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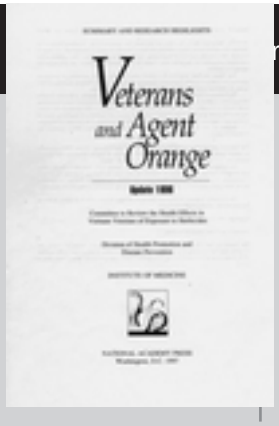

Veterans and Agent Orange: Update 1996: Summary and Research Highlights

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Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, Division of Health Promotion and Disease Prevention

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SUMMARY AND RESEARCH HIGHLIGHTS

Veterans and Agent Orange

Update 1996

Committee to Review the Health Effects in
Vietnam Veterans of Exposure to Herbicides

Division of Health Promotion and
Disease Prevention

INSTITUTE OF MEDICINE

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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About this Summary

The Preface, Contents, and Executive Summary of this document are reproduced in full from *Veterans and Agent Orange: Update 1996*. In addition, excerpts from Chapters 9 and 11 of the full report, which deal with birth defects and acute and subacute transient peripheral neuropathy, respectively, are reproduced here. Research on these two conditions is highlighted in this publication because the committee's conclusions regarding them are based on information that was not available at the time the original report, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (1994), was written. Additional information concerning the incidence of birth defects in the children of Vietnam veterans led the committee that wrote *Update 1996* to reassess all the information regarding a possible association between this health outcome and herbicide exposure and to change a conclusion reached in 1994. Acute and subacute transient peripheral neuropathy were not addressed in the 1994 report, thus the information in *Update 1996* presents the committee's conclusions regarding this new disease category. All chapter references in the text refer to chapters in the full report.

Preface

In response to the concerns voiced by Vietnam veterans and their families, Congress called upon the National Academy of Sciences (NAS) to review the scientific evidence on the possible health effects of exposure to Agent Orange and other herbicides (Public Law 102-4, signed on February 6, 1991). The creation of the first NAS Institute of Medicine committee, in 1992, underscored the critical importance of approaching these questions from a scientific standpoint. The original Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides realized from the beginning that it could not conduct a credible scientific review without a full understanding of the experiences and perspectives of veterans. Thus, to supplement its standard scientific process, the original committee opened several of its meetings to the public in order to allow veterans and other interested individuals to voice their concerns and opinions, to provide personal information about individual exposure to herbicides and associated health effects, and to educate the original committee on recent research results and studies still under way. This information provided a meaningful backdrop for the numerous scientific articles that the original committee reviewed and evaluated.

In its 1994 report *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, the committee reviewed and evaluated the available scientific evidence regarding the association between exposure to dioxin or other chemical compounds contained in herbicides used in Vietnam and a wide range of health effects and provided the committee's findings to the Secretary of Veterans Affairs to consider as the Department of Veterans Affairs carried out its responsibilities to Vietnam veterans. The report also described areas in which the avail-

able scientific data were insufficient to determine whether an association exists and provided the committee's recommendations for future research.

Public Law 102-4 also asked the IOM to conduct biennial updates that would review newly published scientific literature regarding statistical associations between health outcomes and exposure to dioxin and other chemical compounds in these herbicides. The focus of this first updated review is on new scientific studies published since the release of *Veterans and Agent Orange (VAO)* and on updates of scientific studies previously reviewed in *VAO*. To conduct this review, the IOM established a new committee of 16 members representing a wide range of expertise to take a fresh look at the studies reviewed in *VAO* and new scientific studies to determine whether an association exists between herbicide exposure and specific health outcomes. In order to provide a link to *VAO*, half of the committee members had also served on the original committee. All committee members were selected because they are leading experts in their fields, have no conflicts of interest with regard to the matter under study, and have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or dioxin exposure. Biographical sketches of committee members and staff appear in Appendix C.

The committee worked on several fronts in conducting this updated review, always with the goal of seeking the most accurate information and advice from the widest possible range of knowledgeable sources. Consistent with procedures of the IOM, the committee met in a series of closed sessions and working group meetings in which members could freely examine, characterize, and weigh the strengths and limitations of the evidence. Given the nature of the controversy surrounding this issue, the committee deemed it vital to convene an open meeting as well. The public meeting was held in conjunction with the committee's first meeting, in April 1995, and provided the opportunity for veterans and veterans service organizations, researchers, policymakers, and other interested parties to present their concerns, review their research, and exchange information directly with committee members. To solicit broad participation, the committee sent announcements to nearly 1,300 individuals and organizations known to have an interest in this issue. The oral presentations and written statements submitted to the committee are described in detail in Appendix A.

In addition to its formal meetings, the committee actively and continuously sought information from, and explained its mission to, a broad array of individuals and organizations with interest or expertise in assessing the effects of exposure to herbicides. These interactions included meetings with representatives of veterans service organizations, congressional committees, federal agencies, and scientific organizations. The committee also heard from the public through telephone calls and letters, each of which received a response from the IOM staff.

Most of the committee's work involved reviewing the scientific literature bearing on the association between herbicides or dioxin and various health outcomes. The literature included studies of people exposed in occupational and

environmental settings to the types of herbicides used in Vietnam, as well as studies of Vietnam veterans. The committee reviewed the original publications themselves rather than summaries or commentaries. Such secondary sources were used to check the completeness of the review. The committee also reviewed the primary and secondary literature on basic toxicological and animal studies related to dioxin and other herbicides in question.

As explained in the Executive Summary on page 14, the committee found that, in general, it is not possible to quantify the degree of risk likely to be experienced by Vietnam veterans because of their exposure to herbicides in Vietnam. Two members of the committee believe that there are certain circumstances under which the risk to veterans can be quantified. Appendix B presents their analysis and estimates; it represents their opinion alone.

Kelley Brix served as the original study director for this project and deserves credit for drafting sections of the report. The committee would also like to acknowledge the excellent work of the staff members, David Butler, Deborah Katz, and Amy Noel O'Hara. The committee would also like to thank Michael Stoto, Cynthia Abel, Diane Mundt, and Catharyn Liverman, who also served as staff members for the original committee; their knowledge of the subject was helpful in completing the report. Thanks are also extended to Mona Brinegar, who handled the finances for the project; Thomas Burroughs, who provided excellent editorial skills; Michael Edington, who supervised the report through the editorial and publication phases; and Donna Thompson, who provided assistance with editorial changes to the manuscript.

David Tollerud, *Chairman*

Contents

The contents of the entire report, from which this Summary and Research Highlights is extracted, are listed below.

SUMMARY AND RESEARCH HIGHLIGHTS

Veterans and Agent Orange

Update 1996

1

Executive Summary

Because of continuing uncertainty about the long-term health effects of exposure to herbicides used in Vietnam, Congress passed Public Law 102-4, the "Agent Orange Act of 1991." This legislation directed the Secretary of Veterans Affairs to request the National Academy of Sciences (NAS) to conduct a comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of these herbicides, including dioxin. The Institute of Medicine (IOM) of the NAS conducted this review and in 1994 published a comprehensive report, entitled *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (IOM, 1994).

