VETERANS AND AGENT ORANGE — THE U.S. NATIONAL ACADEMY OF SCIENCES DIOXIN EPIDEMIOLOGY REVIEWS

David A. Butler

National Academy of Sciences, Institute of Medicine, 2101 Constitution Avenue, NW, Washington, DC 20418 USA

Introduction

The *Veterans and Agent Orange* series of reports from the National Academy of Sciences[1,2,3] — mandated by the Agent Orange Act of 1991 — review and evaluate the available scientific evidence regarding the association between exposure to the herbicides used in Vietnam or dioxin and various adverse health outcomes. These reports form a major input to the Department of Veterans Affairs policy on compensation to veterans for service-related illnesses.

This paper addresses the methodology used in the evaluation of the epidemiologic literature, the major findings of the report series and how they have changed over time, and the future of this research review effort.

Methods

The Agent Orange Act of 1991 (Public Law 102–4) directed the U.S. Secretary of Veterans Affairs to contract with the National Academy of Sciences (NAS) to undertake a series of reviews and evaluations of the available scientific evidence regarding statistical associations between diseases and exposure to dioxin and other chemical compounds in herbicides used in Vietnam. For each disease, the NAS was asked to determine, to the extent that available scientific data permit meaningful determinations:

1. whether a statistical association of disease 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;
2. the increased risk of the disease in question among those exposed to herbicides during Vietnam service; and
3. whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease in question.

The NAS was asked to provide this scientific information to the Department of Veterans Affairs (DVA) for consideration in making determinations about compensation policy regarding Vietnam veterans. This mandate resulted the creation of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides—which wrote the 1994 report *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam (VAO)*—and successor committees that produced *Veterans and Agent Orange: Update 1996* and *... Update 1998.* Under the mandate of P.L. 104–2, updates will be issued every two years for a total of ten years as measured from the date of the first report.

In fulfilling its charge of judging whether each of a set of human health effects is associated with exposure to herbicides or dioxin, the committee concentrated primarily on reviewing and interpreting epidemiologic studies. The committee began its evaluation presuming neither the presence nor the absence of association. It sought to characterize and weigh the strengths and limitations of the available evidence. These judgments have both quantitative and qualitative aspects that reflect the

nature of the exposures, health outcomes, and populations exposed; the characteristics of the evidence examined; and the approach taken to evaluate this evidence.

To obtain information pertinent to the evaluation of possible health effects of herbicide exposure, the committee reviewed studies of a wide range of groups potentially exposed to the herbicides used in Vietnam (2,4,5-trichlorophenoxyacetic acid [2,4,5-T], 2,4-dichlorophenoxyacetic acid [2,4-D], cacodylic acid, and picloram), or 2,3,7,8-tertachlorodibenzo-*p*-dioxin. These groups include chemical production and agricultural workers and 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. The committee felt that considering studies of other groups could help address the issue of whether these compounds might be associated with particular health outcomes, even though the results would have only an indirect bearing on the increased risk of disease in veterans themselves. Some of these studies, especially those of workers in chemical production plants, provide stronger evidence about health effects than studies of veterans because exposure was generally more easily quantified and measured. Furthermore, the general levels and duration of exposure to the chemicals were greater, and the studies were of sufficient size to examine the health risks among people with varying levels of exposure.

Because of the great differences among the studies, the committee concluded that it was inappropriate to use a quantitative technique such as meta-analysis to combine their individual results into a single summary measure of statistical association. Using such a summary measure would also inappropriately focus attention on one piece of the information used by the committee when, in fact, all the factors discussed above are important to evaluating the literature. Instead, the original committee addressed their charge by assigning each of the health outcomes under study one of four categories on the basis of the epidemiologic evidence reviewed. The categories used by that committee were adapted from those used by the International Agency for Research on Cancer (IARC) in evaluating the evidence for carcinogenicity of various agents[4]. Successor committees adopted these categorizations in their evaluations. Consistent with the charge to the Secretary of Veterans Affairs in P.L. 102-4, the distinctions between categories are based on "statistical association," not on causality, as is common in scientific reviews.

The categories—Sufficient Evidence of an Association, Limited/Suggestive Evidence of an Association, Inadequate/Insufficient Evidence of an Association, and Limited/Suggestive Evidence of *No* Association— are defined below.

