

## 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 myelogenous 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.” Because the committee wished to draw attention to the fact that these three health endpoints merit focused consideration in future updates and might benefit from directed research, these three health outcomes have been listed on the summary table (Table S-1) in the “inadequate evidence” default category with asterisks indicating a footnoted explanation.

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<sup>a</sup>

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**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 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)<sup>b</sup>  
 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<sup>b</sup>

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<sup>a</sup> *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.

<sup>b</sup> 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.