Public Law 102-4 also called for the NAS to conduct subsequent reviews at least every two years for a period of ten years from the date of the first report. The NAS was instructed to conduct a comprehensive review of the evidence that has become available since the previous IOM committee report; and reassess its determinations and estimates of statistical association, risk, and biological plausibility.

This IOM report presents the first updated review and evaluation of the newly published scientific evidence regarding associations between diseases and exposure to dioxin and other chemical compounds in herbicides used in Vietnam. For each disease, the IOM 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 epidemiological 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 biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

In addition to bringing the earlier scientific evidence up to date, the committee has addressed several specific areas of concern, as requested by the Department of Veterans Affairs (DVA). These are: 1) the relationship between exposure to herbicides and the development of acute and subacute peripheral neuropathy; 2) the relationship between exposure to herbicides and the development of prostate cancer, hepatobiliary cancer, and nasopharyngeal cancer; and 3) the relationship between the length of time since first exposure and the possible risk of cancer development.

In conducting its study, the IOM committee operated independently of the DVA and other government agencies. The committee was not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. Rather, the study provides scientific information for the Secretary of Veterans Affairs to consider as the DVA exercises its responsibilities to Vietnam veterans.

ORGANIZATION AND FRAMEWORK

The conclusions in this updated report are based on cumulative evidence from the scientific literature reviewed in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, which will be abbreviated here as *VAO*. This update is intended to supplement rather than replace *VAO*; therefore, most of the background information has not been repeated. Most chapter sections begin with brief summaries of the scientific data in *VAO*, followed by a more thorough discussion of the newly published data and their interpretation. The reader is referred to relevant sections of *VAO* for additional detail and explanation.

Chapter 2 provides an overview of the methods and conclusions of *VAO*. In addition, it provides a summary of the recent activities of several federal government agencies that are relevant to the health effects of Agent Orange and other herbicides used in Vietnam. Chapter 3 provides an update of the recent experimental toxicology data on the effects of the herbicides and of TCDD, a compound found as a contaminant in the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). These data serve as the basis for the biological plausibility of potential health effects in human populations. Chapter 4 describes the methodological considerations that guided the committee's review and its evaluation. Chapter 5 updates the exposure assessment issues in *VAO*. Chapter 8 reviews the methods used to study latency, or time-related effects—a topic of special interest to the DVA—and evaluates the evidence on latency for the cancers under study.

The committee focused most of its efforts on reviewing and interpreting epidemiologic studies, in order to judge whether each of the human health effects is associated with exposure to herbicides or dioxin. The committee weighed the

strengths and limitations of the scientific data in *VAO* as well as the newly published scientific data, and reached its conclusions by interpreting the new evidence in the context of the original report. In particular, each disease has been placed into one of four categories, depending on the strength of evidence for an association (see Conclusions about Health Outcomes, below). The committee used the same criteria to categorize diseases as were used in *VAO*.

In the chapters on the various health outcomes (7, 9, 10, and 11), the committee relied on many of the same epidemiologic studies when assessing the potential associations with herbicides. Therefore, Chapter 6 provides a framework for the methods used in the epidemiologic studies. The chapter is organized to reflect similarities and differences in the nature of exposure among three types of study populations: occupationally exposed, environmentally exposed, and Vietnam veterans.

TOXICOLOGY SUMMARY

Chapter 3 reviews the results of animal studies published during the past three years that investigated the toxicokinetics, mechanism of action, and disease outcomes of TCDD, plus the herbicides themselves.

TCDD elicits a diverse spectrum of biological sex-, strain-, age-, and species-specific effects, including carcinogenicity, immunotoxicity, reproductive/developmental toxicity, hepatotoxicity, neurotoxicity, chloracne, and loss of body weight. These effects vary according to the age, sex, species, and strain of the animals involved. To date, the scientific consensus is that TCDD is not genotoxic and that its ability to influence the carcinogenic process is mediated via epigenetic events such as enzyme induction, cell proliferation, apoptosis, and intracellular communication.

Recent studies on the effects of TCDD and related substances on the immune system amplify earlier findings and suggest that these compounds affect primarily the T-cell arm of the immune response. Direct effects of TCDD on T cells in vitro, however, have not been demonstrated suggesting that the action of TCDD may be indirect. In contrast, a number of animal studies of the reproductive and developmental toxicity of TCDD suggests that developing animals may be particularly sensitive to the effects of TCDD. Specifically, male reproductive function has been reported to be altered following perinatal exposure to TCDD. In addition, experimental studies of the effects of TCDD in the peripheral nervous system suggest that TCDD can cause a toxic polyneuropathy in rats after a single, low dose. Other recent studies provide evidence that hepatotoxicity of TCDD involves AhR-dependent mechanisms.

The most recent studies have focused on the elucidation of the molecular mechanism of TCDD toxicity. The evidence further supports the concept that the toxic effects of TCDD involve AhR-dependent mechanisms. A better appreciation of the complexity of TCDD effects in target cells has led to the development

of refined, physiologically based pharmacokinetic models. These models take into account intracellular diffusion, receptor and protein binding, and liver induction to establish the fractional distribution of the total body burden as a function of the overall body concentration. The association of TCDD with the cytosolic AhR has been shown to require a second protein, known as ARNT, for DNA binding capability and transcriptional activation of target genes. There is also increasing evidence suggesting that events other than receptor binding influence biological response to TCDD. It is now clear that AhR-related signaling influences, and is itself influenced by, other signal transduction mechanisms at low concentrations. Signaling interactions explaining the toxic effects of TCDD may involve growth factors, free radicals, the interaction of TCDD with the estrogen transduction pathway, and protein kinases.

The toxicity of the herbicides used in Vietnam remains poorly studied. In general, the herbicides 2,4-D, 2,4,5-T, cacodylic acid, and picloram have not been identified as particularly toxic substances since high concentrations are often required to modulate cellular and biochemical processes. Impairment of motor function has been reported in rats administered high single oral doses of 2,4-D. The ability of 2,4,5-T to interfere with calcium homeostasis in vitro has been documented and linked to the teratogenic effects of 2,4,5-T on the early development of sea urchin eggs. There is evidence suggesting that both 2,4-D and 2,4,5-T are capable of inducing renal lesions in rats. A series of studies indicates that high concentrations of cacodylic acid results in the formation of a toxic intermediate, the dimethylarsenic radical. No recent studies pertaining to the toxicity of picloram have been published. The half-life in the body of 2,4-D and 2,4,5-T is relatively short and does not appear to extend beyond two weeks. 2,4-D binds covalently to hepatic proteins and lipids, but the molecular basis of this interaction and its biologic consequences are unknown.

