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From 1962 to 1971, the 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; the 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), the most toxic form of dioxin, was an unintended contaminant generated during the production of 2,4,5-T and so was present in Agent Orange and some other formulations sprayed in Vietnam; it is important to remember that Agent Orange is not synonymous with TCDD or dioxin.

In 1991, because of continuing uncertainty about long-term health effects of the sprayed herbicides in Vietnam veterans, Congress passed Public Law (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) convened a committee, whose conclusions IOM published in 1994 in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam (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.

Enacted in 2002, PL 107-103, the Veterans Education and Benefits Expansion Act of 2001, mandated that the *VAO* biennial updates continue through 2014. *Update 2006* was the first report published under that legislation. The current update presents this committee's review of peer-reviewed scientific reports concerning associations between health outcomes and exposure to TCDD and other chemicals in the herbicides used in Vietnam that were published in October 2006– September 2008 and the committee's integration of this information with the previously established evidence database.

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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 (Seventh 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 used by the military in Vietnam:

- 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, as a consequence of congressional and judicial history, both its congressional mandate and the statement of task are phrased with the target of evaluation being “association” between exposure and health outcomes. The rigor of the evidentiary database needed to support a finding of statistical association is weaker than that needed to establish causality, but positive findings for any of the aspects of scientific evidence supportive of causality enhance conviction that an observed statistical association is reliable. Such scientific evidence, of course, would include any information assembled in relation to plausible biologic mechanisms as directed in Article C. In accord with its charge, the committee examined a variety of indicators appropriate for the task, including factors commonly used to evaluate statistical associations, such as the adequacy of control for bias and confounding and the likelihood that an observed association could be explained by chance. Additionally, the committee assessed evidence concerning biologic plausibility derived from laboratory findings in cell-culture or animal models. In particular, associations with multiple supportive indicators are interpreted as having stronger scientific support.

In conducting its study, the present committee operated independently of the Department of Veterans Affairs (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 addition to the above charge, VA made two specific requests to the current committee. First, the committee was asked to consider whether the occurrence of hairy cell leukemia should be regarded as being associated with exposure to the components of herbicides used by the military in Vietnam. Second, the committee was asked to comment on whether effects of herbicide exposure might be manifested at later stages of a child’s development than have

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systematically been evaluated to date or in later generations and on the feasibility of assessing such effects.

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 provided information on whether association between the chemicals of interest and 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 (unless the condition is logically subsumed under a broader disease category that has been evaluated), the committee remains neutral on the basis of the understanding that "absence of evidence is not evidence of absence."

In accord with Congress's mandated presumption of herbicide exposure for all Vietnam veterans, VAO committees have treated Vietnam-veteran status as a proxy for some herbicide exposure when no more specific exposure information is available. To obtain information potentially relevant to the evaluation of health effects related to herbicide exposure in addition to that available from 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 of several occupational groups, including chemical, agricultural, pulp and paper, sawmill, and forestry workers. To the extent that studies of 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 are producing a stream of informative results. A continuing prospective cohort study of agricultural populations with specific information on the chemicals of interest is also steadily contributing new findings to the database. Most important, the Vietnam veterans themselves are advancing in age and, when studied, are capable of providing substantial information on chronic health conditions directly. As the information in the database on populations with established exposures to the chemicals of interest has grown, the committee has come to depend less on data from studies with nonspecific exposure information and has been able to focus more on findings of 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

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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. The search of literature published through September 30, 2008 identified more than 7,000 potentially relevant citations. Screening of those retained about 850 for closer consideration, and roughly 300 ultimately contributed new information to this review. Additional information came from veterans and other interested people 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 (because of confounding, chance, or bias related to errors in selection and measurement) or might accurately represent true associations; although they are not required, data supporting biologic plausibility serve to strengthen confidence that an association is not spurious. 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 new epidemiologic information evaluated in this update and integrated with that previously assembled. The epidemiologic studies have been divided, both here and in the health-outcome chapters, into three categories—Vietnam-veteran, occupational, and environmental—depending on the population addressed.

