

HEALTH EFFECTS OF AGENT ORANGE: THE MORE RECENT NATIONAL ACADEMY OF SCIENCES EFFORTS

Michelle C. Catlin

Institute of Medicine, National Academy of Sciences, 500 5th Street NW, Washington, DC, 20001

Introduction

Public Law 102-4, the Agent Orange Act of 1991, was enacted on February 6, 1991. That legislation, codified as 38 USC Sec. 1116, directed the secretary of veterans affairs to request that the National Academy of Sciences (NAS) conduct an independent, comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange (a 50:50 mixture of the herbicides 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid), and other chemical compounds in the herbicides, including the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, one form of dioxin). The legislation also called for reviews of newly available information to be completed every 2 years after the initial report for a period of 10 years. In addition, the NAS was asked to recommend, as appropriate, additional scientific studies to resolve continuing scientific uncertainties and to comment on particular programs mandated in the law.

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 that committee's work were published in 1994 in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (hereafter referred to as *VAO*)¹. Successor committees were formed to fulfill the requirement for updated reviews. Those committees produced *Veterans and Agent Orange: Update 1996*², *Update 1998*³, and *Update 2000*⁴. The most recent update is *Veterans and Agent Orange: Update 2002*⁷. In 1999, in response to a request from the VA, IOM convened 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*⁵ (hereafter referred to as *Type 2 Diabetes*)⁵. In 2001, VA requested that IOM convene a committee to conduct an interim review of acute myelogenous leukemia (AML). Its review of the literature, including literature available since its review for *Update 2000*, is 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*)⁶.

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 are intended to provide scientific information for the secretary of veterans affairs to consider as VA exercises its responsibilities to Vietnam veterans.

Methods

To fulfill its charge of assessing whether a given human health effect is associated with exposure to at least one of the herbicides or TCDD, the committee concentrated on reviewing and interpreting epidemiologic studies. Experimental investigations that might contribute to biologic plausibility that the chemicals of

interest might be related to a given effect were also reviewed. The committee began its evaluation presuming neither the presence nor the absence of associations.

To obtain all information potentially relevant to the evaluation of health effects related to herbicide exposure, the committee, in addition to reviewing studies of Vietnam veterans, reviewed studies of other groups potentially exposed to the herbicides used in Vietnam (2,4-D, 2,4,5-T and its contaminant TCDD, cacodylic acid, and picloram), other phenoxy herbicides, chlorophenols, and other compounds. Those groups include chemical production and agricultural workers, people possibly exposed heavily to herbicides or dioxins as a result of residing near the site of an accident or near areas used to dispose of toxic waste, and residents of Vietnam.

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 in *VAO*¹ on the basis of diseases and conditions that had been mentioned in the scientific literature or in other documents identified through extensive literature searches. The *VAO*¹ list has been augmented in response to developments in the literature, requests by VA, and concerns of Vietnam veterans.

The information that the committee reviewed for *Update 2002*⁷ was identified through a comprehensive search of relevant databases, including public and commercial databases covering biologic, medical, toxicologic, chemical, historical, and regulatory information. Literature identification continued through July 1, 2002. More than 9,000 potentially relevant studies were identified in those searches, and more than 1,000 were reviewed. Input received from veterans and other interested persons at public hearings and in written submissions served as a valuable source of additional information.

In deciding the strength of the evidence of an association between herbicide exposure and a particular outcome, the committee examined estimates of risk and evaluated whether they might be due to error, bias, confounding, or chance or were likely to represent true associations. The committee recognized that an absolute conclusion about the absence of association may never be attained, because, as is generally the case in science, studies of health outcomes after herbicide exposure are not capable of demonstrating that a purported effect is impossible.

Results and Discussion

The health outcomes reviewed by the committee are categorized as cancer, reproductive and developmental effects, neurobehavioral disorders, and other health effects. The committee weighed the strengths and limitations of all the epidemiologic evidence reviewed in *Update 2002*⁷ and in previous *Veterans and Agent Orange* reports^{1,2,3,4,5,6} and reached its conclusions by interpreting the new evidence in the context of the entire body of literature. It assigned each health outcome being considered to one of four categories on the basis of that evidence. The definitions of the categories and the criteria for assigning particular health outcomes to them are described in Table 1; the health outcomes assigned to each category are also listed in the table.

TABLE 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 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 that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence of an association. There is sufficient evidence of an association between exposure to herbicides and the following health outcomes:

Chronic lymphocytic leukemia (CLL)(category change from *Update 2000*)

Soft-tissue sarcoma

Non-Hodgkin's lymphoma

Hodgkin's disease

Chloracne

Limited or 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 or suggestive evidence of an association between exposure to herbicides and the following health outcomes:

Respiratory cancer (of lung or bronchus, larynx, and trachea)

Prostatic cancer

Multiple myeloma

Acute and subacute transient peripheral neuropathy

Porphyria cutanea tarda

Type 2 diabetes

Spina bifida in the children of veterans

Inadequate or 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

Nasal or nasopharyngeal cancer

Bone cancer

Breast cancer

Female reproductive cancer (cervical, uterine, and ovarian)

Urinary bladder cancer

Renal cancer

Testicular cancer

Leukemia (other than CLL)

Skin cancer

Spontaneous abortion

Birth defects (other than spina bifida)

Neonatal or infant death and stillbirth

Low birthweight

Childhood cancer in offspring, including acute myelogenous leukemia

Abnormal sperm characteristics and infertility

Cognitive and neuropsychiatric disorders

Motor or coordination dysfunction

Chronic peripheral nervous system disorders
Metabolic and digestive disorders (changes in liver enzymes, lipid abnormalities, and ulcers)
Immune system disorders (immune suppression and autoimmunity)
Circulatory disorders
Respiratory disorders
AL-type primary amyloidosis
Endometriosis
Effects on thyroid homeostasis

Limited or Suggestive Evidence of No Association

Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are consistent in not showing a positive association between any magnitude of exposure to herbicides and the outcome. A conclusion of “no association” is inevitably limited to the conditions, exposure, 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 herbicides and the following health outcomes:

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

^a *Herbicides* refers to the major herbicides used 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, or 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.

As mandated by PL 102-4, the distinctions between categories are based on statistical association, not on causality. It should be noted that the committee is charged with reviewing the scientific data, not with making recommendations regarding VA policy; therefore, conclusions reported in Table 1 are not intended to imply or suggest policy decisions. Furthermore, the conclusions are related to associations between exposure to chemicals and health outcomes in human populations, not to the likelihood that any individual's health problem is associated with or caused by the herbicides in question.

References

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