9–1.2)
McDuffie et al., 1990	Saskatchewan farmers applying herbicides (lung)	103	0.6 (* NS)
Zober et al., 1990	BASF employees (trachea, bronchus, lung) — incidence	4	2.0 (0.7–4.6)
Bender et al., 1989	Herbicide sprayers in Minnesota (trachea, bronchus, lung)	54	0.7 (0.5–0.9)
Wiklund et al., 1989a	Swedish pesticide applicators (trachea, bronchus, lung)	38	0.5 (0.4–0.7)
Bond et al., 1988	Dow 2,4-D production workers—lung (Included in the IARC cohort and the NIOSH Dioxin Registry)	8	1.0 (0.5–2.0)
	Low cumulative exposure	1	0.7 (* NS)
	Medium cumulative exposure	2	1.0 (* NS)
	High cumulative exposure	5	1.7 (* NS)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort) (lung, pleura, and retroperitoneal)	117	1.2 (1.0–1.4)
	Background exposure	39	1.0 (0.7–1.4)
	Low-grade exposure	35	1.1 (0.8–1.6)
	High-grade exposure	43	1.3 (1.0–1.8)
Lynge, 1985	Danish production workers—lung, incidence (Included in the IARC cohort)		
	Men	38	1.2 *
	Women	6	2.2 *
Blair et al., 1983	Licensed pesticide applicators in Florida, lawn and ornamental pest category only (lung)	7	0.9 *
Axelson et al., 1980	Swedish herbicide sprayers (lung)	3	1.4 *
ENVIRONMENTAL			
Studies Reviewed in *Update 2004*			
Fukuda et al., 2003	Residents of municipalities in Japan with vs without waste incineration plants (lung)		
	Age-adjusted mortality (100,000), men		39.0 ± 6.7 vs 41.6 ± 9.1 ($p = 0.001$)
	Age-adjusted mortality (100,000), women		13.7 ± 3.8 vs 14.3 ± 4.6 ($p = 0.11$)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Studies Reviewed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia (lung)		
	Men	168	3.1 (2.6–3.5)
	Women	40	0.4 (0.3–0.6)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up—incidence (lung)		
	Zones A, B—men	57	1.3 (1.0–1.7)
	women	4	0.6 (0.2–1.7)
Bertazzi et al., 1998	Seveso residents—15-year follow-up—incidence (lung)		
	Zone A—men	4	1.0 (0.4–2.6)
	Zone B—men	34	1.2 (0.9–1.7)
	women	2	0.6 (0.1–2.3)
	Zone R—men	176	0.9 (0.8–1.1)
	women	29	1.0 (0.7–1.6)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up—incidence (lung)		
	Zone A—men	4	1.0 (0.3–2.5)
	Zone B—men	34	1.2 (0.9–1.7)
	women	2	0.6 (0.1–2.1)
	Zone R—men	176	0.9 (0.8–1.0)
	women	29	1.0 (0.7–1.5)
Svensson et al., 1995	Swedish fishermen		
	East coast (lung and larynx)	16	0.8 (0.5–1.3)
	West coast (lung and larynx)	77	0.9 (0.7–1.1)
Studies Reviewed in *VAO*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence (trachea, bronchus, lung)		
	Zone A—men	2	0.8 (0.2–3.4)
	Zone B—men	18	1.1 (0.7–1.8)
	Zone R—men	96	0.8 (0.7–1.0)
	women	16	1.5 (0.8–2.5)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	576	1.2 (1.1–1.3)
	Branch of Service		
	Navy	141	1.4 (1.2–1.7)
	Army	372	1.2 (1.1–1.3)
	Air Force	63	1.0 (0.7–1.2)
	Histologic type		
	Adenocarcinoma	188	1.5 (1.2–1.7)
	Squamous	152	1.2 (1.0–1.4)
	Small-cell	87	1.2 (0.97–1.5)
	Large-cell	79	1.1 (0.8–1.3)
	Other	70	1.1 (0.8–1.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population–Mortality	544	1.2 (1.1–1.3)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Branch of Service		
	Navy	135	1.4 (1.2–1.6)
	Army	339	1.1 (1.0–1.6)
	Air Force	71	1.1 (0.9–1.4)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence (1982–2000)	78	2.4 (1.6–3.5)
	Histologic type		
	Adenocarcinoma	27	2.7 (1.3–5.6)
	Squamous	19	5.0 (1.8–17.0)
	Small-cell	14	2.1 (0.9–5.5)
	Large-cell	8	1.1 (0.4–3.3)
	Other	10	1.8 (0.6–5.5)
	Mortality (1966–2001)	67	1.8 (1.2–2.7)
Pavuk et al., 2005	White Air Force comparison subjects only (respiratory system)—incidence		
	Serum TCDD levels (pg/g), based on model with exposure variable $\log_e$(TCDD) [f]		
	Per unit increase of -$\log_e$(TCDD) in pg/g	36	1.7 (0.9–3.2)
	Quartiles (pg/g)		
	0.4–2.6	6	1.0
	2.6–3.8	8	1.1 (0.3–3.4)
	3.8–5.2	9	1.2 (0.4–3.5)
	>5.2	13	1.9 (0.7–5.5)
	Number of years served in southeast Asia (SEA)		
	Per year of service	36	1.1 (0.9–1.2)
	Quartiles (years in SEA)		
	0.8–1.3	8	1.0
	1.3–2.1	4	0.5 (0.2–1.8)
	2.1–3.7	11	0.7 (0.3–2.0)
	3.7–16.4	13	0.7 (0.3–2.0)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (trachea, bronchus, lung)	41	1.0 (0.6–1.5)
	Low pay grade at time of discharge	*	1.6 (0.9–3.0)
	High pay grade at time of discharge	*	0.8 (0.6–1.1)
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	White AFHS subjects vs national rates (respiratory system)		
	Ranch Hand veterans		
	Mortality—All	21	0.9 (0.6–1.3)
	Incidence—All	33	1.1 (0.8–1.6)
	With tours between 1966–1970	26	1.1 (0.7–1.6)
	Comparison veterans		
	Mortality—All	38	1.1 (0.8–1.5)
	Incidence—All	48	1.2 (0.9–1.6)
	With tours between 1966–1970	37	1.2 (0.9–1.6)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans (lung and bronchus)	10	3.7(0.8–17.1)
AIHW, 1999	Australian Vietnam veterans—Validation study (lung)	46 [e]	65 expected (49–81)
CDVA, 1998a	Australian Vietnam veterans (lung)	120	65 expected (49–89)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian Vietnam veterans (lung)	212	1.3 (1.1–1.4)
CDVA, 1997b	Australian National Service Vietnam veterans (lung)	27	2.2 (1.1–4.3)
Dalager and Kang, 1997	Army Chemical Corps veterans (respiratory system)	11	1.4 (0.4–5.4)
Mahan et al., 1997	Case–control of Vietnam-era Vietnam veterans—incidence (lung)	134	1.4 (1.0–2.0)
Watanabe and Kang, 1996	US Army and Marine Corps Vietnam veterans (lung)		
	Army Vietnam service	1,139	1.1 * (p <0.05)
	Non-Vietnam	1,141	1.1 * (p <0.05)
	Marine Vietnam service	215	1.2 (1.0–1.3)
	Non-Vietnam	77	0.9 *
Watanabe and Kang, 1995	Marine Vietnam service vs non-Vietnam (lung)	42	1.3 (0.8–2.1)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[e] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have lung cancer?"
[f] The original paper implied that the exposure metric for TCDD was based on actual measured serum levels of TCDD. Subsequent correspondence between the Committee and the investigators indicated that the metric was actually transformed using the natural logarithm of TCDD.
* Information not provided by study authors.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; MCPA, methyl-4-chlorophenoxyacetic acid; NS, not significant; PCDD, polychlorinated dibenzodioxin; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. The SMR of lung cancer was not associated with a JEM-based estimate of exposure to nonvolatile organochlorine compounds (never exposed: 356 cases; SMR = 0.98, 95% CI 0.88–1.08; ever exposed: 314 cases; SMR =1.04, 95% CI 0.93–1.17).

Publications arising from the US AHS have provided findings on the risk of lung cancer in farmers (private pesticide applicators), their spouses, and commercial pesticide applicators, but no results peculiar to any of the herbicides under consideration here have been published. Blair et al. (2005a) reported that farmers and their spouses both had mortality from lung cancer substantially lower than the general population of Iowa and North Carolina, with rate ratios of around 0.4 (see Table 6-14). Such low mortality may have been due to chance, the healthy-worker effect, lower consumption of tobacco, increased level of exercise, or the protective effect of endotoxins to which many agricultural workers may be exposed.

In a publication on the incidence of lung cancer through 2001, Alavanja et al. (2004) stated, without giving quantitative results, that the farmers had a markedly lower incidence of lung cancer

than the general populations of their states, which might be largely attributable to low rates of smoking; 2,4-D was not among the chemicals for which specific rate ratios were provided, although it was implicit that 2,4-D exposure had been analyzed for any association with the occurrence of lung cancer. A later publication on cancer incidence from recruitment through 2002 (Alavanja et al., 2005) presented findings on subgroups (farmers, their spouses, and commercial applicators; see Table 6-14), none of which showed an increased risk of lung cancer.

In a cohort study in New Zealand, 't Mannetje et al. (2005) found that mortality from cancer of the trachea, bronchus, or lung (ICD-9 162) showed a non-significant excess (SMR = 1.4, 95% CI 0.7–2.4) in phenoxy herbicide producers, who also had potential exposure to dioxins. Among phenoxy herbicide sprayers, however, the estimated risk was lower than expected (SMR = 0.5, 95% CI 0.2–1.1).

Torchio et al. (1994) reported on the mortality experience of a cohort of 23,401 male farmers in the Piedmont area of Italy from the time when they registered to use agricultural pesticides (1970–1974) through 1986. The provinces in that area are characterized by higher use of herbicides, particularly 2,4-D and MCPA, than the rest of the country. The estimated risk of lung cancer was significantly reduced (155 cases; SMR = 0.45, 95% CI 0.38–0.52). The authors suggested that the relatively short duration of follow-up and the healthy-worker effect contributed to the observation of reduced mortality.

Reif et al. (1989) performed a series of case–control analyses on the sample of 19,904 people with specified occupations among the 24,762 males 20 years old or older entered from 1980 to 1984 into the the New Zealand Cancer Registry. The focus of their study was on the 134 for whom forestry work was the most recent occupation listed. For each type of cancer, the registrants with any other type of cancer were used as controls. Of 4,224 people with lung cancer, 30 had most recently been forestry workers (OR =1.27, 95% CI 0.84–1.91).

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and respiratory cancer were published since *Update 2004*.

Vietnam-Veteran Studies

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) did not find any excess risk of mortality from lung cancer in the entire cohort (CRR = 0.94, 95% CI 0.62–1.48) but did observe an association in veterans who were classified as having a low pay grade at the time of discharge (RR = 1.64, 95% CI 0.94–2.89). When the first findings of the study (Boyle et al., 1987) were considered in *VAO*, mortality had been too low to support any conclusions.

Pavuk et al. (2005) analyzed the incidences of several types of cancer in subjects in the comparison group in the AFHS in 1982–2003 in terms of their serum TCDD concentrations and the number of years served in Southeast Asia. Their work extends to people with lower TCDD exposures the analyses of cancer incidences observed in the Ranch Hand subjects themselves (Akhtar et al., 2004), which were considered in *Update 2004*. In those analyses, cancers of the lung were included with other cancers of the "respiratory system". There was a non-significant

increase in the incidence of cancer of the respiratory tract with increased serum TCDD (RR = 1.7 per unit increase in $\log_e$[TCDD concentration in picograms per gram], 95% CI 0.9–3.2). However, there was no evidence of an association between the number of years of service in Southeast Asia and the incidence of respiratory cancer (see Table 6-14 for a comparison of the risks estimated for the quartiles of TCDD concentrations with the number of years served in Southeast Asia).

The recent update of the health experience of Australian Vietnam veterans showed significant associations with the incidence of lung cancer (SIR = 1.23, 95% CI 1.13–1.33) (ADVA, 2005a) and mortality (SMR = 1.18, 95% CI 1.08–1.28) (ADVA, 2005b) when all Vietnam veterans (all male, all branches, "defence forces", and "Citizen Military Forces") were compared with the general population of Australia. When conscripted male Army veterans deployed to Vietnam (National Service veterans) were compared with their non-deployed counterparts (National Service non-veterans), the increase in the incidence of lung cancer was more pronounced (SIR = 2.35, 95% CI 1.60–3.49) (ADVA, 2005c). The latter analysis makes use of the presumably more comparable reference group of other veterans and may account for the underestimation of rate ratios obtained when the general population is used (the healthy-warrior effect). There was some variation in rate ratios with branch of service for both incidence of lung cancer (ADVA, 2005a) and mortality from it (ADVA, 2005b); increases were most pronounced in the Navy, substantial in the Army, and equivocal in the Air Force (see Table 6-14). Rate ratios of some histologic subtypes, especially adenocarcinomas and squamous-cell carcinomas, were higher.

Biologic Plausibility

As noted in previous *VAO* reports, there is evidence of increased incidence of squamous-cell carcinoma of the lung in male and female rats exposed to TCDD at high concentrations (Kociba et al., 1978; Van Miller et al., 1977). A more recent study reported a significant increase in cystic keratinizing epitheliomas in female rats exposed to TCDD for 2 years (NTP, 2006), and increases in the incidences of bronchiolar metaplasia, acinar vacuolization, and inflammation were observed in the high-dose (100-ng/kg) group.

A recent 2-year study of F344 rats exposed to cacodylic acid at 0-100 ppm and B6C3F1 mice exposed at 0–500 ppm failed to detect neoplasms in the lung at any dose (Arnold et al., 2006); this finding is consistent with that of previous studies. However, exposure to cacodylic acid has previously been shown to increase tumor multiplicity in mouse strains susceptible to developing lung tumors (for example, A/J strain; Hayashi et al., 1998) or mice pretreated with an intitiating agent (4-nitroquinoline 1-oxide; Yamanaka et al., 1996). The data indicate that cacodylic acid may act as a tumor promoter in the lung.

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

The evidence remains inconclusive but suggestive of an association between exposure to at least one compound of interest and the risk of developing or dying from lung cancer. The best

evidence comes from studies of heavily exposed occupational cohorts. The latest findings from the US AFHS suggest an increase in risk with concentration of serum TCDD even in the subjects who made up the comparison group, whose TCDD exposure was considerably lower than that of the main Ranch Hand group. The American and Australian cohort studies of Vietnam veterans, which presumably cover a large proportion of exposed soldiers, show higher than expected incidence of and mortality from lung cancer. The main limitations of those studies are that there was no assessment of exposure, as there was in, for example, the Ranch Hand study, and that some potential confounding variables, notably smoking, could not be accounted for. It is unlikely that the distribution of smoking would differ greatly between veteran cohorts, so the likelihood of important confounding by smoking is probably low. Those studies therefore lend support to the findings of the Ranch Hand study. The methodologically sound US AHS did not show any increased risks of lung cancer, but, although there was substantial 2,4-D exposure in this cohort (Blair et al., 2005b), dioxin exposure of these contemporary farmers was probably negligible. The evidence from occupational studies remains inconsistent; for example, in the study by Bodner et al. (2003), no excess risks of lung cancer in chemical-company employees were found, but these results must be weighed against results in previously reviewed occupational cohorts that did show evidence of an association (Becher et al., 1996; Ott and Zober, 1996; Steenland et al., 1999).

Also supportive of an association are the numerous lines of mechanistic evidence, discussed in the section on biologic plausibility, which provide further support for the conclusion that the evidence of an association is limited or suggestive.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one compound of interest and carcinomas of the lung, bronchus, and trachea.

BONE AND JOINT CANCER

ACS (2006a) estimated that about 1,500 men and 1,260 women would receive diagnoses of bone or joint cancer (ICD-9 170) in the United States in 2006 and that 730 men and 530 women would die from these cancers. Primary bone cancers are among the least common malignancies, but the bones are frequent sites of tumors secondary to cancers that have metastasized. Only primary bone cancer is considered here. The average annual incidence of bone and joint cancer is shown in Table 6-15.

Bone cancer is more common in teenagers than in adults. It is rare among people in the age groups of most Vietnam veterans (50–64 years). Among the risk factors for adults' contracting of bone or joint cancer are exposure to ionizing radiation in treatment for other cancers and a history of some non-cancer bone diseases, including Paget's disease.

TABLE 6-15 Average Annual Incidence (per 100,000) of Bone and Joint Cancer in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	0.9	0.9	0.7	1.1	1.2	1.1	1.4	1.5	1.00
Females	0.9	1.0	0.4	0.9	1.1	0.3	1.0	1.0	0.4

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and bone and joint cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-16 summarizes the results of the relevant studies.

TABLE 6-16 Selected Epidemiologic Studies—Bone and Joint Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
Merletti et al., 2006	Association of occupational exposure and risk of bone sarcoma	18	2.6 (1.5–4.6)
't Mannetje et al., 2005	Phenoxy herbicide producers and sprayers (men and women)	0	—
Torchio et al., 1994	Italian licensed pesticide users	10	0.8 (0.4–1.4)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	1	1.7 (0.2–13.3)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licenced herbicide applicators	0	—
Studies Reviewed in *Update 2000*			
Rix et al., 1998	Danish paper mill workers—incidence		
	Men	1	0.5 (0.0–2.7)
	Women	0	—
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	1	0.5 (0.0–2.6)
Hertzman et al., 1997	British Columbia sawmill workers		
	Mortality	5	1.3 (0.5–2.7)
	Incidence	4	1.1 (0.4–2.4)
Kogevinas et al., 1997	IARC cohort (men and women)	5	1.2 (0.4–2.8)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	3	1.1 (0.2–3.1)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	2	1.4 (0.2–5.2)
	Workers exposed to any phenoxy herbicide or chlorophenol	5	1.2 (0.4–2.7)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	*
	0-year latency	0	—
	15-year latency	0	—
Studies Reviewed in *Update 1996*			

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Blair et al., 1993	US farmers in 23 states		
	White men	49	1.3 (1.0–1.8)
	White women	1	1.2 (0.0–6.6)
Collins et al., 1993	Monsanto Company workers (Included in the NIOSH cohort)	2	5.0 (0.6–18.1)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish and Italian farm workers		
	Male Danish farmers	9	0.9 *
	Female Danish farmers	0	*
Fingerhut et al., 1991	NIOSH—entire cohort	2	2.3 (0.3–8.2)
	≥1-year exposure, ≥20-year latency	1	5.5 (0.1–29.0)
Zober et al., 1990	BASF employees—basic cohort	0	0 (0.0–65.5)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	— (0.0–31.1)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	1	0.9 (0.0–5.0)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	44	1.0 (0.6–1.4)[d]
Burmeister, 1981	Iowa farmers	56	1.1 (NS)
ENVIRONMENTAL			
Studies Reviewed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Mortality standardized to Samara Region (bone, soft-tissue cancer)		
	Men	7	2.1 (0.9–4.4)
	Women	7	1.4 (0.6–3.0)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 1998	Seveso residents—15-year follow-up		
	Zone B women	1	2.6 (0.3–19.4)
	Zone R men	2	0.5 (0.1–2.0)
	Zone R women	7	2.4 (1.0–5.7)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B women	1	2.6 (0.0–14.4)
	Zone R men	2	0.5 (0.1–1.7)
	Zone R women	7	2.4 (1.0–4.9)
VIETNAM VETERANS			
Studies Reviewed in *Update 1998*			
Clapp, 1997	Massachusetts Vietnam veterans	4	0.9 (0.1–11.3)
AFHS, 1996	Air Force Ranch Hand veterans	0	*
Studies Reviewed in *VAO*			
Breslin et al., 1988	Army Vietnam veterans	27	0.8 (0.4–1.7)
	Marine Vietnam veterans	11	1.4 (0.1–21.5)
Anderson et al., 1986	Wisconsin Vietnam veterans	1	*
Lawrence et al., 1985	New York Vietnam veterans	8	1.0 (0.3–3.0)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 99% CI.

* Information not provided by study authors.
— Denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Update of the Epidemiologic Literature

Occupational Studies

In New Zealand,'t Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers from 1969 and 1973, respectively, through 2000. No deaths from bone and joint cancer (ICD-9 170) were observed in either the producer or sprayer group.

Merletti et al. (2006) reported results from a multicenter case–control study conducted in seven European countries in 1995–1997 and focused on rare cancers, including bone sarcomas. A total of 96 cases were identified, and controls were selected in at least a 1:4 ratio and matched on the basis of age group, sex, and region. Exposure was determined indirectly solely on the basis of self-reported job titles. Although risk was significantly increased in those who reported use of pesticides, insecticides, or herbicides, no data are given with respect to the specific compounds of interest to this report.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of bone cancer was reduced (10 cases; SMR = 0.75, 95% CI 0.36–1.38).

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 49 cases of bone cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with bone cancer (1 case; OR = 1.72, 95% CI 0.22–13.30) was not significantly elevated.

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and bone and joint cancer were published since *Update 2004*.

Vietnam-Veteran studies

The AFHS completed the report on its scheduled 2002 follow-up examination of participants. The examination included questionnaires, physical examinations, and clinical assessments, all of which were used to ascertain bone-cancer risk in participants. Too few events were observed in the cohort to allow assessment of the risk.

The Third Australian Vietnam Veterans Mortality Study 2005 assessed mortality in Australian Vietnam veterans in all branches of service. Mortality experience (through 2001) in the veterans was compared with that in the general population of Australia. However, too few cases of bone cancer were observed in the cohort to allow assessment of RR.

Biologic Plausibility

No animal studies reported an increased incidence of bone and joint cancers after exposure to the compounds of interest. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Results of several pertinent studies have been published since the previous update and were noted above. The studies either reported a non-significant increase in risk of bone and joint cancer, observed too few events to estimate RR adequately, or did not present data that sufficiently linked observed results to specific compounds of interest to this report. Thus, the new results add little to the previous body of results, summarized in Table 6-16, that taken together do not indicate an association between exposure to the compounds of interest and bone cancer.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and bone cancer. That conclusion is based on occupational and environmental studies in which subjects were exposed to a variety of herbicides and herbicide mixtures.

SOFT-TISSUE SARCOMAS

Soft-tissue sarcomas (STS) (ICD-9 164.1, 171) arises in soft somatic tissues within and between organs. Three of the most common types of STS—liposarcoma, fibrosarcoma, and rhabdomyosarcoma—occur in similar numbers in men and women. Because of the diverse characteristics of STS, accurate diagnosis and classification can be difficult. ACS estimated that in 2006 about 5,720 men and 3,810 women would receive diagnoses of STS in the United States

and that about 1,830 men and 1,670 women would die from it (ACS, 2006a). The average annual incidence of STS is shown in Table 6-17.

TABLE 6-17 Average Annual Incidence (per 100,000) of Soft-Tissue Sarcoma (Including Malignant Neoplasms of the Heart) in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	4.2	4.3	4.3	5.0	4.9	6.7	6.7	7.3	3.5
Females	2.9	3.1	3.1	4.2	4.0	7.1	5.1	4.8	7.7

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Among the risk factors for STS are exposure to ionizing radiation during treatment for other cancers and some inherited conditions, including Gardner's syndrome, Li-Fraumeni syndrome, and neurofibromatosis. Several chemical exposures have been identified as possible risk factors (Zahm and Fraumeni, 1997).

Conclusions from *VAO* and Updates

The committee responsible for *VAO* judged that the strong findings in the IARC and NIOSH cohorts, plus extensive Scandinavian case–control studies, complemented by consistency in preliminary reports on the Seveso population and one statistically significant finding in a state study of Vietnam veterans, constituted sufficient information to determine that there is an association between exposure to at least one of the compounds of interest and STS. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-18 summarizes the relevant studies.

TABLE 6-18 Selected Epidemiologic Studies—Soft-Tissue Sarcoma

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	8	1.2 (0.5–2.4)
	Ever	4	0.8 (0.2–2.0)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	0.0 (0.0–19.3)
	Phenoxy herbicide sprayers (>99% men)	1	4.3 (0.1–23.8)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	10	0.7 (0.3–1.2)
	Spouses of private applicators (>99% women)	3	0.5 (0.1–1.4)
	Commercial applicators (men and women)	—	0.0 (0–3.8)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	4	0.7 (0.2–1.8)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
	Spouses of private applicators (>99% women)	3	1.4 (0.3–4.1)
Torchio et al., 1994	Italian licensed pesticide users	2	1.0 (0.1–3.5)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	4	3.2 (1.2–9.0)
Studies Reviewed in *Update 2004*			
Bodner et al., 2003	Dow chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	2	2.4 (0.3–8.6)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	*
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)	0	*
Rix et al., 1998	Danish paper mill workers—incidence		
	Women employed in sorting and packing	8	4.0 (1.7–7.8)
	Men employed in sorting and packing	12	1.2 (0.6–2.0)
Studies Reviewed in *Update 1998*			
Hertzman et al., 1997	Canadian sawmill workers	11	1.0 (0.6–1.7)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	9	2.0 (0.9–3.8)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	6	2.0 (0.8–4.4)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	2	1.4 (0.2–4.9)
Ott and Zober, 1996	BASF employees—incidence	0	0.2 expected
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	0.2 expected
Studies Reviewed in *Update 1996*			
Kogevinas et al., 1995	IARC cohort—incidence (men and women)	11	*
Mack, 1995	US cancer registry data (SEER program) review		
	Men	3,526	*
	Women	2,886	*
Blair et al., 1993	US farmers in 23 states	98	0.9 (0.8–1.1)
Lynge, 1993	Danish production workers—updated incidence for men and women (Included in the IARC cohort)	5	2.0 (0.7–4.8)
Kogevinas et al., 1992	IARC cohort (men and women)		
	10–19 years since first exposure	4	6.1 (1.7–15.5)
Studies Reviewed in *VAO*			
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort)	0	0.0 (0.0–23.1)
Hansen et al., 1992	Danish gardeners—incidence (men and women)		
	Male gardeners	3	5.3 (1.1–15.4)
Smith and Christophers, 1992	Australia residents	30	1.0 (0.3–3.1)
Fingerhut et al., 1991	NIOSH cohort—entire cohort	4	3.4 (0.9–8.7)
	≥1-year exposure, ≥20-year latency	3	9.2 (1.9–27.0)
Manz et al., 1991	German production workers—men and women (Included in the IARC cohort)	0	*
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	4	2.0 (0.6–5.2)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Zober et al., 1990	BASF employees—basic cohort	0	*
Alavanja et al., 1989	USDA forest and soil conservationists	2	1.0 (0.1–3.6)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	*
Wiklund et al., 1988, 1989b	Swedish agricultural workers (men and women)	7	0.9 (0.4–1.9)
Woods et al., 1987	Washington State residents—incidence		
	High phenoxy exposure	*	0.9 (0.4–1.9)
	Self-reported chloracne	*	3.3 (0.8–14.0)
Coggon et al., 1986	British MCPA chemical workers (Included in the IARC cohort)	1	1.1 (0.03–5.9)
Hoar et al., 1986	Kansas residents—incidence		
	All farmers	95	1.0 (0.7–1.6)
	Farm use of herbicides	22	0.9 (0.5–1.6)
Smith and Pearce, 1986	Reanalysis of New Zealand workers	133	1.1 (0.7–1.8) [d]
Vineis et al., 1986	Italian rice growers		
	Among all living females	5	2.4 (0.4–16.1)
Smith et al., 1984	Update of New Zealand workers	17	1.6 (0.7–3.8) [d]
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)		
	Men	5	2.7 (0.9–6.3)
	Women	0	*
Balarajan and Acheson, 1984	Agricultural workers in England		
	Overall	42	1.7 (1.0–2.9)
	Those under 75 years old	33	1.4 (0.8–2.6)
Blair et al., 1983	Florida pesticide applicators	0	*
Smith et al., 1983	New Zealand workers exposed to herbicides	17	1.6 (0.8–3.2) [d]
Hardell, 1981	Swedish residents		
	Exposed to phenoxy acids	13	5.5 (2.2–13.8)
	Exposed to chlorophenols	6	5.4 (1.3–22.5)
Eriksson et al., 1979, 1981	Swedish workers	25	(2.5–10.4) 5:1 matched
ENVIRONMENTAL			
New Studies			
Pahwa et al., 2006	Any phenoxyherbicide	46	1.10 (0.7–1.5)
	2,4-D	41	0.96 (0.6–1.5)
	Mecoprop	12	0.98 (0.5–1.9)
	MCPA	12	1.08 (0.5–2.2)
Studies Reviewed in *Update 2004*			
Comba et al., 2003	Residents near an industrial-waste incinerator in Mantua, Italy—incidence		
	Residence within 2 km of incinerator	5	31.4 (5.6–176.1)
Tuomisto et al., 2004	Finish STS patients and controls	110	
	Quintile 2 (median tissue concentration 20 ng/kg WHO-TEQ)	*	0.4 (0.2–1.1)
	Quintile 5 (median tissue concentration ~60 ng/kg WHO-TEQ)	*	0.7 (0.2–2.0)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Studies Reviewed in *Update 2002*			
Costani et al., 2000	Residents near a chemical plant in Mantua, Italy—incidence	20	2.3 (1.3–3.5)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso—20-year follow-up (men and women)	0	*
Viel et al., 2000	Residents near a French solid-waste incinerator—incidence		
	Spatial cluster	45	1.4 ($p = 0.004$)
	1994–1995	12	3.4 ($p = 0.008$)
Bertazzi et al., 1998	Seveso—15-year follow-up (men and women)		
	Zone R males	4	2.1 (0.7–6.5)
Studies Reviewed in *Update 1998*			
Bertazzi et al. 1997	Seveso residents—15-year follow-up (men and women)		
	Zone R men	4	2.1 (0.6–5.4)
Gambini et al., 1997	Italian rice growers	1	4.0 (0.1–22.3)
Svensson et al., 1995	Swedish fishermen—incidence (men and women)		
	West coast	3	0.5 (0.1–1.4)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—morbidity		
	Zone R men	6	2.8 (1.0–7.3)
	Zone R women	2	1.6 (0.3–7.4)
Studies Reviewed in *VAO*			
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination (men and women)	6	1.6 (0.7–3.5)
Bertazzi et al., 1989a	Seveso residents—10-year follow up		
	Zone A, B, R men	2	5.4 (0.8–38.6)
	Zone A, B, R women	1	2.0 (0.2–1.9)
Bertazzi et al., 1989b	Seveso residents—10-year follow up		
	Zone R men	2	6.3 (0.9–45.0)
	Zone B women	1	17.0 (1.8–163.6)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence	35	1.0 (0.7–1.3)
	Navy	6	0.8 (0.3–1.7)
	Army	29	1.2 (0.8–1.6)
	Air Force	0	0.0 (0.0–1.1)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—mortality	12	0.8 (0.4–1.3)
	Navy	3	0.9 (0.2–2.4)
	Army	9	0.8 (0.4–1.5)
	Air Force	0	0.0 (0.0–2.3)
ADVA, 2005c	Australian men conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		
	Incidence	10	1.0 (0.4–2.4)
	Mortality	3	0.5 (0.1–2.0)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	1	0.8 (0.1–12.8)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
AIHW, 1999	Male Australian Vietnam veterans	14	27 expected (17–37)
CDVA, 1998a	Male Australian Vietnam veterans	398 [e]	27 expected (17–37)
CDVA, 1998b	Female Australian Vietnam veterans	2 [e]	0 expected (0–4)
Studies Reviewed in *Update 1998*			
Clapp, 1997	Massachusetts Vietnam Veterans	18	1.6 (0.5–5.4)
CDVA, 1997a	Australian military Vietnam veterans	9	1.0 (0.4–1.8)
CDVA, 1997b	Australian national service Vietnam veterans	2	0.7 (0.6–4.5)
AFHS, 1996	Ranch Hand veterans	0	*
Watanabe and Kang, 1995	US Marines in Vietnam	0	*
Studies Reviewed in *Update 1996*			
Visintainer et al., 1995	Michigan Vietnam veterans	8	1.1 (0.5–2.2)
Studies Reviewed in *VAO*			
Watanabe et al., 1991	Army Vietnam veterans	43	1.1
	Marine Vietnam veterans	11	0.7
Bullman et al., 1990	Army I Corps Vietnam veterans	10	0.9 (0.4–1.6)
Michalek et al., 1990	Ranch Hand veterans	1	*
	Comparisons	1	*
Breslin et al., 1988	Army Vietnam veterans	30	1.0 (0.8–1.2)
	Marine Vietnam veterans	8	0.7 (0.4–1.3)
Kogan and Clapp, 1988	Vietnam veterans in Massachusetts	9	5.2 (2.4–11.1)
Fett et al., 1987	Australian Vietnam veterans	1	1.3 (0.1–20.0)
Anderson et al., 1986	Wisconsin Vietnam veterans	4	*
Breslin et al., 1986	US Vietnam veterans		
	Army	30	1.0 *
	Marines	8	0.7 *
Kang et al., 1986	Vietnam veterans vs. Vietnam-era veterans	86	0.8 (0.6–1.1)
Lawrence et al., 1985	New York State Vietnam veterans	2	1.1 (0.2–6.7)
Greenwald et al., 1984	New York State Vietnam veterans	10	0.5 (0.2–1.3)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 90% CI.
[e] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have soft-tissue sarcoma?"
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDVA, Commonwealth Department of Veterans' Affairs; CI, Confidence Interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; SEER, Surveillance, Epidemiology, and End Results (SEER) Program; STS, Soft-tissue Sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; WHO TEQ, Toxicity Equivalent as defined by the World Health Organization.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. Mortality rates for soft-tissue sarcoma standardized with the national rates of the 11 contributing countries did not indicate any association to nonvolatile organochlorine compounds, including TCDD (ever exposed: 4 cases, SMR = 0.80, 95% CI 0.22–2.04; never exposed: 8 cases, SMR = 1.22, 95% CI 0.53–2.41) as derived using a job-exposure matrix approach.

In New Zealand, 't Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers from 1969 and 1973, respectively, through 2000. A single death from soft-tissue sarcoma (ICD-9 171) was observed (0.23 expected) in the sprayer group.

In a prospective cohort study of private pesticide applicators, commercial applicators, and spouses of the private applicators, Alavanja et al. (2005) reported 10 and three incident cases of "soft tissue" cancer in the private applicators (SIR = 0.65, 95% CI 0.31–1.20) and their spouses (SIR = 0.48, 95% CI 0.10–1.41), respectively, and none among the commercial applicators; those results led to non-significant risk estimates below the null. In a study of cancer mortality in the same prospective cohort, Blair et al. (2005a) reported four and three deaths from "soft tissue" cancer in the pesticide applicators (SMR = 0.7, 95% CI 0.2–1.8) and their spouses (SMR = 1.4, 95% CI 0.3–4.1), respectively.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of cancer of the connective soft tissue was not increased (two cases; SMR = 0.95, 95% CI 0.11–3.45).

Reif et al. (1989) performed a series of case–control analyses on the sample of 19,904 people with specified occupations among the 24,762 men 20 years old or older entered into the the New Zealand Cancer Registry in 1980–1984. The focus of their study was on the 134 for whom forestry work was the most recent occupation listed. For each type of cancer, the people with any other type of cancer were used as controls. Of 142 people with STS, four had most recently been forestry workers (OR = 3.24, 95% CI 1.17–8.98).

Environmental Studies

In the case–control study of men living in six Canadian provinces, Pahwa et al. (2006) investigated whether exposure to phenoxy herbicides and other pesticides was associated with the incidence of STS. (The results of the study in terms of farm work or residence were reported in Pahwa et al. [2003], which has not been previously reviewed in this series, but the current citation more specifically addresses the VAO charge.) Interviews were completed with 357 men who received new diagnoses of STS in 1991–1994 and with 1,506 control subjects. No associations were found with any exposures to phenoxy herbicides (OR = 1.07, 95% CI 0.80–1.44), to 2,4-D (OR = 0.97, 95% CI 0.71–1.32), to mecoprop (2-[2-methyl-4-chlorophenoxy]propanoic acid [MCPP]) (OR = 1.40, 95% CI 0.86–2.25), or to MCPA (OR = 1.05, 95% CI 0.54–2.02).

Vietnam-Veteran Studies

In a set of three reports updating the health status of Australian Vietnam veterans, no associations between Vietnam service and cancers of connective soft tissue were found in comparing veterans with the general population of Australia in incidence (SIR = 0.99, 95% CI 0.66–1.31) (ADVA, 2005a) and mortality (SMR = 0.75, 95% CI 0.38–1.28) (ADVA, 2005b). When conscripted male Army veterans deployed to Vietnam (National Service veterans) were compared with their non-deployed counterparts (National Service non-veterans), no increases were found in the incidence of STS (SIR = 0.99, 95% CI 0.39–2.44) or mortality from it (SMR = 0.48, 95% CI 0.08–2.01) (ADVA, 2005c).

Biologic Plausibility

In a two year study, dermal application of TCDD to Swiss-Webster mice led to an increase in fibrosarcomas in the females, but not males (NTP, 1982b). There is some concern that the increase in fibrosarcomas may be associated with the treatment protocol, rather than due to the treatment with TCDD. The NTP gavage study (1982a) also found elevated incidences of fibrosarcomas in male and female rats and in female mice. [As *VAO* also reported; but *Update 2004* said there were no animal data specifically supporting STS.]

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Previous committees have concluded that the occupational, environmental, and Vietnam-veteran studies showed sufficient evidence to link herbicide exposure to STS. Three studies of populations exposed to contemporary phenoxy heribicides unlikely to contain TCDD in the United States, Canada, and Italy did not find associations with STS, while the statistical power to detect excess risks in a small cohort of phenoxy herbicide producers and sprayers was low. The findings of a sizable multinational investigation of paper and pulp workers were indeterminant for the rather nonspecific exposure “nonvolatile organochlorines,” but an occupational analysis of those entered into the New Zealand Cancer Registry in the early 1980s did find a strong association between soft-tissue sarcoma and having been a forestry worker.. The studies of Australian veterans did not show any evidence of increased risks amongst deployed soldiers, but the power to detect excess risk was low and there were no data regarding actual exposures. The committee did not find that these new data justified modifying the previous conclusion.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the compounds of interest and STS.

SKIN CANCER—MELANOMA

Skin cancers are generally divided into two broad categories: neoplasms that develop from melanocytes (malignant melanoma, or simply melanoma) and neoplasms that do not. Non-melanoma skin cancers (primarily basal-cell and squamous-cell carcinomas) have a far higher incidence than melanoma but are considerably less aggressive and therefore more treatable. The average annual incidence of melanoma is shown in Table 6-19. The committee responsible for *Update 1998* first chose to address melanoma studies separately from those of non-melanoma skin cancer. Some researchers report results by combining all types of skin cancer without specifying type. The present committee believes that such information is not interpretable (although there is a supposition that mortality figures refer predominantly to melanoma and sizable incidence figures refer to non-melanoma skin cancer). Therefore, the committee is interpreting data only on results that are specified as applying to melanoma or to non-melanoma skin cancer.

TABLE 6-19 Average Annual Cancer Incidence (per 100,000) of Skin Cancers (Excluding Basal and Squamous-Cell Cancers) in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Melanomas of the Skin:									
Males	32.4	38.6	0.5	45.4	52.7	1.1	55.4	64.8	3.5
Females	24.6	30.0	0.2	26.9	32.2	1.8	28.6	34.6	1.2

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.
SEER incidence data are not available for non-melanocytic skin cancer.

ACS estimated that about 34,260 men and 27,930 women would receive diagnoses of cutaneous melanoma (ICD-9 172) in the United States in 2006 and 5,020 men and 2,890 women would die from it (Jemal et al., 2006). More than a million cases of non-melanoma skin cancer (ICD-9 173), primarily basal-cell and squamous-cell carcinomas, are diagnosed in the United States each year (ACS, 2006); it is not required to report them to registries, so the numbers of cases are not as precise as those of other cancers. ACS reports that although melanoma accounts for only about 4% of skin-cancer cases, it is responsible for about 79% of skin-cancer deaths (2006). It estimates that 1,000–2,000 people die each year from non-melanoma skin cancer.

Melanoma occurs more frequently in fair-skinned people than in dark-skinned people; the risk in whites is roughly 20 times that in dark-skinned blacks. The incidence increases with age, although more strikingly in males than in females. Other risk factors include the presence of certain moles on the skin, suppression of the immune system, and excessive exposure to ultraviolet (UV) radiation, typically from the sun. A family history of the disease has been

identified as a risk factor, but it is unclear whether that is attributable to genetic factors or to similarities in skin type and sun exposure patterns.

Excessive exposure to UV radiation is the most important risk factor for non-melanoma skin cancer, although some skin diseases and chemical exposures have also been identified as potential risk factors. Exposure to inorganic arsenic is a risk factor for skin cancer (this does not imply that cacodylic acid, which is a metabolite of inorganic arsenic, can also be assumed to be a risk factor).

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and skin cancer. Additional information available to the committee responsible for *Update 1996* did not change that conclusion. The *Update 1998* committee considered the literature on melanoma separately from that of non-melanoma skin cancer. It found that there was inadequate or insufficient information to determine whether there is an association between the compounds of interest and melanoma. The *Update 2000*, *Update 2002*, and *Update 2004* committees concurred with the findings of the *Update 1998* committee. Table 6-20 summarizes the relevant melanoma studies.

TABLE 6-20 Selected Epidemiologic Studies—Melanoma

Reference	Study Population [a]	Exposed Cases[b]	Estimated Risk (95% CI)[b]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	20	0.8 (0.5–1.3)
	Ever	21	1.2 (0.7–1.8)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	0.0 (0.0–3.0)
	Phenoxy herbicide sprayers (>99% men)	1	0.6 (0.0–3.4)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	100	1.0 (0.8–1.2)
	Spouses of private applicators (>99%women)	67	1.6 (1.3–2.1)
	Commercial applicators (men and women)	7	1.1 (0.4–2.2)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	13	0.7 (0.4–1.3)
	Spouses of private applicators (>99%women)	2	0.4 (0.1–1.6)
Torchio et al., 1994	Italian licensed pesticide users	9	1.2 (0.6–2.3)
Magnani et al., 1987	UK case–control		
	Herbicides	*	1.2 (0.4–4.0)
	Chlorophenols	*	0.9 (0.4–2.3)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators		

Reference	Study Population [a]	Exposed Cases[b]	Estimated Risk (95% CI)[b]
	Melanoma, squamous cell carcinoma, and unknown skin cancer (mortality presumably attributable to melanoma)	5	3.6 (1.2–8.3)
Studies Reviewed in *Update 2002*			
Thörn et al., 2000	Swedish lumberjack workers exposed to phenoxyacetic herbicides–incidence		
	Women	1	3.5 (0.1–19.2)
	Men	0	—
Studies Reviewed in *Update 2000*			
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)	1	2.9 (0.1–15.9)
Studies Reviewed in *Update 1998*			
Hertzman et al., 1997	British Columbia sawmill workers		
	Incidence	38	1.0 (0.7–1.3)
	Mortality	17	1.4 (0.9–2.0)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	9	0.6 (0.3–1.2)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	5	0.5 (0.2–3.2)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	4	1.0 (0.3–2.4)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White men	244	1.0 (0.8–1.1)
	White women	5	1.1 (0.4–2.7)
Lynge, 1993	Danish production workers—updated incidence (Included in the IARC cohort)	4	4.3 (1.2–10.9)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish workers—incidence		
	Men	72	0.7 ($p < 0.05$)
	Women	5	1.2 *
Wigle et al., 1990	Canadian farmers	24	1.1 (0.7–1.6)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	268	0.8 (0.7–1.0)[c]
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—men	1	1.5 (0.2–12.5)
	women	2	1.8 (0.4–7.3)
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Men—counties with high wheat acreage	41	0.8 (0.6–1.1)
	medium wheat acreage	50	0.8 (0.6–1.1)
	Women—counties with high wheat acreage	29	0.7 (0.5–1.2)
	medium wheat acreage	59	1.2 (0.9–1.8)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone A—women	1	9.4 (0.1–52.3)

Reference	Study Population [a]	Exposed Cases[b]	Estimated Risk (95% CI)[b]
	Zone R—men	3	1.1 (0.2–3.2)
	women	3	0.6 (0.1–1.8)
Svensson et al., 1995	Swedish fishermen (men and women)		
	East coast		
	Incidence	0	0.0 (0.0–0.7)
	Mortality	0	0.0 (0.0–1.7)
	West coast		
	Incidence	20	0.8 (0.5–1.2)
	Mortality	6	0.7 (0.3–1.5)
Studies Reviewed in *VAO*			
Bertazzi et al., 1989a	Seveso residents—10-year follow-up		
	Zones A, B, R—men	3	3.3 (0.8–13.9)
	women	1	0.3 (0.1–2.5)
VIETNAM VETERANS			
New Studies			
Pavuk et al., 2005	White Air Force comparison subjects only—incidence		
	Serum TCDD levels (pg/g), based on model with exposure variable $\log_e$(TCDD) [f]		
	Per unit increase of -$\log_e$(TCDD) in pg/g	25	2.7 (1.1–6.3)
	Quartiles (pg/g)		
	0.4–2.6	3	1.0
	2.6–3.8	5	2.1 (0.4–11)
	3.8–5.2	8	3.2 (0.7–15.5)
	>5.2	9	3.6 (0.7–17.2)
	Number of years served in southeast Asia (SEA)		
	Per year of service	25	1.1 (0.9–1.3)
	Quartiles (years in SEA)		
	0.8–1.3	3	1.0
	1.3–2.1	4	1.9 (0.3–10.3)
	2.1–3.7	8	3.2 (0.7–15.3)
	3.7–16.4	10	4.1 (0.9–19.7)
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	756	1.3 (1.2–1.4)
	Navy	173	1.4 (1.2–1.6)
	Army	510	1.2 (1.2–1.4)
	Air Force	73	1.4 (1.1–1.7)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	111	1.1 (0.9–1.3)
	Navy	35	1.6 (1.0–2.1)
	Army	66	1.0 (0.7–1.2)
	Air Force	10	1.0 (0.5–1.8)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		
	Incidence	204	1.1 (0.9–1.4)
	Mortality	14	0.6 (0.3–1.1)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	6	1.4 (0.4–4.9)
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	AFHS subjects vs national rates		
	White AFHS Ranch Hand veterans		

Reference	Study Population [a]	Exposed Cases[b]	Estimated Risk (95% CI)[b]
	Mortality—All	*	
	Incidence—All	17	2.3 (1.4–3.7)
	With tours between 1966–1970	16	2.6 (1.5–4.1)
	White AFHS comparison veterans		
	Mortality—All	*	
	Incidence—All	15	1.5 (0.9–2.4)
	With tours between 1966–1970	12	1.5 (0.8–2.6)
	White AFHS subjects—incidence		
	Who spent at most 2 years in SEA		
	Per unit increase of -$\log_e$(TCDD) in pg/g	14	2.2 (1.3–3.9)
	Comparison group	3	1.0
	Ranch Hand— <10 TCDD pg/g in 1987	4	3.0 (0.5–16.8)
	Ranch Hand— <118.5 TCDD pg/g at end of service	4	7.4 (1.3–41.0)
	Ranch Hand— >118.5 TCDD pg/g at end of service	3	7.5 (1.1–50.2)
	Only Ranch Hands with 100% service in Vietnam and Comparisons with 0% service in Vietnam		
	Per unit increase of -$\log_e$(TCDD) in pg/g	14	1.7 (1.0–2.8)
	Comparison group	2	1.0
	Ranch Hand— <10 TCDD pg/g in 1987	5	3.9 (0.4–35.3)
	Ranch Hand— <118.5 TCDD pg/g at end of service	4	7.2 (0.9–58.8)
	Ranch Hand— >118.5 TCDD pg/g at end of service	3	5.5 (0.6–46.1)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans—incidence	16	1.8 (0.8–3.8)
Ketchum et al., 1999	Ranch Hand (RH) veterans and comparisons through June 1997—incidence		
	Comparisons	9	1.0
	RH background-exposure	4	1.1 (0.3–4.5)
	RH low-exposure	6	2.6 (0.7–9.1)
	RH high-exposure	2	0.9 (0.2–5.6)
AIHW, 1999	Australian Vietnam veterans (Validation study) — incidence	483	380 expected (342–418)
CDVA, 1998a	Australian Vietnam veterans (men)—incidence	2,689 [e]	380 expected (342–418)
CDVA, 1998b	Australian Vietnam veterans (women)—incidence	7 [e]	3 expected (1–8)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian Vietnam veterans (men)	51	1.3 (0.9–1.7)
CDVA, 1997b	Australian national service Vietnam veterans	16	0.5 (0.2–1.3)
Clapp, 1997	Massachusetts Vietnam veterans—incidence	21	1.4 (0.7–2.9)
Studies Reviewed in *VAO*			
Wolfe et al., 1990	Air Force Ranch Hand veterans—incidence	4	1.3 (0.3–5.2)
Breslin et al., 1988	Army Vietnam veterans	145	1.0 (0.9–1.1)
	Marine Vietnam veterans	36	0.9 (0.6–1.5)

[a] Cohorts are male and the endpoint is mortality unless otherwise noted.
[b] Given when available.
[c] 99% CI.
[d] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.

[e] Self-reported medical history. Answer to question: Since your first day of service in Vietnam, have you been told by a doctor that you have melanoma?
[f] The original paper implied that the exposure metric for TCDD was based on actual measured serum levels of TCDD. Subsequent correspondence between the Committee and the investigators indicated that the metric was actually transformed using the natural logarithm of TCDD.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Death from melanoma was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds (*n* = 21; SMR = 1.17, 95% CI 0.72–1.78) than with having never been exposed (*n* = 20; SMR = 0.82, 95% CI 0.5–1.27).

The study by 't Mannetje et al. (2005) is an extension of a cohort study in New Zealand, which is part of an IARC international study of phenoxy herbicide producers and sprayers. Their report describes follow-up from 1969 to 2000 of 813 herbicide producers and 699 sprayers who were classified as exposed to dioxin and phenoxy herbicides. SMRs were computed relative to general New Zealand standards. No cases of melanoma were observed in the production workers, and only one in the sprayers; the estimated SMRs were therefore very unstable and had wide confidence intervals.

In reporting on cancer incidence in the AHS cohort, Alavanja et al. (2005) found that the spouse group showed a significant excess of melanoma, with 67 observed cases (SIR = 1.64, 95% CI 1.27–2.09). Such an excess was not seen in the private applicators (SIR = 0.95, 95% CI 0.78–1.16) or the commercial applicators (SIR = 1.05, 95% CI 0.42–2.17). Melanoma was the only cancer type observed to have a significantly increased risk in the spouses. The authors considered that result to be an "unexpected" and commented that a high percentage of farm spouses engage in outdoor work that involves substantial exposure to sunlight.

Blair et al. (2005a) studied mortality in the AHS cohorts of private applicators (mostly farmers) and their spouses. In the private applicators, there were 13 deaths from melanoma (SMR = 0.7, 95% CI 0.4–1.3). In the spouses, there were two deaths from melanoma (SMR = 0.4, 95% CI 0.1–1.6). The increase in melanoma incidence observed among the AHS spouses is not yet reflected in mortality from melanoma, but the cohort has very low overall mortality compared with the general population. The numbers of melanoma deaths observed in this study are small, and the confidence intervals are relatively wide.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of melanoma was not significantly increased (nine cases; SMR = 1.21, 95% CI 0.56–2.29).

Magnani et al. (1987) conducted a case–control mortality study of 99 people with melanoma and 361 controls in the UK. A JEM was used to predict exposures to various chemical agents on the basis of job title as indicated on the death certificates. Estimated risks of melanoma associated with exposure to herbicides (RR = 1.2, 95% CI 0.4–4.0) and chlorophenols (RR = 0.9, 95% CI 0.4–2.3) were not significantly increased.

For completeness, we note here a letter to the editor by Kennedy et al. (2005). It is not evident that it was peer-reviewed, which is a standard requirement for inclusion in the present committee's evidentiary database of nongovernment reports, but no other publications on the Leiden Skin Cancer Study could be found mentioning herbicides. The letter describes results from a case–control study of squamous-cell carcinoma, basal-cell carcinoma, and melanoma without providing any details about the selection of cases and controls. Data on only male subjects were reported because relevant exposures of women were rare. Of the 47 males with melanoma, only one reported ever being exposed to herbicides. The data are insufficient to support a stable RR estimate, but the authors did document a significant risk of melanoma in men exposed to arsenic (RR = 7.1), although apparently neither organic nor in the form of a herbicide, as would be of interest for the *VAO* reports. Even if it were eligible for inclusion, the paper would provide little information on the potential for an association between exposure to herbicides and melanoma.

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and melanoma were published since *Update 2004*.

Vietnam-Veteran Studies

Pavuk et al. (2005) reported on cancer incidence from 1982 to 2003 in the comparison group in the AFHS. Those Air Force veterans had served in Southeast Asia but had not been involved in spraying herbicides during the Vietnam War, as had the Ranch Hand veterans who were the AFHS primary subjects. Of the roughly 1,800 comparison subjects enrolled in the course of the AFHS, 1,482 had serum-TCDD readings used as the basis of the analyses presented here. The median TCDD concentration in the Southeast Asia comparison group (sampled in 1987) was 3.8 pg/g of lipid, and the values in the highest quartile ranged from 5.2 to 54.8 pg/g. The serum TCDD concentrations in the comparison subjects overlapped considerably with those in the Ranch Hand veterans, 43.2% of whom had TCDD readings in 1987 of less than 10 pg/g (see Akhtar et al., 2004).

The 25 cases of melanoma were distributed as three, five, eight, and nine cases over the quartiles with increasing TCDD. Using the lowest quartile as the referent group for the other three quartiles of Southeast Asia comparison subjects, the second, third, and fourth quartiles of serum TCDD showed increasing RRs of 2.1 (95% CI 0.4–11), 3.2 (95% CI 0.7–15.5), and 3.6 (95% CI 0.7–17.2), respectively. The committee's correspondence with the authors confirmed that the reported significant dose-response relationship was based on a model that used natural-logarithm transformation of the continuous variable, individual serum TCDD concentration (slope per ln [TCDD], 2.7, 95% CI 1.1–6.3; p = 0.02). The results were adjusted for a number of other risk factors, including military occupation, year of birth, number of years served in Southeast

Asia, body-mass index (BMI), skin reaction to sunlight exposure, and eye color. An analogous analysis on the numbers of years that each person had served in Southeast Asia did not yield a significant association with the risk of melanoma (slope per year in Southeast Asia, 1.1, 95% CI 0.9–1.3; p = 0.46). Thus, an increase in the occurrence of melanoma was found to be more specifically associated with TCDD exposure than with service in Southeast Asia.

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported six melanoma deaths in the deployed and four in the non-deployed (CRR = 1.39, 95% CI 0.39–4.93).

A statistically significant increase in melanoma incidence in male Australian Vietnam veterans was found in comparison with the general Australian population (ADVA, 2005a) on the basis of 756 observed cases (SIR = 1.32, 95% CI 1.23–1.41). When the analysis was stratified over the Army, Navy, and Air Force, similar significant associations with the incidence of melanoma were observed in all three branches of service. A potential confounder in the study is exposure to sunlight.

The mortality experience of the above group of male Australian Vietnam veterans through 2001 was analyzed, again by using the rate observed in Australian men in general as the standard (ADVA, 2005b). The 111 deaths from melanoma in all the veterans showed a statistically non-significant increase (SMR =1.10, 95% CI 0.90–1.31). On the basis of 35 deaths from melanoma, mortality was significantly increased in the veterans who had served in the Navy (SMR = 1.56, 95% CI 1.04–2.08), but the findings were neutral for those who had served in the Army or Air Force.

A different Australian study (ADVA, 2005c) compared deployed male Army National Service veterans with non-deployed Vietnam-era veterans. That comparison has the advantage of contrasting health outcomes in groups of men who were of similar age, health, and fitness at the time of enlistment but who differed primarily in Vietnam experience. On the basis of 204 incident cases of and 14 deaths from melanoma in the deployed veterans, neither incidence (SIR = 1.13, 95% CI 0.93–1.37) nor mortality (SMR = 0.56, 95% CI 0.28–1.08) was increased in comparison with the non-deployed veterans.

Biologic Plausibility

No animal studies have reported an increased incidence of melanoma after exposure to the compounds of interest. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

On the whole, the new occupational studies of melanoma were small and could not provide stable estimates of RR associated with herbicide exposure. The Alavanja study had a suggestive result in one subgroup (the female spouses of the private applicators), which the authors had not expected. Increased risks in contemporary users of phenoxy herbicides would not be expected, however, if TCDD were the agent responsible for any increase in melanoma.

Occupational studies reviewed previously by the *VAO* committees have shown a wide range of estimated RRs of melanoma, with only a few results suggesting an increase in the risk of

melanoma in workers potentially exposed to the components of the herbicides sprayed in Vietnam. With respect to melanoma mortality, only the finding of Swaen et al. (2004) based on five skin-cancer deaths in Dutch herbicide applicators was statistically significant (SMR = 3.5, 95% CI 1.2–8.3), and even this result did not explicitly exclude non-melanoma skin cancer. The pooled international IARC cohort (Kogevinas et al., 1997) provides the most comprehensive analysis of cancer mortality in phenoxy herbicide producers and sprayers, with or without concurrent TCDD exposure, but there were only nine melanoma deaths in all the people exposed to phenoxy herbicides and no suggestion of an increased risk with or without TCDD exposure. On the basis of four exposed cases, Lynge (1993) reported a significant increase in the incidence of melanoma (SIR = 4.3, 95% CI 1.2–10.9) in the cohort of Danish phenoxy herbicide producers (whose mortality experience was included in the non-significant findings on the IARC cohort overall).

The limited findings concerning mortality 20 years after environmental exposure arising from the Seveso accident (Bertazzi et al., 2001) show modest increases in the estimated risks in both men (SMR = 1.5, 95% CI 0.2–12.5) and women (SMR = 1.8, 95% CI 0.4–7.3) who resided closest to the release (in zones A and B), but these estimates, being based on only one and two deaths from melanoma, respectively, are extremely unstable.

The newly published studies of Australian servicemen who served in Vietnam show some indication of increases in the occurrence of melanoma, but the overall interpretation is not straightforward. The incidence of melanoma is significantly increased in all male Australian Vietnam veterans in comparison with the general population (ADVA, 2005a). In the parallel study of mortality in the servicemen relative to the Australian population (ADVA, 2005b), the increase in melanoma risk is significant only in those serving in the Navy (SIR = 1.6, 95% CI 1.0–2.1), who might also have had more sunlight exposure. The third Australian study (ADVA, 2005c), comparing deployed and non-deployed National Service veterans (male Army conscripts) with respect to both melanoma incidence and mortality, does not support an effect of deployment (as used as a surrogate for herbicide exposure). The mortality update on the CDC VES (Boehmer et al., 2004) does contain a somewhat higher, but not significantly, incidence of melanoma in deployed than in non-deployed Vietnam-era veterans (SMR = 1.39, 95% CI 0.39–4.93).

The most persuasive evidence comes from the AFHS. The positive findings of an association between TCDD exposure and melanoma presented in Akhtar et al. (2004) are extended down into serum concentrations in the Southeast Asia comparison group in the analyses of Pavuk et al. (2005). Increases in melanoma risk in people in the second, third, and fourth quartiles of serum TCDD concentrations were seen in comparison with the lowest quartile. The overall slope of a dose-response curve in an analytic model based on the logarithm of the continuous variable—each person's serum TCDD concentration—was also statistically significant. In Akhtar et al. (2004), the findings on melanoma incidence in the Ranch Hand veterans were similarly significantly increased; they were stronger and more TCDD-specific than for any other type of cancer.

Melanoma diagnoses are known to increase with screening, as was conducted in the AFHS, but this factor is less likely to bias the estimated risks when the comparison is internal, as in the AFHS reports. It is compelling that a significant dose-response relationship is found when analysis is based on individual readings for the continuous variable (serum TCDD) that is generally regarded as the most precise indicator of herbicide exposure in Vietnam. The analyses in Akhtar et al. (2004) and Pavuk et al. (2005) involve interpretations that were not part of the original study design, but, given some of the insights that have been gained in the course of the AFHS,

such approaches may be justified. The results in those two publications would be more useful if were presented in a more transparent fashion.

In summary, although the collateral evidence from studies of other occupational and environmental populations is inconsistent, significant associations have been demonstrated in studies of populations with well-characterized exposures to the compounds of interest (Lynge et al., 1993; Swaen et al., 2004); they provide evidence of an association with melanoma that may be limited by the possibility of bias or chance. The findings of the ADVA (2005a,b,c) in Australian Vietnam veterans are limited by internal inconsistency. The increase in mortality reported by the CDC VES (Boehmer et al., 2004) is consistent but far from significant.

The results of the AFHS have long been anticipated as the most directly pertinent to the experience of US Vietnam veterans, so the committee was impressed by recent reports (Akhtar et al., 2004; Pavuk et al., 2005) of a strong dose-response relationship between serum TCDD concentrations and melanoma in this population. Some members of the committee were concerned, however, that the findings of the AFHS have not been presented in a complete and systematic fashion. For example, the follow-up for the analysis of the Ranch Hand subjects (Akhtar et al., 2004) represents findings only up to 1999 (not including results of the final examination cycle), whereas the report on the Southeast Asia comparison group (Pavuk et al., 2005) includes diagnoses through 2003. The cross-sectional report (AFHS, 2005) does not provide a definitive statement of cumulative melanoma diagnoses observed in the Ranch Hand subjects through 2003 to match the data analyzed for the Southeast Asia comparison group in Pavuk et al. (2005), but the stated prevalences in the final examination cycle suggest that new melanoma diagnoses in the comparison subjects greatly exceeded those in Ranch Hand subjects (see Table 4-4 in Chapter 4). The committee therefore endorses further evaluation and longitudinal analysis of the entire dataset on cancer outcomes generated in the important AFHS population. The AFHS is of questionable central relevance to the committee's charge, but it had a persisting concern that there was little suggestion of an association in other relevant populations.

The committee members agreed that the two published articles from the AFHS (Akhtar et al., 2004; Pavuk et al., 2005) were very strong findings based on TCDD measurements in a study population of prime interest. Several could not, however, agree to move to melanoma into the limited or suggestive category, given the paucity of support from other investigated populations. Another restraining concern was the hint in the report (AFHS, 2005) on those attending the final AFHS examination that many more new melanomas were diagnosed among the Comparison veterans than in the Ranch Hand subjects, which might produce quite different results if the analyses in Akhtar et al. (2004) were rerun on the final dataset.

Conclusion

After extensive deliberation concerning new evidence and the results of studies reviewed in previous updates, the committee was unable to reach consensus as to whether the evidence concerning an association between exposure to the compounds of interest and melanoma met the criteria for being considered limited or suggestive or this health outcome should remain in the inadequate or insufficient classification primarily because the suggestive findings are almost exclusively from the AFHS, whose final data on both the Ranch Hand and comparison subjects have not yet been analyzed in a satisfactory and uniform manner.

SKIN CANCER: BASAL-CELL AND SQUAMOUS-CELL CANCER (NON-MELANOMA)

The preceding section on melanoma presented background information on non-melanoma skin cancer.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and skin cancer, and additional information available to the committee responsible for *Update 1996* did not change that conclusion. The *Update 1998* committee considered the literature on nonmelanocytic skin cancer separately from that on melanoma and concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and basal-cell or squamous-cell cancer. The *Update 2000* and *Update 2002* committees concurred with that conclusion. Table 6-21 summarizes the relevant studies.

TABLE 6-21 Selected Epidemiologic Studies—Other Nonmelanoma (basal and squamous cell) Skin Cancer

Reference	Study Population [a]	Exposed Cases[b]	Estimated Relative Risk (95% CI)[b]
OCCUPATIONAL			
New Studies			
Torchio et al., 1994	Italian licensed pesticide users	3	0.6 (0.1–1.8)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators		
	Melanoma, squamous cell carcinoma, and unknown skin cancer (mortality presumable attributable to melanoma)	5	3.6 (1.2–8.3)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	Non-melanoma skin cancer	0	—
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides—incidence		
	Foremen	1	16.7 (0.2–92.7)
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	4	0.9 (0.3–2.4)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	4	1.3 (0.3–3.2)

Reference	Study Population [a]	Exposed Cases[b]	Estimated Relative Risk (95% CI)[b]
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	0	—*
Zhong and Rafnsson, 1996	Icelandic pesticide users (men and women—incidence)		
	Men	5	2.8 (0.9–6.6)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White men	425	1.1 (1.0–1.2)
	White women	6	1.0 (0.4–2.1)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	493	0.7 ($p < 0.05$)
	employee	98	0.7 ($p < 0.05$)
	Women—self-employed	5	0.3 ($p < 0.05$)
	employee	10	0.9 (*)
	family worker	90	0.6 ($p < 0.05$)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	3	3.1 (0.6–9.0)
ENVIRONMENTAL			
Studies Reviewed in *Update 1998*			
Gallagher et al., 1996	Alberta, Canada, residents—squamous cell carcinoma (incidence)		
	All herbicide exposure	79	1.5 (1.0–2.3)
	Low herbicide exposure	33	1.9 (1.0–3.6)
	High herbicide exposure	46	3.9 (2.2–6.9)
	Alberta, Canada, residents—basal cell carcinoma		
	All herbicide exposure	70	1.1 (0.8–1.7)
Svensson et al., 1995	Swedish fishermen		
	East coast		
	Incidence	22	2.3 (1.5–3.5)
	Mortality	0	0.0 (0.0–15.4)
	West coast		
	Incidence	69	1.1 (0.9–1.4)
	Mortality	5	3.1 (1.0–7.1)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up (incidence)		
	Zone A—men	1	2.4 (0.3–17.2)
	women	1	3.9 (0.5–28.1)
	Zone B—men	2	0.7 (0.2–2.9)
	women	2	1.3 (0.3–5.1)
	Zone R—men	20	1.0 (0.6–1.6)
	women	13	1.0 (0.6–1.9)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	3	1.0 (0.3–3.0)
	women	3	1.5 (0.5–4.9)
	Zone R—men	20	1.0 (0.6–1.6)
	women	13	1.0 (0.5–1.7)

Reference	Study Population [a]	Exposed Cases[b]	Estimated Relative Risk (95% CI)[b]
Wiklund, 1983	Swedish agricultural workers—incidence	708	1.1 (1.0–1.2)[d]
VIETNAM VETERANS			
New Studies			
Pavuk et al., 2005	White Air Force comparison subjects only (basal and squamous cell)—incidence		
	Serum TCDD levels (pg/g), based on model with exposure variable $\log_e$(TCDD) [f]		
	Per unit increase of -$\log_e$(TCDD) in pg/g	253	1.2 (0.9–1.4)
	Quartiles (pg/g)		
	0.4–2.6	50	*
	2.6–3.8	59	1.2 (0.8–1.8)
	3.8–5.2	71	1.5 (1.1–2.3)
	>5.2	73	1.4 (0.9–2.0)
	Number of years served in southeast Asia (SEA)		
	Per year of service	253	1 (0.9 –1.1)
	Quartiles (years in SEA)		
	0.8–1.3	55	*
	1.3–2.1	50	0.9 (0.6–1.4)
	2.1–3.7	73	1.1 (0.8–1.6)
	3.7–16.4	75	1.2 (0.8–1.7)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans—incidence		
	Basal cell carcinoma (BCC)	121	1.2 (0.9–1.6)
	Squamous cell carcinoma (SCC)	20	1.5 (0.8–2.8)
CDVA, 1998a	Australian Vietnam veterans—men (incidence)	6,936[e]	* *
CDVA, 1998b	Australian Vietnam veterans—women (incidence)	37[e]	* *
Studies Reviewed in *VAO*			
Wolfe et al., 1990	Air Force Ranch Hand veterans—incidence		
	Basal cell carcinoma	78	1.5 (1.0–2.1)
	Squamous cell carcinoma	6	1.6 (0.5–5.1)

[a] Cohorts are male unless otherwise noted.
[b] Given when available.
[c] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[d] 99% CI.
[e] Self-reported medical history. Answer to question: Since your first day of service in Vietnam, have you been told by a doctor that you have other skin cancers (Basal Cell Carcinoma, Squamous Cell Carcinoma)?
* Information not provided by study authors.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: AFHS, Air Force Health Study; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval.

Update of the Epidemiologic Literature

Occupational Studies

In reporting on cancer incidence in the AHS cohort, Alavanja et al. (2005) did not consider non-melanoma skin cancers, because it is not systematically registered in Iowa or North Carolina.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of skin cancer other than melanoma was not increased (three cases; SMR = 0.6, 95% CI 0.12–1.75).

As in the section above on melanoma, we note here a letter to the editor by Kennedy et al. (2005) although it apparently was not peer-reviewed. They reported the frequency of exposure to herbicides of 103 men with squamous-cell carcinoma, 171 with nodular basal-cell carcinoma, and 78 with superficial multifocal basal-cell carcinoma. Separate exposure rates for cases and controls were not reported in their case–control study. The ORs for herbicide exposure were 0.8 for squamous-cell carcinoma, 0.6 for nodular basal-cell carcinoma, and 0.5 for superficial multifocal basal-cell carcinoma; all have wide confidence intervals, and none is statistically significant.

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and non-melanoma skin cancer were published since *Update 2004*.

Vietnam-Veteran Studies

Focusing only on the Southeast Asia comparison subjects in the AFHS, Pavuk et al. (2005) reported 253 cases of basal-cell and squamous-cell carcinoma and an overall RR of 1.2 (95% CI 0.9–1.4) when the second, third, and fourth quartiles combined were compared with the first quartile for serum TCDD concentrations. A significant excess (based on 71 cases) was found for the third quartile (RR = 1.5, 95% CI 1.1–2.3; p = 0.03). The RR for the fourth quartile was 1.4, but it did not achieve statistical significance. The overall dose-response relationship in a model that considered individual values for serum TCDD was not statistically significant. Those results were adjusted for a number of other risk factors, including military occupation, year of birth, number of years served in Southeasast Asia, BMI, skin reaction to sunlight exposure, and eye color.

Biologic Plausibility

Studies in mice that have been designed to determine carcinogenic actions of TCDD generally support the idea that TCDD promotes the formation of skin papillomas and squamous-cell carcinomas (Dunson et al., 2000; Poland et al., 1982; Wyde et al., 2004). However, the observation of the tumor-promoting effects of TCDD only in specific strains (the genetically initiated TgAc [Dunson et al., 2000; Wyde et al., 2004] and the hairless strain [Hebert et al., 1990; Poland et al., 1982] but not such strains as the ICR strain [Wu et al., 2004]) indicates that activation of multiple carcinogenic pathways is required. Similar studies performed in the Syrian golden hamster revealed that treatment with TCDD alone was sufficient for the development of squamous-cell carcinomas of the facial skin (Rao et al., 1988). Cacodylic acid is a well-known

skin carcinogen in humans, but studies in animal models have failed to demonstrate its carcinogenic action in the skin (Cohen et al., 2006).

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

The new results in the Pavuk et al. study, although intriguing, demonstrate only a small RR that is not statistically significant, and the dose-response relationship also is not statistically significant. The only statistically significant result was found in the third, rather than the fourth, quartile of exposure to TCDD, although similar estimated risks were found in the second and fourth quartiles. On the basis of the new studies and in accord with the results of reports previously assessed, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and basal-cell or squamous-cell cancer.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and basal-cell or squamous-cell cancer.

BREAST CANCER

Breast cancer (ICD-9 174 for females, ICD-9 175 for males) is the second-most common type of cancer (after non-melanoma skin cancer) in women in the United States. ACS estimated that 212,920 women would receive diagnoses of breast cancer in the United States in 2006 and that 40,970 would die from it (Jemal et al., 2006). Overall, those numbers represent about 31% of the new cancers and 15% of cancer deaths in women. Incidence data on breast cancer are presented in Table 6-22.

Breast-cancer incidence generally increases with age. In the age groups of most Vietnam veterans, the incidence is higher in whites than in blacks. Established risk factors other than age include personal or family history of breast cancer and some characteristics of reproductive history—specifically, early menarche, late onset of menopause, and either no pregnancies or first full-term pregnancy after the age of 30 years. A pooled analysis of six large-scale prospective studies of invasive breast cancer showed that alcohol consumption over the range of consumption reported by most women was associated with a linear increase in incidence in women (Smith-Warner et al., 1998). The potential of other personal behavioral and environmental factors (including exogenous hormones) to affect breast-cancer incidence is being studied extensively.

TABLE 6-22 Average Annual Incidence (per 100,000) of Breast Cancer in Females in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Male	1.34	1.35	2.17	2.7	2.4	6.4	3.8	4.0	5.5
Female	249.0	258.1	227.6	327.2	340.6	281.3	388.4	408.3	333.1

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Most of the roughly 10,000 female Vietnam veterans who were potentially exposed to herbicides in Vietnam are approaching or have recently reached menopause. Given the high incidence of breast cancer among older and postmenopausal women in general, on the basis of demographics alone it is expected that the breast-cancer burden in female Vietnam veterans will increase in the near future.

Breast cancer occurs primarily in women, and the vast majority of breast-cancer epidemiologic studies involve women, but it also occurs in men (ACS, 2006a). Reported instances of male breast cancer are noted, but the committee's conclusions are based on the studies in women.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and breast cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-23 summarizes the relevant research.

TABLE 6-23 Selected Epidemiologic Studies—Breast Cancer

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	21	0.9 (0.6–1.4)
	Ever	32	0.9 (0.6–1.3)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)		
	Women	1	1.3 (0.0–7.2)
	Men	1	32 (0.8–175)
	Phenoxy herbicide sprayers (>99% men)	0	0.0 (*)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	27	1.1 (0.7–1.6)
	Spouses of private applicators (>99%women)	474	1.0 (0.9–1.1)
	Commercial applicators (men and women)	1	0.6 (0.1–3.5)
Engel et al., 2005	US Agriculture Health Study, wives of private applicators—incidence		

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Wives own use of phenoxy herbicides	41	0.8 (0.6–1.1)
	2,4-D	41	0.8 (0.6–1.1)
	Husbands' use of phenoxy herbicides	110	1.1 (0.7–1.8)
	2,4-D	107	0.9 (0.6–1.4)
	2,4,5-T	44	1.3 (0.9–1.9)
	2,4,5-TP	19	2.0 (1.2–3.2)
Blair et al., 2005a	US Agriculture Health Study—mortality		
	Private applicators (men and women)	3	0.9 (0.2–2.7)
	Spouses of private applicators (>99%women)	54	0.9 (0.7–1.1)
Mills and Young, 2005	Hispanic agricultural farm workers (women)		
	Cancer diagnosis 1987–1994		
	Low 2,4-D use	12	0.6 (0.2–1.9)
	High 2,4-D use	8	0.6 (0.2–1.7)
	Cancer diagnosis 1995–2001		
	Low 2,4-D use	19	2.2 (1.0–4.9)
	High 2,4-D use	21	2.1 (1.1–4.3)
Studies Reviewed in *Update 2000*			
Duell et al., 2000	Female farm workers and residents in North Carolina		
	Used pesticides in the garden	228	2.3 (1.7–3.1)
	Laundered clothes for pesticide user	119	4.1 (2.8–5.9)
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort		
	Women[identical with Manz et al. (1991)]	9	2.2 (1.0–4.1)
	Men	2	2.6 (0.3–9.3)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	Men—white	18	0.7 (0.4–1.2)
	nonwhite	4	1.7 (0.5–4.4)
	Women—white	71	1.0 (0.8–1.3)
	nonwhite	30	0.7 (0.5–1.0)
Kogevinas et al., 1993	IARC cohort—women	7	0.9 (0.4–1.9)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish and Italian farm workers		
	Male farmers	5	0.5 *
	Female farmers	41	0.9 *
	Females family workers	429	0.8 ($p < 0.05$)
Manz et al., 1991	German production workers—men and women (Included in the IARC cohort)		
	Women	9	2.2 (1.0–4.1)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)		
	Male	2	3.5 (0.4–12.5)
	Females	1	0.3 (0.0–1.7)
Lynge, 1985	Danish male and female production workers—incidence (Included in the IARC cohort)		
	Women	13	0.9 *
Wiklund, 1983	Swedish male and female agricultural workers—incidence	444	0.8 (0.7–0.9)[b]

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
ENVIRONMENTAL			
New Studies			
Reynolds et al., 2005	Women undergoing breast biopsies in San Francisco area hospitals - 79 breast cancer cases vs 52 controls with benign breast conditions—incidence		
	Total TEQs (pg/g) in adipose breast tissue		
	≤14.0	24	1.0
	14.1–20.9	22	0.7 (0.3–1.9)
	≤21.0	33	0.3 (0.3–2.0)
			p-trend = 0.99
Reynolds et al., 2004	California Teachers Study cohort		
	Residential proximity to use of "endocrine disruptors" (including 2,4–D and cacodylic acid)		
	Quartiles of use (lb/mi^2)		
	< 1	1,027	1.0
	1–21	274	1.0 (0.8–1.1)
	22–323	114	0.9 (0.7–1.1)
	≥324	137	1.0 (0.9–1.3)
Studies Reviewed in *Update 2002*			
Holford et al., 2000	Patients at Yale-New Haven hospital with breast-related surgery; dioxin-like congener 156	*	0.9 (0.8–1.0)
Revich et al., 2001	Residents of Chapaevsk, Russia—women	58	2.1 (1.6–2.7)
Warner et al., 2002	Seveso Women's Health Study—981 women who were infants to age 40 when exposed—incidence		
	With 10-fold increase in TCDD level	15	2.1 (1.0–4.6)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—females	14	0.7 (0.4–1.3)
Bagga et al., 2000	Women receiving medical care in Woodland Hills, California	73	NS
Demers et al., 2000	Women in Quebec City—newly diagnosed	314	NS
Høyer et al., 2000	Female participants of Copenhagen City Heart Study	195	Overall survival RR 2.8 (1.4–5.6)
Studies Reviewed in *Update 1998*			
Bertazzi et al. 1997	Seveso residents—15-year follow-up		
	Zone A—women	1	0.6 (0.0–3.1)
	Zone B—women	9	0.8 (0.4–1.5)
	Zone R—women	67	0.8 (0.6–1.0)
Studies Reviewed in Update 1996			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone A—women	1	0.5 (0.1–3.3)
	Zone B—women	10	0.7 (0.4–1.4)
	Zone R—women	106	1.1 (0.9–1.3)
	men	1	1.2 (0.1–10.2)
Studies Reviewed in *VAO*			
Bertazzi et al., 1989b	Seveso residents—10-year follow-up		
	Zone A—women	1	1.1 (0.1–7.5)
	Zone B—women	5	0.9 (0.4–2.1)
	Zone R—women	28	0.6 (0.4–0.9)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
VIETNAM VETERANS			
New Studies			
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	0	—
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	7	0.9 (0.4–1.9)
	Navy	1	0.6 (0.0–3.3)
	Army	5	1.0 (0.3–2.2)
	Air Force	1	1.1 (0.0–6.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	4	2.2 (0.6–5.4)
	Navy	1	2.5 (0.0–13.5)
	Army	3	2.5 (0.5–7.2)
	Air Force	0	0.0 (0.0–14.6)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed	0	—
	Incidence	0	0.0 (0.0–2.4)
	Mortality	*	
Studies Reviewed in *Update 2002*			
Kang et al., 2000	Female Vietnam veterans	170	1.2 (0.9–1.5)
Studies Reviewed in *Update 2000*			
CDVA, 1998b	Australian Vietnam veterans—women	17[d]	5 expected (2–11)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans—men	3	5.5 (1.0– >10.0)
Studies Reviewed in *Update 1996*			
Dalager et al., 1995	Female US Vietnam veterans	26	1.0 (0.6–1.8)
Studies Reviewed in *VAO*			
Thomas et al., 1991	Female US Vietnam veterans	17	1.2 (0.6–2.5)

[a] Given when available.
[b] 99% CI.
[c] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[d] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have breast cancer?"
* Information not provided by study authors.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; CI, confidence interval; IARC, International Agency for Research on Cancer; NS, not significant; PCB, polychlorinated biphenyls; RR, relative risk; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Update of the Epidemiologic Literature

Occupational Studies

Three reports on breast-cancer risk in spouses in the AHS have been published since *Update 2004*. Alavanja et al. (2005) identified 474 cases of breast cancer diagnosed through 2002 in the 32,347 spouses of pesticide applicators. No excess breast cancer was observed compared with the general population of North Carolina and Iowa (SIR = 0.99, 95% CI 0.90–1.08). It is unclear whether an association between the compounds of interest andbreast-cancer risk, if one existed,

would be strong enough to increase the estimated risk in such a broadly categorized exposure group. Engel et al. (2005) later conducted more detailed analyses on breast cancer in the same women in relation to type of chemical exposure. The association was null for exposure to phenoxy herbicides as a broad category, considering either direct chemical use by the women (RR = 0.8, 95% CI 0.6–1.1) or use by the husbands of women who did not apply the chemicals themselves (RR = 1.1, 95% CI 0.7–1.8). The results did not vary with duration of exposure, menopausal status, or state of residence (North Carolina vs Iowa). When exposure to 18 specific herbicides was considered, a significant increase in risk was seen only in women whose husbands used trichlorophenoxy propionic acid (2,4,5-TP) (RR = 2.0, 95% CI 1.2–3.2). Results for 2,4-D and 2,4,5-T were null. Blair et al. (2005) analyzed cancer mortality for 1994–2000 in the same cohort and reported no increase in risk of death from breast cancer in the AHS spouses (SMR = 0.9, 95% CI 0.7–1.1); the few women among the private applicators had a similar risk with wider confidence limits. Again, in this analysis the use of broad exposure categories could mask an association with the specific herbicides of interest.

In New Zealand, 't Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers from 1969 and 1973, respectively, through 2000. One woman and one man died from breast cancer in the producer group and none of the sprayers. Estimation of breast-cancer risk in this cohort is extremely imprecise because of the small numbers.

Mills and Yang (2005) conducted a case–control study in Hispanic agricultural workers in California. They estimated breast-cancer risk in relation to union work histories and pesticide use as recorded in state databases. They considered 13 specific chemicals, including 2,4-D. With non-exposed women as the referent group, no association with 2,4-D use was seen in women who had breast cancer diagnosed in 1988–1994. For cases diagnosed in the later period of observation (1995–2001), however, high exposure to 2,4-D was associated with a significant increase in breast cancer (OR = 2.14, 95% CI 1.06–4.32), and low exposure was associated with a similar increase (OR = 2.16, 95% CI 0.95–4.93). It is not clear why a positive association was apparent only in the later years of observation, but it is conceivable that risk increased as latency and exposure duration increased. Individual-level data on established breast-cancer risk factors were not available; county-level data on fertility and socioeconomic status were used as surrogates in adjusted analyses. That is an important limitation in a breast-cancer study because misclassification of established risk factors as covariates can introduce substantial bias. However, fertility rates by county were inversely associated with breast-cancer risk in subjects in this study, so this ecologic variable might have been capturing some of the confounding that could occur because of different reproductive patterns between cases and controls. The strengths of this study—which bears on 2,4-D exposure only, not dioxins—include the use of a comprehensive statewide cancer registry for ascertainment of breast-cancer status and unbiased exposure estimation because of linkage of individual work records to a detailed database on agricultural chemical use.

Environmental Studies

Reynolds et al. (2004) used a Geographic Information System (GIS) to link data on pesticide use to residential histories of women in the California Teachers Study cohort. Two compounds of

interest, 2,4-D and cacodylic acid, were included among 34 chemicals in a category labeled endocrine disruptors but were not addressed in any specific analyses. Residential proximity to use of chemicals in the entire category was not associated with breast-cancer risk (for the heaviest vs the lowest exposure intensity, RR was 1.03, 95% CI 0.86–1.25). It is not clear how many subjects in the analysis had substantial exposure to the compounds.

In another GIS analysis, Brody et al. (2004) compared residential proximity to pesticide sources in people with breast cancer and controls in Massachusetts. No associations were observed; however, the relevance of the study is limited by uncertainty in the extent of exposure to any of the compounds of interest.

Mills and Yang (2006) computed RRs of breast cancer among Latina women in California according to countywide data on pesticide use. Significant increases in risk were reported in association with two organochlorines (methoxychlor and toxaphene); however, risk estimates were not provided for any of the specific compounds of interest. The analysis carries less weight than the previously described study on Latina farm workers by the same authors because, although the number of breast cancers is much greater, the proportion of women significantly exposed to the chemicals is much lower.

Three recent studies are noteworthy for having measured organochlorines in adipose tissue in breast-cancer cases and controls, although two of them are not very informative, because of lack of focus on the specific compounds of interest. The first, a methodologic study by Petreas et al. (2004), is discussed in Chapter 5 in connection with exposure considerations.

Raaschou-Nielsen et al. (2005) compared 409 postmenopausal Danish women with breast cancer to an equal number of matched controls selected from a large research cohort. Fourteen pesticides and 18 polychlorinated biphenyl (PCB) congeners were measured in adipose tissue from the buttocks; women with higher adipose-tissue concentrations of the compounds did not have a higher risk of breast cancer. In fact, the study found strong inverse associations with risk of estrogen-receptor-negative breast cancer in women with the highest concentrations of total PCBs and several organochlorine pesticides ($p = 0.007$ for trend across quartiles of total PCBs). The investigators speculate that the inverse associations could have resulted from higher fish consumption by controls or from more rapid metabolic conversion of precursors to proximal carcinogens by the women with cancer. The study is noteworthy because of its size and because it is the first to use adipose-tissue organochlorines in a prospective analysis of breast-cancer risk. However, its relevance for the purposes of the present committee is limited by the lack of TCDD measurement and by the extreme weakness of the dioxin-like activity of the PCB congeners.

Reynolds et al. (2005) measured dioxin in breast adipose tissue obtained from 79 women with breast cancer and 52 controls with benign breast conditions. They found no associations between any of 17 polychlorinated dibenzodioxins and dibenzofurans with substitutions in the 2, 3, 7, or 8 positions. When all measured compounds were combined as international toxic equivalent units, the OR for the highest tertile vs the lowest was 0.73 (95% CI 0.27–1.95). Although small and lacking in statistical power, the study is unique in its focus on the target-organ exposure and the specific compounds of interest.

Vietnam-Veteran Studies

In the mortality update of the CDC VES of only male subjects through 2000, Boehmer et al. (2004) reported a single case of breast cancer in the non-deployed. Similarly, the updates on the health status of Australian Vietnam veterans reported only on male veterans but included scattered breast-cancer cases. No increase was seen when veterans were compared with the general population of Australia in incidence (SIR = 0.90, 95% CI 0.36–1.86) (ADVA, 2005a), but four deaths produced a non-significant increase in mortality (SMR = 2.15, 95% CI 0.58–5.42) (ADVA, 2005b). In the comparison of deployed with non-deployed Vietnam veterans (ADVA, 2005c), only two breast-cancer cases were identified, both in the non-deployed, and no deaths from this type of cancer.

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Biologic Plausibility

All the experimental evidence indicates that 2,4-D, 2,4,5-T, and TCDD are weakly genotoxic if at all. However, TCDD is a demonstrated carcinogen in animals and is classified as a human carcinogen because of its ability to act as a strong tumor promoter. The possible general mechanisms by which TCDD may exert those effects are discussed in Chapter 3.

With respect to breast cancer, studies performed in laboratory animals (Sprague-Dawley rats) indicate that the effect of TCDD may depend on the age of the animal. For example, TCDD exposure was found to inhibit mammary-tumor growth in the adult rat (Holcombe and Safe, 1994) but to increase tumor growth in the neonatal rat (21 days old) (Desaulniers et al., 2001). Other studies have failed to demonstrate a TCDD effect on mammary-tumor incidence or growth (Desaulniers et al., 2004).

Those observations may indicate a close association between the development of mammary cancers and mammary gland differentiation. Agents capable of disrupting the ability of the normal mammary epithelial cell to enter or maintain its appropriate status (a proliferative, differentiated, apoptotic state), to maintain its appropriate architecture, or to alter key hormone (estrogen) signaling are likely to act as carcinogenic agents (Fenton, 2006; McGee et al., 2006). In that light, it is interesting that postnatal exposure of pregnant rats to TCDD has been found to alter proliferation and differentiation of the mammary gland (Birnbaum and Fenton, 2003; Vorderstrasse et al., 2004). Thus, the effect of TCDD may depend on the timing of the exposure and may affect mammary-tumor development only if the exposure occurs during a specific window during mammary development. The breast is the only human organ that does not fully differentiate until it becomes ready for use; nulliparous women have less-differentiated breast lobules, which are presumably more vulnerable to carcinogenesis.

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Recent results from the AHS cohort generally do not support the hypothesis that exposure to the compounds in Agent Orange increases breast-cancer incidence or mortality in women,

although exposure to the specific compounds of interest was not specified. Increased risks observed in one subgroup whose husbands worked with 2,4,5-TP will require further study and confirmation; this finding could have arisen by chance. Recent studies of environmental exposure found null associations; however, exposures were of questionable relevance. Two studies of organochlorine concentrations in adipose tissue failed to find any evidence of increased risk in association with higher adipose concentrations; in fact, the more relevant study found the risk in the highest tercile of dioxin concentrations in breast fat was lower than in the lowest tercile of dioxin concentrations, although not significantly so.

One study published since the last update does provide some evidence of an association between exposure to 2,4-D and breast-cancer risk in female farmworkers in California (Mills and Yang, 2005). The study is limited by lack of detailed information on potential confounding factors and lack of evidence of a dose-response relationship, but it is large and the investigators were able to estimate individual exposures by linking work histories to an extensive database on pesticide use.

The committee considered the new information in the context of the cumulative data from studies reviewed in previous updates. Results of several prior studies lend support to the hypothesis that there is an association between exposure to the compounds of interest and exposure to the compounds of interest, specifically, studies by Kogevinas et al. (1997), Kang et al. (2000), Revich et al. (2001), and Warner et al. (2002).

The first of those studies is a mortality study of a large multinational cohort of workers exposed to phenoxy herbicides or chlorophenols in manufacturing or spraying (Kogevinas et al., 1997). In women specifically exposed to TCDD and higher chlorinated dioxins, there were nine deaths from breast cancer vs 4.17 expected (SMR = 2.16, 95% CI 0.99–4.10), whereas there was no appreciable risk in other women in the cohort. All nine deaths occurred in the German herbicide plant that accounted for most of the expopsure of women to TCDD. The breast-cancer SMR for this plant alone was 2.84 (95% CI 1.30–5.39). There were also two deaths from breast cancer in the multinational cohort in men exposed to TCDD and higher chlorinated dioxins; this is more than expected for this rare tumor, but such a result could have arisen by chance.

Kang et al. (2000) reported an increased OR for breast cancer in a cross-sectional study comparing female Vietnam veterans with non-Vietnam veterans (multivariate OR = 1.18, 95% CI 0.91–1.51).

Revich et al. (2001) calculated SMRs for women occupationally or environmentally exposed to dioxins in Chapaevsk, Russia, the site of a large chemical plant. Substantially increased concentrations of dioxins were measured in soil, drinking water, and breast milk in Chapaevsk and in the serum of people who worked in the factory or lived nearby. The SMR for breast cancer in the town of Chapaevsk, with 58 observed deaths and expected numbers based on rates for the entire region, was significantly increased (SMR = 2.1, 95% CI 1.6–2.7). That result has limited weight because women in the town were exposed to numerous toxic chemicals, and, although widespread contamination with dioxin was documented, it is difficult to attribute the breast-cancer excess to dioxins alone.

Finally, in a study of women exposed in Seveso (Warner et al., 2002), there was a significant association between lipid-adjusted serum TCDD concentrations and breast-cancer incidence (RR = 2.1 for a 10-fold increase in serum TCDD, 95% CI 1.0–4.6). The study found no difference in the risk estimate after comprehensive adjustment for established or potential breast-cancer risk factors. It is important to note that the Seveso Women's Cohort Study ascertained breast-cancer

status 20–22 years after the Seveso explosion by interview followed by medical-record verification; the study did not include three women who had already died from breast cancer before the interviews took place.

The committee believes that the recent data from the study by Mills and Yang (2005), although not persuasive in themselves, lend additional weight to an association between the relevant herbicide exposures and breast-cancer risk. This study has reasonable size and relatively specific exposure information but is limited chiefly by the data available to control for confounding. Among the four earlier studies contributing to the committee's view, two have highly specific exposure data (related to occupational exposure to phenoxy herbicides and to Seveso), one reports an increased risk in women living in an area with documented heavy dioxin contamination (Chapvaesk), and one reports an increased risk in female Vietnam veterans that does not achieve the conventional level of statistical significance. Each study has limitations or weaknesses that keep its conclusions about the association in question from being definitive. Some members of the committee considered the body of evidence as a whole to be suggestive of an association; for others, the few modestly positive results associated with a diversity of exposures suggested chance findings rather than a coherent picture. Further laboratory and epidemiologic work on this association should be pursued.

The main reason for the unresolved division in the committee's opinion concerning the adequacy of the available evidence to support an association between breast cancer and exposure to the components of the herbicides sprayed in Vietnam was differing individual views about the specificity and relevance of the studied exposures for the population of primary concern to the committee, Vietnam veterans. Overall, the committee was impressed by the positive results from Seveso, but several members considered this a very small sample upon which to anchor an association. The degree to which the profile of chemicals contributing to TEQ in the more positive epidemiologic studies differed from that of Vietnam veterans diminished the conviction of some members that these results constituted fully relevant evidence.

Conclusion

After extensive deliberation concerning the new evidence and the results of studies reviewed in previous updates, the committee was unable to reach consensus as to whether the evidence of an association between exposure to the compounds of interest and breast cancer met the criteria for being considered limited or suggestive or whether concerns about chance, bias, and confounding remained so substantial that breast cancer should remain in the inadequate or insufficient classification.

CANCERS OF THE FEMALE REPRODUCTIVE SYSTEM

This section addresses cancers of the cervix (ICD-9 180), endometrium (also referred to as the corpus uteri; ICD-9 182.0–182.1, 182.8), and ovary (ICD-9 183.0). Other cancers of the female reproductive system that are infrequently reported separately are unspecified cancers of the uterus (ICD-9 179), placenta (ICD-9 181), fallopian tube and other uterine adnexa (ICD-9 183.2–183.9), and other female genital organs (ICD-9 184); any findings on these cancers would be

included in this section. It also presents statistics on other cancers of the female reproductive system. ACS estimates of the numbers of new female reproductive-system cancers in the United States in 2006 are presented in Table 6-24, with genital-system cancers represent roughly 11% of new cancer cases and 10% of cancer deaths in women (Jemal et al., 2006).

Table 6-24 Estimates of New Cases and Deaths in 2004 in United States for Selected Cancers of the Female Reproductive System[a]

Site	New Cases	Deaths
Cervix	9,710	3,700
Endometrium	41,200	7,350
Ovary	20,180	15,310
Other female genital	2,420	2,420

[a]ACS (American Cancer Society), 2006.

The incidences of and risk factors for those diseases vary (Table 6-25). Cervical cancer occurs more often in blacks than in whites, whereas whites are more likely to develop endometrial and ovarian cancer. The incidence of endometrial and ovarian cancer is increased among older women and among those with positive family histories. Use of unopposed estrogen hormone therapy and obesity, which increases endogenous concentrations of estrogen, both increase the risk of endometrial cancer. HPV infection, particularly infection with HPV types 16 and 18, is the most important risk factor for cervical cancer. Use of oral contraceptives is associated with a substantial reduction in the risk of ovarian cancer.