EXPOSURE ASSESSMENT

Assessment of individual exposure to herbicides and dioxin is a key element in determining whether specific health outcomes are linked to these compounds. The committee has found, however, that the definition and quantification of exposure are the weakest methodologic aspects of the epidemiologic studies. Although different approaches have been used to estimate exposure among Vietnam veterans and among various occupationally and environmentally exposed groups, each approach is limited in its ability to determine precisely the intensity and duration of individual exposure.

Since the publication of *VAO*, there has been considerable progress in the use of serum TCDD levels and/or quantitative exposure indices, as summarized in Chapter 5. There also has been progress in characterizing the TCDD body burdens in several groups, including the Ranch Hand cohort, Seveso residents, German herbicide production employees, and Vietnamese civilians (Michalek et

al., 1996; Needham et al., 1994; Flesch-Janys et al., 1994; Ott et al., 1993; and Verger et al., 1994). The mean half-life of TCDD in humans has been calculated to be about 8.7 years in the Ranch Hand cohort (Michalek et al., 1996). Serum TCDD measurements may provide valuable information about past herbicide exposure under some conditions, and they are best used to detect differences in exposure levels among large groups in epidemiologic studies. This additional information on TCDD body burdens in specific groups and information on half-lives allow more accurate comparisons of relative levels of exposure to TCDD among cohorts.

Although definitive data are lacking, the available evidence suggests that Vietnam veterans as a group had substantially lower exposure to herbicides and dioxin than did the subjects in many occupational studies. The participants in Operation Ranch Hand and the Army Chemical Corps are exceptions to this pattern, and it is likely that there are others who served in Vietnam who had exposures comparable in intensity to members of the occupationally exposed cohorts. It is currently not possible to identify this heavily exposed fraction of Vietnam veterans, although exposure reconstruction methods with this capability could perhaps be developed and validated.

CONCLUSIONS ABOUT HEALTH OUTCOMES

Chapters 7, 9, 10, and 11 provide a detailed evaluation of the epidemiologic studies reviewed by the committee and their implications for cancer, reproductive effects, neurobehavioral effects, and other health effects. As is detailed in Chapter 4, the committee used the epidemiologic evidence it reviewed to assign each of the health outcomes being studied into one of the four categories listed in Table 1-1. The definitions of the categories and the criteria for assigning a particular health outcome to them are described in the table, and the specific rationale for each of the findings is detailed in Chapters 7, 9, 10, and 11.

Consistent with the mandate of Public Law 102-4, the distinctions between categories are based on "statistical association," not on causality, as is common in scientific reviews. Thus, standard criteria used in epidemiology for assessing causality (Hill, 1971) do not strictly apply. The committee was charged with reviewing the scientific evidence rather than making recommendations regarding DVA policy, and Table 1-1 is not intended to imply or suggest any policy decisions; these must rest with the Secretary of Veterans Affairs.

Health Outcomes with Sufficient Evidence of an Association

In *VAO*, the committee found sufficient evidence of an association with herbicides and/or TCDD for five diseases: soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, chloracne, and porphyria cutanea tarda (in genetically susceptible individuals). The recent scientific literature continues to sup-

TABLE 1-1 Updated Summary of Findings in Occupational, Environmental, and Veterans Studies Regarding the Association Between Specific Health Problems 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 that are free from bias and confounding 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
Non-Hodgkin's lymphoma
Hodgkin's disease
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, larynx, trachea)
Prostate cancer
Multiple myeloma
Acute and subacute peripheral neuropathy (new disease category)
Spina bifida (new disease category)
Porphyria cutanea tarda (category change in 1996)

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
Nasal/nasopharyngeal cancer
Bone cancer
Female reproductive cancers (cervical, uterine, ovarian)
Breast cancer

TABLE 1-1 Continued

Inadequate/Insufficient Evidence to Determine Whether an Association Exists (continued)

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
Cognitive and neuropsychiatric disorders
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 cancer (category change in 1996)

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)
Bladder cancer
Brain tumors

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.

port the classification of the first four of these diseases in the category of sufficient evidence. Based on the recent literature, the committee has reclassified porphyria cutanea tarda into the category of limited/suggestive evidence, as described below. Based on the recent literature, there are no additional diseases that satisfy this category's criteria—that 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 regards evidence from several small studies that are free from bias and confounding, and that show an association that is consistent in magnitude and direction, as sufficient evidence for an association. The evidence that supports the committee's conclusions for the three cancers is detailed in Chapter 7; for chloracne in Chapter 11.

Health Outcomes with Limited/Suggestive Evidence of Association

In *VAO*, the committee found limited/suggestive evidence of an association for three cancers: respiratory cancer, prostate cancer, and multiple myeloma. The recent scientific literature continues to support the classification of these diseases in the category of limited/suggestive evidence. The literature also indicates that three additional conditions satisfy the criteria necessary for this category: spina bifida, acute and subacute (transient) peripheral neuropathy, and porphyria cutanea tarda (PCT). For outcomes in this category, the evidence must be suggestive of an association with herbicides, 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.

The evidence that supports the committee's conclusions for respiratory cancer and multiple myeloma is detailed in Chapter 7 and is not substantially changed from *VAO*. Because prostate cancer is one of the three cancer types of special interest to the DVA, a brief summary of the relevant scientific evidence is provided here. Because spina bifida, acute and subacute (transient) peripheral neuropathy, and porphyria cutanea tarda have been classified in the category of limited/suggestive since *VAO*, evidence for these associations is also provided.

Several studies have shown an elevated risk for prostate cancer in agricultural or forestry workers. In a large cohort study of Canadian farmers (Morrison et al., 1993), an elevated risk of prostate cancer was associated with herbicide spraying, and the risk increased with increasing number of acres sprayed. The proportionate mortality from prostate cancer was elevated in a study of USDA forest conservationists (PMR = 1.6, CI 0.9-3.0) (Alavanja et al., 1989), and a case-control study of white male Iowans who died of prostate cancer (Burmeister et al., 1983) found a significant association with farming (OR = 1.2) that was not associated with any particular agricultural practice. These results are strengthened by a consistent pattern of nonsignificant elevated risks in studies of chemi-

cal production workers, agricultural workers, pesticide applicators, paper and pulp workers, and the population of Seveso, Italy. The largest recent study demonstrated a significantly increased risk of death from prostate cancer in both white and nonwhite farmers in 22 of the 23 states that were studied (Blair et al., 1993). Studies of prostate cancer among Vietnam veterans or among people who have been exposed environmentally, have not consistently shown an association. However, prostate cancer is generally a disease of older men, and the risk among Vietnam veterans would not be detectable in today's epidemiologic studies. Because there was a strong indication of a dose-response relationship in one study (Morrison et al., 1993) and a consistent positive association in a number of others, the committee felt that the evidence for association with herbicide exposure was limited/suggestive for prostate cancer.

