

# INSTITUTE OF MEDICINE

*Shaping the Future for Health*

## VETERANS AND AGENT ORANGE: UPDATE 2000

**V**eterans and Agent Orange: Update 2000, is the third comprehensive review and evaluation of the newly published scientific evidence regarding associations between health outcomes and exposure to dioxin and other chemical compounds in herbicides used in Vietnam. In accordance with Public Law 102-4—the Agent Orange Act of 1991—a committee of the National Academy of Sciences, Institute of Medicine was asked to determine, to the extent that available data permitted meaningful determinations,

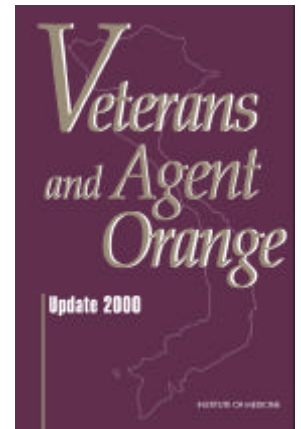
1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. the increased risk of the disease among those exposed to herbicides during Vietnam service; and
3. whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

### New Research Findings in *Update 2000*

In reaching conclusions on whether a health outcome was associated with exposure to dioxin and other chemical compounds in herbicides used in Vietnam, the committee weighed the strengths and limitations of the epidemiologic evidence in previous *Veterans and Agent Orange* reports as well as the newly published scientific data. Each health outcome was assigned to one of four categories, listed in the accompanying table. The findings for the following health outcomes have changed since the *Update 1998* report:

- **Type 2 diabetes:** In a focused report published in 2000, a committee found that there was limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and type 2 (adult-onset) diabetes. Evidence reviewed in this report continues to support that finding. Previous reports had found there was inadequate or insufficient evidence to determine whether an association existed.

- **Acute myelogenous leukemia in children of veterans:** The committee found there was limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and acute myelogenous leukemia



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**The committee found there was limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and acute myelogenous leukemia (AML) in the children of veterans.**

**...the committee examined the possible association between the herbicides of concern in this report and AL-type primary amyloidosis, a rare bone marrow disease not examined in previous *Veterans and Agent Orange* reports. They found that there was inadequate information to determine whether an association existed.**

(AML) in the children of veterans. AML is a cancer of the bone marrow cells that form two types of white blood cells called granulocytes and monocytes.

In particular, two recently published epidemiologic studies support this conclusion. One is a case-control study of AML in which self-reported service in Vietnam or Cambodia was associated with an elevated risk, after adjustment for numerous potentially confounding life-style and sociodemographic factors. The second, a study of the children of Australian Vietnam veterans, found a greater than fourfold risk, although confounding factors other than age and gender were not controlled. While direct measures of exposure are lacking, the committee found the following characteristics of these studies to be particularly persuasive: (1) both were conducted in Vietnam veteran populations; (2) the association was specific for AML, with no excess risk found for other forms of leukemia; (3) one study adjusted for numerous confounders, while the other had an association of sufficiently large magnitude to reduce the likelihood of being completely due to confounding; and (4) the strongest association was seen in children diagnosed at the youngest ages—cases that are considered the strongest candidates for an etiology of parental origin. These characteristics diminish the likelihood that the outcomes were unrelated to service in Vietnam. A third study, which reported a 2.7-fold increased risk of AML in the children of fathers with self-reported exposure of more than 1,000 days to pesticides or weed killers, adds to the plausibility that herbicide exposure could be related to the higher risk observed among those who served in Vietnam.

• **AL-type primary amyloidosis:** In response to a request from the Department of Veterans Affairs, the committee examined the possible association between the herbicides of concern in this report and AL-type primary amyloidosis, a rare bone marrow disease not examined in previous *Veterans and Agent Orange* reports. They found that there was inadequate information to determine whether an association existed.

### **Other Findings**

The report also reaffirms findings in earlier reports that there is sufficient evidence of an association between herbicide or dioxin exposure and soft tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and chloracne in veterans. In *Update 1998*, the committee found limited/suggestive evidence of an association for three cancers—respiratory (larynx, lung or bronchus, and trachea) cancer, prostate cancer, and multiple myeloma—and three other health outcomes—spina bifida in the children of veterans, acute and subacute (transient) peripheral neuropathy, and porphyria cutanea tarda. The recent scientific literature continues to support the classification of these diseases in the limited/suggestive category of evidence.

The scientific data for many of the cancers and other diseases reviewed by the committee were inadequate or insufficient to determine whether an association exists. For two types of cancers—gastrointestinal tumors and brain tumors—the latest literature supported earlier findings that there was limited/suggestive evidence of no association with the exposures of interest. A complete listing of the conditions considered by the committee and their findings concerning them is contained in the accompanying table.

## Updated (2000) Summary of Findings in Occupational, Environmental, and Veterans Studies Regarding the Association Between Specific Health Outcomes and Exposure to Herbicides

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### Sufficient Evidence of an Association

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

Soft-tissue sarcoma	Hodgkin's disease
Non-Hodgkin's lymphoma	Chloracne

### Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent. There is limited/suggestive evidence of an association between exposure to herbicides and the following health outcomes:

Respiratory cancers (lung/bronchus, larynx, trachea)	Porphyria cutanea tarda
Prostate cancer	<i>Type 2 diabetes (category change from Update 1998)</i>
Multiple myeloma	Spina bifida in the children of veterans
Acute and subacute transient peripheral neuropathy	<i>Acute myelogenous leukemia (AML) in the children of veterans (category change from Update 1998)</i>

### Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and the following health outcomes:

Hepatobiliary cancers	Low birthweight
Nasal/nasopharyngeal cancer	Childhood cancer in offspring, other than acute myelogenous leukemia
Bone cancer	Abnormal sperm parameters and infertility
Breast cancer	Motor/coordination dysfunction
Female reproductive cancers (cervical, uterine, ovarian)	Chronic peripheral nervous system disorders
Urinary bladder cancer	Metabolic and digestive disorders (changes in liver enzymes, lipid abnormalities, ulcers)
Renal cancer	Immune system disorders (immune suppression and autoimmunity)
Testicular cancer	Circulatory disorders
Leukemia	Respiratory disorders
Skin cancers	<i>AL-type primary amyloidosis (new health outcome)</i>
Spontaneous abortion	
Birth defects (other than spina bifida)	
Neonatal/infant death and stillbirths	

### Limited/Suggestive Evidence of No Association

Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. *In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.* There is limited/suggestive evidence of no association between exposure to herbicides and the following health outcomes:

Gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, rectal cancer)  
Brain tumors

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NOTE: "Herbicides" refers to the major herbicides used in Vietnam: 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and its contaminant TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), cacodylic acid, and picloram. The evidence regarding association is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

## For More Information...

Copies of *Veterans and Agent Orange: Update 2000* are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at [www.nap.edu](http://www.nap.edu). The full text of this report is available at [www.nap.edu/catalog/10098.html](http://www.nap.edu/catalog/10098.html).

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