TABLE 6-25 Average Annual Incidence (per 100,000) of Female Genital System Cancers in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
All Genital Sites	85.5	89.5	61.7	119.3	126.3	80.0	151.1	156.5	145.3
Cervix	11.7	10.9	15.3	11.8	10.8	17.8	13.2	11.4	25.8
Endometrium	45.5	48.8	24.6	68.6	73.7	36.6	88.6	93.0	77.1
Ovary	22.8	24.2	15.1	31.5	33.9	17.8	39.3	42.0	30.7
Other genital organs	1.1	1.1	0.6	1.5	1.7	0.9	2.7	2.6	1.2

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and female reproductive cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Tables 6-26, 6-27, and 6-28 summarize the results of the relevant studies.

TABLE 6-26 Selected Epidemiologic Studies—Cervical Cancers

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to TCDD (or higher-chlorinated dioxins	0	0.0 (0.0–3.8)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	3	1.8 (0.4–5.2)
	Workers exposed to any phenoxy herbicide or chlorophenol	3	1.1 (0.2–3.3)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	Whites	6	0.9 (0.3–2.0)
	Nonwhites	21	2.0 (1.3–3.1)
Lynge, 1993	Danish phenoxy herbicide workers	7	3.2 (1.3–6.6)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish self-employed farm farmers—incidence		
	Self-employed farmers	7	0.5 ($p < 0.05$)
	Family workers	100	0.5 ($p < 0.05$)
	Employees	12	0.8 *
Wiklund, 1983	Swedish men and women agricultural workers—incidence	82	0.6 (0.4–0.8)[b]
ENVIRONMENTAL			
Studies Reveiwed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia	13	1.8 (1.0–3.1)
VIETNAM VETERANS			
Studies Reveiwed in *Update 2002*			
Kang et al., 2000	Female Vietnam veterans	57	1.1 (0.7–1.7)
Studies Reveiwed in *Update 2000*			
CDVA, 1998b	Australian Vietnam veterans—women	8[d]	1 expected (0–5)

[a] Given when available.
[b] 99% CI.
[c] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[d] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have cancer of the cervix?"
* Information not provided by study authors.
ABBREVIATIONS: CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer.

TABLE 6-27 Selected Epidemiologic Studies—Uterine Cancers

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort (includes cancers of the endometrium)		
	Workers exposed to TCDD (or higher-chlorinated dioxins	3	3.4 (0.7–10.0)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	1	1.2 (0.0–6.5)
	Workers exposed to any phenoxy herbicide or chlorophenol	4	2.3 (0.6–5.9)
Studies Reviewed in *VAO*			
Blair et al., 1993	US farmers in 23 states		
	Whites	15	1.2 (0.7–2.1)
	Nonwhites	17	1.4 (0.8–2.2)
Ronco et al., 1992	Danish self-employed farm farmers—incidence		
	Self-employed farmers	8	0.6 *
	Family workers	103	0.8 ($p < 0.05$)
	Employees	9	0.9 *
Wiklund, 1983	Swedish men and women agricultural workers—incidence	135	0.9 (0.7–1.1)[b]
ENVIRONMENTAL			
Studies Reveiwed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—women	2	0.5 (0.1–1.9)
Weiderpass et al., 2000	Swedish women	154	1.0 (0.6–2.0)
Bertazzi et al., 1998	Seveso residents—15-year follow-up		
	Zone B—women	1	0.3 (0.0–2.4)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B—women	1	0.3 (0.0–1.9)
	Zone R—women	27	1.1 (0.8–1.7)
VIETNAM VETERANS			
Studies Reveiwed in *Update 2002*			
Kang et al., 2000	Female Vietnam veterans	41	1.0 (0.6–1.6)
Studies Reveiwed in *Update 2000*			
CDVA, 1998b	Australian Vietnam veterans—women	4[c]	1 expected (0–5)
Studies Reviewed in *Update 1996*			
Dalager et al., 1995	Female Vietnam veterans	4	2.1 (0.6–5.4)

[a] Given when available.
[b] 99% CI.
[c] Self-reported medical history. Answer to question: Since your first day of service in Vietnam, have you been told by a doctor that you have uterine cancer?
* Information not provided by study authors.
ABBREVIATIONS: CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer.

TABLE 6-28 Selected Epidemiologic Studies—Ovarian Cancer

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	4	3.9 (1.1–10.1)
	Spouses of private applicators (>99%women)	13	0.7 (0.4–1.2)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	8	3.0 (1.3–5.9)
	Spouses of private applicators (>99%women)	32	0.6 (0.4–0.8)
	Commercial applicators (men and women)	0	0.0 (0.0–16.0)
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort		
	Workers exposed to TCDD (or higher-chlorinated dioxins	0	0.0 (0.0–2.6)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	1	0.5 (0.0–2.5)
	Workers exposed to any phenoxy herbicide or chlorophenol	1	0.3 (0.0–1.5)
Studies Reviewed in *Update 1996*			
Kogevinas et al., 1993	IARC cohort	1	0.7 *
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish self-employed farm farmers—incidence		
	Self-employed farmers	12	0.9 *
	Family workers	104	0.8 ($p < 0.05$)
	Employees	5	0.5 *
Donna et al., 1984	Female residents near Alessandria, Italy	18	4.4 (1.9–16.1)
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—women	3	0.7 (0.2–2.0)
Bertazzi et al., 1998	Seveso residents—15-year follow-up		
	Zone A—women	1	2.3 (0.3–16.5)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone A—women	1	2.3 (0.0–12.8)
	Zone R—women	21	1.0 (0.6–1.6)
VIETNAM VETERANS			
Studies Reveiwed in *Update 2002*			
Kang et al., 2000	Female Vietnam veterans	16	1.8 (0.7–4.6)
Studies Reviewed in *Update 2000*			
CDVA, 1998b	Australian Vietnam veterans—women	1[b]	0 expected (0–4)

[a] Given when available.

[b] Self-reported medical history. Answer to question: Since your first day of service in Vietnam, have you been told by a doctor that you have ovarian cancer?

* Information not provided by study authors.

Studies in italics have been superseded by newer studies of the same cohorts.

ABBREVIATIONS: CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer.

Update of the Epidemiologic Literature

Occupational Studies

In the analysis of cancer incidence in the AHS, Alavanja et al. (2005) reported an excess of ovarian cancer in pesticide applicators (SIR = 2.97, 95% CI 1.28–5.85) but a significantly reduced incidence in spouses of farmer applicators (SIR = 0.55, 95% CI 0.38–0.78).

Blair et al. (2005a) observed parallel results for mortality in the same cohort: death from ovarian cancer was increased in applicators (on the basis of only four deaths) but not in farmer spouses. Neither incidence of nor mortality from other female reproductive cancers (combined) was reported to be increased in the analyses.

No new environmental or Vietnam-veteran studies concerning exposure to the compounds of interest and female reproductive cancer were published since *Update 2004*.

Biologic Plausibility

No animal studies have reported an increased incidence of female reproductive cancer after exposure to the compounds of interest. One study (Kociba et al., 1978), however, showed a reduced incidence of uterine tumors in rats fed TCDD at 0.1 mg/kg of diet for 2 years.

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Two analyses of the same cohort found increased incidence of and mortality from ovarian cancer in women who had been engaged in pesticide application. The weight of those studies for the present purposes is limited by the lack of detail on chemical exposures and the absence of data that would allow for control of confounding. Future studies of ovarian cancer should be watched carefully, particularly studies that use biomarkers of exposure or more detailed chemical-exposure histories.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and uterine, ovarian, or cervical cancer.

PROSTATE CANCER

ACS estimated that 234,460 new cases of prostate cancer (ICD-9 185) would be diagnosed in the United States in 2006 and that 27,350 men would die from it (Jemal et al., 2006). That makes prostate cancer the second-most common cancer in men (after non-melanoma skin cancers); it is expected to account for about 33% of new cancer diagnoses and 9% of cancer deaths in men in 2006. The average annual incidence of prostate cancer is shown in Table 6-29.

Incidence varies dramatically with age and race. The risk more than doubles between the ages of 50–54 years and 55–59 years, and it nearly doubles again between the ages of 55–59 years and 60–64 years. As a group, American black men have the highest recorded incidence of prostate cancer in the world (Miller et al., 1996). Their risk is roughly twice that in whites in the United States, 5 times that in Alaska natives, and nearly 8.5 times that in Korean Americans. Little is known about the causes of prostate cancer. Other than race and age, risk factors include a family history of the disease and possibly some elements of the Western diet, such as high consumption of animal fats.

TABLE 6-29 Average Annual Incidence (per 100,000) of Prostate Cancer in United States[a]

50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
All Races	White	Black	All Races	White	Black	All Races	White	Black
146.6	140.6	278.0	356.1	342.9	648.6	620.6	609.2	1,043.0

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

The study of the incidence of and mortality from prostate cancer is complicated by trends in screening for the disease. The recent introduction and widespread adoption of prostate-specific antigen (PSA) for screening have led to improved detection and thus to reports of increased incidence in the United States. The long-term influence of better screening on incidence and mortality, however, is difficult to predict for any country or population, and it will depend on the rapidity with which the screening tool is adopted, its differential use in men of various ages, and the aggressiveness of tumors detected early with this test (Gann, 1997). Because exposure to PSA testing is such a strong determinant of prostate-cancer incidence, epidemiologic studies must be careful to exclude differential PSA testing as an explanation of a difference in risk observed between two populations.

Prostate cancer tends not to be fatal, so mortality studies might miss an increased incidence of the disease. Findings that show an association between an exposure and prostate-cancer mortality should be examined closely to determine whether the exposed group might have had poorer access to treatment that would have increased the likelihood of survival.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to the compounds of interest and prostate cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-30 summarizes results of the relevant studies, including morbidity and mortality studies. The type, quality, and specificity of each study must be considered in the interpretation and weighing of evidence. Because of study

heterogeneity, simply examining all the estimated risks in the table together will not yield a good assessment of the risks.

TABLE 6-30 Selected Epidemiologic Studies—Prostate Cancer

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	117	0.9 (0.7–1.0)
	Ever	84	0.9 (0.7–1.2)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	1	0.4 (0.0–2.1)
	Phenoxy herbicide sprayers (>99% men)	2	0.6 (0.1–2.2)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	1,046	1.3 (1.2–1.3)
	Spouses of private applicators (>99%women)	5	1.2 (0.4–2.8)
	Commercial applicators (men and women)	41	1.4 (1.0–1.9)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	48	0.7 (0.5–0.8)
	Spouses of private applicators (>99%women)	0	0.0 (0–1.6)
Torchio et al., 1994	Italian licensed pesticide users	66	1.0 (0.7–1.2)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	12	0.7 (0.4–1.3)
Studies Reviewed in *Update 2004*			
Alavanja et al., 2003	US Agriculture Health Study—Pesticide appliers from Iowa and North Carolina—incidence	566	1.1 (1.1–1.2)
Bodner et al., 2003	Dow chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	—	1.7 (1.0–2.6)
Swaen et al., 2004	Dutch licensed herbicide applicators	6	1.0 (0.4–2.2)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	7	1.3 (0.5–2.8)
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides		
	Foremen—incidence	2	4.7 (*)
	Male lumberjacks—incidence	3	0.9 (*)
Studies Reviewed in *Update 2000*			
Sharma-Wagner et al., 2000	Swedish citizens		
	Agriculture and stock raising	6,080	1.1 (1.0–1.1) ($p < 0.01$)
	Farmers, foresters, and gardeners	5,219	1.1 (1.0–1.1) ($p < 0.01$)
	Paper mill workers	304	0.9 (0.8–1.0)
	Pulp grinding	39	1.4 (1.0–1.9) ($p < 0.05$)
Fleming et al., 1999a	Florida pesticide appliers	353	1.9 (1.7–2.1)
Fleming et al., 1999b	Florida pesticide appliers	64	2.4 (1.8–3.0)
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	28	1.2 (0.8–1.7)
Dich and Wiklund, 1998	Swedish pesticide appliers	401	1.1 (1.0–1.2)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Born 1935 or later	7	2.0 (0.8–4.2)
	Born before 1935	394	1.1 (1.0–1.2)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	19	1.0 (0.6–1.5)
Hertzman et al., 1997	Canadian sawmill workers		
	Morbidity	282	1.0 (0.9–1.1)
	Mortality from male genital tract cancers	116	1.2 (1.0–1.4)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	68	1.1 (0.9–1.4)
	Workers exposed to TCDD (or higher-chlorinated dioxins	43	1.1 (0.8–1.5)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	25	1.1 (0.7–1.6)
Becher et al., 1996	German production workers (Included in the IARC cohort)	9	1.3 *
Ott and Zober, 1996	BASF employees—incidence		
	TCDD < 0.1 µg/kg of body weight	4	1.1 (0.3–2.8)
	TCDD 0.1–0.99 µg/kg of body weight	1	1.1 (0.0–5.9)
Zhong and Rafnsson, 1996	Icelandic pesticide users	10	0.7 (0.3–1.3)
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators		
	Incidence	6	0.4 (0.1–0.8)
	Mortality	5	0.8 (0.3–1.8)
Blair et al., 1993	US farmers in 23 states (men and women)		
	Whites	3,765	1.2 (1.1–1.2)
	Nonwhites	564	1.1 (1.1–1.2)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort)	3	2.6 (0.5–7.7)
Collins et al., 1993	Monsanto Company workers (Included in the NIOSH cohort)	9	1.6 (0.7–3.0)
Studies Reviewed in *VAO*			
Morrison et al., 1993	Canadian farmers, 45–69 years old, no employees, or custom workers, sprayed ≥250 acres	20	2.2 (1.3–3.8)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	399	0.9 ($p < 0.05$)
	employee	63	0.8 ($p < 0.05$)
Swaen et al., 1992	Dutch licensed herbicide applicators	1	1.3 (0.0–7.3)
Fingerhut et al., 1991	NIOSH—entire cohort	17	1.2 (0.7–2.0)
	≥1-year exposure; ≥20-year latency	9	1.5 (0.7–2.9)
Manz et al., 1991	German production workers—men and women (Included in the IARC cohort)	7	1.4 (0.6–2.9)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	30	1.1 (0.8–1.6)
Zober et al., 1990	BASF employees—basic cohort	0	* (0.0–6.1) [b]
Alavanja et al., 1989	USDA forest conservationists	*	1.6 (0.9–3.0)
	Soil conservationists	*	1.0 (0.6–1.8)
Henneberger et al., 1989	New Hampshire pulp and paper workers	9	1.0 (0.5–1.9)
Solet et al., 1989	US Paper and pulp workers	4	1.1 (0.3–2.9)
Alavanja et al., 1988	USDA agricultural extension agents	*	1.0 (0.7–1.5)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	1.0 (0.0–5.8)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	18	1.3 (0.8–2.1)
Robinson et al., 1986	Northwestern US Paper and pulp workers	17	1.2 (0.7–1.7) [b]
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)	9	0.8 *
Blair et al., 1983	Florida pesticide applicators	2	3.8 expected
Burmeister et al., 1983	Iowa residents—farm exposures	4, 827	1.2 ($p < 0.05$)
Wiklund, 1983	Swedish male and female agricultural workers	3,890	1.0 (0.9–1.0)[c]
Burmeister, 1981	Iowa farmers	1,138	1.1 ($p < 0.01$)
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—men	8	1.1 (0.5–2.2)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B—men	6	1.2 (0.5–2.7)
	Zone R—men	39	1.2 (0.8–1.6)
Svensson et al., 1995	Swedish fishermen—mortality		
	East coast	12	1.0 (0.5–1.8)
	West coast	123	1.1 (0.9–1.3)
	Swedish fishermen—incidence		
	East coast	38	1.1 (0.8–1.5)
	West coast	224	1.0 (0.9–1.1)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone R—men	16	0.9 (0.5–1.5)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	4	1.4 (0.5–3.9)
	Zone R—men	17	0.9 (0.6–1.5)
Bertazzi et al., 1989a	Seveso residents—10-year follow-up		
	Zones A, B, R—men	19	1.6 (1.0–2.7)
Bertazzi et al., 1989b	Seveso residents—10-year follow-up		
	Zone B—men	3	2.2 (0.7–6.9)
	Zone R—men	16	1.6 (0.9–2.7)
VIETNAM VETERANS			
New Studies			
Leavy et al., 2006	606 prostate cancer cases in Western Australia		
	Vietnam service	25	2.1 (0.9–5.1)
Pavuk et al., 2006	AFHS subjects—incidence		
	20-yr cumulative TCDD (ppt-yr)		
	Comparison group	81	1.0
	RH low (≤434 ppt-yr)	31	1.0 (0.7–1.6)
	RH high (>434 ppt-yr)	28	1.2 (0.8–1.9)
			p-trend = 0.42

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Last tour in SEA before 1969 (heavy spraying)		
	Yes		
	Comparison group	17	1.0
	RH low (≤434 ppt-yr)	9	1.0 (0.4–2.3)
	RH high (>434 ppt-yr)	15	2.3 (1.1–4.7)
			p-trend = 0.04
	No		
	Comparison group	64	1.0
	RH low (≤434 ppt-yr)	22	1.1 (0.7–1.8)
	RH high (>434 ppt-yr)	13	0.9 (0.5–1.6)
			p-trend = 0.75
	Less than 2 years served in SEA		
	Yes		
	Comparison group	16	1.0
	RH low (≤434 ppt-yr)	20	1.9 (1.0–3.7)
	RH high (>434 ppt-yr)	14	2.2 (1.0–4.5)
			p-trend = 0.03
	No		
	Comparison group	65	1.0
	RH low (≤434 ppt-yr)	11	0.8 (0.4–1.5)
	RH high (>434 ppt-yr)	14	1.1 (0.6–1.9)
			p-trend = 0.89
Pavuk et al., 2005	White Air Force comparison subjects only—incidence		
	Serum TCDD levels (pg/g), based on model with exposure variable $\log_e$(TCDD) [g]		
	Per unit increase of -$\log_e$(TCDD) in pg/g	83	1.1 (0.7–1.5)
	Quartiles (pg/g)		
	0.4–2.6	13	1.0
	2.6–3.8	24	1.7 (0.8–3.3)
	3.8–5.2	24	1.5 (0.7–2.9)
	>5.2	22	1.2 (0.6–2.4)
	Number of years served in southeast Asia (SEA)		
	Per year of service	83	1.1 (1.0–1.2)
	Quartiles (years in SEA)		
	0.8–1.3	8	1.0
	1.3–2.1	11	1.3 (0.5–3.2)
	2.1–3.7	28	2.2 (1.0–4.9)
	3.7–16.4	36	2.4 (1.1–5.2)
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	692	1.3 (1.2–1.3)
	Navy	137	1.2 (1.0–1.4)
	Army	451	1.8 (1.2–1.4)
	Air Force	104	1.3 (1.0–1.5)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	107	1.2 (1.0–1.5)
	Navy	22	1.3 (0.8–1.8)
	Army	65	1.2 (0.9–1.5)
	Air Force	19	1.4 (0.8–2.1)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Incidence	65	1.2 (0.9–1.5)
	Mortality	0	0.0 (0.0–0.7)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	1	0.4
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	AFHS subjects vs national rates		
	White AFHS Ranch Hand veterans		
	Mortality—All	2	0.7 (0.1–2.3)
	Incidence—All	36	1.5 (1.0–2.0)
	With tours between 1966–1970	34	1.7 (1.2–2.3)
	White AFHS comparison veterans		
	Mortality—All	3	0.8 (0.2–2.1)
	Incidence—All	54	1.6 (1.2–2.1)
	With tours between 1966–1970	42	1.6 (1.2–2.2)
	White AFHS subjects—incidence		
	Who spent at most 2 years in SEA		
	Per unit increase of -$\log_e$(TCDD) in pg/g	28	1.5 (0.9–2.4)
	Comparison group	7	1.0
	Ranch Hand— <10 TCDD pg/g in 1987	10	1.5 (0.5–4.4)
	Ranch Hand— <118.5 TCDD pg/g at end of service	6	2.2 (0.7–6.9)
	Ranch Hand— >118.5 TCDD pg/g at end of service	5	6.0 (1.4–24.6)
	Only Ranch Hands with 100% service in Vietnam and Comparisons with 0% service in Vietnam		
	Per unit increase of -$\log_e$(TCDD) in pg/g	20	1.1 (0.6–1.8)
	Comparison group	3	1.0
	Ranch Hand— <10 TCDD pg/g in 1987	9	2.5 (0.4–16.1)
	Ranch Hand— <118.5 TCDD pg/g at end of service	4	2.4 (0.4–16.0)
	Ranch Hand— >118.5 TCDD pg/g at end of service	4	4.7 (0.8–29.1)
Giri et al., 2004	Veterans using the DVA Medical Center in Ann Arbor, MI		
	All cases	11	OR 2.1 (0.8–5.2)
	Cases in white veterans only	*	OR 2.7 (0.9–8.2)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	26	0.7(0.4–1.3)
AIHW, 1999	Australian Vietnam veterans (Validation study)	212	147 expected (123–171)
CDVA, 1998a	Australian Vietnam veterans	428[e]	147 expected (123–171)
Studies Reviewed in *Update 1998*			
Clapp, 1997	Massachusetts Vietnam veterans—incidence		
	Exposed cancers	15	0.8 (0.4–1.6)
CDVA, 1997a	Australian military Vietnam veterans	36	1.5 (1.0–2.0)
AFHS, 1996	Air Force Ranch Hand veterans	2	0.6 expected
Watanabe and Kang, 1996	US Army and Marine Corps Vietnam veterans		
	Army Vietnam Service	58	1.1 *
	Non-Vietnam	1.0	1.2 *[f]
	Marine Vietnam Service	9	1.2 *

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Non-Vietnam	6	1.3 *
Studies Reviewed in *Update 1996*			
Visintainer et al., 1995	Michigan Vietnam veterans		
	Male genital system—all races	19	1.1 (0.6–1.7)
Studies Reviewed in *VAO*			
Breslin et al., 1988	Army Vietnam veterans	30	0.9 (0.6–1.2)
	Marine Vietnam veterans	5	1.3 (0.2–10.3)
Anderson et al., 1986	Wisconsin Vietnam veterans	0	—

[a] Given when available.
[b] 90% CI.
[c] 99% CI.
[d] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
[e] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have prostate cancer?"
[f] Statistically significant with the 95% CI not including 1.0.
[g]The original paper implied that the exposure metric for TCDD was based on actual measured serum levels of TCDD. Subsequent correspondence between the Committee and the investigators indicated that the metric was actually transformed using the natural logarithm of TCDD.
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; DVA, Department of Veterans' Affairs; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; OR, odds ratio; SEA, southeast Asia; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers with exposure to nonvolatile organochlorine compounds potentially contaminated with TCDD. On the basis of a JEM, the SMR of prostate cancer among men who were ever exposed to nonvolatile organochlorine compounds was not increased (SMR = 0.93, 95% CI 0.74–1.15).

Alavanja et al. (2005) updated their prostate-cancer incidence data on a cohort of private and commercial pesticide applicators who were participants in the AHS. The incidence of prostate cancer was significantly increased in the private applicators, who were mostly farmers (SIR = 1.26, 95% CI 1.18–1.33) and increased with borderline significance in the commercial applicators (SIR = 1.37, 95% CI 0.98–1.86).

A separate report from the AHS examined associations between cumulative exposure to specific chemicals and prostate-cancer mortality (Blair et al., 2005a). Positive associations were observed with several pesticides in applicators with a family history of prostate cancer and a

significantly increased risk in all cohort members with highest exposure to the fumigant methyl bromide. There were no associations between general herbicide exposure and prostate-cancer risk; however, exposure to phenoxy herbicides or dioxin was not reported specifically.

An analysis of mortality in the private applicators in the AHS cohort also appeared recently (Blair et al., 2005a). In contrast with the results on incident prostate cancer, mortality from prostate cancer was significantly reduced in these applicators compared with the general population (SMR = 0.7, 95% CI 0.5–0.8). The relation between exposure to groups of chemicals and mortality was not reported, and the number of deaths available in the AHS for such an analysis is small. Possible explanations of the higher incidence of and lower mortality from prostate cancer in the AHS than in the general population are greater access of cohort members to early detection through PSA screening and greater adoption of aggressive treatment, although their effects on mortality from prostate cancer are not established.

In New Zealand, 't Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers from 1969 and 1973, respectively, through 2000. Although the exposures in this cohort are substantial and highly relevant, the number of deaths due to prostate cancer was too small to provide useful risk estimates.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of prostate cancer was not increased (66 cases; SMR = 0.96, 95% CI 0.74–1.22).

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 2,435 cases of prostate cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with prostate cancer (12 cases; OR = 0.72, 95% CI 0.39–1.31) was not significantly elevated.

Environmental Studies

No new relevant environmental studies concerning exposure to the compounds of interest and prostate cancer were published since *Update 2004*.

Vietnam-Veteran Studies

Two reports on prostate-cancer risk in the AFHS were published since *Update 2004*. A recent publication from Pavuk et al. (2006) focuses solely on prostate cancer in contrast with earlier analyses (Akhtar et al., 2004; Pavuk et al., 2005) and uses information on serum TCDD concentration and years of service in Southeast Asia in both the Ranch Hand and comparison subcohorts. They found no increase in prostate cancer in the Ranch Hand veterans compared with the comparison cohort and no overall association between cumulative serum TCDD and prostate-cancer risk in the Ranch Hand group. In contrast with the comparison veterans, Ranch Hand veterans had no evidence of higher prostate-cancer risk with longer Southeast Asia service. However, more detailed results showed that prostate-cancer risk was significantly higher in Ranch

Hand veterans who had high TCDD and served in Southeast Asia for less than 2 years, or before 1969, than in the control subcohort of Air Force veterans. The authors postulate that those results could be explained by a low risk in comparison veterans who had shorter and earlier service, but further analyses to test this were not presented. Dioxin exposure was presumed to be higher in the Ranch Hand veterans before 1969, and combining this characteristic with serum TCDD concentration might provide more accurate classification of men with truly high exposure and thus reveal an association if one exists. Additional analyses, with different referent groups and simultaneous adjustment for timing and duration of service and serum TCDD, would be helpful, but the data available so far are probably too sparse to provide finely detailed risk estimates.

In a slightly earlier article (Pavuk et al., 2005), prostate cancer was among the cancers whose incidences were analyzed only in the comparison group in the Ranch Hand study—a group presumably not directly exposed to Agent Orange. The authors found a significant increase in prostate-cancer risk in relation to length of service in Southeast Asia, but not to serum TCDD concentration. Those in the highest quartile of length of Southeast Asia service (3.7–16.4 years) had more than twice the risk (RR = 2.4, 95% CI 1.1–5.2) of those in the lowest quartile (0.8–1.3 years). There was evidence of a significant interaction between serum TCDD and years of Southeast Asia service in cancer risk at all sites; however, no such interaction was observed specifically in prostate cancer. Serum TCDD concentrations in this cohort, which was not directly exposed to Agent Orange, were considerably lower than those in the Ranch Hand veterans; moreover, there was no association between serum TCDD and years served in Southeast Asia.

An even earlier study of both the Ranch Hand and AFHS comparison veterans (Akhtar et al., 2004), discussed in *Update 2004*, had reported that prostate-cancer risk in both groups was higher than that in the general US white population (SIR = 1.62 and 1.46, respectively). The differences between the results of that study and the more recent analyses by Pavuk et al. (2005, 2006) are most likely explained by a higher prostate-cancer risk among all veterans who served in Southeast Asia than in the general population; that conclusion would be supported by the observation that prostate-cancer risk in men in the AHFS comparison group, who were not knowingly exposed to herbicides, appeared to increase as length of service in Southeast Asia increased (Pavuk et al., 2005).

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported one prostate-cancer death in the deployed and three in the non-deployed. They did not consider the data sufficient for the calculation of risk estimates unless there were at least 10 deaths from a given type of cancer.

In a set of three reports updating the health status of Australian Vietnam veterans, results were reported concerning a possible association between Vietnam service and prostate-cancer risk. The first report, on cancer incidence, identified 692 prostate cancers in Vietnam veterans—for a small but significant increase in incidence compared with that in the general Australian male population (SIR. 1.25, 95% CI. 1.16–1.34) (ADVA, 2005a). The second, on mortality (ADVA, 2005b), included 107 deaths due to prostate cancer, and mortality was similarly increased (SMR = 1.23, 95% CI 0.99–1.46). Incidence and mortality were increased by about the same degree in veterans who served in the Navy, Army, and Air Force, so a generalized exposure or risk factor might have been responsible. To deal with the possibility of a healthy-worker effect in the Australian veterans, a third report compared men deployed to Vietnam with a National Service cohort that was not deployed (ADVA, 2005c). The results indicate that the incidence of prostate

cancer was similar in the deployed and non-deployed groups; there were too few deaths due to prostate cancer to permit stable risk estimates.

Leavy et al. (2006) reported the results of a case–control study that included 606 people with prostate cancer and 471 controls in Western Australia. A self-report of having served in Vietnam was associated with a non-significant increase in risk (OR = 2.12, 95% CI 0.88–5.06). The low prevalence of reported service in Vietnam (1.6% of controls) resulted in low statistical power of this analysis.

Biologic Plausibility

Prostate cells and prostatic-cancer cell lines are responsive to TCDD in induction of various genes, including those involved in drug metabolism. Simanainen et al. (2004b) used different rat lines (TCDD-resistant Hans/Wistar and TCDD-sensitive Long Evans) and showed that TCDD treatment resulted in a significant decrease in the weight of prostate lobes; however, the effect did not appear to be line-specific. In contrast, the TCDD reduction in sperm does appear to be line-specific and not fully related to the effects of TCDD on serum testosterone (Simanainen et al., 2004a). TCDD effects appear to occur through actions on the urogenital sinus (Lin et al., 2004). In utero and lactational exposure to TCDD appears to retard the aging process in the prostate (Fritz et al., 2005).

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Studies reported since the last update, which are based on occupational cohorts and Vietnam veterans, continue to be limited by nonspecific exposure information, low statistical power, or both. The increased incidence of prostate cancer in chemical applicators in the AHS is of considerable interest and could yield more relevant risk estimates in the future if the number of men with exposures to the compounds of interest is large enough. Updated analyses from the AFHS confirm an association between length of service in Southeast Asia and prostate-cancer incidence in the comparison subcohort. The association appears to be unrelated to serum TCDD concentration and suggests that other factors related to service in Southeast Asia could be responsible. Prostate-cancer risk was not related to serum TCDD in the Ranch Hand veterans either, and subgroup analyses, which suggest increased risk in the men with both higher TCDD and earlier or shorter service in Southeast Asia, cannot now be clearly interpreted.

Although the associations are not large, several studies provide evidence of a small increase in morbidity or mortality due to prostate cancer. The evidence regarding association is drawn from occupational studies in which subjects were exposed to a variety of pesticides, herbicides, and herbicide components and from studies of Vietnam veterans.

Since *Update 2004*, however, new evidence has emerged that service in Vietnam itself may be associated with a higher risk of prostate cancer. Although the explanations for that are unclear, the possibility needs to be taken into account in interpreting studies that bear on the relationship of Agent Orange exposure to prostate cancer.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and prostate cancer.

TESTICULAR CANCER

ACS estimated that 8,250 men would receive diagnoses of with testicular cancer (ICD-9 186.0–186.9) in the United States in 2006 and that 370 men would die from it (Jemal et al., 2006). Other cancers of the male reproductive system that are infrequently reported separately are cancers of the penis and other male genital organs (ICD-9 187). The average annual incidence of testicular cancer is shown in Table 6-31.

TABLE 6-31 Average Annual Incidence (per 100,000) of Testicular Cancer in United States[a]

50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
All Races	White	Black	All Races	White	Black	All Races	White	Black
3.8	4.4	1.2	2.0	2.2	1.8	1.6	1.7	1.0

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Testicular cancer occurs more often in men younger than 40 years old than in older men. On a lifetime basis, the risk in white men is about 4 times that in black men. Cryptorchidism (undescended testes) is a major risk factor for testicular cancer. Family history of the disease also appears to be a risk factor. Several other hereditary, medical, and environmental risk factors have been suggested, but the results of research are inconsistent (Bosl and Motzer, 1997).

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and testicular cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-32 summarizes the results of the relevant studies.

TABLE 6-32 Selected Epidemiologic Studies—Testicular Cancer

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	2	1.1 (0.1–4.1)
	Ever	5	3.6 (1.2–8.4)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	23	1.1 (0.7–1.6)
	Spouses of private applicators (>99%women)	—	0.0 (0–50.2)
	Commercial applicators (men and women)	4	1.2 (0.3–3.2)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	0	—*
	Spouses of private applicators (>99%women)	0	—*
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	6	1.0 (0.4–2.6)
Studies Reveiwed in *Update 2002*			
Burns et al., 2001	Dow chemical production workers	1	2.2 (0.0–12.5)
Studies Reviewed in *Update 2000*			
Flemming et al., 1999b	Florida pesticide appliers	23	2.5 (1.6–3.7)
Hardell et al., 1998	Swedish workers exposed to herbicides	4	0.3 (0.1–1.0)
Studies Reviewed in *Update 1998*			
Hertzman et al., 1997	British Columbia sawmill workers		
	Mortality	116[b]	1.0 (0.8–1.1)
	Incidence	18	1.0 (0.6–1.4)
Kogevinas et al., 1997	IARC cohort	7	1.3 (0.5–2.7)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	—*
Zhong and Rafnsson, 1996	Icelandic pesticide users	2	1.2 (0.1–4.3)
Studies Reviewed in *Update 1996*			
Blair et al., 1993	US farmers in 23 states		
	White men	32	0.8 (0.6–1.2)
	Nonwhite men	6	1.3 (0.5–2.9)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	74	0.9 (*)
	employee	23	0.6 ($p < 0.05$)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	7	2.3 (0.9–4.6)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	4.6 (0.0–25.7)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	4	2.2 (0.6–5.7)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	101	1.0 (0.7–1.2)[c]

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—men	17	1.0 (0.6–1.7)
Bertazzi et al., 1998	Seveso residents—15-year follow-up (genitourinary tract)		
	Zone B—men	10	1.0 (0.5–1.8)
	Zone R—men	73	1.0 (0.8–1.3)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men	1	1.0 (0.1–7.5)
	Zone R—men	9	1.4 (0.7–3.0)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	1	0.9 (0.1–6.7)
	Zone R—men	9	1.5 (0.7–3.0)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	54	0.9 (0.6–1.1)
	Navy	17	1.2 (0.7–1.8)
	Army	34	0.8 (0.5–1.0)
	Air Force	3	0.8 (0.2–2.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	14	0.9 (0.4–1.4)
	Navy	3	0.8 (0.2–2.4)
	Army	10	0.9 (0.4–1.7)
	Air Force	0	0.0 (0.0–3.3)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		
	Incidence	17	0.7 (0.4–1.2)
	Mortality	4	0.8 (0.2–2.0)
Studies Reveiwed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	3	—*
AIHW, 1999	Australian Vietnam veterans	59	110 expected (89–139)
CDVA, 1998a	Australian Vietnam veterans	151[d]	110 expected (89–131)
Studies Reviewed in *Update 1998*			
Clapp, 1997	Massachusetts Vietnam veterans—incidence	30	1.2 (0.4–3.3)
CDVA, 1997a	Australian military Vietnam veterans	4	(NS)
CDVA, 1997b	Australian national service Vietnam veterans	1	1.3
Dalager and Kang, 1997	Army Chemical Corps veterans	2	4.0 (0.5–14.5)
Watanabe and Kang, 1996	Army Vietnam service	114	1.1 *
	MarineVietnam service	28	1.0 *
Studies Reviewed in *Update 1996*			
Bullman et al., 1994	Navy veterans	12	2.6 (1.1–6.2)
Studies Reviewed in *VAO*			
Tarone et al., 1991	Patients at three Washington, DC, area hospitals	31	2.3 (1.0–5.5)
Watanabe et al., 1991	Army Vietnam veterans	109	1.2 (NS)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Marine Vietnam veterans	28	0.8 (NS)
Breslin et al., 1988	Army Vietnam veterans	90	1.1 (0.8–1.5)
	Marine Vietnam veterans	26	1.3 (0.5–3.6)
Anderson et al., 1986	Wisconsin Vietnam veterans	9	1.0 (0.5–1.9)

[a] Given when available.
[b] "Male genital cancers".
[c] 99% CI.
[d] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have cancer of the testis?"
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NS, not significant.

Update of the Epidemiologic Literature

Occupational Studies

In the study by McLean et al. (2006) of mortality in a multinational IARC cohort of 60,468 pulp and paper industry workers, testicular cancer was not considered separately; however, deaths attributed to all male genital cancers were increased among men who were ever exposed to nonvolatile organochlorine compounds potentially contaminated with TCDD. On the basis of only five deaths, the SMR was 3.60 (95% CI 1.17–8.40).

Alavanja et al. (2005) found no evidence of a significant increase in testicular-cancer risk in the AHS cohorts of private pesticide applicators (SIR = 1.05, 95% CI 0.67–1.58) and commercial applicators (SIR = 1.24, 95% CI 0.33–3.17). After investigating the mortality experience of those cohorts, Blair et al. (2005a) reported no deaths from testicular cancer.

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 399 cases of testicular cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with testicular cancer was not elevated (6 cases; OR = 0.99, 95% CI 0.38–2.61).

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and testicular cancer were published since *Update 2004*.

Vietnam-Veteran Studies

A set of three reports updating the health status of Australian Vietnam veterans reported results on a possible association between Vietnam service and testicular cancer. The risk of testicular cancer in the veterans was non-significantly reduced compared with that in the general population (SMR = 0.87, 95% CI 0.63–1.10) (ADVA, 2005a), as was mortality (SMR = 0.85, 95% CI 0.43–1.39) (ADVA, 2005b). The possibility of a healthy-warrior effect was investigated in a separate study that compared the rates of testicular cancer in deployed and non-deployed Vietnam veterans (ADVA, 2005c). Again, risk was slightly lower in the deployed, but the association was below the level of statistical significance because it was based on so few cases (SMR = 0.83, 95% CI 0.42–1.57).

Biologic Plausibility

No animal studies have reported an increased incidence of testicular cancer after exposure to the compounds of interest. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

The evidence from epidemiologic studies is inadequate to link herbicide exposure and testicular cancer. The relative rarity of this cancer makes it difficult to develop risk estimates with any precision. Most cases occur in men 25–35 years old, and men who have received such a diagnosis could be excluded from military service; this could explain the slight reduction in risk observed in some veteran studies.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and testicular cancer.

BLADDER CANCER

Bladder cancer (ICD-9 188) is the most common urinary tract cancer. Cancers of the urethra, paraurethral glands, and other and unspecified urinary cancers (ICD-9_189.3–189.9) are infrequently reported separately; any findings on these cancers would be reported in this section. ACS estimated that 44,690 men and 16,730 women would receive a diagnosis of bladder cancer in the United States in 2006 and that 8,990 men and 4,070 women would die from it (Jemal et al., 2006). In males, in whom this cancer is about twice as common as it is in females, those numbers represent about 6% of new cancer diagnoses and 3% of cancer deaths. Overall, bladder cancer is fourth in incidence among men in the United States.

Bladder-cancer risk rises rapidly with age. In men in the age groups that characterize most Vietnam veterans, bladder-cancer incidence is about twice as high in whites as in blacks. The average annual incidence of urinary bladder cancer is shown in Table 6-33.

TABLE 6-33 Average Annual Incidence (per 100,000) of Bladder Cancer in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	24.0	26.2	15.7	48.0	53.1	30.1	84.2	93.7	45.5
Females	7.4	8.4	4.7	14.0	15.8	8.9	23.5	26.7	14.5

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

The most important known risk factor for bladder cancer is tobacco use, which accounts for about half the bladder cancers in men and one-third of them in women (Miller et al., 1996). Occupational exposure to aromatic amines (also called arylamines), polycyclic aromatic hydrocarbons, and some other organic compounds used in the rubber, leather, textile, paint-products, and printing industries is associated with higher incidence. In some parts of Africa and Asia, infection with the parasite *Schistosoma hæmatobium* contributes to the high incidence.

Exposure to inorganic arsenic is also a risk factor for bladder cancer. Although cacodylic acid is a metabolite of inorganic arsenic as discussed in Chapter 3, the data are insufficient to conclude that studies of inorganic-arsenic exposure are directly relevant to exposure to cacodylic acid, so the literature on inorganic arsenic is not considered in this section.

Conclusions from *VAO* and Updates

The committees responsible for *VAO* and *Update 1996* concluded that there was limited or suggestive evidence of *no* association between exposure to the compounds of interest and urinary bladder cancer. Additional information available to the committee responsible for *Update 1998* led it to change that conclusion to one of inadequate or insufficient information to determine whether there is an association. The *Update 2000, Update 2002*, and *Update 2004* committees did not change that conclusion. Table 6-34 summarizes the results of the relevant studies.

TABLE 6-34 Selected Epidemiologic Studies—Bladder Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	50	1.0 (0.7–1.3)
	Ever	43	1.1 (0.8–1.5)
Alavanja et al., 2005	US Agriculture Health Study (urinary system)—incidence		
	Private applicators (men and women)	184	0.7 (0.6–0.8)
	Spouses of private applicators (>99%women)	17	0.7 (0.4–1.1)
	Commercial applicators (men and women)	13	1.1 (0.6–1.8)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	—*
	Phenoxy herbicide sprayers (>99%men)	0	—*
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	7	0.4 (0.1–0.7)
	Spouses of private applicators (>99% female)	2	0.8 (0.1–2.7)
Torchio et al., 1994	Italian licensed pesticide users	31	0.5 (0.4–0.8)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	4	0.7 (0.3–1.8)
Studies Reviewed in *Update 2004*			
Bodner et al., 2003	Dow chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	—	0.7 (0.1–2.0)
Swaen et al., 2004	Dutch licensed herbicide applicators	2	0.7 (0.1–2.4)
Studies Reveiwed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	0.5 (0.1–2.8)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	Total cohort	16	2.0 (1.1–3.2)
	High-exposure cohort	6	3.0 (1.4–8.5)
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)		
	Total cohort	4	3.7 (1.0–9.5)
	Accidentally exposed subcohort	1	2.8 (0.1–15.5)
Studies Reviewed in *Update 1998*			
Hertzman et al., 1997	Canadian sawmill workers		
	Mortality	33	0.9 (0.7–1.2)
	Incidence	94	1.0 (0.8–1.2)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	34	1.0 (0.7–1.5)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	24	1.4 (0.9–2.1)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	10	0.7 (0.3–1.2)
Ott and Zober, 1996	BASF employees (bladder or kidney)—incidence	2	1.4 (0.4–3.2)
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators—incidence	12	1.6 (0.8–2.8)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort)	1	1.2 (0.0–6.7)
Collins et al., 1993	Monsanto Company workers (Included in the IARC cohort)		
	Bladder and other urinary	16[d]	6.8 (3.9–11.1)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	300	0.6 ($p < 0.05$)
	employee	70	0.7 ($p < 0.05$)
	Women—self-employed	1	0.2 (*)
	employee	2	0.6 (*)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	family worker	25	0.6 ($p < 0.05$)
Fingerhut et al., 1991	NIOSH—entire cohort (bladder and other)	9	1.6 (0.7–3.0)
	≥1-year exposure; ≥20-year latency	4	1.9 (0.5–4.8)
Green, 1991	Herbicide sprayers in Ontario		
	Diseases of the genitourinary system	1	1.0 (0.0–5.6)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	13	0.8 (0.4–1.4)
Zober et al., 1990	BASF employees—basic cohort	0	— (0.0–15.0)
Alavanja et al., 1989	USDA forest or soil conservationists	8	0.8 (0.3–1.6)
Henneberger et al., 1989	New Hampshire pulp and paper workers	4	1.2 (0.3–3.2)
Alavanja et al., 1988	USDA agricultural extension agents	8	0.7 (0.4–1.4)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	— (0–7.2)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	8	0.9 (0.4–1.7)
Robinson et al., 1986	Northwestern US paper and pulp workers	8	1.2 (0.6–2.6)
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)	11	0.8 (*)
Blair et al., 1983	Florida pesticide applicators	3	1.6 (*)
Burmeister, 1981	Iowa farmers	274	0.9 (NS)
ENVIRONMENTAL			
Studies Reveiwed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia (urinary organs)		
	Men	31	2.6 (1.7–3.6)
	Women	17	0.8 (0.5–1.3)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—men	6	1.2 (0.5–2.7)
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Men—counties with high wheat acreage	129	0.9 (0.7–1.1)
	medium wheat acreage	147	0.8 (0.7–1.0)
	Women—counties with high wheat acreage	59	1.1 (0.8–1.6)
	medium wheat acreage	67	1.1 (0.8–1.5)
Bertazzi et al., 1998	Seveso residents—15-year follow-up		
	Zone B—men	1	2.4 (0.3–16.8)
	women	3	0.9 (0.3–3.0)
	Zone R—men	21	0.9 (0.6–1.5)
	women	4	0.6 (0.2–1.8)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	12	1.0 (0.5–1.8)
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		
	East coast	5	1.3 (0.4–3.1)
	West coast	20	1.0 (0.6–1.6)
	Swedish fishermen—incidence (men and women)		
	East coast	10	0.7 (0.4–1.3)
	West coast	55	0.9 (0.7–1.1)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	10	1.6 (0.9–3.1)
	women	1	0.9 (0.1–6.8)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Zone R—men	39	1.0 (0.7–1.4)
	women	4	0.6 (0.2–1.5)
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination (men and women)	14	1.0 (0.6–1.9)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	164	1.0 (0.9–1.2)
	Navy	34	1.0 (0.7–1.4)
	Army	104	1.0 (0.8–1.2)
	Air Force	26	1.3 (0.8–1.8)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	22	0.7 (0.4–1.0)
	Navy	4	0.6 (0.2–1.6)
	Army	13	0.7 (0.3–1.1)
	Air Force	5	1.1 (0.4–2.5)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	19	0.7 (0.4–1.1)
	Mortality	1	0.3 (0.0–1.7)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	1	—*
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	AFHS subjects vs national rates		
	White AFHS Ranch Hand veterans		
	Mortality—All	1	0.9 (*)
	Incidence—All	14	1.1 (0.6–1.7)
	With tours between 1966–1970	14	1.3 (0.7–2.1)
	White AFHS comparison veterans		
	Mortality—All	1	0.6 (*)
	Incidence—All	8	0.4 (0.2–0.8)
	With tours between 1966–1970	4	0.3 (0.1–0.7)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans		
	Bladder and kidney	11	3.1 (0.9–11.0)
Studies Reviewed in *Update 1998*			
Clapp, 1997	Massachusetts Vietnam veterans	80	0.6 (0.2–1.3)
CDVA, 1997a	Australian military Vietnam veterans	11	1.1 (0.6–1.9)
CDVA, 1997b	Australian national service Vietnam veterans	1	0.6 (*)
Studies Reviewed in *VAO*			
Breslin et al., 1988	Army Vietnam veterans	9	0.6 (0.3–1.2)
	Marine Vietnam veterans	4	2.4 (0.1–66.4)
Anderson et al., 1986	Wisconsin Vietnam veterans	1	—*

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] Many of the employees studied were also exposed to 4-aminobiphenyl, a known bladder carcinogen.
[e] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
* Information not provided by study authors.

— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture.

Update of Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers exposed to nonvolatile organochlorines potentially contaminated with TCDD. No excess in mortality due to bladder cancer was observed in men who were ever exposed to nonvolatile organochlorines in this cohort (SMR = 1.09, 95% CI 0.79–1.46).

In the report by Alavanja et al. (2005) on cancer incidence in the AHS prospective cohorts of private pesticide applicators, commercial applicators, and the spouses of the private farmer applicators, statistics are presented for "urinary system cancers", presumably including bladder and kidney cancers. The incidence of this group of cancers was significantly lower than expected in private applicators (SIR = 0.65, 95% CI 0.56–0.75), non-significantly reduced in their spouses (SIR = 0.69, 95% CI 0.40–1.11), and roughly equivalent to that in the general population in the commercial applicators (SIR = 1.08, 95% CI 0.57–1.84).

In a study of cancer mortality in the same prospective AHS cohorts of pesticide applicators and spouses in North Carolina and Iowa, Blair et al. (2005a) reported bladder cancers separately; neither group showed any indication of increased mortality from bladder cancer.

In New Zealand, 't Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers from 1969 and 1973, respectively, through 2000. No deaths from bladder cancer (ICD-9 188) were observed in the producers or sprayers.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of bladder cancer was significantly reduced (31 cases; SMR = 0.54, 95% CI 0.37–0.78). The authors suggested that the relatively short duration of follow-up and the healthy-worker effect contributed to the observed reduction in mortality.

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 912 cases of bladder cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with bladder cancer (4 cases; OR = 0.68, 95% CI 0.25–1.84) was not elevated.

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and bladder cancer were published since *Update 2004*.

Vietnam-Veteran Studies

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported one bladder-cancer death in the deployed and two in the non-deployed. They did not consider the data sufficient for the calculation of risk estimates unless there were at least 10 deaths from cancer of a given type.

A set of three reports updating the health status of Australian Vietnam veterans predented results concerning a possible association between Vietnam service and bladder cancer. Compared with the general population, the Australian veterans did not have an increased incidence (ADVA, 2005a) of bladder cancer (SIR = 1.04, 95%,CI 0.88–1.20), whereas mortality (ADVA, 2005b) from bladder cancer was reduced with borderline statistical significance (SMR = 0.71, 95% CI 0.42–1.01). The possibility that that was attributable to a healthy-warrior effect was investigated in a separate study that compared rates of bladder cancer in deployed and non-deployed Vietnam veterans (ADVA, 2005c). Bladder-cancer incidence was marginally lower in deployed veterans (SIR = 0.63, 95% CI 0.34–1.11); there were too few deaths from bladder cancer to permit reliable risk estimates.

Biologic Plausibility

In laboratory animals, cacodylic acid has been shown to induce primarily bladder tumors (Cohen et al., 2006). In a study of male F344 rats, cacodylic acid administered in drinking water resulted in formation of bladder tumors at the highest concentrations (50 and 200 ppm) (Wei et al., 2002). In another report (Arnold et al., 2006), administration of cacodylic acid in the diet resulted in formation of papillomas and carcinomas in the bladders of both female and male F344 rats but not B6C3F1 mice. No studies have reported an increased incidence of urinary bladder cancer in TCDD-treated animals.

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Available analyses of an association between exposure to the compounds of interest and bladder-cancer risk are characterized by low precision because of the small numbers, low exposure specificity, and lack of ability to control for confounding. No new data have emerged since *Update 2004* to alter the conclusion that the cumulative evidence of such an association is inadequate or insufficient.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and bladder cancer.

RENAL CANCER

Cancers of the kidney (ICD-9 189.0) and renal pelvis (ICD-9 189.1) are often grouped in epidemiologic studies; cancer of the ureter (ICD-9 189.2) is also included sometimes. Although diseases of those organs have different characteristics and could have different risk factors, there is some logic to grouping them: the structures are all exposed to filterable compounds, such as polycyclic aromatic hydrocarbons, that appear in urine. ACS estimated that 24,650 men and 14,240 women would receive diagnoses of renal cancer (ICD-9 189.0, 189.1) in the United States in 2006 and that 8,130 men and 4,710 women would die from it (Jemal et al., 2006). Those figures represent 2–3% of all new cancer diagnoses and cancer deaths. The average annual incidence of renal cancer is shown in Table 6-35.

TABLE 6-35 Average Annual Incidence (per 100,000) of Kidney and Renal Pelvis Cancer in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	22.7	22.5	33.5	35.7	35.6	45.3	54.4	55.5	61.1
Females	10.9	11.1	13.2	18.3	18.9	19.6	24.5	25.2	33.1

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Renal cancer is twice as common in men as in women. In the age groups that include most Vietnam veterans, black men have a higher incidence than white men. With the exception of Wilms' tumor (which is more likely to occur in children), renal cancer is more common in people over 50 years old.

Tobacco use is a well-established risk factor for renal cancer. People with some rare syndromes—notably, von Hippel-Lindau syndrome and tuberous sclerosis—are at higher risk. Other potential risk factors include obesity, heavy acetaminophen use, kidney stones, and occupational exposure to asbestos, cadmium, and organic solvents. Firefighters, who are routinely exposed to numerous pyrolysis products, are in a known higher-risk group.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and renal cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-36 summarizes the results of the relevant studies.

TABLE 6-36 Selected Epidemiologic Studies—Renal Cancer

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	41	0.9 (0.7–1.3)
	Ever	18	0.5 (0.3–0.8)
't Mannetje et al., 2006	Phenoxy herbicide producers (men and women)	1	1.2 (0.0–6.6)
	Phenoxy herbicide sprayers (>99% men)	3	2.7 (0.6–8.0)
Torchio et al., 1994	Italian licensed pesticide users	16	0.6 (0.4–1.0)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	2	0.6 (0.2–2.3)
Magnani et al., 1987	UK case–control		
	Herbicides	*	1.3 (0.6–3.1)
	Chlorophenols	*	0.9 (0.4–1.9)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators	4	1.3 (0.4–3.4)
Studies Reveiwed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	2	0.9 (0.1–3.3)
Studies Reveiwed in *Update 2000*			
Steenland et al., 1999	US chemical workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	13	1.6 (0.8–2.7)
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)		
	Total cohort—kidney cancer	4	4.1 (1.1–10.4)
	Total cohort—"urinary organs"	8	3.9 (1.7–7.6)
Studies Reviewed in *Update 1998*			
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	29	1.1 (0.7–1.6)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	26	1.6 (1.1–2.4)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	3	0.3 (0.1–0.9)
Studies Reviewed in *Update 1996*			
Mellemgaard et al., 1994	Danish Cancer Registry patients		
	Occupational herbicide exposure among men	13	1.7 (0.7–4.3)
	Occupational herbicide exposure among women	3	5.7 (0.6–58.0)
Blair et al., 1993	US farmers in 23 states		
	White men	522	1.1 (1.0–1.2)
	White women	6	0.8 (0.3–1.7)
Studies Reviewed in *VAO*			
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	141	0.6 ($p < 0.05$)
	employee	18	0.4 ($p < 0.05$)
	Women—self-employed	4	0.9 (*)
	employee	3	1.0 (*)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	family worker	30	0.8 (*)
Fingerhut et al., 1991	NIOSH cohort—entire cohort	8	1.4 (0.6–2.8)
	≥1-year exposure, ≥20-year latency	2	1.1 (0.1–3.8)
Manz et al., 1991	German production workers—men and women (Included in the IARC cohort)	3	1.6 (0.3–4.6)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	11	1.0 (0.5–1.7)
Alavanja et al., 1989	USDA forest conservationists	*	1.7 (0.5–5.5)
	Soil conservationists	*	2.4 (1.0–5.9)
Henneberger et al., 1989	New Hampshire paper and pulp workers	3	1.5 (0.3–4.4)
Alavanja et al., 1988	USDA agricultural extension agents	*	1.7 (0.9–3.3)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	* (0.0–6.2)
Robinson et al., 1986	Northwestern US paper and pulp workers	6	1.2 (0.5–3.0)
Coggon et al., 1986	British MCPA production workers (Included in the IARC cohort)	5	1.0 (0.3–2.3)
Lynge, 1985	Danish production workers—incidence	3	0.6 *
Wiklund, 1983	Swedish agricultural workers (men and women)	775	0.8 (0.7–0.9)[d]
Blair et al., 1983	Florida pesticide applicators	1	0.5 *
Burmeister, 1981	Iowa farmers	178	1.1 (NS)
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—men	3	0.8 (0.3–2.6)
	women	3	1.8 (0.6–5.8)
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Men—counties with high wheat acreage	129	1.0 (0.8–1.3)
	medium wheat acreage	147	1.0 (0.8–1.2)
	Women—counties with high wheat acreage	90	1.1 (0.8–1.4)
	medium wheat acreage	85	0.9 (0.7–1.2)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up (kidney and other urinary organs)—incidence		
	Zone R—men	10	0.9 (0.4–1.7)
	women	7	1.2 (0.5–2.7)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	0	—*
	women	1	1.1 (0.2–8.1)
	Zone R—men	11	0.9 (0.5–1.7)
	women	7	1.2 (0.5–2.6)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	125	1.0 (0.8–1.2)
	Navy	34	1.3 (0.9–1.7)
	Army	77	0.9 (0.7–1.1)
	Air Force	14	1.1 (0.6–1.8)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	50	1.0 (0.7–1.2)
	Navy	12	1.1 (0.6–1.9)
	Army	33	0.9 (0.6–1.3)
	Air Force	5	0.8 (0.3–1.8)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		
	Incidence	19	0.7 (0.4–1.0)
	Mortality	4	0.4 (0.1–1.1)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	1	—*
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	11	3.1 (0.9–11.0)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	22	1.2 (0.7–1.8)
CDVA, 1997b	Australian national service Vietnam veterans	3	3.9 (*)
Studies Reviewed in *Update 1996*			
Visintainer et al., 1995	Michigan Vietnam veterans	21	1.4 (0.9–2.2)
Studies Reviewed in *VAO*			
Breslin et al., 1988	Army Vietnam veterans	55	0.9 (0.5–1.5)
	Marine Vietnam veterans	13	0.9 (0.5–1.5)
Kogan and Clapp, 1988	Massachusetts Vietnam veterans	9	1.8 (1.0–3.5)
Anderson et al., 1986	Wisconsin Vietnam veterans	2	—*

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 99% CI.
[e] Incidence rates provided in absence of information on exposed cases or estimated relative risk for morbidity.
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers with exposure to organochlorine compounds potentially contaminated with TCDD. The SMR of kidney cancer was significantly lower than expected in workers who were ever exposed to nonvolatile organochlorine compounds (SMR = 0.53, 95% CI 0.31–0.83).

As noted above in the section on bladder cancer, Alavanja et al. (2005) presented findings on the incidence of "urinary system cancers", presumably including both bladder and kidney cancers, in the AHS cohorts. The incidence of that group of cancers was significantly lower than expected in private applicators but not different from expected in their spouses or commercial pesticide

applicators. In the companion mortality study, Blair et al. (2005a) reported findings only on bladder cancers.

In the mortality study of phenoxy herbicide producers and sprayers in New Zealand (’t Mannetje et al., 2005), the risk of renal cancer (ICD-9 189) could not be reliably estimated, because there were too few cases.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of kidney cancer was not increased (16 cases; SMR = 0.63, 95% CI 0.36–1.02).

Starting with the 19,904 men entered into the the New Zealand Cancer Registry from 1980–1984 with a specified occupation, Reif et al. (1989) contrasted the 542 cases of kidney cancer with the remaining subjects having other types of cancer. Of the 134 cancer registrants for whom forestry worker (with presumed exposure to phenoxyherbicides and chlorophenols) was the most recent occupation, the proportion with kidney cancer (2 cases; OR = 0.58, 95% CI 0.15–2.30) was not elevated.

Magnani et al. (1987) reported a case–control mortality study of 147 people with kidney cancer and 556 controls in the UK. A JEM was used to predict exposures to various chemical agents on the basis of job title as indicated on death certificates. The estimated risks of kidney cancer associated with exposure to herbicides (RR = 1.3, 95% CI 0.6–3.1) and chlorophenols (RR = 0.9, 95% CI 0.4–1.9) were not significantly increased.

Environmental Studies

No new studies concerning exposure to the compounds of interest and renal cancer were published since *Update 2004*.

Vietnam-Veteran Studies

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported one renal-cancer death in the deployed and eight in the non-deployed. They did not consider the data sufficient for the calculation of risk estimates unless there were at least 10 deaths from cancer of a given type.

A set of three reports updated the health status of Australian Vietnam veterans presented results concerning a possible association between Vietnam service and renal cancer. The risk of renal cancer in the veterans was not given numerically but in graphs appeared to be close to that in the general population of Australia (ADVA, 2005a); mortality results were similar (ADVA, 2005b). The possibility that those results were attributable to a healthy-warrior effect was investigated in a separate study that compared rates of renal cancer in deployed and non-deployed Vietnam veterans (ADVA, 2005c); the incidence was somewhat lower in deployed veterans (SIR = 0.59, 95% CI 0.32–1.04), and there were too few renal-cancer deaths to permit reliable analysis.

Biologic Plausibility

No animal studies have reported an increased incidence of renal cancer after exposure to the compounds of interest. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Available analyses of an association between exposure to the compounds of interest and renal-cancer risk are limited by the small number of end points and lack of exposure specificity. No new data have emerged since *Update 2004* to alter that committee's conclusion that the evidence is inadequate or insufficient to determine whether there is an association.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and renal cancer.

CANCERS OF THE EYE AND ORBIT

ACS estimated that 1,230 men and 1,130 women would receive diagnoses of eye cancers (ICD-9 190) in the United States in 2006 and that 110 men and 120 women would die from it (Jemal et al., 2006).

Conclusions from *VAO* and Updates

In response to VA's request that the present committee scan the literature considered by previous VAO committees for overlooked rare cancers, retroactive consideration has been given to ocular cancer in this update. In the course of this review, it was noted that eye cancers are often grouped with brain cancers. The few results reported specifically on cancers of the eye are discussed below, and their findings incorporated into Table 6-38, which contains the cumulative results on brain cancer. Future updates will include eye and orbit cancer with brain cancer.

Update of the Epidemiologic Literature

Occupational Studies

Wiklund (1983) found 93 cases of eye cancer diagnosed in 1961–1973 in people who declared themselves to be agricultural workers in the Swedish census. The SIR was 1.13 (95% CI 0.85–1.47), 1.14 in men.

In a mortality study of 878 Dow chemical workers potentially exposed to 2,4-D in 1945–1983, Bond et al. (1988) noted that there were no cases of eye cancer, whereas 0.2 case was expected. In a mortality study of workers with possible pentachlorophenol exposure followed from 1940 to 1989, Ramlow et al. (1996) reported that no cases of eye cancer were observed, but less than 0.1 case was expected.

Ronco et al. (1992) observed 19 cases of eye cancer in people self-employed as farmers in the Danish census (SIR = 0.91) and six in farming employees (SIR = 1.34). Neither result was statistically significant. No deaths from eye cancer were reported in their similar cancer-mortality study in Italy.

Blair et al. (1993) used death-certificate information on farmers in 23 states in 1984–1988. There were 17 cases of eye cancer in white men and none in any other group. The PMR for eye cancer in white men was 1.58 (95% CI 0.92–2.52). High exposure to sunlight generically associated with farming may be a confounding factor.

The report by Alavanja et al. (2005) on cancer incidence in the AHS prospective cohorts of private pesticide applicators, commercial applicators, and the spouses of the private applicators does not mention eye cancers except for their possible inclusion in “brain and central nervous system cancers”. In the companion study on cancer mortality in the same prospective AHS cohorts of applicators and their spouses, Blair et al. (2005a) report two deaths from eye cancer in the private applicators (SMR = 2.1, 95% CI 0.2–7.6) and one eye-cancer death in their spouses (SMR = 3.7, 95% CI 0.1–20).

In New Zealand, ’t Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers through 2000. No deaths from eye cancer were observed in either group.

Environmental Studies

Schreinemachers (2000) carried out a study in Minnesota, North Dakota, South Dakota, and Montana in which acreage under wheat was used as a surrogate for exposure to chlorophenoxy herbicides; the rationale was that in these states more than 90% of spring wheat and 30% of winter wheat was treated with these herbicides. Cancer mortality was examined during 1980–1999 for selected counties characterized by extent of agriculture and percentage of population that was rural. For eye cancers, the counties were divided into two groups of relatively high or low wheat acreage because of the small number of cases involved. In men, 15 cases were observed, for to an SMR of 1.95 (95% CI 0.69–5.47). In women, 18 cases were observed, for an SMR of 2.77 (95% CI 1.00–7.63), which was of borderline significance.

Vietnam-Veteran Studies

Cancer Incidence in Australian Vietnam Veterans (ADVA, 2005a) reported 27 cases of eye cancer (SIR = 1.75, 95% CI 1.09–2.41); veterans of unknown status were excluded. When results were broken down by branch of service, the Navy Vietnam veterans experienced an SIR that was described as "substantially lower than expected"—0.60 (95% CI 0.07–2.16). In Army veterans, there were 21 cases, for an SIR of 1.99 (95% CI 1.14–2.84). The Air Force veterans experienced 4 cases, giving an SIR of 2.61 (95% CI 0.71–6.69). In deriving all those results, veterans of unknown status were excluded. Similar SIRs were seen when the researchers included the two observed cases of eye cancer in veterans of unknown status in their calculations. The report specifies that most of the eye cancers were melanomas. Increased exposure to ultraviolet radiation in sunlight is postulated as a likely cause of the increased risk of eye melanomas.

The Third Australian Vietnam Veterans Mortality Study 2005 (ADVA, 2005b) extended the 1997 mortality study of Australian servicemen with follow-up to the end of 2001. Mortality is compared through the SMR statistic with the expected number of deaths among male Australians of the same age during the relevant period. In Army Vietnam veterans, there were five cases of eye cancer, which led to a statistically significant SMR of 3.43 (95% CI 1.09–7.85). An analysis was also carried out to investigate eye-cancer mortality. The SMR was significantly increased in 1980–1990 on the basis of three observed cases (5.40, 95% CI 1.10–15.5). In 1963–1979 and 1991–2001, the SMRs were not significantly increased on the basis of one and two cases, respectively.

Australian National Service Vietnam Veterans: Mortality and Cancer Incidence 2005 (2005c) compared National Service veterans and non-veterans. There were 11 cases observed in the deployed vs eight expected, and eight in the non-deployed vs 11 expected. The RR of eye cancer in deployed compared with non-deployed was 1.85 (95% CI 0.68–5.29).

Synthesis

Most of the epidemiologic studies of findings on eye cancer alone reported few or no cases, were of low power, and had statistically non-significant results. The studies with the largest numbers of cases (for example, Schreinemachers, 2000; Wiklund, 1983) did not indicate significant increases in risk associated with herbicide exposure. Some analyses of the Australian Vietnam veterans showed excess risk, but it was probably due to excess exposure to UV radiation, which was not adjusted for. It should be noted that eye cancer is sometimes reported in a combined category with brain cancers.

Conclusion

The sparse data on the occurrence of eye cancer separately constitute inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and eye cancer. Any future findings for this cancer site will be tracked with results on brain cancer.

BRAIN CANCER

"Brain and other nervous system cancers" (ICD-9 191–192) involve the central nervous system (CNS) and include tumors of the brain and spinal cord, the cranial nerves, and the meninges (the outer covering of the brain and spinal cord). Any of the cell types in the CNS can produce cancer. Tumors of the peripheral nerves and autonomic nervous system are considered "soft-tissue" tumors (ICD-9 171). Most cancers in the CNS originate in other parts of the body, such as the lung or breast, but have metastasized to the brain or spinal cord. This section focuses on cancers that originate in the CNS.

In addressing VA's request that gaps in the full array of cancer ICD codes present in the conclusions of prior updates be filled, it was noted that cancer of the eye (ICD-9 190), when reported, is often grouped with brain cancer. Cancer of the eye is considered retrospectively in the previous section; in future updates, findings concerning cancer of the eye will be tracked with results on brain cancer.

The average annual incidence of CNS cancer is shown in Table 6-37. About 95% of cases derive from brain, cranial nerves, and cranial meninges. In adults over 45 years old, about 90% of tumors that originate in the brain are gliomas—astrocytoma, ependymoma, oligodendroglioma, or glioblastoma multiforme. Astrocytoma is the most common; glioblastoma multiforme has the worst prognosis. Meningioma accounts for 20–40% of CNS cancers. It tends to occur in middle age and more commonly in women. Most meningiomas are benign and can be removed surgically. ACS estimated that about 10,730 men and 8,090 women would receive diagnoses of brain and other nervous system cancers in the United States in 2006 and that 7,260 men and 5,560 women would die from them (Jemal et al., 2006). Those numbers represent about 1.3% of new cancer diagnoses and 2.3% of cancer deaths.

In reviewing the descriptive epidemiology of these cancers, it is important to recognize the variation in which specific cancers are included in published reports, often distinguished by a focus on benign or malignant cancers. Another variation is whether cancer from related tissues (such as the pituitary and the eye) is included. Various types of cancer are usually grouped; although this may bias results in unpredictable ways, the most likely consequence is dilution of risk estimates toward the null.

TABLE 6-37 Average Annual Incidence (per 100,000) of Brain and Other Nervous System Cancers in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	9.2	10.1	4.8	12.7	14.0	8.9	17.5	19.7	8.5
Females	6.4	7.3	3.5	8.8	9.3	7.1	9.8	11.1	4.0

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

The only well-established environmental risk factor for brain tumors is exposure to high doses of ionizing radiation (ACS, 2004a; Wrensch et al., 2002). Other environmental exposures—such as to vinyl chloride, petroleum products, and electromagnetic fields—are unproved as risk factors. The causes of most cancers of the brain and nervous system are not known.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the compounds of interest and brain cancer. The committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-38 summarizes the results of the relevant studies.

TABLE 6-38 Selected Epidemiologic Studies—Brain Tumors

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	44	1.0 (0.7–1.4)
	Ever	28	0.8 (0.5–1.2)
't Mannetje et al., 2005	New Zealand phenoxy herbicide workers		
	Phenoxy herbicide producers (men and women)	1	0.8 (0.0–4.6)
	Phenoxy herbicide sprayers (>99% men)	1	0.6 (0.0–3.4)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	33	0.8 (0.6–0.8)
	Spouses of private applicators (>99%women)	15	0.9 (0.5–1.4)
	Commercial applicators (men and women)	5	1.9 (0.6–4.3)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	19	0.7 (0.4–1.1)
	Years handled pesticides		
	≤10 years	5	0.9 (* NS)
	>10 years	12	0.6 (* NS)
	Spouses of private applicators (>99%women)	11	1.1 (0.5–1.8)
Torchio et al., 1994	Italian licensed pesticide users		
	Brain and nervous system	15	0.5 (0.3–0.9)
	Eye	4	2.4 (0.7–6.1)
Lee et al., 2005	Nebraska case–control study—incidence (gliomas)		
	Phenoxy herbicides—combined reports (identical to results for 2,4-D specifically)	32	1.8 (1.0–3.3)
	By self	7	0.6 (0.2–1.6)
	By proxy	25	3.3 (1.5–7.2)
	2,4,5-T—combined reports	7	1.3 (0.5–3.6)
	By self	2	0.4 (0.1–2.3)
	By proxy	5	2.7 (0.7–9.8)
	NIOSH Upper Midwest Health Study—case–control		
Carreon et al., 2005	Women		
	Arsenicals	13	1.0 (0.5–1.9)
	Phenoxy herbicides	25	0.9 (0.5–1.5)
	2,4-D	24	0.9 (0.5–1.6)
Ruder et al., 2004	Men		
	Arsenicals	15	0.7 (0.4–1.4)
	Phenoxy herbicides	67	0.9 (0.6–1.2)
	2,4-D	*	*

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Reif et al., 1989	Case–control study on all men with occupation indicated entered into New Zealand Cancer Registry 1980–1984 (brain or CNS cancers)		
	Forestry workers	4	1.2 (0.4–3.3)
Magnani et al., 1987	UK case–control, JEM used on occupation given on death certificate		
	Herbicides	*	1.2 (0.7–2.1)
	Chlorophenols	*	1.1 (0.7–1.8)
Studies Reviewed in *Update 2004*			
Bodner et al., 2003	Dow chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	*	0.6 (0.1–1.8) [d]
Swaen et al., 2004	Dutch licensed herbicide applicators	4	1.6 (0.4–4.1)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	3	1.1 (0.2–3.2)
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxy acetic herbicides		
	Foreman—incidence	0	*
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	8	0.8 (0.4–1.6) [d]
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	4	0.9 (0.2–2.3) [d]
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	22	0.7 (0.4–1.0)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	12	0.6 (0.3–1.1)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	10	0.8 (0.4–1.5)
Becher et al., 1996	German production workers (Included in the IARC cohort)—cohort I	3	2.3 (0.5–6.8)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	1	* [d]
	15-year latency	1	* [d]
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators (eye and brain)		
	Incidence	3	0.7 (0.1–2.0)
	Mortality	3	1.2 (0.3–3.6)
Dean, 1994	Irish farmers and farm workers		
	Men	195	— *
	Women	72	— *
Blair et al., 1993	US farmers in 23 states		
	White men	447	1.2 (1.1–1.3)
	White women	9	1.1 (0.5–2.1)
Studies Reviewed in *VAO*			
Morrison et al., 1992	Farmers in Canadian prairie province		

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	250+ acres sprayed with herbicides	24	0.8 (0.5–1.2)
Ronco et al., 1992	Danish and Italian farm workers		
	Male Danish farmers—incidence	194	1.1 *[d]
	Female Danish farmers—incidence	5	1.0 *[d]
Swaen et al., 1992	Dutch licensed herbicide applicators	3	3.2 (0.6–9.3)
Fingerhut et al., 1991	NIOSH cohort—entire cohort		
	≥1-year exposure; ≥20-year latency	2	1.1 (0.1–3.8)[d]
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	6	0.4 (0.1–0.8)
Wigle et al., 1990	Canadian farmers	96	1.0 (0.8–1.3)
Alavanja et al., 1989	USDA forest or soil conservationists	6	1.7 (0.6–3.7)
Henneberger et al., 1989	New Hampshire pulp and paper workers	2	1.2 (0.1–4.2)
Alavanja et al., 1988	USDA agricultural extension agents	*	1.0 (0.4–2.4)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	Brain and other system tissues	0	* (0.0–4.1)
Musicco et al., 1988	Brain tumor patients from Milan, Italy (male and female farmers)	61	1.6 (1.1–2.4)
Coggon et al., 1986	British MCPA chemical workers (Included in the IARC cohort)	11	1.2 (0.6–2.2)[d]
Robinson et al., 1986	Northwestern US paper and pulp workers	4	0.6 (0.2–2.1)
Lynge, 1985	Danish production workers—incidence (Included in the IARC cohort)	4	0.7 *
Blair et al., 1983	Florida pesticide applicators	5	2.0 *
Burmeister, 1981	Iowa farmers	111	1.1 (* NS)
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—men	1	0.4 (0.1–3.0)
	women	3	1.9 (0.6–6.0)
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Men—counties with high wheat acreage	130	1.1 (0.9–1.4)[d]
	medium wheat acreage	131	0.9 (0.8–1.2)[d]
	Women—counties with high wheat acreage	95	1.2 (0.9–1.5)[d]
	medium wheat acreage	94	1.0 (0.7–1.2)[d]
Bertazzi et al., 1998	Seveso residents—15-year follow-up		
	Zone B—men	1	0.8 (0.1–5.5)
	women	3	3.2 (1.0–10.3)
	Zone R—men	12	1.3 (0.7–2.5)
	women	8	1.1 (0.5–2.4)
Studies Reviewed in *Update 1998*			
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		
	East coast	2	0.6 (0.1–2.1)
	West coast	15	1.1 (0.6–1.7)
	Swedish fishermen—incidence (men and women)		
	East coast	3	0.5 (0.1–1.5)
	West coast	24	0.9 (0.6–1.4)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone R—men	6	0.6 (0.3–1.4)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	women	6	1.4 (0.6–3.4)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—women	1	1.5 (0.2–11.3)
	Zone R—men	6	0.6 (0.3–1.4)
	women	5	1.2 (0.4–3.0)
Bertazzi et al., 1989a	Seveso residents—10-year follow-up		
	Zones A, B, R—men	5	1.2 (0.4–3.1)
	women	5	2.1 (0.8–5.9)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence (brain)	97	1.1 (0.9–1.2)
	Navy	24	1.2 (0.7–1.7)
	Army	63	1.0 (0.8–1.3)
	Air Force	10	1.1 (0.6–2.1)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality (brain and CNS)	99	1.0 (0.8–1.1)
	Navy	23	1.0 (0.6–1.4)
	Army	66	0.9 (0.7–1.2)
	Air Force	9	0.9 (0.4–1.6)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed (brain and CNS)		
	Incidence (1982–2000)	23	1.4 (0.7–2.6)
	Mortality (1966–2001)	27	1.6 (0.9–3.1)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (meninges, brain, other CNS)	9	1.2 (0.4–3.2)
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	White AFHS subjects vs national rates		
	Ranch Hand veterans		
	Mortality—All (CNS)	3	1.3 (0.3–3.6)
	Incidence—All (Brain and nervous system)	5	1.8 (0.7–4.1)
	With tours between 1966–1970	5	2.2 (0.8–4.8)
	Comparison veterans		
	Mortality—All (CNS)	1	0.3 (*)
	Incidence—All (Brain and nervous system)	2	0.5 (0.1–1.8)
	With tours between 1966–1970	2	0.7 (0.1–2.3)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	39	1.1 (0.7–1.4)
CDVA, 1997b	Australian national service Vietnam veterans	13	1.4
Dalager and Kang, 1997	Army Chemical Corps veterans	2	1.9[e] —
Studies Reviewed in *Update 1996*			
Dalager et al., 1995	US Vietnam veterans—females	4	1.4 (0.4–3.7)
Visintainer et al., 1995	Michigan Vietnam veterans	36	1.1 (0.8–1.5)
Boyle et al., 1987	Vietnam Experience Study	3	— *
Studies Reviewed in *VAO*			
Thomas and Kang, 1990	Army Chemical Corps Vietnam veterans	2	*
Breslin et al., 1988	Army Vietnam veterans	116	1.0 (0.3–3.2)
	Marine Vietnam veterans	25	1.1 (0.2–7.1)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Anderson et al., 1986	Wisconsin Vietnam veterans	8	0.8 (0.3–1.5)
Lawrence et al., 1985	New York Vietnam veterans	4	0.5 (0.2–1.5) [d]

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] Brain and central nervous system combined.
[e] Crude rate ratio of Vietnam to non-Vietnam veterans.
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; CI, confidence interval; CNS, central nervous system; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture.

Update of Epidemiologic Literature

Occupational Studies

Several additional studies concerning a possible association between occupational exposure to the compounds of interest and brain cancer have come to the attention of the committee. Some were published before ***Update 2004*** but were not reviewed previously.

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. The SMR of brain cancer was not associated with a JEM-based estimate of exposure to nonvolatile organochlorine compounds (never exposed: 44 cases; SMR = 1.02, 95% CI 0.74–1.37; ever exposed: 28 cases; SMR = 0.80, 95% CI 0.53–1.15).

't Mannetje et al. (2005) reported on the mortality experience of a New Zealand cohort of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers 2000 from 1969 and 1973, respectively, through 2000. One death from brain cancer (ICD-9 191) was observed in each group and yielded unstable risk estimates less than 1.

Alavanja et al. (2005) reported on a cohort of agricultural pesticide applicators and their spouses in the AHS, using data from the brain-cancer registry of North Carolina and Iowa. Estimates of association with CNS cancer were reported for 4,916 commercial applicators (five cases; SIR = 1.85, 95% CI 0.59–4.31), 52,395 private applicators (33 cases; SIR = 0.80, 95% CI 0.55–1.12), and 32,347 spouses of private applicators (15 cases; SIR = 0.90, 95% CI 0.51–1.49). The estimated risk in applicators was moderately increased, but the increase was not statistically significant.

In a corresponding mortality report from the AHS (Blair et al., 2005a), the findings were non-significant for private applicators (SMR = 1.1, 95% CI 0.5–1.8) and their spouses (SMR = 0.7, 95% CI 0.6–1.0).

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having have high herbicide use, especially of 2,4-D and MCPA. The estimated risk of CNS cancer was significantly

reduced (15 cases; SMR = 0.53, 95% CI 0.3–0.9). The authors suggested that the short duration of follow-up and the healthy-worker effect contributed to the observed reduction in mortality.

Reif et al. (1989) performed a series of case–control analyses on a sample of 19,904 men entered into the New Zealand Cancer Registry from 1980–1984 with an occupation specified. They focused on the 134 registrants for whom forestry worker (presumed to be exposed to phenoxyherbicides and chlorophenols) was the most recent occupation. The brain cancer risk associated with having been a forestry worker (four cases, OR = 1.19, 95% CI 0.44–3.25) was not significantly increased.

Lee et al. (2005) reported a case–control study (251 cases and 498 controls) in Nebraska to investigate an association between agricultural pesticide exposure reported by subjects (24% of cases and 40% of controls) or their proxy respondents (76% of cases and 60% of controls) and adult glioma. When self-reports and proxy reports were combined, the estimated risk of glioma associated with exposure to 2,4-D (32 cases; OR = 1.8, 95% CI 1.0–3.3) was identical with that associated with exposure to phenoxy herbicides in general; the findings on 2,4,5-T (seven cases; OR = 1.3, 95% CI 0.5–3.6) were much sparser. The strengths of the study were case ascertainment and diagnostic certainty. The need to rely on proxy responses for most subjects was a limitation that arose out of interview's being conducted during 1992–1994 whereas the diagnoses occurred in 1988–1993. The pronounced and systematic discrepancy (see table 6-38) between the results on subject-reported exposure (reduced ORs) and proxy-reported exposure (significantly increased ORs), however, underscores concern about recall bias and casts doubt on any interpretations.

Investigators in the NIOSH Upper Midwest Health Study reported case–control studies of women (Carreon et al., 2005; 341 cases and 528 controls) and men (Ruder et al., 2004; 457 cases and 648 controls). Estimated risks of intracranial glioma associated with reported exposure to arsenicals, organochlorines, phenoxy herbicides, or 2,4-D ranged from 0.7 to 1.5; none was statistically significant.

Magnani et al. (1987) reported a case–control mortality study (432 cases of brain cancer and 1,603 controls) in the UK. A JEM was used to predict exposure to various chemical agents on the basis of job title as indicated on death certificates. Estimated risks of brain cancer associated with exposure to herbicides (RR = 1.2, 95% CI 0.7–2.1) and chlorophenols (RR = 1.1, 95% CI 0.7–1.8) were not significantly increased.

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and brain cancer were published since *Update 2004*.

Vietnam-Veteran Studies

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported nine deaths from cancers of the meninges, brain, or other parts of the CNS (ICD-9 191–192) in the deployed and seven in the non-deployed (CRR = 1.19, 95% CI 0.44–3.20).

Pavuk et al. (2005) reported on the risk of cancer in the comparison group of the Ranch Hand cohort study. Only one case of brain or other CNS cancer was reported; the sparseness of the data preclude risk estimation.

The Australian Vietnam Veterans Mortality and Cancer Incidence Studies (ADVA, 2005a,b) reported the risk of brain cancer in a cohort of 59,179 servicemen. The estimated risks of brain cancer (97 cases; SIR = 1.07, 95% CI 0.85–1.28) and brain-cancer mortality (99 cases; SMR = 0.95, 95% CI 0.76–1.13) were not significantly associated with service in Vietnam.

The possibility that the comparisons with the general population might be influenced by a healthy-warrior effect was investigated in a separate study that compared the rates of brain and CNS cancer in deployed and non-deployed Vietnam veterans (ADVA, 2005c). Brain-cancer incidence (RR = 1.36, 95% CI 0.73–2.56) and mortality (RR = 1.64, 95% CI 0.89–3.09) were not significantly associated with deployment in Vietnam.

Biologic Plausibility

No animal studies have reported an association between exposure to the compounds of interest and brain cancer. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Since *Update 2004*, several relevant studies have been identified, including cohort and case–control designs. Many studies rely on surrogate indicators of exposure, such as occupational titles, but several estimated exposure to one or more of the compounds of interest on the basis of a JEM or self-reported exposure history. Most used cancer-registry data with a high degree of diagnostic certainty.

The significant association between occupational exposure to the compounds of interest (2,4-D and phenoxy herbicides) and brain cancer reported in the case–control study by Lee et al. (2005) was severely compromised by the marked difference between self-reported data and proxy-reported data. The cohort study by Alavanja et al. (2005) reported an increased risk in commercial herbicide applicators who were exposed to some of the compounds of interest, but the increase was not statistically significant. And two studies reviewed in prior updates report non-significant increases in risk in herbicide applicators who were exposed to the compounds of interest (Blair et al., 1983; Swaen et al., 2004). Particularly noteworthy are the increased incidence of and mortality from brain cancer (2–3 times those in the comparison groups) in exposed cohorts in both the Air Force Ranch Hands (Akhtar et al., 2004) and the Army Chemical Corps (Dalager and Kang, 1997).

Most of the relevant prior cohort studies do not show substantial risk differences from the null hypothesis, but this may reflect the limited power of the cohort method to identify risk differences in rare diseases, such as brain cancer. With the accumulation of findings that deviate from consistency with the null hypothesis, however, the present committee can no longer retain the original VAO committee's conclusion that the available evidence is suggestive of *no* association.

Conclusion

On the basis of detailed evaluation of the epidemiologic evidence from new and previously reported studies of populations with potential exposure to the compounds of interest, the committee concludes that the categorization in prior updates (limited or suggestive evidence of *no* association) should be revised to inadequate or insufficient to determine whether there is an association between exposure to the compounds of interest and brain cancer and other nervous system cancers.

ENDOCRINE CANCERS

Cancers of the endocrine system as grouped by the Surveillance Epidemiology and End Results (SEER) program (see Table B-2 in Appendix B) represent a disparate group of ICD codes: thymus cancer (ICD-9 164.0), thyroid cancer (ICD-9 193), and other endocrine cancer (ICD-9 194).

ACS estimated that 7,590 men and 22,590 women would receive diagnoses of thyroid cancer in the United States in 2006 and that 630 men and 870 women would die from it (Jemal et al., 2006). It also estimated that 1,100 men and 980 women would receive diagnoses of other endocrine cancer in 2006 and that 390 men and 400 women would die from it (Jemal et al., 2006). Incidence data on cancers of the endocrine system are presented in Table 6-39.

Thyroid cancer is the most prevalent of the endocrine cancers. Many types of tumors can develop in the thyroid gland; most are benign. The thyroid gland contains two main types of cells: follicle cells that make and store thyroid hormone and that make thyroglobulin and C cells that make the hormone calcitonin, which helps to regulate calcium metabolism. Different cancers can develop from each kind of cell, and the classification of thyroid cancer is still evolving (Liu et al., 2006). The several types into which thyroid cancer is currently classified differ in their seriousness. Papillary carcinoma is the most common and usually affects women of childbearing age; it metastasizes slowly and is the least malignant type of thyroid cancer. Follicular carcinoma accounts for about 30% of all cases and has a greater rate of recurrence and metastasis. Medullary carcinoma is a cancer of nonthyroid cells in the thyroid gland and tends to occur in families; it requires different treatment from other types of thyroid cancer. Anaplastic carcinoma (also called giant-cell and spindle-cell cancer) is rare but is the most malignant form of thyroid cancer; it does not respond to radioiodine therapy and metastasizes quickly, invading such nearby structures as the trachea, causing compression and breathing difficulties.

TABLE 6-39 Average Annual Incidence (per 100,000) of Endocrine System in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	7.8	8.1	8.0	10.4	10.8	5.7	11.6	11.8	6.0
Females	21.3	21.6	12.6	19.8	19.4	16.1	19.7	20.3	16.1

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Thyroid cancer can occur in all age groups. People who have had radiation therapy directed at the neck are at higher risk. That therapy was commonly used in the 1950s to treat enlarged thymus glands, adenoids, and tonsils and to treat skin disorders. People who received radiation therapy as children have a higher incidence of thyroid cancer. Other risk factors are a family history of thyroid cancer and chronic goiter.

Conclusions from *VAO* and Updates

The present update is the first to consider endocrine cancers as constituting a separate cancer type. Thus, there is no conclusion from prior VAO committees related to an association between exposure to the compounds of interest and endocrine cancers. That the committee responsible for *VAO* and the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not consider endocrine cancers separately is a reflection of the rarity of thyroid and other endocrine cancers. The present committee searched for studies of rare cancers and identified a number of relevant studies that reported thyroid cancer, in some cases grouped with other endocrine cancers, in populations potentially exposed to the compounds of interest. A number of the studies identified had been considered in *VAO* or previous updates with respect to end points other than thyroid cancer. Those earlier studies are considered below in chronologic order, followed by comments on newer reports identified by the current committee. Table 6-40 summarizes the pertinent results of the relevant studies.

TABLE 6-40 Selected Epidemiologic Studies—Endocrine Cancers (Thyroid, Thymus, and Other)

Reference	Study Population[a]	Exposed Cases[b]	Estimated Relative Risk (95% CI)[b]
OCCUPATIONAL			
Alavanja et al., 2005	US Agriculture Health Study—incidence (thyroid and other endocrine)		
	Private applicators (men and women)	29	1.3 (0.8–1.8)
	Spouses of private applicators (>99% women)	24	0.9 (0.5–1.4)
	Commercial applicators (men and women)	3	1.6 (0.3–5.0)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	*
	Phenoxy herbicide sprayers (>99% men)	0	*
Blair et al., 2004	US Agriculture Health Study—mortality (thyroid)		
	Private applicators (men and women)	3	1.8 (0.4–5.3)
	Spouses of private applicators (>99% female)	0	0.0 (0.0–2.2)
Kogevinas et al. 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol (thyroid, ICD-9 193)	4	1.7 (0.5–4.3)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	2	1.4 (0.2–4.9)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	2	2.2 (0.3–7.9)
	Workers exposed to any phenoxy herbicide or chlorophenol (other endocrine organs, ICD-9 194)	5	3.6 (1.2–8.4)

Reference	Study Population[a]	Exposed Cases[b]	Estimated Relative Risk (95% CI)[b]
	Workers exposed to TCDD (or higher-chlorinated dioxins)	2	2.3 (0.3–8.1)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	3	6.4 (1.3–18.7)
Zhong and Rafnsson 1996	Icelandic men and women exposed to agricultural pesticides, primarily 2,4-D—incidence (other endocrine organs, ICD-9 194)	2	1.3 (0.1–4.7)
Ramlow et al. 1996	Dow cohort of pentachlorophenol factory workers employed between 1940 and 1989 at Michigan Division	0	–
Asp et al., 1994	Finnish phenoxy herbicide applicators—Incidence (thyroid and other endocrine)		
	No latency	2	1.9 (0.3–7.0)
	10-year latency	2	2.4 (0.3–8.6)
	15-year latency	2	3.4 (0.4–12.2)
	Mortality (thyroid)		
	No latency	1	3.8 (0.1–21.3)
	10-year latency	1	4.7 (0.1–26.4)
	15-year latency	1	6.5 (0.2–36.2)
Hallquist et al., 1993	Case-control study of male and female thyroid cancers from Swedish Cancer Registry, 1980–1989		
	Phenoxy herbicide exposure	3	0.5 (0.0–2.0)
	Chlorophenol exposure	4	2.8 (0.5–18)
Blair et al., 1993	US farmers in 23 states (thyroid)		
	White men	39	1.3 (1.0–1.8)
	White women	1	0.8 (0.0–4.4)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	13	0.7 (*)
	Employee	5	1.1 (*)
	Women—self-employed	1	1.3 (*)
	employee	1	1.4 (*)
	family worker	15	1.7 ($p < 0.05$)
Green, 1991	Cohort mortality study of forestry workers exposed to phenoxy acid herbicides	1	*
Wiklund et al., 1989	Cancer risk in licensed pesticide applicators in Sweden	6	1.1 (0.4–2.4)
Bond et al., 1988	Workers engaged in manufacture of phenoxy herbicides	0	*
Coggon et al., 1986	British MCPA procuction workers (Included in IARC cohort) (thyroid)	1	1.8 (0.4–9.8)
Wiklund, 1983	Male and female Swedish agricultural workers—incidence		
	Thyroid	126	0.9 (0.7–1.1)
	Other endocrine gland	117	0.7 (0.5–0.9)
ENVIRONMENTAL			
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Thyroid (ICD-9 193)		
	Men—counties with high wheat acreage	10	1.9 (0.8–4.6)
	medium wheat acreage	9	1.5 (0.6–3.6)

Reference	Study Population[a]	Exposed Cases[b]	Estimated Relative Risk (95% CI)[b]
	Women—counties with high wheat acreage	13	0.9 (0.5–1.9)
	medium wheat acreage	12	0.8 (0.4–1.6)
	Thymus and other endocrine glands (ICD-9 164.0, 194)		
	Men—counties with high wheat acreage	8	1.4 (0.6–3.6)
	medium wheat acreage	5	0.8 (0.3–2.4)
	Women—counties with high wheat acreage	*	*
	medium wheat acreage	*	*
Bertazzi et al., 1998	Cancer mortality in populations following Seveso accident		
	Zone A	*	*
	Zone B—men	1	4.9 (0.6–39.0)
	women	1	3.2 (0.4–24.5)
	Zone R—men	0	–
	women	2	0.8 (0.2–3.6)
VIETNAM VETERANS			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence (thyroid)	17	0.6 (0.3–0.9)
	Navy	3	0.5 (0.1–1.3)
	Army	11	0.5 (0.3–1.0)
	Air Force	3	1.2 (0.2–3.5)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality (thyroid)	2	0.5 (0.0–1.8)
	Navy	1	1.2 (0.0–6.5)
	Army	1	0.4 (0.0–2.0)
	Air Force	0	0.0 (0.0–7.8)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		
	Incidence (thyroid)	4	0.6 (0.1–2.2)
	Mortality (thyroid)	1	1.2 (0.0–91.7)
Breslin et al., 1988	Veterans with service in Vietnam vs. era veterans (thyroid and other endocrine, ICD-9 193–194)		
	Army	15	0.6 (0.3–1.2)
	Marine Corp	4	0.6 (0.1–3.4)
Clapp, 1997	Massachusetts male Vietnam veterans vs era veterans —incidence 1988–1993 (thyroid)	4	1.2 (0.3–4.5)

[a] Results are for mortality and for men unless otherwise specified
[b] Given when available.
* Information not provided by study authors.
— Denoted by a dash in the original study.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; CI, confidence interval; IARC, International Agency for Research on Cancer; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Update of the Epidemiologic Literature

Occupational studies

Wiklund (1983) investigated cancer incidence from 1961 to 1973 in men and women who indicated in the 1960 Swedish census that their economic activity was agricultural. The Swedish Cancer Registry recorded 126 cases of thyroid cancer and 117 cases of other endocrine cancer in this occupational group and found no indication of an increase in risk of either sort of endocrine cancer.

Coggon et al. (1986) examined mortality of workers in the UK exposed to 2-methylchlorophenoxy acid during its manufacture. The study cohort consisted of 4,078 men employed by the company at its factory or spray depots in 1947–1975. The cohort was identified from personnel records, and people were classified as exposed to high, low, or background concentrations on the basis of job titles and dates of employment. Members of the cohort were traced through the National Health Service Registry. There were 1,039 deaths in the cohort, including only one from cancer of the thyroid.

Bond et al (1988) examined mortality in Dow chemical workers engaged in the manufacture of phenoxy herbicides at any time from 1948 to 1983. Mortality was compared with that in all other male workers in the same company location but not engaged in herbicide production. No thyroid cancers were observed.

Wiklund et al. (1989a) reported cancer risk in licensed pesticide applicators in Sweden. The pesticides used were based on occupation and included herbicides. The cohort included 20,245 people who had applied for a license to apply pesticides during 1965–1976. The cohort was followed in the cancer registry until 1982. Six deaths were attributed to thyroid cancer, for a non-significant SIR of 1.10 (95% CI 0.4–2.39).

Green (1991) conducted a cohort mortality study of Ontario forestry workers exposed to phenoxy acid herbicides. The cohort included workers employed at a public electric utility for at least 6 months during 1950–1982 and routinely exposed to herbicides, including phenoxy acid herbicides. The cohort consisted of 1,222 men, and the male population of Ontario was used as the reference group. One death from thyroid cancer was reported. SMRs were calculated for all neoplasms, and not specifically for thyroid cancer.