Vietnam-Veterans Studies

Four studies of Vietnam veterans published since *Update 2006* were reviewed by the committee. The Air Force Health Study produced findings related to cancer incidence, diabetes, serum testosterone concentrations, and benign prostatic hyperplasia. Prostate cancer was studied in Vietnam veterans in the California VA Health System. Mortality from all cancers, occurrences of several individual cancers, and other health outcomes were studied in female Vietnam veterans.

Occupational Studies

Several occupational studies have been published since *Update 2006*. Recent reports from the Agricultural Health Study examined the incidence of respiratory outcomes, neurologic symptoms, Parkinson's disease (PD), diabetes, and cancer in private pesticide applicators (farmers), their spouses, and commercial pesticide applicators. Cancer outcomes were investigated in Danish gardeners exposed to pesticides, including 2,4-D and 2,4,5-T; in German nationals with relevant exposures derived from job–exposure matrices; and in members of the United Farm Workers of America occupationally exposed to 2,4-D. Circulatory diseases and neurologic outcomes were studied in a follow-up of Czech production workers who were exposed to TCDD during the production of 2,4,5-T. New case–control studies have investigated occupational exposures and risk factors for various cancer outcomes and childhood leukemia.

Environmental Studies

Studies of the Seveso cohort that update earlier findings concerning cancer, birth outcomes, diabetes, and circulatory, respiratory, and digestive diseases have been published since *Update 2006*. The continuing Seveso Women's Health Study also published studies of ovarian function and fibroids in Seveso women. Cancer outcomes were evaluated in follow-up studies of residents of Italy, New Zealand, and Besançon, France, and respiratory outcomes in participants of the Ontario Farm Family Health Study were investigated. Data from the National Health and Nutrition Examination Survey were used in several studies of health outcomes, including hypertension, cardiovascular disease, diabetes, and increased concentrations of lipids in relation to serum concentrations of dioxin-like compounds. New case–control studies examined occupational and environmental exposures to the chemicals of interest and other risk factors for various reproductive and cancer outcomes and for PD.

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 VAO reports. Although the studies published since *Update 2006* 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 evidence 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.

Table S-1 defines four categories of association and gives criteria for assigning health outcomes to them. On the basis of its evaluation of veteran, occupational, and environmental studies, the committee allocated particular health outcomes to categories of relative certainty of

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association with exposure to the herbicides that were used in Vietnam or to any of their components or contaminants (with no intention of specifying particular chemicals). The committee notes that experimental data related to biologic plausibility of conditions statistically associated with exposure to Agent Orange has gradually emerged since the beginning of this series of VAO reports and that these findings can inform the decisions about how to categorize the degree of association for individual conditions; a footnote to this effect has been added to Table S-1.

After considering information related to VA's question about hairy-cell leukemia, the committee concluded that not just hairy-cell leukemia, like chronic lymphoid leukemia, but all chronic B-cell neoplasms belong in the category of "sufficient evidence of an association" with Hodgkin's disease and non-Hodgkin's lymphoma. The committee concluded that ischemic heart disease should move from the category of "inadequate or insufficient evidence of an association" into the category of "limited or suggestive evidence of an association". Several pieces of new information specifically on exposure to the chemicals of interest led the committee to decide that PD should also be promoted from the "inadequate or insufficient evidence" category into the "limited or suggestive evidence" category.

As mandated by PL 102-4, the distinctions among categories are based on statistical association, not on strict 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.

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TABLE S–1 Summary of *Seventh Biennial Update* of Findings of Occupational, Environmental, and Veterans Studies Regarding Associations Between Exposure to Herbicides and Specific Health Outcomes^a

Sufficient Evidence of an Association

Epidemiologic 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.^b 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 (including **hairy-cell leukemia and other chronic B-cell leukemias**) (category clarification since *Update 2006*)
- Hodgkin's disease
- Chloracne

Limited or Suggestive Evidence of an Association

Epidemiologic 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.^b For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. 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
- Early-onset transient peripheral neuropathy
- Parkinson's disease** (category change from *Update 2006*)
- Porphyria cutanea tarda
- Hypertension
- Ischemic heart disease** (category change from *Update 2006*)
- Type 2 diabetes (mellitus)
- Spina bifida in offspring of exposed people