There have been three epidemiologic studies that suggest an association between paternal herbicide exposure and an increased risk of spina bifida. In the Ranch Hand study (Wolfe et al., 1995), neural tube defects (spina bifida, anencephaly) were increased among offspring of Ranch Hands with four total (rate of 5 per 1,000), in contrast to none among the comparison infants (exact $p = .04$). The Centers for Disease Control and Prevention (CDC) VES cohort study (Centers for Disease Control, 1989) found that more Vietnam veterans reported that their children had a central nervous system anomaly (OR = 2.3; 95% CI 1.2-4.5) than did non-Vietnam veterans. The odds ratio for spina bifida was 1.7 (CI 0.6-5.0). In a substudy, hospital records were examined in an attempt to validate the reported cerebrospinal defects (spina bifida, anencephaly, hydrocephalus). While a difference was detected, its interpretation is limited by differential participation between the veteran groups and failure to validate negatives reported; that is, the veterans not reporting their children having a birth defect. Thus, the issue of a recall bias is of major concern with this study. In the CDC Birth Defects Study which utilized the population-based birth defects registry system in the metropolitan Atlanta area (Erickson et al., 1984a), there was no association between Vietnam veteran status and the risk of spina bifida (OR = 1.1, CI 0.6-1.7) or anencephaly (OR = 0.9, CI 0.5-1.7). However, the exposure opportunity index (EOI) based upon interview data was associated with an increased risk of spina bifida; for the highest estimated level of exposure (EOI-5) the OR was 2.7 (CI 1.2-6.2). There was no similar pattern of association for anencephaly. Thus, all three epidemiologic studies (Ranch Hand, VES, CDC Birth Defects Study) suggest an association between herbicide exposure and an increased risk of spina bifida in offspring.

In contrast to most other diseases, for which the strongest data have been from occupationally exposed workers, these studies focused on Vietnam veterans. Although the studies were judged to be of relatively high quality, they suffer from methodologic limitations, including possible recall bias, nonresponse bias, small sample size, and misclassification of exposure. For these reasons, the

committee concludes that there is limited/suggestive evidence for an association between exposure to herbicides used in Vietnam and spina bifida in offspring.

There is also limited/suggestive evidence of an association between exposure to herbicides and acute and subacute (transient) peripheral neuropathy. There are several published studies relevant to this health outcome, but they are primarily case histories from occupational studies and chemical reports following the Seveso accident, which describe transient symptoms of peripheral neuropathies in highly exposed intervals (Todd, 1962; Berkley and Magee, 1963; Goldstein et al., 1959; Boeri et al., 1978; Pocchiari et al., 1979; Filippini et al., 1981). Todd (1962) reported a sprayer of 2,4-D weedkiller who developed a gastrointestinal disturbance and, within days, after contact with the chemical, a severe sensory/motor polyneuropathy. Recovery occurred over a period of months. Berkley and Magee (1963) reported another patient who developed a polyneuropathy four days after exposure to a liquid solution of 2,4-D, which was being sprayed in a cornfield. The neuropathy was purely sensory in type. The patient's symptoms gradually resolved over months. Goldstein et al. (1959) described three patients with sensory/motor polyneuropathies that developed over several days and progressed over several weeks after exposure to 2,4-D. All had incomplete recovery after several years. Although these patients were not examined neurologically before their exposure, the temporal relationship between the development of their clinical deficit and the herbicide exposure was clearly documented in the study. Nonetheless, the possibility that their occurrence was unrelated to the herbicide exposure and was due to other disorders such as idiopathic Guillain-Barre syndrome cannot be entirely excluded. The trend to recovery in the individual cases reported and the negative findings of many long-term follow-up studies of peripheral neuropathy suggest that if a peripheral neuropathy indeed develops, it resolves with time.

Case reports and animal studies led to the conclusion in *VAO* that porphyria cutanea tarda (PCT) was associated with TCDD or herbicide exposure in genetically predisposed individuals. However, three recent reports (Jung et al., 1994; Calvert et al., 1994; and Von Benner et al., 1994) failed to support this association. Two studies (Calvert et al., 1994, and Jung et al., 1994) included extensive analysis of porphyrin levels on 451 workers with demonstrated or potential exposure to herbicides and TCDD. The studies found no relationship between porphyrin levels and TCDD levels, and no excess of PCT in these cohorts. However, some workers had evidence of increased porphyrins in urine, suggesting that further investigation is warranted. These new reports, combined with the literature reviewed in *VAO*, led the committee to conclude that there is limited/suggestive evidence of an association between PCT and exposure to herbicides and/or TCDD.

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

The scientific data for the remainder of the cancers and other diseases reviewed by the committee were inadequate or insufficient to determine whether an association exists. For cancers 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 fail to control for confounding or have inadequate exposure assessment. This group includes hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers (cervical, uterine, ovarian), breast cancer, renal cancer, testicular cancer, leukemia, and skin cancer. The scientific evidence for each of these cancers is detailed in Chapter 7. Recent published studies contained enough evidence to warrant moving skin cancer from the limited/suggestive evidence of no association category to this categoty. The scientific evidence for two cancers that are of special interest to the DVA—hepatobiliary cancer and nasopharyngeal cancer—will also be summarized here. Because of its public health importance, breast cancer also receives attention.

Several reproductive effects are classified in this category, including spontaneous abortion, birth defects other than spina bifida, neonatal/infant death and stillbirths, low birthweight, childhood cancer in offspring, and abnormal sperm parameters and infertility. The scientific evidence for reproductive effects is detailed in Chapter 9. Neurobehavioral effects that are classified in this category include cognitive and neuropsychiatric disorders, motor/coordination dysfunction, and chronic peripheral nervous system disorders. The scientific evidence for these effects is detailed in Chapter 10. Other health effects that are classified in this category include metabolic and digestive disorders, immune system disorders, circulatory disorders, and respiratory disorders. The scientific evidence for these effects is detailed in Chapter 11.

On the whole, the estimated relative risks for skin cancer are fairly evenly distributed around the null, and in a number of studies the confidence intervals were relatively narrow. This conclusion led the committee responsible for *VAO* to conclude that there was limited/suggestive evidence of no association between skin cancer and exposure to herbicides used in Vietnam. One other recent study (Lynge, 1993), however, found an excess risk of skin cancer. Based on four cases, a statistically significant increase in the risk of melanoma was observed in the subgroup of men who had been employed for at least one year, using a ten-year latency period (SIR = 4.3, CI 1.2-10.9). However, no information is given about the risk in men with less than 10 years of latency and expected numbers for women are not reported so observed elevated risk in the men with more than 10 years of latency cannot be put into context. Another study found a significant excess risk in men from the Seveso area (SMR = 3.3), based on only three cases (Bertazzi et al., 1989a,b). The committee felt that these results, while not even

suggestive evidence about an association, undermined the evidence of no association in *VAO*, and thus warranted changing skin cancer to the "inadequate/insufficient evidence to determine whether an association exists" category.