Ronco et al. (1992) used database linkage to investigate thyroid-cancer incidence in Danish farmers and farm workers. A cohort of farmers of both sexes, 15–74 years old, was identified in the 1970 census in the Danish Occupational Cancer Registry and followed for 10 years. Categories of farmers were male self-employed, male employee, female self-employed, female employee, and female family worker. There were 13 cases in the self-employed males and five in the male employees, for SIRs of 0.70 and 1.13, respectively (not significant at $p < 0.05$). In the women, there was one case each in the self-employed and employee groups and 15 cases in the family-worker group, for an SIR of 1.67 ($p < 0.05$). The lack of reliable exposure data precludes drawing further conclusions from the study. A similar approach to evaluating cancer mortality within 6 months after the declaration of a farming occupation on the 1981 Italian census did not generate useful findings.

Blair et al. (1993) used information from death certificates from 1984–1988 to assess cancer mortality in farmers in 23 states. There were 39 cases of thyroid cancer in a population of 119,648 white men, for a PMR of 1.34 (95% CI 0.95–1.83). There was once case each in white women,

nonwhite women, and nonwhite men. There was no exposure assessment in the study, and the authors note possible limitations due to the PMR methodology.

Hallquist et al. (1993) examined the possibility of an association between occupational exposures and thyroid cancer in a case–control study. The study involved 180 cases drawn from the Swedish Cancer Registry; the people with cancer were 20–70 years old at diagnosis during the period 1980–1989. Diagnosis was confirmed histologically. There were 360 controls, two for each case, matched on age and sex, drawn from the National Population Registry and in the same regions as the cases. Residence, occupation, and exposures were determined by questionnaire with telephone follow-up. At the time of study, subjects were 123 women and 48 men, and controls were 240 women and 85 men; 9 subjects and 34 controls refused to participate and one control died before being interviewed for the study. Three subjects and 10 controls reported exposure to phenoxy herbicides, for an OR of 0.5 (95% CI 0.01–2.0). Four subjects and three controls were exposed to chlorophenols, which can contain dioxins (OR = 2.8, 95% CI 0.5–18); the increase was not significant.

Asp et al. (1994) reported on a cohort of Finnish chlorophenoxy herbicide applicators that had been assembled in 1972 from personnel records of Finnish employers involved in brush wood control. 2,4-D and 2,4,5-T were used almost exclusively from the middle 1950s to the 1970s. The two herbicides were used in a 2:1 mixture of 2,4-D to 2,4,5-T. Four of the five 2,4,5-T preparations used during the period contained TCDD at 0.1-0.95 mg/kg of herbicide. The use of 2,4,5-T has been suspended since 1980, and exposure since then has been to 2,4-D and MCPA. The original cohort included 1,971 men who had been exposed to phenoxy herbicides for at least 2 weeks during 1955–1971. At the beginning of 1972, the cohort included 1,909 men. Mortality in the cohort was followed to the end of 1989. Cancer incidence was followed from 1972 to the end of 1979. There was a single death from thyroid cancer and an additional incident endocrine cancer case; both occurred at least 15 years after the start of exposure. The estimated risks were high but non-significant, and the results are generally uninformative.

Ramlow et al. (1996) examined mortality in a cohort of pentachlorophenol factory workers employed during 1940–1989 at the Dow Chemical Michigan Division. The cohort is a subset of the larger Dow cohort that was potentially exposed to dioxin. Census lists from the division were used to measure the potential for exposure to herbicides and pentachlorophenol. Some 2,192 workers were identified, and job titles were used to determine potential dioxin exposure. Exposure assessment included a detailed description of dioxin exposure; exposure assessments in the Dow study were discussed more extensively elsewhere (Ott et al., 1987). No deaths from thyroid cancer were identified in the cohort, which was followed for 15 years.

Zhong and Rafnsson (1996) examined a cohort in Iceland of 2,449 people (1,860 men and 589 women) who had encountered pesticides in different ways. Cohort members were classified according to types of activity considered to result in different exposures to pesticides. Exposure was estimated on the basis of amounts of pesticides sold for agricultural purposes during 1976–1993 according to Icelandic records that include amounts of specific chemicals sold. The most-used chemical was 2,4-D; about twice as much of it was used as of the next-most used. 2,4,5-T was used, but it was the leastused chemical in the registry. In the cohort, there were two cases of endocrine cancer (ICD-9 194) (SIR = 1.29, non-significant, 95% CI 0.14–4.66).

Kogevinas et al. (1997) examined cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins in a large international cohort study. The study included 21,863 male and female workers in 36 cohorts exposed to the chemicals in 12 countries. The study was

coordinated by IARC. Subjects were followed from 1939 to 1992. In all the workers exposed to any phenoxy herbicides or chlorophenols, there were four deaths from thyroid cancer (SMR = 1.65, 95% CI 0.45–4.32) and five from other endocrine cancers (SMR = 3.60, 95% CI 1.17–8.39). When the sample was partitioned into those who had and those who had not been exposed to TCDD, the increases in risk were more pronounced in those who had not been exposed to TCDD (thyroid-cancer SMR = 2.17, 95% CI 0.26–7.85; other endocrine cancer SMR = 6.38, 95% CI 1.32–18.65).

In New Zealand, 't Mannetje et al. (2005) followed the mortality experience of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers through 2000. No deaths from thyroid cancer (ICD-9 193) or other endocrine cancer (ICD-9 194) were observed in either group.

Alvanja et al. (2005) published a report on a cohort of agricultural pesticide applicators and their spouses in the AHS using data from cancer registries of North Carolina and Iowa. They reported three cases of thyroid and other endocrine cancers in 4,916 commercial applicators (SIR = 1.58, 95% CI 0.34–4.99), 29 cases in 52,395 private applicators (SIR = 1.29, 95% CI 0.77–1.76), and 24 cases in 32,347 spouses of private applicators (SIR = 0.91, 95% CI; 0.54–1.44). The estimated risks in commercial applicators and private applicators were slightly increased, but none of the estimated risks was statistically significant. Blair et al (2005a) examined mortality in the same AHS prospective cohort of private pesticide applicators and their spouses. In the private applicators, there were three deaths specifically from thyroid cancer (SMR = 1.8, 95% CI 0.4–5.3); there was no mention of other endocrine cancers. There were no deaths from any type of endocrine cancers in the spouses.

Environmental Studies

Bertazzi et al. (1998) summarized cancer mortality in populations in the different zones of exposure after the Seveso accident. Mortality was examined in residents in Zone A (highly exposure; 805 people) and zone B (medium exposure; 5,942 people), and Zone R (low exposure; 38,625 people). There were no deaths from thyroid cancer in Zone A from 1976 to 1991. In Zone B, there was one death from thyroid cancer in males and one in females; these resulted in unstable estimates of increased risk. In Zone R, there were two deaths from thyroid cancer in women but none in men.

A study by Schreinemachers (2000) examined cancer mortality in four wheat-producing states: Minnesota, North Dakota, South Dakota, and Montana. Acreage devoted to raising wheat in counties in those states was used as a surrogate for exposure to chlorophenoxy herbicides; the rationale was that in those states more that 90% of spring wheat and 30% of winter wheat were treated with chlorophenoxy herbicides. Cancer mortality was examined during 1980–1999 in selected counties according wheat acreage per county and the percentage of the population that was rural. Age-standardized mortality rate ratios showed an increasing trend for thyroid-cancer death in white men over 65 years old in the tertiles based on wheat acreage, with eight cases and an SRR of 2.54 (95% CI 0.88–7.35) in the highest tertile. In white women over 65 years old, there were 13 cases, for an SRR of 1.55 (95% CI of 0.88–7.35). The results suggest hypotheses but present the difficulty of uncertainty as to whether results for counties hold for individuals.

Vietnam-Veteran Studies

Anderson et al. (1986a) examined mortality in Vietnam veterans in Wisconsin. Vietnam veterans were compared with veterans who did not serve in Vietnam. No death from thyroid cancer was recorded in the Vietnam veterans.

In a proportionate mortality study of Army and Marine Corps Vietnam veterans, Breslin et al. (1988) examined a sample of 52,253 men who had served in the corps during 1965–1973 and who died during 1965–1982. The cause of death was ascertained for 51,421. Of these, 24,235 had served in Vietnam. Thyroid and other endocrine cancers were grouped. There were 15 deaths in army personnel and four in marine personnel. The PMRs were 0.59 and 0.57, rspectively.

Clapp (1997) evaluated male veterans in Massachusetts for cancer incidence, using data from the Massachusetts Cancer Registry. Over the period 1988–1993, 245 cases of cancer were reported in Vietnam veterans and 999 cases in Vietnam-era veterans. The age-adjusted OR for thyroid cancer (four cases in the Vietnam veterans and 13 in the Vietnam-era veterans) was 1.2 (95% CI 0.3–4.5), which is not statistically significant.

A set of reports updating the health status of Australian Vietnam veterans (ADVA 2005a,b,c), including thyroid cancer, covered a possible association between Vietnam service and thyroid cancer. In a comparison of veterans with the general population of Australia, the SIR was 0.57 (95% CI 0.33–0.92) (ADVA, 2005a), and the SMR was 0.51 (95% CI 0.063–1.78) (ADVA, 2005b). The possibility that the results were attributable to a healthy-warrior effect was investigated in a separate study that compared rates of thyroid cancer in deployed and non-deployed Vietnam veterans (ADVA, 2005c); the decrease in incidence in the deployed did not reach significance (RR = 0.14, 95% CI 0.63–2.24), and the RR of thyroid-cancer mortality based on a single death in each group of veterans was close to 1 with an extremely wide confidence range (RR = 1.17, 95% CI 0.01–91.69).

Biologic Plausibility

The NTP conducted carcinogenesis bioassays in Osborne-Mendel rats and B6C3F1 mice exposed to TCDD by gavage (NTP Report 209, 1982). The incidence of follicular-cell adenoma, but not of carcinoma, increased with increasing TCDD dose in both male and female rats; the increase was significant in male but not female rats. There was a significant increase in follicular-cell adenoma in female but not male mice. The NTP carried out a similar study in female Sprague-Dawley rats more recently (NTP, 2006). Walker et al. (2006) compared the resulting data from that and another study of chronic toxicity and carcinogenicity of TCDD in female Sprague-Dawley rats. They compared the recent results of the NTP assessment and the results of the Dow Chemical assessment of TCDD carcinogenicity. In the NTP and Dow studies, the incidence of thyroid cancer (C-cell adenoma and carcinoma) decreased with increasing dose of TCDD. However, an increased incidence of minimal thyroid follicular-cell hypertrophy was noted in rats given TCDD at 22 ng/kg of body weight or greater.

As indicated in Chapter 3, 2,4-D and 2,4,5-T are at most only weakly mutagenic or carcinogenic. No studies that addressed a possible association between exposure to those herbicides and thyroid cancer in animal models have been identified.

Synthesis

Several relevant studies—including cohort studies, environmental studies, and Vietnam-veteran studies—are considered here for the first time in the series of *VAO* reports. They show low thyroid-cancer incidence and cancer mortality in various populations. The studies assessed exposure to one or more of the compounds of interest although the metrics often were based on surrogate indicators or self-reported exposure. Some of the cohort studies used cancer-registry data with a high degree of diagnostic certainty. Several of the studies show somewhat increased risks of thyroid or other endocrine cancers in association with the compounds of interest. Of the studies with any indication of statistical significance, Blair et al. (1993) and Ronco et al. (1992) both had mixed results; the authors were conducting analyses on large samples whose exposure was no better characterized than "agricultural worker" on a death certificate or census response, whereas in the IARC cohort (Kogevinas et al., 1997), the risks of endocrine cancers were lower in phenoxy herbicide workers who also had exposure to TCDD. Most showed no substantial risk differences in association with the componants of Agent Orange. Many of the studies had very small numbers of cases, and their limitations preclude risk estimation. There were no significant findings in Vietnam-veteran studies. Thus, the studies reviewed do not provide sufficient evidence to determine whether there is an association between exposure to the compounds of interest and thyroid cancer.

Conclusion

On the basis of its evaluation of the epidemiologic evidence reviewed here, the committee concludes that there is insufficient evidence to determine whether there is an association between exposure to the compounds of interest and thyroid or other endocrine cancers.

NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma (NHL, ICD-9 200.0–200.8, 202.0–202.2, 202.8–202.9) is the more common of the two primary types of cancer of the lymphatic system. ACS estimated that 30,680 men and 28,190 women would receive diagnoses of NHL in the United States in 2006 and that 10,000 men and 8,840 women would die from it (Jemal et al., 2006). Collectively, lymphomas (which include Hodgkin's disease) are the fifth-most common form of cancer in the United States. The incidence of NHL is uniformly higher in men than in women and typically higher in whites than in blacks. In the groups that characterize most Vietnam veterans, incidence increases with age. Average annual incidences are shown in Table 6-41.

TABLE 6-41 Average Annual Incidence (per 100,000) of Non-Hodgkin's Lymphoma in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	26.7	28.4	24.1	37.6	38.8	38.2	52.0	55.0	37.5
Females	18.2	18.4	18.7	28.3	29.2	24.4	38.2	41.5	25.4

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003

The causes of NHL are poorly understood. People with suppressed or compromised immune systems are known to be at higher risk, and some studies show increased incidence in people with HIV, human T-cell lymphotropic virus, Epstein-Barr virus, and gastric *Helicobacter pylori* infections. Behavioral, occupational, and environmental risk factors also have been proposed (Blair et al., 1997).

Chronic lymphocytic leukemia (CLL) and hairy-cell leukemia share many traits with NHL (for example, immunohistochemical traits and B-cell origin); it may progress to an acute aggressive form of NHL). CLL is discussed separately after the general section on leukemia.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was sufficient evidence to support an association between exposure to at least one of the compounds of interest and NHL. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-42 summarizes the results of the relevant studies.

TABLE 6-42 Selected Epidemiologic Studies—Non-Hodgkin's Lymphoma

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
OCCUPATIONAL			
New Studies			
Chiu et al., 2006 (based on Zahm et al., 1990, 1993)	Nebraska residents, NHL reclassified according to specific chromosomal translocation (t(14;18)(q32;q21))		
	Translocation present in cases		
	Herbicides	25	2.9 (1.1–7.9)
	Translocation absent in cases		
	Herbicides	22	0.7 (0.3–1.2)
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never		0.9 (0.7–1.3)
	Ever		0.9 (0.6–1.3)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	1	0.9 (0.0–4.9)
	Phenoxy herbicide sprayers (>99% men)	1	0.7 (0.0–3.8)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	114	1.0 (0.8–1.2)
	Spouses of private applicators (>99% women)	42	0.9 (0.6–1.2)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
	Commercial applicators (men and women)	6	1.0 (0.4–2.1)
	Pooled analyses of case–control studies conducted in Iowa, Minnesota, Kansas, Nebraska, 1980s		
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	33	0.9 (0.6–1.2)
	Spouses of private applicators (>99% women)	16	1.2 (0.7–2.0)
Fritschi et al., 2005	Population-based case–control study in New South Wales, Australia, 2000–2001		
	Phenoxy herbicides		
	Non-substantial exposure	10	0.7 (0.3–1.7)
	Substantial exposure	5	1.8 (0.4–7.4)
Mills et al., 2005	Nested case–control analyses of Hispanic workers in cohort of 139,000 California United Farm Workers		
	Ever used 2,4-D	*	3.8 (1.9–7.8)
Chiu et al., 2004	Herbicide usage		
	Farmers	294	1.2 (1.0–1.5)
	Non-farmers	273	1.0 (0.8–1.2)
Lee et al., 2004b	Asthmatics		
	Herbicide exposure-phenoxyacetic acid	17	1.3 (0.7–2.4)
	Exposures among farmers		
	2,4-D	17	1.3 (0.7–2.5)
	2,4,5-T	7	2.2 (0.8–6.1)
	Non-asthmatics		
	Herbicide exposure-phenoxyacetic acid	176	1.0 (0.8–1.3)
	Exposures among farmers		
	2,4-D	172	1.0 (0.8–1.3)
	2,4,5-T	36	1.1 (0.7–1.8)
Hardell et al., 2002	Pooled analysis of Swedish case-control studies of NHL and of hairy cell leukemia		
	Herbicide exposure	77	1.8 (1.3–2.4)
	Phenoxyacetic acids	64	1.7 (1.2–2.3)
	MCPA	21	2.6 (1.4–4.9)
	2,4-D and 2,4,5-T	48	1.5 (1.0–2.2)
	Other	15	2.9 (1.3–6.4)
Torchio et al., 1994	Italian licensed pesticide users	15	0.9 (0.5–1.5)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	7	1.8 (0.9–4.0)
Studies Reviewed in *Update 2004*			
Miligi et al., 2003	Residents from 11 different areas in Italy		
	Phenoxy acid herbicides exposure		
	Men	18 [d]	1.0 (0.5–2.0)
	Women	11 [d]	1.3 (0.5–3.7)
	2,4–D exposure		
	Men	6 [d]	0.7 (0.3–0.19)
	Women	7 [d]	1.5 (0.4–5.7)
Bodner et al., 2003	Dow chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	—	1.4 (0.6–2.7)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	3	1.0 (0.2–2.9)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides—incidence	2	2.3 (0.3–8.5)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	12	1.1 (0.6–1.9)
Hooiveld et al., 1998	Dutch phenoxy herbicide workers (Included in the IARC cohort)	3	3.8 (0.8–11.0)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	4	1.3 (0.3–3.3)
Keller-Byrne et al., 1997	Farmers in central United States		1.3 (1.2–1.6)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	34	1.3 (0.9–1.8)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	24	1.4 (0.9–2.1)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	9	1.0 (0.5–1.9)
Becher et al., 1996	German production workers (Included in the IARC cohort)	6	3.3 (1.2–7.1)
Nanni et al., 1996	Italian farming and animal-breeding workers—incidence (men and women)	3 [d]	1.4 (0.4–5.7)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	7 [e]	1.4 (0.6–2.9)
	15-year latency	5 [e]	1.3 (0.4–3.1)
Amadori et al., 1995	Italian farming and animal-breeding workers—incidence (men and women)	164	1.8 (1.2–2.6)
Studies Reviewed in *Update 1996*			
Kogevinas et al., 1995	IARC cohort—incidence (men and women)		
	Exposed to 2,4,5-T	10	1.9 (0.7–4.8)
	Exposed to TCDD	11	1.9 (0.7–5.1)
Asp et al., 1994	Finnish herbicide applicators		
	Incidence	1	0.4 (0.0–2.0)
Dean, 1994	Irish farmers and farm workers		
	Men	244 [d]	—
	Women	84 [d]	—
Hardell et al., 1994	Umea (Sweden) Hospital patients—incidence		
	Exposure to phenoxy herbicides	25	5.5 (2.7–11.0)
	Exposure to chlorophenols	35	4.8 (2.7–8.8)
Morrison et al., 1994	Farm operators in three Canadian provinces		
	All farm operators	*	0.8 (0.7–0.9)
	Highest quartile of herbicides sprayed	19	2.1 (1.1–3.9)
	Highest quartile of herbicides sprayed relative to no spraying	6	3.0 (1.1–8.1)
Blair et al., 1993	US farmers from 23 states (white men)	843	1.2 (1.1–1.3)
Bloemen et al., 1993	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	2	2.0 (0.2–7.1)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort)	2	3.0 (0.4–10.8)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Lynge, 1993	Danish male and female production workers (Included in the IARC cohort) —updated incidence		
	Exposure to phenoxy herbicides (men)	10	1.7 (0.5–4.5)
Persson et al., 1993	Swedish NHL patients		
	Exposure to phenoxy herbicides	10	2.3 (0.7–7.2)
	Occupation as lumberjack	9	6.0 (1.1–31.0)
Zahm et al., 1993	Females from eastern Nebraska farms	119	1.0 (0.7–1.4)
Kogevinas et al., 1992	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	11	1.0 (0.5–1.7)
Studies Reviewed in *VAO*			
Hansen et al., 1992	Danish gardeners (men and women)—incidence	8	2.0 (0.9–3.9)
Ronco et al., 1992	Danish farm workers—incidence	147	1.0 (*)
	Italian farm workers—mortality	14	1.3 (*)
Smith and Christophers, 1992	Australian residents		
	Exposure >1 day	15	1.5 (0.6–3.7)
	Exposure >30 days	7	2.7 (0.7–9.6)
Swaen et al., 1992	Dutch herbicide applicators	0	—
Vineis et al., 1991	Residents of selected Italian provinces		
	Male residents of contaminated areas	*	2.2 (1.4–3.5)
Wigle et al., 1990	Canadian farmers		
	All farmers	103	0.9 (0.8–1.1)
	Spraying herbicides on 250+ acres	10	2.2 (1.0–4.6)
Zahm et al., 1990	Eastern Nebraska residents		
	Ever done farm work	147	0.9 (0.6–1.4)
	Ever mixed or applied 2,4-D	43	1.5 (0.9–2.5)
Alavanja et al., 1989	USDA forest or soil conservationists	22	2.4 (1.5–3.6)
Corrao et al., 1989	Italian farmers licensed to apply pesticides		
	Licensed pesticide users and nonusers	45 [f]	1.4 (1.0–1.9)
	Farmers in arable land areas	31	1.8 (1.2–2.5)
LaVecchia et al., 1989	Residents of the Milan, Italy, area (men and women)		
	Agricultural occupations	*	2.1 (1.3–3.4)
Persson et al., 1989	Örebro (Sweden) Hospital (men and women)		
	Exposed to phenoxy acids	6	4.9 (1.0–27.0)
Wiklund et al., 1989b	Swedish pesticide applicators (men and women)	27	1.1 (0.7–1.6)
Alavanja et al., 1988	USDA agricultural extension agents	*	1.2 (0.7–2.3)
Dubrow et al., 1988	Hancock County, Ohio residents—farmers	15	1.6 (0.8–3.4)
Olsson and Brandt, 1988	Lund (Sweden) Hospital patients		
	Exposed to herbicides	*	1.3 (0.8–2.1)
	Exposed to chlorophenols	*	1.2 (0.7–2.0)
Wiklund et al., 1988	Swedish agricultural and forestry workers (men and women)		
	Workers in land or animal husbandry		1.0 (0.9–1.1)
	Timber cutters		0.9 (0.7–1.1)
Pearce et al., 1987	New Zealand residents		
	Farming occupations	33	1.0 (0.7–1.5)
	Fencing work	68	1.4 (1.0–2.0)
Woods et al., 1987	Washington state residents		
	Phenoxy herbicide use	*	1.1 (0.8–1.4)
	Chlorophenol use	*	1.0 (0.8–1.2)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
	Farming occupations	*	1.3 (1.0–1.7)
	Forestry herbicide appliers	*	4.8 (1.2–19.4)
Hoar et al., 1986	Kansas residents		
	Farmers compared with nonfarmers	133	1.4 (0.9–2.1)
	Farmers using herbicides ≥21 days/year	7	6.0 (1.9–19.5)
Pearce et al., 1986	New Zealand residents—agricultural sprayers	19 [g]	1.5 (0.7–3.3)
Pearce et al., 1985	New Zealand residents with agricultural occupations, 20–64 years old	224	1.4 (0.9–2.0)
Burmeister et al., 1983	Iowa residents—farming exposures	1,101	1.3 (*)
Riihimaki et al., 1982	Finnish herbicide applicators	0	—
Wiklund, 1983	Swedish male and female agricultural workers—incidence	476	1.1 (0.9–1.2)
Cantor, 1982	Wisconsin residents—farmers	175	1.2 (1.0–1.5)
Hardell et al., 1981	Umea (Sweden) Hospital patients—incidence		
	Exposed to phenoxy acids	41	4.8 (2.9–8.1) [f]
	Exposed to chlorophenols	50	4.3 (2.7–6.9) [f]
ENVIRONMENTAL			
New Studies			
Hartge et al., 2005	NCI SEER case-control study (Iowa, Los Angeles County, Detroit, Seattle) 1998-2000		
	Exposures to 2,4-D in carpet dust (ng/g)		
	Under detection limit	147	1
	<500	257	1.1 (0.8–1.6)
	500–999	86	0.9 (0.6–1.5)
	1000–9999	165	0.7 (0.5–1.0)
	>10000	24	0.8 (0.4–1.7)
Kato et al., 2004	Population-based case–control study in upstate New York state, women, 20–79 years of age, 1995–1998		
	Home usage only of herbicides/pesticides (times)		
	0	231	1
	1–4	33	0.9 (0.5–1.5)
	5–17	30	0.7 (0.4–1.3)
	18–39	27	1.0 (0.6–1.7)
	≥40	40	0.9 (0.5–1.5)
Studies Reviewed in *Update 2004*			
Floret et al., 2003	Residents near a French municipal solid-waste incinerator		
	High exposure category	31	2.3 (1.4–3.8)
Studies Reviewed in *Update 2002*			
Hardell et al., 2001	Case–control study of NHL—TEQ >27.8 and EA >80	8	2.8 (0.5–18.0)
McDuffie et al., 2001	Case–control study of NHL in Canada		
	Exposed to phenoxy herbicides	131	1.4 (1.1–1.8)
	2,4-D	111	1.3 (1.0–1.7)
	Mecoprop	53	2.3 (1.6–3.4)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A,B—men	4	1.8 (0.7–4.9)
	women	3	1.2 (0.4–3.9)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Men—counties with high wheat acreage	176 [h]	0.9 (0.8–1.1)
	medium wheat acreage	186 [h]	0.8 (0.7–1.0)
	Women—counties with high wheat acreage	162 [h]	1.0 (0.8–1.2)
	medium wheat acreage	202 [h]	1.0 (0.8–1.2)
Viel et al., 2000	Residents near a French solid-waste incinerator—incidence		
	Spatial cluster	286	1.3 (p = 0.00003)
	1991–1994	109	1.8 (p = 0.00003)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B—mens	2	1.5(0.2–5.3)
	Zone R—men	10	1.1 (0.5–2.0)
	women	8	0.9 (0.4–1.7)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men	3	2.3 (0.7–7.4)
	women	1	0.9 (0.1–6.4)
	Zone R—men	12	1.3 (0.7–2.5)
	women	10	1.2 (0.6–2.3)
Studies Reviewed in *VAO*			
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination (men and women)	16	2.8 (1.4–5.6)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	3	1.9 (0.6–6.1)
	women	1	0.8 (0.1–5.5)
	Zone R—men	13	1.4 (0.7–2.5)
	women	10	1.1 (0.6–2.2)
Bertazzi et al., 1989b	Seveso residents—10-year follow-up		
	Zone B—women	2	1.0 (0.3–4.2)
	Zone R—men	3	1.0 (0.3–3.4)
	women	4	1.6 (0.5–4.7)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	126	0.7 (0.6–0.8)
	Navy	31	0.8 (0.5–1.0)
	Army	86	0.7 (0.5–0.8)
	Air Force	9	0.8 (0.2–0.9)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	70	0.8 (0.6–1.0)
	Navy	10	0.5 (0.3–0.9)
	Army	52	0.9 (0.6–1085)
	Air Force	8	1.1 (0.4–1.6)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	35	1.1 (0.7–1.9)
	Mortality	21	1.4 (0.7–2.8)
Boehmer et al., 2004	Vietnam Experience Cohort	6	0.9 (0.3–2.9)

Reference	Study Population [a,b]	Exposed Cases [c]	Estimated Relative Risk (95% CI) [c]
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	White Air Force Ranch Hand veterans		
	Lymphopoetic leukemia		
	Ranch Hand Veterans—incidence	10	0.9 (0.4–1.5)
	Comparison Air Force Veterans—incidence	9	0.6 (0.3–1.0)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	1	0.2 (0.0–2.6)
AIHW, 1999	Australian Vietnam veterans	62	48 expected (34–62)
CDVA, 1998a	Australian Vietnam veterans—men	137 [i]	48 expected (34–62)
CDVA, 1998b	Australian Vietnam veterans—women	2 [i]	0 expected (0–4)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans		
	NHL deaths, 1980–1994	33	0.9 (0.6–1.2)
Watanabe and Kang, 1996	Marine Vietnam veterans	46	1.7 (1.2–2.2)
Studies Reviewed in *Update 1996*			
Visintainer et al., 1995	Michigan Vietnam veterans	32	1.5 (1.0–2.1)
Studies Reviewed in *VAO*			
Clapp et al., 1991	Massachusetts Vietnam veterans		1.2 (0.6–2.4)
Dalager et al., 1991	Vietnam veterans diagnosed with NHL	100	1.0 (0.7–1.5)
O'Brien et al., 1991	Army enlisted Vietnam veterans	7 [j]	1.8
Thomas et al., 1991	Women Vietnam veterans	3	1.3 (0.3–1.8)
Watanabe et al., 1991	Army Vietnam veterans vs non-Vietnam veterans	140	0.8 (*)
	Army Vietnam veterans vs combined Army and Marine Vietnam-era veterans	140	0.9 (*)
	Marine Vietnam veterans vs non-Vietnam veterans	42	1.8 (1.3–2.4)
	Marine Vietnam veterans vs combined Army and Marine Vietnam-era veterans	42	1.2 (*)
CDC, 1990b	US Vietnam veterans born 1921–1953	99	1.5 (1.1–2.0)
	Army Vietnam veterans	45	1.2 (0.8–1.8)
	Marine Vietnam veterans	10	1.8 (0.8–4.3)
	Air Force Vietnam veterans	12	1.0 (0.5–2.2)
	Navy Vietnam veterans	32	1.9 (1.1–3.2)
	Blue-water Navy Vietnam veterans	28	2.2 (1.2–3.9)
Michalek et al., 1990	Air Force Ranch Hand veteran mortality	0	*
Wolfe et al., 1990	Air Force Ranch Hand veteran morbidity	1	*
Breslin et al., 1988	Army Vietnam veterans	108	0.8 (0.6–1.0)
	Marine Vietnam veterans	35	2.1 (1.2–3.8)
Garland et al., 1988	Navy enlisted personnel 1974–1983	68	0.7 (0.5–0.9)
Burt et al., 1987	Army combat Vietnam veterans	39	1.1 (0.7–1.5)
	Marine combat Vietnam veterans	17	3.2 (1.4–7.4)
	Army Vietnam veterans (service 1967–1969)	64	0.9 (0.7–1.3)
	Marine Vietnam veterans (service 1967–1969)	17	2.5 (1.1–5.8)
Fett et al., 1987	Australian Vietnam veterans	4	1.8 (0.4–8.0)
Anderson et al., 1986	Wisconsin Vietnam veterans (Includes lymphosarcoma and reticulosarcoma)	4	—
Holmes et al., 1986	West Virginia Vietnam veterans vs West Virginia Vietnam-era veterans	2	1.1 (*)
Lawrence et al., 1985	New York Vietnam veterans vs New York Vietnam-era veterans	10 [f]	1.0 (0.4–2.2)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.

[c] Given when available.
[d] Includes NHL and chronic lymphocytic leukemia combined.
[e] Includes all lymphomas combined.
[f] Includes lymphoma and Hodgkin's disease.
[g] Only NHL other than lymphosarcoma and reticulosarcoma (ICD-9 202).
[h] Includes lymphosarcoma, reticulum cell sarcoma including other lymphoma
[i] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have NHL?"
[j] NHL, four living cases and three deaths originally reported in the CDC Vietnam Experience Study (Boyle et al. 1987).
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid, 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veteran Affairs; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDC, Centers for Disease Control and Prevention; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; EA, Epstein-Barr virus early antigen; IARC, International Agency for Research on Cancer; NHL, Non-Hodgkin's lymphoma; SIR, standard incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, toxin equivalents; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Death from NHL was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds (n = 25; SMR = 0.86, 95% CI; 0.55–1.26) than with having never been exposed (n = 35; SMR = 0.93, 95% CI 0.65–1.30).

Two reports from the US AHS (Alavanja et al., 2005; Blair et al., 2005a) provided findings on the incidence of and mortality from NHL among pesticide applicators, commercial applicators, and their spouses, but no results on any of the specific herbicides under consideration were published. As delineated in Table 6-44, no associations were observed between those occupational categories and NHL.

No associations were found in the cohort study of New Zealand phenoxy producers and sprayers ('t Mannetje et al., 2005), in which a single death from NHL (ICD-9 200, 202) was observed in the producer group and one death in the sprayer group.

A subcohort comprising Hispanic workers drawn from a larger cohort of 139,000 California members of the United Farm Workers of America (UFW) was reanalyzed with a nested case–control design (Mills et al., 2005). A total of 60 people with NHL (45 men and 15 women) were identified, and each case was matched to five control subjects drawn from the original cohort on sex, year of birth, and ethnicity (all were of Hispanic origin). A strong association between use of 2,4-D and NHL was found (OR = 3.80, 95% CI 1.85–7.81); much higher excess risks were found for extranodal cancer (n = 22; OR = 9.73, 95% CI 2.68–35.3) than for nodal NHL (n = 38; OR =

2.29, 95% CI 0.90–5.82). The incidence was significantly increased in both men (*n* = 45; OR = 3.79, 95% CI 1.58–9.11) and women (*n* = 15; OR = 5.23, 95% CI 1.30–20.9).

Fritschi and collaborators (2005) conducted a population-based case–control study in 2000–2001 in men and women 20–74 years old living in New South Wales, Australia. Case subjects were identified with the Central Cancer Registry of New South Wales, and control subjects were selected randomly from electoral rolls that represented almost 100% of Australian citizens. Equal numbers of cases and controls (694 of each) were selected, and response rates were around 69% for cases and 54% for controls. On the basis of detailed questions asked of subjects, occupational exposure to pesticides and herbicides was assessed by a team of industrial hygienists who were unaware of the subjects' case status. For "substantial" exposure to phenoxy herbicides, an OR of 1.75 was found (five exposed case subjects, 95% CI 0.42–7.38).

Chiu et al. (2004) and Lee et al. (2004b) conducted a pooled (combined) analysis of two case–control studies that were carried out in three midwestern American states: Iowa and Minnesota (Cantor et al., 1992) and Nebraska (Zahm et al., 1990). In the Iowa–Minnesota component of the study, 530 white males case subjects 30 years old and older were identified in 1980–1983; in the Nebraska component, 346 male and female case subjects 21 years old and older were identified in 1983–1986. Control subjects were frequency-matched to case subjects by age, sex, and race. Two sampling frames were used to select control subjects: for cases 20–64 years old, random-digit dialing was used; for older control subjects, files from the Health Care Financing Administration (HCFA) were used (2,357 controls). Response rates for case subjects were about 90% and for controls 78% (Iowa and Minnesota) to 85% (Nebraska). In-depth interviews provided information on self-reported use of pesticides and herbicides. Risks were increased by 20% in farmers by use of herbicides (OR = 1.2, 95% CI 1.0–1.5) but not in non-farmer (Table 6-44). In asthmatics, risks were increased by exposure to 2,4-D (OR = 1.3, 95% CI 0.7–2.5) and 2,4,5-T (OR = 2.2, 95% CI 0.8–6.1), but the confidence intervals were broad and included unity. According to the study authors, there was limited statistical power to investigate interactions by asthma status.

A recent analysis of the data from Nebraska (Chiu et al., 2006, based on Zahm et al., 1990, 1993) was used to determine risks of types of NHL. Specifically, tissue samples were analyzed according to the presence of a specific chromosomal translocation (t[14;18][q32;q21]), and only 172 of 385 cases were included. Exposure to herbicides was found to confer a significantly higher risk (OR = 2.9, 95% CI 1.1–7.9) in subjects who had the translocation but not in those who did not (OR = 0.7, 95% CI 0.3–1.2).

Hardell et al. (2002) conducted a pooled analysis of two case–control studies (that were not consider in previous *VAO* reports), one of NHL (Hardell and Eriksson, 1999) and one specifically of a rare form of NHL, hairy cell leukemia (Nordstrom et al., 1998). The increased risk associated with exposure to phenoxy herbicides (OR = 1.65, 95% CI 1.16–2.34) was more strongly associated specifically with exposure to MCPA (OR = 2.62, 95% CI 1.40–4.88) than to 2,4-D and 2,4,5-T (OR = 1.48, 95% CI 0.99–2.20), and the overall association with herbicides (OR = 1.75, 95% CI 1.26–2.42) was stronger for "other herbicides" (OR = 2.90, 95% CI 1.34–6.37).

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The SMR for death from NHL was not significantly increased (15 cases; SMR = 0.9, 95% CI 0.52–1.52).

Reif et al. (1989) performed a series of case–control analyses on the sample of 19,904 people with specified occupations among the 24,762 men 20 years old or older entered into the the New Zealand Cancer Registry from 1980 to 1984. The focus of their report was on the 134 for whom forestry work was the most recent occupation listed. For each type of cancer, people with any other type of cancer were used as controls. Of 535 people with NHL, seven had most recently been forestry workers (OR = 1.84, 95% CI 0.85–3.97).

Environmental Studies

Hartge et al. (2005) conducted a population-based case–control study of NHL, identifying cases from four SEER registries (Iowa, Los Angeles County, Detroit, and Seattle) during the period 1998–2000. (The data were also addressed in Colt et al. [2005], and the study was reanalyzed by Lee WJ et al. [2006].) Control subjects were frequency-matched to case subjects by age, sex, race, and SEER center. Two sampling frames were used to select control subjects: for cases 20–64 years old, random-digit dialing was used; for older subjects, Medicare files were used. The authors investigated residential exposure to pesticides and herbicides in detailed in-person interviews. They also analyzed carpet dust for pesticides. Response rates for cases were 59% and for controls 59%; responses yielded data on 1,321 cases and 1,057 controls. No associations with 2,4-D in carpet dust were found. In a subset of 100 cases and 100 control subjects whose serum concentrations were determined, De Roos et al. (2005a) found a marginal association ($p = 0.06$) with TEQs overall of PCBs, furans, and dioxins but not dioxins alone.

Kato et al. (2004) conducted an incident, population-based, case–control study in upstate New York of women 20–79 years old who received a diagnosis NHL or died from it in 1995–1998. Case subjects were identified in the New York state cancer registry, and linkages with state death certificates were conducted. Control subjects were selected from driver's-license files (for people under 65 years old) and HCFA records (for people at least 65 years old). Response rates were 56% for cases, 30% for controls identified from driver's-license files, and 67% for controls identified from HCFA records. Next of kin were interviewed as surrogate respondents (20.5% for cases and 3.2% for controls). The lack of comparability in interviewing subjects is a cause of concern. Subjects were asked about occupational and home use of herbicides and pesticides, and no associations were found with the use of the combination "herbicides/pesticides".

McDuffie et al. (2005) reported a reanalysis of data gathered in the Cross Canada Study of Pesticides and Health (McDuffie et al., 2001, as described in *Update 2002*). That case–control study identified men with new diagnoses of NHL in 1991–1994 in cancer registries of six Canadian provinces and through active ascertainment; 513 were interviewed. Frequency matching by age and province was used in enrolling 1,506 control subjects. There was evidence of an association with any exposure to 2,4-D (OR = 1.25, 95% CI 0.96–1.62) and any phenoxy herbicide (OR = 1.45, 95% CI 1.13–1.87), although the excess risks posed by exposure to 2,4-D may have been due to concomitant exposure to DEET (OR = 1.17, 95% CI 0.84–1.64).

Vietnam-Veteran Studies

In a follow-up of the CDC VES, Boehmer et al. (2004) compared the mortality experience of US Vietnam veterans with that of non-veterans and did not find an increased rate ratio for death from NHL (crude rate ratio [CRR] = 0.94, 95% CI 0.30–2.93).

A set of three reports updating the health status of Australian Vietnam veterans noted negative associations between Vietnam service and NHL in comparing veterans with the general population of Australia with respect to incidence (SIR = 0.67, 95% CI 0.55–0.79) (ADVA, 2005a) and mortality (SMR = 0.78, 95% CI 0.60–0.96) (ADVA, 2005b). A separate study compared rates of NHL in deployed and non-deployed Vietnam veterans (ADVA, 2005c); the increases in incidence (RR = 1.17, 95% CI 0.72–1.89) and mortality (RR = 1.42, 95% CI 0.73–2.80) in the deployed did not approach significance.

Biologic Plausibility

Increased rates of lymphoma have been reported in female B6C3F mice exposed to TCDD at 1 mg/kg of body weight via gavage twice a week for 2 years (NTP, 1982a). Subsequently, animal studies have not shown an increase in lymphoma in TCDD-exposed animals.

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

In previous *VAO* reports, the evidence was found to be sufficient to support an association between exposure to at least one of the compounds of interest and NHL. Most of the evidence suggests that 2,4-D or 2,4,5-T, rather than TCDD, is responsible for the associations observed in occupational cohorts. For instance, the main cohorts with TCDD exposure, but not herbicide exposure, do not have increased rates of NHL. Some of the new reports of occupational and environmental studies (Chiu et al., 2004; Lee et al., 2004b; McDuffie et al., 2005; Mills et al., 2005) support the previous VAO committee's findings, and others do not. Specifically, the newly reported papers from the US AHS (Alavanja et al., 2005; Blair et al., 2005a) do not provide specific information on the herbicides of interest, and there was no evidence of association in the New Zealand phenoxy herbicide producers and sprayers ('t Mannetje et al., 2005), although statistical power was extremely low in the latter small study. The UFW study showed a strong association between use of 2,4-D and NHL. The occupational case–control studies in New South Wales (Fritschi et al., 2005) showed a positive association, but the number of exposed cases was low. The pooled analyses of previously conducted case–control studies also suggested increased risks posed by exposure to herbicides. The American amd Australian Vietnam-veteran studies, in which there was no specific assessment of exposure, did not indicate that Vietnam veterans had higher rates of NHL than comparison populations.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the compounds of interest and NHL. The evidence is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

HODGKIN'S DISEASE

Hodgkin's disease (HD) (ICD-9 201) is distinct from NHL in its cell of origin, its demographics, and its genetics. ACS estimated that 4,190 men and 3,610 women would receive diagnoses of HD in the United States in 2006 and that 770 men and 720 women would die from it (Jemal et al., 2006). The average annual incidence is shown in Table 6-43.

The possibility that HD has an infectious etiology has been a topic of discussion since its earliest description. An increased incidence in people with a history of infectious mononucleosis has been observed in some studies, and a link with Epstein-Barr virus has been proposed. In addition to the occupational associations discussed below, higher rates of the disease have been observed in people who have suppressed or compromised immune systems.

TABLE 6-43 Average Annual Incidence (per 100,000) of Hodgkin's Disease in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	2.8	3.0	3.1	2.7	2.6	3.5	3.6	3.8	2.5
Females	1.8	1.9	1.6	1.5	1.7	1.2	2.3	2.4	0.8

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* determined that there was sufficient information to support an association between exposure to the compounds of interest and HD. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-44 summarizes the results of the relevant studies.

TABLE 6-44 Selected Epidemiologic Studies—Hodgkin's Disease

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	7	0.6 (0.2–1.2)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Ever	17	1.8 (1.0–2.8)
't Mannetje et al., 2006	Phenoxy herbicide producers (men and women)	1	5.6 (0.1–31.0)
	Phenoxy herbicide sprayers (>99% men)	0	0.0 (0.0–16.1)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	11	0.9 (0.4–1.6)
	Spouses of private applicators (>99% women)	4	0.7 (0.2–1.9)
	Commercial applicators (men and women)	1	0.8 (0.1–4.2)
Blair et al., 2005a	US Agriculture Health Study	3	1.1 (0.2–3.3)
	Private applicators (men and women)	3	1.7 (0.3–4.8)
	Spouses of private applicators (>99% women)	0	0.0 (0.0–2.5)
Torchio et al., 1994	Italian licensed pesticide users	11	1.0 (0.5–1.7)
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dutch licensed herbicide applicators	0	—
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	1.5 (0.0–8.6)
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	3	1.1 (0.2–3.2)
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)	1	3.2 (0.1–17.6)
Rix et al., 1998	Danish paper mill workers—incidence		
	Men	18	2.0 (1.2–3.2)
	Women	2	1.1 (0.1–3.8)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	1	0.7 (0.0–3.6)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	10	1.0 (0.5–1.8)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	8	1.3 (0.6–2.5)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	1	0.3 (0.0–1.5)
Becher et al., 1996	German production workers (Included in the IARC cohort)	0	—
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	0	—
Waterhouse et al., 1996	Residents of Tecumseh, Michigan	13	2.0 (1.1–3.4)
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators	2	1.7 (0.2–6.0)
Blair et al., 1993	US farmers in 23 states	56	1.0 (0.8–1.3)
Kogevinas et al., 1993	IARC cohort—incidence, females	1	*
Persson et al., 1993	Swedish NHL patients—exposure to phenoxy herbicides	5	7.4 (1.4–40.0) [d]
Kogevinas et al., 1992	IARC cohort (men and women)	3	0.6 (0.1–1.7)
Studies Reviewed in *VAO*			
Eriksson et al., 1992	Swedish Cancer Registry patients (men and women)		
	Male sawmill workers	10	2.2 *
	Male farmers	97	1.2 *

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Male forestry workers	35	1.2 *
	Male horticulture workers	11	1.2 *
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	27	0.6 ($p < 0.05$)
	employee	13	1.0 (*)
	Female—self-employed	1	1.1 (*)
	employee	1	1.2 (*)
	family worker	9	0.9 (*)
Swaen et al., 1992	Dutch licensed herbicide applicators	1	3.3 (0.04–18.6)
Fingerhut et al., 1991	NIOSH cohort—entire cohort	3	1.2 (0.3–3.5)
	≥1-year exposure, ≥20-year latency	1	2.8 (0.1–15.3)
Green, 1991	Ontario herbicide sprayers	0	*
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	2	0.4 (0.1–1.4)
Zober et al., 1990	BASF employees—basic cohort	0	*
Alavanja et al., 1989	USDA forest or soil conservationists	4	2.2 (0.6–5.6)
LaVecchia et al., 1989	Residents of the Milan, Italy, area (men and women)		
	Agricultural occupations	*	2.1(1.0–3.8)
	Chemical industry occupations	*	4.3 (1.4–10.2)
Persson et al., 1989	Orebro (Sweden) Hospital patients (men and women)		
	Farming	6	1.2 (0.4–3.5) [d]
	Exposed to phenoxy acids	4	3.8 (0.7–21.0) [d]
Wiklund et al., 1989b	Swedish pesticide applicators	15	1.5 (0.8–2.4)
Alavanja et al., 1988	USDA agricultural extension agents		
	PMR analysis	6	2.7 (1.2–6.3)
	Case–control analysis	6	1.1 (0.3–3.5)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	2.7 (0.0–14.7)
Dubrow et al., 1988	Hancock County, Ohio residents—farmers	3	2.7 *
Wiklund et al., 1988	Swedish agricultural and forestry workers (men and women)		
	Workers in land or animal husbandry	242	1.0 (0.9–1.2)
	Workers in silviculture	15	2.3 (1.3–3.7)
Hoar et al., 1986	Kansas residents		
	All farmers	71	0.8 (0.5–1.2)
	Farm use of herbicides (phenoxy acids and others)	28	0.9 (0.5–1.5)
	Farmers using herbicides >20 days/year	3	1.0 (0.2–4.1)
	Farmers using herbicides >15 years	10	1.2 (0.5–2.6)
Pearce et al., 1985	New Zealand residents with agricultural occupations, ages 20–64	107	1.1 (0.6–2.0)
Hardell and Bengtsson, 1983	Umea (Sweden) Hospital patients—incidence		
	Exposed to phenoxy acids	14	5.0 (2.4–10.2)
	Exposed to high-grade chlorophenols	6	6.5 (2.2–19.0)
	Exposed to low-grade chlorophenols	5	2.4 (0.9–6.5)
Riihimaki et al., 1982	Finnish herbicide applicators	0	*
Wiklund, 1983	Swedish male and female agricultural workers—incidence	226	1.0 (0.9–1.2) [e]

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Burmeister, 1981	Iowa farmers	47	1.2 (NS)
Hardell et al., 1981	Umea (Sweden) Hospital patients—incidence		
	Exposed to phenoxy acids	41	4.8 (2.9–8.1)[f]
	Exposed to chlorophenols	50	4.3 (2.7–6.9)[f]
ENVIRONMENTAL			
New Studies			
Pahwa et al., 2006	Canadian men (≥19 years of age) from 1 of 6 Canadian provinces		
	Any phenoxy herbicide	65	1.0 (0.7–1.4)
	2,4-D	57	1.0 (0.7–1.4)
	Mecoprop	20	1.3 (0.7–2.2)
	MCPA	11	1.2 (0.6–2.6)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—men	2	2.6 (0.6–10.9)
	women	2	3.7 (0.9–16.0)
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Men—counties with high wheat acreage	14	0.8 (0.4–1.5)
	medium wheat acreage	32	1.8 (1.1–2.9)
	Women—counties with high wheat acreage	14	0.9 (0.4–1.7)
	medium wheat acreage	19	1.0 (0.6–1.9)
Viel et al., 2000	Residents around a French municipal solid-waste incinerator—incidence	9	1.5 (NS)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B—men	2	3.3 (0.4–11.9)
	women	2	6.5 (0.7–23.5)
	Zone R—women	4	1.9 (0.5–4.9)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men	1	1.7 (0.2–12.8)
	women	1	2.1 (0.3–15.7)
	Zone R—men	4	1.1 (0.4–3.1)
	women	3	1.0 (0.3–3.2)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population–incidence	51	2.1 (1.5–2.6)
	Navy	7	1.3 (0.5–2.6)
	Army	40	2.3 (1.6–3.0)
	Air Force	4	2.1 (0.6–5.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population–mortality	13	0.9 (0.5–1.5)
	Navy	2	0.6 (0.1–2.1)
	Army	11	1.1 (0.5–1.9)
	Air Force	0	0.0 (0.0–2.9)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Incidence	12	0.9 (0.4–2.0)
	Mortality	4	1.7 (0.3–11.8)
Boehmer et al., 2004	Vietnam Experience Cohort	2	0.9 (*)
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	White Air Force Ranch Hand veterans		
	Lymphopoietic leukemia		
	Ranch Hand Veterans—incidence	10	0.9 (0.4–1.5)
	Comparison Air Force Veterans—incidence	9	0.6 (0.3–1.0)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	1	0.3 (0.0–3.2)
Studies Reviewed in *Update 1998*			
Watanabe and Kang, 1996	Marine Vietnam veterans	25	1.9 (1.2–2.7)
Studies Reviewed in *Update 1996*			
Visintainer et al., 1995	Michigan Vietnam veterans	20	1.1 (0.7–1.8)
Studies Reviewed in *VAO*			
Watanabe et al., 1991	Army Vietnam veterans		
	vs Army non-Vietnam veterans	116	1.0 (*)
	vs all non-Vietnam veterans	116	1.1 (*)
	Marine Vietnam veterans		
	vs Marine non-Vietnam veterans	25	1.9 (*)
	vs all non-Vietnam veterans	25	1.0 (*)
CDC, 1990	US men born 1921–1953		
	Vietnam veterans	28	1.2 (0.7–2.4)
	Army	12	1.0 (0.5–2.0)
	Marine	4	1.7 (0.5–5.9)
	Air Force	5	1.7 (0.6–4.9)
	Navy	7	1.1 (0.4–2.6)
Michalek et al., 1990; Wolfe et al., 1990	Air Force Ranch Hand veteran mortality	0	—*
Breslin et al., 1988	Army Vietnam veterans compared with Vietnam-era Army veterans	92	1.2 (0.7–1.9)
	Marine Vietnam veterans compared with Marine Vietnam-era veterans	22	1.3 (0.7–2.6)
Boyle et al., 1987	Vietnam Experience Study	0	—*
Fett et al., 1987	Australian Vietnam veterans	0	—*
Anderson et al., 1986	Wisconsin Vietnam veterans	4	—*
Holmes et al., 1986	West Virginia Vietnam veterans compared with West Virginia Vietnam-era veterans	5	8.3 (2.7–19.5)
Lawrence et al., 1985	New York Vietnam veterans compared with New York Vietnam-era veterans	10[e]	1.0 (0.4–2.2)[g]

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 90% CI.
[e] 99% CI.
[f] Includes both NHL and HD.
[g] Includes both lymphoma and HD.
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veterans Affairs; AFHS, Air Force Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; IARC, International Agency for Research on Cancer; NHL, Non-Hodgkin's Lymphoma; NIOSH, National Institute for Occupational Safety and Health; NS, not significant; PMR, proportionate-mortality ratio; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Death from HD was significantly increased in those who had ever been exposed to nonvolatile organochlorine compounds (*n* = 17; SMR = 1.76, 95% CI 1.02–2.82) but not in those who had never been exposed (*n* = 7; SMR = 0.58, 95% CI 0.23–1.19).

Two reports from the US AHS (Alavanja et al., 2005; Blair et al., 2005a) found no excess risks of HD among pesticide applicators, commercial applicators, and their spouses, but the numbers of cases were very small. No results on any of the specific herbicides of interest were published (see Table 6-46).

In their small cohort of New Zealand phenoxy herbicide producers and sprayers, 't Mannetje et al. (2005) found only one case of HD.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of HD was not significantly increased (11 cases; SMR = 0.95, 95% CI 0.47–1.69).

Environmental Studies

In the Cross Canada Study of Pesticides and Health, Pahwa et al. (2006) investigated the possibility of an association between exposure to phenoxy herbicides and other pesticides and HD. Interviews were conducted with 316 men with newly diagnosed HD in 1991–1994, and their exposures were compared with those of 1,506 control subjects. No associations were found with any exposure to phenoxy herbicides (OR = 0.99, 95% CI 0.70–1.38), 2,4-D (OR = 0.96, 95% CI 0.67–1.37), mecoprop (OR = 1.26, 95% CI 0.72–2.21), or MCPA (OR = 1.24, 95% CI 0.60–2.60).

Vietnam-Veteran Studies

In an update of mortality in the cohorts of the CDC VES through 2000, Boehmer et al. (2004) reported two deaths from HD in deployed veterans and two in non-deployed veterans.

A set of three reports updating the health status of Australian Vietnam veterans noted a significant association of service in Vietnam with HD in comparing male veterans with the general

population of Australia with respect to incidence (SIR = 2.05, 95% CI 1.49–2.61) (ADVA, 2005a) but not mortality (SMR = 0.89, 95% CI 0.46–1.49) (ADVA, 2005b). In another analysis comparing rates of HD in deployed and non-deployed Vietnam veterans (ADVA, 2005c), the incidence rate ratio was 0.90 (95% CI 0.39–1.97), and the mortality rate ratio was 1.72 (95% CI 0.29–11.77).

Biologic Plausibility

No animal studies have shown an association between exposure to the compounds of interest and HD. It is not clear whether true HD even develops in rats and mice. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

The relative rarity of HD complicates the evaluation of epidemiologic studies that address it. However, earlier studies carried out in Sweden (for example, the work of Hardell and colleagues) were well conducted and included excellent characterization of exposure. The committee believes that the small amount of additional information in the present report does not contradict these findings, especially given that most studies had low statistical power. Although it has not been demonstrated as clearly as for NHL, a positive association between the compounds of interest and the development of HD is biologically plausible because of their common lymphoreticular origin and common risk factors.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the compounds of interest and HD.

MULTIPLE MYELOMA

Multiple myeloma (ICD-9 203.0) is characterized by the proliferation of bone marrow stem cells that results in an excess of neoplastic plasma cells and in the production of excess abnormal proteins, usually fragments of immunoglobulins. Multiple myeloma is sometimes grouped with other immunoproliferative neoplasms (ICD-9 203.8). ACS estimated that 9,250 men and 7,320 women would receive diagnoses of multiple myeloma in the United States in 2006 and that 5,680 men and 5,630 women would die from it (Jemal et al., 2006). The average annual incidence of multiple myeloma is shown in Table 6-45.

TABLE 6-45 Average Annual Incidence (per 100,000) of Multiple Myeloma in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Males	7.0	6.3	15.2	11.4	10.3	26.5	17.9	17.3	32.5
Females	4.8	4.0	12.6	8.2	7.5	15.2	12.2	10.3	29.9

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.

The incidence of multiple myeloma is highly age-dependent, with a relatively low rate in people under 40 years old. The incidence is slightly higher in men than in women, and the difference becomes more pronounced with age.

An increased incidence of multiple myeloma has been observed in several occupational groups, including farmers and other agricultural workers and those with workplace exposure to rubber, leather, paint, and petroleum (Riedel et al., 1991). People with high exposure to ionizing radiation and those who suffer from other plasma-cell diseases, such as monoclonal gammopathy of unknown significance or solitary plasmacytoma, are also at greater risk.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to the compounds of interest and multiple myeloma. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-46 summarizes the results of the relevant studies.

TABLE 6-46 Selected Epidemiologic Studies—Multiple Myeloma

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	21	0.8 (0.5–1.3)
	Ever	20	1.1 (0.7–1.7)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	3	5.5 (1.1–16.1)
	Phenoxy herbicide sprayers (>99% men)	0	0.0 (0.0–5.3)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	43	1.3 (1.0–1.8)
	Spouses of private applicators (>99%women)	13	1.1 (0.6–1.9)
	Commercial applicators (men and women)	0	0.0 (0.0–2.7)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	11	0.6 (0.3–1.2)
	Spouses of private applicators (>99%women)	5	0.9 (0.3–2.1)
Torchio et al., 1994	Italian licensed pesticide users	5	0.4 (0.1–1.0)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	1	0.5 (0.1–3.7)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Studies Reviewed in *Update 2004*			
Swaen et al., 2004	Dow chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	3	2.1 (0.4–6.1)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	1	0.8 (0.0–4.5)
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides—incidence	0	—
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	10	2.1 (1.0–3.8)
Hooiveld et al., 1998	Dutch phenoxy herbicide workers (Included in the IARC cohort)	0	0.0 *
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	0	—*
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	17	1.3 (0.8–2.1)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	9	1.2 (0.6–2.3)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	8	1.6 (0.7–3.1)
Becher et al., 1996	German production workers (Included in the IARC cohort)		
	Plant I	3	5.4 (1.1–15.9)
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators		
	Incidence	2	1.5 (0.2–5.2)
	Mortality	3	2.6 (0.5–7.7)
Dean, 1994	Irish farmers and farm workers (men and women)		
	Men	171	1.0 *
Semenciw et al., 1994	Farmers in Canadian prairie provinces	160	0.8 (0.7–1.0)
Blair et al., 1993	US farmers in 23 states	413	1.2 (1.0–1.3)
Brown et al., 1993	Iowa residents who used pesticides or herbicides	111	1.2 (0.8–1.7)
Lynge, 1993	Danish production workers—updated incidence (Included in the IARC cohort)		
	Men	0	*
	Women	2	12.5 (1.5–45.1)
Zahm et al., 1992	Eastern Nebraska users of herbicides		
	Men	8	0.6 (0.2–1.7)
	Women	10	2.3 (0.8–7.0)
	Eastern Nebraska users of insecticides		
	Men	11	0.6 (0.2–1.4)
	Women	21	2.8 (1.1–7.3)
Studies Reviewed in *VAO*			
Eriksson and Karlsson, 1992	Residents of northern Sweden	20	2.2 (1.2–4.7)[d]
Swaen et al., 1992	Dutch herbicide applicators	3	8.2 (1.6–23.8)
Fingerhut et al., 1991	NIOSH cohort—entire cohort	5	1.6 (0.5–3.9)
	≥1-year exposure, ≥20-year latency	3	2.6 (0.5–7.7)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	4	0.7 (0.2–1.8)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Alavanja et al., 1989	USDA forest or soil conservationists	6	1.3 (0.5–2.8)
Boffetta et al., 1989	ACS Prevention Study II subjects	12	2.1 (1.0–4.2)
	Farmers using herbicides or pesticides	8	4.3 (1.7–10.9)
LaVecchia et al., 1989	Residents of the Milan, Italy, area (men and women)		
	Agricultural occupations	*	2.0 (1.1–3.5)
Morris et al., 1986	Residents of four SEER areas		2.9 (1.5–5.5)
Pearce et al., 1986	New Zealand residents—agricultural sprayers		
	Use of agricultural spray	16	1.3 (0.7–2.5)
	Likely sprayed 2,4,5-T	14	1.6 (0.8–3.1)
Cantor and Blair, 1984	Wisconsin residents—farmers in counties with highest herbicide use	*	1.4 (0.8–2.3)
Burmeister et al., 1983	Iowa residents—farming exposures		
	Born 1890–1900	*	2.7 ($p < 0.05$)
	Born after 1900	*	2.4 ($p < 0.05$)
Riihimaki et al., 1982	Finnish herbicide applicators	1	(0.2 expected)
ENVIRONMENTAL			
New Studies			
Pahwa et al., 2006	Canadian men (≥19 years of age) from 1 of 6 Canadian provinces		
	Any phenoxy herbicide	62	1.2 (0.8–1.8)
	2,4-D	59	1.3 (0.9–1.9)
	Mecoprop	16	1.2 (0.7–2.8)
	MCPA	7	0.5 (0.2–1.2)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A, B—men	1	0.6 (0.1–4.3)
	women	4	3.2 (1.2–8.8)
Schreinemachers, 2000	Rural or farm residents of Minnesota, Montana, and North and South Dakota		
	Men—counties with high wheat acreage	75	0.8 (0.6–1.0)
	medium wheat acreage	108	1.0 (0.8–1.3)
	Females—counties with high wheat acreage	77	1.0 (0.7–1.3)
	medium wheat acreage	91	1.0 (0.8–1.3)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B—men	1	1.1 (0.0–6.2)
	women	4	6.6 (1.8–16.8)
	Zone R—men	5	0.8 (0.3–1.9)
	women	5	1.0 (0.3–2.3)
Studies Reviewed in *Update 1996*			
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men	2	3.2 (0.8–13.3)
	women	2	5.3 (1.2–22.6)
	Zone R—men	1	0.2 (0.0–1.6)
	women	2	0.6 (0.2–2.8)
Studies Reviewed in *VAO*			
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	2	2.7 (0.6–11.3)
	women	2	4.4 (1.0–18.7)
	Zone R—men	1	0.2 (0.0–1.5)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	women	3	0.9 (0.3–3.1)
VIETNAM VETERANS			
New Studies			
Boehmer et al., 2004	Vietnam Experience Cohort	1	0.4 (*)
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	31	0.7 (0.437–0.9)
	Navy	4	0.4 (0.1–1.0)
	Army	21	0.7 (0.4–1.0)
	Air Force	6	1.1 (0.4–2.4)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	24	0.9 (0.5–1.2)
	Navy	3	0.5 (0.1–1.5)
	Army	15	0.8 (0.4–1.3)
	Air Force	6	1.7 (0.6–3.6)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs non-deployed		
	Incidence	8	2.1 (0.7–6.0)
	Mortality	5	0.9 (0.2–3.4)
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	White Air Force Vietnam Veterans		
	Lymphopoetic leukemia		
	Ranch Hand Veterans—incidence	10	0.9 (0.4–1.5)
	Comparison Air Force Veterans—incidence	9	0.6 (0.3–1.0)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	2	0.7 (0.1–5.0)
Studies Reviewed in *Update 1998*			
CDVA, 1997a	Australian military Vietnam veterans	6	0.6 (0.2–1.3)
CDVA, 1997b	Australian military Vietnam veterans	0	
Watanabe and Kang, 1996	Army Vietnam veterans	36	0.9 *
	Marine Vietnam veterans	4	0.6 *
Studies Reviewed in *VAO*			
Breslin et al., 1988	Army Vietnam veterans	18	0.8 (0.2–2.5)
	Marine Vietnam veterans	2	0.5 (0.0–17.1)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] 90% CI
* Information not provided by study authors.
— When information was denoted by a dash in the original study.
Studies in italics have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ACS, American Cancer Society; ADVA, Australian Department of Veterans Affairs; AFHS, Air Force Health Study; CI, confidence interval; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; SEER, Surveillance, Epidemiology, and End Results (SEER) Program; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Multiple myeloma was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds (*n* = 20; SMR = 1.07, 95% CI 0.66–1.66) than with having never been exposed (*n* = 21; SMR = 0.83, 95% CI 0.51–1.27).

Two reports from the US AHS (Alavanja et al., 2005; Blair et al., 2005a) provided findings on multiple myeloma in pesticide applicators, commercial applicators, and their spouses, but no results on any of the specific herbicides under consideration were published. A higher incidence of multiple myeloma than expected was found in private applicators (43 cases; SIR = 1.34, 95% CI 0.97–1.81) (Blair et al., 2005a).

In the cohort study of New Zealand phenoxy herbicide producers and sprayers (’t Mannetje et al., 2005), the sole significant finding reported was higher mortality from multiple myeloma among producers than expected (three deaths; SMR = 5.51, 95% CI 1.14–16.1). No deaths from multiple myeloma were observed in the sprayers.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of multiple myeloma was significantly reduced (five cases; SMR = 0.42, 95% CI 0.14–0.99). The authors suggested that the relatively short duration of follow-up and the healthy-worker effect contributed to the observation of reduced mortality.

Reif et al. (1989) performed a series of case–control analyses of the sample of 19,904 people with specified occupations among the 24,762 men 20 years old or older entered into the the New Zealand Cancer Registry in 1980–1984. Their focus was on the 134 for whom forestry work was the most recent occupation listed. For each type of cancer, the people with any other type of cancer were used as controls. Of 295 people with multiple myeloma, only one had most recently been a forestry worker (OR = 0.53, 95% CI 0.08–3.72).

Environmental Studies

In a case–control study of 342 men with new diagnoses of multiple myeloma in 1991–1994 and 1,506 controls in six Canadian provinces, Pahwa et al. (2006) investigated whether exposure to phenoxy herbicides and other pesticides was associated with multiple myeloma. Suggestions of positive associations were found with any exposure to phenoxy herbicides (OR = 1.25, 95% CI 0.93–1.68) or 2,4-D (OR =1.21, 95% CI 0.89–1.65), but the confidence intervals all included unity; a 66% increase in incidence was found in association with exposure to mecoprop (OR = 1.66, 95% CI 1.02–2.71); and no association was found in association with exposure to MCPA (OR = 0.71, 95% CI 0.32–1.58). In analyses of the subset of subjects who worked or lived on farms, the association with exposure to those phenoxy herbicides was similar, but the association with mecoprop was reduced (OR = 1.21, 95% CI 0.65–2.27).

Vietnam-Veteran Studies

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported one death from multiple myeloma in deployed veterans and one in non-deployed veterans.

A set of three reports updating the health status of Australian Vietnam veterans noted no associations between Vietnam service and multiple myeloma in comparing veterans with the general population of Australia with respect to incidence (SIR = 0.66, 95% CI 0.43–0.90) (ADVA, 2005a) or mortality (SMR = 0.86, 95% CI 0.52–1.20) (ADVA, 2005b). A separate study compared the rates of multiple myeloma in deployed and non-deployed Vietnam veterans (ADVA, 2005c); the incidence of multiple myeloma in deployed veterans was increased (RR = 2.19, 95% CI 0.76–5.98), but mortality from multiple myeloma was not increased (RR = 0.90, 95% CI 0.22–3.29).

Biologic Plausibility

No animal studies have reported an association between exposure to the compounds of interest and multiple myeloma. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

The study by ’t Mannetje et al. (2005) of an occupational group in New Zealand that was involved in the production of phenoxy herbicides and the US AHS (Alavanja et al., 2005) showed higher than expected risks of multiple myeloma. The main limitation of the report of the US AHS is that it did not present findings on any of the compounds of interest, although subjects in the study were indeed exposed to 2,4-D. An environmental case–control study in Canada suggested small excess risks, but the confidence intervals were broad. Recent studies of Australian Vietnam veterans suggested a higher risk of multiple myeloma in male Army veterans deployed to Vietnam than in their non-deployed counterparts.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and multiple myeloma.

AL AMYLOIDOSIS

The committee has moved the section on AL amyloidosis from its position in previous *VAO* updates, where it was grouped with a variety of nonneoplastic health conditions, to put it closer to related conditions, such as multiple myeloma and some types of B-cell lymphoma. The conditions share several biologic features, most notably clonal hyperproliferation of B-cell-derived plasma cells and production of abnormal amounts of immunoglobulins.

The primary feature of amyloidosis (ICD-9 277.3) is the accumulation and deposition in various tissues of insoluble protein, historically termed amyloid. A wide spectrum of disease can stem from this; excessive amyloid protein can have limited clinical consequences or can produce severe, rapidly progressive multiple-organ-system dysfunction. Annual incidence is estimated at 1/100,000; there are about 2,000 new cases each year in the United States. Amyloidosis occurs mainly in people 50–70 years old and occurs more often in males than in females (Solomon, 1999).

Amyloid protein accumulates in the extracellular spaces of various tissues, often affecting multiple organ systems. The pattern of organ involvement depends on the nature of the protein; some amyloid proteins are more fibrillogenic than others. Amyloidosis is classified according to the biochemical properties of the fibril-forming protein, with the letter *A* (for amyloid) as the first designation. AL amyloidosis is the most common form of amyloidosis; the *L* indicates that the amyloid protein is derived from immunoglobin light chains. That links AL amyloidosis with other B-cell disorders that involve overproduction of immunoglobin, such as multiple myeloma and some types of B-cell lymphomas.

AL amyloidosis results from the abnormal overproduction of immunoglobulin light chain protein from a monoclonal population of plasma cells. Clinical findings can include excessive AL protein or immunoglobulin fragments in the urine or serum, renal failure with nephrotic syndrome, liver failure with hepatomegaly, heart failure with cardiomegaly, marcroglossia, carpal tunnel syndrome, and peripheral neuropathy. Bone marrow biopsies commonly show an increased density of plasma cells, suggesting a premalignant state. Historically, that test emphasized routine histochemical analysis, but modern immunocytochemistry and flow cytometry now commonly identify monoclonal populations of plasma cells with molecular techniques. AL amyloidosis can progress rapidly and is often far advanced by the time it is diagnosed (Buxbaum, 2004).

Conclusions from *VAO* and Updates

The Department of Veterans Affairs identified AL amyloidoisis as of concern after the publication of *Update 1998*. AL amyloidosis was considered by the committees responsible for *Update 2000*, *Update 2002*, and *Update 2004*. Those committees concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and AL amyloidosis

Update of the Epidemiologic Literature

Because it is a rare condition, there is little epidemiologic literature specifically on AL amyloidosis. Cohen et al (2004) describe a series of six patients with AL amyloidosis in association with NHL; risk could not be estimated, because the study design did not include a control group for comparison, but the report indicates that the two conditions are closely related.

Rajkumar et al. (2006) review the relationship between AL amyloidosis and other plasma cell disorders. They describe AL amyloidosis as a clonal plasma cell disorder characterized by low tumor burden but profound multisystemic disease.

No new occupational, environmental, or Vietnam-veteran studies concerning exposure to the compounds of interest and amyloidosis of any sort were published since *Update 2004*.

Biologic Plausibility

A 1979 study reported AL amyloidosis in association with chronic skin lesions in Swiss mice after chronic exposure to TCDD (Toth et al., 1979). That finding has not been reported in later studies of TCDD carcinogenicity in mice or rats. The observation of common chromosomal abnormalities in AL amyloidosis and multiple myeloma (Harrison et al., 2002) and of "progression" from AL amyloidosis to multiple myeloma (Rajkumar et al., 1998) support the biologic plausibility of linking AL amyloidosis with multiple myeloma.

It is known that AL amyloidosis is associated with B-cell diseases. ,Roughly 15–20% of the time it occurs with multiple myeloma. Other diagnoses associated with AL amyloidosis include B-cell lymphomas (Cohen et al., 2004), monoclonal gammopathies, agammaglobulinemia, and monoclonal gammopathy of undetermined significance (Rajkumar et al., 2006). Thus, AL amyloidosis can result from such medical conditions as multiple myeloma and B-cell lymphomas for which there is evidence of association with exposure to the compounds of interest.

Synthesis

AL amyloidosis is a very rare condition, and it is not likely that population-based epidemiology will ever provide substantial direct evidence regarding its causation. However, the biologic and pathophysiologic features linking AL amyloidosis, multiple myeloma, and some types of B-cell lymphomas—most notably clonal hyperproliferation of plasma cells and abnormal immunoglobulin production—indicate that AL amyloidosis is pathophysiologically related to those conditions.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the compounds of interest and AL amyloidosis.

LEUKEMIA

There are four primary types of leukemia (ICD-9 202.4, 203.1, 204.0–204.9, 205.0–205.9, 206.0–206.9, 207.0–207.2, 207.8, 208.0–208.9): acute and chronic lymphocytic leukemia and acute and chronic myelogenous (or granulocytic) leukemia. Acute myelogenous leukemia (ICD-9 205) is also commonly called acute myeloid leukemia or acute nonlymphocytic leukemia. There are numerous subtypes of AML; for consistency, the present report uses *acute myelogenous leukemia*, or AML, regardless of designations in the source materials.

ACS estimated that 20,000 men and 15,070 women would receive diagnoses of some form of leukemia in the United States in 2006 and that 12,470 men and 9,810 women would die from it (Jemal et al., 2006). Collectively, leukemia was expected to account for 2.5% of all new diagnoses of cancer and 3.9% of deaths from cancer in 2006. The different forms of leukemia have different patterns of incidence and, in some cases, different risk factors. The incidences of the various forms of leukemia are presented in Table 6-47.

Table 6-47 Average Annual Incidence (per 100,000) of Leukemias in United States[a]

	50–54 Years of Age			55–59 Years of Age			60–64 Years of Age		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
All Leukemias:									
Males	12.6	12.8	11.3	21.0	22.3	16.6	32.8	34.2	26.5
Females	7.8	8.0	5.9	12.0	12.2	10.7	17.5	18.6	11.7
Acute Lymphocytic Leukemia:									
Males	1.0	1.0	1.2	1.0	1.0	1.1	1.5	1.4	1.0
Females	0.7	0.6	1.0	1.0	1.1	0.6	0.6	0.5	0.4
Acute Myeloid Leukemia:									
Males	3.2	3.2	2.4	5.4	5.7	3.5	9.1	9.2	8.5
Females	2.8	2.8	1.6	4.3	4.2	3.6	5.8	5.8	5.6
Chronic Lymphocytic Leukemia:									
Males	5.0	5.4	4.8	9.3	10.2	6.7	14.7	15.6	11.0
Females	2.0	2.2	1.0	4.1	4.5	3.0	6.4	7.3	2.0
Chronic Myeloid Leukemia:									
Males	1.8	1.7	1.5	2.2	2.2	1.8	3.8	3.9	2.5
Females	1.2	1.3	1.0	1.3	1.3	1.5	2.4	2.5	1.2
All Other Leukemia[c]:									
Males	0.4	0.3	0.2	0.8	0.6	2.5	1.2	1.3	1.5
Females	0.3	0.3	0.6	0.6	0.5	0.6	1.0	1.0	0.8

[a] SEER (Surveillance, Epidemiology, and End Results program) nine standard registries, crude age-specific rates, 1999–2003.
[b] Insufficient data to provide a meaningful incidence estimate.
[c] Includes leukemic reticuloendotheliosis (hairy-cell leukemia), plasma-cell leukemia, monocytic leukemia, and acute and chronic erythremia and erythroleukemia.

In adults, acute leukemia is nearly always in the form of AML; see the material below specifically about AML for more background information about this hematopoietic neoplasm.

Acute lymphocytic leukemia (ALL) is a disease of the young and of people over 70 years old. It is relatively uncommon in the age groups that include most Vietnam veterans. The lifetime incidence of ALL is slightly higher in whites than in blacks and higher in men than in women. Exposure to high doses of ionizing radiation is a known risk factor for ALL, but there is little consistent evidence on other factors.

Chronic lymphocytic leukemia (CLL) shares many traits with lymphomas (such as immunohistochemistry, B-cell origin, and progression to an acute, aggressive form of NHL), so the committee reviews it below separately from the other leukemias.

The incidence of chronic myelogenous leukemia (CML) increases steadily with age in people over 30 years old. Its lifetime incidence is roughly equal in whites and blacks and is slightly higher in men than in women. CML accounts for about one-fifth of the cases of leukemia among people in the age groups that include most Vietnam veterans. It is associated with an acquired chromosomal abnormality known as the Philadelphia chromosome, for which exposure to high doses of ionizing radiation is a known risk factor.

Little is known about the risk factors associated with other forms of leukemia. However, two human retroviruses have been linked to human leukemias: HTLV-1 appears to cause adult T-cell leukemia or lymphoma, and HTLV-2 has been linked to hairy-cell leukemia, but with less definitive data.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and leukemia. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 6-48 summarizes the results of the relevant studies.

TABLE 6-48 Selected Epidemiologic Studies—Leukemia

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	49	1.0 (0.7–1.3)
	Ever	35	0.9 (0.6–1.2)
’t Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	0.0 (0.0–5.3)
	Phenoxy herbicide sprayers (>99% men) (myelogenous leukemia)	1	1.2 (0.0–6.4)
Alavanja et al., 2005	US Agriculture Health Study—incidence		
	Private applicators (men and women)	70	0.9 (0.7–1.2)
	Spouses of private applicators (>99%women)	17	0.7 (0.4–1.2)
	Commercial applicators (men and women)	4	0.9 (0.3–2.4)
Blair et al., 2005a	US Agriculture Health Study		
	Private applicators (men and women)	27	0.8 (0.5–1.1)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Spouses of private applicators (>99%women)	14	1.4 (0.8–2.4)
Mills et al., 2005	Cohort study of 139,000 United Farm Workers, with nested case-control analyses restricted to Hispanic workers in California		
	Ever used 2,4-D		
	Total leukemia	*	1.0 (0.4–2.6)
	Lymphocytic leukemia	*	1.5 (0.3–6.6)
	Granulocytic (myelogenous) leukemia	*	1.3 (0.3–5.4)
Hertzman et al., 1997	British Columbia sawmill worker with chlorophenate process (more hexa-, hepta-, & octaCDDs than TCDD), all leukemias—incidence	47	1.2 (0.9–1.5)
	ALL	2	1.0 (0.2–3.1)
	CLL	24	1.7 (1.2–2.4)
	AML	5	0.8 (0.3–1.7)
	CML	7	1.1 (0.5–2.0)
	Other and unspecified	5	0.5 (0.2–1.0)
Torchio et al., 1994	Italian licensed pesticide users	27	0.8 (0.5–1.1)
Reif et al., 1989	Case–control study on all men with occupation indicated entered into New Zealand Cancer Registry 1980–1984 (all leukemias)		
	Forestry workers	4	1.0 (0.4–2.6)
	AML	3	2.2 (*)
Studies Reviewed in *Update 2004*			
Miligi et al., 2003	Case–control of residents of 11 areas in Italy—incidence of leukemia excluding CLL		
	Exposure to phenoxy herbicides	6	2.1 (0.7–6.2)
Swaen et al., 2004	Dutch licensed herbicide applicators—mortality	3	1.3 (0.3–3.7)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	Lymphopoietic mortality in workers with high 2,4-D exposure	4	1.3 (0.4–3.3)
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides	0	—
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	US chemical production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	10	0.8 (0.4–1.5)
Hooiveld et al., 1998	Dutch chemical production workers (Included in the IARC cohort)	1	1.0 (0.0–5.7)
Rix et al., 1998	Danish paper mill workers—incidence		
	Men	20	0.8 (0.5–1.2)
	Women	7	1.3 (0.5–2.7)
Studies Reviewed in *Update 1998*			
Gambini et al., 1997	Italian rice growers	4	0.6 (0.2–1.6)
Kogevinas et al., 1997	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	34	1.0 (0.7–1.4)
	Workers exposed to TCDD (or higher-chlorinated dioxins)	16	0.7 (0.4–1.2)
	Workers not exposed to TCDD (or higher-chlorinated dioxins)	17	1.4 (0.8–2.3)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Becher et al., 1996	German chemical production workers (Included in the IARC cohort)—Cohort I	4	1.8 (0.5–4.7)
Ramlow et al., 1996	Dow pentachlorophenol production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)		
	0-year latency	2	1.0 (0.1–3.6)
	15-year latency	1	—
Waterhouse et al., 1996	Residents of Tecumseh, Michigan—incidence		
	All leukemias		
	Men	42	1.4 (1.0–1.9)
	Women	32	1.2 (0.9–1.8)
	CLL	10	1.4 (1.0–1.9)
Amadori et al., 1995	Italian farming and animal-breeding workers		
	Farmers	5	1.6 (0.5–5.2)
	Farmer-breeders	10	3.1 (1.1–8.3)
Studies Reviewed in *Update 1996*			
Asp et al., 1994	Finnish herbicide applicators		
	Mortality	2	(*)
	Lymphatic	1	0.9 (0.0–5.1)
	Myelogenous	1	0.7 (0.0–3.7)
	Incidence		
	Lymphatic	3	1.0 (0.2–3.0)
Semenciw et al., 1994	Farmers in Canadian prairie provinces	357	0.9 (0.8–1.0)
	Lymphatic	132	0.9 (0.8–1.1)
	Myelogenous	127	0.8 (0.7–0.9)
Blair et al., 1993	US farmers in 23 states		
	White men	1,072	1.3 (1.2–1.4)
	White women	24	1.5 (0.9–2.2)
Kogevinas et al., 1993	IARC cohort (women only, myelogenous leukemia)	1	2.0 (0.2–7.1)
Studies Reviewed in *VAO*			
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (Included in the IARC cohort)		
	Leukemia and aleukemia (ICD-9 204–207)	2	2.2 (0.3–7.9)
	Myelogenous leukemia (ICD-8 205)	2	4.2 (0.5–15.1)
Hansen et al., 1992	Danish gardeners—incidence		
	All gardeners—CLL	6	2.5 (0.9–5.5)
	all other types of leukemia	3	1.2 (0.3–3.6)
	Men—CLL	6	2.8 (1.0–6.0)
	all other types of leukemia	3	1.4 (0.3–4.2)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	145	0.9 (*)
	employee	33	1.0 (*)
	Women—self-employed	8	2.2 ($p < 0.05$)
	employee	3	1.3 (*)
	family worker	27	0.9 (*)
Fingerhut et al., 1991	NIOSH—entire cohort	6	0.7 (0.2–1.5)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	18	1.2 (0.7–1.9)
Brown et al., 1990	Case-control on white men in Iowa and Minnesota, all types of leukemia—incidence	578	
	Ever farmed	335	1.2 (1.0–1.5)
	AML	81	1.2 (0.8–1.8)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	CML	27	1.1 (0.6–2.0)
	CLL	156	1.4 (1.1–1.9)
	ALL	7	0.9 (0.3–2.5)
	Myelodysplasias	32	0.8 (0.5–1.4)
	Any herbicide use	157	1.2 (0.9–1.6)
	AML	39	1.3 (0.8–2.0)
	CML	16	1.3 (0.7–2.6)
	CLL	74	1.4 (1.0–2.0)
	ALL	2	0.5 (0.1–2.2)
	Myelodysplasias	10	0.7 (0.3–1.5)
	Phenoxy acid use	120	1.2 (0.9–1.6)
	2,4-D use	98	1.2 (0.9–1.6)
	2,4,5-T use	22	1.3 (0.7–2.2)
	First use >20 years prior	11	1.8 (0.8–4.0)
	MCPA	11	1.9 (0.8–4.3)
	First use >20 years prior	5	2.4 (0.7–8.2)
Wigle et al., 1990	Canadian farmers	138	0.9 (0.7–1.0)
Zober et al., 1990	BASF employees at plant with 1953 explosion		
	All 3 cohorts (n = 247)	1	1.7 *
	Cohort 3	1	5.2 (0.4–63.1)
	Incident case of AML in Cohort 1		
Alavanja et al., 1988	USDA agricultural extension agents	23	1.9 (1.0–3.5)
	Lymphatic	*	2.1 (0.7–6.4)
	Trend over years worked		($p < 0.01$)
	Myelogenous	*	2.8 (1.1–7.2)
	Trend over years worked		($p < 0.01$)
Bond et al., 1988	Dow 2,4-D production workers (Included in the IARC cohort and the NIOSH Dioxin Registry)	2	3.6 (0.4–13.2) [d]
Blair and White, 1985	1,084 leukemia deaths in Nebraska 1957–1974		
	Farmer–usual occupation on death certificate		1.3 ($p < 0.05$)
	99 ALLs	*	1.3 (*)
	248 CLLs	*	1.7 ($p < 0.05$)
	105 unspecified lymphatics	*	0.9 (*)
	235 AMLs	*	1.2 (*)
	96 CMLs	*	1.1 (*)
	39 unspecified myelogenous	*	1.0 (*)
	39 acute monocytics	*	1.9 (*)
	52 acute unspecified leukemias	*	2.4 (*)
	65 unspecified leukemias	*	1.2 (*)
Burmeister et al., 1982	1,675 leukemia deaths in Iowa 1968–1978		
	Farmer -usual occupation on death certificate		1.2 ($p < 0.05$)
	ALL	28	0.7 (0.4–1.2)
	CLL	132	1.7 (1.2–2.4)
	Lived in one of 33 counties with highest herbicide use	*	1.9 (1.2–3.1)
	Unspecified lymphatic	64	1.7 (1.0–2.7)
	AML	86	1.0 (0.8–1.5)
	CML	46	1.0 (0.7–1.7)
	Unspecified myelogenous	36	0.8 (0.5–1.4)
	Acute monocytic	10	1.1 (0.4–2.6)
	Unspecified leukemia	31	1.1 (0.6–2.0)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
ENVIRONMENTAL			
Studies Reviewed in *Update 2002*			
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Mortality standardized to Samara Region		
	Men	11	1.5 (0.8–2.7)
	Women	15	1.5 (0.8–2.4)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zones A, B—men	9	2.1 (1.1–4.1)
	women	3	1.0 (0.3–3.0)
Schreinemachers., 2000	Rural or farm residents of Minnesota, Montana, North Dakota, South Dakota		
	Men—counties with wheat acreage 23,000–110,999	246	1.0 (0.8–1.1)
	Men—counties with wheat acreage ≥111,000	248	1.1 (1.0–1.3)
	Women—counties with wheat acreage 23,000–110,999	183	1.0 (0.8–1.2)
	Women—counties with wheat acreage ≥111,000	146	0.9 (0.8–1.2)
Bertazzi et al., 1998	Seveso residents—15-year follow-up		
	Zone B—men	7	3.1 (1.4–6.7)
	women	1	0.6 (0.1–4.0)
	Zone R—males	12	0.8 (0.4–1.5)
	women	12	0.9 (0.5–1.6)
Studies Reviewed in *Update 1998*			
Bertazzi et al., 1997	Seveso residents—15-year follow-up		
	Zone B—men	7	3.1 (1.3–6.4)
	women	1	0.6 (0.0–3.1)
	Zone R—men	12	0.8 (0.4–1.4)
	women	12	0.9 (0.4–1.5)
Studies Reviewed in *Update 1996*			
Swensson et al., 1995	Swedish fishermen		
	All leukemias—mortality		
	East coast (higher serum TEQs)	5	1.4 (0.5–3.2)
	West coast (lower serum TEQs)	24	1.0 (0.6–1.5)
	Lymphocytic—incidence		
	East coast (higher serum TEQs)	4	1.2 (0.3–3.3)
	West coast (lower serum TEQs)	16	1.3 (0.8–2.2)
	Myelogenous—incidence		
	East coast (higher serum TEQs)	2	0.9 (0.1–3.1)
	West coast (lower serum TEQs)	6	0.5 (0.2–1.1)
Bertazzi et al., 1993	Seveso residents—10-year follow-up—incidence		
	Zone B—men	2	1.6 (0.4–6.5)
	Myelogenous leukemia (ICD-9 205)	1	2.0 (0.3–14.6)
	women	2	1.8 (0.4–7.3)
	Myelogenous leukemia (ICD-9 205)	2	3.7 (0.9–15.7)
	Zone R—men	8	0.9 (0.4–1.9)
	Myelogenous leukemia (ICD-9 205)	5	1.4 (0.5–3.8)
	women	3	0.4 (0.1–1.2)
	Myelogenous leukemia (ICD-9 205)	2	0.5 (0.1–2.1)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Studies Reviewed in *VAO*			
Bertazzi et al., 1992	Seveso residents—10-year follow-up		
	Zones A, B, R—men	4	2.1 (0.7–6.9)
	women	1	2.5 (0.2–27.0)
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence		
	All branches	130	1.1 (1.0–1.4)
	Lymphocytic leukemia	72	1.4 (1.1–1.7)
	Myelogenous leukemia	54	1.0 (0.8–1.3)
	Navy	35	1.5 (1.0–2.0)
	Lymphocytic leukemia	14	1.3 (0.7–2.1)
	Myelogenous leukemia	19	1.7 (1.0–2.6)
	Army	80	1.1 (0.8–1.3)
	Lymphocytic leukemia	50	1.4 (1.0–1.8)
	Myelogenous leukemia	28	0.8 (0.5–1.1)
	Air Force	15	1.2 (0.7–2.0)
	Lymphocytic leukemia	8	1.4 (0.6–2.7)
	Myelogenous leukemia	7	1.3 (0.5–2.6)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—mortality		
	All branches	84	1.0 (0.8–1.3)
	Lymphocytic leukemia	24	1.2 (0.7–1.7)
	Myelogenous leukemia	55	1.1 (0.8–1.3)
	Navy	17	1.3 (0.8–1.8)
	Lymphocytic leukemia	4	0.2 (0.0–1.2)
	Myelogenous leukemia	11	1.6 (0.9–2.5)
	Army	48	0.1 (0.7–1.2)
	Lymphocytic leukemia	17	1.3 (0.7–2.0)
	Myelogenous leukemia	30	0.8 (0.5–1.1)
	Air Force	14	1.6 (0.8–2.6)
	Lymphocytic leukemia	6	2.7 (1.0–5.8)
	Myelogenous leukemia	8	1.3 (0.5–2.5)
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	16	0.6 (0.3–1.1)
	Lymphocytic leukemia	9	0.8 (0.3–2.0)
	Myelogenous leukemia	7	0.5 (0.2–1.3)
	Mortality	11	0.6 (0.3–1.3)
	Lymphocytic leukemia	2	0.4 (0.0–2.4)
	Myelogenous leukemia	8	0.7 (0.3–1.7)
Boehmer et al., 2004	Vietnam Experience Cohort	8	1.0 (0.4–2.5)
Studies Reviewed in *Update 2004*			
Akhtar et al., 2004	White Air Force Ranch Hand veterans—lymphopoietic cancers[†]		
	All Ranch Hand veterans		
	Incidence (SIR)	10	0.9 (0.4–1.5)
	Mortality (SMR)	6	1.0 (0.4–2.0)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
	Veterans with tours between 1966–1970—incidence	7	0.7 (0.3–1.4)
	White Air Force Comparison veterans—lymphopoietic cancers[†]		
	All comparison veterans		
	Incidence (SIR)	9	0.6 (0.3–1.0)
	Mortality (SMR)	5	0.6 (0.2–1.2)
	Veterans with tours between 1966–1970—incidence	4	0.3 (0.1–0.8)
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	2	0.7 (0.1–5.0)
AIHW, 1999	Australian Vietnam veterans	27	26 expected (16–36)
CDVA, 1998a	Australian Vietnam veterans—men	64[e]	26 expected (16–36)
CDVA, 1998b	Australian Vietnam veterans—women	1[e]	0 expected (0–4)
Studies Reviewed in *Update 1998*			
Dalager and Kang, 1997	Army Chemical Corps veterans		1.0 (0.1–3.8)
CDVA, 1997a	Australian military Vietnam veterans	33	1.3 (0.8–1.7)
Studies Reviewed in *Update 1996*			
Visintainer et al., 1995	Michigan Vietnam veterans	30	1.0 (0.7–1.5)

[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
[d] $p < 0.01$.
[e] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have leukemia?"
* Information not provided by study authors.
—When information was denoted by a dash in the original study.
[†] Lymphopoietic cancers comprise all of the forms of lymphoma (including Hodgkin's Disease and non-Hodgkin's lymphoma) and leukemia (ALL, AML, CLL, CML).
Studies in "italics" have been superseded by newer studies of the same cohorts.
ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid, 2,4-D, 2,4-dichlorophenoxyacetic acid; ADVA, Australian Department of Veterans Affairs; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; CLL, Chronic lymphocytic leukemia; IARC, International Agency for Research on Cancer; USDA, US Department of Agriculture.

Update of the Epidemiologic Literature

Occupational Studies

McLean et al. (2006) reported on a multinational IARC cohort of 60,468 pulp and paper industry workers. A JEM was applied to individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). The occurrence of leukemia was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds (n = 35; SMR = 0.89, 95% CI 0.62–1.24) than with having never been exposed (n = 49; SMR = 0.95, 95% CI 0.70–1.26).

Two reports of the US AHS (Alavanja et al., 2005; Blair et al., 2005a) presented no results on any of the specific herbicides under consideration but noted no increases in the incidence of or mortality from leukemia in pesticide applicators, commercial applicators, or their spouses (Table 6-44).

't Mannetje et al. (2005) found only one case of leukemia, specified as a myelogenous tumor (ICD-9 205), in their small cohort of phenoxy herbicide producers and sprayers.

A subcohort of Hispanic workers drawn from a larger cohort of 139,000 California UFW members was assembled for a nested case–control study (Mills et al., 2005). A total of 51 people with leukemia (35 men and 16 women; 23 lymphocytic, 20 granulocytic, and eight other) were identified. Control subjects (in a 5:1 ratio) matched by sex, ethnicity, and age were drawn from the UFW cohort by using incidence density sampling. Exposure to pesticides and herbicides was determined by linking the subjects' job titles to records of pesticide application in the California Department of Pesticide Regulation. Use of 2,4-D was not found to be associated with all types of leukemia (OR = 1.03, 95% CI 0.41–2.61) or with leukemias specified as habing arisen from myelogenous or lymphocytic cell lines.

Torchio et al. (1994) reported on a cohort of 23,401 Italian licensed pesticide users in the Piedmont region, which the Italian National Institute of Statistics reports as having high herbicide use, especially of 2,4-D and MCPA. The estimated risk of leukemia was not increased (27 cases; SMR = 0.75, 95% CI 0.49–1.08).

Reif et al. (1989) performed a series of case–control analyses on the sample of 19,904 people with specified occupations among the 24,762 men 20 years old or older entered into the the New Zealand Cancer Registry during 1980–1984. The focus of their report was on the 134 for whom forestry work was the most recent occupation listed. For each type of cancer, people with any other type of cancer were used as controls. Of 534 people with leukemia, four had most recently been forestry workers (OR = 0.96, 95% CI 0.36–2.61).

Environmental Studies

No relevant environmental studies concerning a possible association between exposure to the compounds of interest and leukemia were published since those reviewed in *Update 2004*.

Vietnam-Veteran Studies

In the mortality update of the CDC VES through 2000, Boehmer et al. (2004) reported eight deaths from leukemia in both the deployed and non-deployed veterans (CRR = 0.95, 95% CI 0.36–2.53).

A set of three reports updating the health status of Australian Vietnam veterans noted non-significantly increased risks of leukemia after Vietnam service in comparing veterans with the general population of Australia with respect to incidence (SIR = 1.88, 95% CI 0.98–1.38) (ADVA, 2005a) and mortality (SMR = 1.07, 95% CI 0.84–1.30) (ADVA, 2005b). A separate study compared rates of leukemia in deployed and non-deployed Vietnam veterans (ADVA, 2005c); no increased risks leukemia (RR = 0.60, 95% CI 0.31–1.13) or leukemia mortality (RR = 0.61, 95% CI 0.27–1.30) were seen in the deployed. The reports on the Australian Vietnam

veterans also presented risks broken down by leukemia type (see Table 6-49); only in CLL did the veterans have a significant increase over the general public (ADVA, 2005a).