Inadequate or Insufficient Evidence to Determine an Association

The available epidemiologic 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 in the respiratory system and intrathoracic organs
- Esophageal cancer
- Stomach cancer
- Colorectal cancer (including small intestine and anus)
- Hepatobiliary cancers (liver, gallbladder, and bile ducts)
- Pancreatic cancer
- Bone and joint cancer
- Melanoma
- Nonmelanoma skin cancer (basal cell and squamous cell)

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Breast cancer
 Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
 Urinary bladder cancer
 Renal cancer (kidney and renal pelvis)
 Cancers of brain and nervous system (including eye)
 Endocrine cancers (thyroid, thymus, and other endocrine organs)
 Leukemia (**other than all chronic B-cell leukemias**, including chronic lymphocytic leukemia and hairy-cell leukemia)
 Cancers at other and unspecified sites
 Infertility
 Spontaneous abortion (other than after 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)
 Neurodegenerative diseases, excluding Parkinson's disease
 Chronic peripheral nervous system disorders
 Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
 Gastrointestinal, metabolic, and digestive disorders (changes in hepatic enzymes, lipid abnormalities, and ulcers)
 Immune system disorders (immune suppression, allergy, and autoimmunity)
 Circulatory disorders (other than hypertension and 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 after paternal exposure to TCDD

^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 Evidence for an association is strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.

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 of 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 chemicals 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 to a given health outcome has been placed in. 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 in Vietnam veterans attributable to exposure to the chemicals of interest (at least for the conditions, exposures, and lengths of observation covered by the studies reviewed). 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 information needed for assigning 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, the committee states as 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.

COMMITTEE 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 the herbicides used in Vietnam and to TCDD and in elucidating the mechanisms that underlie the effects, but there are still subjects on which increased knowledge could be very useful.

While presenting the charge, VA asked that the committee comment on whether effects of herbicide exposures might be manifested at later stages of a child’s development than have

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systematically been evaluated or in later generations and comment on the feasibility of assessing such effects. The chapter on reproductive effects contains the committee's synopsis of toxicologic and epidemiologic information relevant to the request, little of which to date is directly related to the chemicals of interest to the VAO series. Developing understanding of epigenetic mechanisms leads this committee to conclude that it is considerably more plausible than previously believed that exposure to the herbicides sprayed in Vietnam might have caused paternally-mediated transgenerational effects. Such potential would most likely be attributable to the TCDD contaminant in Agent Orange. Consequently, this committee recommends that laboratory research be conducted to address and characterize TCDD's potential for inducing epigenetic modifications. As the offspring of Vietnam veterans grow older, the possibility of a parental effect on the incidence of adult cancers, cognitive problems, and other diseases of maturity are of increasing interest. While information concerning the applicability of epigenetic mechanism to TCDD is being gathered, the committee further recommends innovative epidemiologic protocols be developed to address the logistically challenging task of determining whether adverse effects are being manifested in the adult children and grandchildren of Vietnam veterans.

This committee recommends the pursuit of additional research in toxicology. 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 compromise the health of aging Vietnam veterans. Additional health problems, such as metabolic syndrome and male-mediated effects in offspring, merit laboratory investigation and study in human populations.

The 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 outcomes represented in the complete database assembled in the course of the Air Force Health Study. Consideration should also be given to restarting the congressionally mandated National Vietnam Veterans Longitudinal Study, derived from the cohort originally studied in the National Vietnam Veterans Readjustment 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.

The committee notes that its recommendations are similar to those offered in previous updates and that there has been little activity in several critical areas. The fate of the assemblage of data and biologic samples from the Air Force Health Study remains unsettled; in the interim, critical integrative analyses such as longitudinal evaluation of the cancer data have not yet been made public, and the unique potential of this resource languishes. It is the committee's conviction that work needs to be undertaken promptly to resolve questions regarding several health outcomes, most urgently tonsil cancer, melanoma, and paternally transmitted transgenerational effects. Creative analysis of VA's own data resources and further work on cohorts that have already been established may well be the most effective way to address those outcomes and to gain a better understanding of the role of herbicide exposure in development of PD in Vietnam veterans.