There are relatively few occupational, environmental, and veterans studies of hepatobiliary cancer, and most of these are small in size and have not controlled for lifestyle-related factors. The estimated relative risk in the various studies range from 0.3 to 3.3, usually with broad confidence intervals. Given the methodological difficulties associated with most of these studies, the evidence regarding hepatobiliary cancer is not convincing with regard to either an association or lack of association with herbicides or TCDD. The few studies that have been published since *VAO* (Asp et al., 1994; Bertazzi et al., 1993; Blair et al., 1993; Collins et al., 1993; and Cordier et al., 1993) do not change the conclusion that there is inadequate evidence to determine whether an association exists between exposure to herbicides and hepatobiliary cancer.

There are only a few occupational studies, one environmental study, and one veterans study of nasal and/or nasopharyngeal cancer, including two recently published studies (Asp et al., 1994, and Bertazzi et al., 1993). The estimated relative risks in the various studies range from 0.6 to 6.7, usually with broad confidence intervals. Thus, there is inadequate/insufficient evidence to determine whether an association exists between exposure to herbicides and nasal/nasopharyngeal cancer.

There have been a few occupational studies, two environmental studies, and two veterans studies of breast cancer among women exposed to herbicides and/or TCDD. These include four recently published studies (Bertazzi et al., 1993; Blair et al., 1993; Dalager et al., 1995; and Kogevinas et al., 1993). Most of these studies reported a relative risk of approximately 1.0 or less, but it is uncertain whether or not the female members of these cohorts had substantial chemical exposure. TCDD appears to exert a protective effect on the incidence of mammary tumors in experimental animals (see Chapter 3), which is consistent with the tendency for the relative risks to be less than 1.0. In summary, however, the committee believes that there is insufficient evidence to determine whether an association exists between exposure to herbicides and breast cancer.

Health Outcomes with Limited/Suggestive Evidence of No Association

In *VAO*, the committee found a sufficient number and variety of well-designed studies to conclude that there is limited/suggestive evidence of no association between a small group of cancers and exposure to TCDD or herbicides. This group includes gastrointestinal tumors (colon, rectal, stomach, and pancreatic), brain tumors, and bladder cancer. The recent scientific evidence continues to support the classification of these cancers in this category, and it is detailed in Chapter 7. Based on the recent literature, there are no additional diseases that satisfy the criteria necessary for this category.

For outcomes in this category, several adequate studies covering the full range of levels of herbicide exposure that human beings are known to encounter are mutually consistent in not showing a positive association between exposure and health risk at any level of exposure. These studies have relatively narrow confidence intervals. 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.

The Relationship Between the Length of Time Since Exposure and the Possible Risk of Cancer Development

The importance of latency effects and other time-related factors in determining cancer risk has long been recognized, and statistical methodologies have been developed to study this issue. A variety of practical difficulties relating to exposure assessment and other data requirements, however, have limited the use of these methods in epidemiological studies of environmental carcinogens. In response to the request from the DVA to explore latency issues related to herbicides used in Vietnam, the committee attempts in Chapter 8 to establish a methodology to address the timing of herbicide exposure and the risk of cancer. This chapter also reviews the literature on herbicide exposure and cancers classified in the "Sufficient Evidence of an Association" and "Limited/Suggestive Evidence of an Association" categories for results that describe how timing of exposure affects the relative risk due to exposure.

For four of the cancers studied—soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma—the committee concluded that there was not enough information in the literature about the timing of exposure and subsequent risk to further discuss latency issues. The committee did find that there was enough information about the timing of exposure and respiratory and prostate cancers, with considerably more information about the former than the latter, to warrant analysis of results. Both of these cancers are in the "Limited/Suggestive Evidence of an Association" category, and this conclusion has not changed after this investigation of time-related factors.

The evidence in the literature suggests that the time from exposure to TCDD to increased risk of respiratory cancer is less than ten years, and that the increase in relative risk continues for somewhat more than 20 years. The available literature does not indicate how long it takes for relative risks to return to one. These conclusions are based primarily on the study conducted by the National Institute for Occupational Safety and Health (Fingerhut, 1991), since this study is the most informative about the changes in risk of respiratory cancer with time since first exposure to TCDD, but the calculations are supported by other studies that have investigated time-related effects. The epidemiological literature was not infor-

mative on the effect of the age at which the exposure was received, or whether the carcinogen appeared to act at an early or late stage of the carcinogenic process.

The limited data do not indicate any increase in the relative risk of prostate cancer with time since exposure to TCDD. For prostate cancer, the epidemiological literature was not informative on how long the effects of exposure last, the effect of the age at which the exposure was received, or whether the carcinogen acts at an early or late stage of the carcinogenic process.

Increased Risk of Disease in Vietnam Veterans

Although there have been numerous health studies of Vietnam veterans, most have been hampered by relatively poor measures of exposure to herbicides or TCDD, in addition to other methodological problems. Most of the evidence on which the findings in Table 1-1 are based comes from studies of people exposed to dioxin or herbicides in occupational and environmental settings, rather than from studies of Vietnam veterans. The committee found this body of evidence sufficient for reaching the conclusions about statistical associations between herbicides and the health outcomes summarized in Table 1-1; however, the lack of adequate data on Vietnam veterans per se complicates the second part of the committee's charge, which is to determine the increased risk of disease among individuals exposed to herbicides during service in Vietnam. Given the large uncertainties that remain about the magnitude of potential risk from exposure to herbicides in the epidemiologic studies that have been reviewed (Chapters 7, 9, 10, and 11), the inadequate control for important confounders, and the uncertainty about the nature and magnitude of exposure to herbicides in Vietnam (Chapter 5), the necessary information to undertake a quantitative risk assessment is lacking. Thus, in general, it is not possible for the committee to quantify the degree of risk likely to be experienced by veterans because of their exposure to herbicides in Vietnam. The quantitative and qualitative evidence about herbicide exposure among various groups studied suggests that most Vietnam veterans (except for selected groups with documented high exposures, such as participants in Operation Ranch Hand) had lower exposure to herbicides and TCDD than the subjects in many occupational and environmental studies. However, individual veterans who had very high exposures to herbicides could have risks approaching those in the occupational and environmental studies.

2

Research Highlights

BIRTH DEFECTS

Introduction

This section taken from Chapter 9 of the full report summarizes published scientific literature on exposure to herbicides and birth defects. A complete discussion of the evidence is presented for these adverse reproductive/developmental outcomes because the committee has changed its assessment of this literature since the release of *VAO*. In *VAO*, the committee concluded that the evidence at that time was inadequate or insufficient to determine whether an association existed between exposure to herbicides and birth defects.