Biologic Plausibility

Male rats fed TCDD at a dose of 1 ng/kg of body weight per week for 78 weeks and sacrificed at week 95 of the study showed an increased incidence of lymphocytic leukemia (Van Miller et al., 1977), but female rats and mice of both sexes did not show increased incidences. Later studies of TCDD's carcinogenicity have not shown an increased incidence of leukemia in mice or rats.

Two recent in vitro studies suggest that TCDD exposure does not promote leukemia. Grevenynghe et al. (2006) reported that proliferation of cultured human bone marrow stem cells (the source of leukemic cells) was not influenced by addition of TCDD to the culture medium. And Mulero-Navarro et al. (2006) reported that the AhR promoter is silenced in ALL—an effect that could lead to reduced expression of the receptor that binds TCDD and mediates its toxicity. No reports of animal studies have noted an increased incidence of leukemia after exposure to the phenoxy herbicides or other compounds of interest.

Synthesis

The new studies from the US AHS and on Vietnam veterans did not provide any new evidence of an association between exposure to the compounds of interest and leukemia, although it is important to recognize that analyses of possible effects of exposure to TCDD and other compounds of interest were not reported. Exposure to 2,4-D was assessed in UFW members, but no association with leukemia incidence was found.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and leukemias other than CLL.

Chronic Lymphocytic Leukemia

In the proposed World Health Organization classification of non-Hodgkin's lymphoid neoplasms CLL (ICD-9 204.1) and its lymphomatous form, small-cell lymphocytic lymphoma, are mature B-cell neoplasms (IARC, 2001). ACS estimated that about 6,280 men and 3,740 women would receive diagnoses of CLL in the United States in 2006 and that 2,590 men and 2,070 women would die from it (Jemal et al., 2006). Nearly all cases occur after the age of 50 years. For average annual incidence, see Table 6-47.

The requirements for diagnosis of CLL include an absolute peripheral-blood lymphocyte count of more than 10×10^9,per liter, a predominant population of mature-looking lymphocytes, and hypercellular or normal cellular bone marrow that contains more than 30% lymphocytes. The malignant cells in CLL exhibit a characteristic membrane phenotype with coexpression of pan-B-cell antigens—including CD19, CD20, and CD23—with CD5. However, the cell surface membranes express only weak surface-membrane immunoglobulin.

Patients with CLL are staged according to the Rai classification: stage 0, clinical features of lymphocytes in the blood and marrow only; stage I or II (intermediate risk), lymphocytosis, lymphadenopathy, and splenomegaly with or without hepatomegaly; and stage III or IV (high risk), lymphocytosis and either anemia or thrombocytopenia or both. The most consistent abnormal finding at initial diagnosis is lymphadenopathy—from small lymph nodes to nodes as large as an orange. Patients with large lymphadenopathy, white-cell counts higher than 100×10^9 per liter, or thrombocytopenia require therapy. The disease is complicated by autoimmune anemias and recurrent infection because of hypogammaglobulinemia.

Diffuse small-cell lymphocytic lymphoma is the term for the condition of patients who have lymphomatous CLL. Patients seek medical attention for painless generalized lymphadenopathy that in many cases has lasted for several years. Unlike the situation in CLL, the peripheral blood may be normal or reveal only mild lymphocytosis. However, the bone marrow has abnormal cells in 75–95% of cases. Both small-cell lymphocytic lymphoma and CLL can transform into aggressive NHL, known as Richter's syndrome. Richter's syndrome is characterized by diffuse large-cell lymphoma or its immunoblastic variant. It is resistant to current therapies, and the median survival is about 6 months. Hairy-cell leukemia has recently been classified as a rare form of CLL (AJCC, 2002).

Conclusions from VAO and Updates

Update 2002 was the first to discuss CLL separately from other leukemias. The epidemiologic studies indicated that farming, especially with exposure to 2,4-D and 2,4,5-T, is associated with significant mortality from CLL. Many more studies support the hypothesis that herbicide exposure can contribute to NHL risk. Most cases of CLL and NHL reflect malignant transformation of B-lymphocyte progenitor cells, so these diseases could have a common etiology. Studies reviewed in *Update 2002* and *Update 2004* and in the present report are summarized in Table 6-49.

TABLE 6-49 Selected Epidemiologic Studies—Chronic Lymphocytic Leukemia

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
OCCUPATIONAL			
New Studies			
Hertzman et al., 1997	British Columbia sawmill worker with chlorophenate process (more hexa-, hepta-, & octaCDDs than TCDD), all leukemias—incidence	47	1.2 (0.9–1.5)
	ALL	2	1.0 (0.2–3.1)
	CLL	24	1.7 (1.2–2.4)
	AML	5	0.8 (0.3–1.7)
	CML	7	1.1 (0.5–2.0)
	Other and unspecified	5	0.5 (0.2–1.0)

Reference	Study Population [a,b]	Exposed Cases[c]	Estimated Relative Risk (95% CI)[c]
Studies Reviewed in *Update 1998*			
Waterhouse et al., 1996	Residents of Tecumseh, Michigan—incidence (men and women)	10	1.8 (0.8–3.2)
Amadori et al., 1995	Workers in northeast Italy (men and women)		
	Farming and animal-breeding workers	15	2.3 (0.9–5.8)
	Farming workers only	5	1.6 (0.5–5.2)
	Animal-breeding workers only	10	3.1 (1.1–8.3)
Studies Reviewed in *VAO*			
Hansen et al., 1992	Danish gardeners (men and women)		
	All gardeners	6	2.5 (0.9–5.5)
	Male gardeners	6	2.8 (1.0–6.0)
Brown et al., 1990	Residents of Iowa and Minnesota		
	Ever farmed	156	1.4 (1.1–1.9)
	Any herbicide use	74	1.4 (1.0–2.0)
Blair and White, 1985	1,084 leukemia deaths in Nebraska 1957–1974		
	Farmer -usual occupation on death certificate	*	1.3 ($p < 0.05$)
	248 CLLs	*	1.7 ($p < 0.05$)
Burmeister et al., 1982	1,675 leukemia deaths in Iowa 1968–1978		
	Farmer -usual occupation on death certificate		1.2 ($p < 0.05$)
	CLL	132	1.7 (1.2–2.4)
	Lived in 33 counties with highest herbicide use	*	1.9 (1.2–3.1)
ENVIRONMENTAL			
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Lymphatic leukemia		
	Zones A, B—men	2	1.6 (0.4–6.8)
	women	0	—
VIETNAM VETERANS			
New Studies			
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence		
	All branches	58	1.20 (0.7–1.7)
	Navy	12	1.51 (0.8–2.6
	Army	42	1.68 (1.2–2.2)
	Air Force	4	0.87 (0.2–2.2)

NOTE: USDA = United States Department of Agriculture.
[a] Table shows mortality unless otherwise noted.
[b] Cohorts are male unless otherwise noted.
[c] Given when available.
— When information was denoted by a dash in the original study.
ABBREVIATION: ADVA, Australian Department of Veterans Affairs

Update of the Epidemiologic Literature

Occupational Studies

In the review responding to VA's request that all evidence on AML be assessed in this update, the committee noted a large study of sawmill workers in which the dioxin exposure from chlorophenols tended to involve less TCDD than hexachlorinated, heptachlorinated, and octachlorinated dioxins. Hertzman et al. (1997) reported on cancer incidence in 1969–1989 in a cohort of 23,829 workers in 11 sawmills in British Columbia that used chlorophenate. The risk of all types of leukemias neared significance (SIR = 1.18, 95% CI 0.91–1.50), which was dominated largely by 24 cases of CLL (SIR = 1.67, 95% CI 1.16–2.36).

Environmental Studies

No new environmental studies concerning exposure to the compounds of interest and CLL were published since *Update 2004*.

Vietnam-Veteran Studies

An increase in the incidence of CLL was observed in the comparison between Australian Vietnam veterans and the general public (SIR = 1.55, 95% CI 1.15–1.95) (ADVA, 2005a). Only in the group of Army veterans was a significant effect shown (SIR = 1.68, 95% CI 1.18–2.19), although the rate was also increased in the smaller group of Navy veterans (SIR = 1.51, 95% CI 0.78–2.63). In the corresponding mortality study (ADVA, 2005b), cases of lymphocytic leukemia were too few to separate into acute and chronic types. In the study that compared the incidence of CLL in deployed and non-deployed Australian forces (ADVA, 2005c), no increase was found in the deployed (RR = 0.90, 95% CI 0.31–2.45); again, there were too few deaths from lymphocytic leukemia to analyze acute and chronic types separately.

Biologic Plausibility

No animal studies have reported an increase specifically in the incidence of CLL after exposure to the compounds of interest. However, given the similarities between CLL and B-cell lymphomas, a similar argument for biologic plausibility can be made. An increased incidence of lymphoma was reported in female B6C3F mice exposed to TCDD at 1 mg/kg of body weight via gavage twice a week for 2 years (NTP, 1982a). The finding was confirmed and extended in recent NTP studies in which a dose-related increase in the incidence of lymphoma was observed in female mice given TCDD orally at 0.04, 0.2, or 2.0 μg/kg twice a week for 104 weeks.

Laboratory animal studies of 2,4-D found no induction of lymphomas. (See Chapter 3 for more information on 2,4-D toxicity.)

The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Although considerably more studies support the hypothesis that herbicide exposure can contribute to the development of NHL, exposure to 2,4-D and 2,4,5-T also appears to be associated with the occurrence of CLL. Malignant transformation of B-lymphocyte progenitor cells is apparent in most cases of CLL and NHL, so it is plausible that these diseases could have a common etiology.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to the compounds of interest and CLL.

Acute Myelogenous Leukemia

In adults, acute leukemia is nearly always in the form of AML (ICD-9 205.0, 207.0, 207.2). ACS estimated that about 6,350 men and 5,580 women would receive new diagnoses of AML in the United States in 2006 and that 5,090 men and 3,950 women would die from it (Jemal et al., 2006). Seven distinct morphologic groups were described in the French-American-British (FAB) classification system. FAB M0 and M1 without maturation are characterized by the presence of Auer rods in the leukemic cell. FAB M-2 myelogenous leukemia with maturation also has Auer rods and is more likely to have chromosomal abnormalities. FAB M-3 progranulocytic leukemia has distinct morphologic, clinical, and cytogenetic features that include a tendency toward disseminated intravascular coagulation. FAB M-4 myelomonocytic leukemia is characterized by a mixture of large myeloid and monocytic elements. Some patients have prominent eosinophilia. Patients who present with the FAB categories M-2 to M-4 generally are 30–40 years old and experience a favorable outcome of induction chemotherapy. Patients with FAB M-5, monocytic leukemia; FAB M-6, erythroleukemia; or FAB M-7, megakaryocytic leukemia, often are over 60 years old, and the prognosis generally is poor.

AML is the most common leukemia among adults; its incidence increases steadily with age in people over 40 years old. In the age groups that typically include Vietnam veterans, AML makes up roughly one-fourth of cases of leukemia in men and one-third in women. Overall, AML is slightly more common in men than in women. Risk factors associated with an increased risk of AML include high doses of ionizing radiation, occupational exposure to benzene, and exposure to some medications used in cancer chemotherapy (such as melphalan). Fanconi's anemia and Down syndrome are associated with an increased risk of AML, and tobacco use is thought to account for about 20% of AML cases.

Conclusions from VAO and Updates

In this update, at the request of VA, AML is being considered as an independent cancer type to determine whether there is evidence that its occurrence is associated with exposure to the herbicides sprayed in Vietnam.

The search strategies that have been in use since the VAO project was undertaken in the Institute of Medicine would have identified any articles addressing AML specifically and articles that reported on leukemia in general. All the studies previously reviewed in this series with respect to leukemia were revisited to locate any reported results specifically on AML. Perhaps the complexity of the leukemia classification systems and the fact that they have been in flux throughout the 20th century have caused epidemiologists to question whether diagnoses of specific leukemia types made over decades could be compiled and reliably reallocated to appropriate types for analysis. For whatever reasons, virtually no usable information on types of leukemia has been reported in the epidemiologic literature on cohorts reviewed to date. Occasionally, leukemia is partitioned into lymphocytic and myelogenous (Alavanja et al., 1988; Asp et al., 1994; Bertazzi et al., 1993; Bueno de Mesquita et al., 1993; Kogevinas et al., 1993; Semenciw at al., 1994; Svensson et al., 1995), but no instances of partitioning into acute and chronic were observed. Findings characterized in both respects are extremely uncommon (Green, 1991; Hertzman et al., 1997; Reif et al., 1989; Zober et al., 1990). Thse instances are likely to occur without associated statistics and for such small numbers of cases would not be useful. The rarity of individual specific leukemias makes them a more suitable topic for the case–control design, but the committee found only a small number of studies that followed such a protocol and yielded results for AML (Blair and White, 1985; Brown et al. 1990; Burmeister et al., 1982). The statistics that are available for AML in particular have been entered with the results for leukemia overall in Table 6-48.

Green (1991) noted that the one case of leukemia observed in the 17 people who died from cancer in a cohort of 1,222 forestry worker who worked with phenoxy herbicides and picloram was AML. In reporting on the 534 men entered in the New Zealand Cancer Registry from 1980–1984 with a diagnosis of leukemia, Reif et al. (1989) mentioned that, of the four cases who were forestry workers, three had AML, giving an elevated risk in association with that occupation (OR = 2.24) that was characterized as being “imprecise.” In describing the cohort of 247 at the BASF plant that had an explosion in 1953, Zober et al. (1990) mentioned only that there was an incident case of AML. Kogevinas et al. (1993) mentioned one death from myelogenous leukemia in the 701 women in the IARC cohort, for an increased risk estimate with a very wide confidence range (SMR = 1.96, 95% CI 0.24–7.08). The findings of Asp et al. (1994) on leukemia incidence and mortality in 1,909 Finnish phenoxy herbicide applicators were so sparse that partitioning into lymphocytic and myelogenous types was unilluminating. The observation by Bueno de Mesquita et al. (1993) that both the leukemia deaths observed in their cohort of Dutch chemical workers involved the myeloid cell type pratically doubled the estimated risk (SMR = 4.17, 95% CI 0.50–15.05), but the confidence interval remained exceedingly large. The situation was similar when Bertazzi et al. (1993) distinguished between myelogenous and lymphocytic leukemias in the 10-year follow-up of morbidity in the Seveso cohort. Svensson et al. (1995) reported separately on the incidence of lymphocytic and myelogenous leukemias in fishers residing on the east and west coasts of Sweden; on the basis of a modest number of cases, the incidence of neither type of

leukemia differed from no effect, but the estimated risks of lymphatic leukemias were greater than 1, and those of the myelogenous type fell below 1.

A cohort of farmers in Alberta, Saskatchewan, and Manitoba was defined by identification of specified occupation in the 1971 Canadian census and linked to the Canadian Mortality Data Base (Semenciw at al., 1994). Findings based on 357 leukemia deaths (SMR = 0.85, 95% CI 0.77–0.95) were robust enough that they could be usefully partitioned to yield a significantly reduced risk of myelogenous leukemias (SMR = 0.78, 95% CI 0.65–0.93) but not lymphatic leukemias (SMR = 0.94, 95% CI 0.79–1.12).

In the leukemia results on agricultural extension workers (Alavanja et al., 1988), the phenomenon was similar, but the message was reversed. The significant increase in leukemias overall (SMR = 1.92, 95% CI 1.04–3.54) was intensified when the analysis was restricted to myelogenous leukemias (SMR = 2.80, 95% CI 1.09–7.19).

Hertzman et al. (1997) reported on the cancer incidence in 1969–1989 in a cohort of 23,829 workers in 11 sawmills in British Columbia that used chlorophenate, which tends to be contaminated with hexachlorinated, heptachlorinated, and octachlorinated, rather than tetrachlorinated, dioxins. The risk of all types of leukemias neared significance (SIR = 1.18, 95% CI 0.91–1.50) and was dominated by 24 cases of CLL (SIR = 1.67, 95% CI 1.16–2.36); the five cases of AML, however, did not indicate an increased risk (SIR = 0.81, 95% CI 0.32–1.70).

For every white man 30 years old or older who died of any type of leukemia in Nebraska in 1957–1974, Blair and White (1985) selected two non-leukemia deaths matched on sex, race, county of residence, age at death (within 2 years), and calendar year of death. Usual occupations were obtained from death certificates, and 1,084 of the people with leukemia were coded as farmers (farm owners, tenants, or laborers), for a risk ratio of 1.25, which was said to be significant at the 0.05 level. When the risks of nine different leukemia types were calculated, only the risk of CLL (OR = 1.67) was significantly increased; the estimated risk of AML in 235 farmers was 1.18.

Burmeister et al. (1982) conducted an analogous investigation of the association between a usual occupation of farming and death from leukemia in 1968–1978 in Iowa. There was an increased risk of leukemias overall (OR = 1.24; $p < 0.05$), but no increase in risk was associated with AML in particular.

Brown et al. (1990) not only broke down leukemia cases by type but provided a substantial amount of information on the use of specific phenoxy herbicides and AML and CLL. A companion case–control study was conducted on lymphomas. Screening of white men 30 years old or older in the Iowa Tumor Registry (March 1981–October 1983) and a surveillance network established for this study in Minnesota (October 1980–September 1982) identified 578 newly diagnosed cases of leukemia. Stratifying on age, vital status, and state assembled a population-based sample of 1,245 white men without lymphohematopoietic cancer. Detailed information on personal habits, family medical history, and occupation (particularly farming and aspects of pesticide use) was gathered from in-person interviews conducted with the subjects or close relatives. For leukemias overall, the results suggested an association with phenoxy herbicide use (SIR = 1.2, 95% CI 0.9–1.6). For AML in particular, the association with having ever used herbicides (SIR = 1.3, 95% CI 0.8–2.0) was slightly more pronounced than that with having ever lived on a farm (SIR = 1.2, 95% CI 0.8–1.8).

Update of the Epidemiologic Literature

In light of the overall paucity of information on a possible association between exposure to the herbicides sprayed in Vietnam and AML specifically, the information published on this subject since *Update 2004* is relatively rich.

Occupational Studies In their small cohort of phenoxy herbicide producers and sprayers, 't Mannetje et al. (2005) found a single case of leukemia, which was specified as myloid (ICD-9 205).

Environmental Studies No new environmental studies concerning the compounds of interest and AML were published since *Update 2004*.

Vietnam-Veteran Studies The reports on the Australian Vietnam veterans (ADVA, 2005a,b,c) were unusual in presenting risks broken down by leukemia type (see Table 6-49). Compared with the incidence in the general public (SIR = 1.04, 95% CI 0.67–1.42) (ADVA, 2005a) or non-deployed veterans (RR = 0.30, 95% CI 0.06–1.11) (ADVA, 2005c), the incidence of AML in deployed veterans was not perceptibly increased. With respect to mortality, however, the findings for leukemia were broken down only to the level of lymphocytic vs myelogenous but not specifically for AML (ADVA, 2005b,c).

Biologic Plausibility

No animal studies have reported an increase in the incidence of AML after exposure to the compounds of interest. The biologic plausibility of the carcinogenicity of the compounds of interest in general is summarized at the end of this chapter.

Synthesis

Taken together, the occupational, environmental, and veteran studies are limited by the paucity of reports related to the types of leukemia and to AML in particular.

In concluding its review of the available findings related to the occurrence of AML in veterans exposed to the herbicides sprayed in Vietnam, the committee notes the finding in *Update 2000* of limited or suggestive evidence of an association between exposure to the compounds of interest and AML in the children of Vietnam veterans and the reversal of the finding in *Acute Myelogenous Leukemia* (2002). The recognition of an error in a key publication and new information on the illness resulted in reclassification AML in children to inadequate evidence to determine whether there is an association.

Conclusion

The committee concludes that there is inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and AML or other specific types of leukemia except CLL.

SUMMARY

Biologic Plausibility

The biologic plausibility of an association between exposure to the compounds of interest and human cancers is summarized as follows. The studies considered in this chapter with respect to biologic plausibility have been restricted primarily to those performed in laboratory animals (rats, mice, hamsters, and monkeys). Mechanistic studies pertaining to the possible carcinogenic actions of the compounds of interest have been described in Chapter 3. The evidence obtained from cellular and molecular studies indicates that a connection between human exposure to TCDD and cancers is biologically plausible. In considering the relevance of the studies in laboratory animals to the effect that human exposure to TCDD (and other compounds of interest) may have on the development of cancers in the veterans of the Vietnam War, a few notes of caution should be observed. First, the effects of TCDD vary widely among species. For example, there are differences among various experimental animals in susceptibility to a number of TCDD-induced effects, and the sites at which tumors are induced vary among species. Second, the exposures used in the animal studies may or may not appropriately represent human exposures (discussed in Chapter 3). Third, the dose or body burden that would be expected to affect either the incidence or the progression of a specific human cancer significantly is not clear. Fourth, given that human cancers are complex diseases most frequently observed in the aging population and influenced by genetic, dietary, hormonal, and environmental factors, it is not yet clear whether the studies have been performed in a manner that appropriately models the development of the specific human cancers of interest.

With respect to 2,4-D, 2,4,5-T, and picloram, several studies have been performed in laboratory animals. In general, the results were negative, although some of them would not meet current standards for cancer bioassays; others produced equivocal results. Thus, it is impossible to have confidence in conclusions regarding the carcinogenicity of those compounds. Most of the evidence indicates that 2,4-D is genotoxic only at very high concentrations. Although 2,4,5-T was shown to increase the formation of DNA adducts by cytochrome P450-derived metabolites of benzo[*a*]pyrene, most available evidence indicates that 2,4,5-T is genotoxic only at high concentrations.

There is some evidence that cacodylic acid is carcinogenic. Studies performed in laboratory animals have shown that it can induce neoplasms of the kidney (Yamamoto et al., 1995) and bladder (Arnold et al., 2006; Wei et al., 2002). In the lung, treatment with cacodylic acid induced formation of neoplasms when administered to mouse strains that are genetically susceptible to them (Hayashi et al., 1998). Other studies have used the two-stage model of carcinogenesis in which animals are exposed first to a known genotoxic agent and then to a suspected tumor-

promoting agent. With that model, cacodylic acid has been shown to act as a tumor-promoter with respect to lung cancer (Yamanaka et al., 1996).

A number of health agencies have concluded that TCDD is a human carcinogen. Studies in laboratory animals in which only TCDD has been administered have reported that TCDD can increase the incidence of a number of neoplasms, most notably of the liver, lung, thyroid, and oral mucosa (Kociba et al., 1978; NTP 2006). Some studies have used the two-stage model of carcinogenesis and shown that TCDD can act as a tumor-promoter to increase the incidence of ovarian (Davis et al., 2000), liver (Beebe et al., 1995), and skin cancers (Wyde et al., 2004). When Cheng et al. (2006) applied the concentration- and age-dependent elimination model of Aylward and colleagues (2005b) in estimating the cancer risk associated with occupational TCDD exposure in the NIOSH cohort, they found that the model predicted cumulative serum TCDD concentrations 4–5 times higher than those obtained with the first-order elimination model and an 8.7-year fixed-half-life model. As to the mechanisms by which TCDD exerts its carcinogenic effects, it is thought to act primarily as a tumor-promoter. In many of the animal studies reviewed, treatment with either TCDD has resulted in hyperplasia and/or metaplasia of epithelial tissues. In addition, in both laboratory animals and cultured cells, TCDD has been shown to exhibit a wide array of effects on growth regulation, hormone systems, and other factors associated with the regulation of cellular processes that involve growth, maturation, and differentiation. Thus, it may be that TCDD (and perhaps other compounds of interest) may increase the incidence or progression of human cancers through an interplay between multiple cellular factors. Tissue-specific protective cellular mechanisms may also affect the response to TCDD and further complicate our understanding of its carcinogenic effects.

In conclusion, the evidence indicates that a connection between TCDD and cacodylic acid and cancer in humans is, in general, biologically plausible. Experiments with 2,4-D, 2,4,5-T, and picloram in animals and cells have not provided a strong biologic basis for the presence or absence of carcinogenic effects. Considerable uncertainty remains about how to apply the available information to the evaluation of the carcinogenic potential of herbicide or TCDD exposure in Vietnam veterans.

Conclusions

The committee had four categories available to classify the strength of the evidence from the occupational, environmental, and veteran-studies reviewed regarding an association between exposure to the compounds of interest and each of the kinds of cancer studied. In categorizing diseases according to the strength of the evidence, the committee applied the same criteria (discussed in Chapter 2) that were used in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004*. To be consistent with the charge to the committee by the Secretary of Veterans Affairs in Public Law 102-4 and with accepted standards for scientific reviews, the committee distinguished among the four conclusions on the basis of statistical association, not causality.

Despite extensive consideration of all the evidence available, the committee could not reach consensus on whether breast cancer and melanoma skin cancer satisfy the criteria for inclusion in the category of limited or suggestive evidence of an association or should be retained in the category of inadequate or insufficient evidence to determine whether there is an association.

Health Outcomes with Sufficient Evidence of an Association

For outcomes in this category, a positive association with at least one of the compounds of interest must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regarded evidence from several small studies that were free of bias and confounding and that showed an association that was consistent in magnitude and direction as sufficient evidence of an association.

Previous VAO committees found sufficient evidence of an association between exposure to at least one of the compounds of interest and four kinds of cancer: soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia. The scientific literature continues to support the classification of those four cancers in the category of sufficient evidence.

Health Outcomes with Limited or Suggestive Evidence of an Association

For outcomes in this category, the evidence must suggest an association with at least one of the compounds of interest that could be limited because chance, bias, or confounding could not be ruled out with confidence. A high-quality study may have demonstrated a strong positive association amid a field of less convincing positive findings, or, more often, several studies yielded positive results, but the results of other studies were inconsistent.

Previous VAO committees found limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and laryngeal cancer; cancer of the lung, bronchus, or trachea; prostatic cancer; and multiple myeloma. The literature continues to support the classification of those diseases in the category of limited or suggestive evidence. The evidence of an association between the chemicals of interest and AL amyloidosis was found to be limited or suggestive on the basis primarily of biologic similarities to multiple myeloma.

The committee could not reach consensus on whether breast cancer and melanoma skin cancer satisfy the criteria for inclusion in the category of limited or suggestive evidence of an associationor should be retained in the category of inadequate or insufficient evidence to determine whether there is an association.

Health Outcomes with Inadequate or Insufficient Evidence to Determine Whether There Is an Association

This is the default category for any disease outcome for which there is no information upon which to base even a discussion. For many of the kinds of cancer reviewed by the committee, some scientific data were available, but they were inadequate or insufficient in terms of quality, consistency, or statistical power to support a conclusion of the presence or absence of an association. Some studies fail to control for confounding or to provide adequate exposure assessment. In addition to any specific kinds of cancer that have not been directly addressed in the present report, this category includes hepatobiliary cancer (cancer of the liver, gallbladder, and bile ducts); cancer of the buccal cavity, pharynx, and nose; bone and joint cancer, non-melanoma

skin cancer (including basal-cell carcinoma and squamous-cell carcinoma); cancer of the male and female reproductive systems (excluding prostate cancer); urinary bladder cancer; renal cancer (cancer of the kidney and renal pelvis); and the various forms of leukemia other than CLL. Some kinds of cancer (cancer of the brain, colon, rectum, stomach, and pancreas) previously deemed to have limited or suggestive evidence of *no* association have been moved to this category.

The committee could not reach consensus on whether breast cancer and melanoma skin cancer satisfy the criteria for inclusion in the category of limited or suggestive evidence of an association or should be retained in the category of inadequate or insufficient evidence to determine whether there is an association.

Health Outcomes with Limited or Suggestive Evidence of No Association

For outcomes in this category, several adequate studies covering the full known range of human exposure are consistent in *not* showing a positive association with exposure to one of the compounds of interest. The studies have relatively narrow confidence intervals. A conclusion of "*no* association" is inevitably limited to the conditions, magnitude of exposure, and length of observation of the available studies. The possibility of a very small increase in risk associated with a given exposure can never be excluded. Inclusion in this category does, however, presume evidence of lack of association between each of the compounds of interest and a particular health outcome, but there has been virtually no cancer epidemiology specifically evaluating the consequences of exposure to picloram or cacodylic acid.

Previous VAO committees found a sufficient number and variety of well-designed studies to conclude that there was limited or suggestive evidence of *no* association between the compounds of interest and a small group of cancer types: gastrointestinal tumors (of the colon, rectum, stomach, and pancreas) and brain tumors. In light of the presumption noted above and re-evaluation of previously reviewed evidence, those types of cancer have been reclassified as having inadequate or insufficient evidence to determine whether there is an association. On the basis of evaluation of the scientific literature, no additional types of cancer satisfy the criteria for inclusion in this category.

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7

Reproductive and Developmental Effects

This chapter summarizes the scientific literature published since *Veterans and Agent Orange: Update 2004*, hereafter referred to as *Update 2004* (IOM, 2005), on the association between exposure to herbicides and adverse reproductive or developmental effects. (Analogous shortened names are used to refer to the updates for 1996, 1998, 2000, and 2002 [IOM, 1996, 1999, 2001, 2003].) The categories of association and the approach to categorizing the health outcomes are discussed in Chapters 1 and 2. The literature discussed includes papers that describe environmental, occupational, and Vietnam-veteran studies that evaluate herbicide exposure and the risk of birth defects, declines in sperm quality and fertility, spontaneous abortion, stillbirth, neonatal and infant mortality, low birth weight and preterm birth, and childhood cancer. In addition to studies of herbicides and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), studies of populations exposed to polychlorinated biphenyls (PCBs) were reviewed when relevant because TCDD is sometimes a contaminant of PCBs. For new studies that report only a single reproductive health outcome and that are not revisiting a previously studied population, design information is summarized here with the results; design information on all other new studies can be found in Chapter 4.

This chapter's primary emphasis is on the potential adverse reproductive effects of herbicide exposure in men because the vast majority of Vietnam veterans are men. About 8,000 women served in Vietnam (H. Kang, US Department of Veterans Affairs, personal communication, December 14, 2000), so findings relevant to female reproductive health are also included. Studies that investigated the potential reproductive consequences of exposure of either parent were considered; whenever the information was available, an attempt was made to evaluate the effects of maternal and paternal exposure separately.

FERTILITY

Male reproductive function is under the control of several components whose proper coordination is important for normal fertility. Several of the components and some endpoints related to male fertility, including reproductive hormones and sperm characteristics, can be studied as indicators of fertility. The reproductive neuroendocrine axis involves the central nervous system, the anterior pituitary gland, and the testis. The hypothalamus integrates neural inputs from the central and peripheral nervous systems and regulates the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Both are secreted into the circulation in episodic bursts by the anterior pituitary gland and are necessary for normal spermatogenesis. In the testis, LH interacts with receptors on Leydig cells, where it stimulates increased testosterone synthesis. FSH and the testosterone from the Leydig cells interact with the

Sertoli cells in the seminiferous tubule epithelium to regulate spermatogenesis. More detailed reviews of the male reproductive hormones can be found elsewhere (Knobil et al., 1994; Yen and Jaffe, 1991). Several agents, such as lead and dibromochloropropane, affect the neuroendocrine system and spermatogenesis (for reviews, see Bonde and Giwercman, 1995; Tas et al., 1996).

Whereas many studies have investigated the relationship between chemicals and male fertility, studies among women are sparse. Some chemicals may disrupt the female hormonal balance necessary for proper functioning. Normal menstrual-cycle functioning is also important in the risk of hormonally related diseases, such as osteopenia, breast cancer, and cardiovascular disease. Chemicals can have multiple effects on the female system, including modulation of hormone concentrations, such menstrual- or ovarian-cycle irregularities as changes in menarche and menopause, and impairment of fertility (Bretveld et al., 2006a,b). In this chapter, we discuss studies that have focused on menstrual-cycle characteristics and age of menarche or age of menopause. Studies of the association between the chemicals of interest and endometriosis are reviewed in Chapter 9.

Conclusions from *VAO* and Updates

The committee responsible for *Veterans and Agent Orange*, hereafter referred to as *VAO* (IOM, 1994), concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, or cacodylic acid and altered sperm characteristics or infertility. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that finding. Reviews of the relevant studies are presented in the earlier reports. Table 7-1 summarizes the studies.

TABLE 7-1 Selected Epidemiologic Studies—Fertility (altered hormone concentrations, decreased sperm counts or quality, subfertility, or infertility)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
Farr et al., 2006	Age of menopause women who self-reported pesticide exposure	8,038	0.9 (0.8–1.0)
Farr et al., 2004	Menstrual cycle characteristics of premenopausal women in AHS aged 21-40	1,754	
	Short menstrual cycle		0.8 (0.6–1.0)
	Long menstrual cycle		1.4 (0.9–2.1)
	Irregular		0.6 (0.4–0.8)
	Missed Period		1.6 (1.3–2.0)
	Intermenstrual bleeding		1.1 (0.9–1.4)
Oh et al. 2005	Male fertility-dioxin exposure with air monitoring	31	1.4 *
Studies Reviewed in *Update 2000*			
Abell et al., 2000	Female greenhouse workers in Denmark—(maternal exposure)		
	>20 hours manual contact per week	220	0.7 (0.5–1.0)[b]
	Never used gloves	156	0.7 (0.5–1.0)[b]

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	High exposure	202	0.6 (0.5–0.9)[b]
Larsen et al., 1998	Danish farmers who used any potentially spermatotoxic pesticides, including 2,4-D		
	Farmers using pesticides vs. organic farmers	523	1.0 (0.8–1.4)[b]
	Used three or more pesticides		0.9 (0.7–1.2)[b]
	Used manual sprayer for pesticides		0.8 (0.6–1.1)[b]
Studies Reviewed in *Update 1998*			
Heacock et al., 1998	Workers at sawmills using chlorophenates		
	Standardized fertility ratio	18,016 (births)	0.7 (0.7–0.8)[c]
	Mantel-Haenszel rate ratio estimator	18,016 (births)	0.9 (0.8-0.9)[c]
	Cumulative exposure (hours)		
	120–1,999	7,139	0.8 (0.8–0.9)[c]
	2,000–3,999	4,582	0.9 (0.8–1.0)[c]
	4,000–9,999	4,145	1.0 (0.9–1.1)[c]
	≥10,000	1,300	1.1 (1.0–1.2)[c]
Lerda and Rizzi, 1991	Argentinean farmers exposed to 2,4-D	32	
	Sperm count (millions/ml)		exposed: 49.0 vs. control: 101.6
	Motility (%)		exposed: 24.8 vs. control: 70.4
	Sperm death (%)		exposed: 82.9 vs. control: 37.1[d]
	Anomalies (%)		exposed: 72.9 vs. control: 33.4 (p<0.01 overall)
ENVIRONMENTAL			
New Studies			
Eskanazi et al., 2005	Seveso cohort-serum dioxin concentrations and age of menopause	616	
	Premenopause	260	43.6 (0.2–0.9)
	Natural Menopause	169	45.8 (0.3–1.0)
	Surgical menopause	83	43.4 (0.3–1.0)
	Impending menopause	13	43.8 (0.2–0.9)
	Perimenopause	33	36.5 (0.2–0.9)
	Other	58	39.6 (0.2–0.9)
Greenlee et al., 2003	Women from Wisconsin, US ± infertility (maternal exposure)		
	Mixed or applied herbicides	21	2.3 (0.9–6.1)
	Used 2,4,5-T	9	9 cases (2.7%) 11controls (3.4%)
	Used 2,4-D	4	4 cases (1.2%) 4 controls (1.2%)
Swan et al., 2003	Men from Missouri, US ± low sperm quality		
	Elevated urinary metabolite marker for 2,4-D	5	0.8 (0.2–3.0)
Warner et al. 2004	Age of menarche at time of exposure	282	1.0 (0.8–1.1)
Studies Reviewed in *Update 2002*			
Staessen et al., 2001	Adolescents in communities close to industrial sources of heavy metals, PCBs, VOCs, and PAHs—delays in sexual maturity		

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	In Hoboken, Belgium	8	4.0 (*)
	In Wilrik, Belgium	15	1.7 (*)
VIETNAM VETERANS			
Studies Reviewed in *Update 1996*			
Henriksen et al., 1996	Effects on specific hormone levels or sperm count in Ranch Hands		
	Low testosterone		
	High dioxin (1992)	18	1.6 (0.9–2.7)
	High dioxin (1987)	3	0.7 (0.2–2.3)
	Low dioxin (1992)	10	0.9 (0.5–1.8)
	Low dioxin (1987)	10	2.3 (1.1–4..9)
	Background (1992)	9	0.5 (0.3–1.1)
	High FSH		
	High dioxin (1992)	8	1.0 (0.5–2.1)
	Low dioxin (1992)	12	1.6 (0.8–3.0)
	Background (1992)	16	1.3 (0.7–2.4)
	High LH		
	High dioxin (1992)	5	0.8 (0.3–1.9)
	Low dioxin (1992)	5	0.8 (0.5–3.3)
	Background (1992)	8	0.8 (0.4–1.8)
	Low sperm count		
	High dioxin	49	0.9 (0.7–1.2)
	Low dioxin	43	0.8 (0.6–1.0)
	Background	66	0.9 (0.7–1.2)
Studies Reviewed in *VAO*			
CDC, 1989	Vietnam Experience Study		
	Lower sperm concentration	42	2.3 (1.2–4.3)
	Proportion of abnormal sperm	51	1.6 (0.9–2.8)
	Reduced sperm motility	83	1.2 (0.8–1.8)
Stellman et al., 1988	American Legionnaires who served in Southeast Asia		
	Difficulty having children	349	1.3 ($p < .01$)

Unless otherwise indicated, studies show paternal exposure.

[a] Given when available.

[b] For this study, relative risk has been replaced with the fecundability ratio, for which a value less than 1.0 indicates an adverse effect.

[c] For this study, relative risk has been replaced with the standardized fertility ratio, for which a value less than 1.0 indicates an adverse effect.

[d] Table 1 in the reference reverses these figures—control: 82.9%; exposed: 37.1%—but the text ("The percentages of asthenospermia, mobility, necrosperma and teratospermia were greater in the exposed group than in controls…") suggests that this is a typographic error.

* Information not provided by study authors.

Update of the Epidemiologic Literature

Occupational Studies

After exclusion of women who were pregnant, were nursing, were taking oral contraceptives, had extreme body-mass indexes, or had missing values, Farr et al. (2004) reported on the menstrual-cycle characteristics of 3,103 premenopausal women in the Agricultural Health Study (AHS) who were 21–40 years old when they completed a female health and family health

questionnaire. They examined the association between pesticide mixing or applying and menstrual characteristics of short cycles, long cycles, irregular cycles, missed periods, and bleeding or spotting between periods in the preceding 12 months. Women who had never mixed or applied pesticides were considered the control group. The investigators reported a significant relationship between increased cycle length and ever mixing or applying any type of pesticide ($p = 0.02$) and increased reports of missed periods (OR = 1.6). There was a trend toward increased odds of long cycles ($p = 0.08$) and missed periods ($p < 0.001$) with increasing days of pesticide exposure. Although using hormonally active pesticides was found to be associated with increased cycle length and increased frequency of missed cycles, the pesticides with this observed association did not include any of the chemicals of interest to the present review committee. The study used self-reported information on menstrual cycle that may have been unreliable, and no hormonal confirmation of menstrual dysfunction was available. Overall, there was no indication of an association with menstrual-cycle characteristics and the specific chemicals of interest in this review.

There also has been a report from the AHS (Farr et al., 2006) concerning age at menopause in 8,038 women who were 35–55 years old at the time of enrollment. Women were classified according to their self-reported pesticide exposure. Overall, women who ever mixed or applied pesticides were found to have a higher age at menopause (hazard ratio [HR] by Cox proportional hazard analysis = 0.87, 95% CI 0.78–0.97) that translates into a delay of about 3 months. The estimate did not vary much when restricted to herbicides (HR = 0.88, 95% CI 0.74–1.05) or to phenoxy herbicides (HR = 0.85, 95% CI 0.65–1.11).

One study of male fertility outcomes has been published since the last update. Oh et al. (2005) studied a group of 31 male incinerator workers and 84 controls in Seoul, South Korea. They measured dioxin exposure with air monitoring in the facility and found that levels were 100 times higher than those reported for the general Seoul area (31.17 ng TEQ/m^3 compared with 0.32 ng TEQ/m^3). Sperm characteristics were analyzed for eight controls and six workers. No statistically significant differences were observed in the number of sperm ($p = 0.05$) or sperm mobility ($p = 0.35$). The fractions of sperm with DNA damage in waste-incineration workers and control subjects were measured at 1.40% ± 0.08% and 1.26% ± 0.03%, respectively ($p = 0.001$).

Environmental Studies

The committee reviewed two reports from the Seveso Women's Health Study (SWHS) published since the last update that focused on age at menarche and age at menopause in the Seveso population, which was exposed to high concentrations of TCDD as the result of an industrial explosion in 1976. Warner et al. (2004) examined age at menarche in 282 women who were premenarcheal at the time of the explosion. TCDD was measured in archived blood samples. Subjects had a mean age of 6.9 years at the time of the explosion. The median serum TCDD concentration was 140.3 ppt for all premenarcheal women. Serum TCDD did not vary with self-reported age at menarche in all subjects or in a group that were less than 8 years old at the time of the explosion. A major limitation of the study was that age at menarche was based on recall, and the time between onset of menarche and study interview ranged from 5 to 19 years. The finding of no association between age at menarche and exposure of young girls to TCDD may be related to the possibility that susceptibility is greater in utero than during childhood.

The committee reviewed a second SWHS paper by Eskenazi et al. (2005) on serum dioxin concentrations and age at menopause in the Seveso cohort. The study included 616 women who were premenopausal at the time of the explosion and were older than 35 years at the time of the interview. The median lipid-adjusted serum TCCD concentration was 43.7 ppt and did not vary significantly among the menopausal categories of premenstrual, natural menopause, surgical menopause, impending menopause, and perimenopause. The HRs of the serum TCDD quintiles (1.0, 1.1, 1.4, 1.6, and 1.1) suggested a trend between TCDD exposure (up to about 100 ppt) and earlier onset of natural menopause but also suggested that women with the highest serum TCDD did not have the earliest onset of menopause. Age at which the subjects of this study were exposed represents an appropriate match for the experience of female Vietnam veterans. The literature suggests, however, that ovarian follicles are most susceptible to effects in the prepubertal period.

A publication by Swan (2006) only reiterated the findings in Swan et al. (2003), which were considered in *Update 2004*.

Vietnam-Veteran Studies

No new Vietnam-veteran studies concerning exposure to the compounds of interest and fertility were published since *Update 2004*.

Biologic Plausibility

There is little evidence that 2,4-D or 2,4,5-T has substantial effects on reproductive organs or fertility. One recent study has demonstrated that 2,4,5-T competes with 17β-estradiol for binding to estrogen receptor α and can function as an antiestrogen in cell culture (Lemaire et al., 2006), suggesting 2,4,5-T may have the potential to disrupt female reproductive function.

In contrast with the lack of evidence on 2,4-D and 2,4,5-T, many diverse laboratory studies provide evidence that TCDD can affect reproductive organ function and reduce fertility in both males and females. TCDD exposure can reduce fertility in male rats and is associated with histologic changes in the testis (Chahoud et al., 1989). More recent studies of TCDD's effects on the testis have shown that it can induce significant changes in gene expression (Lai et al., 2005a, Kuroda et al., 2005; Volz et al., 2005; Yamano et al., 2005), leading to modification of steroidogenesis in particular (Lai et al., 2005b). Those changes are associated with disruption or complete inhibition of spermatogenesis (Fisher et al., 2005; Simanainen et al., 2004; Volz et al., 2005). Furthermore, the TCDD-induced reduction in spermatogenesis has been associated with reduced erectile function in one study (Moon et al., 2004) and reduced serum testosterone in another (Simanainen et al., 2004).

In females, TCDD has been shown to reduce reproductive success, and this reduction could be mediated by alterations in the ovaries, uterus, and placenta. TCDD has been shown to disrupt ovarian steroidogenesis, impair ovulation, reduce circulating progesterone and estradiol, and decrease fertility (Li et al., 2006; Petroff and Mizinga, 2003; Ushinohama et al., 2001). Recent studies demonstrate that TCDD at low concentrations suppresses gene expression essential to ovarian function and down-regulates estrogen-dependent signaling (Hombach-Klonisch et al., 2006; Miyamoto, 2004). TCDD-induced reduction in fertility in females could also be mediated

by changes in the uterus. TCDD has antiestrogenic activity on the uterus, causing impairment of uterine epithelial function (Buchanan et al., 2000) that may contribute to TCDD-induced reduction in the survival of implanted embryos early in gestation (Kitajima et al., 2004). TCDD-induced reduction in reproductive success may also be mediated by altered placental function, which can lead to fetal death. TCDD alters gene expression in the placenta, suppresses placental vascular remodeling, and induces placental hypoxia (Ishimura et al., 2002, 2006; Mizutani et al., 2004).

The biologic plausibility of reproductive effects in general arising from exposure to the chemicals of interest is discussed at the end of this chapter.

Synthesis

Although there is much evidence of the biologic plausibility of disruption of male and female fertility by exposure to the chemicals of interest, there continues to be a lack of substantive epidemiologic data that demonstrate any association in human populations.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous Veterans and Agent Orange (VAO) reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and altered hormone concentrations, menstrual-cycle abnormalities, decreased sperm counts or sperm quality, subfertility, or infertility.

SPONTANEOUS ABORTION

Spontaneous abortion is the expulsion of a nonviable fetus, generally before 20 weeks of gestation, that is not induced by physical or pharmacologic means. The background risk of recognized spontaneous abortion is generally 7–15% (Hertz-Picciotto and Samuels, 1988), but it is established that many more pregnancies terminate before women become aware of them (Wilcox et al., 1988)—these terminations are known as subclinical pregnancy losses and generally are not included in studies of spontaneous abortion. Estimates of the risk of recognized spontaneous abortion vary with the design and method of analysis. Study designs include cohorts of women asked retrospectively about pregnancy history, cohorts of pregnant women (usually those receiving prenatal care), and cohorts of women who are monitored for future pregnancies. Retrospective reports can be limited by memory loss, particularly of spontaneous abortions that took place a long time before. Studies that enroll women who appear for prenatal care require the use of life tables and specialized statistical techniques to account for differences in the times at which women seek medical care during pregnancy. Enrollment of women before pregnancy provides the theoretically most valid estimate of risk, but it can attract non-representative study groups because protocols are demanding.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and spontaneous abortion. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, and *Update 2000* did not change that conclusion. Information available to the committee responsible for *Update 2002*, however, led to the conclusion that there was suggestive evidence that paternal exposure to TCDD is *not* associated with the risk of spontaneous abortion, but that there was insufficient information to determine whether an association exists between maternal exposure to TCDD and the risk of spontaneous abortion or between maternal or paternal exposure to 2,4-D, 2,4,5-T, picloram, or cacodylic acid and the risk of spontaneous abortion. The additional information reviewed by the committee responsible for *Update 2004* did not change this conclusion. The relevant studies are reviewed in the earlier reports. Table 7-2 summarizes them.

TABLE 7-2 Selected Epidemiologic Studies—Spontaneous Abortion

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
Studies Reviewed in *Update 2002*			
Schnorr et al., 2001	Wives and partners of men in the NIOSH cohort		
	Estimated paternal TCDD serum level at the time of conception		
	<20 ppt	29	0.8 (0.5–1.2)
	20 to <255 ppt	11	0.8 (0.4–1.6)
	255 to <1120	11	0.7 (0.3–1.6)
	≥ 1120 ppt	8	1.0 (0.4–2.2)
Studies Reviewed in *Update 2000*			
Driscoll, 1998	Women employed by the US Forest Service—miscarriages (maternal exposure)	141	2.0 (1.1–3.5)
Studies Reviewed in *VAO*			
Moses et al., 1984	Follow-up of 2,4,5-T production workers	14	0.9 (0.4–1.8)
Suskind and Hertzberg, 1984	Follow-up of 2,4,5-T production workers	69	0.9 (0.6–1.2)
Smith et al., 1982	Follow-up of 2,4,5-T sprayers vs non-sprayers	43	0.9 (0.6–1.3)**
Townsend et al., 1982	Wives of men employed involved in chlorophenol processing at Dow Chemical Co.	85	1.0 (0.8–1.4)
Carmelli et al., 1981	Wives of men occupationally exposed to 2,4-D		
	All reported work exposure to herbicides (high and medium)	63	0.8 (0.6–1.1)**
	Farm exposure	32	0.7 (0.4–1.5)
	Forest and commercial exposure	31	0.9 (0.6–1.4)
	Exposure during conception period		
	Farm exposure	15	1.0 (0.5–1.8)
	Forest and commercial exposure	16	1.6 (0.9–1.8)
	All exposures, father aged 18–25 years		
	Forest and commercial exposure	8	3.1 (1.2–7.8)
	Exposure during conception period		
	Father aged 31–35 years, farm exposure	10	2.9 (0.8–10.9)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
ENVIRONMENTAL			
New Studies			
Eskenazi et al., 2003	Seveso (Italy) Women's Health Study participants living in exposure Zones A and B in 1976 (maternal exposure)		
	Pregnancies 1976–1998	97	0.8 (0.6–1.2)
	Pregnancies 1976–1984	44	1.0 (0.6–1.6)
Studies Reviewed in *Update 2002*			
Arbuckle et al., 2001	Ontario farm families (maternal and paternal exposure)		
	Phenoxyacetic acid herbicide exposure in the preconception period & spontaneous abortion risk	48	1.5 (1.1–2.1)
Revich et al., 2001	Residents of the Samara Region, Russia (maternal and paternal exposure)		
	Chapaevsk		24.4% (20.0–29.5%)[b]
	Samara	*	15.2% (14.3–16.1%)[b]
	Toliatti	*	10.6% (9.8–11.5%)[b]
	Syzran	*	15.6% (13.4–18.1%)[b]
	Novokuibyshevsk	*	16.9% (14.0–20.3%)[b]
	Other small towns	*	11.3% (9.4–13.8%)[b]
Tuyet and Johansson, 2001	Vietnamese women who were or whose husbands were exposed to herbicides sprayed during the Vietnam war	*	(*) [anecdotal reports of miscarriage in pilot study]
Studies Reviewed in *Update 2000*			
Axmon et al., 2000	Wives of Swedish fishermen		
	Before gestation week 12		0.5 (0.3–1.0)
	East coast residents	12	
	West coast residents	54	
Petrelli et al., 2000	Wives of pesticide appliers	26	3.8 (1.2–12.0)
VIETNAM VETERANS			
Studies Reviewed in *Update 2002*			
Kang et al., 2000	Female Vietnam-era veterans (maternal exposure)		1.0 (0.82–1.21)
	Vietnam veterans (1,665 pregnancies)	278	(*)
	Vietnam-era veterans who did not serve in Vietnam (1,912 pregnancies)	317	(*)
Studies Reviewed in *Update 2000*			
Schwartz, 1998	Female Vietnam veterans (maternal exposure)		
	Women who served in Vietnam	113	(*)
	Women who did not Serve in the war zone	124	(*)
	Civilian Women	86	(*)
Studies Reviewed in *Update 1996*			
Wolfe et al., 1995	Air Force Ranch Hand veterans	157	
	Background	57	1.1 (0.8–1.5)
	Low level exposure	56	1.3 (1.0–1.7)
	High level exposure	44	1.0 (0.7–1.3)
Studies Reviewed in *VAO*			
Aschengrau and Monson, 1989	Wives of Vietnam veterans presenting at Boston Hospital for Women		
	27 weeks gestation	10	0.9 (0.4–1.9)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	13 weeks gestation	*	1.2 (0.6–2.8)
CDC, 1989	Vietnam Experience Study		
	Overall	1,566	1.3 (1.2–1.4)
	Self-reported low exposure	489	1.2 (1.0–1.4)
	Self-reported medium exposure	406	1.4 (1.2–1.6)
	Self-reported high exposure	113	1.7 (1.3–2.1)
Field and Kerr, 1988	Follow-up of Australian Vietnam veterans	199	1.6 (1.3–2.0)
Stellman et al., 1988	American Legionnaires with service 1961–1975		
	Vietnam-era veterans vs. Vietnam veterans		
	All Vietnam veterans	231	1.4 (1.1–1.6)
	Low exposure	72	1.3 (1.0–1.7)
	Medium exposure	53	1.5 (1.1–2.1)
	High exposure	58	1.7 (1.2–2.4)
	Vietnam-era veterans vs. Herbicide handlers	9	1.6 (0.7–3.3)
	Vietnam veterans with medium or high exposure vs. Vietnam veterans with low exposure		
	Medium exposure	53	1.2 (0.8–1.7)
	High exposure	58	1.4 (0.9–1.9)

Unless otherwise indicated, studies show paternal exposure.
[a] Given when available.
[b] Spontaneous abortion rate per 100 full-term pregnancies for the years 1991–1997.
* Information not provided by study authors.
**90% Confidence Interval

ABBREVIATIONS: CDC, Centers for Disease Control and Prevention; CI, confidence interval; NIOSH, National Institute for Occupational Safety and Health.

Update of the Epidemiologic Literature

Environmental Studies

Tango et al. (2004) studied the distribution of several birth outcomes around Japanese municipal-waste incinerators with elevated dioxin emissions. They found fetal death after the 12th week of gestation (with or without congenital malformations) was not associated with the distance the mother lived from an incinerator at the time of birth or whether her residence was in the area known to have the highest dioxin soil concentrations.

No new occupational or Vietnam-veteran studies concerning exposure to the compounds of interest and spontaneous abortion were published since *Update 2004*.

Biologic Plausibility

Laboratory animal studies demonstrate that TCDD exposure during pregnancy can alter circulating steroid hormone concentrations (Simanainen et al., 2004) and disrupt placental development and function (Ishimura et al., 2006; Mizutani et al., 2004) and thus contribute to a reduction in survival of implanted embryos and to fetal death (Kitajima et al., 2004). However, the reproductive significance of those effects and the risk of recognized pregnancy loss before 20

weeks of gestation in humans are not clear. There is no evidence of a relationship between paternal or maternal exposure to TCDD and spontaneous abortion. Exposure to 2,4-D or 2,4,5-T causes fetal toxicity and death after maternal exposure in experimental animals. However, that effect occurs only at high doses and in the presence of maternal toxicity. No fetal toxicity or death has been reported to occur after paternal exposure to 2,4-D.

The biologic plausibility of reproductive effects in general arising from exposure to the chemicals of interest is discussed at the end of this chapter.

Synthesis

No additional information was available to the committee responsible for *Update 2006* to motivate changing the assessment of the last two committees. Given the age of the Vietnam-veteran cohort, it is highly unlikely that additional information on this outcome among the population will appear.

Conclusions

The present committee concurs with the overall conclusion of the previous committees that paternal exposure to TCDD is *not* associated with risk of spontaneous abortion and that insufficient information is available to determine whether an association exists between the risk of spontaneous abortion and maternal exposure to TCDD or either maternal or paternal exposure to 2,4-D, 2,4,5-T, picloram, or cacodylic acid.

STILLBIRTH, NEONATAL DEATH, AND INFANT DEATH

Stillbirth or *late fetal death* typically refers to the delivery at or after 20 weeks of gestation of a fetus that shows no signs of life, including fetuses that weigh more than 500 g regardless of gestational age (Kline et al., 1989). *Neonatal death* refers to the death of a liveborn infant within 28 days of birth, while *infant death* includes deaths occurring before the first birthday.

Because the causes of stillbirth and early neonatal death overlap considerably, they are commonly analyzed together in a category referred to as *perinatal mortality* (Kallen, 1988). Stillbirths make up less than 1% of all births (CDC, 2000). The most common causes of perinatal mortality (Kallen, 1988) among low-birth weight (500-g to 2,500-g) liveborn and stillborn infants are placental and delivery complications—abruptio placenta, placenta previa, malpresentation, and umbilical-cord complications. Among infants weighing more than 2,500 g at birth, the most common causes of perinatal death are complications of the cord, placenta, and membranes and congenital malformations (Kallen, 1988).

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid

and stillbirth, neonatal death, or infant death. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Reviews of the relevant studies are presented in the earlier reports.

Update of the Epidemiologic Literature

The only relevant study published since the last update was a large study of multiple pregnancy outcomes in Japan (Tango et al., 2004). The study found no associations between proximity of the mother's residence at the time of birth (defined in terms of 1-km bands around the incinerators) and rates infant deaths (<1 yr, <1 mo, <1 wk with and without congenital malformations). Analyses were conducted for a "peak-decline" relationship with "peak" dioxin soil concentrations (known to occur about 2 km from an incinerator); only death within the first year of life, overall ($p = 0.023$) or with congenital malformations ($p = 0.047$), showed a significant results. This study had several methodologic weaknesses, including the lack of individual-level information on other risk factors and of individual exposure data. In addition, the birth-outcome effects might be associated with socioeconomic differences in residents in the different zones.

No new occupational or Vietnam-veteran studies concerning exposure to the compounds of interest and stillbirth, neonatal death, or infant death were published since *Update 2004*.

Biologic Plausibility

Laboratory studies of maternal TCDD exposure during pregnancy have demonstrated the induction of fetal death; neonatal death, however, is only rarely observed and is usually the result of cleft palate leading to an inability to nurse. Studies addressing the potential for perinatal death as a result of paternal exposure to TCDD or herbicides are too limited to support conclusions.

The biologic plausibility of reproductive effects in general arising from exposure to the chemicals of interest is discussed at the end of this chapter.

Synthesis

The study reviewed for this update did not find significant associations between the relevant exposures and rates of infant or fetal deaths. The study was limited in that exposure was based on environmental concentrations of dioxin and individual exposure data were not obtained. Furthermore, several risk factors that could confound associations between exposure and outcome were not assessed.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and stillbirth, neonatal death, or infant death.

BIRTH WEIGHT AND PRETERM DELIVERY

The World Health Organization recommends 2,500 g as the threshold for designation of low birth weight (Alberman, 1984). Low infant weight at birth is among the important predictors of neonatal death and morbidity in the United States. The concept of low birth weight actually encompasses two causal pathways, often treated as a single entity: low birth weight secondary to intrauterine growth retardation (IUGR), in which case a fetus or baby is referred to as small for gestational age, and low birth weight secondary to preterm delivery (PTD), which can have other long-term consequences. The concept of IUGR represents birth weight adjusted for gestational age. The current definition of PTD is delivery at less than 259 days, or 37 completed weeks, of gestation, calculated on the basis of the date of the first day of the last menstrual period (Bryce, 1991). About 7% of live births are low birth weight. The incidence of IUGR is much more difficult to quantify because there are no standards for distributing birth weight by gestational age. When no distinction is made between the causes of low birth weight (IUGR or PTD), the factors most strongly associated with it are maternal tobacco use during pregnancy, multiple births, and race or ethnicity. Other potential risk factors are socioeconomic status (SES), maternal weight, birth order, maternal complications during pregnancy (such as severe pre-eclampsia) and obstetric history, job stress, and cocaine or caffeine use during pregnancy (Kallen, 1988). Established risk factors for PTD include race (black), marital status (single), low SES, previous low birth weight or PTD, multiple gestations, tobacco use, and cervical, uterine, or placental abnormalities (Berkowitz and Papiernik, 1993).

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence of an association between exposure to the compounds of interest and low birth weight or preterm delivery. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Reviews of the relevant studies are presented in the earlier reports.

Update of the Epidemiologic Literature

Update 2000, *Update 2002*, and *Update 2004* discussed change in the sex-ratio at birth from the usual ratio of male-to-female newborns, which is approximately as a possible adverse reproductive outcome. If the herbicides used in Vietnam did alter this endpoint in humans, it would not represent an outcome for which an individual veteran could be compensated. Such an alteration would, however, be indicative of some impact on reproductive function, as mentioned in the section on biologic plausibility at the end of this chapter. Of the new articles reporting reproductive effects, two environmental studies that presented findings on birth weight and gestational age also assessed possible changes in the sex-ratio at birth; their findings for this additional endpoint are included below.

Occupational Studies

Lawson et al. (2004) conducted a follow-on study of PTD and birth weight among the children of men in the National Institute for Occupational Safety and Health (NIOSH) cohort in comparison to age- and race-matched neighborhood referents. The analysis of birth weight considered 1,117 singleton, full-term births (at least 37 weeks gestation) to 217 referent wives (604 referent births) and 176 worker wives (513 births; 221 pre-exposure and 292 exposed). The suggestion of an increase in birth weight with high TCDD concentrations vanished when adjustment was made for mother's education, parity, smoking during pregnancy, length of gestation, and the infant's sex. In order to consider the possibility that the mothers might have experienced direct exposure from materials carried home by the fathers when they were engaged in their NIOSH employment during a pregnancy, another analysis was restricted to such pregnancies for the cohort members and pregnancies occurring while the NIOSH plants were in operation for the referents, or 334 referent births and 98 exposed births. In this case, the adjusted analysis found a statistically significant increase of 31 g in birth weight with each log increase in TCDD concentration ($p = 0.03$).

Lawson et al. (2004) also conducted an analysis of preterm births based on a total of 1,153 births: 618 referent, 238 pre-exposed, and 297 during-exposure. With or without adjustment for age of mother and for the occurrence of an accident, smoking, or medication use during pregnancy, no increase in risk of prematurity was observed (OR = 0.8, 95% CI 0.6–1.1).

Environmental Studies

Another study of the effect of dioxins on reproductive outcomes was conducted in an area surrounding a municipal waste incinerator located 10 km from Taipei that began operating in 1992 (Lin et al., 2006). The incinerator's average emission concentration of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) for 1997 (6.47 ng TEQ/m^3) was used as the input for a dispersion model (EPA's Industrial Source Complex Model—Short Term Model), which was used to estimate annual averages for each administrative district of Taipei. A cut point of 0.03 pg TEQ/m^3, between the background concentrations for rural (0.02 pg TEQ/m^3) and urban air (0.05 pg TEQ/m^3), was selected. The dispersion model predicted concentrations greater than 0.03 pg TEQ/m^3 for 40 districts; those were retained as the "exposed" districts, which were further subdivided at 0.05 pg TEQ/m^3. Among the districts with predicted concentrations of zero, 40 "reference" districts were randomly selected; those were all in non-industrial areas at least 12 km from the incinerator.

From Taiwan's birth registry, Lin et al. (2006) assembled newborn gender, birth order, gestational age, and birth weight, plus maternal age, address, and educational level, for all singleton live births in the study districts for 1991 and 1997. After excluding those with birth weights less than 500 g, with gestational ages less than 20 weeks, or born to unwed women, 6,697 and 6,282 infants born in 1991 and 1997, respectively, were available for analysis.

Analyses were adjusted for maternal age and education, sex of newborn, and birth order; information on other potential confounders (such as maternal smoking) was not available. Categorical comparisons of the predicted high and low exposed districts with the reference districts found no associations for low birth weight (under 2,500 g), PTD (less than 37 weeks of gestation), or sex ratio for 1991 (as might have been expected before exposure began) nor for

1997 (after the incinerator had been in operation for 5 years). Regression on the continuous variables determined the difference between the exposed and reference districts in 1991 and in 1997 for mean birth weight or mean gestational age. In 1997, the adjusted decrease in birth weight of 5.87 g for the exposed districts was non-significant, but the relative reduction in gestational age of 0.09 week was significant ($p < 0.05$). (For 1991, both these endpoints had non-significantly higher values in the "not yet" exposed districts than in the reference districts; therefore, a comprehensive before-and-after analysis might have revealed stronger effects in the districts that ultimately were exposed.) In light of no suggestion of an increased risk of PTD, the small reported reduction in gestational age is of questionable biological significance.

The study's large size gave it considerable sensitivity. On the whole it used appropriate methods, but apparently an analysis was not conducted to make full use of the 1991 data as self-control information to determined the relative changes between the exposed and reference districts from 1991 to 1997. The exposure assessment is only as reliable as the estimates generated by EPA's dispersion model for the districts of Taipei, so exposure misclassification could have contributed to biasing the generally negative results toward the null.

In their study of birth outcomes for mothers living within about 10 km of Japanese municipal-waste incinerators emitting high concentrations of dioxin, Tango et al. (2004) found no relationship between proximity of the mother's residence to the incinerator for low or extremely low (under 1,500 g) birth weight. Analyses for association with peak dioxin concentrations in soil (known to occur about 2 km from the incinerators) were also negative. The sex ratio at birth, evaluated in terms of deviation in the proportion of female live births from the national proportion, was also found not to be related to the distance of the maternal residence from an incinerator.

Vietnam-Veteran Studies

No new Vietnam veteran studies concerning exposure to the compounds of interest and birth weight or preterm delivery were published since *Update 2004*.

Biologic Plausibility

Laboratory studies of the potential male-mediated developmental toxicity of TCDD and herbicides as a result of exposure of adult male animals are too limited to permit conclusions. TCDD and herbicides are known to cross the placenta leading to direct exposure of the fetus. Data from studies in experimental animals also suggest that the pre-implantation embryo and developing fetus are sensitive to the toxic effects of 2,4-D and TCDD after maternal exposure. However, the significance of those animal effects for humans is not clear.

The biologic plausibility of reproductive effects in general arising from exposure to the chemicals of interest is discussed at the end of this chapter.

Synthesis

The three studies reviewed here (two environmental and one based on an occupational cohort) did not find an association between exposure to the compounds of interest and the risk of

low birth weight or prematurity. The two new weakly significant findings may simply be spurious results arising among many comparisons; a modest increase in average birth weight would not be construed as an adverse effect, and the small decrease in average gestation is of questionable biologic importance. Although the results overall suggest a lack of an association, they should be interpreted with caution because of some methodologic limitations, such as a long recall period in the cohort study and exposure misclassification in the environmental studies.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and low birth weight or preterm delivery.

BIRTH DEFECTS

The March of Dimes defines a birth defect as "an abnormality of structure, function or metabolism, whether genetically determined or as the result of an environmental influence during embryonic or fetal life" (Bloom, 1981). Other terms, often used interchangeably, are *congenital anomaly* and *congenital malformation.* Major birth defects, which occur in 2–3% of live births, are abnormalities that are present at birth and are severe enough to interfere with viability or physical well-being. Birth defects are detected in another 5% of babies through the first year of life. The causes of most birth defects are unknown. Genetic factors, exposure to some medications, exposure to environmental contaminants, occupational exposures, and lifestyle factors have been implicated in the etiology of birth defects (Kalter and Warkany, 1983). Most etiologic research has focused on the effects of maternal and fetal exposures, but some work has addressed paternal exposures. Paternally mediated exposures might occur by several routes and exert effects in various ways. One way is through direct genetic damage to the male germ cell transmitted to the offspring and dominantly expressed as a birth defect. A hypothesized route is the transfer of toxic compounds through a man's body into his seminal fluid, resulting in intermittent fetal exposures throughout gestation (Chia and Shi, 2002). Another, even more indirect route of paternally mediated exposure could be contact of family members with contamination brought into the home from the workplace, but this would not be applicable to offspring of Vietnam veterans conceived during the post-deployment period.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* determined that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T or its contaminant TCDD, picloram, or cacodylic acid and birth defects among offspring. Additional information available to the committee responsible for *Update 1996* led it to conclude that there was limited or suggestive evidence of an association between at least one of the compounds of interest and spina bifida in the children of veterans; there was no change in the conclusions regarding other birth defects. The committee for *Update 2002*, which reviewed the study of female Vietnam veterans (Kang et al.,

2000) reporting significant increases in the occurrence of birth defects among their offspring, did not find those results adequate to modify prior conclusions. Later VAO committees have not encountered additional data to merit changing the conclusion that the evidence is inadequate to support an association between exposure to the chemicals of interest and birth defects (aside from spina bifida) among the offspring of either male or female veterans.

Summaries of the results from studies of birth defects and specifically neural-tube defects that were reviewed here and in earlier reports can be found in the Tables 7-3 and 7-4, respectively.

TABLE 7-3 Selected Epidemiologic Studies—Birth Defects in the Offspring of Subjects

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
Lawson et al., 2004	Wives of workers with serum TCDD levels in NIOSH cohort	14	* (*)
Studies Reviewed in *Update 1998*			
Kristensen et al., 1997	Norwegian farmers (maternal & paternal exposure)	4,189	1.0 (1.0–1.1)[b]
Dimich-Ward et al., 1996	Sawmill workers		
	Cataracts	11[c]	5.7 (1.4–22.6)
	Genital organs	105[c]	1.3 (0.9–1.5)
Garry et al., 1996	Private pesticide appliers		
	Circulatory–respiratory	17	1.7 (1.0–2.8)
	Gastrointestinal	6	1.7 (0.8–3.8)
	Urogenital	20	1.7 (1.1–2.6)
	Musculoskeletal–integumental	30	
	Maternal age < 30	11	0.9 (0.5–1.7)
	Maternal age > 30	19	2.5 (1.6–4.0)
	Chromosomal	8	1.1 (0.5–2.1)
	Other	48	
	Maternal age < 35	36	1.1 (0.8–1.6)
	Maternal age > 35	12	3.0 (1.6–5.3)
	All births with anomalies	125	1.4 (1.2–1.7)
Studies Reviewed in *VAO*			
Moses et al., 1984	Follow-up of 2,4,5-T male production workers	11	1.3 (0.5–3.4)
Suskind and Hertzberg, 1984	Follow-up of 2,4,5-T male production workers	18	1.1 (0.5–2.2)
Smith et al., 1982	Follow-up of 2,4,5-T sprayers—sprayers vs. non-sprayers	13	1.2 (0.6–2.5)[e]
Townsend et al., 1982	Follow-up of Dow Chemical plant workers	30	0.9 (0.5–1.4)
ENVIRONMENTAL			
New Studies			
Cordier et al. 2004	Residents of the Rhône-Alpes region of France living near municipal solid waste incinerators (maternal and paternal exposure)		
	Minor anomalies	518	0.9 (0.8–1.1)
	Chromosomal anomalies	204	1.0 (0.9–1.2)
	Monogenic anomalies	83	1.1 (0.8-1.4)
	Unknown or multifactoral etiology	964	1.1 (1.0–1.2)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Schreinemachers, 2003	Rural or farm residents of Minnesota, Montana, North and South Dakota (maternal and paternal exposure)		
	Any birth anomaly	213	1.1 (0.9–1.3)
	Central nervous system anomalies	12	0.8 (0.5–1.4)
	Circulatory or respiratory anomalies	39	1.7 (1.1–2.6)
	Digestive system anomalies	24	0.9 (0.6–1.5)
	Urogenital anomalies	44	1.0 (0.7–1.5)
	Musculoskeletal or integumental anomalies	70	1.5 (1.1–2.1)
	Chromosomal anomalies	17	0.9 (0.6–1.6)
Tango, 2004	Investigated multiple pregnancy outcomes in Japan-infant deaths from congenital defects	42	(*) NS
Studies Reviewed in *Update 2002*			
Loffredo et al., 2001	Mothers in the Baltimore-Washington Infant Study exposed to herbicides during the first trimester (maternal exposure)	8	2.8 (1.2–6.9)
Revich et al., 2001	Residents of Chapaevsk, Russia—congenital malformations	*	(*) NS
ten Tusscher et al., 2000	Infants born in Zeeburg, Amsterdam clinics 1963–1965 with orofacial cleft (maternal exposure)		
	Births in 1963	5	(*) SS
	Births in 1964	7	(*) SS
Studies Reviewed in *Update 2000*			
García et al., 1998	Residents of agricultural areas in Spain—≥median score on chlorophenoxy herbicides exposure duration (months) index	14	3.1(0.6–16.9)
Studies Reviewed in *VAO*			
Fitzgerald et al., 1989	Persons exposed to an electrical transformer fire—total birth defects (maternal or paternal exposure)	1	2.1 (0.05–11.85)
Mastroiacovo et al., 1988	Seveso residents (maternal, paternal, and in utero exposure)		
	Zones A and B total defects	27	1.2 (0.9–1.6)[e]
	Zones A, B, R total defects	137	1.0 (0.8–1.1)[e]
	Zones A and B mild defects	14	1.4 (0.9–2.2)[e]
Stockbauer et al., 1988	Persons in Missouri with documented TCDD soil contamination near residence (maternal; paternal; in utero exposure)		
	Total birth defects	17	0.8 (0.4–1.5)
	Major defects	15	0.8 (0.4–1.7)
	Midline defects	4	0.7 (0.2–2.3)
Hanify et al., 1981	Residents of areas of Northland New Zealand subject to aerial 2,4,5-T spraying[d]		
	All birth malformations	164	1.7 (1.4–2.1)[e]
	All heart malformations	20	3.9 (2.1–7.4)[e]
	Hypospadias, epispadias	18	5.6 (2.7–11.7)[e]
	Talipes	52	1.7 (1.2–2.3)[e]
	Cleft lip	6	0.6 (0.3–1.3)[e]
	Isolated cleft palate	7	1.4 (0.6–3.2)[e]

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
VIETNAM VETERANS			
Studies Reviewed in *Update 2002*			
Kang et al., 2000	Female Vietnam-era veterans – deployed vs non-deployed (maternal exposure)		
	"Likely" birth defects	*	1.7 (1.2–2.2)
	"Moderate-to-severe" birth defects	*	1.5 (1.1–2.0)
Studies Reviewed in *Update 2000*			
AIHW, 1999	Australian Vietnam veterans—Validation Study		
	Down syndrome	67	92 expected (73–111)
	Tracheo-oesophageal fistula	10	23 expected (14–32)
	Anencephaly	13	16 expected (8–24)
	Cleft lip or palate	94	64 expected (48–80)
	Absent external body part	22	34 expected (23–45)
	Extra body part	74	74 expected (*)
Michalek et al., 1998a	Air Force Ranch Hand veterans		
	before service in Southeast Asia	*	0.7 (*)
	after service in Southeast Asia	*	1.5 (*)
Studies Reviewed in *Update 1996*			
Wolfe et al., 1995	High exposure Ranch Hands relative to comparisons		
	All anomalies	57	1.0 (0.8–1.3)
	Nervous system	3	(*)
	Eye	3	1.6 (0.4–6.0)
	Ear, face, and neck	5	1.7 (0.6–4.7)
	Circulatory system and heart	4	0.9 (0.3–2.7)
	Respiratory system	2	(*)
	Digestive system	5	0.8 (0.3–2.0)
	Genital system	6	1.2 (0.5–3.0)
	Urinary system	7	2.1 (0.8–5.4)
	Musculoskeletal	31	0.9 (0.6–1.2)
	Skin	3	0.5 (0.2–1.7)
	Chromosomal anomalies	1	(*)
Studies Reviewed in *VAO*			
AFHS, 1992	Air Force Operation Ranch Hand veterans—birth defects in conceptions following service in Southeast Asia		
	Congenital anomalies	229	1.3 (1.1–1.6)
	Nervous system	5	1.9 (0.5–7.2)
	Respiratory system	5	2.6 (0.6–10.7)
	Circulatory system or heart	19	1.4 (0.7–2.6)
	Urinary system	21	2.5 (1.3–5.0)
	Chromosomal	6	1.8 (0.6–6.1)
	Other	5	2.6 (0.6–10.7)
Aschengrau and Monson, 1990	Vietnam veterans whose children were born at Boston Hospital for Women		
	All congenital anomalies (crude OR)		
	Vietnam veterans vs. to men without known military service	55	1.3 (0.9–1.9)
	Vietnam veterans vs. to non-Vietnam veterans	55	1.2 (0.8–1.9)
	One or more major malformations (crude OR)		
	Vietnam veterans vs. men without known	18	1.8 (1.0–3.1)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	military service		
	Vietnam veterans vs. non-Vietnam veterans	18	1.3 (0.7–2.4)
CDC, 1989	Vietnam Experience Study—interview data		
	Total anomalies	826	1.3 (1.2–1.4)
	Nervous system defects	33	2.3 (1.2–4.5)
	Ear, face, neck defects	37	1.6 (0.9–2.8)
	Integument	41	2.2 (1.2–4.0)
	Musculoskeletal defects	426	1.2 (1.1–1.5)
	Hydrocephalus	11	5.1 (1.1–23.1)
	Spina bifida	9	1.7 (0.6–5.0)
	Hypospadias	10	3.1 (0.9–11.3)
	Multiple defects	71	1.6 (1.1–2.5)
	Children of veterans reporting high exposure	46	1.7 (1.2–2.4)
CDC, 1989	General Birth Defects Study—hospital records		
	Birth defects	130	1.0 (0.8–1.3)
	Major birth defects	51	1.2 (0.8–1.9)
	Digestive system defects	18	2.0 (0.9–4.6)
	Birth defects—black Vietnam veterans only	21	3.4 (1.5–7.6)
Donovan et al., 1984	Australian Vietnam veterans		
	Vietnam veterans vs all other men	127	1.02 (0.8–1.3)
	National Service veterans—Vietnam service vs no Vietnam service	69	1.3 (0.9–2.0)
Erikson et al., 1984a	Vietnam veterans identified through the CDC Metropolitan Atlanta Congenital Defects Program		
	Any major birth defects	428	1.0 (0.8–1.1)
	Multiple birth defects with reported exposure	25	1.1 (0.7–1.7)
	EOI-5: spina bifida	1	2.7 (1.2–6.2)
	EOI-5: cleft lip with or without cleft palate	5	2.2 (1.0–4.9)

Unless otherwise indicated, studies show paternal exposure.

[a] Given when available.

[b] 95% confidence intervals contained one for all outcomes. Anencephaly and spina bifida included in this calculation.

[c] Number of workers with maximal index of exposure (upper three quartiles) for any job held up to three months prior to conception.

[d] Excludes stillbirths, neonatal death, or dislocated or dislocatable hip.

[e] 90% confidence interval

* Information not provided by study authors.

ABBREVIATIONS: AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDC, Centers for Disease Control and Prevention; CI, confidence interval; EOI, exposure opportunity index; NS, not significant; SIR, standardized incidence ratio; SS, statistically significant.

TABLE 7-4 Selected Epidemiologic Studies—Neural Tube Defects in the Offspring of Subjects

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
Studies reviewed in *Update 1998*			
Blatter et al., 1997	Dutch farmers		
	Spina Bifida—Moderate/Heavy Exposure		
	Pesticide use	8	1.7 (0.7–4.0)
	Herbicide use	7	1.6 (0.6–4.0)[g]
Kristensen et al., 1997	Norwegian farmers—spina bifida (maternal and paternal exposure)		
	Tractor spraying equipment	28	1.6 (0.9–2.7)
	Tractor spraying equipment and orchards or greenhouses	5	2.8 (1.1–7.1)
Dimich-Ward et al., 1996	Sawmill workers		
	Spina bifida or anencephaly	22[b]	2.4 (1.1–5.3)
	Spina bifida only	18[b]	1.8 (0.8–4.1)
Garry et al., 1996	Private pesticide appliers—central nervous system defects	6	1.1 (0.5–2.4)
ENVIRONMENTAL[c]			
New Studies			
Cordier et al. 2004	Residents of the Rhône-Alpes region of France (maternal and paternal exposure)	49	0.9 (0.6–1.2)
Studies Reviewed in *VAO*			
Stockbauer et al., 1988	Persons in Missouri with documented TCDD soil contamination—central nervous system defects (maternal; paternal; in utero exposure)	3	3.0 (0.3–35.9)
Hanify et al., 1981	Spraying of 2,4,5-T in New Zealand (all exposures)		
	Anencephaly	10	1.4 (0.7–2.9)[d]
	Spina bifida	13	1.1 (0.6–2.1)[d]
VIETNAM VETERANS			
Studies Reviewed in *Update 2000*			
AIHW, 1999	Australian Vietnam veterans—Validation Study		
	Spina bifida—maxima	50	33 expected (22–44)
	Anencephaly	13	16 expected (8–24)
Studies Reviewed in *Update 1996*			
Wolfe et al., 1995	Air Force Operation Ranch Hand personnel—neural tube defects[e]	4	(*)
Studies Reviewed in *VAO*			
CDC, 1989	Vietnam Experience Study		
	Spina bifida		
	Vietnam veterans' children	9	1.7 (0.6–5.0)
	Non-Vietnam veterans' children	5	(*)
	Anencephaly		
	Vietnam Veterans' children	3	(*)
	Non-Vietnam veterans' children	0	(*)
Erickson et al., 1984a,b	Birth Defects Study - Vietnam veterans		
	Spina Bifida	19	1.1 (0.6–1.7)
	Anencephaly	12	0.9 (0.5–1.7)
	EOI-5: spina bifida	20[f]	2.7 (1.2–6.2)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	EOI-5: anencephaly	7[f]	0.7 (0.2–2.8)
ADVA, 1983	Australian Vietnam veterans—neural tube defects		
		16	0.9

Unless otherwise indicated, studies show paternal exposure.
[a] Given when available.
[b] Number of workers with maximal index of exposure (upper three quartiles) for any job held up to 3 months prior to conception.
[c] Either or both parents potentially exposed.
[d] 90% confidence interval
[e] Of the four neural tube defects reported among Ranch Hand offspring there were two spina bifida (high dioxin level), one spina bifida (low dioxin), and one anencephaly (low dioxin). No neural tube defects were reported in the comparison cohort. 454 post-service births were studied in Ranch Hand veterans; 570 in comparison cohort.
[f] Number of Vietnam veterans fathering a child with a neural tube defect given any exposure opportunity index.
[g] Calculated from data presented in the paper
* Information not provided by study authors.

ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AIHW, Australian Institute of Health and Welfare; CDC, Centers for Disease Control and Prevention; EOI, exposure opportunity index; NR, not reported.

Update of the Epidemiologic Literature

Occupational Studies

Lawson et al. (2004) reported on the pregnancy outcomes among wives of men from the NIOSH cohort of workers who were highly exposed to chemicals contaminated with TCDD compared to those of matched neighborhood referents. The analysis of birth defects was performed on 1,153 live-born and 13 stillborn infants. Because only a modest number of birth defects were reported, pre-exposed and referent pregnancies were combined when they were qualitatively contrasted to the approximately 300 exposed pregnancies. Confirmation from vital and medical records was attempted, but was successful for only about 50% of the reported birth defects. The reported categories included 6 major central nervous system defects (4 among the exposed pregnancies), plus clubfoot, hip and lower limb defects, genitourinary defects, cardiovascular defects, and cleft lip or palate. Although the numbers were too small for reliable conclusions and only descriptive data were presented, there did not appear to be any trend of increased incidence of birth defects among offspring of exposed workers.

Environmental Studies

The only relevant environmental study published since *Update 2004* was Tango et al. (2004). The study found no associations between proximity to the incinerators and rates of fetal loss or infant deaths (before 1 week, 1 month, or 1 year) due to congenital malformation. In analyses using a "peak-decline" approach based on soil concentrations that had been shown to peak approximately 2 km from the incinerators, a significant outcome was found for infant death in the first year of life due to any congenital defect ($p = 0.047$), but the relationship was slightly more significant for all deaths in the first year ($p = 0.023$); no relationship was found for the intervals

closer to birth. This study had several methodologic weaknesses, including the lack of individual-level information on other risk factors and of individual exposure data. No data on specific types of congenital defects were included.

Vietnam-Veteran Studies

No new Vietnam veteran studies concerning exposure to the compounds of interest and birth defects were published since *Update 2004*.

Biologic Plausibility

Laboratory studies have established that maternal exposure to TCDD during pregnancy is associated with a wide variety of birth defects, which depend on the timing of exposure and the species being studied. However, laboratory studies of potential male-mediated developmental toxicity attributable to exposure to TCDD and herbicides, specifically with regard to birth defects, are too limited to permit conclusions. It is notable that both the aryl hydrocarbon receptor (AhR) and the AhR nuclear translocator are expressed in the human testis and sperm (Khorram et al., 2004; Shultz et al., 2003), and studies in rodents have shown that TCDD exposure results in significant changes in gene expression in spermatocytes and Sertoli cells; hence, cells of the testis are responsive to TCDD exposure (Kuroda et al., 2005; Yamano et al., 2005). Furthermore, laboratory studies have shown that TCDD inhibits spermatogenesis and reduces erectile function in animals (Moon et al., 2004; Simanainen et al., 2004). Thus, there is biologic potential for paternal exposure to contribute to TCDD-induced reproductive and developmental toxicity.

The only study assessing paternal TCDD exposure in humans that was reviewed for the present update failed to show any evidence that paternal TCDD exposure of male chemical workers caused an increase in birth defects in their offspring. In a previous laboratory study, paternal exposure of rats to TCDD failed to result in any birth defects in the F1 generation (Chahoud et al., 1991). And an epidemiologic study of maternal serum TCDD failed to establish any link with maternal thyroid dysfunction, which might contribute to cognitive or motor impairment in offspring (Foster et al., 2005).

The biologic plausibility of reproductive effects in general arising from exposure to the chemicals of interest is discussed at the end of this chapter.

Synthesis

For this update, the only new occupational study of birth defects and exposures to the chemicals of interest was a follow-on study of the children of men in the NIOSH cohort (Lawson et al., 2004). Because only 1,166 live born and stillborn infants were available for analyses, the information generated was too sparse to provide additional insights into the risks of birth defects. Birth defects were addressed indirectly by a new environmental study of residents in areas surrounding metropolitan waste-incineration facilities in Japan (Tango et al., 2004). On the basis of large numbers of births, the Japanese study found an association between residence in the areas with the highest soil dioxin concentrations and deaths before the first birthday due to any

congenital abnormality, but this relationship did not carry over to deaths occurring in the first month or in the first week of life.

Ngo et al. (2006) conducted a systematic review and meta-analysis of the association between Agent Orange and birth defects. Relevant studies published from 1966 to 2002 were identified by search engines, and the authors also included unpublished conference proceedings and information from researchers on findings from unpublished studies. They reviewed 22 studies, including 13 Vietnamese studies (11 of them unpublished) and nine of Vietnam veterans (two unpublished). Secondary analyses of primary data reviewed by previous VAO committees fall outside the type of findings ordinarily factored into the evidence bases evaluated in the VAO reviews, but given the nature of the reported results, the present committee wanted to comment on the Ngo et al. review. Unpublished studies are outside VAO's inclusion criteria, so the 13 unpublished studies considered by Ngo et al. were not included in previous VAO reviews of the association between the chemicals of interest and birth defects. All the studies that Ngo et al. indicate as published were reviewed in the VAO series. The Vietnam-veteran study that provided the highest risk estimates for birth defects (Field and Kerr, 1988) was excluded from consideration by previous VAO committees because of serious methodologic issues (IOM, 1994). In limiting their review to Agent Orange, Ngo et al. also excluded the broader array of occupational and environmental studies on the components of Agent Orange that previous VAO reviews have addressed.

Ngo et al. (2006) reported a substantially greater strength of association between exposure to Agent Orange and birth defects in the studies of Vietnamese populations (RR = 3.00, 95% CI 2.19–4.12) than in those of non-Vietnamese populations (RR = 1.29, 95% CI 1.04–1.59). The non-Vietnamese study populations consisted of Vietnam veterans, who were almost exclusively male, whereas the Vietnamese populations had a much greater likelihood of maternal exposure. Only Kang et al. (2000) addressed birth defects among the offspring of female Vietnam War veterans, who overall constitute fewer than 10,000 of the roughly 3 million US Vietnam veterans.

Ngo et al. (2006) also conducted subgroup meta-analyses based on presumed exposure intensity. They reported no significant increased risk of birth defects among non-Ranch Hand veterans (RR = 1.04, 95% CI 0.93–1.16). Combining three sequential studies of Ranch Hand veterans, who were presumed to have been more highly exposed, risk was increased (RR = 1.20, 95% CI 1.08–1.34), but they were unable to control for non-independent observations among the studies of Ranch Hand veterans studies. Combined risks from studies of North Vietnamese veterans and of sprayed Vietnamese civilians were successively higher. The numbers of cases reported in the studies reviewed by Ngo et al. (2006) were too small to allow meta-analysis of specific types of birth defects.

In general, the relatively small number of offspring among Vietnam veterans seriously restricts the ability to detect statistically significant increases in specific birth defects, and meta-analytic methods are the best approach to assessing the overall import of the studies of exposures to the chemicals of interest and the risk of specific birth defects. In addition, as the offspring of veterans become older, the risk of diseases stemming from congenitally transmitted defects that alter normal physiologic function, such as endocrine and reproductive function, merits increasing attention.

Conclusions

There were no new relevant studies on the association between parental exposure to 2,4-D, 2,4,5-T, TCDD, cacodylic acid, or picloram and spina bifida in offspring. The committee

concludes that the evidence is still limited or suggestive of an association between exposure to the compounds of interest and spina bifida.

Its evaluation of the evidence reviewed here and in previous VAO reports leads the committee to conclude that there is still inadequate or insufficient evidence of an association between exposure to the compounds of interest and all other birth defects.

CHILDHOOD CANCER

The American Cancer Society estimated that 9,200 children under the age of 15 years would have a diagnosis of cancer in the United States in 2004 (ACS, 2004). Treatment and supportive care of children with cancer have improved greatly, and mortality has declined by 49% over the last 30 years. Despite those advances, cancer remains the leading cause of death from disease in children under the age of 15 years, and 1,510 deaths were projected for 2004 (ACS, 2004).

Leukemia is the most common cancer in children. It accounts for about one-third of all childhood cancer cases; leukemia is expected to be diagnosed in nearly 2,760 children in 2004 (ACS, 2004). Of those, nearly 2,000 will have acute lymphocytic leukemia (ALL); most of the rest will have acute myelogenous leukemia (AML). Acute myelogenous leukemia (*International Classification of Diseases*, Ninth Edition [ICD-9] 205) is commonly referred to as acute myeloid leukemia and acute nonlymphocytic leukemia. For consistency, this report uses *acute myelogenous leukemia,* or simply *AML,* regardless of usage in the source materials. ALL is most common in early childhood, peaking between the ages of 2 and 3 years, and AML is most common during the first 2 years of life. ALL incidence is consistently higher in boys than in girls; AML incidence is similar in boys and girls (NCI, 2001). Through early adulthood, ALL rates are about twice as high in whites as in blacks; AML exhibits no consistent pattern in this respect. Chapter 6 contains additional information on leukemia as part of the discussion of adult cancer.

The second-most common group of cancers in children are those of the central nervous system—the brain and the spinal cord. Other cancers in children include lymphomas, bone cancers, soft-tissue sarcomas, kidney cancers, eye cancers, and adrenal gland cancers. Compared with adult cancers, relatively little is known about the etiology of most childhood cancers, especially about potential environmental risk factors and the effect of parental exposures.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and childhood cancers. Additional information available to the committees responsible for *Update 1996* and *Update 1998* did not change that conclusion. The committee responsible for *Update 2000* reviewed the material in earlier VAO reports and newly available published literature and determined there was limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and AML. After the release of *Update 2000*, investigators involved in one study discovered an error in their published data. The committee reconvened to evaluate the previously reviewed and new literature regarding AML, and *Acute Myelogenous Leukemia* (IOM, 2002) was produced. It reclassified AML from

"limited/suggestive evidence of an association" to "inadequate evidence to determine whether an association exists". Table 7-5 summarizes the results of the relevant studies. The committees responsible for *Update 2000*, *Update 2002*, and *Update 2004* reviewed the material in earlier VAO reports and in newly available published literature and agreed that there remained inadequate or insufficient evidence of an association between exposure and childhood cancers

TABLE 7-5 Selected Epidemiologic Studies—Childhood Cancers

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
Chen et al., 2005	Parental occupational exposure to pesticide and childhood GCTs		
	Maternal	32	1.1 (0.7–1.6)
	Paternal	39	0.9 (0.6–1.3)
Reynolds et al., 2005b	Maternal exposure to agricultural pesticide in class of "probable human carcinogens" (including cacodylic acid) during 9 months prior to delivery		
	All sites	223	1.0 (0.9–1.2)
	Leukemias	179	1.2 (0.9–1.5)
	Central nervous system tumors	31	0.9 (0.5–1.4)
Studies Reviewed in *Update 2004*			
Flower et al., 2004	Offspring of male pesticide applicators in Iowa from AHS		
	Maternal exposure to chlorophenoxy herbicides	7	0.7 (0.3–1.5)
	Paternal exposure to chlorophenoxy herbicides	28	1.3 (0.6–2.6)
	Maternal exposure to 2,4-D	7	0.7 (0.3–1.6)
	Paternal exposure to 2,4-D	26	1.29 (0.7–2.4)
Studies Reviewed in *Update 2000*			
Heacock et al., 2000	Offspring of sawmill workers exposed to fungicides contaminated with PCDDs and PCDFs		
	Leukemia		
	All workers offspring—incidence	11	1.0 (0.5–1.8)
	Offspring of workers with high chlorophenate exposure	5	0.8 (0.2–3.6)[b]
	Brain cancer		
	All workers offspring—incidence	9	1.3 (0.6–2.5)
	Offspring of workers with high chlorophenate exposure	5	1.5 (0.4–6.9)[b]
Buckley et al., 1989	Children's Cancer Study Group—exposure to pesticides and weed killers—AML		
	Any paternal exposure	27	2.3 (p = 0.5)
	Paternal exposure >1,000 days	17	2.7 (1.0–7.0)
	Maternal exposure >1,000 days	7	undefined
ENVIRONMENTAL			
New Studies			
Chen et al., 2006	Childhood GCTs and residential exposure to herbicides 6 months before conception, during gestation, or through breastfeeding period		

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Maternal exposure	47	1.3 (0.9–1.7)
	Daughters	36	1.4 (1.0–2.0)
	Sons	11	1.0 (0.5–1.8)
	Paternal exposure	90	1.0 (0.7–1.3)
	Daughters	32	1.2 (0.7–2.0)
	Sons	58	1.0 (0.7–1.4)
Studies Reviewed in *Update 2002*			
Daniels et al., 2001	Neuroblastoma risk in children (case–control study) (as reported by both parents)		
	Pesticides in the home (used ever)	*	1.6 (1.0–2.3)
	Herbicides in the garden	*	1.9 (1.1–3.2)
	Pesticides in the garden	*	2.2 (1.3–3.6)
Buckley et al., 2000	NHL diagnosed at the age of $\leq$ 20 years in children with potential prenatal exposure to herbicides	*	(*)[c]
Kerr et al., 2000	Neuroblastoma risk in children		
	Maternal occupational exposure to insecticides	40	2.3 (1.4–3.7)
	Paternal exposure to dioxin	7	6.9 (1.3–68.4)
Studies Reviewed in *Herbicide/Dioxin Exposure and AML in the Children of Veterans*			
Kristensen et al., 1996	Children of agricultural workers in Norway		
	Children with AML whose parents purchased pesticides	12	1.4 (0.6–2.9)
Studies Reviewed in *Update 2000*			
Meinert et al., 2000	Childhood cancer—population-based case-control study		
	Leukemia		
	Paternal exposure; year before pregnancy	62	1.5 (1.1–2.2)
	Paternal exposure; during pregnancy	57	1.6 (1.1–2.3)
	Maternal exposure; year before pregnancy	19	2.1 (1.1–4.2)
	Maternal exposure, during pregnancy	15	3.6 (1.5–8.8)
	Lymphomas		
	Paternal exposure, year before pregnancy	11	1.5 (0.7–3.1)
	Paternal exposure, during pregnancy	10	1.6 (0.7–3.6)
	Maternal exposure, year before pregnancy	3	2.9 (0.7–13)
	Maternal exposure, during pregnancy	4	11.8 (2.2–64)
Pearce and Parker, 2000	Kidney cancer in subjects (1-15 yrs) with paternal occupation in agriculture	21	0.9 (0.2–3.8)
Infante-Rivard et al., 1999	Childhood ALL in households using herbicides—population-based case-control study		
	Exposure during pregnancy	118	1.8 (1.3–2.6)
	Exposure during childhood	178	1.4 (1.1–1.9)
Studies Reviewed in *Update 1996*			
Pesatori et al., 1993	Seveso residents aged 0–19 years—10-year follow-up, morbidity, all exposure zones		
	All cancers	17	1.2 (0.7–2.1)
	Ovary and uterine adnexa	2	— (0 expected)
	Brain	3	1.1 (0.3–4.1)
	Thyroid	2	4.6 (0.6–32.7)
	Hodgkin's lymphoma	3	2.0 (0.5–7.6)
	Lymphatic leukemia	2	1.3 (0.3–6.2)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Myeloid leukemia	3	2.7 (0.7–11.4)
Bertazzi et al., 1992	Seveso residents aged 0–19 years—10-year follow-up, mortality, all exposure zones		
	All cancers	10	7.9 (3.8–13.6)
	Leukemias	5	3.9 (1.2–1.8)
	Lymphatic leukemia	2	1.6 (0.1–4.5)
	Myeloid leukemia	1	0.8 (0.0–3.1)
	Leukemia, others	2	1.6 (0.1–4.6)
	Central nervous system tumors	2	1.6 (0.1–4.6)
VIETNAM VETERANS			
Studies Reviewed in *Herbicide/Dioxin Exposure and AML in the Children of Veterans*			
AIHW, 2001	Australian Vietnam veterans' children—Revised Validation Study – AML	12[d]	1.3 (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 AML cases, is superseded by AIHW, 2001 above.		
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—outcomes in the offspring of veterans		
	Cancer	25	1.5 (0.7–2.8)
	Leukemia	12	1.6 (0.6–4.0)
Field and Kerr, 1988	Cancer in children of Australian Vietnam veterans	4	(*)
Erikson et al, 1984b	CDC Birth Defects Study—children of Vietnam veterans		
	"Other" neoplasms	87	1.8 (1.0–3.3)

Unless otherwise indicated, studies show paternal exposure.