Results and Discussion

Health Outcomes with Sufficient Evidence of an Association

The original (1994 report) committee found sufficient evidence of an association with herbicides and/or TCDD for three cancers—soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease—and two other health outcomes, chloracne and porphyria cutanea tarda (PCT). After reviewing the whole of the literature available two years later, the committee responsible for the 1996 update concluded that the statistical evidence still supported this classification for the three cancers and chloracne. However, new data regarding porphyria cutanea tarda combined with the studies reviewed in *VAO* justified moving PCT to the category of *limited/suggestive evidence of an association with herbicide exposure.* The *Update 1998* committee concluded that the literature continued to support the *'96* categorizations.

For diseases in this category, a positive association between herbicides and the outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regarded evidence from several small studies that are free from bias and

confounding, and show an association that is consistent in magnitude and direction, as sufficient evidence for an association.

Health Outcomes with Limited/Suggestive Evidence of an Association

The committee responsible for *VAO* found limited/suggestive evidence of an association for three cancer outcomes: respiratory cancers (lung/bronchus, larynx, trachea), prostate cancer, and multiple myeloma. The *Update 1996* committee added three health outcomes to this list: PCT (as explained above), acute and subacute transient peripheral neuropathy, and spina bifida in the children of veterans. Transient peripheral neuropathies had not been addressed in *VAO* since, by virtue of their transient nature, they were not amenable to epidemiologic study. In response to a request from DVA, the *Update 1996* committee added them to the list of reviewed health outcomes and made its determination on the basis of evidence available from case histories. A 1995 analysis of birth defects among the offspring of Ranch Hands, in combination with earlier studies of neural tube defects in the children of Vietnam veterans published by the Centers for Disease Control and Prevention (CDC), led the *Update 1996* committee to distinguish spina bifida from other adverse reproductive outcomes and classify it in the *limited/suggestive* category. The literature did not support any changes to these conclusions for the *Update 1998* report.

For diseases in this category, the evidence must be suggestive of an association between herbicides and the outcome considered, but the association may be limited because chance, bias, or confounding could not be ruled out with confidence. Typically, at least one high-quality study indicates a positive association, but the results of other studies may be inconsistent.

Health Outcomes with Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Scientific data for many of the cancers and other diseases reviewed by the *VAO*, *Update 1996*, and *Update 1998* committees were inadequate or insufficient to determine whether any association exists. There was one change in the health outcomes in this category between the first two reports: skin cancer was moved into this category in *Update 1996* when available evidence no longer supported its classification as a condition with limited/suggestive evidence of no association. Two years later, the *Update 1998* report reclassified urinary bladder cancers into this category for the same reason. A complete list of outcomes in this category in *Update 1998* report is given below:

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

For diseases in this category, the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies may fail to control for confounding or have inadequate exposure assessment.

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

For a small group of health outcomes, the *VAO* committee found a sufficient number and variety of well-designed studies to conclude that there is limited/suggestive evidence of *no* association between these cancers and TCDD or the herbicides under study. This group included gastrointestinal tumors (colon, rectal, stomach, and pancreatic), skin cancer, brain tumors, and bladder cancer. As noted above, the *Update 1996* committee came to the same conclusions in all but one circumstance. It concluded that studies on skin cancer published since *VAO*, considered in combination with the evidence addressed in that report, no longer supported the classification of this health outcome in the *no-association* category. Urinary bladder cancers were removed from this category by the *Update 1998* committee on the basis of evidence that had become available since the *Update 1996* effort.

For outcomes in this category, 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, and have relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, levels 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.

Acknowledgments

Support for this research was provided by the U.S. Department of Veterans Affairs. The National Academies reports cited in this abstract could not have been done without the work of volunteer committees of experts and the assistance of scientists and researchers who generously lent their time and expertise to the efforts.

References

1. Institute of Medicine. (1994) Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam, National Academy Press, ISBN 0-309-04887-7.
2. Institute of Medicine. (1996) Veterans and Agent Orange: Update 1996, National Academy Press, ISBN 0-309-05487-7.
3. Institute of Medicine. (1999) Veterans and Agent Orange: Update 1998, National Academy Press, ISBN 0-309-06326-4.
4. International Agency for Research on Cancer (IARC). (1977) Some Fumigants, The Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Vol. 15. Lyon, France: World Health Organization (WHO), IARC.