Background

The March of Dimes defines a birth defect as "an abnormality of structure, function or metabolism, whether genetically determined or as the result of an environmental influence during embryonic or fetal life" (Bloom, 1981). Other terms often used interchangeably with birth defects are "congenital anomalies" and "congenital malformations." Major birth defects are usually defined as those abnormalities that are present at birth and severe enough to interfere with viability or physical well-being. Major birth defects are seen in approximately 2 to 3 percent of live births (Kalter and Warkany, 1983). An additional 5 percent of birth defects can be detected with follow-up through the first year of life. Given the general frequency of major birth defects of 2 to 3 percent and the number of

men who served in Vietnam (2.6 million), and assuming that they had at least one child, it has been estimated that 52,000 to 78,000 babies with birth defects have been fathered by Vietnam veterans, even in the absence of an increase due to exposure to herbicides or other toxic substances (Erickson et al., 1984a).

Epidemiologic Studies of Birth Defects

Because the publication of new data from the Ranch Hand study has caused the committee to change its conclusion about the strength of the evidence regarding the association between exposure to herbicides used in Vietnam and birth defects, the following material was included from *VAO* to present a complete picture about the evidence for the committee's conclusions. The section entitled "Ranch Hand Study," however, is based on the new information. Chapter 6 of the full report discusses in greater detail the characteristics of each study.

Occupational Studies

Four occupational epidemiology studies have examined the potential association between herbicide exposure of male workers and birth defects. The Townsend study (Townsend et al., 1982) of workers with potential dioxin exposure at a Dow Chemical plant did not find an increased risk of birth defects among dioxin-exposed workers (30 births with anomalies; 47/1,000 births) compared to unexposed workers (87 births with anomalies; 49/1,000 births; OR = 0.9, CI 0.5-1.4). A major limitation of this study is its limited statistical power to detect an elevated odds ratio for specific defects. The authors noted that the study had 26 percent power to detect a doubling of risk due to exposure for a group of indicator malformations (anomalies thought to be easily recognized and reported by the mother, such as an oral cleft, spina bifida, and Down's syndrome). An additional problem is that despite the use of these "indicator malformations," without medical records, validation of the accuracy of maternal self-report of birth defects is questionable for many conditions.

Two studies of workers from a 2,4,5-T plant in Nitro, West Virginia, did not report an association with birth defects among offspring (Moses et al., 1984; Suskind and Hertzberg, 1984). The relative risk estimates for any birth defect were 1.3 (CI 0.5-3.4) for Moses et al. and 1.1 (CI 0.5-2.2) from the Suskind and Hertzberg study. Both studies had limited statistical power, given the small number of subjects (204 exposed workers in the Suskind and Hertzberg study; 117 exposed workers in the Moses study). This is especially problematic for the evaluation of most specific birth defects. Both studies also relied on self-reports for the ascertainment of birth defects.

A study of 2,4,5-T sprayers found only a slightly elevated odds ratio for congenital anomalies (OR = 1.2, CI 0.5-3.0) associated with the spraying group (Smith et al., 1982). The study used self-administered questionnaires to deter-

mine outcomes. Like the other studies, it had limited power for the analysis of individual birth defects.

Environmental Studies

A variety of environmental studies have examined the relationship between herbicide exposure and prevalence of birth defects (Nelson et al., 1979; Gordon and Shy, 1981; Hanify et al., 1981; Mastroiacovo et al., 1988; Stockbauer et al., 1988; White et al., 1988; Fitzgerald et al., 1989; Jansson and Voog, 1989). Some studies reported a statistical association with specific birth defects (clubfoot, Fitzgerald et al., 1989; cleft lip with or without cleft palate, Gordon and Shy, 1981; heart, hypospadias, clubfoot, Hanify et al., 1981; oral clefts, Nelson et al., 1979), although others have not reported an association (Stockbauer et al., 1988; Fitzgerald et al., 1989; Jansson and Voog, 1989), including the Seveso study (Mastroiacovo et al., 1988). Interpretation of the results of these environmental studies is difficult, because most of the studies were inconsistent, were based on ecologic correlations, had inadequate statistical power, did not validate birth defects recorded from vital statistics or self-reports, and included both male and female exposures.

A recently published study from Vietnam evaluated the risk of birth defects among the offspring of mothers who resided in a village in the southern part of the country that had been sprayed during the conflict (Phuong et al., 1989); 81 cases of birth defects (diagnosis not specified) were identified. No differences were reported between cases and controls for the potentially confounding factors investigated. Strong associations were found for birth defects (calculated from data presented; OR = 3.8, CI 1.1-13.1). The paper is difficult to evaluate given the sparse details presented. Study design factors such as how birth defects were diagnosed and what types were detected, the size of the original case and control groups from which the final groups were sampled, the pattern of patient accrual for this hospital, the method of data collection, and how the potential herbicide spraying histories were determined were not specified. Finally, to put the study in the context of this review, the potential exposure 17 to 22 years earlier pertains to both the mother and the father.

Results from a number of other studies from Vietnam, both of sprayed villages in the southern part of the country and of veterans returning to the unsprayed northern regions, have been reported, mostly in a review by Constable and Hatch (1985). These studies indicate an increased risk of birth defects, including anencephaly, oral clefts, and a variety of other anomalies. Nonetheless, these studies generally suffer from poor reporting and a variety of methodologic problems such as limited control of confounding factors, use of a referral hospital, lack of comparison groups, uncertainty of exposure classification, and no validation of reported birth defects. Although the findings are suggestive of an association

between herbicide spraying and birth defects, the available studies are insufficient to draw firm conclusions.

Vietnam Veterans Studies

As part of the CDC Vietnam Experience Study (1989), the reproductive outcomes and the health of children of male veterans were examined. The VES assessment included a telephone interview, a review of hospital birth defect records for a subsample of veterans who underwent a medical examination, and a review of the medical records of selected birth defects for all study subjects.

The interview data revealed that Vietnam veterans reported more birth defects (64.6 per 1,000 total births) among offspring than did non-Vietnam veterans (49.5 per 1,000 total births). The adjusted odds ratio estimate for congenital anomalies as a group was 1.3 (CI 1.2-1.4). When examined by specific defect category, elevated adjusted odds ratios were found for defects of the nervous system (OR = 2.3, CI 1.2-4.5); ear, face, neck (OR = 1.6, CI 0.9-2.8); and integument (OR = 2.2, CI 1.2-4.0). A small but statistically significant odds ratio of 1.2 (CI 1.1-1.5) was found for musculoskeletal defects. An analysis of specific defects considered by the investigators to be relatively common and reliably diagnosed was also conducted. Elevated (crude) odds ratios were reported for hydrocephalus (OR = 5.1, CI 1.1-23.1), spina bifida (OR = 1.7, CI 0.6-5.0), and hypospadias (OR = 3.1, CI 0.9-11.3). Vietnam veterans also reported having more children with multiple defects (OR = 1.6, CI 1.1-2.5) than non-Vietnam veterans. An analysis of Vietnam veterans' self-reported herbicide exposure found a dose-response gradient, with an adjusted odds ratio for birth defects of 1.7 (CI 1.2-2.4) at the highest level of exposure.