[a] Given when available.

[b] OR estimated using low exposure subjects as the comparison cohort.

[c] No information on herbicides as a class, distinct from insecticides or other pesticides, was available; exposures before conception were not singled out, and no distinction between maternal and paternal exposure was made.

[d] Of the 12, 9 were observed and 3 additional cases were estimated to have occurred in the portion of the cohort whose data were not validated.

* Information not provided by study authors.

ABBREVIATIONS: AFHS, Air Force Health Study; AHS, Agricultural Health Study, AIHW, Australian Institute of Health and Welfare; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CDC, Centers for Disease Control and Prevention; CI, confidence interval; EOI, exposure opportunity index; GCT, germ-cell tumor; NS, not significant; SS, statistically significant.

Update of Epidemiologic Literature

Occupational Studies

Two related papers from the Children's Oncology Group addressed exposures to pesticides and the risk of childhood germ-cell tumors (GCTs). One focused on residential pesticides and chemicals (Chen et al., 2006) and the other on parental occupational exposures (Chen et al., 2005), but they were based on the same overall case–control study. GCTs are very rare childhood cancers, so recruitment was done throughout the United States and included incident cases diagnosed from 1993 to 2001 in children under the age of 15 years. Controls were selected by random-digit dialing and frequency-matched on sex, year of birth, and state. Data were collected via two questionnaires (telephone and self-administered). Maternal exposure to herbicides at home from 6 months before pregnancy until termination of breastfeeding was associated with a slightly increased risk among female offspring (OR = 1.4, 95% CI 1.0–2.0), but not among male offspring (OR = 1.0, 95% CI 0.5–1.8).

Similarly, Chen et al. (2005) reported on maternal and paternal exposures to pesticides before, during, and after pregnancy from occupational exposures. The data on analyses for exposures to herbicides, insecticides, or fungicides were not presented, but it was stated that the only a positive association was for maternal exposure to herbicides at work during the postnatal period and and GCTs in female offspring (OR = 2.3, 95% CI 1.0–5.2); therefore, exposures with timing relevant to this review were not associated with increased risks of GCTs in the offspring. Both studies are limited by the questionable reliability of the self-reported exposures, reporting of the results only for full the preconception through postnatal period, the small numbers of subjects, and the failure to consider residential and occupational herbicide exposures simultaneously.

Environmental Studies

Reynolds et al. (2005b) conducted a case–control study on childhood cancer and gestational exposure to pesticides. Compilation in California's Pesticide Use Reporting Database (CPUR) of information of amount and location of application by specific product began in 1990. Considering children born after September 1990 and diagnosed with cancer before the age of 5, they identified 2,189 children entered in California's population-based cancer registry by the end of 1997. A total of 4,335 live controls were randomly selected from California birth certificates and matched on date of birth and sex. A geographic information system (GIS) approach was 99% successful in geocoding residence at time of birth for 2,189 case mothers and 4,388 control mothers, permitting linkage to the CPUR. Considering the amount of pesticide applied and the distance of the treated areas from the mother's residence, cumulative exposures for the 9 months before birth were determined for several different classifications of pesticides. California's category of pesticides that are "probable human carcinogens," which includes cacodylic acid, is the only classification of possible relevance for this review. Cases of all types of cancer were no more likely than controls to have experienced high exposure during gestation to "probable human carcinogens" (OR = 1.01, 95% CI 0.85–1.20); the same was true for the subset of leukemias (OR = 1.17, 95% CI 0.90–1.54) or CNS cancers (OR = 0.86, 95% CI 0.54–1.36). No individual-level data were obtained for the study participants or their parents regarding lifestyle

or other personal characteristics to permit adjustment for possible confounder. The exposure assessment assumes that residential proximity is a good indicator of exposure. Distance to pesticide exposure sources was based on the children's residences at birth, which would lead to at least some misclassification due to residential mobility. Finally, although the study included many subjects, most of them lived in areas that experienced little or no agricultural pesticide use, so the risk estimates for the high exposure categories were based on small numbers.

Vietnam-Veteran Studies

No new Vietnam veteran studies concerning exposure to the compounds of interest and childhood cancer were published since *Update 2004*.

Biologic Plausibility

Paternal or maternal exposure to xenobiotics potentially could increase the susceptibility of offspring to developing cancer through multiple mechanisms. Susceptibility could be increased by inheriting a genetic predisposition, which by itself could increase the development of cancer or the likelihood of developing cancer after future exposure to a carcinogen; the mother or father would transmit either an acquired genetic defect or an epigenetic alteration that predisposed the child to cancer. Alternatively, a maternally-mediated increased susceptibility to childhood cancer could result from direct exposure of a child in utero or via lactation to a xenobiotic that induces epigenetic alterations that increase cancer susceptibility or is itself carcinogen.

It has been shown that prenatal TCDD exposure of rats is associated with altered mammary gland differentiation and an increase in the number of mammary adenocarcinomas (Brown et al., 1998). A recent study's demonstration that early postnatal TCDD exposure does not increase mammary-cancer risk (Desaulniers et al., 2004) suggests that TCDD-induced changes in utero mediate the increase in cancer susceptibility. Developmental epigenetic alterations may be involved in those prenatal effects. TCDD has been shown to suppress the expression of two tumor-suppressor genes, $p16^{Ink4a}$ and p53, via an epigenetic mechanism that appears to involve DNA methylation (Ray and Swanson, 2004). Similarly, it was reported that prenatal TCDD exposure increases methylation of two growth-related imprinted genes, H19 and Igf2, in the developing fetus (Wu et al., 2004).

Although there is no direct evidence from animal models that TCDD increases the risk of childhood cancers, such as acute leukemia or GCTs, emerging research suggests that prenatal TCDD exposure can disrupt epigenetic imprinting patterns and alter organ differentiation, and this could contribute to an increased susceptibility to cancer later in life. A recent study has shown that chromosomal rearrangements associated with childhood ALL are evident in the neonatal blood spots; this suggests that childhood leukemias begin before birth and that maternal and perinatal exposures to xenobiotics may contribute to genetic mutations (Smith et al., 2005).

Synthesis

The studies reviewed for this update did not find significant associations between the relevant exposures and childhood cancers. As with other outcomes in the offspring of Vietnam veterans, the small number of these rare childhood cancers expected among the circumscribed number of Vietnam veterans would seriously hinder detection of any actual increases; meta-analytic methods may be the best approach for assessing the overall significance of the association between exposures to the chemicals of interest and the risk of specific childhood cancers.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and childhood cancers.

SUMMARY

Overall Biologic Plausibility of Reproductive and Developmental Effects

This section summarizes the general biologic plausibility of a connection between exposure to the compounds of interest and reproductive and developmental effects on the basis of data from animal and cellular studies. Chapter 3 presents details of the committee's evaluation of data from the recent studies.

TCDD induces a variety of adverse reproductive and developmental effects in laboratory animals. The administration of TCDD to male animals elicits reproductive toxicity by affecting testicular and seminal vesicle weight and function and by decreasing the rate of sperm production. The mechanisms of those effects are not known, but a primary hypothesis is that they are mediated through dysregulation of testicular steroidogenesis. Exposure to TCDD is associated with increased estradiol secretion and decreased testosterone secretion; both hormones regulate sperm production. However, high doses of TCDD were required to elicit those effects, and TCDD-exposed male rats were able to sire viable fetuses. Thus, there is little evidence from laboratory studies that TCDD exposure of males contributes to reduced fertility.

Many studies also have examined the effects of TCDD on the female reproductive system. Two primary mechanisms that probably contribute to abnormal follicle development and decreased numbers of ova after TCDD exposure are crosstalk of the AhR with the estrogen receptor and dysregulation of the hypothalamic-pituitary-gonadal axis. Interaction of the activated AhR leads to inhibition of estradiol-induced gene expression and to enhancement of estrogen-receptor protein degradation; both activities may contribute to TCDD's antiestrogenic effects. TCDD also dysregulates the secretion pattern of preovulatory gonadotropin hormones, and this leads to abnormal and reduced follicle development. In addition, oocytes are directly responsive to TCDD. Thus, TCDD's effects on hormone concentrations, hormone-receptor signaling, and ovarian responsiveness to hormones all probably contribute to TCDD-induced female reproductive toxicity. On the basis of animal data, male and female reproductive effects of TCDD in humans are biologically plausible. Furthermore, a recent study has shown that dioxins and dibenzofurans

significantly correlate with dysregulation of estrogen metabolism in pregnant women (Wang et al 2006)—evidence of a biologically plausible mechanism of TCDD's adverse effects on human reproduction.

In animal studies, TCDD crosses the placenta and is transferred via breast milk. In humans, TCDD has been measured in circulating maternal blood, cord blood, placenta, and breast milk (Suzuki et al., 2005), and it is estimated that an infant breast-fed for 1 year accumulates a dose of TCDD that is 6 times higher than an infant not breast-fed (Lorber and Phillips., 2002). Thus, the exposure of human infants in utero and via lactation has been demonstrated.

In animal studies, TCDD exposure during pregnancy can reduce body weight at birth, but this typically occurs at high doses. Thus, there is little evidence that TCDD exposure is associated with reduction in birth weight.

TCDD is a potent teratogen in all laboratory species that have been studied, although the pattern of induced birth defects is often species-specific. For example, fish, mice, and avian embryos exhibit substantial alterations in craniofacial development—shortened jaw in piscine species, cleft palate in mice, and beak malformations in birds. The developing cardiovascular system is also a common target for TCDD-induced teratogenicity, and it has been shown that cardiac myocytes and the endothelial lining of the heart and blood vessels are primary target sites of TCDD's effects. Cytochrome P450 1A1 induction or alterations in pathways controlled by vascular endothelial growth factor might mediate the early lesions that result in TCDD-related vascular derangements. That antioxidant treatment provides protection against TCDD-induced embryotoxicity in some systems suggests that reactive oxygen species might be involved in the teratogenic effects of exposure to TCDD. Several reports of studies in exposed animals and humans suggest that low perinatal exposure to TCDD and 2,4-D could impair brain development. Outcomes can be subtle, ranging from altered learning and memory to modified sex-related behavior. The mechanisms of those effects are unclear.

Studies in rodents show that a single maternal dose of TCDD produces malformations of the external genitalia and functional reproductive alterations in female progeny, including decreased fertility rate, reduced fecundity, cystic endometrial hyperplasia, and disrupted estrous cycles. Those effects depend on the timing of exposure. Similarly, male progeny exhibit alterations in reproductive-organ development and function. Maternal exposure to TCDD impairs prostate growth and seminal vesicle weight and branching and decreases sperm production and caudal epididymal sperm number in offspring.

Little research has been conducted on the offspring of male animals exposed to herbicides. Feeding of simulated Agent Orange mixtures to male mice produced no adverse effects in offspring; a statistically significant excess of fused sternebrae in the offspring of the two most highly exposed groups was attributed to an anomalously low rate of this defect in the controls (Lamb et al., 1981).

Altered sex ratio might reflect the effects of exposure to the chemicals of interest on reproductive capability. It has been hypothesized that concentrations of parental hormones at conception or induction of lethal mutations before birth could affect sex ratio. There has been no work with experimental animals that specifically examined the effects of TCDD on sex ratios of offspring, nor have any alterations in sex ratio been reported in animal studies that examined developmental effects of TCDD on offspring.

The mechanisms by which TCDD induces birth defects have not been established and are probably species- and organ-specific. Nonetheless, studies have consistently demonstrated that TCDD-induced developmental toxicity required the AhR. That has been definitively established in

mice that lack AhR expression. When pregnant AhR-null mice are exposed to TCDD, the fetuses fail to exhibit any of the typical developmental malformations associated with TCDD exposure. The activated AhR mediates changes in gene transcription, so the inappropriate and sustained activation of AhR by TCDD during development appears to be a key first step in mediating TCDD's developmental toxicity. Although structural differences in the AhR have been identified among species, it functions similarly in animals and humans. Therefore, a common mechanism probably underlies the reproductive and developmental toxicity of TCDD in humans and animals, and data on animals support a biologic basis of TCDD's toxic effects.

Little information is available on the reproductive and developmental effects of exposure to the herbicides discussed in this report. Studies indicate that 2,4-D does not affect male or female fertility and does not produce fetal abnormalities. Offspring of pregnant rodents exposed to 4-(2,4-dichlorophenoxy)butyric acid (2,4-DB) exhibit a reduced growth rate and increased mortality (Charles et al., 1999), but only after very high doses. Exposure to 2,4-D also alters the concentration and function of reproductive hormones and prostaglandins. One study reported an increased incidence of malformed offspring of male mice exposed to a mixture of 2,4-D and picloram in drinking water; however, paternal toxicity was observed in the high-dose group, and there was no clear dose–response relationship (Blakley et al., 1989). Picloram alone produced fetal abnormalities in rabbits at doses that are also toxic to the pregnant animals (John-Greene et al., 1985), but that effect has not been seen in many studies. 2,4,5-T was toxic to fetuses when administered to pregnant rats, mice, and hamsters; its ability to interfere with calcium homeostasis in vitro has been documented and linked to its teratogenic effects on the early development of sea urchin eggs. Cacodylic acid is toxic to rat, mouse, and hamster fetuses at high doses that are also toxic to the pregnant mother.

There is growing evidence from laboratory animal and human studies that exposures during fetal or postnatal development can lead to adverse effects later in life that are not immediately apparent as structural malformations or functional deficits. For example, exposure of humans and rats to TCDD in early postnatal life induces dental aberrations and reduces enamel maturation of teeth (Alaluusa et al., 2004; Gao et al., 2004). A study of human exposure to background concentrations of dioxins, furans, and PCBs during prenatal development (Nakajima et al., 2006) suggests possibly more relationship with reduced motor development in 6-month-old infants than with their mental development; however, the few significant correlations found among dozens of comparisons made were for specific congeners with low relative potency (TEFs), so the study is essentially negative for developmental effects arising from prenatal exposure to TCDD.

The foregoing suggests that a connection between TCDD exposure and human reproductive and developmental effects is, in general, biologically plausible. However, more definitive conclusions about the potential for such TCDD toxicity in humans are complicated by differences in sensitivity and susceptibility among individual animals, strains, and species; by the lack of strong evidence of organ-specific effects among species; by differences in route, dose, duration, and timing of exposure; and by substantial differences in the toxicokinetics of TCDD between laboratory animals and humans. Experiments with 2,4-D and 2,4,5-T indicate that they have subcellular effects that could constitute a biologically plausible mechanism for reproductive and developmental effects. Evidence from animals, however, indicates that they do not have reproductive effects and that they have developmental effects only at very high doses. There is insufficient information on picloram and cacodylic acid to assess the biologic plausibility of those compounds' reproductive or developmental effects.

Considerable uncertainty remains about how to apply toxicologic information to the evaluation

of potential health effects of herbicide or TCDD exposure on the offspring of Vietnam veterans. Scientists disagree over the extent to which information derived from animal and cellular studies can be used to predict human health outcomes and over the extent to which the health effects of high-dose exposure can be extrapolated to low-dose exposure. The biologic mechanisms that underlie TCDD's toxic effects continue to be a subject of active research, and future VAO updates are likely to have more and better information on which to base conclusions, at least for TCDD.

Synthesis

The studies reviewed for this update did not find any significant associations between the relevant exposures and reproductive outcomes. The scientific evidence supports the biologic plausibility of a connection between exposure to the chemicals of interest and reproductive effects, but the epidemiologic studies of occupational cohorts, exposed communities, and Vietnam veterans have not provided conclusive evidence of any additional associations between exposures and an array of reproductive outcomes and conditions among the offspring of exposed parents. The mechanisms by which the chemicals exert their biologic effects are still subjects of scientific investigation. With the aging of the Vietnam-veteran population, additional studies on fertility, spontaneous abortion, and sex ratio cannot be expected, although there may be additional studies of reproductive outcomes in other populations with exposure to the chemicals of interest. The possibility of structural or functional abnormalities in the offspring of exposed people will continue to be of interest.

Conclusions

There is inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and altered hormone concentrations; semen quality; infertility; spontaneous abortion; late fetal, neonatal, or infant death; low birth weight or preterm delivery; birth defects other than spina bifida; and childhood cancers.

There is limited or suggestive evidence of an association between exposure to the compounds of interest and spina bifida.

There is limited or suggestive evidence that the specific combination of paternal exposure to TCDD is *not* associated with risk of spontaneous abortion.

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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8

Neurologic Disorders

Neurologic disorders include a wide variety of medical conditions. The nervous system can be divided anatomically and functionally into the central nervous system (CNS) and the peripheral nervous system (PNS). Distinguishing between CNS dysfunction and PNS dysfunction is a useful starting point for understanding and evaluating neurologic disorders.

The CNS consists of the brain and the spinal cord. CNS disorders can be broadly divided into neurobehavioral disorders and movement disorders. Neurobehavioral disorders can involve cognitive syndromes, including memory problems, dementia, and Alzheimer's disease; and neuropsychiatric problems, including neurasthenia (a collection of such symptoms as difficulty in concentrating, headache, insomnia, and fatigue), post-traumatic stress disorder (PTSD), anxiety disorder, depression, and suicide. Those disorders result from problems in the cerebral cortex or limbic system. Movement disorders, such as Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), involve weakness, tremors, involuntary movements, incoordination, or gait abnormalities. Those disorders result from problems in the basal ganglia, cerebellum, or spinal cord.

The PNS includes the spinal nerve roots that leave the spinal cord through the vertebral column, traverse the brachial and lumbar plexuses, and end in the peripheral nerves that connect with muscles, skin, and internal organs. PNS disorders are classified as various types of peripheral neuropathy, which can involve sensory changes, motor weakness, or autonomic instability. Those disorders result from problems in somatic or autonomic nerves or both.

Neurologic disorders can also be classified on the basis of anatomic distribution as global or focal, on the basis of timing relative to exposure a causative agent, as early or of delayed onset, or on the basis of duration as transient or persistent. For example, global CNS dysfunction can lead to a general abnormality, such as an altered level of consciousness, whereas focal CNS dysfunction might lead to an isolated abnormality, such as difficulty with language function (aphasia). Early-onset disorders are seen within days or weeks of exposure; delayed onset may occur after months or years. Transient disorders are short-lived; persistent disorders produce lasting deficits. Timing is important in assessing the effects of chemical exposure on neurologic function and must be considered in the design and critique of epidemiologic studies. In the original *Veterans and Agent Orange* report, hereafter referred to as *VAO* (IOM, 1994), attention was deliberately focused on persistent neurobehavioral disorders. *Veterans and Agent Orange: Update 1996,* or *Update 1996* (IOM, 1996); *Veterans and Agent Orange: Update 1998,* or *Update 1998* (IOM, 1999); *Veterans and Agent Orange: Update 2000,* or *Update 2000* (IOM, 2001); *Veterans and Agent Orange: Update 2002,* or *Update 2002* (IOM, 2003); *Veterans and Agent Orange: Update 2004,* or *Update 2004* (IOM, 2005); and this report review data pertinent to all neurologic disorders.

Case identification in neurologic disorders is often difficult because there are few disorders for which there are specific diagnostic tests. Many disorders involve cellular or molecular biochemical

effects, so even the most advanced imaging techniques can miss an abnormality. Because the nervous system is not readily accessible for biopsy, pathologic confirmation usually is not feasible. Furthermore, neurologic disorders are by their nature largely subjective, so there often is no objective evidence with which to confirm a diagnosis.

Many studies have addressed the possible contribution of various chemical exposures to neurologic disorders, but the committee's focus is on the health effects of a particular set of chemicals: four herbicides (2,4-dichlorophenoxyacetic acid [2,4-D], 2,4,5-trichlorophenoxyacetic acid [2,4,5-T], 4-amino-3,5,6-trichloropicolinic acid [picloram], and cacodylic acid [dimethyl arsinic acid or DMA]) and a contaminant of 2,4,5-T, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Thus, the specificity of exposure assessment is an important consideration in weighing evidence relevant to the committee's charge, as described earlier (Chapters 2 and 5).

This chapter reviews the association between exposure to the compounds of interest and neurobehavioral disorders, movement disorders, and peripheral neuropathy. The scientific evidence supporting biologic plausibility also is reviewed briefly here; a more thorough discussion of updated toxicologic studies is in Chapter 3. More complete discussions of the categories of association and of this committee's approach to categorizing health outcomes are presented in Chapters 1 and 2. If a study new to this update reports only a single neurologic outcome and is not revisiting a previously studied population, its design information is summarized with its results; design information on other new studies is in Chapter 4.

NEUROBEHAVIORAL (COGNITIVE OR NEUROPSYCHIATRIC) DISORDERS

This section summarizes the findings of *VAO* and previous updates on neurobehavioral disorders and incorporates information published in the last 2 years into the evidentiary database.

Conclusions from *VAO* and Updates

On the basis of the data available at the time, it was concluded in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* that there was inadequate or insufficient evidence to determine the existence of an association between exposure to the compounds of interest and neurobehavioral disorders. Many of the data that informed that conclusion came from the Air Force Health Study (AFHS, 1984, 1987, 1990, 1991, 1995, 2000, 2003). *VAO* and the updates offer more complete discussions of the results. The AFHS study design and methods of exposure assessment are discussed in Chapters 4 and 5, respectively.

The studies reviewed in *VAO* (IOM, 1994) revealed no association between serum TCDD concentration and reported sleep disturbance or variables on the Symptom Checklist-90-Revised (SCL-90-R). In contrast, serum TCDD was significantly associated with responses on some scales of the Millon Clinical Multiaxial Inventory (MCMI).

In *Update 2000* (IOM, 2001), results from the AFHS indicated that although the frequency of several self-reported neuropsychiatric symptoms differed between exposure groups, the associations were not significant after adjustment for covariates. In addition, a repeat psychologic assessment with the SCL-90-R in conjunction with self-reported psychologic disorders verified through medical-record review showed that among five diagnostic categories (psychosis, alcohol dependence, drug dependence, anxiety, and other neurosis), a dose–response

pattern with serum TCDD concentration was found only for "other neuroses" in the enlisted ground crew. When the entire cohort was evaluated, there were no significant associations between serum TCDD and various psychologic diagnoses.

Update 2002 (IOM, 2003) reviewed three studies. Neuropsychologic tests of cognitive functioning indicated significant group differences on some scales, but the findings did not support a dose–response relationship with serum TCDD: poorer performance was seen in groups with background or low exposure, and the lower performance on only one memory test for one subgroup of subjects suggested a chance finding.

Update 2004 (IOM, 2005) reviewed five new studies. Among them was a report on the AFHS cohort (Barrett et al., 2003) in which the authors conclude that there were "few consistent differences in psychological functioning" between groups categorized by serum dioxin concentrations. Another report described increased prevalence of PTSD among Korean military who served in Vietnam, although there was no association with estimated exposure to Agent Orange. The remaining three studies were uninformative because of methodologic limitations.

Prior committees have maintained the conclusion that there has been inadequate or insufficient evidence of an association between exposure to the compounds of interest and neurobehavioral disorders (cognitive or neuropsychiatric).

Update of the Epidemiologic Literature

Since *Update 2004*, Park et al. (2005) investigated the association between occupational factors and mortality from neurodegenerative diseases, including Alzheimer's disease and presenile dementia (PSD), PD, and motor neuron disease (see also the section on PD and parkinsonism below). The authors examined data from 1992–1998 death certificates for over 2.6 million deaths in 22 states. They report mortality odds ratios associated with subjects' "usual occupation" and with a subgroup of "pesticide-exposed" occupations. Subjects who had worked in "pest control" had significantly increased risk for PSD (odds ratio [OR] = 2.96). However, the exposure assessment was too imprecise for the results to inform the present committee's conclusions.

A study of Australian Vietnam veterans reported an association between deployment in Vietnam and "mental disorders" (ADVA, 2005c). The authors state that "there was a borderline significant elevation in mortality from mental disorders, with a relative rate of 2.75 (95% confidence interval [CI] 0.98–8.83). The number of deaths for this group of diseases was small enough for an examination to be made for the 19 deaths involved. All of the deaths were due to conditions associated with alcohol or drug misuse." Therefore, that report did not inform the committee's conclusions regarding the possible association between neurobehavioral disorders and exposure to herbicides in Vietnam.

Biologic Plausibility

A few animal studies suggesting possible involvement of chemicals of interest in neurobehavioral effects were identified in this review. Mitsui et al. (2006) suggested that hippocampus-dependent learning could be impaired in male rats exposed in utero to TCDD. effects on fear conditioning, via hippocampus effects, in adult male rats exposed to TCDD while

in utero. Lensu et al. (2006) examined areas in the hypothalamus for possible involvement in TCDD effects on food consumption, potentially related to wasting syndrome caused by TCDD, and suggest that their results are not consistent with the hypothalamus a primary role for the hypothalamus. Although this study does not address cognitive or neuropsychiatric disorders, it involves behaviour (food consumption). There also were studies in rodents that detected molecular effects in cerebellar granule cells or neuroblasts, which are involved in cognitive and motor processes (Kim and Yang, 2005; Williamson et al., 2005) A general summary of the biologic plausibility of neurologic effects of exposure to the herbicides used in Vietnam is presented at the end of this chapter, and detailed discussion is in Chapter 3.

Synthesis

There is not consistent epidemiologic evidence of an association between neurobehavioral disorders (cognitive or neuropsychiatric) and Agent Orange exposure. Difficulties in case identification and diagnosis, misclassification of exposures because of a lack of contemporaneous measures, subject ascertainment and selection bias, and uncontrolled confounding from many comorbid conditions are common weaknesses in the studies reviewed. The variability of the test results over time, the weak and inconsistent associations, and a lack of consistent dose–response relationships also detract from evidence of an association between the exposures of interest and neurobehavioral disorders.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is still inadequate or insufficient evidence to determine the existence of an association between exposure to the compounds of interest and neurobehavioral disorders (cognitive or neuropsychiatric).

MOVEMENT DISORDERS

This section summarizes the findings of previous *VAO* reports on movement disorders, including PD and ALS, and incorporates information published in the last 2 years into the evidentiary database.

Parkinson's Disease and Parkinsonism

PD is a progressive neurodegenerative disorder that affects millions of people worldwide. Its primary clinical manifestations are bradykinesia, resting tremor, cogwheel rigidity, and gait instability. Those signs were first described in 1817 as a single entity by James Parkinson, who believed that severe fright from a traumatic experience was a probable cause. Despite nearly 2 centuries of investigation, the true causes of the disease remain enigmatic, and the diagnosis still relies on a characteristic constellation of signs found in a clinical neurologic examination.

However, the signs are not pathognomonic; they are seen in other disorders, including parkinsonism resulting from syndromes that are virtually indistinguishable from PD. Ultimately, a diagnosis of PD can be confirmed with postmortem pathologic examination of brain tissue for the characteristic loss of neurons from the substantia nigra and telltale Lewy body intracellular inclusions. Pathologic findings in other causes of parkinsonism show different patterns of brain injury.

Estimates of population-based incidence of PD range from 2 to 22 per 100,000 person-years, and estimates of prevalence range from 18 to 182 per 100,000 person-years. That makes PD the second-most common neurodegenerative disease (after Alzheimer's disease). Age is the only definite risk factor for PD; peak incidence and prevalence are consistently found in the seventh and eighth decades of life.

Heredity has long been suspected as a primary risk factor for PD, and identification of evidence of genetic transmission—marked by the determination of specific mutations in two genes, Parkin and α-synuclein—has accumulated over the last decade. However, it has become clear that simple Mendelian transmission can account only for some rare forms of familial and early-onset PD.

Conclusions from VAO and Updates

On the basis of growing concerns about a possible link between PD and pesticide exposures, the original *VAO* committee suggested that attention be paid to the pattern of new cases in Vietnam veterans as they enter the decades when PD is most prevalent to determine whether there is evidence of an association between PD and exposure to the compounds of interest. That recommendation has been echoed in each update.

Prior studies have identified PD on the basis of clinical signs or diagnostic coding (ICD-9 332) from death certificates or hospital admission records. Although exposure would be relevant to causation if it occurred before disease onset, the specific timing of exposure and disease onset is often unknown. The *Update 1996* and *Update 1998* committees considered the detection of early-onset cases to be vital to test the hypothesis that cases are related to a toxic exposure.

The *Update 2000* committee noted that most studies had grouped cases of all ages; studies that separated early-onset cases have yielded inconsistent results (Butterfield et al., 1993; Stern et al., 1991). Estimates of relative risk have also been inconsistent: five studies demonstrate positive associations (Butterfield et al., 1993; Gorell et al., 1998; Liou et al., 1997; Seidler et al., 1996; Semchuk et al., 1992), two demonstrate negative associations (Kuopio, 1999; Stern, 1991), and one shows no association (Taylor et al., 1999). A meta-analysis indicated significant heterogeneity in the published work (Priydarshi et al., 2000). Evidence supporting a dose–response relationship was limited to one study (Gorell et al., 1998), which demonstrated an increased incidence of PD with increasing dose as measured by duration of exposure.

Update 2002 reviewed reports of two cohort studies (Engel et al., 2001; Petrovich et al., 2002), whose results were similar to those of the many other studies reviewed for earlier updates. Long duration of agricultural work was associated with parkinsonism in many reports, but the results did not show consistent dose–response trends, and no association with any specific compound of interest was identified.

Update 2004 reviewed reports of three epidemiologic studies: a cohort study (Baldi et al., 2003a) and a nested case–control study (Baldi et al., 2003b) in France and a case–control study

in Belgium (Pals et al., 2003). None showed significant associations with the compounds of interest.

None of the studies has described specific exposures to the compounds of interest. Table 8-1 summarizes the relevant studies.

TABLE 8-1 Epidemiologic Studies of Pesticide [a] Exposure and Parkinson's Disease [b]

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides [a]	OR (95 % CI)	Neurologic Dysfunction
Ascherio et al., 2006; US	413 confirmed cases of PD diagnosed after 1992	142,485 respondents to 2001 survey without self-report of PD	1992 baseline self-report of exposure to pesticides	+	1.7 (1.2−2.3)	2001 follow-up of health outcomes; confirmation of PD self-report with medical records
Kamel et al., 2005			Questionnaire—self-reported pesticide use by number of days per year			Symptoms that might be indicative of Parkinson's disease, but no formal diagnosis
Park et al., 2005; US	33,678 cases of PD, during 1992 to 1998		Death certificates—any mention of PD along with an occupation associated with probable pesticide exposure	+	Farming 1.2 (1.1−1.2)	Death certificates from 22 states with any mention of PD
Baldi et al., 2003a; France	585 men (age > 70 years)		Questionnaire—detailed occupational histories	+	Occupational pesticides (mostly fungicides) 5.6 (1.5–21.6)	Self-report at 8 and 10 year follow-ups
Baldi et al., 2003b; France	84 (age > 70 years)	252 (age > 70 years)	Interview –Occupational history coded by experts –Residential history	+	Occupational pesticides (mostly fungicides) 2.2 (1.1–3.4)	UK PD Society Brain Bank clinical criteria
Pals et al., 2003; Belgium	423	205	Questionnaire–occupational history not interpreted with respect to pesticide use			Neurologic exam
Petrovitch et al., 2002; US	2,623	5,363	Total years plantation work and years of pesticide exposure	+	Plantation work >20 years 1.9 (1.0–3.5)	Medical records and neurologic exam
Engel et al., 2001; US	238	72	Self-administered questionnaire for occupational exposure	+	Pesticides 0.8 (0.5–1.2) Highest tertile pesticide 2.0 (1.0–4.2)	Neurologic exam by trained nurse

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides [a]	OR (95 % CI)	Neurologic Dysfunction
					Herbicide 0.9 (0.6–1.3)	
Ritz and Yu, 2000; US	7,516 (PD cause of death 1984–1994)	498,461 (ischemic heart disease cause of death 1984–1994)	Counties ranked by pesticide use from pesticide registry and agricultural census data	+	Prevalence OR: Moderate pesticide 1.36 (1.3–1.5)	ICD-9 332
Tuchsen and Jensen, 2000; Denmark	134	128,935 expected cases 101.5	Occupations in farming, Horticulture, and landscape expected to have exposure to pesticides	+	Age-standardized hospitalization ratio for all men in agriculture and horticulture 1.34 (1.09–1.62)	First-time hospitalization for PD
Fall et al., 1999; Sweden [c]	113	263	Questionnaire—any job handling pesticides		Pesticides 2.8 (0.9–8.7)	Neurologic exam
Kuopio et al., 1999; Finland	123 (onset of PD before 1984)	279	Interview—pesticides or herbicides regularly or occasionally used		Regular use of herbicides 0.7 (0.3–1.3)	Neurologic exam
Taylor et al., 1999; US	140	147	Interview—exposure recorded as total days for lifetime		Pesticides 1.02 (0.9–1.2) Herbicides 1.06 (0.7–1.7)	Neurologic exam
Chan et al., 1998; Hong Kong [c]	215	313	Interview—exposure to pesticides during farming (years)	+	Pesticides in women 6.8 (1.9–24.7) Pesticides in men 0.7 (0.3–1.8)	Neurologic exam
Gorrell et al., 1998; US [c]	144 (age > 50 years)	464	Interview—herbicide and insecticide use while working on a farm or gardening	+	Occupational herbicides 4.1 (1.4–12.2)	Standard criteria of PD by history
Hubble et al., 1998; US	3 PD with dementia	51 PD without dementia	Interviews—pesticide exposure >20 days in any year and presence of allele for poor drug metabolism	+	Pesticide exposure and genetic trait 3.17 (1.1–9.1)	Neurologic exam
McCann et al., 1998; Australia [c]	224	310	Questionnaire—daily or weekly exposure to industrial herbicides and pesticides >6 months		Herbicides or pesticides 1.2 (0.8–1.5)	Neurologic exam
Menegon et al., 1998;	96	95	Interview—pesticide exposure		Pesticides	Standard criteria of

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides [a]	OR (95 % CI)	Neurologic Dysfunction
Australia			more than once weekly for >6 months before onset of PD	+	2.3 (1.2–4.4)	PD by history
Smargiassi et al., 1998; Italy[c]	86	86	Interview—occupational exposure for at least 10 consecutive years		Pesticides or herbicides 1.15 (0.6–2.4)	Standard criteria of PD by history
Liou et al., 1997; Taiwan [c,d]	120	240	Interview—Occupational exposures to herbicides or pesticides	+	Herbicides or pesticides, no paraquat 2.2 (0.9–5.6) Paraquat use 3.2 (2.4–4.3)	Neurologic exam
Schulte et al., 1996; US [d]	43,425 PD cause of death in 27 states 1982–1991		Occupational exposure to what?	+	PMR excess in male pesticide appliers, horticultural farmers, farm workers, and graders and sorters of agricultural products	ICD-9 332
Seidler et al., 1996; Germany [c,d]	380 (age < 66 years with PD after 1987)	755	Interview—dose-years = years of application weighted by use	+	Neighborhood controls for herbicide 1.7 (1.0–2.7) Regional controls for herbicide 1.7 (1.0–2.6)	Neurologic exam
Chaturvedi et al., 1995; Canada [c]	87 (age > 64 years)	2,070	Survey—exposure positive if frequently used		Pesticides 1.8 (0.9–3.4)	History of PD
Hertzman et al., 1994; Canada[c]	127	245	Interview—occupation with probable pesticide exposure	+	Pesticides in men 2.3 (1.1–4.9)	Neurologic exam
Morano et al., 1994; Spain[c]	74	148	Interview—direct and indirect exposure to pesticides		Pesticides 1.73 (1.0–3.0)	Neurologic exam
Butterfield et al., 1993; US [b,c]	63 (age < 50 years)	68	Questionnaire—pesticide or insecticide use 10 times in any year	+	Insecticides 5.8 Past dwelling fumigated 5.3 Herbicides 3.2 (2.5–4.1)	Standard criteria of PD by history
Hubble et al.,	63	76	Questionnaire—		Pesticides or	Neurologic exam

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides [a]	OR (95 % CI)	Neurologic Dysfunction
1993; US [c]			pesticide or herbicide use 20 days per year for >5 years	+	herbicides 3.4 (1.3–7.3)	
Jimenez-Jimenez et al., 1992; Spain [c]	128	256	Interview—exposure: applied pesticides, or lived and ate vegetables where pesticides use		Pesticides 1.3 (0.9–2.1)	Standard criteria of PD by history
Semchuk et al., 1992; Canada[c,d]	130	260	Interview—occupational exposure for each job held >1 month	+	Pesticides 2.25 (1.3–4.0) Herbicides 3.06 (1.3–7.0)	Neurologic exam
Stern et al., 1991; US [c]	69 (age < 40 years) 80 (age > 59 years)	149	Interview—insecticides and pesticides measured by self-report of home or garden use		Herbicides—young onset 0.9 (0.5–1.7) Herbicides—old onset 1.3 (0.7–2.4)	Standard criteria of PD by history
Wechsler et al., 1991; US	34 (age > 39 years)	22	Questionnaire—duration of occupational and home pesticide use		Home pesticides used more frequently by cases	Standard criteria of PD by history
Wong et al., 1991; US [c]	38 (19 sibling pairs with PD)	38 (age and sex matched and 19 sibling pairs with essential tremor)	Interview—acre-years = number of years exposed multiplied by number of acres applied herbicides or pesticides		Herbicides or pesticides 1.0 (0.7–1.4)	Neurologic exam
Golbe et al., 1990; US [b,d]	106	106	Telephone survey—sprayed pesticides or insect spray once a year for a total of 5 years	+	Sprayed pesticide 7.0 (5.8–8.5)	Neurologic exam
Hertzman et al., 1990; Canada	57	122	Questionnaire—ever worked in an orchard	+	Working in orchards 3.7 (1.3–10.3)	Neurologic exam
Koller et al., 1990; US [c]	150	150	Interview—acre-years = acres multiplied by years of herbicide or pesticide used		Herbicide or pesticide use 1.1 (0.9–1.3)	Neurologic exam
Ho et al., 1989; Hong Kong[c]	35 (age >60 years)	105	Interview—use of insecticides or herbicides (Y/N), farming, eating	+	Herbicides and pesticides 3.6 (1.0–12.9)	Neurologic exam

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides [a]	OR (95 % CI)	Neurologic Dysfunction
			raw vegetables			
Tanner et al., 1989; China	100	200	Interview—exposure to what? for at least 1 year before onset of PD		Fruit growing 1.00 (1.0–1.0) Corn growing 0.54 (0.3–1.1) Rice growing 1.29 (0.7–2.3)	Neurologic exam

Abbreviations: PMR, proportionate mortality ratio.
[a] For the objective of this Veterans and Agent Orange review series, only associations with herbicides are of possible relevance; only the phenoxy herbicides, cacodylic acid, and picloram are of specific interest.
[b] Modified from Le Couteur et al. (1999).
[c] Studies used in meta-analysis (Priyadarshi et al., 2000).
[d] Reviewed in *Update 1996* or *Update 1998*.

Update of the Epidemiologic Literature

Since *Update 2004*, several reports have examined the possible associations between PD and pesticide exposures, but none has addressed exposure to herbicides in particular or specifically to the chemicals of interest for this series of reviews. One was a mortality study described in the section on neurobehavioral disorders (Park et al., 2005), another was a prospective cohort study (Ascherio et al., 2006), and one was derived from the AHS cohort (Kamel et al., 2005).

Ascherio et al. (2006) investigated the relationship between PD and exposures self-reported in 1992 among the 143,325 participants in the Cancer Prevention Study II Nutrition Cohort who responded to the 2001 health status survey. From the 840 reported cases of PD, medical records were obtained for 677, permitting confirmation by a movement disorder specialist of 588 cases (413 diagnosed after 1992). After adjusting for age, sex, and smoking, the risk for PD was higher among the 5.7% of the participants (n = 7,864) reporting exposure to pesticides or herbicides compared to those not reporting such exposure (RR = 1.7, 95% CI 1.2–2.3, p = 0.002); this risk remained unchanged whether occupation was a farmer or not. The statistical significance the findings for "pesticides/herbicides" in this large prospective study with information on some possible confounders is worthy of note in light of the absence of association with the other 11 exposures studied, but again any elevation in the risk of PD cannot be attributed specifically to the chemicals of interest in this report with any certainty.

The design of the mortality study by Park et al. (2005) was not as strong. Information from death certificates was used to identify subjects with PD and their usual occupations. A primary limitation of the study is that "exposure to pesticides" was inferred on the basis of a retrospective job-exposure matrix that was not constructed to account for specific compounds; thus, although the authors indicated that exposure to pesticides was associated with mortality from PD, exposure to specific compounds of interest was not assessed.

From the baseline (cross-sectional) data collected in the Agricultural Health Study, exposure to various herbicides was more common in subjects who reported at least 10 neurologic symptoms than in those who reported fewer than 10 (Kamel et al., 2005). However, diagnosis of a neurologic condition, such as PD, generally relies on full clinical assessment that integrates

symptoms and signs with other historical information; it is not at all clear how to interpret nonspecific symptom groupings.

Biologic Plausibility

Interest in possible environmental causes of PD was increased by the observation that 1-methyl-4-phenyl-1,2,4,6-tetrahydropyridine (MPTP) poisoning induces a movement disorder that recapitulates the classic features of PD. The effects of MPTP and its bioactive metabolite MPP+ have become well known, and MPTP toxicity has become the pre-eminent animal model for PD research. It is notable that MPP+ is similar in chemical structure to paraquat (a commonly used herbicide, although not one used in Vietnam), but it is different from the compounds of interest in this report.

Studies detailed in Chapter 3 addressed a hypothesis that 2,4-D may cause significant damage to dopaminergic terminals and contribute to nigrostriatal degeneration. The results did not support a link between acute exposure to 2,4-D and nigrostriatal injury in the mouse model. However, various studies have addressed neurologic systems in animal models, and several studies support effects of 2,4-D on the developing brain in animal models.

The etiology of PD remains unclear. Chemicals including chemicals of concern are known to be distributed to all organs including the CNS. Some chemicals have been associated with PD in the literature, including the herbicide paraquat, although that is not among the chemicals of concern here. Elbaz et al. (2004) reported results of a case-control study, indicating an association between specific alleles of cytochrome P450 2D6 (CYP2D6), unspecified pesticide exposure, and the risk of PD. These results suggest that the lowered enzyme activity associated with some alleles of CYP2D6 may represent a susceptibility factor for response to exposure to certain neurotoxicants. This study is consistent with earlier reports suggesting some as yet undefined involvement of CYP2D6 in the etiology of PD. This supports an implication that chemicals may be involved in PD, although not specifically the chemicals of concern.

A summary of biologic plausibility of neurologic effects arising from exposure to the herbicides used in Vietnam is presented at the end of this chapter, and in Chapter 3 there are detailed descriptions of the studies.

Synthesis

Epidemiologic studies have pursued various occupational exposures as potential risk factors for PD; pesticide use is among those receiving the most attention, but it has rarely been possible to isolate the effects of selected chemical herbicides, because exposures often are mixed and assessments usually are retrospective, relying on such broad categories as “ever exposed to any pesticide”, which, as noted above, is not considered informative for this report. In addition, reported associations have been inconsistent, and only rarely has evidence supported dose–response relationships. Thus, the data are weakened for the committee’s purposes by persistent methodologic limitations and by the lack of specificity for the compounds of interest.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that evidence of an association between exposure to the compounds of interest and PD remains inadequate or insufficient.

Amyotrophic Lateral Sclerosis

ALS is a progressive, adult-onset, motor neuron disease that presents with muscle atrophy, weakness, and fasciculations. Most cases of ALS are sporadic; only 5–10% of cases are familial. One-fifth of familial-ALS patients have mutations in the gene that encodes superoxide dismutase-1 (Rosen et al., 1993). The incidence of sporadic ALS is 1–2 per 100,000 person-years, and the incidence of ALS peaks between the ages of 55 and 75 years (Brooks, 1996). A specific diagnostic test does not exist, but clinical diagnosis has a high degree of accuracy (Rowland, 1998; Rowland and Shneider, 2001).

Summary of Update 2002 and Update 2004

ALS was first considered by the committee for *Update 2002*. Although multiple potential etiologic factors have been investigated (Breland and Currier, 1967; Deapen et al., 1986; Gallagher and Sander, 1987; Hanisch et al., 1976; Kurtzke and Beebe, 1980; McGuire et al., 1997; Roelofs-Iverson et al., 1984; Savettieri et al. 1991), associations have not been consistently identified.

Pesticide or herbicide exposure has been associated with increased risk of ALS, including a doubling of the risk from long-term occupational exposure to pesticides (Deapen et al., 1986) and a tripling of the risk from exposure to agricultural chemical products (Savettieri et al., 1991) and from exposure to herbicides (McGuire et al., 1997), although none of those risk estimates was statistically significant. A population-based case–control study demonstrated associations between exposure to agricultural chemical products and ALS in men, with a statistically significant 2.4-fold increased risk and a statistically significant trend with duration of exposure (McGuire et al., 1997). A mortality study of Dow Chemical Company employees exposed to 2,4-D included three deaths from ALS, with a significant positive association (RR = 3.45, 95% CI 1.10–11.11; Burns et al., 2001). Table 8-2 summarizes the results of the relevant studies.

Table 8-2. Epidemiologic Studies of Pesticide [a] Exposure and Amyotrophic Lateral Sclerosis

Reference; Country	Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides [a]	OR (95% CI)	Neurologic Dysfunction
Morahan and Pamphlett, 2006	179	179	Questionnaire – exposure to environmental toxicants		Herbicide or pesticide exposure 1.6 (1.0–2.4); Industrial exposure 5.6 (2.1–15.1)	Self-reported
ADVA, 2005c			Deployment to Vietnam		4.7 (1.0–22.8)	
Weisskopf et al., 2005			Self-administered questionnaire		1.5 (1.1–2.1) $p = 0.007$	Self-reported military services and death certificates
Burns et al., 2001; US	1,567	40,600	Industrial hygienist ranked job exposure. cumulative exposure, years, or each job times weighted exposure 2,4-D	+	3.45 (1.1–11.1)	Death certificates
McGuire et al., 1997; US	174	348	Self-reported lifetime job history and workplace exposures reviewed by panel of four industrial hygienists	+	Herbicide exposure - 2.4 (1.2–4.8); significant trend analysis for dose-effect relationship with agricultural chemicals - $p = 0.03$	Newly diagnosed with ALS 1990–1994 in western Washington state
Chancellor et al., 1993; Scotland	103	103	Required regular occupational exposure to pesticides for 12 months or more		1.4 (0.6–3.1)	Scottish Motor Neuron Register
Savettieri et al., 1991; Italy	46	92	Continual exposure to agricultural chemicals		3.0 (0.4–20.3)	Cases reviewed by neurologists
Deapen et al., 1986; US	518	518	Ever worked in presence of pesticides		2.0 (0.8–5.4)	ALS Society of America

[a] For the objective of this Veterans and Agent Orange review series, only associations with herbicides are of possible relevance; only the phenoxy herbicides, cacodylic acid, and picloram are of specific interest.

Update of the Epidemiologic Literature

Since *Update 2004*, three studies relevant to the committee's charge have been identified. One evaluated the possible association between ALS and occupational exposures to herbicides and pesticides, and two evaluated the possible association between ALS and military service in Vietnam.

Morahan and Pamphlett (2006) published a case–control study from Australia (179 cases and 179 convenience controls matched by age, sex, and ethnicity) in which they analyzed possible associations between ALS and exposures to various environmental toxicants. Exposures were based on subjects' self-reports with a structured questionnaire. The authors report increased risk associated with exposure to herbicides or pesticides (OR = 1.57, 95% CI 1.03–2.41). A dose-reponse was suggested by higher risk estimates for subjects reporting regular exposure (OR = 4.65, 95% CI 1.82–11.87) and industrial exposure (OR = 5.58, 95% CI 2.07–15.06); the relationship was apparent for use in hobby gardening, but not in farming. Those estimates remained significantly increased after Bonferroni correction for multiple comparisons, and this reduced the likelihood that the results were due to chance alone. Although materials from the cases' neurologists were reviewed to confirm a probable or definite ALS diagnosis by well-established clinical criteria, the cases in this study were self-referred members of Australian ALS associations; similarly, the controls were a non-random collection of spouses, relatives, and acquaintances of the patients, and community volunteers. Thus the means of identifying subjects raises concerns about possible selection bias. The findings were also limited by the imprecise exposure assessment.

By following up the vital status of the American Cancer Society's cohort for the Cancer Prevention Study II, Weisskopf et al. (2005) conducted a prospective cohort study of the relationship between self-reported military service and death from ALS as coded on death certificates listed in the US National Death Index in 1989–1998. Among 408,288 men without self-reported "serious illness" at enrollment (1982) and alive at the beginning of 1989, 280 deaths from ALS were observed. With control for age and smoking history, the risk of dying from ALS was significant (RR = 1.58, 95% CI 1.14–2.19); further adjustment for several factors that have been suggested to contribute to the risk of ALS (education, alcohol intake, several occupations, and self-reported exposure to pesticides and herbicides) only slightly modified by adjustment (RR = 1.53, 95% CI 1.12–2.09). Risk estimates were similarly elevated for all branches of the military except the Marines and for service during the World-War-II, Korean-War, and Vietnam-War eras. Largely on the basis of that report, with supporting evidence from three other studies related to service in the Gulf War, the Institute of Medicine has recently concluded that the evidence linking ALS with military service is limited or suggestive (IOM, 2006). This VAO committee reviewed the findings carefully and concluded that they are not directly relevant to its charge, however, because the reported association is with military service itself rather than with exposure to specific compounds of interest. The insensitivity of the findings to adjustment for exposure to herbicides and pesticides (simultaneously with other factors) further reduces the support of these data for an association between ALS and the herbicides sprayed in Vietnam.

The third study focused on Vietnam veterans from Australia and reporting an association between deployment in Vietnam and ALS (ADVA, 2005c). The study compared troops deployed in Vietnam with those who did not serve in Vietnam and is described in more detail in Chapter 4.

The authors identified a large increase in relative risk of ALS that was of borderline statistical significance (9 cases; RR = 4.73, 95% CI 0.98–22.76).

Biologic Plausibility

Several studies have been published since Update 2004 that deal with mechanisms of neurotoxicity that might be ascribed to chemicals of concern, notably 2,4-D and TCDD. Molecular effects of the chemicals of concern are described in detail in Chapter 3. Some of those effects suggest possible pathways by which there could be effects on the neural systems involved in this outcome. A number of the studies suggest that there are neurological effects of chemical of interest in animal models when exposure is during development. There also are some studies that further support suggestions that the level of reactive oxygen species could alter the functions of specific signaling cascades and may be involved in neurodegeneration. Although not specifically concerning the chemicals of interest, such studies are potentially relevant to the chemicals of concern, as TCDD and herbicides have been reported to elicit oxidative stress (Celik et al., 2006; Shen et al., 2005). The mechanistic studies suggest possible avenues to pursue to determine linkages between the chemicals of concern and the neurological outcomes that could result in adult humans. A summary of biologic plausibility of neurologic effects arising from exposure to the compounds of interest is presented at the end of this chapter and in Chapter 3.

Synthesis

Epidemiologic studies of ALS have pursued a variety of occupational exposures as potential risk factors; pesticide and herbicide exposures are among those receiving the most attention. Although it has rarely been possible to isolate the effects of selected compounds of interest, a study of a cohort of 2,4-D production workers did identify significantly increased risk (Burns et al., 2001); however, this result is considered unstable, given the low number of cases and the wide confidence interval. Case–control studies of occupational exposures to pesticides and herbicides have identified significantly increased risks (McGuire et al., 1997; Morahan and Pamphlett, 2006), but they did not weigh heavily, because of imprecise exposure assessments and other design limitations. Although recent prospective (Weisskopf et al., 2005) and retrospective (ADVA, 2005b) studies have identified increased risk in veterans who served in Vietnam, they tend to implicate military service itself rather than exposure to the specific compounds of interest.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous *VAO* reports, the committee concludes that the evidence of an association between exposure to the compounds of interest and ALS remains inadequate or insufficient.

PERIPHERAL NEUROPATHY

Peripheral neuropathy consists of disorders of the PNS. Manifestations of this syndrome can include a combination of sensory changes, motor weakness, and autonomic instability. Clinically, various forms of peripheral neuropathy can be characterized by the distribution of nerve abnormalities and their patterns of progression. For example, a peripheral neuropathy resulting from toxic exposure usually affects the limbs in a symmetric pattern, beginning distally (in the toes) and moving proximally (toward the spine) and providing the basis of the term "dying-back neuropathy," now more rigorously referred to as "distal axonopathy." Thus, sensory deficits at the ankle generally occur after deficits in the toes. Physiologically, various forms of peripheral neuropathy can be characterized by results of electrodiagnostic testing to indicate which neural structures are affected. Most toxicant-induced neuropathies involve injury to the nerve cell bodies (neurons) or nerve fibers (axons) that produces changes in the amplitude of a nerve's response to an electric stimulus. In severe cases, there also can be slowing in the speed of nerve impulses. Those conditions contrast with the prominent slowing of nerve-conduction velocity (NCV) that results from injury to myelin, as seen in such inflammatory conditions as Guillain-Barré syndrome.

The clinical appearances of several peripheral neuropathies can be virtually identical, so it is often difficult to determine whether a peripheral neuropathy is caused by a toxic exposure. Sometimes, clues in particular features of the clinical history and presentation suggest toxic exposure, but complaints of peripheral nerve disorders often occur in isolation and are monotonously similar, so etiologic determination can be difficult. As many as 30% of cases are "idiopathic"; that is, no etiology is determined despite exhaustive clinical evaluation.

The most common toxicant-induced neuropathy occurs as a result of chronic alcohol exposure. Peripheral neuropathy also occurs commonly as a complication of diabetes: its reported prevalence in people with chronic diabetes is up to 50%. It is important to include assessment of alcohol use and diabetes as covariates in epidemiologic studies because the neuropathies that are related to these conditions are clinically and physiologically indistinguishable from other toxicant-induced neuropathies.

Clinically, in cases of toxicant-induced peripheral neuropathy, stabilization or improvement is the rule after exposure ends. Recovery might not be complete, however, and the degree of recovery can depend on the severity of the initial deficits. Furthermore, there is a possibility of "subclinical" effects, and a person might be unaware of symptoms although evidence of nerve dysfunction can be found in a detailed neurologic examination or through electrodiagnostic testing.

In *VAO*, peripheral neuropathy was considered a single category of disease. Before revising the conclusion regarding neuropathies, the committee for *Update 1996* divided them into "acute and subacute" and "chronic" classifications (on the basis of when an outcome occurs relative to exposure). In this section of this report, however, the terms "acute" (brief) and "chronic" (prolonged or protracted) describe the time course of toxicant exposure. "Early" and "delayed onset" are used to describe the time course of the neuropathy. The distinction between "transient" and "persistent" is not always clear, because recovery may be protracted and incomplete. The committee considers a neuropathy to be of early onset and transient if abnormalities appear and resolve within 2 years after cessation of external exposure.

Conclusions from *VAO* and Updates

VAO and subsequent updates noted that the literature on peripheral neuropathy had been difficult to integrate because it is characterized by variable methods that lack uniform operational definitions. The techniques used to identify affected persons, to define comparison populations, and to assess exposures differ considerably among studies. Also, many of the studies are limited by nonrandom selection, which raises a concern about bias, and by the relatively small number of participants, which decreases confidence in risk estimates and limits the power to detect a true association. There have been variable results, with some studies demonstrating abnormalities of peripheral nerve function and others not.

In *VAO*, the committee reviewed results of four occupational-cohort studies of workers who had been exposed to the compounds of interest (Moses et al., 1984; Singer et al., 1982; Suskind and Hertzberg; 1984; Sweeney et al., 1993). Singer et al. (1982) reported decreased NCVs in 2,4-D and 2,4,5-T production workers who were examined 2 months after exposures were reduced. In former 2,4,5-T production workers with a history of chloracne (10 years after last exposure), Moses et al. (1984) found diminished pin-prick sensation, but Suskind and Hertzbert (1984) did not find differences in NCVs. Similarly, Sweeney et al. (1993) reported decreased pin-prick sensation but no differences in NCVs in former herbicide production workers (evaluated 15 years or more after their last exposure).

VAO also reviewed epidemiologic studies of populations potentially exposed to TCDD in the environment. A series of studies in Italy evaluated peripheral neuropathy in the Seveso population after the industrial accident on July 10, 1976 (Assennato et al., 1989; Barbieri et al., 1988; Boeri et al., 1978; Filippini et al., 1981; Gilioli et al., 1979). Boeri et al. (1978) reported more frequent symptoms and signs of neuropathy in a cohort of residents living in the contaminated area than in a comparison group who were last examined 7–10 months after the explosion. There was no statistical difference in conduction velocity between groups. Gilioli et al. (1979) noted electrodiagnostic abnormalities in laboratory technicians potentially exposed to TCDD from analytic samples; however, the technicians were also exposed to solvents used in the analytic process. Fillipini et al. (1981) reported an increased prevalence of peripheral neuropathy in Seveso residents with evidence of high exposure to TCDD (chloracne or liver enzyme abnormalities) who were last examined 21 months after the accident. Barbieri et al. (1988) reported a higher rate of abnormalities on neurologic examination and electrodiagnostic testing in subjects with a history of chloracne who were examined 6 years after the accident, but there was no significant increase in peripheral neuropathy as defined by World Health Organization (WHO) criteria. Assennato et al. (1989) described electrodiagnostic evaluation of that group 9 years after the accident; no differences were observed in NCV or neuropathy as defined by WHO criteria. Other environmental studies reviewed in *VAO* were of Missouri residents potentially exposed to TCDD in the early 1970s when waste oil was sprayed to control dust (Hoffman et al., 1986; Stehr et al., 1986; Webb et al., 1987). Although more frequent sensory abnormalities were reported in potentially exposed subjects, the differences were not statistically significant, and the semi-ecologic study design was not suited to causal inference. Some of the data from epidemiologic studies of environmental exposures have suggested an increased risk of peripheral nerve abnormalities, but evidence of an association between exposure to the compounds of interest and peripheral neuropathy is inconsistent.

Studies of Vietnam veterans were also reviewed in *VAO* (AFHS, 1984, 1987, 1991; CDC, 1988). A study by the Centers for Disease Control and Prevention (CDC, 1988) focused on

service in Vietnam, not on exposure to the compounds of interest, and therefore provided no evidence of the possible effects of specific exposures. There was no indication of increased risk of peripheral neuropathy in the first reports on Ranch Hand (RH) veterans (AFHS, 1984, 1987, 1991). Studies reviewed in *VAO* did not indicate an association between exposure and peripheral neuropathy in Vietnam veterans.

Update 1996 reviewed two new epidemiologic studies. Using an administrative database, Zorber et al. (1994) found no evidence of increased use of medical services for diagnosis of peripheral neuropathy in workers previously exposed to TCDD at a BASF plant. Decoufle et al. (1992) reported no association between self-reported exposure to herbicides in Vietnam and peripheral neuropathy. The limitations of those studies were such that they did not confirm or refute a possible relationship between exposure and neuropathy.

In addition, the committee responsible for *Update 1996* reviewed case reports that described peripheral neuropathy after exposures to the compounds of interest (Berkley and Magee, 1963; Goldstein et al., 1959; Todd, 1962). In each instance, the peripheral neuropathy improved gradually but had not resolved completely even after several months or years. The possibility cannot be entirely excluded that the five cases reported in those publications were unrelated to herbicide exposure and were examples of other disorders, such as idiopathic Guillain-Barré syndrome. The committee also considered several supportive animal models (Grahmann et al., 1993; Grehl et al., 1993; see "Biologic Plausibility" below). The committee concluded that there was limited or suggestive evidence of an association between exposure to the compounds of interest and early-onset transient peripheral neuropathy.

Update 1998 reviewed no new studies. The context for the issue of peripheral neuropathy, its relationship with toxic exposures, and the occurrence of diabetes mellitus was discussed. In particular, it was noted that neuropathy is a common consequence of diabetes. That was particularly relevant because the committee issued a special report a year later that concluded that there was limited or suggestive evidence of an association between diabetes and exposure to Agent Orange.

Update 2000 reviewed what was then the most recent report on RH veterans (AFHS, 2000), which combined signs of peripheral neuropathy to produce increasingly specific, graded indexes of neuropathy—a common approach in epidemiologic studies. RH veterans were significantly more likely than were comparison subjects to have abnormalities in the indexes, and the prevalence of abnormalities increased with dioxin concentration. Although the clinical relevance of epidemiologic indexes of neuropathy is never certain, the strong associations described between the indexes and the conditions known to produce peripheral neuropathy, such as diabetes and alcohol use, supported their validity in this study. The AFHS investigators included those conditions as potential confounders in the statistical analysis. However, the effect of diabetes could not be eliminated in the most specific neuropathy index, because there were not enough non-diabetic subjects. It therefore was impossible, lacking any effect of diabetes, to estimate the association between dioxin exposure and neuropathy.

Update 2002 considered one peer-reviewed article that described the peripheral-neuropathy data on the AFHS cohort (Michalek et al., 2001). In a primary analysis, the investigators had included diabetes as a potential confounder in the statistical model. In a secondary analysis, subjects with conditions that were known to be associated with neuropathy were excluded, and subjects with diabetes were enumerated. In both analyses, there were strong and significant associations between possible and probable neuropathy and dioxin concentration, and significant trends were found with increasing concentrations of dioxin. However, there were too few non-

diabetic subjects to produce meaningful estimates of risk in the absence of the contribution of diabetes. Thus, questions remained about the specific association between exposure to the compounds of interest and peripheral neuropathy in the absence of any effect of diabetes.

Update 2004 also considered one peer-reviewed article (Kim et al., 2003), which reported an association between Korean veterans' service in Vietnam and peripheral neuropathy. Methodologic limitations, such as a concern about recall bias and residual confounding due to diabetes, and issues related to the TCDD dose estimation prevented a strong inference.

Update of the Scientific Literature

Since *Update 2004* (IOM, 2005), no reports dealing with peripheral neuropathy as a diagnosis have been published, although a cohort report (Kamel et al., 2005) assessed neurologic symptoms, some of which could arise from peripheral neuropathy. As mentioned in the section on PD, it is not clear how to interpret studies that simply rely on nonspecific clinical findings. Furthermore, it is not possible to rule out bias or residual confounding.

There is no compelling new evidence that supports an association between peripheral neuropathy and exposure to the compounds of interest.

Biologic Plausibility

No new studies directly pertinent to peripheral neuropathy were identified in this update. However, it is worth reiterating findings from earlier updates. Neuronal cell cultures treated with 2,4-D showed decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis. Those mechanisms are important for maintaining synaptic connections between nerve cells and supporting the mechanisms involved in axon regeneration during recovery from peripheral neuropathy. Grahmann et al. (1993) and Grehl et al. (1993) reported on abnormalities in electrophysiology and pathology, respectively, observed in the peripheral nerves of rats treated with TCDD. When the animals were sacrificed 8 months after exposure, there was pathologic evidence of persistent axonal nerve damage and histologic findings typical of toxicant-induced injury. Those results constitute evidence of the biologic plausibility of an association between peripheral neuropathy and exposure to the compounds of interest. A summary of biological plausibility of neurologic effects arising from exposure to the compounds of interest is presented at the end of this chapter and more detailed discussion appears in Chapter 3.

Synthesis

Over the last 50 years, a body of literature has accumulated that suggests an association between the compounds of interest and peripheral neuropathy. Past committees have concluded that there is evidence of an association between "acute and subacute transient" peripheral neuropathy and exposure to at least one compound of interest (*Update 1996*). However, there remained questions about whether evidence supported an association with persistent neuropathy.

Human case reports have documented peripheral neuropathy after acute exposure to large amounts of 2,4-D as shown by neurologic examination and electrodiagnostic testing. Reports have indicated eventual symptom stabilization and improvement, but sensory and motor deficits have persisted in some people for months or years after exposure ended.

Several epidemiologic studies have reported increased risk of peripheral neuropathy in populations exposed to the compounds of interest in a variety of occupational and environmental settings. However, the literature is inconsistent and suffers from methodologic limitations. The most dramatic exposures have involved industrial accidents that caused environmental contamination, such as the one in Seveso, Italy, in 1976. Studies of residents in that region have shown early-onset neuropathy, and subclinical abnormalities in some subjects have been demonstrated with electrodiagnostic testing.

Epidemiologic studies that used appropriate comparison groups and standard techniques for diagnosis and assessment of exposure have not demonstrated consistent associations between exposure to the compounds of interest and the development of peripheral neuropathy. Several reports have shown no significant association, and in the reports that did indicate an association, chance, bias, or confounding could not be ruled out with confidence. In particular, diabetes might confound the results, inasmuch as many of the subjects with neuropathy also had diabetes, which is a known cause of neuropathy. Controlling for the effects of diabetes is a technical challenge because there is evidence of an association between diabetes and exposure to at least one of the compounds of interest (IOM, 2003); in many cases, diabetes could be in the causal pathway that links exposure and peripheral neuropathy.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the compounds of interest and early-onset transient peripheral neuropathy.

On the basis of its evaluation of the evidence reviewed here and previous *VAO* reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and delayed or persistent peripheral neuropathy.

SUMMARY

Biologic Plausibility

Experimental data continue to accrue regarding the biologic plausibility of a connection between exposure to the compounds of interest and various neurologic disorders. This section summarizes in a more general way some of this information reviewed in the current update, as well as information from the prior update, for a more complete summary. A more detailed discussion of the newer research can be found in Chapter 3.

The effects of TCDD are mediated by interaction with the AhR, a protein found in animal and human cells. The AhR complex is known to bind DNA and produce changes in transcription, thereby influencing genetic function. The AhR complex can produce an array of molecular effects that influence cell growth, hormone regulation, and normal cellular metabolism. Although some

structural differences have been identified in the AhRs of different species, the AhR is functionally similar among species. Therefore, data from animal studies can be used to support the biologic plausibility of human neurotoxicity.

Several studies have been published since Update 2004 that deal with mechanisms of neurotoxicity that might be ascribed to chemicals of concern, notably 2,4-D and TCDD. Molecular effects of the chemicals of concern are described in detail in Chapter 3. Some of those effects suggest possible pathways by which there could be effects on the neural systems involved in this outcome. A number of the studies suggest that there are neurological effects of chemicals of interest in animal models when exposure is during development. There also are some studies that further support suggestions that the level of reactive oxygen species could alter the functions of specific signaling cascades and may be involved in neurodegeneration. Although not specifically concerning the chemicals of interest, such studies are potentially relevant to the chemicals of concern, as TCDD and herbicides have been reported to elicit oxidative stress. The mechanistic studies suggest possible avenues to pursue to determine linkages between the chemicals of concern and the neurological outcomes that could result in adult humans.

Basic scientific studies have emphasized the importance of alterations in neurotransmitter systems as potential mechanisms that underlie TCDD-induced neurobehavioral disorders. Neuronal cultures treated with 2,4-D exhibited decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis. Those mechanisms are important for maintaining the connections between nerve cells that are necessary for neuronal function and that are involved in axon regeneration and recovery from peripheral neuropathy. Animal experiments have demonstrated that TCDD treatments affect the fundamental molecular events that underlie neurotransmission initiated by calcium uptake. Mechanistic studies have demonstrated that 2,4,5-T can alter cellular metabolism and cholinergic transmission necessary for neuromuscular transmission.

TCDD treatment of rats at doses that do not cause general systemic illness or wasting disease produces electrodiagnostic changes in peripheral nerve function and pathologic findings that are characteristic of toxicant-induced axonal peripheral neuropathy.

As discussed in Chapter 3, extrapolation of observations of cells in culture or animal models to humans is complicated by differences in sensitivity and susceptibility among animals, strains, and species; by the lack of strong evidence of organ-specific effects across species; and by differences in route, dose, duration, and timing of chemical exposures. Thus, although the observations in themselves cannot support a conclusion that Agent Orange produces neurotoxic effects in humans, the studies provide evidence of the biologic plausibility of an association.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest (2,4-D, 2,4,5-T, TCDD, picloram, and cacodylic acid) and neurobehavioral disorders (cognitive or neuropsychiatric), PD, or ALS.

In *Update 1996*, the committee concluded that there was limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and “acute and subacute transient” peripheral neuropathy. The evidence was drawn from occupational and other

studies in which subjects were exposed to a variety of herbicides and herbicide components. Information available to the committees responsible for *Update 1998*, *Update 2000*, and *Update 2002* supported that conclusion. The committee for *Update 2004* exhaustively reviewed the data on peripheral neuropathy and concluded that there was limited or suggestive evidence of an association between exposure and "early onset, transient" peripheral neuropathy, but that the evidence was inadequate or insufficient to support an association between exposure to the compounds of interest and "delayed or persistent" peripheral neuropathy.

The present committee did not reviewed new evidence that would modify the conclusions of prior VAO committees concerning possible associations between exposure to the chemicals sprayed in Vietnam and adverse neurologic health outcomes.

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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9

Other Health Effects

This chapter discusses data on the possible association between exposure to the herbicides used in Vietnam—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid)—and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a contaminant of 2,4,5-T, and the following non-cancer health outcomes: chloracne, porphyria cutanea tarda (PCT), respiratory disorders, immune-system disorders, diabetes, lipid and lipoprotein disorders, gastrointestinal and digestive disease (including liver toxicity), circulatory disorders, endometriosis, and adverse effects on thyroid homeostasis.

For each type of health outcome, background information is followed by a brief summary of the findings described in earlier reports by the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. In the discussion of the most recent scientific literature, studies are grouped by exposure type (occupational, environmental, or Vietnam veteran). For articles on that report on only a single health outcome and that are not revisiting a previously studied population, design information is summarized with the results; design information on other studies can be found in Chapter 4 and in Appendix B. A synopsis of toxicologic and clinical information related to the biologic plausibility of the chemicals of interest influencing the occurrence of the health effect is presented next, followed by a synthesis of all the material reviewed. Each health outcome section ends with the present committee's conclusions regarding the strength of the evidence for support of an association with the chemicals of interest. The categories of association and the committee's approach to categorizing the health outcomes are discussed in Chapters 1 and 2.

CHLORACNE

Chloracne is a skin disease that is characteristic of exposure to TCDD and other diaromatic organochlorine compounds. It shares some pathologic processes (such as the occlusion of the orifice of the sebaceous follicle) with more common forms of acne (such as acne vulgaris), but it can be differentiated by the presence of epidermoid inclusion cysts, which are caused by proliferation and hyperkeratinization (horn-like cornification) of the epidermis and sebaceous gland epithelium. Although chloracne is typically distributed over the eyes, ears, and neck, among chemical-industry workers exposed to TCDD it can also occur on the trunk, genitalia, and buttocks (Neuberger et al., 1998).

Chloracne has been exploited as a marker of exposure in epidemiologic studies of populations exposed to TCDD and related chemicals. It is one of the few findings in humans that are consistently associated with such exposure, and it is a well-validated indicator of high-dose exposure to TCDD and related compounds (Sweeney et al., 1997/98). If chloracne occurs, it

appears shortly after the chemical exposure, not after a long latent period. Although it is resistant to acne treatments, it usually regresses over time. Therefore, new cases of chloracne in Vietnam veterans would not be the result of exposure during Vietnam and are not of concern for this report. It should be noted that absence of chloracne does not necessarily indicate absence of substantial exposure to TCDD, as is apparent from studies of people with documented exposure to TCDD after the Seveso accident (Baccarelli et al., 2005a). And there is not necessarily a correlation between serum TCDD concentrations and the occurrence or severity of chloracne.

Conclusions from *VAO* and Updates

The committee responsible for *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam,* hereafter referred to as *VAO* (IOM, 1994), determined that there was sufficient evidence of an association between exposure to at least one compound of interest and chloracne. Additional information available to the committees responsible for *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), and *Update 2004* (IOM, 2005) did not change that conclusion. Reviews of the studies that underlie the conclusion can be found in the earlier reports.

Update of the Epidemiologic Literature

Environmental Studies

Since *Update 2004*, there has been a single environmental study concerning chloracne and a publication of case reports, one of which involved a high-profile news story.

Baccarelli et al. (2005b) conducted a case–control study of chloracne in the population of Seveso, Italy. They studied 101 cases of chloracne diagnosed after the accident and 211 controls in two subsets: 101 controls matched to the individual cases by sex, age, and zone of residence at the time of the accident and 110 drawn as a random sample of noncases recruited previously by Landi et al. (1997, 1998) from residents of contaminated and noncontaminated areas. The second control group was much older (median age, 31 years compared with 8 years for the cases and the matched control group). Serum TCDD had been measured in the middle 1990s.

People with high plasma TCDD (over 10 ppt) had an increased risk of chloracne, which remained significant after adjustment for age, sex, and place of residence (odds ratio [OR] = 3.7, 95% confidence interval [CI] 1.6–8.8). Higher risks of having developed chloracne were observed among subjects who were younger than 9 years old at the time of the accident (OR = 7.4, 95% CI 1.8–30.3) and among those with relatively light hair color (OR = 9.2, 95% CI 2.6–32.5). The results were described as being similar with and without inclusion of the second set of controls.

Sterling and Hanke (2005) described several individual case reports involving acute dioxin exposures. The first concerns Viktor Yushchenko, president of Ukraine, who may have been poisoned at a dinner party. An extremely high concentration of dioxin in blood samples were documented—the second highest concentration recorded in humans. Severe chloracne symptoms were also described. The second case report concerns a 30-year-old secretary who may have

ingested TCDD in the chemical laboratory where she worked. During the first year after exposure, facial inflammation and acne were observed; they gradually progressed to dense cysts on the entire face and a few lesions on the body. Various other symptoms were described. The patient has had several surgical interventions for the deep inflammation and cysts. An exposed colleague of the patient also had high serum TCDD but had only mild symptoms, which resolved after treatment. The Sterling and Hanke (2005) paper appears to be a second-hand report of these cases, and it is not clear that the authors had direct clinical contact with the patients.

No new occupational or Vietnam veteran studies concerning exposure to the compounds of interest and chloracne were published since *Update 2004*.

Biologic Plausibility

As noted in previous reports, chloracne-like skin lesions have been reported in several animal species in response to exposure to TCDD but not to purified phenoxy herbicides. Most data that have accrued in the last 2 decades have demonstrated that TCDD alters differentiation of human keratinocytes. The most recent studies (Geusau et al., 2005) support the idea that TCDD accelerates the events associated with early differentiation but also obstructs completion of differentiation. In fact, it has recently been proposed (Panteleyev and Bickers, 2006) that the major mechanism that underlies TCDD-induced chloracne is activation of the stem cells in the basal layer of the skin to differentiate and inhibition of their ability to commit fully to a differentiated status. Recent work using a constitutively activated form of the aryl hydrocarbon receptor (AhR) implicates additional inflammation-related mechanisms by which TCDD exposure may lead to chloracne (Tauchi et al., 2005). The data provide a biologically plausible mechanism for the induction of chloracne by TCDD.

Synthesis

The new information supports the conclusion of previous committees that there is sufficient evidence of an association between exposure to at least one compound of interest and chloracne.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one compound of interest and chloracne.

PORPHYRIA CUTANEA TARDA

Porphyrias are uncommon disorders caused by deficiencies of enzymes involved in the pathway of biosynthesis of heme, the iron-containing, nonprotein portion of the hemoglobin molecule. PCT is a heterogeneous group of disorders caused by a deficiency of a specific enzyme, uroporphyrinogen decarboxylase. PCT, the most common of the porphyrias, can be

inherited but usually is acquired. Type I PCT, which accounts for 80–90% of all cases, is an acquired disease that typically becomes evident in adulthood. Type I PCT can occur spontaneously but usually occurs in conjunction with environmental factors, such as alcohol consumption, exposure to estrogens, or use of some medications.

The most important clinical finding is cutaneous photosensitivity. Sensitivity to sunlight is thought to result from the excitation of excess porphyrins in the skin by long-wave ultraviolet radiation, which leads to cell damage. Fluid-filled vesicles and bullae develop on sun-exposed areas of the face and on the dorsa of the hands, feet, forearms, and legs. Other features include hypertrichosis (excess hair) and hyperpigmentation (increased pigment), especially on the face. People with PCT have increased porphyrins in the liver, plasma, urine, and stools. Iron, estrogens, alcohol, viral hepatitis, and chlorinated hydrocarbons can aggravate the disorder. Iron overload is almost always present in people who have PCT.

Conclusions from *VAO* and Updates

On the basis of strong animal studies and case reports demonstrating induction of PCT with exposure and resolution following removal of exposure, the committee responsible for *VAO* determined that there was sufficient evidence of an association between exposure to TCDD and PCT in genetically susceptible people. Because PCT is manifested shortly after exposure to TCDD, new cases of PCT attributable to exposure during the Vietnam War are not expected to occur.

The committee responsible for *Update 1996* reviewed studies of three cohort populations with substantial exposures to TCDD, which all had non-positive results for even changes in urinary porphyrin levels that usually occur at lower exposure levels than clinical signs of PCT. These new data led it to conclude that there was only limited or suggestive evidence of an association. *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not further change the revised conclusion. Reviews of the relevant studies are found in the earlier reports.

Update of the Epidemiologic Literature

No new occupational, environmental, or Vietnam-veteran studies concerning exposure to the compounds of interest and porphyria cutanea tarda were published since *Update 2004*.

Biologic Plausibility

PCT has not been replicated in animal studies with TCDD, although other porphyrin abnormalities have been reported. However, administration of TCDD to mice results in an accumulation of uroporphyrin that occurs in manner that requires the AhR, CYP1A1, and CYP1A2 (Robinson et al., 2002; Smith et al., 2001; Uno et al., 2004).

Synthesis

No new studies provide evidence of a direct risk of PCT in adults since those reviewed in *Update 2004*.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one compound of interest and PCT.

RESPIRATORY DISORDERS

For the purposes of this report, nonmalignant respiratory disorders are acute and chronic lung diseases other than cancer. Acute nonmalignant respiratory disorders include pneumonia and other respiratory infections; they can be increased in frequency and severity when the normal defense mechanisms of the lower respiratory tract are compromised. Chronic nonmalignant respiratory disorders generally take one of two forms: Airways disease encompasses disorders characterized by obstruction of the flow of air out of the lungs, among them asthma and chronic obstructive pulmonary disease (COPD); COPD is also known as chronic obstructive airways disease and includes emphysema and chronic bronchitis. Parenchymal disease, or interstitial disease, generally includes disorders that cause inflammation and scarring of the deep lung tissue, including the air sacs and supporting structures; parenchymal disease is less common than airways disease, and its disorders are characterized by reductions in lung capacity, although they can include a component of airway obstruction. Some severe chronic lung disorders, such as cystic fibrosis, are hereditary. Because Vietnam veterans received health screenings before entering military service, few severe hereditary chronic lung disorders are expected in that population.

The major risk factor for many nonmalignant respiratory disorders is cigarette-smoking. Although cigarette-smoking is not associated with all diseases of the lungs, it is the major cause of many airways disorders, especially COPD; it contributes to some interstitial disease; and it compromises host defenses in such a way that people who smoke are generally more susceptible to some types of pneumonia. Cigarette-smoking also makes almost every respiratory disorder more severe and symptomatic than it would be in its absence. The frequency of habitual cigarette-smoking varies with occupation, socioeconomic status, and generation. For those reasons, cigarette-smoking can be a major confounding factor in interpreting the literature on risk factors for respiratory disease. Vietnam veterans are reported to smoke more heavily than are non-Vietnam veterans (McKinney et al., 1997).

It is well known that causes of death from respiratory diseases, especially chronic ones, are highly misclassified on death certificates. Grouping various respiratory diseases for analysis, unless they all are associated with a given exposure, will lead to attenuations of the estimates of relative risk as well as a diminution of statistical power. Moreover, deaths from respiratory and cardiovascular diseases are often confused. In particular, when persons have both conditions concurrently and both contributed to death, there may be some uncertainty about which cause should be selected as the primary underlying cause. In other instances, errors may arise in selecting one underlying cause in a complex chain of health events (for example, if COPD leads to congestive heart failure and then to respiratory failure). Many study populations were rather small, so investigators grouped deaths from all nonmalignant respiratory diseases into one category, combining pneumonia, influenza, and other diseases with COPD and asthma.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine an association between exposure to the compounds of interest and the respiratory disorders specified above. Additional information available to the committees responsible for *Update 1996* and *Update 1998* did not change that finding. *Update 2000* drew attention to findings from the Seveso cohort that suggested a higher mortality from nonmalignant respiratory disorders among study subjects, particularly males, who were more heavily exposed to TCDD. Those findings were not replicated in several other relevant studies, although one showed an increase (which did not attain statistical significance). The committee for *Update 2000* concluded that although new evidence suggested an increased risk of nonmalignant respiratory disorders, particularly COPD, among people exposed to TCDD, the observation was tentative and the information insufficient to determine an association between the exposures of interest and respiratory disorders. Additional information available to the committee responsible for *Update 2002* did not change that finding. *Update 2004* included a new cross-sectional study among residents near a wood-treatment plant (Dahlgren et al., 2003). Soil and sediment samples from a ditch in the neighborhood contained dioxins and furans. Although exposed residents reported greater frequency of chronic bronchitis by history (17.8% vs 5.7%, $p < 0.0001$) and asthma by history (40.5% vs 11.0%, $p < 0.0001$) compared with a "non-exposed" control group, the committee concluded that selection bias and recall bias limited the utility of the results and that there was a possibility of confounding because history of tobacco use was not accounted for adequately. Table 9-1 summarizes the results of the relevant studies.

TABLE 9-1 Selected Epidemiologic Studies—Non-Malignant Respiratory Disease

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
Cohort studies			
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers, non-malignant respiratory mortality (ICD-9 480–519)	9	0.9 (0.4–1.8)
	New Zealand phenoxy herbicide sprayers, non-malignant respiratory mortality (ICD-9 480–519)	6	0.65 (0.2–1.2)
Blair et al., 2005	US Agriculture Health Study —COPD mortality		
	Private applicators	50	0.2 (0.2–0.3)
	Spouses	15	0.3 (0.2–0.7)
Hoppin et al., 2006	US Agriculture Health Study, commercial applicators exposed to 2,4-D—cross-sectional study of wheeze	225	1.3 (1.0–1.7)
Studies Reviewed in *Update 2002*			
Burns et al., 2001	Males employees of the Dow Chemical Company—manufacture exposed to 2,4-D between 1945–1994, non-malignant respiratory mortality (ICD-8 460–519)		
	All non-malignant respiratory	8	0.4 (0.2–0.7)
	Pneumonia	4	0.6 (0.2–1.4)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Studies Reviewed in *Update 2000*			
Steenland et al., 1999	NIOSH mortality study of chemical workers at 12 plants in US exposed to TCDD, non-malignant respiratory mortality (ICD-9 460–519)	86	0.9 (0.7–1.1)
Sweeney et al., 1997/98**	NIOSH follow-up study of production workers of sodium trichlorophenol and of 2,4,5-T ester contaminated with TCDD, chronic bronchitis and COPD	2	--
Studies Reviewed in *Update 1998*			
Becher et al., 1996	Four German production facilities of phenoxy herbicides and chlorophenols, non-malignant respiratory mortality (ICD-9 460–519)		
	Boehringer Ingelheim	10	0.52(0.3–1.0)
	Bayer Uerdingen	2	0.9 (0.1–3.1)
	Bayer Dormagen	0	0.00
	BASF Ludwigshafen	4	0.6 (0.2–1.6)
Svensson et al., 1995	Swedish fisherman exposed to TCDD, mortality from bronchitis or emphysema (ICD-7 490–493)		
	East coast	4	0.5 (0.2–1.2)
	West coast	43	0.8 (0.6–1.1)
Ott and Zober, 1996*	German workers exposed to trichlorophenol contaminated with TCDD from an accident at a BASF plant, 1953–1993, non-malignant respiratory mortality	1	0.1 (0.0–0.8)
Ramlow et al., 1996	Mortality of workers at a Dow Chemical plant, Michigan, producing pentachlorophenol contaminated with polychlorophenol dibenzodioxins (PCDD), 1940–1989		
	Non-malignant respiratory mortality (ICD-8 460–519)	14	0.9 (0.5–1.5)
	Cumulative PCP exposure		
	<1 Unit	3	0.6 (0.2–1.9)
	≥1 Unit	11	1.4 (0.8–2.5)
	Pneumonia (ICD-8 480–486)	6	1.1 (0.4–2.4)
	Emphysema (ICD-8 492)	4	1.3 (0.4–3.3)
Kogevinas et al., 1997	Mortality of male and female international workers producing or applying phenoxy herbicides, non-malignant respiratory mortality (ICD-9 460–519), 1939–1992		
	Men	252	0.8 (0.7–0.9)
	Women	7	1.1 (0.4–2.2)
Studies Reviewed in *Update 1996*			
Senthilselvan et al., 1992	Cross-sectional study of self-reported prevalence of asthma among male farmers in Saskatchewan (1982–1983)		
	Chlorinated hydrocarbons	31	0.8 (0.5–1.3)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Zober et al., 1994*	German workers exposed to trichlorophenol contaminated with TCDD from an accident at a BASF plant, 1953–1989. 175 of 247 cohort members compared to unexposed workers for prevalence of non-malignant respiratory conditions.		
	Illness episodes per 100 person-years (cohort/reference):		
	All non-malignant respiratory diseases (ICD-9 460–51)	--	33.7/31.0 (p = 0.22)
	Upper respiratory tract infections (460–478)	--	12.0/9.0 (p = 0.00)
	Pneumonia or influenza (480–487)		17.4/18.8 (p = 0.08)
	COPD (490–496)		8.0/7.5 (p = 0.31)
Studies Reviewed in *VAO*			
Coggon et al., 1991	Production of phenoxy herbicides and chlorophenols in four British plants, mortality from non-malignant respiratory diseases, 1963–1985	8	0.7 (0.3–1.3)
Coggon et al., 1986	British plant manufacturing MCPA, mortality from non-malignant respiratory diseases (ICD-9 460–519), 1947–1983	93	0.6 (0.5–0.8)
Alavanja et al., 1989	PMR study of USDA soil and forest conservationists, mortality from non-malignant respiratory diseases (ICD-9 460–519), 1970–1979	80	0.8 (0.6–1.0)
Calvert et al., 1991**	NIOSH Cross-sectional study of production workers of sodium trichlorophenol and of 2,4,5,-trichlorophenoxyacetic ester (2,4,5-T ester) contaminated with TCDD comparing exposed to unexposed workers		
	Odds ratios for an increase in 1 ppt of serum TCDD		
	Chronic bronchitis	--	0.5 (0.1–2.6)
	COPD	--	1.2 (0.5–2.8)
Suskind and Hertzberg, 1984	Cross-sectional study of the Nitro, West Virginia, plant that manufactured 2,4,5-T, comparing exposed to unexposed workers, 1979.		
	Odds ratios comparing exposed to unexposed for the outcome of "abnormal" pulmonary functions tests:		
	FEV_1	203	2.82 (p = 0.0159)
	FVC	203	2.25 (p = 0.319)
	FEV_1/FVC	203	2.97 (p = 0.0099)
	FEF_{25-75}	203	1.86 (p = 0.0517)
Blair et al., 1983	Licensed pesticide applicators, Florida, non-malignant respiratory diseases, (ICD-8 460–519)	20	0.9
	Analyses by length of licensure		
	≤10 years	8	0.6
	10–19 years	8	1.5
	≥20 years	4	1.7

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
ENVIRONMENTAL			
Studies Reviewed in *Update 2004*			
Dahlgren et al., 2003	Cross-sectional study among residents living near a wood treatment plant (creosote and pentachlorophenol), Mississippi, who were plaintiffs in a lawsuit against the plant compared to subjects living in another comparable area with no known chemical exposures.		
	Adjusted scores comparing exposed to unexposed (<0 means exposed subjects had more symptoms):		
	Shortness of breath		
	Adults	--	-2.5 ($p<0.05$)
	Children	--	-3.8 ($p<0.05$)
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Follow-up of 1976 accident in Seveso, Italy, who were exposed to pure TCDD in an industrial accident, 1976–1996		
	Non-malignant respiratory diseases (ICD-9 460–519)	44	1.0 (0.8–1.4)
	Zone A	9	1.9 (1.0–3.6)
	Zone B	35	1.3 (0.9–2.0)
	COPD (ICD9 490–493)	29	1.5 (1.1–2.2)
	Zone A	7	3.3 (1.6–6.9)
	Zone B	22	1.3 (0.9–2.0)
Bertazzi et al., 1998; Pesatori et al., 1998 (results from Bertazzi)	Follow-up of residents in Seveso, Italy who were exposed to pure TCDD in an industrial accident, 1976–1991		
	Non-malignant respiratory diseases (ICD-9 460–519)		
	Zone A	5	2.4 (1.0–5.7)
	Men	2	1.3 (0.3–5.3)
	Women		
	Zone B	13	0.7 (0.4–1.2)
	Men	10	1.0 (0.5–1.9)
	Women		
	Zone R	133	1.1 (0.9–1.3)
	Men	84	1.0 (0.8–1.2)
	Women		
	COPD (ICD9 490–493)		
	Zone A	4	3.7 (1.4–9.8)
	Men	1	2.1 (0.3–14.9)
	Women		
	Zone B	9	1.0 (0.5–1.9)
	Men	8	2.5 (1.2–5.0)
	Women		
	Zone R	74	1.2 (0.9–1.5)
	Men	37	1.3 (0.9–1.9)
	Women		

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Studies Reviewed in *VAO*			
Bertazzi et al, 1989a; Bertazzi et al, 1989b (results from Bertazzi et al, 1989a)	Follow-up of residents in Seveso, Italy who were exposed to pure TCDD in an industrial accident, 1976-1986		
	Men		
	Non-malignant respiratory diseases (ICD-9 460–519)	55	1.0 (0.7–1.3)
	Pneumonia (ICD-9 480–486)	14	0.9 (0.5–1.5)
	COPD (ICD-9 490–493)	31	1.1 (0.8–1.7)
	Women		
	Non-malignant respiratory diseases (ICD-9 460–519)	24	1.0 (0.7–1.6)
	Pneumonia (ICD-9 480–486)	9	0.8 (0.4–1.6)
	COPD (ICD-9 490–493)	8	1.0 (0.5–2.2)
VIETNAM VETERANS			
New Studies			
Boehmer et al., 2004	Vietnam Experience Cohort		
	Non-malignant respiratory mortality (ICD-9 460–519)	20	0.8 (0.5–1.5)
Ketchum and Michalek, 2005	US Air Force Health Study		
	Non-malignant respiratory mortality (ICD-9 460–519)	8	1.2 (0.6–2.5)
Kang et al., 2006	US Army Chemical Corps personnel		
	Self-reported, non-malignant respiratory problems diagnosed by a doctor		
	Deployed vs non-deployed	129	1.4 (1.1–1.8)
	Sprayed herbicides in Vietnam versus never	*	1.6 (1.3–2.1)
ADVA, 2005b	Third Australian Vietnam Veterans Mortality Study.		
	Deployed veterans vs. Australian population		
	All branches		
	Respiratory system diseases	239	0.8 (0.7–0.9)
	Chronic obstructive pulmonary disease	128	0.8 (0.7–1.0)
	Navy		
	Respiratory system diseases	50	0.8 (0.6–1.0)
	Chronic obstructive pulmonary disease	28	0.9 (0.6–1.3)
	Army		
	Respiratory system diseases	162	0.8 (0.7–0.9)
	Chronic obstructive pulmonary disease	81	0.8 (0.7–1.0)
	Air Force		
	Respiratory system diseases	28	0.6 (0.4–0.9)
	Chronic obstructive pulmonary disease	18	0.8 (0.4–1.2)
ADVA, 2005c	Australian National Service Vietnam Veterans: Mortality and Cancer Incidence study.		
	National Serviceman (SMR)		
	Respiratory diseases	38	0.5 (0.3–0.6)
	Chronic obstructive pulmonary disease	18	0.9 (0.5–1.4)
	National Serviceman, deployed (SMR)		
	Respiratory diseases	18	0.5 (0.3–0.8)
	Chronic obstructive pulmonary disease	8	0.9 (0.4–1.8)
	National Serviceman, non-deployed (SMR)		
	Respiratory diseases	20	0.4 (0.2–0.6)
	Chronic obstructive pulmonary disease	10	0.9 (0.4–1.7)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Studies Reviewed in *Update 1998*			
Bullman & Kang, 1996	Post-service study among male Vietnam veterans who were wounded in combat.		
	Non-malignant respiratory mortality (ICD9 460–519) compared to the US population	43	0.9 (0.7–1.2)
O'Toole et al., 1996	Australian Army Vietnam veterans self-reported health status that between 1989 and 1990 compared to a random sample from the general Australian population. Prevalence ratios, adjusted for differences in response.		
	Acute conditions that required recent medical intervention		
	Asthma	--	1.4 (0.6–2.1)
	Bronchitis, emphysema	--	2.1 (0.2–4.0)
	Other	--	2.1 (1.6–2.8)
	Chronic conditions		
	Asthma	--	0.9 (0.5–1.4)
	Bronchitis, emphysema	--	4.1 (2.8–5.5)
	Other	--	4.0 (2.2–5.9)
Watanabe et al., 1996; Watanabe et al., 1991 (results from 1996 paper)	Mortality of US Vietnam veterans who died during 1965–1988, PMR analysis of non-malignant respiratory mortality (ICD8 460–519)		
	Army	648	0.81 ($p<0.05$)
	Marine Corps	111	0.68 ($p<0.05$)
Crane et al., 1997a	Mortality of male Australian Vietnam veterans compared to the general Australian population		
	Non-malignant respiratory mortality (ICD-9 460–519)		
	1964–1979	3	0.1 (0.0–0.3)
	1980–1994	92	0.9 (0.7–1.1)
	Chronic obstructive airways disease (ICD-9 490–496)		
	1980–1994	47	0.9 (0.7–1.2)
Crane et al., 1997b	Australian mortality veterans study of national servicemen that compared those who served in Vietnam to those who did not, 1982-1994		
	1965–1982	2	2.6 (0.2–30.0)
	1982–1994	6	0.9 (0.3–2.7)
AFHS, 1996	Cause-specific mortality among Rand Hand personnel compared to Air Force veterans	2	0.5 (0.1–1.6)
Studies Reviewed in *VAO*			
Anderson et al., 1986	Mortality study comparing Wisconsin Vietnam veterans with Wisconsin Vietnam era veterans.		
	SMR analysis of non-malignant respiratory mortality (ICD-8 460–519)		
	Vietnam veterans compared to Wisconsin	32	0.3 (0.2–0.5)
	Vietnam veterans compared to other veterans	32	0.5 (0.4–0.7)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
CDC, 1988	Cross-sectional study, with medical examinations, of US Army veterans who served in Vietnam compared to US Army veterans who had not served		
	Odds ratios from pulmonary function tests (case definition: ≤80% predicted value)		
	FEV_1	254	0.9 (0.7–1.1)
	FVC	177	1.0 (0.8–1.3)
	FEV_1/FVC	152	1.0 (0.8–1.3)
Eisen et al., 1991	Study of monozygotic twins who served in US military during Vietnam era		
	Respiratory conditions		
	Present at time of survey	--	1.4 (0.8–2.4)
	At any time since service	--	1.4 (0.9–2.0)
	Required hospitalization	--	1.8 (0.7–4.2)

[a] Given when available.
[b] Self-reported medical history. Answer to question: "Since your first day of service in Vietnam, have you been told by a doctor that you have leukemia?"
* Information not provided by study authors.
—When information was denoted by a dash in the original study.
ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid, 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDVA, Commonwealth Department of Veterans' Affairs; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEF_{25-75}, forced mid-expiratory flow; USDA, US Department of Agriculture.