The VES also examined serious health problems in the veterans' children; that is, the veterans were asked to report physician-diagnosed major health problems or impairments during the first five years of their children's lives. About half of the health conditions reported were respiratory disease (mostly asthma and pneumonia) and otitis media. For most of the conditions, the veterans reported more health conditions than non-Vietnam veterans (all conditions, OR = 1.3, CI 1.2-1.4). After excluding children with a serious health condition or either a birth defect or cancer, the overall crude OR was 1.2 (CI 1.1-1.3). Elevated crude odds ratios were found for anemias (OR = 2.0, CI 1.2-3.3), diseases of the skin (OR = 1.5, CI 1.1-1.9), rash (OR = 2.3, CI 1.1-4.9), and allergies (OR = 1.6, CI 1.2-2.1). Without medical records that validate for many of these types of common conditions and health problems, recall bias may be an explanation for many of these findings.

The CDC (1989) did conduct two substudies using hospital records to identify birth defects among the veterans' offspring. The first, the General Birth Defects Study (GBDS), compared the occurrence of birth defects recorded on hospital records for the children of Vietnam and of non-Vietnam veterans (130

cases and 112 cases, respectively) who participated in the medical examination component of the VES. For a variety of characteristics, there were no apparent differences between the group of men who participated in the exam and the total interview group. There was no difference in the prevalence of birth defects between the two groups of children (crude OR = 1.0, CI 0.8-1.3). There was a slight but nonsignificant excess for major birth defects (OR = 1.2, CI 0.8-1.9). When analyzed by organ system, only digestive system defects appeared to be elevated (OR = 2.0, CI 0.9-4.6), although the small number of defects precluded the analysis of several broad categories. The number of defects was also too small for the analysis of specific individual defects. An analysis by race did indicate an elevated odds ratio (3.4, CI 1.5-7.6) for black Vietnam veterans. An examination of the specific defects listed on hospital records for children of black veterans did not reveal any particular pattern. A comparison of interview and hospital records was also conducted to evaluate the extent of potential misclassification of veteran responses. In general, interview responses were not predictive of the presence of a defect for either veteran group. The agreement between interview and hospital records was slightly poorer for Vietnam veterans. For example, the positive predictive value of the interview response for the presence of a defect in the hospital record was 24.8 percent among Vietnam veterans and 32.9 percent among non-Vietnam veterans. Sensitivity was 27.1 percent among Vietnam veterans and 30.3 percent among non-Vietnam veterans. The kappa measure of agreement was also lower (20.9 percent versus 27.6 percent) among Vietnam veterans.

The second substudy, the Cerebrospinal Malformation (CSM) Study, involved the analysis of medical records for all cases of cerebrospinal malformations (spina bifida, anencephalus, hydrocephalus) and stillbirths reported by veterans in the interview study. The substudy found 26 cerebrospinal malformations (live and stillbirths) among children of Vietnam veterans and 12 among children of non-Vietnam veterans. No formal analysis of the difference in malformations between the veteran groups was conducted, because negative responses (i.e., children without a reported malformation) were not verified and the participation rates differed between groups (7.8 percent of Vietnam veterans and 22.1 percent of non-Vietnam veterans refused to participate).

The VES did find suggestive associations for birth defects. It is interesting to note that some potential associations were found for birth defects considered by the investigators to be "relatively common, easily diagnosed, and observable at birth" (CDC, 1989). These include hydrocephalus (OR = 5.1, CI 1.1-23.1) and hypospadias (OR = 3.1, CI 0.9-11.3). The GBDS did not replicate these findings, but this sample had limited power for the analysis of specific defects. Although associations were not found for all conditions, there was clearly a general pattern of a greater prevalence of birth defects in the offspring of Vietnam veterans, according to self-reports. The authors properly note the potential for recall bias as an explanation for the pattern of excess risk. As an attempt to evaluate recall bias, two record validation studies of birth defects were conducted. Overall, the

GBDS did not find any association with an increased risk of birth defects among offspring of Vietnam veterans. However, this validation study had limited power to detect an increased risk for specific birth defects. The second validation substudy, the CSM review, was flawed by the differentially poor response rate among the non-Vietnam veteran group. This result and the fact that negative responses were not pursued discouraged the investigators from estimating the relative risk for cerebrospinal malformations.

Another important study of Vietnam veterans was the CDC Birth Defects Study (Erickson et al., 1984a,b). In this study, children with birth defects among 428 fathers who were reported to have been Vietnam veterans were compared to children with birth defects among 268 control fathers who were non-Vietnam veterans. The odds ratio for Vietnam veteran status in relation to any major birth defect among offspring was 1.0 (CI 0.8-1.1). Analysis of the Agent Orange exposure opportunity index (EOI; see *VAO* Chapter 6 for details) based on both military records and self-reports did not indicate a statistically significant trend of increasing risk of all types of birth defects (combined) with increasing levels of Agent Orange exposure. No association was noted between Vietnam veteran status or self-reported Agent Orange exposure and risk of fathering a child with multiple birth defects (OR = 1.1, CI 0.7-1.7). The odds ratios for Vietnam veteran status, self-reported Agent Orange exposure, and logistic regression coefficients for EOI based on self-report and military records for most of the 95 birth defect groups were not significantly elevated. Although the odds ratio for spina bifida was not elevated with Vietnam veteran status (OR = 1.1), the EOI indices showed a pattern of increasing risk. For example, the odds ratios for the EOI based on information obtained during the interview for low to high levels of exposure (levels 1 to 5) were 1.2 (CI 1.0-1.4), 1.5 (CI 1.1-2.1), 1.8 (CI 1.1-3.0), 2.2 (CI 1.2-4.3), 2.7 (CI 1.2-6.2). A similar pattern was found for cleft lip with/without cleft palate— namely, EOI-1 (OR = 1.2, CI 1.0-1.4), EOI-2 (OR = 1.4, CI 1.0-1.9), EOI-3 (OR = 1.6, CI 1.0-2.6), EOI-4 (OR = 1.9, CI 1.0-3.6), and EOI-5 (OR = 2.2, CI 1.0-4.9). The category "specified anomalies of nails" had an increased odds ratio for Vietnam veteran status and elevated coefficients (not statistically significant) for the two exposure indices. The category "other neoplasms" was related to the EOI based on the father's self-reported Agent Orange exposure. This group included a variety of congenital neoplasms such as cysts, teratomas, and benign tumors. In an attempt to search for a Vietnam veteran birth defect "syndrome," pairs and triplets of defects were examined for combinations that yielded significant differences in the distribution among Vietnam veterans and controls. According to the authors, these analyses did not produce any important associations or patterns among defect combinations.

The results of this study were generally negative; that is, there was not a general pattern of increased risk for birth defects among the offspring of Vietnam veterans. However, the analysis of the Agent Orange EOIs based on military records found a significant trend for increased risk for spina bifida with increased

exposure. As the authors note, this finding must be viewed with caution, because a related defect, anencephalus, was not found to be associated with a significant EOI trend. Another positive association was noted for cleft lip without cleft palate, where a significant regression coefficient was found for the EOI index based on the father's interview. No association was found for the EOI from military records.