* Ott and Zober (1996) and Zober et al. (1994) refer to the same study population.
** Calvert et al. (1991) and Sweeney et al. (1997/98) refer to the same study population.

Update of the Epidemiologic Literature

Occupational Studies

In a mortality analysis of the Agricultural Health Study (AHS), Blair et al. (2005) found a decrease in deaths from COPD among private applicators and their spouses (standardized mortality ratio [SMR] = 0.2, 95% CI 0.2–0.3) based on 50 deaths. There were no differences based on the number of years of handling pesticides. The deficit may have arisen because of the healthy-worker effect, lower consumption of tobacco in this cohort, increased exercise, or the protective effect of endotoxin exposure that many agricultural workers experience (Lange, 2000).

In a new report from the AHS, Hoppin et al. (2006) used a cross-sectional design to investigate the prevalence of wheeze among 2,375 commercial pesticide applicators. The authors defined wheeze as a positive response to the question, "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?". Exposure to pesticides was defined as having occurred in the year before administration of the baseline questionnaire. After adjusting for age, smoking status, physician diagnosis of asthma or atopy (allergy-proneness), and body-mass index (BMI), they found an association with the prevalence of wheeze and

"current" exposure to 2,4-D (prevalence OR = 1.27, 95% CI 0.96–1.68). (An association was not found for "former" use (unadjusted OR = 0.89, 95% CI 0.68–1.17 [computed by the present committee from Table 2 of the paper.]) The interpretation of such findings may be controversial, inasmuch as self-reported health conditions may not be reported accurately and there may be overreporting if people believe that their exposures were hazardous. The study showed positive associations with all of 16 herbicides (including 2,4-D), eight of 14 insecticides, and one of seven fungicides. At first glance, that seems to be a large proportion of positive findings, perhaps greater than what would be expected if some of the compounds were causal agents. Because many of the exposures were correlated, it is difficult to judge whether the number of positive associations was greater than what would be expected by chance. The authors indicated in the paper that self-reported wheeze is reported reasonably accurately and quoted a paper from Australia on a general-population survey of asthma (Jenkins et al., 1996). Although the Australian study did show excellent accuracy of self-reported wheeze, important differences between the two cohorts lead to questions as to whether the results of the Australian study are applicable to the AHS.

Mortality from diseases of the respiratory system were reported in a cohort study of 813 chemical producers (who worked during about 1950–1980) and 699 sprayers of phenoxy herbicides in New Zealand (who worked during 1973–1984) who were followed during the period 1970–2000 ('t Mannetje et al., 2005). The researchers found no associations with mortality from diseases of the respiratory system (International Classification of Diseases-9 [ICD-9] 480–519). The SMR for production workers was 0.93 (95% CI 0.42–1.76, nine deaths) and for sprayers 0.55 (95% CI 0.20–1.21, nine deaths).

Environmental Studies

No new environmental studies concerning the compounds of interest and nonmalignant respiratory diseases were published since those reviewed in *Update 2004*.

Vietnam-Veteran Studies

In the Centers for Disease Control and Prevention (CDC) Vietnam Experience Study (VES), Boehmer et al. (2004) compared cause-specific mortality among Vietnam veterans with that among service personnel who did not participate in the war. They found that among Vietnam veterans the rate ratio for mortality from diseases of the respiratory system (ICD-9 460–519) was 0.82 (95% CI 0.45–1.49).

Ketchum and Michalek (2005) published findings from 20 years of follow-up for mortality in the US Air Force Health Study (AFHS) that compared Ranch Hands with referent subjects. Respiratory diseases were identified from physical and other clinical examinations conducted during the periodic visits. The estimated relative risk for all nonmalignant respiratory causes of death (ICD-9 460–519) was 1.2 (95% CI 0.6–2.5).

In the cohort study of US Army Chemical Corps (ACC) personnel, Kang et al. (2006) conducted a cross-sectional survey among 2,247 Vietnam veterans and 2,242 non-Vietnam veterans. The Vietnam veterans served at least one tour of duty during 1965–1973 and were likely to have been involved in chemical operations. The survey was conducted by the Veterans

Health Administration in 1999–2000; 1,499 Vietnam veterans (66.7% response rate) and 1,428 comparison subjects (63.7%) participated. The prevalence of self-reported nonmalignant respiratory problems diagnosed by a doctor was significantly higher in the Vietnam veterans (adjusted OR = 1.41, 95% CI 1.13–1.76). When those who reported spraying herbicides in Vietnam were compared with those who did not, the adjusted OR was 1.57 (95% CI 1.20–2.07); and the OR for spraying herbicides in both cohorts was 1.62 (95% CI 1.28–2.05). However, amont a subset of workers whose serum TCDD was measured, there was no difference in the prevalence of respiratory problems between those whose serum TCDD was above and below 2.5 ppt.

In the *Third Australian Vietnam Veterans Mortality Study 2005* (ADVA, 2005b), Army (n = 41,084), Navy (n = 13,538), and Air Force (n = 4,570), no associations were found comparing military personnel serving in Vietnam to the general population of Australia (nonmalignant respiratory diseases SMR, 0.77, and 95% CI 0.67–0.87; COPD SMR = 0.85, and 95% CI 0.70–1.00). In *Australian National Service Vietnam Veterans: Mortality and Cancer Incidence 2005* (ADVA, 2005c), which involved 19,240 Vietnam veterans and 24,729 non-deployed veterans, there was no excess risk of death from nonmalignant respiratory diseases among those deployed to Vietnam compared with non-deployed veterans (RR = 1.12, 95% CI 0.56–2.23) and no excess risk of death from COPD (RR = 1.00, 95% CI 0.34–2.80).

Biologic Plausibility

As discussed in Chapter 3, new animal studies have shown that TCDD exposure increases mortality of mice infected with influenza virus. That effect was shown to depend on expression of the AhR; the mechanism underlying increased mortality was not related to the suppression of the immune response to influenza by TCDD but appeared to involve an increase in the inflammatory response in the lung. On the basis of those findings, it is biologically plausible that exposure to TCDD results in exacerbation of acute or chronic lung diseases associated with inflammatory responses. In addition, cigarette-smoking is a major risk factor for respiratory disease. TCDD is known to induce cytochrome P450 enzymes that are responsible for the activation of several chemicals found in tobacco smoke to more toxic intermediates. Thus, it is also biologically plausible that exposure to TCDD synergizes the toxic effects of a variety of compounds present in tobacco smoke and increases respiratory disease.

Synthesis

Results of the new studies of mortality from nonmalignant respiratory diseases (ADVA, 2005 b,c; Blair et al., 2005; Ketchum and Michalek, 2005; ’t Mannetje et al., 2005) do not support the hypothesis that herbicides increase mortality from them. The results of the Seveso accident showed a positive association (Bertazzi et al., 2001), although it is based on only nine deaths in the high-exposure area (zone A), and this finding could have been due to chance or misclassification of causes of death. More important, although it recognizes that mortality studies are limited by small numbers of events and misclassification of causes of death, especially respiratory conditions, the committee does not believe that scientific conclusions can be based on

health outcomes that are defined vaguely, for example, by combining a wide array of disparate respiratory health outcomes into one large category.

Two new cross-sectional studies have reported positive associations between exposure and the prevalence of various chest conditions. To summarize (see Table 9-1 and the report of findings above), Hoppin et al. (2006) found in the AHS an association between "current" exposure to 2,4-D and the prevalence of self-reported wheeze (adjusted OR = 1.27) and Kang et al. (2006) found in a study of ACC personnel an association between exposure and the prevalence of self-reported physician-confirmed respiratory problems (OR = 1.41). Other cross-sectional prevalence studies considered in previous updates that bear on this matter include the study of an accident at a BASF plant (Zober et al., 1994) that found no association of exposure with episodes of COPD, the NIOSH cross-sectional study of production workers exposed to 2,4,5-T ester contaminated with TCDD (Calvert et al., 1991) that found no increase in COPD associated with serum TCDD concentration, a cross-sectional study in Saskatchewan (Senthilselvan et al., 1992) that found no association between exposure to chlorinated hydrocarbons and the prevalence of self-reported asthma, and the study of residents exposed environmentally to emissions from a plant that produced creosote and pentachlorophenol (Dahlgren et al., 2003) that found positive associations with chronic bronchitis. This latter study was judged in *Update 2004* to have been biased.

The nonspecificity of the types of respiratory conditions reported in Kang et al. (2006) make it exceedingly difficult to draw any conclusions regarding specific respiratory conditions, and the lack of observed association with serum TCDD concentrations also argues against the existence of an association. The issue of nonspecificity is key to interpreting this study. The study by Hoppin et al. (2006) is also unclear about what wheeze represents: the definition of *wheeze* was very broad and included any episode in the year before administration of the questionnaire, and the authors reported that only 28% of subjects with wheeze reported having asthma or atopic conditions.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and the prevalence of wheeze and asthma.

IMMUNE-SYSTEM DISORDERS

The immune system defends the body against infection by viruses, bacteria, and other disease-producing microorganisms, known as pathogens. The immune system also plays a role in cancer surveillance, destroying mutated cells that might otherwise develop into tumors. To recognize the wide array of pathogens in the environment, the immune system relies on many cell types that operate together to generate immune responses. Those cells arise from stem cells in the bone marrow; they are found throughout the body's lymphoid tissues, and they circulate in the blood as white blood cells (WBCs). The main types of WBCs are granulocytes, monocytes, and lymphocytes.

Immune Suppression

Suppression of immune responses can result in reduced resistance to infectious disease and increased risk of cancer. Infection with HIV is a well-recognized example of an acquired immune deficiency in which a specific type of lymphocyte (CD4+ T cells) is the target of the virus. The decline in the number of CD4+ T cells after HIV infection correlates with an increased incidence of infectious diseases, including fatal opportunistic infections, and with an increased incidence of several types of cancer. Treatment of cancer patients with toxic chemotherapeutic drugs also suppresses the immune system by inhibiting the generation of new WBCs from the bone marrow and by blocking proliferation of lymphocytes during an immune response. Immune suppression can result from exposure to chemicals in the workplace or in the environment, including dioxin (see Chapter 3). However, unless the immune suppression is severe, it is often difficult to obtain clinical evidence that directly links chemical-induced changes in immune function to increased infectious disease or cancer, because many confounding factors can influence a person's ability to combat infection. Such confounders include age, vaccination status, the virulence of the pathogen, the presence of other diseases (such as diabetes), stress, smoking, and the use of drugs or alcohol.

Allergy

Sometimes the immune system responds to a foreign substance that is not pathogenic. Such immunogenic substances are called allergens. The response to some allergens, like pollen or bee venom, results in the production of immunoglobulin E (IgE) antibodies. Once produced, IgE antibodies bind to specialized cells—mast cells—that occur in tissues throughout the body, including lung airways, the gut wall, and blood-vessel walls. When a person is exposed again to the allergen, the allergen binds to the antibodies on the mast cells, causing them to release histamine and leukotrienes, which cause the symptoms associated with an allergic response. Other allergens, such as poison ivy and nickel, activate allergen-specific lymphocytes at the site of contact (usually the skin) that release substances that cause inflammation and tissue damage.

Autoimmune Disease

Autoimmune disease is another example of the immune system's causing rather than preventing disease. The immune system attacks the body's own cells and tissues as though they are foreign. For example, the autoimmune reaction in multiple sclerosis is directed against the myelin sheath of the nervous system; in Crohn's disease, the gut is the target of attack; in type 1 diabetes mellitus, the insulin-producing cells of the pancreas are destroyed by the immune response. Rheumatoid arthritis (RA) is an autoimmune disease that arises from immune attack on the joints. Genetic predisposition and such environmental factors as infectious diseases and stress are thought to facilitate the development of autoimmune diseases.

Systemic lupus erythematosus (SLE) is an autoimmune disease that has no specific target organ of immune attack. Instead, patients have a variety of symptoms that often occur in other diseases, and diagnosis is difficult. A characteristic rash across the cheeks and nose and sensitivity to sunlight are common symptoms; oral ulcers, arthritis, pleurisy, proteinuria, and neurologic disorders may be present. Almost all people with SLE test positive for antinuclear antibodies in the absence of drugs known to induce them. The causes of SLE are unknown, but environmental and genetic factors have been implicated. Some of the environmental factors that may trigger it are infections, antibiotics (especially those in the sulfa and penicillin groups), ultraviolet radiation, extreme stress, drugs, and hormones. Occupational exposures to such chemicals as crystalline silica, solvents, and pesticides have also been associated with risk of SLE (Cooper and Parks, 2004; Parks and Cooper, 2005).

Conclusions from *VAO* and Updates

The committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* concluded that there was inadequate or insufficient information to determine whether an association exists between exposure to the chemicals of concern and immune-system disorders. Reviews of the studies that underlie that conclusion are presented in the previous reports (IOM, 1994, 1996, 1999, 2001, 2003, 2005).

Update of the Epidemiologic Literature

Occupational studies

De Roos et al. (2005b) studied risk factors for RA in 57,000 licensed pesticide applicators and their spouses in association with the AHS. Pesticide application itself did not increase risk of RA, nor did the use of herbicides. However, the broad grouping of chlorophenoxy herbicides was associated with a significantly decreased risk of RA (OR = 0.05); the risk was attributable specifically to 2,4-D. In a subanalysis restricted to incident cases, an inverse association between risk of RA and use of 2,4-D was again observed (OR = 0.02).

Oh et al. (2005) evaluated aspects of the immune response in waste-incineration workers that were exposed to increased aerial concentrations of dioxin and in control subjects. There was no difference in the frequency of types of lymphocytes or in concentrations of circulating lymphocytes between the workers and the controls.T cells that expressed a marker of activation were significantly more highly concentrated in the incineration workers, but the relevance of this observation is unknown.

Environmental Studies

Baccarelli et al. (2005b) carried out a 20-year follow-up study of the long-term health effects of TCDD exposure in Seveso residents. The incidences of various health conditions associated with the immune system were the same in exposed and control subject, including allergic diseases, infectious diseases, respiratory diseases, anemia, and psoriasis (an autoimmune

disorder). The 101 exposed subjects all had chloracne, and their mean plasma TCDD concentrations were higher than those of the 211 nonchloracne control subjects.

Vietnam-Veteran Studies

Boehmer et al. (2004) compared post-service mortality in male US Army Vietnam veterans with that in non-Vietnam veterans and found no significant difference in death due to "endocrine, nutritional and metabolic diseases, and immunity disorders" (ICD-9 240–279) (crude RR = 1.32, 95% CI 0.50–3.47).

Biologic Plausibility

Exposure of laboratory animals to phenoxy herbicides has not been associated with immunotoxicity. In contrast, TCDD is a known immunosuppressive chemical in laboratory animals, and exposure to TCDD has been shown to increase the incidence and severity of various infectious diseases. TCDD exposure also suppresses the allergic immune response of rats and decreases allergen-associated lung pathology. Feeding juvenile and adult mice various quantities of TCDD for 5 weeks or more produced no evidence of increased IgE synthesis, and it suppressed skin sensitization to dinitrofluorobenzene. No animal studies have specifically addressed the effects of TCDD or other compounds of interest on autoimmune disease. Chapter 3 updates recent toxicologic studies that demonstrate the effects of the compounds of interest on the immune system.

Synthesis

TCDD is a well-known immunosuppressive agent in laboratory animals. Therefore, one would expect that exposure of humans to sufficiently high doses would result in immune suppression. However, several studies of various measures of human immune function have failed to reveal consistent correlations with TCDD exposure, and no detectable pattern of increased infectious disease has been documented in veterans exposed to TCDD or other herbicides used in Vietnam. Although suppression of the immune response by TCDD could increase the risk of some cancers in Vietnam veterans, there is no evidence to support that connection.

Epidemiologic studies have been inconsistent with regard to TCDD's influence on IgE production in humans (*Update 2004*). No animal or human studies have specifically addressed the influence of the TCDD on autoimmune disease. The Boehmer et al. (2004) study of post-service mortality associated with various causes showed no increase in deaths of Vietnam veterans that could be attributed to immune-system disorders.

Few effects of phenoxy herbicide exposure on the immune system have been reported in animals or humans, and clear association between phenoxy herbicide exposure and autoimmune or allergic disease has been found.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and immune suppression, allergy, or autoimmune disease.

DIABETES

Diabetes mellitus is a group of heterogeneous metabolic disorders characterized by hyperglycemia and quantitative or qualitative deficiency of insulin action (Orchard et al., 1992). Although all forms share hyperglycemia, the pathogenic processes involved in its development differ. Most cases of diabetes mellitus are in one of two categories: type 1 diabetes is characterized by a lack of insulin caused by the destruction of insulin-producing cells in the pancreas (β cells), and type 2 diabetes is characterized by a combination of resistance to the actions of insulin and inadequate secretion of insulin (called relative insulin deficiency). In old classification systems, type 1 diabetes was called insulin-dependent diabetes mellitus or juvenile-onset diabetes mellitus, and type 2 diabetes was called non-insulin-dependent diabetes mellitus or adult-onset diabetes mellitus. The modern classification system recognizes that type 2 diabetes can occur in children and also can require insulin treatments. Long-term complications of both types can include cardiovascular disease, nephropathy, retinopathy, neuropathy, and increased vulnerability to infections. Maintaining blood sugar concentrations within the normal range is crucial for preventing complications.

About 90% of all cases of diabetes mellitus are of type 2. Onset can occur before the age of 30 years, and incidence increases steadily with age thereafter. The main risk factors are age, obesity, central fat deposition, a history of gestational diabetes (in women), physical inactivity, ethnicity (prevalence is greater in blacks and Hispanics than in whites), and—perhaps most important—family history. The relative contributions of those features are not known. Prevalence and mortality statistics in the US population for 2004 are presented in Table 9-2.

TABLE 9-2 Prevalence and Mortality in US for 2004 from Diabetes, Lipid Disorders, and Circulatory Disorders

ICD-9 Range	Diseases of the Circulatory System	Prevalence (% of Americans 20 years of age and older) Men	Prevalence (% of Americans 20 years of age and older) Women	Mortality (number of deaths, all ages) Men	Mortality (number of deaths, all ages) Women
250	Diabetes	-	-	35,000	37,800
	Physician diagnosed	7.4 [a]	7.9 [a]	-	-
	Undiagnosed	2.9 [a]	2.1 [a]	-	-
	Prediabetes	33.8 [a]	22.2 [a]	-	-
	Lipid disorders				
	Total cholesterol ≥ 200 mg/dL	47.8	55.2	-	-
	Total cholesterol ≥ 240 mg/dL	16.2	17.1	-	-
	LDL cholesterol ≥ 130 mg/dL	32.2	32.4	-	-
	HDL cholesterol < 40 mg/dL	25.1	9.1	-	-

ICD-9 Range	Diseases of the Circulatory System	Prevalence (% of Americans 20 years of age and older) Men	Prevalence (% of Americans 20 years of age and older) Women	Mortality (number of deaths, all ages) Men	Mortality (number of deaths, all ages) Women
390–459	All circulatory disorders	37.5	36.6	410,400	461,200
390–398	Rheumatic fever and rheumatic heart disease	-	-	1,022	2,226
401–404 [b]	Hypertensive disease			22,800	31,400
401	Essential hypertension	-	-	-	-
402	Hypertensive heart disease	-	-	-	-
403	Hypertensive renal disease	-	-	-	-
404	Hypertensive heart and renal disease	-	-	-	-
410–414, 429.2	Ischemic or coronary heart disease	8.9	6.1	233,300	219,100
410, 412	Acute or old myocardial infarction	5.1	2.5	83,100	74,500
411	Other acute and subacute forms of ischemic heart disease	-	-	-	-
413	Angina pectoris	4.4	3.9	-	-
414	Other forms of chronic ischemic heart disease	-	-	-	-
429.2	Cardiovascular disease, unspecified	8.9	6.1	233,300	219,100
415–417 [b]	Diseases of pulmonary circulation	-	-	-	-
420-429	Other forms of heart disease (e.g., pericarditis, endocarditis, myocarditis,cardiomyopathy)	-	-	-	-
426–427	Arrhythmias	-	-	-	-
428	Heart failure	2.8	2.2	22,500	35,200
430–438 [b]	Cerebrovascular disease (e.g., hemorrhage, occlusion, transient cerebral ischemia; includesmention of hypertension in 401)	2.6	2.8	58,700	91,500
440–448 [b]	Diseases of arteries, arterioles, and capillaries	-	-	-	-
451–459	Diseases of veins and lymphatics, and other diseases of circulatory system	-	-	-	-

SOURCE: AHA, 2007.
- Specific information not available.
[a] For ages 18 years and above.
[b] Gap in ICD-9 sequence follows.

The etiology of type 2 diabetes is unknown, but three major components have been identified: peripheral insulin resistance (thought by many to be primary) in target tissues (muscle, adipose tissue, and liver), a defect in β-cell secretion of insulin, and overproduction of glucose by the liver. In states of insulin resistance, insulin secretion is initially higher for each concentration of glucose than in people without diabetes. That hyperinsulinemic state is a compensation for peripheral resistance and often can maintain normal glucose concentrations for years. Eventually, β-cell compensation becomes inadequate, and there is progression to overt diabetes with concomitant hyperglycemia. Why the β cells cease to produce sufficient insulin is not known.

Type 1 diabetes occurs as a result of immunologically mediated destruction of β cells in the pancreas, which often occurs during childhood but can occur at any age. As in many

autoimmune diseases, genetic and environmental factors influence pathogenesis. Some viral infections are believed to be important environmental factors that can trigger the autoimmunity associated with type 1 diabetes.

Pathogenetic diversity and diagnostic uncertainty are among the important problems associated with epidemiologic study of diabetes mellitus. Given the multiple likely pathogenetic mechanisms that lead to diabetes mellitus—which include diverse genetic susceptibilities (as varied as autoimmunity and obesity) and the all sorts of potential environmental and behavioral factors (such as viruses, nutrition, and activity)—many agents or behaviors can contribute to risk, especially in genetically susceptible people. The multiple mechanisms also can lead to heterogeneous responses to various exposures. Because up to half the cases of diabetes are undiagnosed, the potential for ascertainment bias in population-based surveys is high (more intensively followed groups or those with more frequent health-care contact are more likely to get the diagnosis); this emphasizes the need for formal standardized testing (to detect undiagnosed cases) in epidemiologic studies.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether an association between exposure to the compounds of interest and diabetes mellitus exists. Additional information available to the committees responsible for *Update 1996* and *Update 1998* did not change that conclusion.

In 1999, in response to a request from the Department of Veterans Affairs, IOM called together a committee to conduct an interim review of the scientific evidence regarding type 2 diabetes. That review focused on information published after the deliberations of the *Update 1998* committee and resulted in the report *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*, hereafter referred to as *Type 2 Diabetes* (IOM, 2000). The committee responsible for that report determined that there was limited or suggestive evidence of an association between type 2 diabetes and exposure to at least one compound of interest. The committees responsible for *Update 2000*, *Update 2002*, and *Update 2004* upheld that finding. Reviews of the pertinent studies are found in the earlier reports; Table 9-3 presents a summary.

TABLE 9-3 Selected Epidemiologic Studies—Diabetes and health outcomes related to diabetes

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
New Studies			
Blair et al., 2005a	US Agriculture Health Study—mortality		
	Private applicators (male and female)	26	0.3 (0.2–0.5)
	Spouses of private applicators (>99% female)	18	0.6 (0.4–1.0)
Studies Reviewed in *Update 2002*			
Steenland et al., 2001	Ranch Hand veterans and workers exposed to TCDD-contaminated products compared to unexposed comparison cohorts		
	Ranch Hands	147	1.2 (0.9–1.5)
	Workers	28	1.2 (0.7–2.3)
Kitamura et al., 2000	Workers exposed to PCDD at a municipal waste incinerator	8	*(NS)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Studies Reviewed in *Update 2000*			
Calvert et al., 1999[b]	Workers exposed to 2,4,5-T and derivatives	26	1.5 (0.8–2.9)
	Serum TCDD pg/g of lipid		
	<20	7	2.1 (0.8–5.8)
	20–75	6	1.5 (0.5–4.3)
	75–238	3	0.7 (0.2–2.6)
	238–3,400	10	2.0 (0.8–4.9)
Steenland et al., 1999[b]	Highly exposed industrial cohorts (n = 5,132)		
	Diabetes as underlying cause	26	1.2 (0.8–1.7)
	Diabetes among multiple causes	89	1.1 (0.9–1.3)
	Chloracne subcohort (n = 608)	4	1.1 (0.3–2.7)
Vena et al., 1998[b]	Production workers and sprayers in 12 countries[b]	33	2.3 (0.5–9.5)
Steenland et al., 1992[b,c]	Dioxin-exposed workers–mortality rates		
	Diabetes as underlying cause	16	1.1 (0.6–1.8)
	Diabetes among multiple causes	58	1.1 (0.8–1.4)
Studies Reviewed in *Update 1998*			
Sweeney et al., 1997/1998	Dioxin-exposed workers from 2 chemical plants		1.1 , $p < 0.003$
Ramlow et al., 1996	Pentachlorophenol production workers—mortality	4	1.2 (0.3–3.0)
Studies Reviewed in *Update 1996*			
Ott et al., 1994	Trichlorophenol production workers		$p = .06$
Von Benner et al., 1994	West German chemical production workers	N/A	N/A
Zober et al., 1994	BASF production workers	10	0.5 (0.2–1.0)
Studies Reviewed in *VAO*			
Sweeney et al., 1992	NIOSH production workers	26	1.6 (0.9–3.0)
Henneberger et al., 1989	Paper and pulp workers	9	1.4 (0.7–2.7)
Cook et al., 1987	Production workers—mortality	4	0.7 (0.2–1.9)
Moses et al., 1984	2,4,5-T and TCP production workers with chloracne	22	2.3 (1.1–4.8)
May, 1982	TCP production workers	2	*
Pazderova-Vejlupkova et al., 1981	2,4,5-T and TCP production workers	11	*
ENVIRONMENTAL			
New Studies			
Chen HL et al., 2006	Residents around 12 municipal waste incinerators in Taiwan—Prevalence of physician diagnosed diabetes Serum TCDD/TCDF (international TEQs) in logistic model adjusted for age, sex, smoking, BMI	29	2.4 (0.2–31.9)
Baccarelli et al., 2005	Children residing in Seveso at time of accident—Development of diabetes		
	101 with chloracne	1	*
	211 without chloracne	2	*
Studies Reviewed in *Update 2004*			
Fierens et al., 2003	Belgium residents (142 women; 115 men) exposed to dioxins and PCBs		
	Subjects in the top decile for dioxins		5.1 (1.2–21.7)
Studies Reviewed in *Update 2002*			
Masley et al., 2000	Population-based survey in Saskatchewan	28	*
Studies Reviewed in *Update 2000*			
Bertazzi et al., 2001	Seveso residents—20-year follow-up		
	Zone A and B—males	6	0.8 (0.3–1.7)
	—females	20	1.7 (0.1–2.7)
Cranmer et al., 2000[b]	Vertac/Hercules Superfund site residents (n = 62)—		

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	OR for High Insulin among non-diabetic subjects at varying times and levels for TCDD >15 ppt compared to persons with TCDD < 15 ppt		
	Fasting (insulin level, >4.5 μIU/ml)	3	8.5 (1.5–49.4)
	30-min (insulin level, >177 μIU/ml)	3	7 (1.3–39.0)
	60-min (insulin level, >228 μIU/ml)	4	12 (2.2–70.1)
	120-min (insulin level, >97.7 μIU/ml)	6	56 (5.7–556)
Bertazzi et al., 1998[b]	Seveso residents—15-year follow-up		
	Zone A—females	2	1.8 (0.4–7.0)
	Zone B—males	6	1.2 (0.5–2.7)
	—females	13	1.8 (1.0–3.0)
Pesatori et al., 1998[b]	Zone R—males	37	1.1 (0.8–1.6)
	—females	74	1.2 (1.0–1.6)
VIETNAM VETERANS			
New Studies			
Kang et al., 2006	US Army Chemical Corps personnel		
	Deployed vs non-deployed	226	1.2 (0.9–1.5)
	Sprayed herbicides in Vietnam vs never	123	1.5 (1.1–2.0)
AFHS, 2005	Air Force Health Study—2002 exam cycle Ranch Hand veterans—relative risk with 2-fold increase in 1987 TCDD level		1.3 (1.1–1.5)
Kern et al., 2004	Air Force Health Study—Ranch Hand–Comparison subject pairs—within-pair differences: lower Ranch Hand insulin sensitivity with greater TCDD levels		
	1997 exam (29 pairs)		(p = 0.01)
	2002 exam (71 pairs)		(p = 0.02)
ADVA, 2005b	Australian Vietnam veterans vs Australian population –mortality	55	0.5 (0.4–0.7)
	Navy	12	0.5 (0.3–0.9)
	Army	37	0.5 (0.4–0.7)
	Air Force	6	0.5 (0.2–1.0)
ADVA, 2005c	Australian men conscripted into Army National Service—deployed vs non-deployed–mortality	6	0.3 (0.1–0.7)
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	*	*
CDC, 1988b	Vietnam Experience Study—deployed vs non-deployed		
	Interviewed–self-reported diabetes	155	1.2 (p > 0.05)
	Subset with physical exam		
	—self-reported diabetes	42	1.1 (p > 0.05)
	—fasting serum glucose (geometric mean)		93.4 vs 92.4 mg/dL (p < 0.05)
Studies Reviewed in *Update 2004*			
JS Kim et al., 2003	Korean veterans of Vietnam—Vietnam Veterans	154	2.7 (1.1–6.7)
Michalek et al., 2003	Air Force Ranch Hand Veterans (n = 343)	92	NS
Studies Reviewed in *Update 2000*			
AFHS, 2000[b]	Air Force Heath Study—1997 exam cycle Ranch Hand veterans and comparisons	(Numerous analyses discussed in the text of *Herbicide/Dioxin Exposure and Type 2 Diabetes*)	
Longnecker and Michalek, 2000[b]	Air Force Heath Study—Comparison veterans only, OR by quartiles of serum dioxin concentration		
	Quartile 1: <2.8 ng/kg	26	1.00—referent

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Quartile 2: 2.8–<4.0 ng/kg	25	0.9 (0.5–1.7)[d]
	Quartile 3: 4.0–<5.2 ng/kg	57	1.8 (1.0–3.0)[d]
	Quartile 4: ≥5.2 ng/kg	61	1.6 (0.9–2.7)[d]
CDVA, 1998a[b]	Australian Vietnam veterans—male	2,391 reported[e] (6% of respon-dents)	1,780 expected (1,558–2,003)
CDVA, 1998b[b]	Australian Vietnam veterans—female	5 reported[e] (2% of respon-dents)	10 expected (9–11)
Studies reviewed in *Update 1998*			
Henriksen et al., 1997[b]	Air Force Health Study—through 1992 exam cycle Ranch Hand veterans—high-exposure group		
	Glucose abnormalities	60	1.4 (1.1–1.8)
	Diabetes prevalence	57	1.5 (1.2–2.0)
	Use of oral medications for diabetes	19	2.3 (1.3–3.9)
	Serum insulin abnormalities	18	3.4 (1.9–6.1)
O'Toole et al., 1996	Australian Vietnam veterans	12	1.6 (0.4–2.7)[e]
Studies Reviewed in *VAO*			
AFHS, 1991	Air Force Heath Study—1987 exam cycle Ranch Hand veterans and comparisons	85	$p = 0.001$, $p = 0.028$
AFHS, 1984	Air Force Heath Study—1982 exam cycle Ranch Hand veterans and comparisons	158	$p = 0.234$

[a] Given when available.
[b] Study is discussed in greater detail in *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (IOM, 2000).
[c] May include some of the same subjects covered in the NIOSH cohorts addressed in the other references cited in the Occupational cohorts category.
[d] Adjusted for age, race, body mass index, waist size, family history of diabetes, body mass index at the time dioxin was measured, serum triglycerides, and military occupation.
[e] Self-reported medical history; answer to question, Since your first day of service in Vietnam, have you been told by a doctor that you have diabetes?
* = Information not provided by study authors.
ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ADVA, Australian Department of Veterans Affairs AFHS, Air Force Health Study; AIHW, Australian Institute of Health and Welfare; CDC, Centers for Disease Control and Prevention; CI, confidence interval; EOI, exposure opportunity index; HDL, high-density lipoprotein; N/A, not applicable; NS, not significant; SS, statistically significant; TCP, trichlorophenol.

Update of the Epidemiologic Literature

Occupational Studies

Blair et al. (2005a) reported mortality results from a prospective study of 57,309 licensed private and commercial pesticide applicators and 32,345 spouses of private applicators who lived in Iowa and North Carolina and were enrolled in the AFS in 1994–1997 through 2000. The mortality experience of that cohort was compared with that of the general population in the two states. Among the 52,393 private applicators, who were mostly male, 1,558 deaths were observed, for an overall SMR of 0.5 (95% CI 0.4–0.5); 26 of the deaths were due to diabetes, for

an SMR of 0.3 (95% CI 0.2–0.5). Among the spouses, 497 deaths were observed, for an overall SMR of 0.6 (95% CI 0.5–0.6); 18 of the deaths were due to diabetes, for an SMR of 0.6 (95% CI 0.4–1.0). The publication further reports that the low relative mortality generally varied little with such factors as years of handling pesticides and length of follow-up.

Environmental Studies

Chen H-L et al. (2006) investigated the prevalence of diabetes in Taiwanese who lived near municipal waste incinerators for at least 5 years. Health information was obtained from an interviewer-administered questionnaire on which people were asked about their medical histories, including physician-diagnosed diabetes, and serum samples were collected for analysis of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). A logistic regression analysis found the prevalence of diabetes to be non-significantly associated with serum PCDD and PCDF concentrations, on the basis of international toxic equivalents (TEQs) (OR = 8.64, 95% CI 0.87–93.3). Any relationship was even less apparent after adjustment for age, sex, smoking status, and BMI (OR = 2.44, 95% CI 0.21–31.90).

Baccarelli et al. (2005b) reported the results of a case–control study of residents of Seveso, Italy, who experienced dioxin exposure during the accident of 1976. The accident resulted in a large outbreak of chloracne, primarily among the resident children (of the 193 cases, 88% were in people less than 14 years old). From 1993 to 1998, the study recruited 101 people with chloracne and 211 controls, 101 of whom were pair-matched on age, sex, and zone of residence and 110 of whom had lived in the Seveso area at the time of the accident. The object was to investigate the association between dioxin and chloracne occurrence. Plasma TCDD was measured with high-resolution gas chromatography–mass spectrometry. Of the 211 control subjects, 104 were characterized as having been exposed to dioxin as a result of the accident and 107 as unexposed. As a part of subject follow-up, enrollees were interviewed with respect to the occurrence of various diseases since the accident. Only one of the cases and two of the controls (one characterized as exposed and the other as unexposed) reported a diabetes diagnosis since the accident.

Vietnam-Veteran Studies

Kang et al. (2006) reported results of a study of Vietnam-era veterans of the US ACC and compared data on 1,499 who had been deployed to Vietnam with data on 1,428 who had not. Self-reported data were collected from the participants by telephone interview. Medical and hospital records were sought to document reported cases of diabetes; such support was obtained for 79.2% of the 362 reported cases; available records for 39 lacked confirmatory information, and no records could be obtained for the remaining 36. Serum dioxin concentrations measured in a subgroup of 897 of the participants confirmed the reliability of self-reports of herbicide spraying as a surrogate for TCDD exposure. With respect to diabetes risk, the OR for Vietnam veterans relative to non-Vietnam veterans was 1.16 (95% CI 0.91–1.49) adjusted for age, race, BMI, rank, and smoking. Among the Vietnam veterans, comparison of those who reported a history of spraying herbicides with those who did not yielded an OR of 1.49 (95% CI 1.10–2.02) adjusted for the same factors. Similarly, when Vietnam service and herbicide spraying were both

included with the previous risk factors in a logistic model for diabetes applied to all the ACC subjects, the risk associated with deployment to Vietnam was not significant (OR = 1.04, 95% CI 0.80–1.37), whereas the risk associated with herbicide spraying was increases (OR = 1.50; 95% CI 1.15–1.95). The study concludes that Vietnam veterans employed as sprayers carried a significantly higher risk of diabetes than non-Vietnam veterans.

The final examination cycle of the AFHS was conducted in 2002–2003 and used questionnaires, physical examinations, and clinical assessments to ascertain diabetes prevalence. The official report (AFHS, 2005) presents findings cumulated from the study's beginning in 1982 but only on subjects who participated in the final examination cycle. Significant associations were reported between dioxin concentrations and diabetes risk and severity. In particular, among the Ranch Hand participants with dioxin measurements, there was a significantly increased risk of being diabetic (RR = 1.29, 95% CI 1.10–1.51) for a doubling in 1987 dioxin concentrations after adjustment for age, race, military occupation, BMI, waist-to-hip ratio, smoking, and family history. Similarly, time to diabetes onset was significantly shorter among the Ranch Hand subjects with higher 1987 dioxin concentrations. Those results underscore and strengthen previous AFHS findings with respect to diabetes.

Kern et al. (2004) report results from a substudy of the AFHS. Two subsets of AFHS participants were formed: one subset of those who participated in the 1997 AFHS physical examination and the other of those who participated in the 2002 AFHS physical examination. The subsets consisted of pairs of subjects without prior indications of diabetes that were matched one for one (on age, BMI, black vs nonblack race, and first-order family history of diabetes) and consisted of a Ranch Hand veteran with serum TCDD over 10 ppt and a comparison veteran with serum TCDD under 10 ppt. A total of 29 matched pairs from the 1997 examination and 71 matched pairs from the 2002 examination were studied. Insulin sensitivity was measured in serum samples with two methods: a frequent-sampling intravenous-glucose tolerance test in 1997 and a quantitative insulin-sensitivity check index based on fasting glucose and insulin in 2002. There were no significant group differences in any of the measures of insulin sensitivity between the Ranch Hands and their matched comparisons. Regressions of within-pair differences for insulin sensitivity on within-pair differences in TCDD concentrations found the greater depression in the Ranch Hands' insulin sensitivity to be significantly related to higher TCDD concentrations. The authors suggested that high blood TCDD may modestly promote insulin resistance.

The Australian Department of Veterans' Affairs (DVA) Third Vietnam Veterans Mortality Study (ADVA, 2005b) assessed mortality among Australian Vietnam veterans from all branches of service. The mortality experience (through 2001) of the veterans was compared with that of the general population of Australia. The investigators report an SMR of 0.52 (95% CI 0.38–0.66) with respect to diabetes, which suggests a significant decrease in the rate of death from diabetes among the veterans. Similarly, in the study comparing deployed and non-deployed Australian National Service veterans (ADVA, 2005c), the risk of death from diabetes was reduced among those sent to Vietnam (SMR = 0.3, 95% CI 0.1–0.7). However, the investigators noted that in Australia people with type 1 diabetes were not allowed to be sent to Vietnam, so there was considerable selection bias in the study cohort.

It was brought to the present committee's attention that the original *VAO* report had overlooked data related to diabetes in the report on the CDC VES (CDC, 1988). The incidence of self-reported diabetes did not differ ($p > 0.05$) between the deployed and non-deployed among the 15,288 subjects who completed telephone interviews (1.9% vs 1.4%; OR, 1.2) or the subset

of 4,362 subjects who had physical examinations (1.7% vs 1.5%; OR, 1.1). Among the examined veterans, however, although there was no difference in the risk of exceeding the reference limit of 140 mg/dL, the modest difference in the geometric means of fasting glucose between the deployed (93.4 mg/dL) and the non-deployed (92.4 mg/dL) was significant ($p < 0.05$). The recent 30-year follow-up on mortality in the cohort (Boehmer et al., 2004) did not report findings with respect to deaths associated with diabetes, and there has not been any follow-up on the morbidity profile.

Biologic Plausibility

The toxicity of TCDD in laboratory animals has been historically linked with body weight loss through inhibition of gluconeogenesis and enhanced lipid metabolism. Despite alterations in these key metabolic processes, diabetes (defined as significant and prolonged elevation of blood glucose levels) has not been reported in TCDD-exposed rodents. Chronic active inflammation, acinar cytoplasmic vacuolization, and acinar atropy were found in the pancreata of rats exposed to TCDD for two years without lesions in the insulin-secreting islet beta cells. Nonetheless, several recent in vitro studies provide evidence that TCDD exposure could contribute to the development of type 2 diabetes. Three different laboratories reported that key regulators of insulin action are altered by TCDD. Marchand et al. (2005) showed that IGFBP-1 is transcriptionally activated by TCDD in hepatocyes; Liu and Matsumura (2006) showed that TCDD suppresses insulin responsive glucose transporter (GLUT-4) gene expression in adipocytes; and Hokanson et al. (2004) showed insulin receptor substrate -1 (IRS-1) was downregulated in MCF-7 cells co-treated with TCDD and estrogen. In addition, pancreatic islets from rats treated with a single 1 ug/kg dose of TCDD showed impaired insulin secretion in response to glucose and reduced glucose uptake without an effect on GLUT2 protein level (Novelli et al., 2005). These changes could contribute to insulin resistance of cells and elevated blood sugar. Results reported by Yang and Bleich (2004) also contribute to plausibility by showing that the COX2 promoter in a pancreatic beta cell line is responsive to TCDD via direct transcriptional activation of a DRE. Induction of COX2 in beta cells is suspected to contribute to beta cell dysfunction as a part of diabetes development.

Synthesis

The study by Blair et al. (2005) has several acknowledged weaknesses. The AHS cohort is a working cohort being compared with the general population of two states. The possibility of bias due to the healthy-worker effect cannot be dismissed. In addition, most of the pesticide workers and their spouses in the AHS cohort were farmers. Adults in farm families are known to have significantly lower cause-specific mortality than the general population, and this limits the generalizability of results. Furthermore, although the subjects have considerable potential for exposure to phenoxy herbicides, in the period under consideration exposure to 2,4,5-T and its contaminant TCDD was unlikely.

Baccarelli et al. (2005b) studied a relatively small sample consisting almost entirely of people who were children at the time of dioxin exposure. Their ages at the time of exposure do not correspond to those of soldiers in Vietnam, and at the time of the study they had not yet

reached the age at which diabetes becomes prevalent. This study comparing morbidity in those with and without chloracne has limited utility for studying an association between dioxin exposure and specific diseases, such as diabetes.

The finding of an association between herbicide exposure and diabetes risk among Vietnam-era US ACC veterans (Kang et al., 2006) is consistent with the results of several previous studies. Moreover, the study investigated a group of Vietnam veterans with documented herbicide exposure, and individual self-reports of herbicide spraying were effectively validated by measurements of serum TCDD in a subsample. The study's reliance on self-reported data for disease classification was mitigated by fairly complete verification with medical records only for diabetes. Results of substudies implied that recall bias was unlikely to have affected the comparison appreciably. There was a potential for selection bias, but the authors strongly argued that the study group was reasonably representative of non-Vietnam veterans, as well as exposed Vietnam veterans.

The Australian Vietnam-veteran study did not find a positive association between exposure and diabetes risk, but it had limitations that suggest bias in the risk estimates. Other Vietnam-veteran studies, particularly those based on the AFHS cohort, continue to provide the strongest support for a positive association between dioxin exposure and diabetes risk. The AFHS report (2005) on the 2002 examination reinforced earlier findings of a significant increase in risk, severity, and speed of disease onset associated with higher serum dioxin concentrations.

Increased blood dioxin levels resulting from recommended weight loss subsequent to diagnosis of diabetes are a possible source of bias in analyses of association between serum TCDD levels and the development of diabetes. Mobilization from fat stores during dieting is known to increase blood levels of dioxin, but the degree or persistence of such elevations is not well characterized. The cross-sectional analyses of Ranch Hand and comparison subjects took account of BMI, but not changes in weight (AFHS, 2005). The serum TCDD levels used in those exam cycle analyses, however, were based upon samples drawn primarily in 1989 or later that may have pre- or post-dated an individual's diabetes diagnosis. The questionnaire for the study by Kang et al. (2006) included questions regarding weight loss as well as the year in which diabetes developed, but the analysis determining risk of developing diabetes with respect to degree of herbicide exposure (qualitatively and indirectly derived for all subjects from self-reports of spraying and serum levels in sprayers) also adjusted for BMI, but not for change in BMI over time. All blood samples from Army Chemical Corps subjects were drawn after administration of the questionnaire ascertaining diabetes status, but at various intervals after diagnosis, so a perceptible trend of diet-induced TCDD elevation in the subjects with diabetes would not be anticipated. The committee found it implausible that a bias related to post-diagnosis weight loss could be responsible for repeated findings of association between diabetes and herbicide exposure.

All together, the newly added studies do not counter previous findings with respect to the association between exposure and diabetes risk. In some cases, they lend additional support to previous findings. The new studies are not, however, sufficient to merit a stronger conclusion with respect to the association.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one compound of interest and diabetes.

LIPID AND LIPOPROTEIN DISORDERS

Plasma lipid (notably cholesterol) concentrations have been shown to predict cardiovascular disease and are considered fundamental to the underlying atherosclerotic process (Kuller and Orchard, 1988). Cholesterol and triglycerides, the two major types of lipids, are carried in the blood attached to proteins to form lipoproteins, which are classified by density. Very-low-density lipoprotein (VLDL, the major "triglyceride" particle) is produced in the liver and is progressively catabolized (hydrolyzed), mainly by an insulin-stimulated enzyme (lipoprotein lipase), to form intermediate-density lipoprotein (IDL), or VLDL remnants. Most of the VLDL remnants are rapidly cleared by low-density lipoprotein (LDL) receptors (types B and E) in the liver, and the rest form LDL, the major "bad cholesterol". LDL is cleared by LDL receptors in the liver and other tissues. High-density lipoprotein (HDL), the "good cholesterol", is produced in the small intestine and liver. It also results from the catabolism of VLDL. LDL is involved in the delivery of cholesterol to the tissues, and HDL is involved in "reverse" transport and facilitates the return of cholesterol to the liver for biliary excretion (LaRosa, 1990).

Disorders of lipoprotein metabolism usually result from overproduction or decreased clearance of lipoproteins or both. Common examples are hypercholesterolemia, which can be familial (because of an LDL-receptor genetic defect) or polygenic (because of multiple minor genetic susceptibilities); familial hypertriglyceridemia (sometimes linked to susceptibility to diabetes); and mixed hyperlipidemias, in which both cholesterol and triglycerides are elevated. The mixed hyperlipidemias include familial combined hyperlipidemia, which could result from hepatic overproduction of VLDL and apoprotein B, and type III dyslipidemia, which involves defective clearance of IDL and VLDL remnants and a buildup of these atherogenic particles. Although the bulk of blood lipid concentration is genetically determined, diet, activity, and other factors (such as concurrent illness, use of drugs, age, sex, and hormones) have major effects. In particular, the saturated-fat content of the diet might raise LDL concentrations through decreased LDL-receptor activity; obesity and a high-carbohydrate diet can increase VLDL and possibly are linked to insulin resistance and reduced lipoprotein lipase activity. Diabetes mellitus and metabolic syndrome are associated with increased triglycerides and decreased HDL. Other diseases (thyroid and renal disorders) often result in hypercholesterolemia. It is evident that multiple host and environmental factors influence lipid and lipoprotein concentrations and that those influences must be considered before the effect of a new factor can be assessed (LaRosa, 1990). Any analysis should control for obesity as a primary determinant of triglyceride and TCDD concentrations. Finally, the ability of chronic diseases to raise triglycerides, glucose, and LDL and/or to lower HDL must be recognized.

Statistics on the prevalence in the US population for 2004 of reading in the ranges defining various lipid disorders are presented in Table 9-2.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of concern and lipid and lipoprotein disorders. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. Table 9-4 provides a summary of relevant studies that have been reviewed.

TABLE 9-4 Selected Epidemiologic Studies—Lipid and Lipoprotein Disorders

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
OCCUPATIONAL			
Studies Reviewed in *Update 2004*			
Hu et al., 2003	Workers exposed to PCDDs/PCDFs in Taipei City		
	Comparison between high and low exposure groups using the low exposures group as controls	67 high; 66 low	
	Total cholesterol		2.8 (1.0–7.9)
	Triglycerides		1.5 (0.5–4.3)
Pelclová et al., 2002	Workers exposed to 2,3,7,8-TCDD in Spolana, Czech Republic	12	
	Correlation between the year (1968 to 2001) in which the highest level of the parameter was measured and serum 2,3,7,8-TCDD level in 1966		
	Cholesterol		r = 0.78; $p = 0.01$
	Triglycerides		r = 0.66; $p = 0.02$
Studies Reviewed in *Update 2002*			
Kitamura et al., 2000	Workers exposed to PCDDs—hyperlipidemia	8	6.1, $p = 0.02$
Studies Reviewed in *Update 1998*			
Calvert et al., 1996	Workers exposed to 2,4,5-T derivatives vs matched referents OR		
	Abnormal total cholesterol		
	Overall	95	1.1 (0.8–1.6)
	High TCDD	18	1.0 (0.5–1.7)
	Abnormal HDL cholesterol		
	Overall	46	1.2 (0.7–2.1)
	High TCDD	16	2.2 (1.1–4.7)
	Abnormal mean total/HDL cholesterol ratio		
	Overall	131	1.1 (0.8–1.6)
	High TCDD	36	1.5 (0.8–2.7)
	Abnormal mean triglyceride		
	Overall	20	1.0 (0.5–2.0)
	High TCDD	7	1.7 (0.6–4.6)
Ott and Zober, 1996	Production workers exposed to 2,3,7,8-TCDD	42	
	Cholesterol		[no significant effect][b]
	Triglycerides		[no significant effect][b]
	HDL cholesterol		Increased; $p = 0.05$[b]
Studies Reviewed in *VAO*			
Martin, 1984	Production workers exposed to TCDD		
	No chloracne	53	
	Cholesterol		Increased; $p < 0.005$[b]
	Triglycerides		Increased; $p < 0.005$[b]
	HDL cholesterol		[no significant effect][b]
	With chloracne	39	

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
	Cholesterol		Increased; $p < 0.05$[b]
	Triglycerides		Increased; $p < 0.01$[b]
	HDL cholesterol		[no significant effect][b]
Moses et al., 1984	TCP and 2,4,5-T production workers	118	
	Cholesterol		[no significant effect][c]
	Triglycerides		[no significant effect][c]
Suskind and Hertzberg, 1984	TCP production workers	204	
	Cholesterol		[no significant effect][b]
	Triglycerides		[no significant effect][b]
	HDL cholesterol		[no significant effect][b]
May, 1982	TCP production workers	94	
	Cholesterol		[no significant effect][b]
	Triglycerides		[no significant effect][b]
Pazderova-Vejlupkova et al., 1981	TCP and 2,4,5-T production workers	55	
	Cholesterol		[no significant effect][b]
	Triglycerides		Increased VLDL; $p = .01$[b]
ENVIRONMENTAL			
Studies Reviewed in *VAO*			
Assennato et al., 1989	Seveso Zone A adult subjects chloracne	193	
	Cholesterol		[no significant effect][b]
	Triglycerides		[no significant effect][b]
Mocarelli et al., 1986	Children exposed near Seveso	63	
	Cholesterol		[no significant effect][b]
	Triglycerides		[no significant effect][b]
VIETNAM VETERANS			
New Studies			
AFHS, 2005	Air Force Ranch Hand veterans (2002 exam data)	762	
	Model 3 Low + High TCDD Exp vs comparisons		
	Cholesterol		reduced, p = 0.039
	Model 1 Ranch Hand vs comparisons		
	Triglycerides		increased for enlisted groundcrew, p = 0.034
	Model 3 Low + High TCDD exp vs comparisons		
	Triglycerides		increased, p = 0.001
	Model 4 ORH 1987 Serum TCDD Levels		
	Triglycerides		increased, p = 0.02
Studies Reviewed in *Update 2000*			
AFHS, 2000	Air Force Ranch Hand veterans	858	
	Cholesterol		[no significant effect]
	Triglycerides		[no significant effect]
Studies reviewed in *Update 1998*			
AFHS, 1996	Air Force Ranch Hand veterans (1992 exam data)	884	
	Cholesterol	884	[no significant effect][d] (cholesterol:HDL ratio)
	Triglycerides		[no significant effect][d]
	HDL cholesterol		[no significant effect][d] (cholesterol:HDL ratio)
O'Toole et al., 1996	Australian Vietnam veterans, compared with the Australian population	20	
	Cholesterol		3.0 (1.3–4.7)

Reference	Study Population	Exposed Cases[a]	Estimated Relative Risk (95% CI)[a]
Studies reviewed in *VAO*			
AFHS, 1991	Air Force Ranch Hand veterans—Serum dioxin analysis (1987 exam data)	283–304[f]	
	Cholesterol		$p = 0.175$[e]
	Triglycerides		$p < 0.001$[e,g]
	HDL cholesterol		$p < 0.001$[e]
AFHS, 1990[h]	Air Force Ranch Hand veterans—Original exposure group analysis (1987 exam data)	8–142[f]	
	Model 1, Ranch Hand vs comparisons		
	Cholesterol		1.2 (0.9–1.5)
	Triglycerides		1.3 (0.9–1.8)
	HDL cholesterol		1.0 (0.4–2.4)
AFHS, 1984; Wolfe et al., 1990	Air Force Ranch Hand veterans exposed to herbicide spraying (1982 data)	1,027	
	Cholesterol		[no significant effect][h]
	Triglycerides		[no significant effect][h]
	HDL cholesterol		[no significant effect][h]

[a] Given when available.
[b] *p*-values comparing means of subjects and controls in univariate analysis.
[c] *p*-values comparing means in production workers with subsequent chloracne to those without.
[d] Comparing change over time between exposed and comparison groups.
[e] Comparing mean dioxin across lipid groups.
[f] Number of exposed Ranch Hand with "high" lipid values.
[g] Continuous analysis.
[h] Comparing means.

NOTE: Estimated risk and 95% CI reported unless *p*-values are specified.
ABBREVIATIONS: AFHS, Air Force Health Study; HDL, High-density lipoprotein; PCDD, polychlorinated dibenzodioxins; TCP, trichlorophenol; VLDL, very low density lipoprotein

Update of the Epidemiologic Literature

No new occupational or environmental studies concerning exposure to the compounds of interest and lipid and lipoprotein disorders were published since *Update 2004*.

Vietnam-Veteran Studies

In the study of Ranch Hand veterans by the US Air Force (AFHS, 2005), assessment of lipid and lipoprotein disorders was conducted on the basis of physical examinations in 2002. Analysis included total serum cholesterol, HDL, the ratio of total cholesterol to HDL, and triglycerides. Covariates used in the adjusted analyses of the lipid and lipoprotein values included age, race, military occupation, smoking history, alcohol-consumption history, BMI, and degreasing and industrial chemical exposure.

No significant associations between dioxin exposure and total serum cholesterol, HDL, or the ratio of total cholesterol to HDL in Ranch Hand veterans were found. However, significantly *fewer* Ranch Hand veterans with 1987 serum TCDD over 10 ppt (43 of 416, or 10.3%) than other veterans who served in Southeast Asia (153 of 1,149, or 13.3%) exhibited abnormally high serum total cholesterol (over 240 mg/dL), for an adjusted RR of 0.68 (95% CI 0.47–0.98, p =

0.039). In contrast, the concentration of serum triglycerides showed a trend for a positive association when Ranch Hand veterans were categorized into low, medium, or high serum TCDD (p = 0.077). However, the mean serum triglyceride in the three exposure categories ranged from 114 to 130 mg/dL—all within the normal physiologic range.

In a second set of analyses, the percentage of veterans with abnormally high serum triglycerides (over 250 mg/dL) was compared between Ranch Hand veterans and other veterans who served in Southeast Asia. The percentage with abnormally high serum triglycerides was significantly higher in Ranch Hand enlisted ground-crew personnel (17.9% with abnormally high serum triglycerides vs 11.9% in the comparison group; adjusted RR = 1.54, 95% CI 1.03–2.29, p = 0.034), Ranch Hand veterans categorized as having low TCDD exposure (15.4% vs 9.8%; adjusted RR = 1.72, 95% CI 1.11–2.66, p = 0.015), and Ranch Hand veterans with high TCDD exposure (20.4% vs 9.8%; adjusted RR = 1.70, 95% CI 1.12–2.57, p = 0.012). Finally, a weak but significant positive association between the percentage of Ranch Hand veterans with abnormally high serum triglycerides and their 1987 serum TCDD (adjusted RR = 1.20, 95% CI 1.03–1.40, p = 0.02) was found.

Biologic Plausibility

The induction of lipid mobilization and alterations in lipid metabolism are well-known effects of high-dose exposure to TCDD in laboratory animals that results in hyperlipidemia and loss of body fat. Increases in serum triglycerides were also seen in TCDD-exposed rhesus monkeys (Reir et al., 2001) and mice. For example, Boverhof et al.(2005) found that exposure of mice to a single high dose of TCDD (30 µg/kg of body weight) increased serum triglycerides 1–7 days after exposure, and the increase was associated with changes in hepatic gene expression that were consistent with mobilization of peripheral fat. Similarly, Dalton et al.(2001) found that exposure of mice to a cumulative TCDD dose of 15 µg/kg over 3 days increased serum triglycerides and LDL when measured 4 weeks after exposure. The mechanism underlying altered lipid metabolism has not been elucidated, but the high-dose studies in animal models provide some evidence of biologic plausibility that TCDD exposure can directly alter serum lipid and lipoprotein concentrations.

Synthesis

Previously reviewed literature showed inconsistent changes in serum lipids or lipoproteins after exposure to the compounds of interest, and in most cases the sample sizes were insufficient to support any conclusions. The recent report on Ranch Hand veterans (AFHS, 2005) shows that serum TCDD concentrations are positively associated with serum triglycerides; however, even in Ranch Hand veterans with the highest TCDD exposure, the mean serum triglyceride concentration (130 mg/dL) is well below that considered to be abnormal (250 mg/dL). It is notable that the Ranch Hand veterans with abnormally high serum triglycerides tend to be those with the highest TCDD exposure.

Hypertriglyceridemia is considered to be a major risk factor for acute pancreatitis when serum triglyceride concentrations exceed 1,000 mg/dL, and there is some evidence that it is an independent but weak risk factor for ischemic heart disease at concentrations over 150 mg/dL

(Austin et al., 1998; Jeppesen et al., 1998; Miller et al., 1998). More commonly, however, high serum triglyceride concentrations (150–500 mg/dL) are considered to be a consequence of other underlying diseases, particularly diabetes mellitus and metabolic syndrome, and hypertriglyceridemia is a well recognized marker of these diseases, especially when associated with low HDL concentrations (NCEP, 2002).

The VAO committee responsible for *Type 2 Diabetes* concluded that there was limited or suggestive evidence of an association between type 2 diabetes mellitus and exposure to herbicides in Vietnam (IOM, 2000). Although the latest Ranch Hand study (USAF, 2006) adjusted the RR of hypertriglyceridemia for smoking and BMI, it failed to account for the presence of diabetes mellitus. Diabetes mellitus is strongly associated with hypertriglyceridemia, as discussed above, so it is plausible that the increased percentage of Ranch Hand veterans with abnormally high serum triglycerides may be a consequence of diabetes mellitus. In that regard, the percentage of all Ranch Hand veterans with a diagnosis of diabetes mellitus (about 23%) could include the percentage with hypertriglyceridemia (about 13%).

Hypertriglyceridemia itself was not considered a health outcome by the present committee, but it was recognized that its presence may indicate the emergence of a more significant health concern, metabolic syndrome. Metabolic syndrome is characterized by obesity, high triglycerides (over 150 mg/dL), low HDL (under 40 mg/dL), hypertension (over 130/85 mm Hg), and high fasting plasma glucose or diagnosed diabetes mellitus (Alberti et al., 2006). As noted above, the committee responsible for *Update 2004* concluded that there is suggestive evidence of a link between exposure to herbicides in Vietnam and type 2 diabetes mellitus, whereas the present committee has concluded that there is suggestive evidence of a link between exposure to herbicides in Vietnam and hypertension (see section on circulatory disorders). Thus, an increasing number of Vietnam veterans may be exhibiting at least three of the diagnostic criteria for metabolic syndrome: hypertriglyceridemia, diabetes mellitus, and hypertension. It will be important to analyze the incidence of those individual outcomes as potential components of a larger disease syndrome.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is insufficient or inadequate evidence to determine whether there is an association between exposure to the compounds of interest and lipid or lipoprotein disorders.

GASTROINTESTINAL AND DIGESTIVE DISEASE, INCLUDING LIVER TOXICITY

This section discusses a variety of conditions encompassed by ICD-9 520–579: diseases of the esophagus, stomach, intestines, rectum, liver, and pancreas. Details on peptic ulcer and liver disease, the two conditions most often discussed in the literature reviewed, are provided below. The symptoms and signs of gastrointestinal disease and liver toxicity are highly varied and often vague.

The essential functions of the gastrointestinal tract are to absorb nutrients and eliminate waste. Those complex tasks involve numerous chemical and molecular interactions on the mucosal surface and complex local and distant neural and endocrine activity. One common condition of the gastrointestinal tract is motility disorder, which could be present in 15% of adults. The most convenient way to categorize diseases that affect the gastrointestinal system is according to the affected anatomic segment. Esophageal disorders predominantly affect swallowing; gastric disorders are related to acid secretion; and conditions that affect the small and large intestines are reflected in alterations in nutrition, mucosal integrity, and motility. Some systemic disorders (inflammatory, vascular, infectious, and neoplastic conditions) also affect the gastrointestinal system.

Peptic Ulcer Disease

Peptic ulcer disease refers to ulcerative disorders of the gastrointestinal tract that are caused by the action of acid and pepsin on the stomach or duodenal mucosa. Peptic ulcer disease is characterized as gastric or duodenal ulcer, depending on the site of origin. Peptic ulcer disease occurs when the corrosive action of gastric acid and pepsin overcomes the normal mucosal defense mechanisms that protect against ulceration. About 10% of the population have clinical evidence of duodenal ulcer at some period in life; a similar percentage are affected by gastric ulcer. The incidence of duodenal ulcer peaks in the fifth decade, and the incidence of gastric ulcer about 10 years later.

Evidence increasingly indicates that the bacterium *Helicobacter pylori* is linked to peptic ulcer disease (both duodenal and gastric). *H. pylori* colonizes the gastric mucosa in 95–100% of patients with duodenal ulcer and in 75–80% of patients with gastric ulcer. Healthy subjects in the United States under 30 years old have gastric colonization rates of about 10%. Over the age of 60 years, colonization rates exceed 60%. Colonization alone, however, is not sufficient for the development of ulcer disease; only 15–20% of subjects with *H. pylori* colonization will develop ulcers in their lifetimes. Other risk factors include genetic predisposition (for instance, certain blood and HLA types), cigarette smoking, and psychological factors (chronic anxiety and stress).

Liver Disease

Blood tests that reflect liver function are the mainstay of diagnosis of liver disease. Increases in serum bilirubin and in the serum concentrations of some hepatic enzymes—aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyltransferase (GGT)—are commonly noted in liver disorders. The relative sensitivity and specificity of those enzymes for diagnosing liver disease vary, and several tests can be required for diagnosis. The only regularly reported abnormality in liver function associated with TCDD exposure in humans is an increase in GGT. Estimated serum activity of that enzyme constitutes a sensitive indicator of a variety of conditions, including alcohol and drug hepatotoxicity, infiltrative lesions of the liver, parenchymal liver disease, and biliary tract obstruction. Increases are noted after many chemical and drug exposures that are not followed by evidence of liver injury. The confounding effects of alcohol use (often associated with increased GGT) make interpretation of changes in

GGT in exposed people difficult (Calvert et al., 1992). An increase in GGT can be considered a normal biologic adaptation to chemical, drug, or hormone exposure.

Cirrhosis is the most commonly reported liver disease in epidemiologic studies of herbicide or TCDD exposure. Cirrhosis is irreversible chronic injury of the liver with extensive scarring and resulting loss of liver function. Clinical symptoms and signs include jaundice, edema, abnormalities in blood clotting, and metabolic disturbances. Cirrhosis can lead to portal hypertension with associated gastroesophageal varices, enlarged spleen, abdominal swelling attributable to ascites, and ultimately hepatic encephalopathy that can progress to coma. It generally is impossible to distinguish the various causes of cirrhosis by using clinical signs and symptoms or pathologic characteristics. The most common cause of cirrhosis in North America and many parts of Western Europe and South America is excessive alcohol consumption. Other causes are chronic viral infection (hepatitis B or hepatitis C), a poorly understood condition called primary biliary cirrhosis, chronic right-sided heart failure, and a variety of less common metabolic and drug-related causes.

Conclusions from *VAO* and Updates

Studies that have been reviewed by previous committees have consisted of those focusing on liver enzymes and others that have reported specific liver diseases. Evaluation of the effect of herbicide and TCDD exposure on non-cancer gastrointestinal ailments is challenging in that clinical experience suggests that medical history and physical examination are undependable diagnostic tools for some ailments, so incidence data are sometimes problematic. The strong interdependence among the characteristics of a given person (such as weight and laboratory indexes of hepatic function and health) and TCDD body burden complicates the already difficult task of assessing association.

Most of the analyses of occupational or environmental cohorts have had insufficient numbers of cases to support confident conclusions. The one study with a relatively large number of observations (Vena et al., 1998) found lower digestive system disease and cirrhosis mortality among exposed workers than among unexposed controls. A set of studies of Australian veterans suggested a higher incidence of stomach and duodenal ulcers in men and women, but the information was self-reported and the analyses were not controlled for confounding influences. A report on the Ranch Hand study (AFHS, 2000) found a significantly higher percentage of other liver disorders among veterans in the high-dioxin category than among comparisons. The excesses were primarily of transaminase and other nonspecific liver abnormalities. Data were consistent with an interpretation of a dose–response relationship, but other explanations were also plausible. Although there have been sporadic reports of increased gastrointestinal disease potentially related to exposure to herbicides or TCDD, the results are inconsistent among studies. In addition, interpretation of individual studies was generally subject to a lack of information on alcohol consumption and other risk factors. In the studies that showed the strongest association between potential exposure and gastrointestinal disease (specifically cirrhosis), there was strong evidence that excess alcohol consumption was the etiology of the cirrhosis.

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and gastrointestinal and digestive disease, including liver toxicity. Additional

information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion.

Update of the Epidemiologic Literature

Occupational Studies

't Mannetje et al. (2005) completed a mortality study in New Zealand of 813 TCDD-exposed phenoxy herbicide producers and 699 sprayers whose vital status was followed from 1969 and 1973, respectively, to 2000. No increased mortality from diseases of the digestive system were found (ICD-9 530–579) in production workers (SMR = 1.3, 95% CI 0.4–3.3) or sprayers (SMR = 0.8, 95% CI 0.16–2.34).

Environmental Studies

Baccarelli et al. (2005b) conducted a case–control study of Seveso residents who had chloracne and were about 8 years old at the time of exposure. They were no more likely to report gastrointestinal disease during the 20-year follow-up period than controls, and no cases of liver disease were reported.

Lee et al. (2006) studied the association between fatty liver and hepatic function in residents of the vicinity of a closed pentachlorophenol manufacturing factory (exposure area) and nearby areas (control area). A total of 85 subjects were studied (52 in the exposure area). All subjects were identified from prior investigations of serum PCDD and PCDF measurements. The average serum PCDD and PCDF concentration was 80.1 pg ± 50.9 pg WHO-TEQ/g of lipid among subjects in the exposure area and 25.5 pg ± 18.2 pg in subjects in the control area. Statistically higher ORs for fatty liver and GGT were found in subjects with the higher PCDD concentrations and high BMI. Fatty liver was diagnosed with ultrasonographic examination by a senior radiologist blinded to subject status or PCDD concentration. Diagnostic criteria of fatty liver were "bright liver", blaring of hepatic vessels and diaphragm, and fat attenuation. With control for a substantial age difference between the groups, the findings suggest a synergistic effect of BMI, serum PCDD, and the risk of fatty liver.

Vietnam-Veteran Studies

Boehmer et al. (2004) in a mortality analysis of the VES reported a crude RR of 1.10 for all deaths from gastrointestinal disease (95% CI 0.73–1.66).

Kang et al. (2006) reported 101 hepatitis cases among 1,499 Vietnam veterans (adjusted OR = 1.85, 95% CI 1.30–2.64). The cases were associated with Vietnam service, being nonwhite, and regular smoking but not with a history of spraying herbicide.

Ketchum and Michalek (2005) reported on mortality in Ranch Hand veterans. The RR of death caused by disease of the digestive system was not significantly increased on the basis of small numbers of Ranch Hand deaths (RR = 1.6, 95% CI 0.8–3.0).

The 2002 examination report of the Ranch Hand cohort (AFHS, 2005) included seven self-reported liver disorders verified by medical-record review, hepatomegaly noted on physical examination, and 28 laboratory measures that are commonly used to assess liver function. No significant increases were found in self-reported liver disorders or hepatomegaly on examination. Several findings were increased among Ranch Hand veterans, including increased occult stool among Ranch Hand officers and decreasing C4 complement as dioxin increased. Increased risk for abnormal alkaline phosphatase and triglyceride level concentrations were reported in the Ranch Hand ground crew. The percentage of Ranch Hand veterans with abnormal triglyceride concentrations increased significantly as the 1987 dioxin concentration increased. The only regularly reported abnormality in liver function associated with TCDD exposure in humans, increased GGT, was not increased in any of the comparisons made in the report.

The Australian Vietnam-veterans study (ADVA, 2005b) reported 292 cases of liver disease (SMR = 1.03, 95% CI 0.91–1.15) and a subset of 161 cases of alcoholic liver disease (SMR = 1.19, 95% CI 1.01–1.38) among military personnel serving in Vietnam compared to cases of liver disease among the general population of Australia.

Biologic Plausibility

TCDD effect on the intestine is not well understood. Ishida et al. (2005) examined the effect of dioxin on the pathology and function of the intestine in AhR-sensitive and -less-sensitive mice, after oral administration of TCDD (100 µg/kg). C57BL/6J mice showed changes in villous structure and nuclear/cytoplasm ratio in the epithelial cells of the intestine. In an oral glucose tolerance test, the serum glucose level was significantly increased in the C57BL/6J mouse but not in the DBA/2J mouse. The expression of intestinal mRNAs coding sodium-glucose co-transporter 1 (SGLT1) and glucose transporter type 2 were increased only in C57BL/6J mice. The intestinal activity of sucrase and lactase also was significantly increased in C57BL/6J mice by TCDD.

Synthesis

There is no evidence that Vietnam veterans are at greatly increased risk for serious liver disease, and reports of increased risk of abnormal liver-function tests have been mixed. Although increased rates of gastrointestinal disease have not been reported, the possibility of a relationship between dioxin exposure and subtle alterations in the liver and in lipid metabolism cannot be ruled out.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and gastrointestinal and digestive diseases.

CIRCULATORY DISORDERS

This section covers a variety of conditions encompassed by ICD-9 390–459, such as acute and chronic rheumatic fever (390–398), hypertension (401–404), ischemic heart disease (410–414), heart failure (428), cerebrovascular disease (430–438), and peripheral vascular disease (443). *Coronary heart disease* is a specific term related to atherosclerosis; *ischemic heart disease* is a broader term that typically includes atherosclerosis and its symptoms. The American Heart Association reports mortality related to coronary heart disease, not to its symptoms, which include angina and myocardial infarction. Table 9-2 contains estimates of prevalence and associated mortality in the US population for 2004 for the individual disorders of the circulatory system.

Various methods have been used in morbidity studies to assess the circulatory system, including analysis of symptoms or history, physical examination of the heart and peripheral arteries, Doppler measurements of peripheral pulses, electrocardiography (ECG), and chest radiography. Doppler measurements and physical examination of pulses in the arms and legs are used to detect decreases in pulse strength, which can be caused by thickening and hardening of the arteries. ECG can be used to detect heart conditions and abnormalities, such as arrhythmias (abnormal heart rhythms), heart enlargement, and heart attacks. Chest radiography can be used to assess the consequences of ischemic heart disease and hypertension, such as the enlargement of the heart seen with heart failure. However, clinical testing is often nonspecific; similar test results can be observed as a consequence of various medical conditions. A common limitation of mortality studies is that they attribute death to circulatory disorders with various degrees of diagnostic confirmation.

Conclusions from *VAO* and Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and circulatory disorders. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. New studies since *Update 2004* and a study not previously discussed with respect to cardiovascular outcomes are reviewed below. In light of the newer findings, the present committee reconsidered all studies related to ischemic heart disease and hypertension that had been discussed in previous updates. Those studies are all summarized in Table 9-5.

TABLE 9-5 Selected Epidemiologic Studies—Circulatory Disorders

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Studies of Vietnam Veterans				
	Studies on US Army Chemical Corps			
Kang et al., 2006 and supplemental data	**Army Chemical Corps — Morbidity**			
	Vietnam Vets vs Non-Vietnam Vets			
	Hypertension requiring Rx	496	1.06 (0.89–1.27)[b]	Diagnoses not confirmed by medical record review
	Heart disease diagnosed by MD	243	1.09 (0.87–1.38)[b]	
	Sprayers vs Non-sprayers			
	All (diabetics & non-diabetics)			
	Hypertension requiring Rx	247	1.26 (1.00–1.58)[b]	
	Heart disease diagnosed by MD	129	1.41 (1.06–1.89)[b]	
	All Veterans, contribution of spraying to logistic regression model			
	All (diabetics & non-diabetics)			
	Hypertension requiring Rx		1.32 (1.08–1.61)[b]	
	Heart disease diagnosed by MD		1.52 (1.18–1.94)[b]	
	Non-diabetics only			
	Hypertension requiring Rx		1.23 (0.99–1.52)[b]	
	Heart disease diagnosed by MD		1.52 (1.14–2.01)[b]	
	Controlling for diabetic status			
	Hypertension requiring Rx		1.27 (1.04–1.55)[c]	
	Heart disease diagnosed by MD		1.45 (1.13–1.86)[c]	
Thomas and Kang, 1990	**US Army Chemical Corps vs US male population—Mortality**			
	Circulatory diseases (390–458)	6	0.55	Not adjusted for known risk factors

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
	Air Force Health Study of Ranch Hand Veterans			
AFHS, 2005 1,951 participants in 2002 exam Number in analysis	**AFHS, 2002 Exam Cycle Report—Morbidity** <u>Model 1: RH Subjects vs SEA Comparisons</u> (also available separately for Officer, Enlisted flyer, Enlisted groundcrew)			
	Essential hypertension			
1,885	Heart disease (except essential hypertension)	412 of 759	0.92 (0.53–1.13)[a]	82% overall
1,902	Enlisted flyer	644 of 767	1.20 (0.94–1.54)[a]	
308	Myocardial infarction	120 of 131	2.46 (1.19–5.11)[a]	
1,902	Stroke or transient ischemic attack	77 of 767	0.81 (0.59–1.12)[a]	
1,902		29 of 767	1.39 (0.82–2.34)[a]	
	<u>Model 2: RH Subjects with extrapolated initial serum TCDD (>10 ppt in 1987)</u>			
	Essential hypertension			
406	Heart disease (except essential hypertension)	244	1.12 (0.91–1.37)[a]	Relative risk
411	Myocardial infarction	344	1.08 (0.85–1.38)[a]	for a 2x
411	Stroke or transient ischemic attack	42	1.31 (0.97–1.77)[a]	increase in
411		17	1.26 (0.78–2.03)[a]	serum TCDD
	<u>Model 3: All Subjects with serum TCDD readings (RH group vs Comp)</u>			
	Essential hypertension			
1,344	Comparison			
	RH background (<10 ppt, 1987)	644	1.0	
	RH low (10–118 ppt, initial)	168	0.88 (0.67–1.16)[a]	
	RH high (>118 ppt, initial)	109	0.74 (0.53–1.04)[a]	
	Heart disease (except essential hypertension)	135	1.32 (0.94–1.87)[a]	
1,355	Comparison			
	RH background (<10 ppt, 1987)	937	1.0	
	RH low (10–118 ppt, initial)	299	1.33 (0.94–1.89)[a]	
	RH high (>118 ppt, initial)	171	1.03 (0.68–1.54)[a]	
	Myocardial infarction	173	1.21 (0.81–1.82)[a]	
1,355	Comparison			
	RH background (<10 ppt, 1987)	132	1.0	
	RH low (10–118 ppt, initial)	34	0.81 (0.53–1.25)[a]	
	RH high (>118 ppt, initial)	18	0.60 (0.34–1.04)[a]	
	Stroke or transient ischemic attack	24	1.04 (0.63–1.74)[a]	
1,355	Comparison			
	RH background (<10 ppt, 1987)	36	1.0	
	RH low (10–118 ppt, initial)	12	1.21 (0.59–2.45)[a]	
	RH high (>118 ppt, initial)	7	1.10 (0.47–2.57)[a]	
		10	2.16 (0.98–4.77)[a]	
	<u>Model 4: RH Subjects with 1987 serum TCDD readings</u>			
	Essential hypertension			
748	Heart disease (except essential hypertension)		1.11 (0.98–1.25)[a]	
755	Myocardial infarction		0.90 (0.78–1.06)[a]	Relative risk
755	Stroke or transient ischemic attack		1.03 (0.85–1.24)[a]	for a 2x
755			1.04 (0.76–1.44)[a]	increase in serum TCDD

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
AFHS, 2000 [*largely superseded by AFHS, 2005*]	**Operation Ranch Hand—**Results of 1997 exam Hypertension–medical record review Model 3: RH high TCDD vs background Model 4: RH Vets 1987 serum TCDD		 1.27 (0.93–1.74) [a] 1.18 (1.04–1.34)[a]	 Relative risk for a 2x increase in serum TCDD
AFHS, 1995 [*largely superseded by AFHS, 2005*]	**Operation Ranch Hand—**Results of 1992 exam Hypertension–medical record review Model 3: RH high TCDD vs background Model 4: RH Vets 1987 serum TCDD		 1.20 (0.88–1.63) [a] 1.14 (1.02–1.28)[a]	 Relative risk for a 2x increase in serum TCDD
Wolfe et al., 1992 [*largely superseded; summary of results in AFHS, 1991b*]	**Operation Ranch Hand—**Results of 1987 exam**–Morbidity** Essential hypertension Model 3: RH high TCDD vs background Verified heart disease (w/o HT) Model 4: RH high TCDD vs background	 NR NR	 Increase ($p < 0.05$) Decrease ($p < 0.05$)	
AFHS, 1990 [*largely superseded by AFHS, 2005*]	**Operation Ranch Hand—**Results of 1987 exam Model 1: before analyses on serum TCDD levels All verified by medical record review Essential hypertension Heart disease (w/o HT) Myocardial infarction	 297 337 39	 1.07 (0.89–1.29) [a] 1.06 (0.88–1.26) [a] 0.96 (0.63–1.47) [a]	
AFHS, 1987 [*largely superseded by AFHS, 2005*]	**Operation Ranch Hand—**Results of 1985 exam Model 1: before analyses on serum TCDD levels All verified by medical record review Essential hypertension Heart disease (w/o HT) Myocardial infarction	 195 224 9	 1.03 (0.83–1.27) [a] 1.22 (1.00–1.50) [a] 0.88 (0.38–2.08) [a]	
AFHS, 1984 [*largely superseded by AFHS, 2005*]	**Operation Ranch Hand—**Results of 1982 baseline exam Model 1: before analyses on serum TCDD levels All verified by medical record review Heart disease Myocardial infarction	 147 7	 $p = 0.982$ $p = 0.432$	

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Ketchum and Michalek, 2005 *[Supersedes Michalek et al., 1990, 1998]*	**AFHS—Circulatory disease—mortality** Ranch Hand Subjects vs all SEA veterans Pilots and navigators Administrative Officers Enlisted Flight Engineers Ground Crew Atherosclerosis Hypertensive disease Stroke AFHS Veterans with serum TCDD SEA comparison group Background (0.6–10 ppt) Low (10–29.2 ppt) High (18–617.8 ppt)	 66 18 2 6 40 28 2 5 31 8 12 9	 1.3 (1.0–1.6) 1.1 (0.7–1.8) 1.8 (0.4–7.8) 0.5 (0.2–1.1) 1.7 (1.2–2.4) 1.7 (1.1–2.5) 2.5 (0.6–10.8) 2.3 (0.9–6.0) 1.0 0.8 (0.4–1.8)[d] 1.8 (0.9–3.5)[d] 1.5 (0.7–3.3)[d]	Not adjusted for known risk factors
Watanabe and Kang, 1996	**US Army and Marine Corps Vietnam-era veterans—Mortality** (PMR, 1965–1988) Served in Vietnam vs never deployed to SEA Circulatory diseases (390–458) Army Marine Corps	 5,756 1,048	 0.97 (p >0.05) 0.92 (p <0.05)	Not adjusted for known risk factors
Bullman and Kang, 1996	**US wounded Vietnam veterans vs US men—Mortality** (through 1981, focus on suicide) Circulatory disease	 246	 0.72 (0.55–0.91)	
Boehmer et al., 2004	**CDC Vietnam Experience Study—Mortality** Deployed vs non-deployed Circulatory disease Year of death 1970–1984 1985–2000 Discharged before 1970 Discharged after 1970 Ischemic heart diseases 0–15 years since discharge >15 years since discharge	 185 NR NR NR NR 125 8 117	 1.01 (0.82–1.24) 0.56 (0.28–1.15)[e] 1.06 (0.85–1.32)[e] 0.83 (0.62–1.12)[e] 1.43 (1.02–1.99)[e] 0.77 (0.31–1.55) 1.14 (0.87–1.50)	Partition at 1970 arbitrary
CDC, 1988	**Vietnam Experience Study—Morbidity** Deployed vs non-deployed Hypertension postdischarge Interviewed Examined	 2,013 623	 1.3 (p <0.05) 1.2 (p <0.05)	Not adjusted for known risk factors
Stellman et al., 1988	**American Legionnaires serving during Vietnam-era—Morbidity**			

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
	Service in SEA vs not, with medically diagnosed			
	High blood pressure	592	1.12 (p >0.05)	Not age adjusted
	Heart disease	97	1.45 (p <0.05)	Age adjusted
Anderson et al., 1986	**Wisconsin Vietnam veterans—all diseases of circulatory system—Mortality**			
	White male Vietnam veterans vs	100		
	National population		0.69 (p <0.05)	
	State population		0.62 (p <0.05)	
	Non-veterans		0.58 (p <0.05)	
	All veterans		0.86 (p >0.05)	
	Vietnam–era veterans		0.99 (0.80–1.20)	
Kogan and Clapp, 1985	**Massachusetts Vietnam-era veterans** (1958–1973)**—Mortality** (1972–1983)			
	Deployed vs non-deployed			Not adjusted for age; Vietnam veterans thought to be younger
	Deaths 1972–1983			
	Circulatory system (except cerebrovascular)	139	PMR = 0.88 (p >0.05)	
	Cerebrovascular	28	PMR = 1.11 (p >0.05)	
	Deaths 1978–1983			
	Circulatory system (except cerebrovascular)	85	PMR = 0.80 (p <0.05)	
	Cerebrovascular	19	PMR = 1.64 (p <0.05)	Expect less "diluted" effect for later time?
	Studies of Austrian Vietnam Veterans			
Australian Dept Veterans Affairs, 2005b	**Australian Vietnam Veterans vs General Male Population—Mortality**			
	Circulatory disease	1,767	0.88 (0.84–0.92)	
	1963–1979	186	0.69 (0.59–0.79)	
	1980–1990	546	0.88 (0.80–0.95)	
	1991–2001	1,035	0.93 (0.87–0.99)	Dissipation of healthy worker effect perhaps
	Ischemic heart disease	1,297	0.94 (0.89–0.99)	
	1963–1979	124	0.70 (0.58–0.82)	
	1980–1990	421	0.95 (0.86–1.04)	
	1991–2001	753	0.99 (0.92–1.06)	
	Stroke	223	0.80 (0.70–0.91)	
	1963–1979	35	0.81 (0.54–1.07)	
	1980–1990	59	0.73 (0.54–0.92)	
	1991–2001	129	0.83 (0.69–0.97)	
Australian Dept Veterans Affairs, 2005c	**Australian National Service Veterans Deployed vs Non-deployed—Mortality**			
	Circulatory disease	208	1.05 (0.87–1.27)	
	Ischemic heart disease	159	1.18 (0.94–1.47)	
	Stroke	15	0.61 (0.30–1.15)	

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Crane et al., 1997a [*largely superseded by ADVA, 2005b*]	**Australian Vietnam veterans—Mortality** (1980–1994) Circulatory disease Ischemic heart disease Cerebral hemorrhage		 0.96 (0.88–1.05) 1.04 (0.94–1.14) 0.80 (0.53–1.22)	 Not adjusted for known risk factors
Crane et al., 1997b [*largely superseded by ADVA, 2005c*]	**Australian National Service Vietnam-era veterans—Mortality** (1982–1994) Deployed vs non-deployed Circulatory disease Ischemic heart disease Cerebral hemorrhage Other	 77 57 3 17	 0.95 (0.70–1.28) 0.97 (0.68–1.39) 0.96 (0.14–5.66) 0.88 (0.44–1.69)	 Not adjusted for known risk factors
O'Toole et al., 1996	**Australian male Army Vietnam veterans** (random sample)**—Morbidity** Self-report in telephone interview Hypertension Heart disease Other circulatory diseases (excluding above & hemorrhoids) Self-report in telephone interview (adjusted for non-response) Hypertension Heart disease Other circulatory diseases (excluding above & hemorrhoids)	 NR NR NR NR NR NR	 99% CIs 2.08 (1.63–3.31) 2.02 (0.96–4.77) 2.07 (1.35–3.97) 99% CIs 2.17 (1.71–2.62) 1.98 (0.91–3.05) 2.39 (1.61–3.17)	 Not adjusted for known risk factors Not adjusted for known risk factors
Kim J-S et al., 2003	**Korean veterans of Vietnam—Morbidity** Deployed vs Non-deployed (unadjusted) Valvular heart disease Congestive heart failure Ischemic heart disease Hypertension Adjusted for risk factors	 8 5 34 383	 p = 0.0019 p = 0.5018 p = 0.0045 p = 0.0143 2.29 (1.33–3.95)[g]	Concerns of selection bias, quality of diagnosis, low participation, gross pooling of blood samples made TCDD levels useless
Occupational Studies				
McLean et al., 2006	**IARC Cohort of Pulp and Paper Workers—** Circulatory disease—**Mortality** Never exposed to nonvolatile organochlorines Ever exposed to nonvolatile organochlorines	 2,727 2,157	 0.92 (0.89–0.96) 0.99 (0.95–1.04)	Not adjusted for known risk factors
Blair et al., 2005a	**Agricultural Health Study—Mortality** Private applicators (farmers) and spouses			

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
	Circulatory disease (1994–2000)	619	0.5 (0.5–0.6)[f]	
't Mannetje et al., 2005 [IARC subcohort]	**New Zealand phenoxy herbicide workers—Mortality**			Not adjusted for known risk factors
	Producers (1969–2000)			
	Circulatory disease	51	1.0 (0.7–1.3)	All causes
	Hypertensive disease	0	0.0 (0.0–3.5)	SMR = 1.0
	Ischemic heart disease	38	1.0 (0.7–1.4)	(0.8–1.2)
't Mannetje et al., 2005 (continued)	Sprayers (1973–2000)			
	Circulatory disease	33	0.5 (0.4–0.7)	All causes
	Hypertensive disease	1	0.8 (0.0–4.5)	SMR = 0.6
	Ischemic heart disease	22	0.5 (0.3–0.8)	(0.5–0.8)
Vena et al., 1998 [same dataset as Kogevinas et al., 1997 (emphasis on cancer) reviewed in *Update 1998*]	**IARC Cohort of Phenoxy Herbicide Workers—Mortality** (1939–1992)			
	All male phenoxy herbicide workers			
	All circulatory disease (390–459)	1,738	0.91 (0.87–0.95)	Not adjusted for known risk factors
	Ischemic heart disease (410–414)	1,179	0.92 (0.87–0.98)	
	Cerebrovascular disease (430–438)	254	0.86 (0.76–0.97)	
	Other diseases of the heart (415–429)	166	1.11 (0.95–1.29)	
	All female phenoxy herbicide workers			
	All circulatory disease (390–459)	48	1.00 (0.73–1.32)	Not adjusted for known risk factors
	Ischemic heart disease (410–414)	24	1.07 (0.68–1.59)	
	Cerebrovascular disease (430–438)	9	0.73 (0.33–1.38)	
	Other diseases of the heart (415–429)	6	0.92 (0.34–2.00)	
	Workers with phenoxy herbicide exposure only			
	All circulatory disease (390–459)	588	0.86 (0.79–0.93)	Not adjusted for known risk factors
	Ischemic heart disease (410–414)	394	0.85 (0.77–0.94)	
	Cerebrovascular disease (430–438)	96	0.86 (0.70–1.05)	
	Other diseases of the heart (415–429)	32	0.80 (0.55–1.13)	
	TCDD-exposed workers			
	All circulatory disease (390–459)	1,170	0.94 (0.88–0.99)	Not adjusted for known risk factors
	Ischemic heart disease (410–414)	789	0.97 (0.90–1.04)	
	Cerebrovascular disease (430–438)	162	0.84 (0.71–0.98)	
	Other diseases of the heart (415–429)	138	1.20 (1.01–1.42)	
	Contribution of TCDD exposure to Poisson regression analysis			
	All circulatory disease	1,151	1.51 (1.17–1.96)	Only adjusted for age and timing of exposure
	Ischemic heart disease	775	1.67 (1.23–2.26)	
	Cerebrovascular disease	161	1.54 (0.83–2.88)	

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Hooiveld et al., 1998	**Dutch herbicide factory workers** (IARC subcohort)**—Mortality** (1955–1991) <u>549 exposed vs 482 non-exposed male workers</u>			
	All circulatory diseases (390–459)	45	1.4 (0.8–2.5)	Only adjusted for age and timing of exposure
	>124 ng/kg TCDD	NR	1.5 (0.8–2.9)	
	Ischemic heart diseases (410–414)	33	1.8 (0.9–3.6)	
	>124 ng/kg TCDD	NR	2.3 (1.0–5.0)	
	Cerebrovascular diseases (430–438)	9	1.4 (0.4–5.1)	
	>124 ng/kg TCDD	NR	0.8 (0.2–4.1)	
	Other heart disease (415–429)	3	0.7 (0.1–4.3)	
	>124 ng/kg TCDD	NR	0.4 (0.0–4.9)	

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Flesch-Janys, 1997/1998 (TEQ info); Flesch-Janys et al., 1998 (in German, also TCDD info)	**Hamburg, Germany herbicide production workers <u>vs national FRG population</u>** (IARC subcohort)**—Mortality** (1952–1992; estimated of PCDD/F and TCDD blood levels from work history & measures on 190 of 1,189 men, divided into 4 lowest quintiles & top 2 deciles)			Potential for exposure misclassification
	<u>Estimated final PCDD/F TEQs (ng/kg)</u>			
	Circulatory disease (390–459)	156	1.06 (0.90–1.24)	
	1.0–12.2		0.71 (0.44–1.17)	Not adjusted for known risk factors
	12.3–39.5		0.73 (0.46–1.16)	
	39.6–98.9		1.20 (0.82–1.76)	
	99.0–278.5		1.22 (0.84–1.78)	
	278.6–545.0		1.18 (0.73–1.92)	
	545.1–4361.9		1.70 (1.02–2.85)	
			p-trend = 0.04	
	Ischemic heart disease (410–414)	76	0.97 (0.77–1.22)	
	1.0–12.2		0.80 (0.42–1.56)	
	12.3–39.5		0.76 (0.40–1.45)	
	39.6–98.9		0.75 (0.40–1.42)	
	99.0–278.5		0.88 (0.50–1.58)	
	278.6–545.0		1.26 (0.67–2.39)	
	545.1–4361.9		2.17 (1.18–4.00)	
			p-trend = 0.03	
	<u>Estimated final TCDD (ng/kg)</u>			
	Circulatory disease (390–459)	156	1.06 (0.90–1.24)	
	0–2.8		0.94 (0.62–1.43)	Not adjusted for known risk factors
	2.81–14.4		0.69 (0.42–1.14)	
	14.5–49.2		1.13 (0.75–1.68)	
	49.3–156.7		1.29 (0.88–1.89)	
	156.8–344.6		1.10 (0.69–1.78)	
	344.7–3890.2		1.62 (0.95–2.77)	
			p-trend = 0.04	
	Ischemic heart disease (410–414)	76	0.97 (0.77–1.22)	
	0–2.8		1.13 (0.65–1.95)	
	2.81–14.4		0.63 (0.31–1.27)	
	14.5–49.2		0.94 (0.51–1.73)	
	49.3–156.7		0.70 (0.36–1.36)	
	156.8–344.6		1.17 (0.61–2.23)	
	344.7–3890.2		1.99 (1.05–3.75)	
			p-trend = 0.10	

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Flesch-Janys et al., 1995	**Hamburg, German herbicide production workers vs gas workers** (IARC subcohort)— **Mortality**			
	Estimated final PCDD/F TEQs (ng/kg)			
	Circulatory disease (390–459)	156		
	1.0–12.2		0.93 (0.57–1.50)	Not adjusted for known risk factors
	12.3–39.5		0.92 (0.59–1.46)	
	39.6–98.9		1.48 (1.01–2.17)	
	99.0–278.5		1.55 (1.07–2.24)	
	278.6–545.0		1.63 (1.01–2.64)	
	545.1–4361.9		2.06 (1.23–3.45)	
			p-trend <0.01	
	Ischemic heart disease (410–414)	76		
	1.0–12.2		1.02 (0.54–1.95)	
	12.3–39.5		0.96 (0.51–1.82)	
	39.6–98.9		0.97 (0.52–1.81)	
	99.0–278.5		1.13 (0.64–2.00)	
	278.6–545.0		1.73 (0.92–3.27)	
	545.1–4361.9		2.72 (1.49–4.98)	
			p-trend <0.01	
	Estimated final TCDD (ng/kg)			
	Circulatory disease (390–459)	156	1.22 (0.81–1.83)	Not adjusted for known risk factors
	0–2.8		0.88 (0.54–1.44)	
	2.81–14.4		1.35 (0.91–2.01)	
	14.5–49.2		1.64 (1.12–2.39)	
	49.3–156.7		1.53 (0.95–2.44)	
	156.8–344.6		1.96 (1.15–3.34)	
	344.7–3890.2		p-trend = 0.01	
	Ischemic heart disease (410–414)	76	1.43 (0.83–2.44)	
	0–2.8		0.81 (0.41–1.61)	
	2.81–14.4		1.18 (0.65–2.16)	
	14.5–49.2		0.90 (0.47–1.75)	
	49.3–156.7		1.61 (0.85–3.04)	
	156.8–344.6		2.48 (1.32–4.66)	
	344.7–3890.2		p-trend < 0.01	
Becher et al., 1996 [mortality through 1992 for I. Hamburg reported above by Flesch-Janys]	**Phenoxy herbicide workers at 4 German plants** (4 IARC subcohorts, including Hamburg)–Flesch-Janys)— **Mortality** (through 1989)			
	Circulatory diseases (390–458)	12	0.74 (0.38–1.30)	
	Bayer Uerdingen	3	0.34 (0.07–0.99)	
	Bayer Dormagen	32	0.78 (0.53–1.10)	
	BASF Ludwigshafen			

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Coggon et al., 1991	**British Chemical Manufacturers from 4 Plants** (4 IARC subcohorts)**—Mortality**			
	Circulatory disease	74	1.16 (0.91–1.46)	
	Plant A (1975–1987)	34	1.67 (adjusted = 1.39, p ≈ 0.05)	
	Plant B (1969–1987)	5	0.95	
	Plant C (1963–1987)	12	0.84	
	Plant D (1969–1987)	23	0.97	
Coggon et al., 1986	**British MCPA manufacturers** (5th of 7 UK IARC cohorts)**—Mortality**			
	Hypertensive & ischemic heart disease (401–414, 428–429)	337		
	Vs national rates		0.81 (0.73–0.90)	
	With rural adjustment		0.86 (0.77–0.96)	
	US Cohorts in NIOSH Cohort (and also in IARC Cohort)			
Burns et al., 2001 [part of IARC & NIOSH cohorts]	**Dow 2,4-D Production Workers—Mortality** (1945–1994)			
	Circulatory disease			Not adjusted for known risk factors
	0 years latency	158	0.95 (0.80–1.11)	
	≥20 years latency	130	1.05 (0.87–1.24)	
Ramlow et al., 1996	**Dow PCP workers (1930-1980)** (subcohort)**—Mortality** (1940–1989)			
	Circulatory diseases (390–458)	115	0.95 (0.79–1.14)	
	Arteriosclerotic heart disease (410–414)	86	1.02 (0.82–1.26)	
	Cerebrovascular disease (430–438)	15	1.02 (0.57–1.68)	
Steenland et al., 1999	**NIOSH Cohort (subcohorts of IARC cohort from 12 US plants)—Mortality** (through 1993)			
	Total Cohort (5,132) vs US population			
	Cerebrovascular disease (430–438)		0.96 (0.74–1.21)	Not adjusted for known risk factors
	Ischemic heart disease (410–414)	69	1.09 (1.00–1.20)	
	Chloracne subcohort (608) vs US population	456	1.17 (0.94–1.44)	
	Exposure subcohort (3,538)	92		
	<19 cumulative TCDD		1.0	Adjusted for age
	19–139	NR	1.23 (0.75–2.00)	
	139–580	NR	1.34 (0.83–2.18)	
	581–1,649	NR	1.30 (0.79–2.13)	(no units for JEM-derived exposure)
	1,650–5,739	NR	1.39 (0.86–2.24)	
	5,740–20,199	NR	1.57 (0.96–2.56)	
	≥20,200	NR	1.75 (1.07–2.87)	
		NR	p-trend cum expo = 0.05	
			p-trend log[cum expo] <0.001	

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Calvert et al., 1998	**2 US Chemical Plants (part of NIOSH & IARC cohorts)—Morbidity**			
	Verified conditions			
	TCDD-exposed (281) vs unexposed (260)			
	Myocardial infarction	17	1.33 (0.62–2.84)	Not adjusted for known risk factors
	Current systolic hypertension	64	1.05 (0.70–1.58)	
	Current diastolic hypertension	77	1.23 (0.83–1.82)	
	TCDD effect vs unexposed in logistic model			
	Self-reported and verified conditions combined			
	Myocardial infarction			
	Serum TCDD <238 pg/g lipid	NR	1.14 (0.29–4.49) [i]	
	Serum TCDD ≥238 pg/g lipid	NR	1.09 (0.23–5.06) [i]	
	Hypertension			
	Serum TCDD <238 pg/g lipid	NR	1.34 (0.89–2.02) [i]	
	Serum TCDD ≥238 pg/g lipid	NR	1.05 (0.58–1.89) [i]	
	Verified conditions			
	Current systolic hypertension			
	Serum TCDD <238 pg/g lipid	NR	1.09 (0.65–1.83) [i]	
	Serum TCDD ≥238 pg/g lipid	NR	1.20 (0.61–2.34) [i]	
	Current diastolic hypertension			
	Serum TCDD <238 pg/g lipid	NR	1.35 (0.88–2.09) [i]	
	Serum TCDD ≥238 pg/g lipid	NR	0.97 (0.51–1.87) [i]	
Suskind and Hertzberg, 1984	**Monsanto Workers at Nitro, WV—Morbidity**			
	Workers exposed to 2,4,5-T production (n = 204)			
	vs not exposed (n = 163) (self-report)			
	Hypertension	70	(p >0.05)	Adjusted for age
	Coronary artery disease	22	(p >0.05)	
Zack and Gaffey, 1983	**Monsanto Workers at Nitro, WV** (n = 884)**—Mortality** (1955–1977)			
	Circulatory diseases (390–458)	92	1.11 (p >0.05)	Not adjusted for known risk factors
	Atherosclerosis and CHD (410–413)	79	1.33 (p <0.05)	
	All other	13	0.56 (p <0.05)	
Zack and Suskind, 1980	**Monsanto Workers at Nitro, WV—Mortality** (1955–1978)			
	Workers with chloracne (n = 121)			Not adjusted for known risk factors
	Circulatory diseases (390–458)	17	0.68 (p >0.05)	
	Atherosclerosis and CHD (410–413)	13	0.73 (p >0.05)	
Swaen et al., 2004 *[Supersedes Swaen et al., 1992]*	**Dutch licensed herbicide applicators—Mortality** (1980–2000)			
	Circulatory disease	70	0.68 (0.53–0.86)	

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
Ott and Zober, 1996 *[Supersedes Zober et al., 1994 & Von Benner et al., 1994 (translation from German)]*	**Clean-up workers at German TCP reactor (BASF)—Mortality** (1953–1992) Circulatory diseases <0.1 estimated TCDD µg/kg bw 0.1–0.99 ≥1.0 Ischemic heart disease <0.1 estimated TCDD µg/kg bw 0.1–0.99 ≥1.0	 37 13 11 13 16 7 4 5	 0.8 (0.6–1.2) 0.8 (0.4–1.4) 1.0 (0.5–1.7) 0.8 (0.4–1.3) 0.7 (0.4–1.1) 0.9 (0.3–1.8) 0.7 (0.2–1.7) 0.6 (0.2–1.3)	Reliability of estimated body burden?
	Other Occupational Studies			
Kitamura K et al., 2000	**Municipal waste incinerator workers—Morbidity** Hypertension by PCDD/PCDF levels	 14 of 94	 No increases observed [h]	
Gambini et al., 1997	**Italian rice growers—Mortality** (1957–1992) (Phenoxy herbicide use common 1960–1980) Myocardial infarction Other ischemic heart diseases Stroke	 67 72 155	 0.72 (0.56–0.92) 0.41 (0.32–0.52) 0.96 (0.81–1.12)	
Alavanja et al., 1989	**US Forest and Soil Conservationists—Mortality** Ischemic heart disease (410–414) Cerebrovascular disease (430–438)	 543 99	 PMRs 1.0 (0.9–1.1) 0.9 (0.8–1.1)	Not adjusted for known risk factors
Blair et al., 1983	**Florida, US Licensed Pesticide Applicators—Mortality** Circulatory diseases (390–458)	 159	 0.88 (p >0.05)	Not adjusted for known risk factors
Environmental Studies				
Chen HL et al., 2006	**Residents around 12 municipal waste incinerators in Taiwan—Prevalence** Hypertension diagnosed by a physician Serum PCDD/PCDF levels (international TEQs in logistic model)	 118	 5.6 (1.6–19.6) 0.9 (0.2–3.7) [j]	
Bertazzi et al., 2001 [*Supersedes Pesatori et al., 1998, Bertazzi et al., 1989a,b, 1998*]	**Seveso, Italy—Mortality–20 yr** (1976–1996) **Zones A&B, sexes combined** All circulatory diseases (390–459) Chronic rheumatic heart diseases (393–398) Hypertensive vascular disease (401–405) Ischemic heart diseases (410–414)	 265 3 9 97	 1.0 (0.8–1.1) 0.9 (0.3–3.0) 0.6 (0.3–1.2) 1.0 (0.8–1.2)	Adjusted for age and gender only

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)	Comments
	Acute myocardial infarction (410)	50	0.8 (0.6–1.1)	
	Chronic ischemic heart diseases (412, 414)	46	1.2 (0.9–1.6)	
	Cerebrovascular diseases (430–438)	88	1.1 (0.9–1.3)	

[a] Adjusted for age, race, rank, smoking, alcohol history, cholesterol, HDL, cholesterol-HDL ratio, uric acid, diabetes, BMI or percent body fat, waist-to-hip ratio, and family history of heart disease.
[b] Adjusted for age, race, rank, BMI, and smoking.
[c] Adjusted for age, race, rank, BMI, smoking, and diabetes.
[d] Adjusted for smoking and family history of heart disease.
[e] Adjusted for age, race, and military occupation.
[f] Adjusted for age, race, state, sex, and calendar year of death.
[g] Adjusted for age, smoking, alcohol, BMI, education, and martial status.
[h] Adjusted for age, BMI, and smoking.
[i] Adjusted for age, sex, BMI, smoking, drinking, diabetes, triglycerides, total cholesterol, HDL. family history of heart disease, and which plant.
[j] Adjusted for age, sex, BMI, and smoking.
NR–Not reported

Update of the Epidemiologic Literature

Occupational Studies

In a report not previously reviewed for circulatory disorders, Coggon et al. (1991) studied mortality from circulatory diseases at four British herbicide-producing factories that were part of the multinational International Agency for Research on Cancer (IARC) cohort of workers exposed to phenoxy herbicides. There was a non-significant increase in mortality from circulatory diseases overall (SMR = 1.16, 95% CI 0.91–1.46), but the increase was concentrated in Plant A, which had a higher potential for TCDD exposure. A nested case–control study of the Plant A subcohort demonstrated a significant increase in risk among a group of small departments within the plant (RR = 6.2, 95% CI 2.3–16.4) with no evident defining common characteristic.

In another study of a subcohort of the IARC cohort, mortality records for 1969–2000 were analyzed for New Zealand workers exposed to phenoxy herbicides and dioxins (’t Mannetje et al., 2005). In comparison with national rates, they found that mortality from circulatory diseases in production workers was close to the expected (SMR = 0.96, 95% CI 0.72–1.27) but significantly lower in sprayers (SMR = 0.52, 95% CI 0.36–0.73). There was no significant difference in mortality from specific circulatory diseases, except for ischemic heart disease, which was significantly decreased in sprayers (SMR = 0.49, 95% CI 0.31–0.75).

McLean et al. (2006) reported on another multinational IARC cohort of 60,468 pulp and paper industry workers. A job exposure matrix was applied to 58,162 individual work histories to estimate exposure to nonvolatile organochlorine compounds (which would include TCDD). Death from circulatory diseases was not more strongly associated with having ever been exposed to nonvolatile organochlorine compounds, including TCDD (SMR = 0.99, 95% CI 0.95–1.04) than with having never had this exposure (SMR = 0.92, 95% CI 0.89–0.96). That the confidence intervals scarcely overlap raises the possibility that exposure to TCDD counters the expected healthy-worker effect.

Blair et al. (2005a) analyzed mortality records for 1994–2000 for participants of the Agricultural Health Study, which included licensed pesticide applicators and their spouses. Mortality from circulatory diseases was significantly lower (SMR = 0.5, 95% CI 0.5–0.6) than in the general population. Furthermore, the reduction in SMR for circulatory diseases remained significant after control for the effects of farm size, years of handling pesticides, presence of farm animals, and whether corn was grown on the farm. That finding is consistent with the noncomparability of a rural working population with the general population (the healthy-worker effect).

Environmental Studies

Chen HL et al. (2006) investigated the prevalence of hypertension in Taiwanese residents who lived near municipal waste incinerators for at least 5 years. Health information was obtained with an interviewer-administered questionnaire for which people were asked about their medical histories, including physician-diagnosed high blood pressure, and serum samples were collected for analysis of PCDDs and PCDFs. A logistic regression analysis showed that the incidence of hypertension was significantly associated with serum PCDD and PCDF concentrations on the basis of international TEQs (OR = 5.58, 95% CI 1.63–19.62). However, the incidence of hypertension was no longer increased when the model was adjusted for age, sex, smoking status, and BMI (OR = 0.91, 95% CI 0.23–3.73). Furthermore, the significant increases in PCDDs and PCDFs in older subjects, in women, and in passive smokers and the marginally significant ($p = 0.075$) increase with BMI demonstrate that PCDD and PCDF concentrations co-vary with hypertension risk factors.

Vietnam-Veteran Studies

A 30-year follow-up study was conducted on post-service mortality from the date of discharge through 2000 for the Army Vietnam veterans in CDC's cohort for the VES. Boehmer et al. (2004) compared mortality rates in those deployed to Vietnam with those in non-deployed Vietnam-era veterans. Mortality from circulatory diseases was lower, but not significantly, among Vietnam veterans in the first 15 years after discharge (RR = 0.56, 95% CI 0.28–1.15) and was more comparable with that among the non-deployed men in the 15- to 30-year follow-up period (RR = 1.06, 95% CI 0.85–1.32). Analysis of only the 15- to 30-year period after discharge revealed that mortality from circulatory diseases was increased among Veterans discharged after 1970 (RR = 1.43, 95% CI 1.02–1.99) but not among those discharged before 1970 (RR = 0.83, 95% CI 0.62–1.12); it is unclear how to interpret this finding.

The Australian DVA (ADVA, 2005b) reported a significantly lower mortality from circulatory diseases among Australian Vietnam veterans than among the male Australian population (SMR = 0.88, 95% CI 0.84–0.92). More specifically, the reduction associated with stroke was stronger (SMR = 0.80, 95% CI 0.70–0.91), and the reduction associated with ischemic heart disease was less pronounced over the entire observation period (SMR = 0.94, 95% CI 0.89–0.99) and was no longer evident after 1980 (see Table 9-5). When the data were analyzed for each of the three branches of service, Army and Air Force veterans exhibited a significant reduction in mortality from all circulatory diseases, which was reflected by decreases

in mortality from stroke among Army veterans and from ischemic heart disease among Air Force veterans. Navy veterans did not exhibit any differences in circulatory-disease mortality. It is also notable that the reduction in circulatory-disease mortality in Australian Vietnam veterans was most apparent from 1963 to 1979 (SMR = 0.69, 95% CI 0.59–0.79), less apparent from 1980 to 1990 (SMR = 0.88, 95% CI 0.80–0.95), and nearly equivalent to that in the general male population from 1991 to 2001 (SMR = 0.93, 95% CI 0.87–0.99). As in the CDC VES (Boehmer et al., 2004), the change in mortality over time could reflect the fading of a "healthy-warrior effect" as the cohort matures. As noted above, however, although the pattern was clear for ischemic heart disease, there was no such trend for mortality from stroke.

In a parallel study, the Australian DVA (ADVA, 2005c) reported the RR of death from all circulatory diseases in Vietnam-era Australian National Service veterans, comparing those deployed to those not deployed to Vietnam. The rate of death from all circulatory diseases did not differ between the deployed and non-deployed (RR = 1.05, 95% CI 0.87–1.27), whereas among the deployed veterans the rate of death from ischemic heart disease was non-significantly higher (RR = 1.18, 95% CI 0.94–1.47) and that from stroke was non-significantly lower (RR = 0.61, 95% CI 0.30–1.15).

Ketchum and Michalek (2005) assessed the cumulative post-service mortality from 1982 to 1999 in veterans of Operation Ranch Hand. When all Ranch Hand veterans were considered as a group, mortality from circulatory diseases was marginally higher (RR = 1.3, 95% CI 1.0–1.6) than in Vietnam-era Air Force veterans who did not spray herbicides. However, in analyses that were restricted to enlisted ground crew, Ranch Hand veterans had increased mortality from circulatory diseases (RR = 1.7, 95% CI 1.2–2.4). When mortality from circulatory diseases in all enlisted ground crew was divided into five categories (atherosclerotic heart disease, cardiomyopathy, stroke, hypertension, and other), only mortality from atherosclerotic heart disease, which accounted for most of the deaths, was significantly higher in the Ranch Hand personnel (RR = 1.7, 95% CI 1.1–2.5).

Ketchum and Michalek (2005) also analyzed mortality in a subgroup of 1,016 Ranch Hand veterans and 1,436 Vietnam-era comparison veterans who had at least one physical examination during 1982–1997 and had their serum dioxin measured. Potential risk factors were also assessed, including smoking, alcohol consumption, and family history of heart disease. When categorized according to serum TCDD concentration, mortality from circulatory diseases was non-significantly higher in the Ranch Hand veterans in the low-TCDD group (RR = 1.8, 95% CI 0.9–3.5) and the high-TCDD group (RR = 1.5, 95% CI 0.7–3.3).

In the final examination cycle of Ranch Hand veterans by the US Air Force (AFHS, 2005), cardiovascular diseases were identified through medical-record verification of questionnaire data and physical examination and were classified into four conditions based on ICD-9: essential hypertension (401), heart disease excluding essential hypertension (391, 392, 393–398, 402, 404, and 410–429), myocardial infarction (410 and 412), and stroke or transient ischemic attack (435.0[sic]–436). Participants who had verified heart conditions before service in Southeast Asia were excluded. Covariates used in the adjusted analyses of the cardiovascular assessment included age, race, military occupation, smoking history, alcohol-consumption history, uric acid, BMI, waist-to-hip ratio, cholesterol, HDL, cholesterol-to-HDL ratio, family history of heart disease, diabetes mellitus, and use of blood-pressure medication. The analyses revealed a significant positive association between essential hypertension and 1987 serum dioxin concentration for all Ranch Hand veterans (unadjusted RR = 1.18, 95% CI 1.08–1.29), which remained after adjustment for covariates (adjusted RR = 1.11, 95% CI 0.98–1.25). The relative

risk of heart disease excluding essential hypertension in all Ranch Hand veterans was not associated with 1987 serum dioxin concentrations (adjusted RR = 0.90, 95% CI 0.78–1.06).

In a separate study, Kang et al. (2006) assessed the incidence of hypertension and heart disease in 1,499 US ACC veterans who handled or sprayed Agent Orange in Vietnam and 1,428 veterans from the same era who did not serve in Vietnam. Health information was gathered through telephone interviews that asked whether a medical doctor had diagnosed any type of heart condition, including coronary arterial disease, angina pectoris, myocardial infarction, and heart attack. In addition, the veterans were asked whether a medical doctor had diagnosed hypertension, whether a doctor had recommended weight loss or prescription medicine for the hypertension, and in what year the diagnosis and/or therapy had begun. Of the individual heart conditions that were reported, 68% of the cases were in the category of ischemic heart disease (ICD-9 410–414), including myocardial infarction, coronary arterial disease, and surgery required for coronary arterial disease (Kang, personal communication). The accuracy of self-reports of chronic medical conditions was supported by medical-record review, which confirmed 79% of self-reported diabetes diagnoses.

When the entire cohort was considered, the prevalence of neither hypertension nor heart disease was significantly associated with service in Vietnam. However, in analyses restricted to ACC veterans who served in Vietnam, men who reported having sprayed exhibited a higher incidence of hypertension (adjusted OR = 1.26, 95% CI 1.00–1.58) and a significantly incidence of heart disease (adjusted OR = 1.41, 95% CI 1.06–1.89) than veterans who did not report spraying herbicides. In an effort to evaluate the possibility of over-reporting of medical conditions among former sprayers compared with non-sprayers, the analysts compared prevalence proportions in subsets of sprayers who were grouped according to a serum TCDD concentration obtained after the study interviews. Those who had serum TCDD above the median (2.5 ppt) had reported a greater prevalence of heart conditions (22.9% vs 15.7%; two-sided $p = 0.08$) and of hypertension (43.6% vs 33.7%; two-sided $p = 0.05$) than had those who had lower serum TCDD. In contrast no such difference in frequency of reporting of, for instance, respiratory problems, was associated with serum TCDD concentration.

To evaluate whether service in Vietnam itself was responsible for the higher prevalence of hypertension and heart conditions in the ACC veterans, Kang et al. (2006) conducted a logistic regression analysis that included deployed and non-deployed veterans. In a model containing Vietnam service and herbicide spraying, service in Vietnam was not independently associated with hypertension or heart disease; herbicide spraying, however, was a significant covariate with adjusted ORs of 1.32 (95% CI 1.08–1.61) for hypertension and 1.52 (95% CI 1.18–1.94) for heart disease. The analysis included adjustment for age, race, BMI, and smoking.

Because there is suggestive evidence of an association between exposure to herbicides in Vietnam and type 2 diabetes (IOM, 2005) and diabetes is a major risk factor for hypertension and heart disease, additional analyses were conducted to elucidate the degree to which hypertension and heart disease may have been attributable to diabetes in the ACC cohort (Kang, personal correspondence). When a logistic regression analysis was conducted on only non-diabetic ACC veterans, herbicide spraying was associated with the prevalence of heart disease (OR = 1.52, 95% CI 1.14–2.01) and with the prevalence of hypertension (OR = 1.23, 95% CI 0.99–1.52). Analysis of all ACC veterans that controlled for diabetic status revealed that herbicide spraying was associated with the prevalence of heart disease (OR = 1.45, 95% CI 1.13–1.86) and with the prevalence of hypertension (OR = 1.27, 95% CI 1.04–1.55), but merely being deployed to Vietnam was not significantly associated with either. Although the prevalence of

heart disease or hypertension was greater in diabetic veterans than in non-diabetic veterans, herbicide spraying increased the prevalence equally in the two groups. Those results imply that the increases in the risk of heart disease and hypertension in Vietnam veterans who sprayed herbicides are associated with spraying herbicides, regardless of diabetes status.

Biologic Plausibility

It is well established that the vasculature is a target of TCDD toxicity, which leads to significant increases in oxidative stress and induces major changes in gene expression regulating numerous signaling pathways (Puga et al., 2004). There is also growing evidence from a variety of experimental models that TCDD induces or promotes cardiovascular disease in adult animals. For example, chronic exposure of the ApoE knockout mouse to TCDD increased the incidence, severity, and progression of atherosclerotic plaques (Dalton et al., 2001), and rats chronically exposed to TCDD exhibited significant arterial remodeling characterized by endothelial cell hypertrophy, extensive smooth muscle cell proliferation, and inflammation (Jokinen et al., 2003). The rats in this study also showed a dose-related increase in cardiomyopathy. Other studies have shown that TCDD exposure increased myocardial fibrosis (Riecke et al., 2002) and led to cardiac hypertrophy and alteration in control of heart rhythm (Lin et al., 2001; Thackaberry et al., 2005). In one study, acute exposure of mice to a relatively high dose of TCDD significantly increased the release of vasoconstricting eicosanoids and induced hypertension (Dalton et al., 2001). Those data demonstrate that activation of the AhR by xenobiotics induces cardiovascular injury and leads to cardiovascular disease in animal models.

Recently, the role of the AhR in normal cardiovascular function in adult animals has been established with studies of AhR-null mice. The animals develop hypertension, cardiac hypertrophy, and reduction in cardiac function with age; hence, the AhR has a role in cardiovascular function (Lund et al., 2003, 2005, 2006; Thackaberry et al., 2002; Vasquez et al., 2003). That both the sustained activation of the AhR by TCDD and the genetic deletion of the AhR result in cardiovascular disease suggests that the AhR acts to maintain the physiologic balance of the cardiovascular system and that either its excessive activation or its insufficient activation disrupts this homeostasis. However, additional studies are needed to confirm the relationships and to determine their relevance to humans. Specifically, future research studies are needed to establish animal models of TCDD-induced cardiovascular disease to increase understanding of the physiologic and pathologic mechanisms that mediate the increased morbidity and mortality from circulatory diseases, including hypertension and ischemic heart disease, that have been suggested to be associated with herbicide and TCDD exposure in epidemiologic studies.

Synthesis

In this section, the committee synthesizes information on circulatory disorders from the new studies described above and reconsiders studies that were reviewed in prior updates. Because circulatory diseases constitute a broad group of diverse conditions, hypertension is discussed separately from other circulatory diseases so that the new studies can be adequately synthesized and integrated with the earlier studies.

Hypertension

Hypertension, typically defined as blood pressure above 140/90 mm Hg, affects more than 70 million adult Americans and is a major risk factor for coronary heart disease, myocardial infarction, stroke, and heart and renal failure. The major quantifiable risk factors for hypertension are well established and include age, race, BMI or percentage body fat, and diabetes; and the strongest conclusions regarding a potential increase in the incidence of hypertension come from studies that have controlled for these risk factors.

The study by Kang et al. (2006 and personal correspondence) has several strengths. In studying the ACC, one of the most highly exposured Vietnam-veteran cohorts, it addresses subjects of primary concern to the VAO committee. Exposure to TCDD was directly measured in a subset of the study population and linked to the entire sample by establishing correlations of high values with self-reported spraying. It also had the merit of controlling for established risk factors for hypertension. Although the absolute increase in prevalence among ACC-veteran sprayers (about 25%) is not large, it is consistent with the fact that there are several other well-established contributors to the development if hypertension.

One limitation of this study is the potential for information bias, inasmuch as the data on hypertension and on herbicide spraying were self-reported. That concern is diminished, in part, because a patient is more likely to report accurately a chronic disorder that requires continuing management, including hypertension and diabetes; this accuracy rate typically exceeds 90% (Okura et al., 2004). Although self-reported hypertension was not verified by medical-record review in the Kang et al. study, self-report of diabetes was found to be quite reliable: 79% of the reported cases were verified, confirmatory information was not found in the medical records available for 11% of the reported cases, and medical records were not obtained for the remaining 10%. A high level of verification of a health outcome, however, does not guarantee the absence of bias due to under-reporting and the related differential misclassification among exposure groups. Recall bias that leads to over-reporting of herbicide spraying among men who have serious health conditions must also be considered in evaluating this study. Although there is evidence that ex-sprayers were more likely to report several health conditions besides hypertension, comparison within the ex-sprayer subgroup according to serum TCDD concentration suggests that recall bias does not fully explain the associations.

Selection bias could arise from the cross-sectional nature of the study, which accounts for disease prevalence only among people in the original deployed and non-deployed ACC cohorts who were still alive and participated. Concern for that type of selection bias is tempered by the high and nearly equal rates of participation by deployed veterans (72%) and non-deployed veterans (69%). Furthermore, the prevalence of hypertension among the non-deployed veterans (30%) was similar to that among US men of comparable age (32%) (Fields et al., 2004). Despite those data, it remains unknown whether the observed relationship of spraying to the prevalence of hypertension is equivalent to what one would have observed if the cohort had been followed longitudinally. Nonetheless, that the primary population of concern to VA is the current living cohort of Vietnam veterans makes findings from the study particularly relevant.

The results of the Kang et al. study are not consistent with those of a previously reviewed study by Calvert et al. (1998), which investigated cardiovascular outcomes in a cohort of herbicide-factory workers exposed to TCDD. The report of the earlier study failed to identify a

significant association between measured serum TCDD and hypertension after controlling for hypertension risk factors. The negative findings argue against an association between TCDD exposure and hypertension although the study was limited by self-reported diagnosis of hypertension and possibly by selection bias due to low response rates (28% for neighborhood referents, 70% for living and located cohort members, and 48% for the original cohort). The study by Kang et al. (2006) is also not consistent with the new environmental study of Chen HL et al. (2006), which showed that serum concentrations of dioxin-like PCDDs and PCDFs are not associated with an increased incidence of hypertension when major risk factors are adjusted for; the interpretation of this study was limited by lack of information on the criteria for diagnosing hypertension and by a very narrow range of serum TEQ concentrations.

Two other occupational studies were uninformative because they failed to define hypertension (Kitamura et al., 2000) or used a definition that was not comparable with that in veteran studies (Suskind and Hertzberg, 1984).

In contrast, the results of Kang et al. (2006) are consistent with those of other studies of Vietnam veterans, including the other most highly exposed cohort composed of Vietnam veterans who served in Operation Ranch Hand (AFHS, 1995, 2000, 2005). Multiple examination cycles of the AFHS have consistently reported an increase in the prevalence of hypertension with a doubling of serum dioxin concentration. The analyses controlled for the major risk factors for hypertension, and diagnosis was confirmed with medical-record review. Limitations of the AFHS studies include the potential for selection bias and the variation in the comparison group over examination cycles. Selection bias is reduced, in part, by the relatively high participation rates across (cycles 4-6, 74–83% in Ranch Hand veterans and 57–73% in the comparison group).

The study by Kang et al. (2006) is also consistent with other veteran studies, including those of Australian Vietnam veterans (O'Toole et al., 1996) and American Legion Vietnam veterans (Stellman et al., 1988) and the VES (CDC, 1988). All those studies reported significant increases in the incidence of hypertension, but only the study by Kang et al. controlled for potential confounding variables and used an index of herbicide-related exposure. Finally, the Korean-veteran study by Kim et al. (2003) was not considered despite an increased prevalence of hypertension and control for established risk factors, because of concern regarding selection bias when the study population was assembled, the very low participation in each group (by 28% and 6% of Vietnam and non-Vietnam veterans, respectively), the inability to assess the quality or definition of hypertension as a diagnosis, and the relatively low values and narrow range of reported serum TCDD concentrations (IOM, 2005).

Circulatory Diseases

Circulatory diseases constitute a group of diverse conditions—of which hypertension, coronary heart disease, and stroke are the most prevalent—that account for 75% of mortality from circulatory diseases in the United States. The major quantifiable risk factors for circulatory diseases are similar to those for hypertension and include age, race, smoking, serum cholesterol, BMI or percentage of body fat, and diabetes.

Reported results of new morbidity and mortality studies of the most highly exposed Vietnam-veteran cohorts (ACC and Operation Ranch Hand) were not entirely consistent. ACC veterans who sprayed Agent Orange reported a significant increase in the prevalence of heart disease, with ischemic heart disease representing nearly 70% of the conditions reported (Kang et al.,

2006). In contrast, the AFHS did not find the prevalence of heart disease, myocardial infarction, or stroke to be significantly associated with either current or back-extrapolated serum TCDD concentrations in Ranch Hand veterans (AFHS, 2005). Ketchum and Michalek (2005) found a significant increase in mortality due to atherosclerotic heart disease in Ranch Hand ground crew personnel, but the increase in mortality from circulatory disease among all Ranch Hand veterans based on back-extrapolated serum TCDD was not significant. The strengths and limitations of the cross-sectional studies of veterans are the same as discussed above for hypertension.

The new evidence of an increase in the incidence of heart disease is consistent with results of previously reviewed studies on herbicide-factory workers occupationally exposed to TCDD. In the IARC cohort of phenoxy-herbicide workers overall (Vena et al., 1998), an internal comparison found that being in the subgroup with the highest likelihood for TCDD exposure was associated with increased mortality from ischemic heart disease (RR = 1.67, 95% CI 1.23–2.26). In analyses of three IARC subcohorts, herbicide-factory workers with high serum TCDD exhibited significant increases in mortality from ischemic heart disease (RR = 1.99, 95% CI 1.05–3.75 compared with national rates [Flesch-Janys et al., 1997/1988] or RR = 2.48, 95% CI 1.32–4.66 compared with gas workers [Flesch-Janys et al., 1995]; RR = 2.3, 95% CI 1.0–5.0 [Hooiveld et al., 1998]; RR = 1.75, 95% CI 1.07–2.87 [Steenland et al., 1999]). Furthermore, in two of the studies a significant trend was observed with increasing TCDD exposure (Flesch-Janys et al., 1995; Steenland et al., 1999). Although those studies did not control for potential disease confounders, the effect of confounding on the studies was reduced by the use of comparison groups of workers who probably have similar cardiovascular risk characteristics. So, for example, although BMI is a risk factor for ischemic heart disease and people who have a higher BMI will eliminate TCDD more slowly, it is unlikely that BMI would influence the choice of jobs associated with higher TCDD exposure.

The evidence from the cohort studies is based on the association of ischemic heart disease mortality with back-extrapolated TCDD concentrations derived by using a first-order elimination model. New physiologically based pharmacokinetic models that use a dose-dependent elimination rate to back-extrapolate peak blood concentrations (discussed in Chapter 3) predict a much larger range of initial exposures and probable changes in relative exposure rankings (Emond et al., 2005). Other limitations on the evidence of an association between the compounds of interest and ischemic heart disease are the lack of control for known risk factors and reporting (in many earlier studies) in terms of less specific classifications of cardiac mortality. It is also problematic that only cross-sectional analyses are available on Vietnam veterans; results derived from longitudinal analyses could be interpreted with greater confidence.

Although the evidence for an association of exposure to the chemicals of interest with hypertension may appear similar to that for an association with ischemic heart disease, many of the overtly positive findings for ischemic heart disease were derived from mortality studies that did not have access to the information necessary to adjust for known risk factors, as was possible in the ACC and AFHS analyses. In the studies with data on potential confounders, however, endpoints comparable to ischemic heart disease were only defined in a relatively imprecise fashion. The primary reason approximately half the committee could not agree to a conclusion of limited or suggestive evidence for an association for ischemic heart disease was that uncontrolled confounders might be distorting the results, while the remainder was not concerned that this was likely to be a major problem in occupational cohort studies.

Conclusion

Following extensive deliberations regarding the strengths and weaknesses of the new evidence and evidence from studies reviewed in previous VAO reports, the present committee deemed that the strengths of the evidence related to hypertension out weighed the weaknesses and concluded that there is limited or suggestive evidence of an association between exposure to the compounds of interest and hypertension (ICD-9 401–405), but that issues of chance, bias, and confounding could not be ruled out entirely. In contrast, members of the committee were divided on the relative weight to be given to the weaknesses of the heart disease studies and thus remained divided in their judgments as to whether the evidence related to ischemic heart disease (ICD-9 410–414) and exposure to the compounds of interest was adequately informative to advance this health outcome from the "inadequate or insufficient" category into the "limited or suggestive" category. For all other types of circulatory disease, the committee found that the evidence is inadequate or insufficient to determine whether there is an association with exposure to the compounds of interest.

AL AMYLOIDOSIS

VA identified AL amyloidoisis (ICD-9 277.3) as of concern after the publication of *Update 1998*. AL amyloidosis has been considered by the committees responsible for *Update 2000*, *Update 2002*, and *Update 2004*. Those committees concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and AL amyloidosis. The committee responsible for the current update has moved the section on AL amyloidosis to Chapter 6, on neoplastic endpoints, where it is considered with multiple myeloma and B-cell lymphoma. The available scientific literature indicates that the three conditions are closely related in that they share many biologic features, most notably a clonal hyperproliferation of B cells and underlying chromosomal damage.

ENDOMETRIOSIS

Endometriosis (ICD-9 617) affects 5.5 million women in the United States and Canada at any given time (NICHD, 2007). The endometrium is the tissue that lines the inside of the uterus and is built up and shed each month during menstruation. In endometriosis, endometrium is found outside the uterus—usually in other parts of the reproductive system, the abdomen, or surfaces near the reproductive organs. That misplaced tissue develops into growths or lesions that continue to respond to hormonal changes in the body and break down and bleed each month in concert with the menstrual cycle. Unlike blood released from endometrium in the uterus, blood released in endometriosis has no way to leave the body, and the results are inflammation, internal bleeding, and degeneration of blood and tissue that can cause scarring, pain, infertility, adhesions, and intestinal problems.

There are several theories about the etiology of endometriosis, including genetics, but the cause remains unknown. It has been proposed that endometrium is distributed through the body via blood or the lymphatic system; that menstrual tissue backs up into the fallopian tubes, implants in the abdomen, and grows; and that all women experience some form of tissue backup

during menstruation but only those with immune-system or hormonal problems experience the tissue growth associated with endometriosis. Despite numerous symptoms that can indicate endometriosis, diagnosis is possible only through laparoscopy or a more invasive surgical technique. Several treatments for endometriosis are available, but there is no cure.

The suspicion that TCDD can be involved in the etiology of endometriosis began after the observation that the incidence of endometriosis was higher in monkeys that had been treated with low doses of TCDD than in control monkeys (Reir et al., 1993). Experimental and epidemiologic studies have been conducted. Several epidemiologic studies have investigated non-dioxin-like polychlorinated biphenyls (PCBs), and some have examined a possible association with TCDD or dioxin-like compounds.

Conclusions from *VAO* and Updates

Endometriosis was first reviewed in this series of reports in *Update 2002*, which identified two relevant studies, and *Update 2004* examined three environmental studies. The present review updates the literature review with two additional studies. Table 9-6 provides a summary of relevant studies that have been reviewed.

TABLE 9-6 Selected Epidemiologic Studies—Endometriosis

Reference	Study Population	Study Results
ENVIRONMENTAL		
New Studies		
Heilier et al., 2005	Endometriosis in Belgium women with overnight fasting serum levels of PCDD/PCDF and PCB	50 exposed cases; OR = 2.6 (95% CI 1.3–5.3)
Porpora et al., 2006	Italian women with endometriosis with increased levels of polychlorobiphenyls	Cases = Mean cumulative value of 410 ng g_1 Control = value of 250 ng g_1 OR = 4.0, CI 95% 1.3–13; (p = 0.0003).
Studies Review in Update 2004		
De Felip et al., 2004	Pilot study of Italian and Belgian women of reproductive age; compared concentrations of TCDD and total TEQ in pooled blood samples from women diagnosed with endometriosis to controls	*Mean Concentration TCDD (pg/g lipid)*
		Italy: Controls (10 pooled samples) = 1.6; Cases (2 sets of 6 pooled samples) = 2.1, 1.3
		Belgium: Controls (7 pooled samples) = 2.5; Cases (Set I, 5 pooled samples; Set II, 6 pooled samples) = 2.3,2.3
		Mean Concentration (pg TEQ/g lipid)
		Italy: Controls (10 pooled samples) = 8.9±1.3 (99% CI, 7.2–11); Cases (2 sets of 6 pooled samples) = 10.7±1.6; 10.1±1.5
		Belgium: Controls (7 pooled samples) = 24.7±3.7 (99% CI, 20–29); Cases (Set I, 5 pooled samples; Set II, 6 pooled samples) = 18.1±2.7; 27.1±4.0

Fierens et al., 2003	Belgian women with environmental exposure to PCDDs/PCDFs or dioxins; compared analyte concentrations[a] in cases vs controls	Mean concentrations (pg TEQ/g lipid): Cases (n = 10) = 26.2 (95% CI, 18.2–37.7) Controls (n = 132) = 25.6 (95% CI, 24.3–28.9) No significant difference
Eskenazi et al., 2002	Residents of Seveso Zones A and B ≤30 years of age in 1976; compared incidence of endometriosis across serum TCDD concentrations	Serum TCDD 20.1–100 ppt: 8 exposed cases; OR = 1.2 (90% CI, 0.3–4.5) Serum TCDD >100 ppt: 9 exposed cases; OR = 2.1 (90% CI, 0.5–8.0)

Studies Reviewed in *Update 2002*		
Pauwels et al., 2001	Patients undergoing infertility treatment in Belgium; compared number of women with endometriosis and without endometriosis who had serum dioxin levels ≥100 pg TEQ/g serum lipid	6 exposed cases; OR = 4.6 (95% CI, 0.5–43.6)
Mayani et al., 1997	Residents of Jerusalem being evaluated for infertility; compared number of women with elevated TCDD concentrations in diagnosed with endometriosis (n=44) with subjects not diagnosed with endometriosis (n=35)	8 exposed cases; OR = 7.6 (95% CI, 0.9–169.7)

[a] Dioxin TEQs calculated using the WHO (1998) Toxic Equivalency Factor methodology.
ABBREVIATIONS: PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofurans; TCDD, tetrachlorodibenzo-*p*-dioxin; TEQ, toxicity equivalents.

Update of the Epidemiologic Literature

Environmental Studies

Heilier et al. (2005) conducted a case–control study of endometriosis in Belgium. Overnight fasting serum concentrations of PCDDs, PCDFs, and PCBs, expressed as TEQs, were compared among three groups of women: 25 with peritoneal endometriosis and 25 with deep endometriosis—both those groups were recruited from a hospital—and 21 healthy controls recruited concurrently from the consultations of the same gynecologists who referred the deep-endometriosis cases. The controls were of similar age as the other two groups and showed no clinical signs of peritoneal or deep endometriosis or clinical evidence of another gynecologic abnormality.

A significant association was found between PCDDs and PCDFs together and dioxin-like PCBs and the two endometriosis outcomes combined, with an OR of 2.6 (95% CI 1.3–5.3) for an increase of 10 pg in total TEQ/g lipids in serum PCDDs and PCDFs and dioxin-like PCBs. The analysis included consideration of and adjustment for potential confounders (including age, age at menarche, menstrual irregularities, BMI, oral-contraceptive use, breastfeeding, parity, and

family history). The association with PCDD and PCDF serum concentrations was strongest when comparing those with deep endometriosis to the controls (OR = 7.7 [per 10 pg/g], 95% CI 1.97–30.17). The distinction between the two types of endometriosis contributed to the strength of this study, as did the fact that the healthy controls were likely not to have either (although this was not confirmed laparoscopically).

A study of endometriosis in Italy included a group of women who were undergoing laparoscopy for suspected endometriosis or other benign gynecologic conditions during April 2000–January 2004 in a hospital in Rome (Porpora et al., 2006). The selection of study subjects allowed investigators to rule out the presence of endometriosis among controls. The final study group consisted of 40 cases and 40 controls; all provided blood specimens for analysis of dioxin-like compounds. Women with endometriosis had higher overall concentrations of PCBs than the controls (410 vs 250 ng/g of lipid base). In addition, several specific PCBs were measured, and dose–response relationships were observed across tertile groups for PCB 118 and 138 with increasing risk of endometriosis, although the confidence limits were very wide and overlapped. The analysis included proper control for confounders (with either statistical analysis or eligibility restrictions). However, because the study indicated higher concentrations of both doxin-like and non-dioxin-like PCBs among cases than among controls, the contribution of dioxin-like PCBs alone to the increased risk of endometriosis cannot be determined.

No new occupational or Vietnam-veteran studies concerning exposure to the compounds of interest and endometriosis were published since *Update 2004*.

Biologic Plausibility

Laboratory studies that used animal models and examined gene-expression changes associated with human endometriosis and TCDD exposure provide evidence to support the biologic plausibility of a link between that TCDD exposure and endometriosis. The first suggestion that TCDD exposure may be linked to endometriosis came as a secondary finding from a study that exposed female rhesus monkeys (*Macaca mulatta*) chronically to low concentrations of dietary TCDD for 4 years (Rier et al., 1993). Ten years after the exposure ended, the investigators documented an increased incidence of endometriosis in the monkeys that correlated with the dioxin exposure concentration. The small sample prevented a definitive conclusion that TCDD was a causal agent in the development of the endometriosis, but it led to numerous studies of the ability of TCDD to promote the growth of pre-existing endometriotic lesions.

When fragments of uterine tissue were implanted in the peritoneal cavity to mimic eutopic endometrial lesions, TCDD exposure was shown to promote the survival and growth of the lesions in rhesus monkeys and in mice (Cummings et al., 1996; Johnson et al., 1997; Yang et al., 2000). In mice, direct treatment of endometrial tissue with TCDD before placement into the peritoneal cavity resulted in increased size and number of endometrial lesions (Bruner-Tran et al., 1999).

A number of proposed mechanisms by which TCDD may promote endometrial lesions provide additional biologic plausibility of the link between TCDD and endometriosis. Human endometrial tissue expresses both the AhR and its dimerization partner, the aryl hydrocarbon nuclear translocator (Khorram et al., 2002), and three AhR target genes: CYP1A1, 1A2, and 1B1 (Bulun et al., 2000). That suggests that endometrial tissue is responsive to TCDD. Furthermore,

TCDD significantly decreases the ratio of progesterone receptor B to progesterone receptor A in normal human endometrial stromal cells and blocks the ability of progesterone to suppress matrix metalloproteinase (MMP) expression; these actions may promote endometrial-tissue invasion. Both the reduced ratio and the resistance to progesterone-mediated MMP suppression are observed in endometrial tissue from women with endometriosis (Igarashi et al., 2005; Nayyar et al., 2006).

TCDD induces changes in gene expression that mirror those observed in endometrial lesions. For example, TCDD can induce expression of histamine-releasing factor, which is increased in endometrial lesions and accelerates their growth (Oikawa et al., 2002, 2003). Similarly, TCDD stimulates expression of RANTES (regulated on activation, normal T cell expressed, and secreted) in endometrial stromal cells, and RANTES concentration and bioactivity are increased in women with endometriosis (Zhao et al., 2002).

Although those studies do not establish the degree to which TCDD may cause or promote endometriosis, they do provide evidence that supports the biologic plausibility of a link between TCDD exposure and endometriosis.

Synthesis

The two studies described above were of similar design and were strengthened by appropriate consideration of potential confounders, differentiation of cases and controls, and serum measurements of dioxin-like compounds. Both studies resulted in similar findings of a significant association between blood concentrations of dioxin-like chemicals and risk of endometriosis. Although the Porpora et al. (2005) study was limited by not being able to distinguish dioxin-like and non-dioxin-like PCBs, the two studies produced similar and consistent results.

The studies reviewed previously in *Updates 2002* and *2004* were limited primarily by their small study sizes, which did not produce statistically significant associations between the compounds of interest and endometriosis. However, they showed positive associations that can be considered consistent with the results of the two studies reviewed above.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in *Update 2002* and *Update 2004*, the committee concludes that there is inadequate or insufficient evidence to support an association between exposure to the compounds of interest and endometriosis.

THYROID HOMEOSTASIS

Clinical disruptions of thyroid function include various disorders grouped in ICD-9 242.8 and 246.8. The thyroid gland secretes the hormones thyroxine (T4) and triiodothyronine (T3), which stimulate and help to regulate metabolism throughout the body. The thyroid also secretes calcitonin, a hormone that controls calcium concentration in the blood and storage of calcium in bones. Secretion of T4 and T3 is under the control of thyroid-stimulating hormone (TSH), which

is secreted by the anterior pituitary gland. Iodine operates in thyroid physiology both as a constituent of thyroid hormones and as a regulator of glandular function. Control of circulating concentrations of those hormones is regulated primarily by a negative-feedback pathway that involves three organs: the thyroid, the pituitary, and the hypothalamus. In the hypothalamus–pituitary–thyroid feedback scheme, the hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the pituitary to produce TSH, which triggers the thyroid to produce T4 and T3. Cells in the hypothalamus and pituitary respond to concentrations of circulating T4 and T3. When T4 and T3 are low, the pituitary is stimulated to deliver more TSH to the thyroid, which increases T4 and T3 output. When circulating T4 and T3 are high, they signal to reduce the output of TRH and TSH. This negative-feedback loop maintains hormone homeostasis.

Disruption of thyroid homeostasis can be stimulatory (hyperthyroidism) or suppressive (hypothyroidism). Both conditions are diagnosed by analysis of blood concentrations of thyroid hormones, TSH, and other proteins (anti-thyroid antibodies). The prevalence of thyroid dysfunction among adults in the general population ranges from 1 to 10%, depending on the group, the testing setting, sex, age, method of assessment, and the presence of conditions that might affect thyroid function. People with subclinical (biochemical) conditions may or may not show other evidence (signs or symptoms) of thyroid dysfunction.

In hypothyroidism, the body lacks sufficient thyroid hormone. Overt hypothyroidism is seen as a high serum concentration of TSH and a low serum concentration of free T4. Subclinical hypothyroidism is defined as a high serum concentration of TSH and a normal serum concentration of free T4. People with hypothyroidism typically have symptoms of low metabolism. Studies consistently show that subclinical hypothyroidism is common and occurs more frequently in women than in men (Canaris et al., 2000; Hollowell et al., 2002; Sawin et al., 1985). In the Framingham study, for example, among 2,139 people 60 years old or older, 14% of women and 6% of men had subclinical hypothyroidism (Sawin et al., 1985). Subclinical hypothyroidism is a risk factor for overt hypothyroidism. Studies have reported an association of hypothyroidism with a wide variety of other conditions.

The term *hyperthyroidism* may involve any disease that results in overabundance of thyroid hormone. Clinical or overt hyperthyroidism is characterized as a low serum concentration of TSH and high serum concentration of free T4. Subclinical hyperthyroidism is defined as a low serum concentration of TSH and a normal serum concentration of free T4. The prevalence of subclinical hyperthyroidism was estimated at about 1% in men and 1.5% in women over 60 years old (Helfand and Redfern, 1998). Conditions associated with hyperthyroidism include Graves disease and diffuse toxic goiter. Like hypothyroidism, hyperthyroidism is more common in women than in men, and, although it occurs at all ages, it is most likely to occur in people over 15 years old. A form of hyperthyroidism called neonatal Graves disease occurs in infants born of mothers who have Graves disease. Occult hyperthyroidism may occur in patients over 65 years old and is characterized by a distinct lack of typical symptoms.

It is important to distinguish between potential effects on adults and effects that may occur during development. In adults, the thyroid gland is able, within reason, to compensate for mild or moderate disruption (such as that caused by hyperplasia or goiter). In contrast, the fetus is highly sensitive to alterations in thyroid hormones, and alterations in thyroid homeostasis can hamper the development of many organ systems, including the nervous and reproductive systems. Both adult and developmental outcomes are considered here.

Summary of Updates

The thyrotoxic potential of the compounds of interest was addressed first in *Update 2002* and again in *Update 2004* (IOM, 2003; 2005). The committee responsible for *Update 2002* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the compounds of interest and adverse effects on thyroid homeostasis in Vietnam veterans. Some effects on thyroid homeostasis have been observed in humans, mainly after exposure in the perinatal period. The *Update 2004* committee also concluded that there was inadequate or insufficient evidence of an association between exposure to the compounds of interest and adverse effects on thyroid homeostasis. Although additional effects had been observed in human studies, the committee concluded that the functional importance of those changes remained unclear because adaptive capacity could be adequate to accommodate them.

Update of the Scientific Literature

Occupational Studies

No new occupational studies concerning the compounds of interest and thyroid homeostasis were published since *Update 2004*.

Environmental Studies

The one environmental study published since *Update 200*2 involved anglers chronically exposed to dioxin-like compounds in the diet (Bloom et al., 2006). The study group was part of the New York State Angler Cohort Study, a prospective study of health effects in consumers of sport fish from the Great Lakes (Vena et al., 1996). The study population was licensed anglers between 18–40 years old. The subset of people in the Dioxin Exposure Substudy included 23 who had reported eating sport fish and who had serum concentrations of PCB 153 (a marker of general exposure) that placed them in the 75th percentile and 15 nonconsumers. Serum concentrations of eight PCDDs, nine PCDFs, and four coplanar PCBs were measured in all 38 people by CDC, and the sum of dioxin-like compounds was compared the concentrations of T3, T4, free T4, and TSH. A significant inverse relationship was seen between the sum of dioxin-like compounds and the concentration of free T4. However, there was no association between the sum of dioxin-like compounds and TSH. The study results are based on the sum of dioxin-like compounds, not TCDD specifically. However, the results add to information that indicates that such chemicals do show association with change in some measure of thyroid function.

In a study published in 2001 but not included in earlier reports, Nagayama et al. (2001) examined relationships between dioxin and dioxin-related compounds and thyroid hormones in patients with so-called Yusho disease. The study population was drawn from among 83 patients whose blood was examined in 1994–1995 for PCDD congeners (including TCDD), PCDFs, and PCB congeners. There were 16 in the study (three males and 13 females), and blood drawn in 1996 and 1997 was analyzed for T3, T4, free T4, and TSH. TEQ concentrations in the study population ranged from less than 100 to over 1,000 pg/g of lipid. The average TEQ concentration was 7-fold greater than average serum TEQ concentrations in the Japanese population. However,

there were no significant correlations between serum TEQ and the concentrations of T3, T4, free T4, or TSH, all of which were in the normal range except for one serum T4 value that was slightly higher than the normal range.

In a study by Foster et al. (2005), dioxin-like activity and thyroid hormone concentrations were examined in 150 women who were undergoing amniocentesis. Subjects were excluded if they had language problems, daily alcohol-consumption or drug-use history, other health conditions that required medical intervention, or a history of endocrine disease, including thyroid disease. On entrance into the study, subjects completed questionnaires that addressed other factors, such as diet and tobacco use. Serum TSH and T4 were measured with radioimmunoassay. Serum dioxin-like compounds were measured only with a cell-based bioassay to yield TEQs. There was no association between thyroid function and TEQ. The qualitative measure of TEQ precludes conclusions regarding specific chemicals of concern. Similar studies of adults by Nagayama et al. (2001) on 16 Yusho patients but with TEQs determined from direct measurements of PCDD, PCDF, and PCB congeners showed no association with thyroid function.

Wang et al. (2005) examined the associations between transplacental exposure to various chlorinated dioxin, dibenzofuran, and PCB congeners and thyroid-hormone status in 118 newborn-mother pairs in Tiawan. The mothers were all healthy, were 25–34 years old, had a single pregnancy, and had no tobacco use or alcohol use during pregnancy. Dioxin and other congeners were measured chemically in placentas; the 2,3,7,8-substituted congeners of dioxins were examined specifically. Indexes of infant thyroid function were measured in cord blood taken 1 minute after delivery. Significant ($p < 0.05$) effects on TSH and thyroid-binding globulin were detected.

In a study by Matsuura et al. (2001), thyroid function was examined in infants who had been breast-fed and those who had been bottle-fed. Breast milk was collected at various times over a year from 80 primaparous mothers, 25–34 years old, in four prefectures in Japan and analyzed for PCDDs, PCDFs, and PCBs. Blood was taken from infants at 1 year. Blood also was taken from 30 bottle-fed infants at 1 year. Serum T4, T3, and free T4 were not different between the groups. Serum TSH was significantly higher in the breast-fed group ($p = 0.027$), but values in both groups were in the normal range.

Vietnam-Veteran Studies

No new publications examining thyroid function in the AFHS cohort or in other Vietnam veterans since *Update 2004* were identified (IOM 2005). However, two studies that evaluated post-service mortality in Vietnam veterans considered individual causes and all causes of death (Boehmer et al., 2004; Ketchum and Michalek, 2005). Among individual causes, both studies examined mortality from endocrine disorders, which would include thyroid disorders. In the Boehmer et al. (2004) study, deaths ascribed to “endocrine, nutritional and immunity disorders” (ICD-9 240–279) included 10 of Vietnam veterans and seven of non-Vietnam veterans (RR = 1.32, 95% CI 0.50–3.47). Ketchum and Michalek (2005) examined mortality in the Ranch Hand and comparison veteran groups. There were three deaths from endocrine diseases in the Ranch Hand group and 31 in the comparison group (RR = 1.4, 95% CI 0.4–4.7).

Biologic Plausibility

TCDD has been demonstrated to affect concentrations of T4, T3, and TSH in experimental animals, but the effects appear to be species-dependent, and they lack consistency in demonstrating either definite hyperthyroidism or hypothyroidism after exposure to TCDD. Nevertheless, long-term exposure of animals to TCDD usually results in suppressed T4 and T3 and stimulated TSH. The National Toxicology Program reported that female rats exposed chronically to TCDD showed a follicular-cell hyperplasia and hypertrophy of thyroid follicles.

Chapter 3 discusses recent toxicologic studies of TCDD effects on thyroid indexes relevant to the biologic plausibility of effects of TCDD and the herbicides of interest on the thyroid gland. TCDD influences the metabolism of thyroid hormones and TSH. Notably, the study by Nishimura et al. (2005) confirmed that induction of the glucuronyl transferase UGT1A6, thought to be involved in the reduction in serum thyroid hormone in mice, depends on the AhR. Thus, some dioxin-like PCB congeners (such as PCB-77) can be metabolized to hydroxy derivatives that more closely resemble the structure of T4 and displace it from thyroid-binding proteins, such as transthyretin—a mechanism not likely with TCDD. Not all mechanisms by which chemicals might affect thyroid homeostasis are understood, and dioxin may act on thyroid function via different mechanisms.

Synthesis

The synthesis of this review is similar to that in *Update 2004*. Numerous animal experiments and several epidemiologic studies have shown that TCDD and dioxin-like compounds appear to exert an influence on thyroid homeostasis. Two occupational studies were considered in that 2004 report. Johnson et al. (2001) measured serum hormone and TCDD concentrations in 37 men who had sprayed 2,4,5-T in Victoria, Australia. In correlation analysis, TCDD concentrations were inversely related to T3 and TSH concentrations. The association was strongest when historical, but not current, serum TCDD concentrations were considered. In a paper reviewed in *Update 1998*, Zober et al. (1994) examined 138 BASF workers exposed to TCDD in a 1953 industrial incident and reported that thyroid disease was increased ($p < 0.05$) in the exposed population.

In the AFHS study considered in *Update 2004*, Pavuk et al. (2003) reported on thyroid-hormone status in the AFHS cohort, which was examined in 1982, 1985, 1987, 1992, and 1997. At each time, there was a trend toward an increasing concentration of TSH that was not accompanied by changes in circulating T4 or in the percentage uptake of T3 (measured only in the earlier years). In a repeated-measures linear regression adjusted for age, race, and military occupation, the low-exposure and high-exposure Ranch Hand veterans had TSH significantly higher than the comparison population, and the trend test showed a significant linear increase over the comparison and background-, low-, and high-exposure groups ($p = 0.002$). No changes in microsomal or antithyroid antibodies were observed, nor was there any evidence of changes in clinical thyroid disease. The percentage with abnormally high TSH was higher at each examination in the high-exposure Ranch Hand group than in the comparison population, but the confidence intervals were wide and included 1 at each examination (1982: OR = 1.8, 95% CI 0.7–5.9; 1985: OR = 1.4, 95% CI 0.7–3.2; 1987: OR = 1.9, 95% CI 0.8–4.5; 1992: OR = 1.7, 95% CI 0.8–3.9; 1997: OR = 1.8, 95% CI 0.9–3.4). Also reiterated, in an earlier study of the

Ranch Hand cohort (AFHS, 1991) was reviewed in *VAO* but not reconsidered in *Update 2002*. The assessment of endocrine function in that study included a series of thyroid-function tests that showed no difference in thyroid function between exposed and control veterans.

The effects on maternal or fetal thyroid status are evident in numerous studies and are of concern because TCDD and dioxin–like compounds may affect the early development of neurologic and sensory organs and of motor function if exposure occurs in utero or during lactation. In animal studies, effects of TCDD on thyroid homeostasis have been observed in adults exposed in the laboratory, and there are indications of similar effects in the wild. In human studies, increases in TSH have been seen without evidence of increases in T4. In the new studies of adults reviewed here, there was lack of correlation between dioxin-like compounds and TSH concentrations. Likewise, in the studies in infants, there were not significant associations between magnitude of exposure to dioxin or dioxin-like compounds and measures of thyroid function. Those studies, then, suggest that people were able to adapt to changes in thyroid status that might have been induced by exposure to TCDD and other dioxin-like compounds.

Conclusions

There is inadequate or insufficient evidence of an association between exposure to the compounds of interest and clinical or overt adverse effects on thyroid homeostasis. Some effects have been observed in humans, but the functional importance of the changes reported in the studies reviewed remains unclear to the present committee, because adaptive capacity could be adequate to accommodate them.

SUMMARY

On the basis of the occupational, environmental, and veterans studies reviewed and in light of information concerning biologic plausibility, the committee reached one of four conclusions about the strength of the evidence regarding an association between exposure to the compounds of interest and each of the health effects discussed in this chapter. In categorizing diseases according to the strength of the evidence, the committee applied the same criteria (discussed in Chapter 2) that were used in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004*. To be consistent with the charge to the committee by the Secretary of Veterans Affairs in Public Law 102-4 and with accepted standards of scientific reviews, the distinctions between conclusions are based on statistical association, not on causality.

Despite extensive consideration of the full evidentiary databases, the committee could not reach consensus as to whether ischemic heart disease satisfied the criteria for inclusion in the category of limited or suggestive evidence of an association or should be retained in the category of inadequate or insufficient evidence.

Health Outcomes with Sufficient Evidence of an Association

For diseases in this category, a positive association between exposure and outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable

confidence. The committee regarded evidence from several small studies that were free of bias and confounding and that showed an association that was consistent in magnitude and direction as sufficient to conclude that there is an association.

The committes responsible for *VAO, Update 1996, Update 1998, Update 2000, Update 2002,* and *Update 2004* concluded that there was sufficient evidence of an association between exposure to at least one compound of interest and chloracne. The scientific literature continues to support the classification of chloracne in the category of sufficient evidence. On the basis of the literature, no additional health effects discussed in this chapter satisfy the criteria necessary for inclusion in this category.

Health Outcomes with Limited or Suggestive Evidence of an Association

For this category, the evidence must suggest an association between exposure and outcome, although it can be limited because chance, bias, or confounding could not be ruled out with confidence.

The committees responsible for *Update 1996, Update 1998, Update 2000, Update 2002,* and *Update 2004* concluded that there was limited or suggestive evidence of an association between exposure to at least one compound of interest and porphyria cutanea tarda. The scientific literature continues to support the classification of this disorder in the category of limited or suggestive evidence.

On the basis of its evaluation of available scientific evidence, the committee responsible for *Type 2 Diabetes* concluded that there was limited or suggestive evidence of an association between exposure to at least one compound of interest and type 2 diabetes; the committee responsible for *Update 2004* reached the same conclusion. Evidence reviewed in the present report continues to support that conclusion.

The present committee has added the cardiovascular condition hypertension to the list of health outcomes in the category of limited or suggestive evidence. The committee was unable to reach consensus as to whether another cardiovascular endpoint, ischemic heart disease, belonged in this category or in the classification below, “inadequate or insufficient evidence to determine whether there is an association”.

Health Outcomes with Inadequate or Insufficient Evidence to Determine Whether There Is an Association

The scientific data on many of the health effects reviewed by the present committee were inadequate or insufficient to determine whether there is an association between exposure to the compounds of interest and the health outcomes. For the health effects in this category, the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. Some studies failed to control for confounding or used inadequate exposure assessment. This category includes nonmalignant respiratory disorders, such as asthma in isolation, pleurisy, pneumonia, and tuberculosis; immune-system disorders (immune suppression and autoimmunity); lipid and lipoprotein disorders; gastrointestinal diseases; digestive diseases; liver toxicity; circulatory disorders (except as qualified above); endometriosis; and disorders of thyroid homeostasis.

The committee was unable to reach consensus as to whether another cardiovascular endpoint, ischemic heart disease, belonged in this category or in the classification below, "inadequate or insufficient evidence to determine whether there is an association".

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

To classify outcomes in this category, several adequate studies covering the full range of known human exposure must be consistent in not showing a positive association between exposure and outcome at any magnitude of exposure. The studies also must have relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, magnitudes of exposure, and periods of observation covered by the available studies. The possibility of a very small increase in risk at the exposure studied can never be excluded.

The committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* concluded that none of the health outcomes discussed in this chapter had limited or suggestive evidence of *no* association with the exposures to the compounds of interest. The most recent scientific evidence continues to support that conclusion.

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Research Recommendations

As part of its charge, the committee was asked to make recommendations concerning the need, if any, for additional scientific studies to resolve uncertainties concerning the health effects of the chemicals of interest sprayed in Vietnam: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid. This chapter summarizes the committee's research recommendations.

Although great strides have been made over the last several years in understanding the health effects of exposure to the chemicals of interest and in elucidating the mechanisms underlying them, gaps in our knowledge remain. The scope of potential research on the chemicals is wide, and what follows in this chapter is not an exhaustive listing of future research that might have value. There are many additional opportunities for progress in such subjects as toxicology, exposure assessment, the conduct of continuing or additional epidemiologic studies, and systematic and comprehensive integration of existing data that have not been explicitly noted here.

- **There is a need for new animal models to elucidate mechanisms of diseases and disease progression.**

The committee believes that experimental research in the mechanisms that underlie human health outcomes (particularly cardiovascular disease) could provide valuable information related to the risk of disease in Vietnam veterans. The central role of the aryl hydrocarbon receptor (AhR) in animal models is clear, and AhR gene differences in animals clearly affect susceptibility to the effects of TCDD. Although work to date on the AhR in humans has been sparse, variations in this specific genetic factor alone are likely to affect human susceptibility to the toxic effects of TCDD, other dioxin-like chemicals, and herbicide formulations containing these chemicals. In addition, recent research makes clear that variations in the genetic regulation of the expression or activity of other factors, including proteins that interact with the AhR and the gene products that are regulated by the AhR, are critical in determining susceptibility to the effects of TCDD and the types of toxic effects observed. Studies addressing the identification, distribution, and functional consequences of polymorphisms of the AhR and the other cofactors in human populations should be pursued.

- **A biphasic physiologically-based pharmacokinetic (PBPK) model for TCDD is needed.**

The committee recognizes the importance of accurate back-extrapolation of serum TCDD concentrations to predict exposure levels at the time of Vietnam service and to categorize veterans accurately into appropriate exposure classifications. As noted in Chapter 3, new human

PBPK models have been developed in an effort to incorporate the increasing evidence that TCDD exhibits dose-dependent elimination. The models seriously challenge the paradigm of a one-compartment, first-order elimination model for back-extrapolation of estimates of earlier exposures; however, it remains unclear which type of model should be used for dose reconstruction. Thus, the committee recommends additional validation of the PBPK models and direct comparisons of the resulting exposure classifications when the new models and the standard first-order elimination models are applied to large data sets.

- **Potential emergence of metabolic syndrome should be analyzed.**

The committee recognized that, within the study populations reviewed in preparing *Update 2006*, the values of serum components and specific health outcomes may be interrelated, including hypertriglyceridemia, type 2 diabetes mellitus, hypertension, and ischemic heart disease. The first three of those outcomes are key criteria for the diagnosis of metabolic syndrome, and the fourth is a major consequence of it. Thus, the committee recommends that—in addition to analysis of the association of exposure to the chemicals of interest with individual health outcomes—the incidence of multiple health outcomes that define metabolic syndrome should be analyzed as a group.

- **Possible effects in offspring merit further investigation.**

The assessment of any link between exposure of Vietnam veterans to the chemicals of interest and *birth defects or developmental disease* in their offspring presents distinct challenges. The Department of Veterans Affairs (VA) should review all the possible cognitive and developmental effects in offspring of veterans. Such a review should include the possibility of effects in grandchildren, which are of growing concern to veterans and their families. A recent review of the literature and meta-analysis by Ngo et al. (2006) noted a significant association for veterans, who served in Ranch Hand, pointing to the need to examine closely both the biologic plausibility of paternally mediated birth defects and existing epidemiologic evidence. In addition, reviews have focused on epidemiologic studies of data from birth-defect registries or parental reports of birth defects. Those studies often exclude alterations in function that could appear later in a child's life, such as in neurologic function, endocrine function, or reproductive capacity. The findings of the Air Force Health Study (AFHS) on birth defects in veterans' offspring have not yet been (and, if funding is not provided, may never be) formally and systematically integrated and analyzed in a longitudinal fashion.

Most etiologic research has focused on the effects of maternal and fetal exposures, but some work addressing paternal exposures has been discussed in previous reviews. With increasing concern about male reproductive function, increasing numbers of epidemiologic studies of the role of paternal exposures in the risk of birth defects among offspring are being published. This work is particularly relevant in assessing health outcomes in offspring among a largely male service population. The plausibility of birth defects arising from parental exposure, especially from *paternal exposure,* merits a careful review in light of newly hypothesized mechanisms (such as heritable forms of gamete imprinting) that might make paternal transmission of a TCDD effect more plausible. The committee recommends that an ad hoc group be established to review current mechanistic studies that could further knowledge of a possible paternally mediated link between exposure to the chemicals of interest and health conditions (including birth defects) among offspring. Given the rarity of birth defects, the committee also recommends that the ad

hoc group conduct a meta-analysis of the current epidemiologic studies of male populations exposed to the chemicals of interest and the risk of birth defects among offspring.

- **Available information should be gleaned from existing cohort studies.**

Members of the Army Chemical Corps constitute the largest cohort of Vietnam veterans exposed directly to herbicides and TCDD. They were involved in the handling and distribution of the chemicals in Vietnam. Army Chemical Corps veterans who reported spraying herbicides as part of their duties have been demonstrated to have increased serum TCDD concentrations; that more highly exposed population (herbicide sprayers) has also been shown to be at increased risk for several diseases. The population should be the focus of additional study, with new resources devoted to it, because it represents our best opportunity to understand the health effects of exposure to TCDD and the herbicides used in Vietnam.

The present VAO committee concurs with the recommendations of the recent Committee on the Disposition of the Air Force Health Study (IOM, 2006). That committee concluded that the various assets of the study should be retained, that a custodian should be identified to house and administer the data, and that the data should be made available for future research. The future availability of the data implies that full longitudinal analysis using the data collected in the various medical cycle examinations, data on medical interventions (such as hospitalizations and emergency-department visits), cancer incidence, mortality, and other data on exposure could be used profitably to investigate further some of or all the endpoints that may be associated with the exposures under consideration in the present report. The present *VAO* committee concurs with the AFHS-disposition committee that prioritizing which endpoints to investigate ought to be left to independent investigators making appropriate choices based on scientific criteria.

There is regrettably little data available on the women who served in Vietnam. The cohort of nurses studied in Kang et al. (2000) largely exhausted the source population, but now that an additional 10 years has elapsed following up the health status of this group and determining their TCDD levels be worthwhile.

At the direction of Congress, the National Vietnam Veterans Readjustment Study (1986-1988) investigated primarily psychiatric sequellae in a representative cohort of about 1,600 men and women. In 2000, Congress mandated (Public Law 106-419) that the VA assess the current physical and mental wellbeing of the individuals in that cohort. In 2001, VA contracted for the work, named the National Vietnam Veterans Longitudinal Study, but unfortunately progress ceased within two years. The VA Office of Inspector General (2005) ruled that "the Study was not properly, planned, procured, or managed," but directed that the study be completed, making provisions to avoid the previous problems. Because baseline information is available on symptoms and chronic health problems in the original cohort, the committee thinks completion of this study could generate meaningful information for future updates and concurs that serious consideration should be given to restarting the National Vietnam Veterans Longitudinal Study.

Starting in 1978, the National Institute for Occupational Safety and Health (NIOSH**)** began to study US workers potentially exposed to TCDD. A total of 5,132 workers in 12 large manufacturing companies were included in the cohort. The NIOSH cohort has been an extremely valuable source of data in assessing the health effects associated with TCDD exposure. The studies have included high-quality exposure assessment, and evaluations of a wide array of health outcomes have been published. Given its value as an important source of epidemiologic data, the committee recommends that studies of the NIOSH cohort be extended.

The committee also notes that future analyses of health outcomes in those and other important study populations should be as specific as possible because generic findings, such as for "all respiratory outcomes," are not useful in addressing this committee's charge of determining associations of herbicide exposures with specific health conditions.

- **VA should evaluate possibilities for studying health outcomes among Vietnam-era veterans by using the existing administrative and health-services databases.**

The original *VAO* committee recommended that the Department of Defense (DoD) and VA identify Vietnam service in the computerized index of records. By linking that information with the VA electronic medical-record and associated administrative databases, such as discharge-diagnosis and pharmacy-use records, it should be possible to assemble epidemiologic information on common health conditions for evaluation of possible associations with military service in Vietnam.

Particular attention should be paid to the feasibility of conducting epidemiologic studies of conditions that have been noted to be of special interest but on which the current evidence is inadequate or insufficient to determine whether there is an association with herbicide exposure (such as tonsil and breast cancers, melanoma, Parkinson's disease, amyotrophic lateral sclerosis, lupus, ischemic heart disease, and stroke). For very uncommon health outcomes, a case-control design would probably be most appropriate.

Although applications for compensation and appeals constitute a non-representative, self-selected sample that is influenced by which conditions are already judged to be service-related, an effort to use existing VA information should include a more systematic review of the distribution of health outcomes in the database.

- **Exposure-reconstruction study should be put to use.**

The Institute of Medicine's Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam oversaw the development of a herbicide-exposure model for Vietnam veterans (the "Stellman model"), which was described in detail in recent publications (IOM, 2003a,b). That committee concluded that the model was adequate for use in epidemiologic studies. The present committee recommends that the model be incorporated into new epidemiologic studies where feasible, as is being investigated by a newly convened IOM committee, the Committee on Making Best Use of the Agent Orange Reconstruction Model.

- **Studies of the Vietnamese population would be worthwhile.**

As discussed in earlier updates, the Vietnamese are an understudied population. Although there are likely to be serious logistical challenges, the many Vietnamese people with substantial exposure constitute a potentially informative study sample. It will be important to include appropriate exposure measures, such as tissue TCDD concentrations, when studying Vietnamese residents. Because such research has the potential to close a number of gaps in understanding of the long-term health consequences of exposure to TCDD and herbicides used in Vietnam, the committee supports any further steps that can be taken to develop collaborative programs of research.

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[1] Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

APPENDIX A

Agendas of Public Meetings Held by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Sixth Biennial Update)

FIRST PUBLIC MEETING

Thursday, March 30, 2006
Keck Center, Room 201
Washington, DC

Presentations

- **Welcome; Goals and Conduct of the Public Meeting; Introductions**
  John Stegeman, Committee Chair

- **Charge to the Committee**
  Mark Brown, PhD, US Department of Veterans Affairs

- **IOM Veterans and Agent Orange Reports: A Brief History**
  David Butler, PhD, Institute of Medicine

- **Service in Vietnam and Melanoma**
  David A. Lamenzo, Vietnam Veteran

- **The Role of Dioxins in Cancer Risk in Highly Exposed Populations (Biomarkers of Exposure and Early Effects)**
  Maria Teresa Landi, MD, PhD, Investigator, National Cancer Institute

SECOND PUBLIC MEETING

Thursday, June 15, 2006
The Hyatt Regency Phoenix
Civic Plaza, 122 North Second Street
Phoenix, AZ

Presentations

- **Welcome; Goals and Conduct of the Public Meeting; Introductions**
  John Stegeman, Committee Chair

- **The Possible Effects of Contaminated Herbicides on the Pituitary**
  Debra Kraus, Artist

- **Vietnam Experience**
  Denis Dermody, Vietnam Veteran

- **Conference call concerning conventions for ICD coding and grouping health outcomes**
  Theodore R. Holford, PhD, Yale School of Public Health
  Kyle Steenland, PhD, Professor, Rollins School of Public Health, Emory University

APPENDIX B

Clarification of Cancer Groupings Used in Reporting Results, with Correspondence to NIOSH Cause-of-Death Codes and ICD Codes for Cancers

For *Update* 2006, the Department of Veterans Affairs (VA) requested two refinements in the system used in previous *Veterans and Agent Orange* (*VAO*) updates to present conclusions about the adequacy of evidence concerning associations between cancer types and exposure to the herbicides sprayed in Vietnam. First, conclusions should be provided for the full range of cancer types; that is, the cancer groupings for which conclusions are drawn used should be exhaustive. Second, it should be apparent into which groupings specific cancer diagnosis falls.

The explicitly stated cancer grouping reviewed in prior updates left a few gaps in the full range of cancer types (as indicated in italics in Table B-1). Those gaps represent quite specific types of cancer on which no data compatible with review had been found; the endpoint by default was in the "inadequate or insufficient evidence" category. The major portion of evidence compiled for review in this series comes from cohort studies, primarily of mortality but some of incidence. Other data have been generated by case-control studies, which follow the only design amenable to studying very infrequent or very specific health outcomes. How researchers are able to group, analyze, and report their findings is influenced by the distribution of cases that they observe, so the data that *VAO* committees have had available for review reflect mortality experience at a level of specificity concordant with statistical analysis.

Previous updates have referred to the International Classification of Diseases (ICD) system, which is used by physicians and researchers around the world to group related diseases and procedures so that morbidity and mortality information cab be classified for statistical purposes in a standard form amenable to data storage and retrieval. It is a comprehensive hierarchic system that permits great detail, but that can be collapsed into broad categories. Codes mentioned in *VAO* reports are stated in terms of ICD, Version 9 (ICD-9). ICD-7, ICD-8, and ICD-9 were in effect for deaths that occurred in 1960-1967, 1968-1978, and 1979-1998, respectively; the differences among them are fairly subtle. Although ICD-10, which went into effect for coding causes of deaths that occurred from 1999 on, appears radically different from the earlier versions, it corresponds in large part to basically the same disease entities (see Table B-2). To date, most published epidemiologic studies have been related to health outcomes that occurred and were encoded before ICD-10 went into effect.

Since 1983, the National Institute for Occupational Safety and Health (NIOSH) has maintained software for generating standardized expectations, as derived from US mortality data assembled by the National Center for Health Statistics, for ICD-encoded mortality datasets. An article by Robinson et al. (2006) discusses revisions to that standard software to incorporate deaths coded according to ICD-10 and includes conversions and equivalencies between ICD-7, -8, -9, and -10 for 119 exhaustive categories for cause of death. Codes for malignant neoplasms span the ICD-9 range 140.0-208.9, NIOSH's major categories 02-10, or NIOSH's more specific minor categories 004-040.

The NIOSH death codes for neoplasms provide comprehensive scaffolding for organizing the committee's reviews and conclusions by cancer type that is somewhat simpler than ICD classifications,

but maps completely to the ICD system as it has evolved. Because the NIOSH system has been used to mediate analysis of many sets of cohort data, its groupings correspond quite closely with the published research findings available for *VAO* review. In general cohort studies, one is unlikely to encounter results on more specific groupings than NIOSH's minor categories.

As discussed in Chapter 2, this committee has not framed its conclusions strictly in terms of ICD codes, but the ICD system has been a valuable tool for the work of *VAO* committees. There can be coding errors on hospital records or death certificates, but when researchers present their results labeled with ICD codes, there can be little ambiguity about what they intended. When their most definitive indication is something like "respiratory cancers," however, there can be uncertainty about where the evidence should be considered. In such cases, the committee has done its best to follow the hierarchy laid out in Table B-1.

As indicated above, many of the studies reviewed by the committee use or were written at a time when ICD-9 was in place. Accordingly, ICD references in this report use that scheme. ICD-10 began to be implemented in the United States in 1999. It differs from ICD-9 in level of detail (about 8,000 categories versus about 5,000 in ICD-9) and nomenclature (alphanumeric versus the numeric codes of ICD-9); additions and modifications were also made with regard to some coding rules and the rules for selecting an underlying cause of death (Anderson et al., 2001). Table B-2 lists the ICD-9 and ICD-10 codes for the various forms of malignant neoplasm addressed in this report. In situ neoplasms, benign neoplasms, neoplasms of uncertain behavior, and neoplasms of unspecified behavior have separate codes in both schemes.

Table B-1 Mapping of Groupings of Malignant Neoplasms That are the Subjects of Conclusions in *Update 2004* with ICD-9 Codes

NIOSH Category for Cause of Death		**NIOSH Groupings of Cancer Sites**	Subsites **"*Update 2004* Characterization of Grouping"** [a]	**ICD-9 codes (Gaps** [b] **in *Italics*)**
Major	**Minor**			
02		Buccal cavity and pharynx	**"Oral, nasal, and pharyngeal"**	
	004	Lip		**140**
	005	Tongue		**141**
	006	Other parts of buccal cavity		
			Salivary glands	**142**
			Floor of mouth	**144**
			Gum and other mouth	**143, 145**
	007	Pharynx		
			Oropharynx	**146**
			Tonsil	146.0–146.2
			Nasopharynx	**147**
			Hypopharynx	**148**
			Other buccal cavity and pharynx	*149*
				(**160** = nasal below)
03		Digestive organs and peritoneum	**"Gastrointestinal"**	
	008	Esophagus		**150**
	009	Stomach		**151**
	010	Intestine except rectum		
			Small intestine	*152*
			Colon (large intestine)	**153**
	011	Rectum		**154**
	012	Biliary passages, liver, and gall bladder	**"Hepatobiliary"**	
			Liver and intrahepatic bile ducts	**155**
			Gallbladder and extrahepatic	*156*

NIOSH Category for Cause of Death		NIOSH Groupings of Cancer Sites	Subsites "*Update 2004* Characterization of Grouping" [a]	ICD-9 codes (Gaps [b] in *Italics*)
Major	**Minor**			
			bile ducts	
	013	Pancreas		157
	014	*Retroperitoneum and other and unspecified digestive organs*		*158-159*
04		Respiratory system	**"Respiratory"**	
	015	Larynx		**161**
	016	Trachea, bronchus, and lung		162
			Trachea	*162.0* (there is no ICD 162.1)
			Lung and bronchus	**162.2-162.9**
	017	*Pleura*		*163*
	018	*Other respiratory*		
			Nasal cavity, middle ear, and accessory sinuses	(**160**, above with oral and pharyngeal)
			Thymus, heart, *and mediastinum*	*164* (*164.0,* below with endocrine; **164.1**, below with soft tissue sarcoma)
			Other respiratory, unspecified	*165* (discontinuity with ICD codes)
05	019	Breast (male and female)	**"Breast"**	**174**, *175*
06		Female genital organs	**"Female reproductive"**	
	020	Cervix uteri		**180**
	021	Other unspecified parts of uterus		179, 181, 182
			Uterus, parts unspecified	*179*
			Placenta	*181*
			Body of uterus	**182**
	022	Ovary, fallopian tube, and broad ligament		183
			Ovary	**183.0** (there is no ICD 183.1)
			Fallopian tube and other uterine adnexa	*183.2-183.9*
	023	*Other female genital organs*		*184*
07		Male genital system		185, 186
	024	Prostate	**"Prostate"**	**185**
	025	Testis	**"Testicular"**	**186**
		Penis and other male genital organs	*[for NIOSH in minor group 036]*	*187*
08		Urinary system		
	026	Kidney (including renal pelvis and ureter)	**"Renal"**	**189.0-189.2**
	027	Bladder and other urinary organs	**"Urinary bladder"**	188, 189.3–189.9
			Bladder	**188**
			Urethra, paraurethral glands, other and unspecified urinary	*189.3–189.9*
				(discontinuity with ICD codes)
09		Other and unspecified sites		
	028	Bone ("and articular cartilage" in ICD nomenclature)	**"Bone and joint"**	**170**
			"Skin"	
	029	Melanoma		**172**

NIOSH Category for Cause of Death		NIOSH Groupings of Cancer Sites	Subsites "*Update 2004* Characterization of Grouping" [a]	ICD-9 codes (Gaps [b] in *Italics*)
Major	**Minor**			
	030	Other malignant skin neoplasm		**173**
	031	*Mesothelioma*		No codes (new minor code)
	032	Connective ("and other soft" in ICD nomenclature) tissue	**"Soft-tissue sarcoma"**	**171**
			(heart)	**(164.1)**
	033	Brain and other parts of nervous system (ICD "soft tissue" includes peripheral nerves and autonomic nervous system)	**"Brain"**	**191-192**
	034	*Eye*		*190*
	035	*Thyroid*		*193*
			(thymus)	*164.0*
	036	*Other and unspecified sites*	*Other endocrine cancers*	*194*
			Other and ill-defined sites	*195*
			Stated or assumed to be secondary of specified sites	*196-198*
			Site unspecified	*199*
10		Lymphatic and hematopoietic tissue		
		Lymphoma		
	037	**Hodgkin's disease**		**201**
	038	**Non-Hodgkin's lymphoma**		**200, 202** (excluding 202.4), 273.3
	039	**Multiple myeloma**		**203** (excluding 203.1)
	040	Leukemia and aleukemia	**"Leukemia (other than CLL)"**	204-208
		Lymphocytic		
			Acute lymphocytic	**204.0**
			Chronic lymphocytic	**204.1**
			Other lymphocytic	**202.4**; **204.2–204.9**
		Myeloid (granulocytic)		
			Acute myeloid	
			Acute	**205.0**
			Acute erythremia and erythroleukemia	**207.0**
			Megakaryocytic leukemia	**207.2**
			Chronic myeloid	**205.1**
			Other myeloid	**205.2–205.3, 205.8–205.9**
		Monocytic		
			Acute monocytic	**206.0**
			Chronic monocytic	**206.1**
			Other monocytic	**206.2–206.9**
		Other leukemia		
			Other acute	**208.0**
			Other chronic	**207.1, 208.1**
			Aleukemic, subleukemia and "not otherwise specified"	**203.1**, **207.2, 207.8, 208.2–208.9**

[a] **Boldface cancer (sub)site:** most comprehensive grouping for which conclusion was drawn in *Update 2004.*
[b] *Italicized cancer (sub)site*: prior gap in coverage of cancers (not explicitly addressed in text).

Table B-2 Surveillance, Epidemiology, and End Results (SEER) Program Malignant Neoplasm Site Groupings for ICD-9 and ICD-10

Cancer Site	ICD-9 codes	ICD-10 codes
Buccal cavity and pharynx		
Lip	140.0–140.9	C00.0–C00.9
Tongue	141.0–141.9	C01, C02.1–C02.9
Salivary glands	142.0–142.9	C07, C08.0–C08.9
Floor of mouth	144.0–144.9	C04.0–C04.9
Gum and other mouth	143.0–143.9, 145.0-145.6, 145.8-145.9	C03.0–C03.9, C05.0–C05.9, C06.0–C06.9
Nasopharynx	147.0–147.9	C11.1–C11.9
Tonsil	146.0–146.2	C09.0–C09.9
Oropharynx	146.3–146.9	C10.1–C10.9
Hypopharynx	148.0–148.9	C12, C13.0–C13.9
Other buccal cavity and pharynx	149.0–149.9	C14.0–C14.9
Digestive system		
Esophagus	150.0–150.9	C15.0–C15.9
Stomach	151.0–151.9	C16.0–C16.9
Small intestine	152.0–152.9	C17.0–C17.9
Colon excluding rectum	153.0–153.9, 159.0	C18.0–C18.9, C26.0
Rectum and rectosigmoid junction	154.0–154.1	C19, C20
Anus, anal canal, and anorectum	154.2–154.3, 154.8	C21.0–C21.9
Liver and intrahepatic bile duct		
Liver	155.0,155.2	C22.0, C22.2–C22.4, C22.7–C22.9
Intrahepatic bile duct	155.1	C22.1
Gallbladder	156.0	C23
Other biliary	156.1–156.9	C24.0–C24.9
Pancreas	157.0–157.9	C25.0–C25.9
Retroperitoneum	158.0	C48.0
Peritoneum, omentum, and mesentery	158.8–158.9	C48.1–C48.2
Other digestive organs	159.8–159.9	C26.8–26.9, C48.8
Respiratory system		
Nasal cavity, middle ear, and accessory sinuses	160.0–160.9	C30.0, C30.1, C31.0–C31.9
Larynx	161.0–161.9	C32.0–C32.9
Lung and bronchus	162.2–162.9	C34.0–C34.9
Pleura	163.0–163.9	C38.4
Trachea, mediastinum, and other respiratory organs	162.0, 164.2–165.9	C33, C38.1–C38.3, C38.8, C39
Bones and joints	170.0–170.9	C40.0–C40.9, C41.0–C41.9
Soft tissue (including heart)	171.0–171.9, 164.1	C38.0, C47.0–C47.9, C49.0–C49.9
Skin		
Malignant melanomas	172.0–172.9	C43.0–C43.9
Other malignant skin neoplasms	173.0–173.9	C44.0–C44.9
Breast (male and female)	174.0–174.9, 175	C50.0–C50.9
Female genital system		
Cervix	180.0–180.9	C53.0–C53.9
Corpus	182.0–182.1, 182.8	C54.0–C54.9
Uterus, not otherwise specified	179	C55
Ovary	183.0	C56.0–C56.9
Vagina	184.0	C52
Vulva	184.1–184.4	C51.0–C51.9
Other female genital organs	181, 183.2–183.9, 184.8, 184.9	C57.0–C57.9, C58

Cancer Site	ICD-9 codes	ICD-10 codes
Male genital system		
Prostate	185	C61
Testis	186.0–186.9	C62.0–C62.9
Penis	187.1–187.4	C60.0–C60.9
Other male genital organs	187.5–187.9	C63.0–C63.9
Urinary system		
Urinary bladder	188.0–188.9	C67.0–C67.9
Kidney and renal pelvis	189.0, 189.1	C64.0–C64.9, C65.0–C65.9
Ureter	189.2	C66.0–C66.9
Other urinary organs	189.3–189.4, 189.8–189.9	C68.0–C68.9
Eye and orbit	190.0–190.9	C69.0–C69.9
Brain and other nervous system		
Brain	191.0–191.9	C71.0–C71.9
Meninges	192.1	C70.0–C70.9
Other nervous system[1]	192.0, 192.2–192.9	C72.0–C72.9
Endocrine system		
Thyroid	193	C73
Other endocrine (including thymus)	164.0, 194.0–194.9	C37, C74.00–C74.92, C75.0–C75.9
Lymphomas		
Hodgkin's disease	201.0–201.9	C81.0–81.9
Non-Hodgkin's lymphomas	200.0–200.8, 202.0–202.2, 202.8–202.9	C82.0–C82.9, C83.0–C83.9, C84.0–C84.5, C85.0–C85.9, C96.3
Multiple myeloma	203.0, 238.6	C90.0, C90.2
Leukemias		
Lymphocytic		
Acute lymphocytic	204.0	C91.0
Chronic lymphocytic	204.1	C91.1
Other lymphocytic	202.4, 204.2–204.9	C91.2-C91.4, C91.7, C91.9
Myeloid (granulocytic)		
Acute myeloid	205.0, 207.0, 207.2	C92.0, C92.4–C92.5, C94.0, C94.2
Chronic myeloid	205.1	C92.1
Other myeloid	205.2–205.3, 205.8–205.9	C92.2–C92.3, C92.7, C92.9
Monocytic		
Acute monocytic	206.0	C93.0
Chronic monocytic	206.1	C93.1
Other monocytic	206.2–206.9	C93.2, C93.7, C93.9
Other leukemia		
Other acute	208.0	C94.4, C94.5, C95.0
Other chronic	207.1, 208.1	C94.1, C95.1
Aleukemic, subleukemic and "not otherwise specified"	203.1, 207.2, 207.8, 208.2–208.9	C90.1, C91.5, C94.3, C94.7, C95.2, C95.7, C95.9
Miscellaneous malignant neoplasms	159.1, 195.0–195.8, 196.0–196.9, 199.0–199.1, 202.3, 202.5–202.6, 203.8	C26.1, C76.0–C76.8, C77.0–C77.9, C78.0–C78.8, C79.0–C79.8, C80, C88.0–C88.9, C96.0–C96.2, C96.7, C96.9, C97

Adapted from Ries et al., Table A-4.

[1] Cancers of the peripheral nerves and the autonomic nervous system are classified as "soft tissue" in ICD.

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APPENDIX C

Epidemiologic Tables for Chapter 4

In Tables C-1 (page C-2), C-2 (page C-25), and C-3 (page C-32), respectively, studies are grouped according to whether their subjects had occupational exposures, had environmental exposures, or were specifically Vietnam veterans. The tables provide an overview of design aspects of those epidemiologic studies reviewed in this and earlier reports that presented results on more than one health outcome or that investigated populations that have been repeatedly studied. The summaries include the study's design type, the numbers of subjects in the study and comparison populations, and a synopsis of how subjects were selected, how data were collected, what inclusion criteria were used, and how exposure was determined. Results were discussed in the appropriate health outcome chapter of the *Veterans and Agent Orange* document in which the publication was reviewed. The citations for the articles in this appendix can be found in the reference list at the end of Chapter 4.

Contents of TABLE C-1 Epidemiologic Studies—Occupational Exposure

TABLE C-1 Epidemiologic Studies—Occupational Exposure

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
PRODUCTION WORKERS				
NIOSH Studies Reviewed in *Update 2006*				
Lawson et al. 2004	Cohort	Continues NIOSH cross-sectional medical study Sweeny et al. 1989, 1993. Wives of chemical workers vs. referent neighbors exposed to TCDD at the time of conception using pharmacokinetic model.	217 referent wives 176 workers wives	1,117
NIOSH Studies Reviewed in *Update 2002*				
Steenland et al., 2001	Cohort	Reexamine and compare diabetes data from the NIOSH cohort and the United States Air Force Ranch Hand study; to reconcile differences between study methods and protocols.	267 NIOSH workers; 990 Ranch Hand subjects	227 NIOSH comparisons 1,275 Ranch Hand comparisons
NIOSH Studies Reviewed in *Update 2000*				
Calvert et al., 1999	Cohort	Follow-up of workers employed more than 15 years before at 2 plants that manufactured substances contaminated with TCDD; to evaluate associations between serum TCDD and serum glucose (diabetes), TSH, total T_4, T_3	281	260

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Steenland et al., 1999	Cohort	Mortality of workers at 12 industrial plants that produced TCDD-contaminated materials, using a job–exposure matrix to estimate TCDD exposure categories; endpoints were all cancers, lung cancer, ischemic heart disease, diabetes, smoking-related cancer, and all other cancers	5,132 (3,538 subjects with exposure data divided into septiles of cumulative exposure; 608 with chloracne)	—
Calvert et al., 1998	Cohort	Follow-up of workers employed more than 15 years before at 2 plants that manufactured TCDD-contaminated materials; to evaluate association between TCDD exposure and cardiovascular outcomes	281	260
Halperin et al., 1998	Cohort	Follow-up of a cohort of TCDD-exposed workers at 2 plants that manufactured TCDD-contaminated materials; to assess association between serum TCDD and immunologic outcome variables for eligible workers and matched neighborhood controls	259	243
NIOSH Studies Reviewed in *Update 1998*				
Sweeney et al., 1996, 1997/1998	Cross sectional	Non-cancer endpoints for liver function, gastrointestinal disorders, chloracne, serum glucose, hormone, lipid concentrations, diabetes in the group studied by Calvert et al. (1991)	281	260
Halperin et al., 1995	Cross sectional	Surrogates for cytochrome P-450 induction in group studied by Calvert et al. (1991)	281	260
NIOSH Studies Reviewed in *Update 1996*				
Calvert et al., 1994	Cross-sectional	PCT in group studied by Calvert et al. (1991)	281	260
Egeland et al., 1994	Cohort	Total serum testosterone and gondadotropin in chemical production workers exposed to dioxin, in group studied by Calvert et al. (1991)	248	231
NIOSH Studies Reviewed in *VAO*				
Sweeney et al., 1993	Cohort	Peripheral neuropathy in group studied by Calvert et al. (1991)	281	260
Alderfer et al., 1992	Cohort	Psychological Assessment to determine depression in group studied by Calvert et al. (1991)	281	260
Calvert et al., 1992	Cohort	Liver and gastrointestinal systems assessment in group studied by Calvert et al. (1991)	281	260

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Calvert et al., 1991	Cohort	Workers employed at 1 of 2 plants manufacturing TCDD-contaminated materials at least 15 years before; to assess chronic bronchitis, COPD, ventilatory function, thorax, lung abnormalities; compared with matched neighborhood controls	281	260
Fingerhut et al., 1991	Cohort	Cancer mortality in male workers from 12 plants producing TCDD-contaminated materials (1942–1984), compared with US population	5,172	—
Monsanto Studies Reviewed in *VAO*				
Collins et al., 1993	Cohort	Mortality of workers (through 1987) exposed and unexposed to dioxin between March 8, 1949, and Nov. 22, 1949, as indicated by presence of chloracne, compared with local population mortality rates	122 (Chloracne); 632 (without Chloracne)	—
Moses et al., 1984	Cohort	Health outcomes in Monsanto workers (1948–1969) with chloracne reported as a surrogate for 2,4,5-T exposure, compared with health outcomes in workers without chloracne as surrogate for no exposure	117	109
Suskind and Hertzberg, 1984	Cohort	Health outcomes (1979) at clinical examination among workers exposed to 2,4,5-T (1948–1969) compared with non-exposed workers at same Monsanto plant	204	163
Zack and Gaffey, 1983	Cohort	Mortality of all white male workers (1955–1977) employed at a Monsanto plant through Dec. 31 1977, compared with mortality of standardized U.S. population	884	—
Zack and Suskind, 1980	Cohort	Mortality experience among employees with chloracne exposed to TCP process accident in 1949 at Monsanto, compared with US male population standard	121	—
Dow Studies in *Update 2004*				
Bodner et al., 2003	Cohort	Additional 10-year follow-up of cohort studied by Cook et al. (1986), through 1995; Dow cohort findings compared with IARC International Study and NIOSH Dioxin Registry.	2,187	—
Dow Studies Reviewed in Update 2002				
Burns et al., 2001	Cohort	Mortality in chemical workers who manufactured or formulated 2,4-D, 1945—1994	1,567	US population; 40,600 non-exposed chemical workers

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Dow Studies Reviewed in *Update 1998*				
Ramlow et al., 1996	Cohort	Mortality in PCP-exposed workers	770	US population 36,804 non-exposed workers
Dow Studies Reviewed in *Update 1996*				
Bloeman et al., 1993	Cohort	Follow-up of cohort studied by Bond et al. (1988), through 1986	878	U.S. population; 36,804 unexposed workers
Dow Studies Reviewed in *VAO*				
Bond et al., 1989a	Cohort	Chloracne incidence among workers potentially exposed to TCDD; association with other risk factors	2,072	Internal Comparison
Bond et al., 1989b	Cohort	Extension of Ott et al. (1987), through 1984	2,187	—
Bond et al., 1988	Cohort	Mortality (through 1982) among workers potentially exposed to 2,4-D (1945–1983) compared with US white males and all other male employees not exposed	878	US white male population; 36,804 non-exposed employees
Bond et al., 1987	Cohort	Extension of Cook et al. (1980); mortality through 1982	322	US white male population; 2,026 employees without chloracne
Cook et al., 1987; Ott et al., 1987	Cohort	Extension of Cook et al. (1986) through 1982	2,187	—
Sobel et al., 1987	Case–control	STS among Dow employees (1940–1979), compared with employees without STS, for possible association with several exposures	14	126
Cook et al., 1986	Cohort	Mortality experience (1940–1979) of men manufacturing chlorinated phenols, compared with US white men	2,189	—
Bond et al., 1983	Cross-sectional	Differences in potentially exposed and non-exposed workers for TCDD during chemical production, for (1) morbidity and (2) medical examination frequency, 1976–1978	(1) 183 (2) 114	(1) 732 (2) 456
Townsend et al., 1982	Cohort	Adverse reproductive outcomes among wives of Dow employees potentially exposed to TCDD (1939–1975), compared with wives whose husbands were not exposed	370	345

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Cook et al., 1980	Cohort	Mortality experience (through 1978) of male workers involved in a chloracne incident (1964) from TCDD exposure, compared with mortality experience of US white men	61	—
Ott et al., 1980	Cohort	Mortality experience among workers exposed to 2,4,5-T in manufacturing (1950–1971), compared with mortality experience of US white men	204	—
BASF Studies Reviewed in *Update 2000*				
Zober et al., 1997	Cohort (1953 accident) Cross-sectional (1988 cohort)	Review and summary of previous BASF studies of morbidity and mortality in workers exposed to TCDD after BASF accidents in 1953 and 1988	154 Surviving (as of 1989) members of 1953 accident cohort; 42 exposed (1988) extruder personnel	None
BASF Studies Reviewed in *Update 1998*				
Ott and Zober, 1996	Cohort	Cancer incidence and mortality experience (through 1992) of workers exposed to TCDD after the BASF accident, during reactor cleanup, maintenance, or demolition (based on the cohort of Zober et al., 1990)	243	—
BASF Studies Reviewed in *Update 1996*				
Zober et al., 1994	Cohort	Morbidity experience in the group studied Zober et al. (1990)	158	161
BASF Studies Reviewed in *VAO*				
Zober et al., 1990	Cohort	Mortality experience of TCDD-exposed workers (1954–1987) at BASF plant, compared with population of FRG	247	—
Thiess et al., 1982	Cohort	Mortality experience among BASF employees potentially exposed to TCDD during Nov. 17, 1953, accident, compared with population and other workers not exposed	74	180,000 (Town); 1.8 million (district); 60.5 million (FRG); 2 groups of 74 each from other cohort studies
IARC Studies Reviewed in *Update 2006*				
't Mannetje et al., 2005	Cohort	New Zealand phenoxy herbicide workers exposed TCDD & phenoxy herbicides	813 Production workers; 699 sprayers	

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
IARC Studies Reviewed in *Update 2000*				
Neuberger et al., 1999	Austrian chloracne cohort	Morbidity up to 1993 of exposed chemical workers assessed by health insurance data and health examination, laboratory measures, interviews with participating survivors and control subjects.	159; 50 Participated in examination	Two control groups, comparable to 50 examination participants; numbers not given
Hooiveld et al., 1998	Cohort	Mortality (through 1991), using SMR, of Dutch factory workers assessed in relation to work and exposure history; SMR and relative risk analyses	562 (Serum samples for 50); 140 males at accident	567
Jäger et al., 1998	Cohort	Preliminary data from Neuberger et al., 1999 [English abstract only]	159, Original cohort; 56 screened; 49 full data	Matched non-exposed controls
Neuberger et al., 1998	Cohort of exposed cases	Preliminary data from Neuberger et al., 1999	50	Age and sex-matched controls; number not given
Vena et al., 1998	Cohort	36 Worker cohorts from 12 countries, produced or sprayed phenoxyacid herbicides and chlorophenols, categorized in 1 of 3 TCDD or higher-chlorinated dioxin categories; non-cancer mortality (1939–1992) analyzed by SMR comparison and Poisson multiple regression	21,863	None
Flesch-Janys, 1997	Cohort	Mortality (1952–1984) of German workers exposed to TCDD and other contaminants in herbicide and insecticide production; SMR and Cox regression model	1,189	—
IARC Studies Reviewed in *Update 1998*				
Kogevinas et al., 1997	Cohort	Mortality (through 1992) of workers engaged in production or application of phenoxy herbicides and composed of (1) the Saracci et al. (1991) cohorts, (2) the German cohorts of Becher et al. (1996), and (3) the NIOSH cohorts of Fingerhut et al. (1991)	26,615 Total (21,863 exposed; 4,160 probably exposed; 592 unknown exposure)	—
Becher et al., 1996	Cohort	Cancer mortality (through 1989) among German workers in 4 chemical factories exposed to 2,4,5-T and/or trichlorophenol (subcohorts I and II), and phenoxy herbicides and chlorophenols (subcohorts III and IV)	2,479	—

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Flesch-Janys et al., 1995	Cohort	Cancer and circulatory system mortality among chemical plant workers in Hamburg, Germany, exposed to herbicides contaminated with PCDD/F	1,189	2,528 gas workers
IARC Studies Reviewed in *Update 1996*				
Kogevinas et al., 1995	Case–control	Nested studies of the relationship between STS and NHL and occupational exposures in the IARC cohort	11 cases, STS; 32 cases, NHL	5 Controls per case
Kogevinas et al., 1993	Cohort	Cancer incidence and mortality experience of female workers in 7 countries, potentially exposed to chlorophenoxy herbicides, chlorophenols, and dioxin, compared with national death rates and cancer incidence rates	701	—
Lynge, 1993	Cohort	Cancer incidence in the group studied by Lynge (1985); follow-up extended through 1987	3,390 Men; 1,071 Women	—
Kogevinas et al., 1992	Cohort	STS and malignant lymphoma mortality in an international cohort of production workers and herbicide sprayers (group studied by Saracci et al., 1991)	14,439 (13,482 Exposed, 416 probably exposed, 541 unknown exposure)	3,951 Non-exposed employees
IARC Studies Reviewed in *VAO*				
Bueno de Mesquita et al., 1993	Cohort	Mortality experience of production workers exposed to phenoxy herbicides and chlorophenols in the Netherlands, compared with national rates	2,310	—
Coggon et al., 1991	Cohort	Mortality experience among 4 cohorts of workers potentially exposed (1963–1985) to phenoxy herbicides and chlorophenols, compared with national (England and Wales) and local population expected numbers	1,104, Factory A; 271, Factory B; 345, Factory C; 519, Factory D	—
Manz et al., 1991	Cohort	Mortality experience of workers (1952–1984) at Hamburg, Germany, Boehringer plant exposed to TCDD, compared with national mortality and workers from another company	1,184 Men 399 Women	(a) population (b) 3,120 gas workers
Saracci et al., 1991	Cohort	Mortality experience of 20 international cohorts of herbicide sprayers and production workers, compared with national expected mortality experience	16,863 Men; 1,527 Women	—
Coggon et al., 1986	Cohort	Mortality experience (through 1983) among workers manufacturing and spraying MCPA (1947–1975), compared with expected number of deaths among men of England and Wales and for rural areas	5,754	—

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Lynge, 1985	Cohort	Cancer incidence among Danish workers exposed to phenoxyherbicides compared with expected results from the general population	3,390 Men; 1,069 Women	—
Studies from Other Chemical Plants Reviewed in *Update 2000*				
Hryhorczuk et al., 1998	Cohort	Morbidity (chloracne, prophyria, general health status) of workers involved in pentachlorophenol production 1938–1978, compared with unexposed workers at the same factory.	366	303
Jung et al., 1998	Cohort	Self-selected group of former workers at pesticide factory: physical examination, laboratory measures, questionnaires; associations between serum PCDD/F, infectious disease, immunologic measures	192	—
		Lymphocyte proliferation and chromate resistance tests compared for subgroup of most highly exposed workers at the study factory and non-exposed workers in another industry	29 Highly exposed subgroup	28 External unexposed group
Studies from Other Chemical Plants Reviewed in *Update 1998*				
Tonn et al., 1996	Cohort	Long-term immune system effects of TCDD in industrial workers (1966–1976) in production and maintenance at a German chemical factory producing 2,4,5-T	11	10
Studies from Other Chemical Plants Reviewed in *VAO*				
Jennings et al., 1988	Cohort	Immunologic abnormalities among TCDD-exposed workers in a 2,4,5-T–manufacturing accident, compared with matched controls	18	15
Thomas, 1987	Cohort	Mortality experience as of Jan. 1, 1981, for white men employed in fragrance and flavors plant with possible exposure to TCDD, compared with US white men and for cancers compared with local men	1,412	—
May, 1982, 1983	Cohort	Health outcomes among workers exposed and probably exposed to TCDD after a 1968 accident, compared with non-exposed workers	41 Exposed; 54 possibly exposed	31
Pazderova-Vejlupkova et al., 1981	Descriptive	Development of TCDD intoxication among men in Prague (1965–1968)	55	None
Poland et al., 1971	Cross-sectional	PCT, chloracne, hepatotoxicity, neuropsychiatric symptoms among 2,4-D and 2,4,5-T workers, compared with other plant workers	73 Workers (20 administrators; 11 production supervisors; 28 production; 14 maintenance)	Internal comparison

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Bashirov, 1969	Cross-sectional	Descriptive results of examination of workers involved in production of herbicides, study of workers for examination of cardiovascular and digestive systems, compared with non-exposed controls	292 Descriptive; 50 Examined	20 Examined
AGRICULTURAL–FOREST PRODUCTS				
Studies from US Agricultural Health Study (AHS) Reviewed in *Update 2006*				
Farr et al., 2006	Cohort	US Agriculture Health Study – age at menopause for women 35-55	8,038	
Hoppin et al., 2006		US Agriculture Health Study – cross sectional design to investigate the prevalence of wheeze among commercial pesticide applicators	2,375	
Alavanja et al., 2005	Cohort	US Agriculture Health Study – incidence Farmers, spouses of farmers, commercial applicators	87,286 – Total; 51,211 private applicators; 31,350 spouses; 4,725 commercial applicators	
Blair et al., 2005	Cohort	US Agriculture Health Study – mortality Farmers (yrs used pesticides ≤10 or >10), spouses of farmers		
De Roos et al., 2005b	Cohort	US Agriculture Health Study reported on rheumatoid arthritis (RA) for women applicators and spouses	135	675
Engel et al., 2005	Cohort	US Agriculture Health Study, wives of private applicators – incidence of breast cancer	309	
Kamel et al., 2005		AHS cross-sectional analysis of white male licensed private pesticide applicators	18,782	
Farr et al., 2004		AHS – menstrual cycle characteristics in premenstrual women aged 21-40	3,103	
Kern et al. 2004	Cohort	AHS –serum TCDD and insulin sensitivity in Air Force veterans exposure to herbicides	567	815
Studies from US Agricultural Health Study (AHS) Reviewed in *Update 2004*				
Flower et al., 2004	Prospective cohort	Parental pesticide application and cancer risk in offspring of pesticide appliers in AHS cohort	150	—
Alavanja et al., 2003	Prospective cohort	Correlation between pesticide exposure (including 2,4-D and 2,4,5-T) and prostate cancer in pesticide appliers	55,332	—
Studies from US Agricultural Health Study (AHS) Reviewed in *Update 2002*				

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Hoppin et al., 2002	Cohort	Study predicting wheeze among farm pesticide appliers in AHS	3,838 appliers with wheeze	16,630 appliers without wheeze
Studies from US Agricultural Health Study (AHS) Reviewed in *Update 2000*				
Alavanja et al., 1998	Cohort	Analysis of self-reported health care visits resulting from pesticide use by Iowa and North Carolina pesticide applicators	35,879	None
Studies of Other Agricultural Workers Reviewed in *Update 2006*				
United Farm Workers				
Mills and Yang, 2005	Nested case-control	California United Farm Workers evaluated effects of specific pesticides including 2,4,D on breast cancer	128 breast cancer cases	640 cancer free
Mills et al., 2005	Nested case-control	California United Farm Workers evaluated effects of specific pesticides including 2,4,D on lymphohematopoeitic cancers (LHC)	131	
Lee et al., 2004a	Case-control	Population based–agricultural pesticide use and adenocarcinoma of stomach or esophagus	170 stomach; 137 esophagus	502
Torchio et al., 1994	Cohort	Men licensed to use agricultural pesticides in Piedmont area of Italy	23,401	2,683
Reif et al., 1989	Case-control	Men with occupation indicated entered into New Zealand Cancer Registry 1980-1984 (brain or CNS cancers)	134	
Upper Midwest Health Study				
Lee et al., 2005	Case-control	Nebraska–incidence (gliomas)		
Carreon et al., 2005	Case-Control	Upper Midwest Health Study evaluated effects of rural herbicide exposure (arsenicals, phenoxys) on female farmers	341 (female glioma)	528
Ruder et al., 2004	Case-Control	Upper Midwest Health Study evaluated effects of rural herbicide exposure (arsenicals, phenoxys) on male farmers	(male glioma)	
Chiu et al., 2004	Nested case control	Examined the association between agricultural pesticide use and familial cancer with NHL	973	2,853
Lee et al., 2004b	Nested case control	NHL among asthmatics who reported previous pesticide exposure		
Studies of Other Agricultural Workers Reviewed in *Update 2002*				
Arbuckle et al., 2001	Cohort	Spontaneous abortions in couples living on full-time, family-run farms in Ontario, Canada	2,110 Women; 3,936 pregnancies	None
Masley et al., 2000	Cross-sectional survey	Targeted survey of households in an agriculture-based rural area of Saskatchewan, Canada	548 households; 1,407 individuals	None

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Curtis et al., 1999	Cohort	Time to pregnancy in couples living on full-time, family-run farms in Ontario, Canada	2,012 Pregnancies	None
Savitz et al., 1997	Cohort	Male pesticide exposure and pregnancy outcome for full-time, family-run farms in Ontario, Canada	1,898 Couples; 3,984 pregnancies	None
Studies of Other Agricultural Workers Reviewed in *Update 2000*				
Arbuckle et al., 1999	Cohort	Spontaneous abortions in couples living on full-time, family-run farms in Ontario, Canada	2,110 Women ; 3,936 pregnancies	None
Studies of Other Agricultural Workers Reviewed in *Update 1998*				
Gambini et al., 1997	Cohort	Cancer mortality (1957–1992) among rice growers in Novara Province, northern Italy	958	—
Kristensen et al., 1997	Cohort	Birth defects among offspring of Norwegian farmers born after 1924	192,417 Births	61,351 Births
Faustini et al., 1996	Cohort	Immune system components and function among farmers who mixed and applied commercial formulations containing 2,4-D and MCPA	10	Internal comparison
Studies of Other Agricultural Workers Reviewed in *Update 1996*				
Dean, 1994	Cohort	Brain and hematopoietic cancer mortality in agricultural workers, compared with non-agricultural workers in Ireland (1971–1987)	Population size unclear	—
Morrison et al., 1994	Cohort	Update of mortality experience in the group studied by Wigle et al., (1990), through 1987, with addition of farmers from Alberta and Manitoba	155,547	—
Semenciw et al., 1994	Cohort	Leukemia mortality in group studied by Morrison et al., (1993)	155,547	—
Blair et al., 1993	Cohort	Causes of death, including cancer, among farmers in 23 states (1984–1988)	119,648 White men; 2,400 white women; 11,446 non-white men; 2,066 non-white women	—
Semenciw et al., 1993	Cohort	Multiple myeloma mortality of male farmers, compared with male population of the 3 prairie provinces of Canada (1971–1987)	155,547	—
Senthilselvn et al., 1992	Cross sectional	Association between pesticide exposure and asthma in male farmers	1,939	None
Studies of Other Agricultural Workers Reviewed in *VAO*				

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Morrison et al., 1993	Cohort	Mortality experience of male Canadian farmers 45 years or older in Manitoba, Saskatchewan, Alberta (1971–1987), compared with Canadian prairie province mortality rates	145,383	—
Eriksson et al., 1992	Cohort	Incidence of NHL, HD, multiple myeloma (1971–1984) among selected occupational groups in Swedish men and women, compared with rates expected in general population	Number in occupational group unknown	—
Hansen et al., 1992	Cohort	Study of cancer incidence among male and female Danish gardeners compared to incidence expected among the general population	4,015 (859 women; 3,156 men)	—
Morrison et al., 1992	Cohort	Mortality experience, male farmers 35 years or older (1971–1987), compared with Canadian prairie province rates	155,547	—
Ronco et al., 1992	Cohort	Cancer incidence (1970–1980) among male and female Danish farm workers 15–74 years old, compared with expected number of cancers among persons economically active; cancer mortality (November 1981–April 1982) among male and female Italian farmers 18–74 years old, compared with persons in other occupational groups	None given	None given
Lerda and Rizzi, 1991	Cohort	Farmers exposed to 2,4-D, as measured in urine, compared with non-exposed men, for differences in sperm volume, death, count, motility, abnormalities, March–June 1989	32	25
Wigle et al., 1990	Cohort	NHL mortality experience in male farmers 35 years or older (1971–1985) in Saskatchewan, Canada, compared with age- and period-specific mortality rates expected for Saskatchewan males	69,513	—
Corrao et al., 1989	Cohort	Cancer incidence among male farmers licensed (1970–1974) to use pesticides, compared with number expected among licensed non-users	642	18,839
Wiklund et al., 1988a	Cohort	Malignant lymphoma incidence among agricultural and forestry workers in Sweden, compared with the general population of men; 1960 census	354,620	1,725,845
Wiklund and Holm, 1986	Cohort	STS incidence among agricultural and forestry workers in Sweden, compared with the general population of men; 1960 census	354,620	1,725,845
Wiklund, 1983	Cohort	Cancer incidence (diagnosed 1961–1973) among agricultural workers in Sweden, compared with expected rates; 1960 census	19,490	—

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Burmeister, 1981	Cohort	Mortality of farmers, compared with non-farmers, Iowa (1971–1978)	6,402	13,809
Studies of Forestry Workers Reviewed in *Update 2002*				
Thörn et al., 2000	Cohort	Mortality and cancer incidence in Swedish lumberjacks exposed to phenoxy herbicides	261	243
Studies of Forestry Workers Reviewed in *VAO*				
Green, 1991	Cohort	Mortality experience, male forestry workers (1950–1982) in Ontario, compared with expected mortality of male Ontario population	1,222	—
Green, 1987	Cohort	Suicide experience in Canadian forestry workers by number of years in forestry trade as a surrogate for exposure to phenoxy herbicides, compared with population	1,222	—
Van Houdt et al., 1983	Cross sectional	Acne and liver dysfunction in 2,4,5-T–exposed and non-exposed Dutch forestry workers	54	54
Studies of Herbicides–Pesticide Appliers Reviewed in *Update 2006*				
Foster et al., 2005	Cross sectional	Dioxin levels and thyroid hormones in maternal serum as possible contributor to cognitive or motor impairment in offspring.	20,625 appliers and spouses; 21,375 children born during or after 1975	—
Studies of Herbicide–Pesticide Appliers Reviewed in *Update 2004*				
Swaen et al., 2004	Cohort	Mortality follow-up in Dutch male herbicide appliers.	1,341	—
Studies of Herbicide–Pesticide Appliers Reviewed in *Update 2000*				
Dich and Wiklund, 1998	Cohort	Men licensed for pesticide application in Sweden; cancer cases ascertained from cancer registry and reported standardized incidence ratio for prostate cancer	20,025	—
Studies of Herbicide–Pesticide Appliers Reviewed in *Update 1998*				
Heacock et al., 1998	Cohort	Fertility among British Columbia workers potentially exposed to chlorophenate wood preservatives in 14 sawmills, 1955–1988; includes the cohort studied by Hertzman et al. (1997)	18,016 Births	1,668 Births
Hertzman et al., 1997	Cohort	Mortality among British Columbia workers potentially exposed to chlorophenate wood preservatives in 11 sawmills, 1950–1985	23,829	2,658
Dimich-Ward et al., 1996	Cohort; nested case–control	Birth defects among offspring (1952–1988) of the cohort studied by Hertzman et al. (1997)	19,675 Births among 9,512 fathers	5 control subjects, non-anomalous birth, per case

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Garry et al., 1996a	Cohort	Chromosome abnormalities based on the cohort of Garry et al. (1994)	23 Fumigant appliers; 18 insecticide appliers; 20 herbicide appliers	33
Garry et al., 1996b	Cohort	Birth defects among offspring (1989–1992) of male pesticide appliers in Minnesota	4,935 Births among 34,772 pesticide appliers (125 with birth anomalies)	3,666 Births with anomalies, general population
Zhong and Rafnsson, 1996	Cohort	Cancer mortality among various subgroups of pesticide users in Iceland	2,449 (1,860 males, 589 females)	—
Studies of Herbicide–Pesticide Appliers Reviewed in *Update 1996*				
Asp et al., 1994	Cohort	Mortality and cancer morbidity experience of male chlorophenoxy herbicide appliers (cohort studied by Riihimaki et al., 1982, 1983) in Finland (1955–1971), through 1989, compared with general population morbidity and mortality	1,909	—
Garry et al., 1994	Cross-sectional	Health outcomes resulting from exposure in male pesticide appliers in Minnesota	719	None
Studies of Herbicide–Pesticide Appliers Reviewed in *VAO*				
Swaen et al., 1992	Cohort	Cancer mortality experience (through 1987) among Dutch male herbicide appliers licensed before 1980, compared with total Dutch male population	1,341	—
Bender et al., 1989	Cohort	Cancer mortality of Minnesota highway maintenance workers, compared with numbers expected in white Minnesota men	4,849	—
Wiklund et al., 1989a	Cohort	Risk of cancer in cohort studied by Wiklund et al. (1987), through 1982	20,245	—
Wiklund et al., 1989b	Cohort	Risk of STS, HD, NHL in cohort studied by Wiklund et al. (1987) through 1984	20,245	—
Wiklund et al., 1988b	Cohort	Risk of STS in cohort studied by Wiklund et al. (1987), through 1984	20,245	—
Wiklund et al., 1987	Cohort	Risk of HD, NHL among Swedish pesticide appliers from date of license through 1982, compared with expected total population cases	20,245	—
Blair et al., 1983	Cohort	Mortality experience of white male Florida pesticide appliers compared with US and Florida men	3,827	—
Riihimaki et al., 1983	Cohort	Cancer morbidity, mortality in cohort (Riihimaki et al., 1982), through 1980.	1,926	—

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Riihimaki et al., 1982	Cohort	Mortality among herbicide appliers exposed to 2,4-D and 2,4,5-T in Finland, compared with expected population mortality	1,926	—
Smith et al., 1982	Cohort	Adverse reproductive outcomes among chemical appliers and agricultural contractors by category of exposure: none; compounds other than 2,4,5-T; 2,4,5-T	113 Pregnancies (compounds other than 2,4,5-T); 486 pregnancies (2,4,5-T)	401 Pregnancies (non-exposed)
Barthel, 1981	Cohort	Cancer incidence (1948–1972) in male agricultural production workers, compared with expected population incidence rates	1,658	—
Smith et al., 1981	Cohort	Differences in adverse reproductive outcomes in chemical appliers (1973–1979) in New Zealand, compared with agricultural contractors	459	422
Axelson et al., 1980	Cohort	Additional years of follow-up of cohort established in Axelson and Sundell (1974)	348	—
Axelson and Sundell, 1974	Cohort	Mortality and cancer incidence among Swedish railroad workers spraying herbicides (>45 days), compared with expected deaths by age and sex (1957–1972) in Sweden	348, Total herbicide exposure; 207, phenoxy acids and combinations; 152, amitrole and combinations; 28, other herbicides and combinations	—
PAPER AND PULP WORKERS				
Paper and Pulp Studies Reviewed in *Update 2006*				
McLean et al., 2006	Cohort	IARC pulp and paper works exposure to Exposure to nonvolatile organochlorine compounds	27 Never exposed ; 16 Ever exposed	
Paper and Pulp Studies Reviewed in *Update 2000*				
Schildt et al., 1999	Case–control	Histopathologically verified oral-cancer cases, matched control subjects; mailed exposure questionnaire on lifetime occupational history, oral cancer risk factors, pesticide use, smoking, SES, place of residence	410	410
Rix et al., 1998	Cohort	Cancer incidence in blue-collar workers at 3 Danish paper mills, compared with population rates from national population and mortality registers	14,788 (14,362 Identified for follow-up)	—
Paper and Pulp Studies Reviewed in *VAO*				
Jappinen and Pukkala, 1991	Cohort	Cancer incidence (through 1987) in male Finnish pulp and paper workers (1945–1961), compared with rates in local central hospital district	152	~135,000

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Henneberger et al., 1989	Cohort	Mortality experience through August 1985, white men employed in Berlin, New Hampshire, pulp and paper industry, compared with mortality expected in US white men	883	—
Solet et al., 1989	Cohort	Mortality (1970–1984) in white male United Paperworkers International Union members, compared with expected number of deaths in US men	201	—
Robinson et al., 1986	Cohort	Mortality experience through March 1977, white male workers employed in 5 paper and pulp mills, compared with expected number of deaths in US population	3,572	—
CASE–CONTROL STUDIES				
Case–Control Studies Reviewed in *Update 2006*				
De Roos et al., 2005a	Nest case–control	AHS limited to female participants to determine association of 2,4-D and rheumatoid arthritis	135	675
De Roos et al., 2005b	Case–control	Investigation of PCBs and other organchlorines and risk of NHL	100	100
Hartge et al., 2005	Case–control	Estimate the effects of residential herbicide exposure on NHL risk.	1,057	1,321
Heilier et al., 2005	Case–control	Endometriosis among Beligan surgical patients vs healthly gyn patients	50 women (25 w/ peritoneal endometriosis, 25 w/ deep adenomyotic nodules	21
McDuffie et al., 2005	Case–control	Test contradictory results in studies of phenoxyherbicides and NHL, rubber gloves use by farmers when mixing or applying pesticides	513	1506
Chen et al., 2006	Case–control	Residential exposure to pesticides and chemicals		
Chen et al. 2005	Case–control	Parental occupational exposure to pesticide and childhood germ cell-tumors (GCTs)	253	394
Oh et al., 2005	Case–control	South Korean study evaluated male fertility-dioxin exposure with air monitoring	84	31
Park et al., 2005	Case–control	Investigated the association between occupational factors and mortality from neurodengerative diseases		

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Reynolds et al., 2005a	Case–control	Evaluated breast cancer risk associated with body burden levels of PCDDs and PCDFs	79 women diagnosed with invasive breast cancer	52 women diagnosed with benign breast conditions
Reynolds et al., 2005b	Case–control	Evaluated association between cancers diagnosed at 0–4 years in 1990–1997 and maternal exposure to "probable human carcinogens" (including cacodylic acid) during gestation at residence based on application of GIS approach to pesticides data from CPUR	2,216 cases in state cancer registry matched to California birth certificate	4,388 controls matched on DOB and sex
Tango et al., 2004	Case–control	Examined multiple pregnancy outcomes in Japan-infant deaths from congenital defects		
Magnani et al., 1987	Case–control	Mortality study that examined five cancer − oesophageal, pancreatic, cutaneous melanoma, kidney, and brain in deceased male residents		
Case–Control Studies Reviewed in *Update 2000*				
Ekström et al., 1999	Case–control	All new cases of histologically confirmed gastric adenocarcinoma in 2 areas in Sweden; age- and sex- matched control group randomly selected by computerized population register	565	1,164
Hardell and Eriksson, 1999	Case–control	Male cases, 25 years or older, with histopathologically confirmed NHL during 1987–1990 in northern and central-Sweden; age-matched controls from National Population Registry	404	741
García et al., 1998	Case–control	Match-paired study of congenital malformations or defects in an agricultural region of Spain	261	261
Case–Control Studies Reviewed in *Update 1998*				
Blatter et al., 1997	Case–control	Multicenter Dutch study of paternal occupation and risk of spina bifida in offspring (1980–1992)	222	764
Liou et al., 1997	Case–control	Occupational and environmental risk factors and PD in Taiwan (1993–1995)	120	240
Tatham et al., 1997	Nested case–control	Occupational risk factors (population based) for subgroups of NHL patients based on the CDC Selected Cancers Study (CDC, 1990a,b,c,d)	1,048	1,659
Nanni et al., 1996	Case–control	Occupational and chemical risk factors (population-based) in northeastern Italy for CLL and NHL (1987–1990)	187	977

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Schulte et al., 1996	PMR Analysis, Nested case–control	Neurodegenerative diseases and occupational risk factors from 27 states	Based on 130,420 death certificates	
Seidler et al., 1996	Case–control	PD and rural factors, including exposure to herbicides and wood preservatives, in Germany	380	379 neighborhood controls; 376 regional controls
Case-Control Studies Reviewed in *Update 1996*				
Hardell et al., 1994	Case–control	Association between occupational exposures, parameters related to NHL in white males in Sweden	105	335
Mellemgaad et al., 1994	Case–control	Cases of renal-cell carcinoma (20–79 years) in Denmark, compared with population-based sample without cancer for identification of occupational risk factors	365	396
Nurminen et al., 1994	Case–control	Structural defects in infants born to mothers engaged in agriculture in first trimester, compared with those from mothers not in agricultural work during the first trimester	1,306	1,306
Brown et al., 1993	Case–control	Multiple myeloma (population-based) in Iowa men, for association with pesticide exposures	173	650
Persson et al., 1993	Case–control	Risk factors potentially associated with HD and NHL in males identified from the Regional Cancer Registry in Sweden	31 HD ; 93 NHL	204
Semchuk et al., 1993	Case–control	PD cases (36–90 years of age) in Canada, compared with population-based sample, for association with occupational exposure to herbicides and other exposures	75 Men; 55 Women	150 Men; 110 Women
Zahm et al., 1993	Case–control	NHL and pesticide exposure in white women diagnosed from July 1, 1983, to June 30, 1986	206	824
McDuffie et al., 1990	Case–control	Pesticide exposure in male cases of primary lung cancer in Saskatchewan, Canada, compared with age-, sex-, and location of residence–matched control subjects	273	187
Case–Control Studies Reviewed in *VAO*				
Cantor et al., 1992	Case–control	NHL (population-based) in Iowa and Minnesota men, association with farming exposures	622	1,245
Smith and Christophes, 1992	Case–control	STS, malignant lymphomas in men diagnosed 1982–1988 in Australia, compared with other cancers, for association with exposure to phenoxy herbicides and chlorophenols	82	82 Other cancers; 82 population

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Brown et al., 1990	Case–control	Leukemia (population based) in Iowa and Minnesota men for association with farming exposures	578	1,245
Eriksson et al., 1990	Case–control	Male cases of STS (25–80 years) diagnosed 1978–1986 in central Sweden, compared with population-based sample without cancer, for association with occupational exposure to phenoxyacetic acids and chlorophenols	218	212
Wingren et al., 1990	Case–control	Male cases of STS (25–80 years) diagnosed 1975–1982 in southeast Sweden, compared with 2 referent groups: population-based sample and other cancers, for association with phenoxyacetic acids and chlorophenols	71	315 Population based; 164 other cancers
Zahm et al., 1990	Case-control	White men 21 years or older diagnosed with NHL (1983–1986) in Nebraska, compared with residents of the same area without NHL, HD, multiple myeloma, CLL for association with herbicides (2,4-D) on farms	201	725
Alavanja et al., 1989	PMR Analysis, nested case–control	Mortality experience, USDA forest–soil conservationists (1970–1979) evaluated for specific cancer excess; case–control study of specific cancers identified from PMR analysis	1,411	—
Boffetta et al., 1989	Nested case–control	Multiple myeloma (national), compared with other cancer controls, for association with exposures including pesticides and herbicides	282	1,128
LaVecchia et al., 1989	Case–control	Italian men and women with HD, NHL, and multiple myeloma (1983–1988), compared with population of Italy, for occupational and herbicide use associations	69 HD; 153 NHL; 110 Multiple Myeloma	396
Persson et al., 1989	Case–control	HD, NHL among living men and women in Sweden, compared with subjects without cancers, for association with occupational exposures, including phenoxy herbicides	54 HD; 106 NHL	275
Woods and Polissar, 1989	Case–control	NHL from the study of Woods et al. (1987), association with phenoxy herbicides in farmworkers	576	694
Alavanja et al., 1988	PMR Analysis, nested case–control	USDA extension agents mortality experience (1970–1979), evaluated for specific cancer excess; case–control study of specific cancers identified from PMR analysis	1,495	—
Dubrow et al., 1988	Case–control	NHL, HD (death certificates, 1958–1983) among white male residents of Hancock County, Ohio, compared with a random sample of those dying from other causes, for association with farming	61 NHL; 15 HD	304

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Hardell and Eriksson, 1988	Case–control	Male cases of STS (25–80 years) diagnosed between 1978–1983 in northern Sweden, compared to two referent groups: population based, and with other cancers, for association with occupational exposure to phenoxyacetic acids and chlorophenols	55	330 Population based; 190 other cancers
Musicco et al., 1988	Case–control	Brain gliomas diagnosed 1983–1984 in men and women in Italy, compared with (1) patients with non-glioma nervous system tumors and (2) patients with other neurologic diseases, for association with chemical exposures in farming	240	(1) 465 (2) 277
Olsson and Brandt, 1988	Case–control	NHL (1978–1981) in Swedish men, compared with 2 groups of men without NHL for association with occupational exposures including phenoxy acids	167	50, Same area; 80, other parts of Sweden
Hardell et al., 1987	Case–control	Kaposi's sarcoma in AIDS patients (23–53 years) in Sweden, compared with controls, for association with TCDD and pesticide exposure	50	50
Pearce et al., 1987	Case–control	Expansion of study by Pearce et al. (1986b) of NHL to include ICD 200 diagnosed cases and additional controls, for association with farming exposures	183	338
Woods et al., 1987	Case–control	STS or NHL in men 20–79 years old (1983–1985) in western Washington State, compared with non-cancer population sample, for association with occupational exposure to phenoxy herbicides and chlorinated phenols	128 STS ; 576 NHL	694
Hoar et al., 1986	Case–control	STS, NHL, HD in Kansas (1976–1982), compared with non-cancer control subjects, for association with 2,4-D, 2,4,5-T, and other herbicides in white men 21 years or older	133 STS; 121 HD; 170 NHL	948
Morris et al., 1986	Case–control	Multiple myeloma (1977–1981) in four SEER areas, compared with population control subjects, for risk factors associated with the disease, including farm use of herbicides	698	1,683
Pearce et al., 1986a	Case–control	Male multiple myeloma cases diagnosed 1971–1981 in New Zealand, compared with control subjects with other cancers, for potential association with phenoxy herbicides and chlorophenols	76	315
Pearce et al., 1986b	Case–control	NHL cases (ICD-9 202) in men diagnosed 1977–1981 in New Zealand, compared with control group sample with other cancers and population sample, for association with occupational exposure to phenoxy herbicides and chlorophenols	83	168 Other cancer; 228 general population

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Smith and Pearce, 1986	Case–control	Update of Smith et al. (1983), diagnoses through 1982	51 Update cases (133, combined with data from Smith et al., 1983)	315 (407)
Vineis et al., 1986	Case–control	STS cases in men and women diagnosed 1981–1983 in northern Italy, compared with population sample of control subjects, for association with phenoxy herbicide exposure	37 Men; 31 women	85 Men; 73 women
Blair and White, 1985	Case–control	Leukemia cases by cell type in Nebraska (1957–1974), compared with non-leukemia deaths, for association with agricultural practices	1,084	2,168
Pearce et al., 1985	Case–control	Malignant lymphoma, multiple myeloma in men diagnosed 1977–1981 in New Zealand, compared with men with other cancers, for association with agricultural occupations	734	2,936
Balarajan and Acheson, 1984	Case–control	STS (1968–1976) diagnosed in men in England and Wales, compared with men with other cancers, for association with farming, agriculture, forestry occupations	1,961	1,961
Donna et al., 1984	Case–control	Ovarian cancer in women (1974–1980), compared with women without ovarian cancer, for association with herbicide use	60	127
Hardell et al., 1984	Case–control	Primary liver cancer diagnosed 1974–1981 in men (25–80) , residing in northern Sweden, compared with population-based control subjects, for association with occupational exposure to phenoxyacetic acid and chlorophenols	98	200
Smith et al., 1984	Case–control	STS in New Zealand residents (1976–1980), compared with subjects without cancer, for association with occupational exposures, including phenoxy herbicides	82	92
Burmeister et al., 1983	Case–control	Multiple myeloma, NHL, prostate, stomach cancer mortality (1964–1978) in white men 30 years or older, compared with mortality from other causes, for association with farming practices, including herbicide use, in Iowa	550 Multiple myeloma 1,101 NHL; 4,827 prostate; 1,812 stomach	1,100; 2,202; 9,654; 3,624
Hardell and Bengtsson, 1983	Case–control	HD diagnosed (1974–1978) in men (25–85) in northern Sweden, compared with population-based sample without cancer, for association with occupational exposure to phenoxyacetic acid and chlorophenols	60	335
Smith et al., 1983	Case–control	Preliminary report, men with STS reported 1976–1980 in New Zealand, compared with control subjects with other cancers, for association with phenoxyacetic acid exposure	80	92

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Burmeister et al., 1982	Case–control	Leukemia deaths (1964–1978) in white men 30 years or older in Iowa, compared with nonleukemia deaths, for association with farming	1,675	3,350
Cantor, 1982	Case–control	NHL in Wisconsin males (1968–1976), compared with men dying from other causes, for association with farming	774	1,651
Hardell et al., 1982	Case–control	Nasal, nasopharyngeal cancers diagnosed 1970–1979 in men (25–85) residing in northern Sweden, compared with controls selected from previous studies (Hardell and Sandstrom, 1979; Hardell et al., 1981), for association with occupational exposure to phenoxyacetic acid and chlorophenols	44 nasal; 27 nasopharyngeal	541
Carmelli et al., 1981	Case–control	Cases of spontaneous abortion (1978–1980), compared with live births, for association with paternal exposure to 2,4-D	134	311
Eriksson et al., 1979, 1981	Case–control	Cases of STS diagnosed 1974–1978 in southern Sweden, compared with population-based sample without cancer, for association with occupational exposure to phenoxyacetic acid and chlorophenols	110	219
Hardell, 1981	Case–control	(1) Cases of STS (Hardell and Sandstrom, 1979) and malignant lymphomas (Hardell et al., 1981), compared with colon cancer cases, and (2) Colon-cancer cases compared to population-based controls for association with occupational exposure to phenoxyacetic acids and chlorophenols	(1) 221 (2) 154	154 541
Hardell et al., 1980 Hardell et al., 1981	Case–control	Cases of malignant lymphomas (HD, NHL, unknown) diagnosed (1974–1978) in men (25–85) in northern Sweden, compared with population-based controls, for association with occupational exposure to phenoxyacetic acid and chlorophenols	60 HD 109 NHL	338
Blair and Thomas, 1979	Case–control	Cases in Nebraska (1957–1974), compared with deaths from other causes, for association with agricultural practices	1,084	2,168
Hardell and Sandstrom, 1979	Case–control	Cases of STS (26–80 years) diagnosed (1970–1977) in northern Sweden, compared with population-based controls, for association with occupational exposure to phenoxyacetic acid and chlorophenols	52	206

[a]The dash (—), Comparison group based on a population (e.g., US white males, country rates); details are given in the text for population specifics.

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CLL, Chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; FRG, Federal Republic of Germany; HD, Hodgkin's

disease; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, methyl-4 chlorophenoxyacetic acid; NIOSH, National Institute for Occupational Safety and Health; NHL, non-Hodgkin's lymphoma; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofurons; PD, Parkinson's disease; PCP, pentachlorophenol; PCT, porphyria cutanea tarda; PMR, proportionate mortality ratio; SEER, Surveillance, Epidemiology, and End Results program of National Cancer Institute; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; STS, soft-tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, 2,4,5-trichlorophenol; TSH, thyroid-stimulating hormone; T3, triiodothryonine; T4, thyroxine; USDA, US Department of Agriculture; Update *2000,* Veterans and Agent Orange: *Update 2006, Veterans and Agent Orange: Update 2006 (*IOM, 2007); *Update 2004, Veterans and Agent Orange: Update 2004 (*IOM, 2005); *Update 2002, Veterans and Agent Orange: Update 2002 (*IOM, 2003); *Update 2000* (IOM, 2001); *Update 1998, Veterans and Agent Orange: Update 1998* (IOM, 1999); *Update 1996, Veterans and Agent Orange: Update 1996* (IOM, 1996); and *VAO, Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (IOM, 1994).

Contents of TABLE C-2 Epidemiologic Studies—Environmental Exposure

TABLE C-2 Epidemiologic Studies—Environmental Exposure

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Seveso Studies Reviewed in *Update 2006*				
Baccarelli et al., 2005	Population based	Investigate health status of chloracne cases, TCDD-chloracne exposure relationship, and factors modifying TCDD toxicity	101 chlorance cases	211 control
Eskenazi et al., 2005	Population based	Seveso Women's Health Study examining the relationship of TCDD (serum dioxin) and age at menopause	616	None
Landi et al., 2005	Population based	Effects of CYP1A1, CYP1B1 variant genotypes and haplotypes on mRNA expression and EROD activity in lymphocytes.	62	59
Warner et al., 2004	Population based	Examined the age of menarche in SWHS women who were premenarcheal at the time of the explosion	282	
Seveso Studies Reviewed in *Update 2004*				
Baccarelli et al., 2004	Population based	mRNA concentrations, AhR, ARNT, CYP1A1, CYP1B1 genes, and EROD activity in peripheral blood lymphocytes in a Seveso, Italy cohort	62	59
Eskenazi et al., 2004	Cohort	Relationship between serum TCDD concentration and age at exposure in SWHS participatants	899	None
Eskenazi et al., 2003a	Cohort	Association between maternal serum TCDD and birth outcome SWHS participants	888	None
Landi et al., 2003	Population based	Effect of TCDD-mediated alterations in AhR-dependent pathway in Seveso zone A and B residents	62	59
Baccarelli et al., 2002	Population based	Immunologic effects in Seveso residents, compared with previous published results	62	59
Eskenazi et al., 2002a	Cohort	Association between menstrual cycle characteristics and serum TCDD in SWHS participatants	381	None
Eskenazi et al., 2002b	Cohort	Association between endometriosis and serum TCDD concentration in SWHS participants	601	None

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Seveso Studies Reviewed in *Update 2002*				
Warner et al., 2002	Cohort	Association between individual serum TCDD and breast cancer risk in SWHS participants	15	981
Seveso Studies Reviewed in *Update 2000*				
Bertazzi et al., 2001	Cohort	Mortality (through 1996) of residents in 3 exposure zones	804, Zone A; 5,941, Zone B; 38,624, Zone R	232,745
Pesatori et al., 1998	Cohort	Mortality (through 1991) of residents in 3 exposure zones	805, Zone A; 5,943, Zone B; 38,625, Zone R	232,747
Seveso Studies Reviewed in *Update 1998*				
Bertazzi et al., 1997, 1998	Cohort	Cancer incidence among residents of contaminated zones (A, B, R) after 15 years of follow-up, through 1991	45,373 Total: 805, Zone A; 5,943, Zone B; 38,625, Zone R	232,747
Mocarelli et al., 1996	Cohort	Sex ratio among offspring of Seveso Zone A residents (1) 1977–1984, (2) 1985–1994	(1) 74 births (28 male, 48 female) (2) 124 births (60 male, 48 female)	—
Seveso Studies Reviewed in *Update 1996*				
Bertazzi et al., 1993	Cohort	Cancer incidence in residents (20–74 years) of contaminated zones (A, B, R) exposed to TCDD on July 10, 1976, compared with neighboring residents in nonexposed areas	724, Zone A; 4,824, Zone B; 31,647, Zone R	181,579
Pesatori et al., 1993	Cohort	Cancer incidence in Seveso residents (1–19) in first postaccident decade, compared with age-matched residents of neighboring non-exposed areas	~20,000	167,391
Seveso Studies Reviewed in *VAO*				
Bertazzi et al., 1992	Cohort	Mortality for exposed children (1976–1986), compared with children in non-exposed areas	306, Zone A; 2,727, Zone B; 16,604, Zone R	95,339
Pesatori et al., 1992	Cohort	Cancer incidence (1976–1986) in zone A, B, R, compared with non-exposed areas	Data in person-years	Data in person-years
Assennato et al., 1989a	Cohort	Dermatologic, laboratory results in children during periodic exams	193 Chloracne	123
Assennato et al., 1989b	Cohort	Health outcomes in workers assigned to cleanup or referent group after Seveso accident	36	36
Bertazzi et al., 1989a,b	Cohort	Mortality experience (1976–1986) in Zone A, B, R residents, compared with non-exposed residents in neighboring towns	556, Zone A; 3,920, Zone B; 26,227, Zone R	167,391

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Barbieri et al., 1988	Cohort	Prevalence of peripheral nervous system involvement among Seveso residents with chloracne, compared with residents of non-exposed areas	152	123
Mastroiacovo et al., 1988	Cohort	Birth defects to Zone A, B, R mothers with live and stillbirths, compared with mothers from non-exposed areas	26, Zone A 435, Zone B 2,439, Zone R	12,391
Mocarelli et al., 1986	Cross sectional	Laboratory measures of serum and urine in Seveso Zone A and B children measured over 6 years (1977–1982), compared with Zone R children	69, Zone A; 528, Zone B; 874, Zone R	241, Subset of zone R
Ideo et al., 1985	Cross sectional	Enzyme activity among residents of Seveso Zone B and an uncontaminated community	117 Adults	127 Adults
Tenchini et al., 1983	Cross sectional	Cytogenetic analysis, maternal and fetal tissue among Seveso exposed, compared with control sample	19	16
Ideo et al., 1982	Cross sectional	Hepatic enzymes in exposed children, compared with normal	16, Zone A ; 51, Zone B	60 Bristo Assizio 26 Cannero
Caramaschi et al., 1981	Cohort	Chloracne among Seveso children, compared with children with no chloracne, association with other health outcomes between chloracne and no chloracne groups	146	182
Filippini et al., 1981	Cohort	Prevalence of peripheral neuropathy on 2 screening examinations in Seveso residents, compared with residents of non-exposed areas	308	305
Bisanti et al., 1980	Descriptive	Selected health outcomes in residents of Zone A, B, R	730, Zone A; 4,737, Zone B; 31,800, Zone R	None
Boeri et al., 1978	Cohort	Neurologic disorders in exposed residents on July 10, 1976, compared with residents of non-exposed areas	470, Zone A	152, Zone R
Times Beach/Quail Run Studies Reviewed in *VAO*				
Evans et al., 1988	Cross sectional	Retesting for skin delayed-type hypersensitivity among non-responders in earlier test (Stehr et al., 1986)	28	15
Stockbauer et al., 1988	Cohort	Adverse reproductive outcomes (1972–1982) among mothers potentially exposed to TCDD-contaminated areas of Missouri (1971) compared with births among non-exposed mothers	402 births	804 births
Hoffman et al., 1986; Stehr-Green et al., 1987	Cohort	Health effects (1971–1984) in Quail Run Mobile Home Park residents compared with residents of noncontaminated mobile home parks	154	155

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Webb et al., 1987	Cross sectional	Pilot, Missouri residents exposed to TCDD in the environment (1971) for health effects, comparing potentially high-exposed to low-exposed residents	68 High-exposed	36 Low-exposed
Stehr et al., 1986	Cross sectional	Pilot, Missouri residents exposed to TCDD in the environment (1971) for health effects, comparing potentially high-exposed to low-exposed residents	68 High-exposed	36 Low-exposed
Studies in Vietnamese Reviewed in *Update 1996*				
Cordier et al., 1993	Case control	Hepatocellular carcinoma (1989–1992) in males living in Vietnam, compared with other hospitalized patients, for association with a range of exposures, including herbicides	152	241
Studies in Vietnamese Reviewed in *VAO*				
Dai et al., 1990	Cohort	Infant mortality (1966–1986) in 2 South Vietnam villages exposed to Agent Orange spraying, compared with infant mortality in an unsprayed area	5,609	3,306
Phuong et al., 1989a	Case control	Birth defects, hydatidiform mole, compared with normal births (1982) in Ho Chi Minh City, for association with maternal exposure to Agent Orange and TCDD	15 Birth defects; 50 hydatidiform moles	104 134
Phuong et al., 1989b	Cohort	Reproductive anomalies among births to women (May 1982–June 1982) living in heavily sprayed areas with herbicides in southern Vietnam, compared with births among women from Ho Chi Minh City	7,327 Births	6,690 Births
Constable and Hatch, 1985	Review	Summaries, reproductive outcomes among Vietnamese populations, including 9 unpublished studies		
Other Environmental Studies Reviewed in *Update 2006*				
Chen et al., 2006		Investigated the prevalence of hypertension in Taiwanese residents near municipal waste incinerators for a least 5 years		
Lee C-C et al., 2006	Cohort	From prior survey identified residence near Taiwan PCP factory to examine associations fatty liver and hepatic function and PCDD/Fs in serum	85 subjects (52 from exposure)	33
De Roos et al., 2005a		Studied associations for TEQs overall from PCBs, furans, and dioxins were NHL cases serum levels had been determined	100	100
Hartge et al., 2005	Population based case-control	Identified cases of NHL from four SEER registries (Iowa, Los Angeles County, Detroit, Seattle) during 1998-2000	1,321	1,057

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
McDuffie et al., 2005	Case-control	NHL in males in Canada exposed to phenoxy herbicides	513	1,056
Mills and Yang 2005	Nested case-control	Breast cancer in Californian farm labor union members	128	640
Mills et al., 2005	Nested case-control	Lymphohematopoietic cancer (NHL leukemia) in Californian Hispanic farm workers	131	139,000
Pahwa et al., 2006	Case-control	HD, multiple myeloma, STS diagnosed 1991-1994 in men ≥19 years of age living in six Canadian provinces, exposed to phenoxy herbicides and other pesticides	316 HD cases 342 multiple myeloma cases 357 STS cases	1,056
Vermeir et al., 2005	Cross-sectional	Flemish Environmental and Health Study on neuro-behavior and dioxin-like compounds		
Wang et al., 2005	Cross-sectional	Thyroid function in newborns with exposure to PCBs	118	
Other Environmental Studies Reviewed in *Update 2004*				
Fierens et al., 2003	Population-based, cross-sectional	Association between serum dioxin, prevalence of diabetes, endometriosis in several Belgian towns	194	63
Fukuda et al., 2003	Ecologic cohort	Correlation between incinerator dioxin emissions and mortality in 803 Japanese municipalities	426 Municipalities with plants	164 Municipalities without plants
Other Environmental Studies Reviewed in *Update 2002*				
Revazova et al., 2001	Cohort	Cytogenetic effects in women exposed to different amounts of dioxin while living in Chapaevsk, Russia	15 Possibly exposed workers;	30 Non-exposed but living close to plant
Revich et al., 2001	Cohort	Dioxin exposures in Chapaevsk, Russia, and various health outcomes in children and adults	Children and adults in Chapaevsk, Russia	Samara region and all of Russia
Other Environmental Studies Reviewed in *Update 2000*				
Schreinemachers 2000	Cross sectional	Cancer mortality rates in 4 northern wheat-producing states using wheat acreage per county as surrogate for exposure.	—	—
Other Environmental Studies Reviewed in *Update 1998*				
Gallagher et al., 1996	Case control	Community-based study of primary BCC and primary SCC in Alberta, Canada	226 BCC; 180 SCC	406
Lovik et al., 1996	Cohort	Immune system parameters in hobby fishermen in the Frierfjord, southeastern Norway	24	10

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Masala et al., 1996	Case–control	Multicenter study, NHL, HD, multiple myeloma, AML by region in Italy	421 HD; 1,822 NHL; 325 multiple myeloma; 263 AML	Internal comparison by region
Waterhouse et al., 1996	PMR analysis, nested case–control	NHL, HD, CLL in rural Michigan	42 Males; 32 females	4 Controls per case
Svensson et al., 1995	Cohort	Mortality and cancer incidence experience in 2 cohorts of Swedish fishermen	2,896 East coast	8,477 West coast
Weisglas-Kuperus et al., 1995	Cohort	Immunologic effects of pre- and postnatal PCB or TCDD exposure in 207 Dutch infants from birth to 18 months	105 Breast-fed	102 Bottle-fed
Wolf and Karmaus, 1995	Cross sectional	Effects of inhalation exposure to TCDD and related compounds in wood preservatives on cell-mediated immunity in German day care center employees	221	189
Other Environmental Studies Reviewed in *Update 1996*				
Butterfield et al., 1993	Case control	Possible environmental risk factors associated with young-onset PD	63	68
Peper et al., 1993	Descriptive	Environmental exposure in Germany to dioxins and furans, potential association with adverse neuropsychological effects	19	None
Other Environmental Studies Reviewed in *VAO*				
Lampi et al., 1992	Nested case-control/ Cohort	Cancer incidence in Finland community residents exposed to chlorophenol-contaminated water and food (1987), compared with residents of other communities; several cancers, compared with population controls, for association with potential risk factors, including food and water consumption	56 Colon cancer; 40 bladder cancer; 8 STS; 7 HD; 23 NHL; 43 leukemia	688
Vineis et al., 1991	Ecological	Presentation rates (1985–1988) NHL, HD, STS in men and women (15–74) living in provinces in Italy where phenoxy herbicides are used in rice weeding and defined in 2 categories	63 HD; 253 NHL; 49 STS	No non-exposed control
Fitzgerald et al., 1989	Cohort	Health outcomes in group exposed to electrical transformer fire (1981), compared with standardized rates among upstate New York residents	377	—
Jansson and Voog, 1989	Cohort, Case study	Case study of facial cleft (April–August 1987), facial cleft (1975–1987), compared with expected rates in Swedish county with incinerators	20,595 Births after incineration 6 case study	71,665 Births before incineration

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Cartwright et al., 1988	Case–control	Living NHL cases (1979–1984) in Yorkshire, England, compared with other hospitalized patients, for association with a range of exposures including fertilizers, herbicides	437	724
Michigan Department of Public Health, 1983	Descriptive	Comparison of Michigan county rates, for STS and connective tissue cancer mortality (1960–1981), compared with state and national rates, for potential excess in areas where dioxin could be in the environment	County rates	State and national rates
Gordon and Shy, 1981	Case–control	Agricultural chemical exposures and potential association with cleft palate–lip in Iowa and Michigan, compared with other live births	187	985
Hanify et al., 1981	Ecological design	Study of adverse birth outcomes (1960–1966), compared for association with 2,4,5-T spraying (1972–1977)	9,614 Births	15,000 Births
Nelson et al., 1979	Ecological design	Prevalence of oval cleft palate in high, medium, and low 2,4,5-T-sprayed areas in Arkansas (1948–1974)	—	—
US EPA, 1979	Ecological design	Spontaneous abortion (1972–1977) in herbicide-sprayed areas around Alsea, Oregon compared with spontaneous abortion in nonsprayed areas	2,344 Births	1,666 Births, nonsprayed area; 4,120 Births, urban area

[a]The dash (---) indicates the comparison group is based on a population (e.g., US white males, country rates), with details given in the text for specifics of the actual population.

ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AhR, arylhydrocarbon receptor; AML, acute myelogenous leukemia; ARNT, arylhydrocarbon receptor nuclear transporter; BCC, basal cell carcinoma; CYP1A1, cytochrome p450 1A1; CYP1B1, cytochrome P450 1B1; EROD, 7-ethoxyresorufun-*O*-deethylase; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; PCB, polychlorinated biphenyls; PD, Parkinson's disease; SCC, squamous cell carcinoma; SWHS, Seveso Women's Health Study; STS, soft-tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; *Update 2006, Veterans and Agent Orange: Update 2006 (*IOM, 2007); *Update 2004, Veterans and Agent Orange: Update 2004 (*IOM, 2005); *Update 2002, Veterans and Agent Orange: Update 2002 (*IOM, 2003); *Update 2000, Veterans and Agent Orange: Update 2000 (*IOM, 2001); *Update 1998, Veterans and Agent Orange: Update 1998 (*IOM, 1999); *Update 1996, Veterans and Agent Orange: Update 1996* (IOM, 1996); US EPA, United States Environmental Protection Agency; and *VAO, Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (IOM, 1994).

Contents of TABLE C-3 Epidemiologic Studies—Vietnam Veterans Exposed

TABLE C-3 Epidemiologic Studies—Vietnam Veterans Exposed

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
STUDIES OF AMERICAN VIETNAM VETERANS				
Reports from the Air Force Health Study (AFHS) on Ranch Hand Veterans Reviewed in *Update 2006*				
Pavuk, 2006	Cohort	Focus on prostate cancer using information on serum TCDD and years of service in Southeast Asia (SEA)	59	81
AFHS, 2005		Air Force Health Study – 2002 exam cycle Ranch Hand veterans		
Ketchum and Michalek 2005	Cohort	Ranch Hand mortality analysis summarizing current all-cause and cause-specific post-service mortality rates for veterans sprayed between 1962 to 1971	1,262 Ranch Hand Veterans	19,078 comparison Veterans
Pavuk et al., 2005	Cohort	Examine cancer incidence in Air Force veterans who served in Southeast Asia and who were not occupationally exposed to herbicides	1482	No comparison group
Kern et al., 2004	Cohort	Observe whether insulin sensitivity was related to TCDD in Vietnam veterans exposed to Agent Orange and other herbicides in Vietnam from 1962 to 1971	?	?
Reports from AFHS Reviewed in *Updated 2004*				
Akhtar et al., 2004	Cohort	Follow-up to Ketchum et al. (1999), comparing cancer incidence among Ranch Hands with Vietnam veterans who served in Southeast Asia but did not spray herbicides and with US national cancer rates	1,189 Net Ranch Hands for external analysis; 1,009 net Ranch Hands for internal analysis	1,776 Net comparison subjects for external analysis; 1,429 net comparison subjects for internal analysis
Barrett et al., 2003	Cohort	Serum TCDD measurement and psychological functioning among Ranch Hand veterans	1,109	1,493

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Michalek et al., 2003	Cohort	Correlation for TCDD elimination and Ranch Hands with diabetes	343	No comparison group
Pavuk et al., 2003	Cohort	Study to examine the relationship between serum TCDD and thyroid function in Ranch Hand veterans	1,009	1,429
Barrett et al., 2001	Cohort	Based on tests of cognitive functioning in 1982 and dioxin concentrations measured in 1987 and 1992, analyzed association between serum dioxin levels and cognitive functioning	937 Ranch Hand	1,052 Ranch Hand comparisons
Michalek et al., 2001a	Cohort	Based on physical examination through 1992 and medical records reviewed through March 1993, association between serum dioxin levels and hepatic abnormality	1109 Ranch Hand	1493 Ranch Hand comparisons
Michalek et al., 2001b	Cohort	Based on physical examination in 1982, 1985, 1987, 1992, and 1997 and medical records through 1997, association between serum dioxin and peripheral neuropathy	761 Ranch Hand	1,086 Ranch Hand comparisons
Michalek et al., 2001c	Cohort	Based on physical examination in 1982, 1985, 1987, and 1992 and medical records through 1997, association between serum dioxin and hematologic function	953 Ranch Hand	1,280 Ranch Hand comparisons
Steenland et al., 2001	Cohort	Reexamine and compare diabetes data from the NIOSH cohort and the United States Air Force Ranch in order to reconcile differences between the two study methods and protocols.	267 NIOSH workers; 990 Ranch Hands	227 NIOSH comparisons 1,275 Ranch Hand comparisons
Reports from AFHS Reviewed in *Updated 2000*				
AFHS, 2000	Cohort	266 Health-related endpoints, including assessments of 10 clinical areas: general health, neoplasia, neurologic, psychological, gastrointestinal, cardiovascular, hematologic, endocrine, immunologic, pulmonary	995	1,299
Longnecker and Michalek, 2000	Cohort	Based on physical examination and medical records review through 1992, association between serum dioxin and diabetes mellitus among comparison group (no Ranch Hands)	—	1,197
Ketchum et al., 1999	Cohort	Based on physical examination and medical records review through 1992, association between serum dioxin and cancer, skin cancer, cancer other than skin cancer	980 Ranch Hand	1,275 Ranch Hand comparisons
Michalek et al., 1999a	Cohort	Further elucidate relationship between dioxin and diabetes mellitus, effect of dioxin body burden on sex-hormone-binding globulin and insulin and fasting glucose	871 Ranch Hand	1,121 Ranch Hand comparisons

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Michalek et al., 1999b	Cohort	Based on physical examinations in 1982, 1985, 1987, and 1992, immunologic response and exposure to dioxin among Ranch Hand and comparison cohorts	914 Ranch Hand 372 (lymphocyte counts conducted)	1,186 Ranch Hand comparisons 491 (lymphocyte counts conducted)
Burton et al., 1998	Cohort	Based on physical examination and medical record review through 1992, association between serum dioxin and occurrence and timing (relative to Southeast Asia service) of chloracne and acne	930 Ranch Hand	1,200 Ranch Hand comparisons
Michalek et al., 1998b	Cohort	Updates, all-cause and cause-specific post-service mortality (through 1993) among veterans of Operation Ranch Hand, using standardized mortality ratios	1,261 Ranch Hand	19,080 Ranch Hand comparisons
Michalek et al., 1998c	Cohort	Prospective study, exposure and long-term health, survival, reproductive outcome	1,208 Veterans; 903 offspring	1,549 Veterans; 1,254 offspring
Michalek et al., 1998d	Cohort	Third report in a series investigating dioxin body burden and preterm birth, intrauterine growth retardation, infant death among offspring of Ranch Hand veterans	859	1,223
Reports from AFHS Reviewed in *Updated 1998*				
Michalek et al., 1998a	Cohort	Paternal serum dioxin levels and infant death among Ranch Hand offspring	859 Children: 323 background exposure; 267 low exposure; 269 high exposure	1,223 Children
Henriksen et al., 1997	Cohort	Relationship between serum dioxin and glucose, insulin, and diabetes mellitus in Ranch Hands through 1992	989	1,276
AFHS, 1996 Michalek et al., 1998b	Cohort	Mortality update, Ranch Hands through the end of 1993 in the AFHS cohort (1983, 1984b, 1985, 1986, 1989, 1991a, 1995)	1,261	19,080
Henriksen et al., 1996	Cohort	Serum dioxin and reproductive hormones in Ranch Hands, 1982, 1985, 1987, and 1992	1,045 Participants (1982); 474 provided semen	1,224 Participants (1982); 532 provided semen
Reports from AFHS Reviewed in *Update 1996*				
AFHS, 1995	Cohort	Mortality updates of Ranch Hands who sprayed herbicides in Vietnam , compared with Air Force C-130 air and ground crew veterans in Southeast Asia who did not spray herbicides	1,261, Original cohort	19,101, Original cohort

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Wolfe et al., 1995	Cohort	Paternal serum dioxin and reproductive outcomes of Ranch Hand veterans, compared with Air Force veterans from Southeast Asia who did not spray herbicides	932	1,202
Reports from AFHS Reviewed in *VAO*				
AFHS, 1992	Cohort	Reproductive outcomes of AFHS participants	791	942
AFHS, 1984a, 1987, 1990, 1991b	Cohort	Baseline morbidity, follow-up examination results	1,208 Baseline	1,668 Baseline
AFHS, 1983, 1984b, 1985, 1986, 1989, 1991a	Cohort	Mortality updates, Ranch Hands who sprayed herbicides in Vietnam, compared with Air Force C-130 air and ground crew veterans in Southeast Asia who did not spray herbicides	1,261 (original cohort)	19,101 (original cohort)
Michalek et al., 1990	Cohort	Mortality of Ranch Hands, compared with Air Force C-130 air and ground crew veterans in Southeast Asia	1,261	19,101
Wolfe et al., 1990	Cohort	Health status of Ranch Hands at second follow-up, compared with Air Force C-130 air and ground crew veterans in Southeast Asia	995	1,299
CDC Studies Reviewed in Updated 2006				
Boehmer et al., 2004	Cohort	Vietnam Experience Study − post service mortality	18,313	
CDC Studies Reviewed in VAO				
Decoufle et al., 1992	Cohort	Association between self-reported health outcomes and perception of exposure to herbicides based on Vietnam Experience Study	7,924	7,364
O'Brien et al., 1991	Cohort	Interview report and mortality for NHL based on Vietnam Experience Study	8,170	7,564
CDC, 1990a	Case–control	Selected Cancers Study: population-based case–control study of all men born 1921–1953; cases diagnosed area covered by 8 cancer registries, controls selected by random-digit dialing	1,157 NHL; 342 STS; 310 HD; 48 nasal carcinoma; 80 nasopharyngeal carcinoma; 130 primary liver cancer	1,776
CDC, 1990b	Case-control	Selected Cancers Study: population-based case–control study of all men born 1921–1953; cases diagnosed in area covered by 8 cancer registries, controls selected by random-digit dialing for NHL	1,157	1,776
CDC, 1990c	Case-control	Selected Cancers Study: STS	342	1,776

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
CDC, 1990d	Case-control	Selected Cancers Study: HD, nasal cancer, nasopharyngeal cancer, primary liver cancer	310 HD; 48 nasal carcinoma; 80 nasopharyngeal carcinoma; 130 primary liver cancer	1,776
CDC, 1989b	Cohort	Vietnam Experience Study: random sample, US Army enlisted men, 1965–1971	2,490	1,972
CDC, 1988a	Cohort	Vietnam Experience Study: random sample, US Army enlisted men, 1965–1971, psychosocial outcomes	2,490	1,972
CDC, 1988b	Cohort	Vietnam Experience Study: physical health outcomes	2,490	1,972
CDC, 1988c	Cohort	Vietnam Experience Study: reproductive outcomes	12,788 Children	11,910 Children
CDC, 1987; Boyle et al., 1987	Cohort	Vietnam Experience Study: mortality	9,324	8,989
Erickson et al., 1984 a,b	Case–control	CDC birth defects study, children born in the Atlanta, Georgia, area 1968–1980, comparing paternal Vietnam experience and potential Agent Orange exposure for birth defects cases and normal controls	7,133	4,246
Department of Veterans Affairs Studies Reviewed in *Update 2006*				
Kang et al. 2006	Cohort	Army Chemical Corp; serum TCDD, Vietnam veterans {sprayers vs. not sprayers} vs. not Vietnam vet	1,499	1,428
Department of Veterans Affairs Studies Reviewed in *Update 2002*				
Kang et al., 2001	Cohort	Health of Army Chemical Corps Vietnam veterans, compared with Army Chemical Corps veterans who did not serve in Vietnam	2,872	2,737
Kang et al., 2000a	Cohort	Self-report pregnancy outcomes for female Vietnam veterans, compared with contemporary veterans not deployed to Vietnam; odds ratios calculated for reproductive history and various birth defects	3,392 Women; 1,665 women with indexed pregnancy	3,038 Women; 1,912 women with indexed pregnancy
Kang et al., 2000b	Cohort	Gynecologic cancers among female Vietnam veterans, compared with veteran controls	484	5,946
Department of Veterans Affairs Studies Reviewed in *Update 1998*				
Dalager and Kang, 1997	Cohort	Morbidity and mortality experience (1968–1987), Army Chemical Corps Vietnam veterans, compared with US men; extension of Thomas and Kang (1990)	2,872	2,737
Mahan et al., 1997	Case–control	Lung cancer among Vietnam veterans (1983–1990)	329	269 111

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
McKinney et al., 1997	Cross–sectional	Tobacco use in veterans and non-veterans by 1987 NMES	15,000	—
Bullman and Kang, 1996	Cohort	Mortality of veterans with non-lethal (combat and noncombat) wounds sustained during the Vietnam war	34,534	—
Watanabe and Kang, 1996	Cohort	Mortality experience (1965–1988) of Army and Marine Corps Vietnam veterans; extension of Breslin et al. (1988) and Watanabe et al. (1991)	33,833	36,797
Dalager et al., 1995b	Case–control	HD Cases diagnosed 1969–1985 among Vietnam-era veterans	283	404
Watanabe and Kang, 1995	Cohort	Postservice mortality among Marine Vietnam veterans	10,716	9,346
Department of Veterans Affairs Studies Reviewed in *Update 1996*				
Dalager et al., 1995a	Cohort	Update of Thomas et al. (1991) through Dec. 31, 1995	4,586	5,325
Bullman et al., 1994	Case–control	Association between testicular cancer and surrogate measures of exposure to Agent Orange in male Vietnam veterans	97	311
Department of Veterans Affairs Studies Reviewed in *VAO*				
Bullman et al., 1991	Case–control	PTSD cases in Vietnam veterans, compared with Vietnam veterans without PTSD, for association with traumatic combat experience	374	373
Dalager et al., 1991	Case–control	NHL cases diagnosed 1969–1985 among Vietnam era veterans, compared with cases of other malignancies among Vietnam-era veterans, for association with Vietnam service	201	358
Eisen et al., 1991	Cohort	Health effects in male monozygotic twins serving in the armed forces during Vietnam era (1965–1975)	2,260	2,260
Thomas et al., 1991	Cohort	Mortality experience (1973–1987) among female Vietnam veterans, compared with female non-Vietnam veterans and for each cohort compared with US women	4,582	5,324
Watanabe et al., 1991	Cohort	Mortality experience (1965–1984) in Army and Marine Corps Vietnam veterans, compared with: (1) branch-specific (Army and Marine) Vietnam-era veterans, (2) all Vietnam-era veterans combined, (3) the US male population	24,145 Army 5,501 Marines	(1) 27,145 Army 4,505 Marines (2) 32,422 combined Vietnam era (3) US male population
Bullman et al., 1990	Cohort	Mortality experience in Army I Corps Vietnam veterans, compared with Army Vietnam-era veterans	6,668 Deaths	27,917 Deaths

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Farberow et al., 1990	Case-control	Psychological profiles, military factors associated with suicide and MVA fatalities in Los Angeles County Vietnam-era veterans (1977–1982)	22 Vietnam suicides; 19 Vietnam-era suicides	21 Vietnam MVA; 20 Vietnam-era MVA
Thomas and Kang, 1990	Cohort	Morbidity and mortality experience (1968–1987) in Army Chemical Corps Vietnam veterans compared with U.S. men	894	—
True et al., 1988	Cross-sectional	PTSD and Vietnam combat experience among Vietnam-era veterans	775	1,012
Breslin et al., 1988 Burt et al., 1987	Cohort	Mortality experience (1965–1982) in Army and Marine Corps Vietnam veterans, compared with Vietnam-era veterans who did not serve in Southeast Asia, standardized by age and race; nested NHL case–control study	24,235	26,685
Kang et al., 1987	Case–control	STS cases (1975–1980) diagnosed at the Armed Forces Institute of Pathology, compared with controls identified from patient logs of referring pathologists or their departments, for association with Vietnam service and likelihood of Agent Orange exposure	217	599
Kang et al., 1986	Case–control	STS (1969–1983) in Vietnam-era veterans, for association with branch of Vietnam service as a surrogate for Agent Orange exposure	234	13,496
American Legion Studies Reviewed in *VAO*				
Snow et al., 1988	Cohort	PTSD in association with traumatic combat experience among American Legion members serving in Southeast Asia (1961–1975)	2,858	Study group subdivided for internal comparison
Stellman et al., 1988b	Cohort	Physical health, reproductive outcomes among American Legion members who served in Southeast Asia (1961–1975), for association with combat and herbicide exposure	2,858	3,933
Stellman et al., 1988c	Cohort	Social, behavioral outcomes among American Legion members who served in Southeast Asia (1961–1975), association with combat and herbicide exposure	2,858	3,933
State Studies Reviewed in *Update 2006*				
Engel et al., 2005	Cohort	AHS examine phenoxy herbicides and breast cancer incidence among farmer wives in Iowa and North Carolina	?	?
Kirrane et al., 2005	Cross-sectional	AHS in Iowa and North Carolina; phenoxy herbicide exposure and retinal degeneration in wives of farmers	31,173	

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Lee et al., 2004	Population based /case-control	Continues Ward et al., 1997 study on diet. Evaluate risk of the stomach and oesophageal adenocarcinomas associated with farming and agricultural pesticide use in eastern Nebraska	170 (adenocarcinoma of stomach) 137 (oesophagus)	502
State Studies Reviewed in *Update 1998*				
Clapp, 1997	Case-control	Selected cancers identified (1988–1993) among Massachusetts Vietnam veterans, compared with Massachusetts Vietnam-era veterans with cancers of other sites; update of Clapp et al., 1991	245	999
State Studies Reviewed in *Update 1996*				
Visintainer et al., 1995	Cohort	Mortality experience (1965–1971) in male Michigan Vietnam veterans, compared with non-Vietnam veterans from Michigan	3,364 Deaths	5,229 Deaths
State Studies Reviewed in *VAO*				
Fiedler and Gochfeld, 1992 Kahn et al., 1992a,b,c	Cohort	New Jersey: outcomes in select group of herbicide-exposed Army, Marine, and Navy Vietnam veterans, compared with veterans self-reported as unexposed	10 Pointman I 55 Pointman II	17 Pointman I 15 Pointman II
Clapp et al., 1991	Case–control	Massachusetts: selected cancers identified (1982–1988) among Vietnam veterans, compared with Massachusetts Vietnam-era veterans with cancers of other sites	214	727
Deprez et al., 1991	Descriptive	Maine: Vietnam veterans, compared with atomic test veterans and general population, for health status and reproductive outcomes	249	113 Atomic test veterans
Levy, 1988	Cross-sectional	Massachusetts: PTSD in chloracne as indicator of exposure to TCDD; control Vietnam veterans	6	25
Anderson et al., 1986a	Cohort	Wisconsin: mortality experience, veterans compared with non-veterans (Phase 1); mortality experience of Vietnam veterans and Vietnam-era veterans, compared with non-veterans and other veterans (Phase 2) (Superseded by Anderson et al. 1986b)	110,815 White male veteran deaths; 2,494 white male Vietnam-era veteran deaths; 923 white male Vietnam veteran deaths	342,654 White male non-veteran deaths; 109,225 white male other veteran deaths
Anderson et al., 1986b	Cohort	Wisconsin: mortality experience in Vietnam-era veterans and Vietnam veterans, compared with US men, Wisconsin men, Wisconsin non-veterans, and Wisconsin other veterans	122,238 Vietnam-era veterans; 43,398 Vietnam veterans	—
Goun and Kuller, 1986	Case-control	Pennsylvania: STS, NHL, selected rare cancer cases, compared with controls without cancer for Vietnam experience in men (1968–1983)	349	349 Deceased

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Holmes et al., 1986	Cohort	West Virginia: mortality experience (1968–1983) of veterans, Vietnam veterans, Vietnam-era veterans, compared with non-veterans; Vietnam veterans compared with Vietnam-era veterans	615 Vietnam veterans 610 Vietnam era veterans	—
Pollei et al., 1986	Cohort	New Mexico: chest radiographs of Agent Orange Registry Vietnam veterans, compared with radiographs of control Air Force servicemen, for pulmonary and cardiovascular pathology	422	105
Kogan and Clapp, 1985, 1988	Cohort	Massachusetts: mortality experience (1972–1983) among white male Vietnam veterans, compared with non-Vietnam veterans and all other non-veteran white males in Massachusetts	840 Deaths	2,515 Deaths in Vietnam-era veterans
Lawrence et al., 1985	Cohort	New York: mortality experience in (1) Vietnam-era veterans, compared with non-veterans and (2) Vietnam veterans, compared with Vietnam-era veterans	(1) 4,558 (2) 555	17,936 941
Rellahan, 1985	Cohort	Hawaii: health outcomes in Vietnam-era (1962–1972) veterans residing in Hawaii, associated with Vietnam experience	232	186
Wendt, 1985	Descriptive	Iowa: health effects and potential exposure to Agent Orange among veterans who served in Southeast Asia	10,846	None
Greenwald et al., 1984	Case–control	New York: STS cases, compared with controls without cancer for Vietnam service and herbicide exposure including Agent Orange, dioxin, or 2,4,5-T	281	281 Live controls; 130 deceased controls
Newell, 1984	Cross–sectional	Texas: preliminary (1) cytogenetic, (2) sperm, (3) immune response tests in Vietnam veterans, compared with controls	(1) 30; (2) 32; (3) 66	(1) 30; (2) 32; (3) 66
Other Studies American Vietnam Veterans Reviewed in *VAO*				
Tarone et al., 1991	Case–control	Testicular cancer (18–42 years old) cases, January 1976–June 1981, compared with hospital controls, for association with Vietnam service	137	130
Aschengrau and Monson, 1990	Case–control	Cases with late adverse pregnancy outcomes compared with normal control births, for association with paternal Vietnam service (1977–1980)	857 Congenital anomalies 61 stillbirths; 48 neonatal deaths	998
Goldberg et al., 1990	Cohort	Male twin pairs who served in Vietnam era (1965–1975), for association between Vietnam service and PTSD	2,092	2,092

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Aschengrau and Monson, 1989	Case–control	Association between husband's military service and spontaneous abortion at or by 27 weeks, compared with women delivering at 37 weeks	201	1,119
STUDIES OF AUSTRALIAN VIETNAM VETERANS				
Studies of Australian Vietnam Veterans in Reviewed Update *2006*				
ADVA 2005a	Cohort	Cancer incidence from 1982 to 2000 among Australian male Army, Navy, & Air Force veterans who served in Vietnam between May 1962 and July 1973	59,179–total; 41,084 (Army); 13,538 (Navy); 4,570 (Air Force)	
ADVA 2005b	Cohort	Retrospective mortality study of male Australian personnel who served between May 1962 and July 1973 vs. Australian males in general community	59,179	
ADVA 2005c	Cohort	Retrospective cohort study of male National Service personnel who served in the Vietnam era between 1966 and July 1973. Examined all deaths identified from the end of service to 31 December 2001 and all cancers diagnosed from 1982 to 31 December 2000	43,969–Total; 19,240 Veterans; 24,729 Non-Veterans	
Leavy et al. 2006	Case--control	Cancer registry of Western Australia and prostate cancer; deployment to Vietnam	606	471
Studies of Australian Vietnam Veterans Reviewed in *Update 2000*				
AIHW, 1999	Cohort	Validation of the male veterans' study (CDVA, 1998a) by medical documents, doctors' certification, records on a disease or death registry	6,842	—
CDVA, 1998a	Cohort	Self-reported data on male members of the Australian Defence Force and the Citizen Military Force who landed in Vietnam or entered Vietnamese water. Questions on physical (including reproductive history) and mental health, and that of their partner(s) and children	49,944 mailed; 39,955 responded	—
CDVA, 1998b	Cohort	Self-reported data on female members of the Australian Defence Force and the Citizen Military Force who landed in Vietnam or entered Vietnamese water. Questions on physical (including reproductive history) and mental health, and that of their partner(s) and children	278 mailed 225 responded	—
Studies of Australian Vietnam Veterans Reviewed in *Update 1998*				
Crane et al., 1997a	Cohort	Mortality experience (through 1994) of Australian veterans who served in Vietnam	59,036 Males 484 females	—

Reference	Study Design	Description	Study Group (*n*)	Comparison Group (*n*)[a]
Crane et al., 1997b	Cohort	Mortality experience (through 1994) of Australian national servicemen who served in Vietnam	18,949	24,646
O'Toole et al., 1996a,b,c	Cross–sectional	Survey of self-reported health status (1989–1990) of Australian Army Vietnam veterans	641	—
Studies of Australian Vietnam Veterans Reviewed in *VAO*				
Field and Kerr, 1988	Cohort	Tasmanian Vietnam veterans, compared with neighborhood controls for adverse reproductive and childhood health outcomes	357	281
Fett et al., 1987a	Cohort	Mortality experience in Vietnam veterans, compared with Vietnam-era veterans through 1981	19,205	25,677
Fett et al., 1987b	Cohort	Cause-specific mortality experience in Vietnam veterans, compared with Vietnam-era veterans through 1981	19,205	25,677
Forcier et al., 1987	Cohort	Mortality in Vietnam veterans by job classification, location, time of service	19,205	Internal comparison
Donovan et al., 1983, 1984	Case–control	Congenital anomalies in children (1969–1979), compared with infants born without anomalies, for association with paternal Vietnam service	8,517	8,517
STUDIES OF VIETNAM VETERANS FROM OTHER COUNTRIES				
Other Vietnam-Veteran studies Reviewed in *Update 2004*				
Kim H-A et al., 2003	Cohort	Immunotoxicologic effects of Agent Orange exposure on Korean Vietnam veterans	51 (24 Veterans–patient; 27 veterans–normal)	36
Kim J-S et al., 2003	Cross–sectional	Agent Orange exposure and Korean Vietnam veterans	1,224	154
Mo et al., 2002	Cohort	Skin and general disease patterns among Korean Vietnam veterans	332	None
Other Vietnam-Veteran studies Reviewed in *Update 1998*				
Chinh et al., 1996	Cohort	Antinuclear antibodies and sperm autoantibodies among Vietnamese veterans who served 5–10 years in a "dioxin-sprayed zone"	25	63; 36

[a] — Comparison group based on a population (e.g., US white males, country rates); details are given in the text for population specifics.

ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; CDC, Centers for Disease Control; CDVA, Commonwealth Department of Veterans' Affairs; HD, Hodgkin's disease; MVA, motor vehicle accidents; NIOSH, National Institute for Occupational Safety and Health; NHL, non-Hodgkin's lymphoma; NMES; National Medical Expenditure Survey; PTSD, posttraumatic stress disorder; SMR, standardized mortality ratio; STS, soft-tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; *Update 2006, Veterans and Agent Orange: Update 2006 (*IOM, 2007); *Update 2004, Veterans and Agent Orange: Update 2004 (*IOM, 2005); *Update*

*2002, Veterans and Agent Orange: Update 2002 (*IOM, 2003); *Update 2000, Veterans and Agent Orange: Update 2000* (IOM, 2001); *Update 1998, Veterans and Agent Orange: Update 1998* (IOM, 1999); *Update 1996, Veterans and Agent Orange: Update 1996* (IOM, 1996); and *VAO, Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (IOM, 1994).

APPENDIX D

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

John J. Stegeman, Ph.D. *(Chair),* is a Senior Scientist, former Chair of the Biology Department at the Woods Hole Oceanographic Institution, and Director of the Woods Hole Center for Oceans and Human Health, 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. Dr. Stegeman served on the committees for *Veterans and Agent Orange: Update 2000* and *Update 2002 committees*, and chaired the committee for *Veterans and Agent Orange: Update 2004*.

Richard A. Fenske, Ph.D., M.P.H., is a Professor and Associate Chair of Environmental and Occupational Health Sciences at the University of Washington School of Public Health and Community Medicine, and is the Director of the Pacific Northwest Agricultural Safety and Health Center at the University of Washington in Seattle. Dr. Fenske's work has focused on the evaluation of environmental health risks in special populations. Specialty areas include health risks of pesticide exposures, development of new exposure assessment methods, children's exposure to hazardous chemicals, and investigation of the role of dermal exposure for workers. Dr. Fenske serves on the Science Advisory Board of the US Environmental Protection Agency, and also serves as a member of EPA's Human Studies Review Board. He had previously served on the committees for *Veterans and Agent Orange: Update 2002* and *Update 2004*.

Jordan Firestone, M.D., Ph.D., M.P.H., is Assistant Professor of Medicine, with Adjunct appointments in Neurology and Occupational and Environmental Health Sciences. He is Director of the University of Washington Occupational and Environmental Medicine Clinic at Harborview Medical Center in Seattle. Dr. Firestone's research involves chemical exposures and their interactions with individual genetic susceptibility in neurological disease, with a special focus on Parkinson's Disease. His clinical specialty is in occupational neurotoxicology. Dr. Firestone previously served on the committee for *Veterans and Agent Orange: Update 2004*.

Peter H. Gann, M.D., Sc.D., is a Professor and Director of Pathology Research at the University of Illinois at Chicago. A physician-epidemiologist by training, his research work focuses on the causes of breast and prostate cancer, with particular emphasis on the development and application of novel biological markers. His interest in biological markers actually originates with his service as a Project Director at the National Academy of Sciences in the 1980s. Prior to his current position, Dr. Gann spent 13 years in the Department of Preventive Medicine at Northwestern University Medical School. He received a B.A. degree from Swarthmore College, MD and MS (epidemiology/biostatistics) degrees from the University of Pennsylvania, and his doctorate in epidemiology from Harvard University. Dr. Gann

serves on a number of national and international advisory and peer review panels in the field of cancer prevention.

Mark S. Goldberg, Ph.D., Associate Professor in the Department of Medicine, McGill University, Montreal, associate member in the Joint Departments of Epidemiology and Biostatistics and Occupational Health, the Department of Oncology, and Medical Scientist, Royal Victoria Hospital, McGill University Health Centre. Dr. Goldberg is an occupational and environmental epidemiologist and holds an Investigator Award from the Canadian Institute for Health Research. His current research interests include the investigation of occupational and environmental risk factors for breast cancer and the health effects associated with exposures to ambient air pollution. In addition to being a member of grant review panels, Dr. Goldberg is also a member of Health Canada's Science Advisory Board. He has served on the committee for *Disposition of the Air Force Health Study* and the Division of Earth and Life Sciences (DELS) committee for *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues.*

Claudia Hopenhayn, Ph.D., is a Associate Professor in the Department of Epidemiology at the University of Kentucky, College of Public Health. Her primary research interests have focused on cancer and reproductive outcomes, within the context of environmental and occupational epidemiology and cancer control. Dr. Hopenhayn's expertise combines toxicology, biomarkers of exposure and effect, statistics, risk factors, and assessment of intervention, within a framework of epidemiology and multidisciplinary collaborations, both in the United States and internationally. Dr. Hopenhayn previously served on the committee for *Veterans and Agent Orange: Update 2004*.

Nancy I. Kerkvliet, Ph.D., is a Professor in the Department of Environmental and Molecular Toxicology at Oregon State University, Corvallis, Oregon. Dr. Kerkvliet's research is focused on using animal models to understand how chemicals of environmental concern alter immune function. Her primary interest is focused on understanding how activation of the Ah receptor by TCDD and other ligands suppresses immune responses. She previously served on the Committee on Toxicology, the Subcommittee of Jet Propulsion Fuel 8, and the committee for *Veterans and Agent Orange: Update 2004*.

Linda A. McCauley, Ph.D., FAAN, R.N., is a Nightingale Professor of Nursing and Associate Dean for Nursing Research at the University of Pennsylvania, School of Nursing. Dr. McCauley received her doctoral degree in environmental health/epidemiology from the University of Cincinnati. Dr. McCauley has special expertise in the design of epidemiological investigations of occupational and environmental hazards and is nationally recognized for her expertise in occupational and environmental health nursing. Dr. McCauley's research interests are in the areas of chemical exposure among working populations and young children.

DeJuran Richardson, Ph.D., is a Professor and Associate Dean of the Faculty at Lake Forest College and an Adjunct Professor at the University of Illinois at Chicago and the University of Wisconsin-Madison. Dr. Richardson's areas of expertise include Biostatistics and clinical trial data management. He received his B.A., M.S., and Ph.D. degrees from Northwestern University. His professional activities have included appointments to the National Cancer Institute's ECOG Data Monitoring Committee, the National Institute of Neurological Disorders and Stroke (NINDS) Initial Grant Review Committee, and the Advisory Board for the Harvard School of Public Health Initiatives for Minority Student Development (IMSD) Program in the Department of Biostatistics. Dr. Richardson's research interests include the design and analysis of large multi-center clinical trials, the recruitment and retention of underrepresented minorities in clinical trials, and performing statistical survival analyses in the presence of informative censoring. Dr. Richardson's research articles have appeared in many scientific journals. He has served on the committee for *Disposition of the Air Force Health Study.*

Hollie I. Swanson, Ph.D., is Associate Professor in the Department of Molecular and Biomedical Pharmacology and with a joint position with the Toxicology Department at the University of Kentucky

College of Medicine. She received her M.S. from Oregon State University, Ph.D. from Purdue University and postdoctoral training from Michigan State University and Northwestern University. Her research focuses on the study of the aryl hydrocarbon pathway and its role in altering cell fate. She currently serves as Councilor of the Drug Metabolism Specialty Section of the National Chapter of the American Society for Pharmacology and Experimental Therapeutics, is a member of the National and Ohio Valley Chapters of the Society of Toxicology. She is an editorial board member of Toxicology and Applied Pharmacology. Dr. Swanson has published numerous articles pertaining to the molecular and cellular aspects of the Ah receptor and dioxin.

Mary K. Walker, Ph.D., is a Professor of Pharmacology and Toxicology at the University of New Mexico, College of Pharmacy. Her research interests focus on the mechanisms by which high affinity ligands for the AHR increase the risk of cardiovascular disease; and the structural, functional, and molecular changes in adult cardiovascular physiology in a genetic mouse model which lacks the AHR gene. Dr. Walker has also authored and coauthored several articles on these topics.

Stephen D. Walter, Ph.D., is Professor of Clinical Epidemiology and Biostatistics in the Faculty of Health Sciences at McMaster University. Dr. Walter has published extensively on epidemiology and biostatistical methods. His research interests include disease screening and diagnosis; risk assessment; environmental health; and analysis of spatial and temporal data patterns. He is a former Editor of the American Journal of Epidemiology and is the Section Editor for Clinical Epidemiology in the Wiley Encyclopedia of Biostatistics. Dr. Walter has served previously on the IOM Committee on Medicare Coverage of Routine Thyroid Screening.

Staff Biographies

Mary Burr Paxton, Ph.D., is Senior Program Officer in the Institute of Medicine (IOM) Board on Population Health and Public Health Practice. Before joining IOM, she worked as a consultant on the regulation of toxic substances and managed the conduct and analysis of several epidemiology studies on veterans' health. She received a master's of science in biostatistics from the Johns Hopkins School of Hygiene and Public Health and a doctorate in genetics from the George Washington University. She is a diplomate of the American Board of Toxicology. Dr. Paxton has worked on several National Academies reports, including *Issues in Risk Assessment*; *Environmental Neurotoxicology*; *Gulf War and Health: Insecticides and Solvents*; *Gulf War and Health: Fuels, Combustion Products, and Propellants*; *Asbestos: Selected Cancers*; and *Veterans and Agent Orange: Update 2004.*

Jennifer A. Cohen is a Program Officer in the Institute of Medicine (IOM) Board on Population Health and Public Health Practice. She received her undergraduate degree in art history from the University of Maryland. She is also currently attending the University of Maryland where she is working towards her masters in public health. 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; Veterans and Agent Orange: Update 2000, Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans,* and *Veterans and Agent Orange: Update 2004.*

Rose Marie Martinez, Sc.D., is Director of the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. Before joining IOM, she was Senior Health Researcher at Mathematica Policy Research, where she studied the effects of health-system change on the public-health infrastructure, access to care for vulnerable populations, managed care, and the health care workforce. Dr. Martinez is former Assistant Director for Health Financing and Policy with the US General Accounting Office, for

which she directed evaluations and policy analysis on national and public-health issues. Dr. Martinez received her doctorate from the Johns Hopkins School of Hygiene and Public Health.

Tia S. Carter is a senior program assistant on the IOM Board on Population Health and Public Health Practices. She is working on a master's in health-care administration at the University of Maryland University College. She received her undergraduate degree in community health from the University of Maryland, College Park. Before coming to IOM, she worked at the Greater Washington Urban League in the Division of Aging and Health Services as the health promotions coordinator, where she was responsible for health-promotion and disease-prevention education services and activities among the elderly. She has been involved with IOM committee on *Asbestos: Selected Cancers. Veterans and Agent Orange: Update 2006* is Tia's second report with IOM.

Sonia J. Cheruvillil, M.P.H., is a senior program assistant (until June 2006) in the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. She received her masters in public health from George Washington University School of Public Health. She received her undergraduate degrees in English Literature (BA) and Microbiology (BS) from the University of Iowa. She has been involved with the IOM committee on the Disposition of the Air Force Health Study (AFHS) and *Veterans and Agent Orange: Update 2002* and *Update 2004 committee.*

Norman Grossblatt, ELS(D), is a senior editor at the National Academies. Before joining the National Research Council Division of Medical Sciences in 1963, he worked as an analyst in information storage and retrieval at Documentation Incorporated and as a technical editor at the Allis-Chalmers Manufacturing Co., Nuclear Power Department, in Washington, DC. He received a BA in English from Haverford College. Mr. Grossblatt is a diplomate editor in the life sciences and was the founding president of the Board of Editors in the Life Sciences. He is a fellow of the American Medical Writers Association and a recipient of its President's Award; a member of the Council of Science Editors and since 1997 the manuscript editor of its journal, *Science Editor;* and a member of the European Association of Science Editors. At the National Academies, he has edited over 300 reports.