The CDC Birth Defects Study has many strengths, including the use of a population-based registry system with careful classification of birth defects for analysis. The statistical power of the study was excellent for many major birth defects. Use of the Agent Orange EOIs is an attempt to refine exposure assessment procedures compared to measures used in most other studies. The study did have several important limitations. First, the response rates among cases and controls were problematic, with approximately 56 percent of eligible case and control fathers interviewed. Examination of the nonparticipation group revealed lower participation among persons classified as "nonwhite." The analyses by race did not find important differences, but the potential for bias should not be overlooked. Another problem relates to the fact that case births occurred from 1968 through 1980, but interviews took place during 1982 and 1983, up to 14 years after the birth. To minimize the potential recall bias induced by this long lag period, controls were matched on year of birth.

Aschengrau and Monson (1990) studied late adverse pregnancy outcomes among 14,130 obstetric patients who delivered at Boston Hospital for Women from August 1977 to March 1980. History of the fathers' military service in Vietnam was determined from Massachusetts and national military records by using the husbands' names and Social Security numbers. The likelihood of combat experience, based on branch of service and military occupation, was used to estimate potential herbicide exposure. The analyses compared the risk of malformations among children of 107 Vietnam veterans to that for children of 1,432 men without known military service; the risk in 313 non-Vietnam veterans compared to the men without military service; and the risk in the Vietnam veterans compared with the non-Vietnam veterans. There was a slight, nonsignificant increase in the odds ratio for all congenital anomalies for Vietnam veterans compared to men without known military service (OR = 1.3, CI 0.9-1.9) and for Vietnam veterans compared with non-Vietnam veterans (OR = 1.2, CI 0.8-1.9). For major malformations, the odds ratio was elevated for Vietnam veterans compared with men without military service (OR = 1.8, CI 1.0-3.1), but the ratio decreased for Vietnam veterans compared with non-Vietnam veterans (OR = 1.3, CI 0.7-2.4). Only slight increases were found for the analysis of minor malformations and "only normal variants." Although based on small numbers, the analyses of 12 malformation groups found that children of Vietnam veterans, compared to children of men with no known military service, had an increased risk of malformations of the nervous system, cardiovascular system, genital organs, urinary tract, and musculoskeletal system. Confidence intervals were not

presented with the odds ratio estimates, but it was noted that they included 1.0, so elevated risks were not significantly increased. Further examination of specific anomaly diagnoses for the 18 infants of Vietnam veterans with major malformations did not reveal any pattern of association with potential herbicide exposure.

Although the study did find a positive association between paternal military service in Vietnam and the risk of major malformations in offspring, the authors suggest cautious interpretation of their findings, given the small number of subjects in many of the comparisons involving specific groups of birth defects. Additionally, it was noted that some of the malformations observed can also be due to maternal and delivery factors (endocrine condition and fetal presentation). An important problem relates to misclassification of herbicide exposure due to equating exposure to service in Vietnam.

Two state health surveys of veterans (Iowa and Hawaii) did not indicate an increased prevalence of birth defects (Rellahan, 1985; Wendt, 1985), but a survey in Maine did report an increased risk of birth defects among veterans (Deprez et al., 1991). The limitations of these general survey studies affect their usefulness in this evaluation.

As part of the National Vietnam Veterans Birth Defects/Learning Disabilities Registry and database, a joint project of the Association of Birth Defect Children and the New Jersey Agent Orange Commission, a self-administered questionnaire was sent to Vietnam veterans to inquire about birth defects and a variety of conditions and disabilities in the children of Vietnam veterans and non-Vietnam veterans (Lewis and Mekdeci, 1993). A preliminary analysis indicated no differences in birth defects between the two groups; however, for a variety of conditions, including allergies, frequent infections, benign tumors, cysts, and chronic skin disorders, the veterans showed a higher frequency. The possibility of recall bias and the self-selected nature of the registry are of concern. Nonetheless, a carefully designed and comprehensive epidemiologic study with review of medical records could address the possibility of an association with some of these childhood health conditions.

A study of birth defects among offspring of Australian Vietnam veterans was conducted using a total of 8,517 matched case-control pairs, with 127 infant cases and 123 infant controls having a father who served in Vietnam (Donovan et al., 1984). There were 202 cases and 205 controls whose fathers were in the Army but did not serve in Vietnam. The adjusted odds ratio for birth defects among children of Vietnam veterans versus all other men was 1.02 (CI 0.8-1.3). Analysis of subgroups based on the type of Army veteran (Australian Regular Army enlistees, National Service draftees) did not detect any increased odds ratios for these comparisons. There was a slight, statistically nonsignificant increase in the odds ratio for National Service Vietnam veterans versus those who did not serve in Vietnam (OR = 1.3, CI 0.9-2.0). The risk was independent of the length of Vietnam service and the time between service and conception. Analyses by diagnostic group (central nervous system, cardiovascular, oral clefts, hypospadias,

musculoskeletal, dislocation of hip, chromosomal anomalies) did not show an excess risk for Vietnam veterans. However, two defects had odds ratios above 1.5 (statistically nonsignificant)—ventricular septal defects (OR = 1.8) and Down's syndrome (OR = 1.7).

Overall, this study was negative; that is, there was no evidence of an increased risk of fathering a child with a congenital anomaly for Australian Army veterans who served in Vietnam. As indicated by the upper confidence limit (1.3), this study had adequate power to rule out an odds ratio greater than 1.3 for congenital anomalies. Assessment of potential Agent Orange exposure in this study is limited, because "history of service" in Vietnam was used as the primary "exposure" variable. This uncertainty is further compounded by potential differences in the location and nature of service of Australian veterans in Vietnam and their resultant herbicide exposure.

The Australian study of veterans living in Tasmania reported more congenital anomalies among the 357 Vietnam veterans than among the comparison families (Field and Kerr, 1988). The authors suggested that the results indicated a pattern of association with congenital heart disease and anomalies of the central nervous system. As described earlier in the section on spontaneous abortion, there are several notable problems with this study, including inadequate presentation of results, potential selection bias, self-reported health outcomes, and using service in Vietnam as a surrogate for herbicide exposure.

Ranch Hand Study The latest report from the Air Force Health Study (AFHS) of Operation Ranch Hand veterans ("Ranch Hands") and their children was published in 1995 (Wolfe et al., 1995). The Air Force released a first report on the analysis of reproductive effects in 1982, and this report was reviewed in *VAO* (AFHS, 1992). The original study cohort comprised 1,098 Ranch Hands who regularly handled and sprayed herbicides in Southeast Asia from 1962 to 1971 ("exposed cohort") and a comparison group of 1,549 Air Force veterans who were in Southeast Asia at the same time but presumably were not exposed to herbicides. In 1987, 995 Ranch Hands (91 percent of original study group) and 1,299 comparison veterans (84 percent of original group) participated in a physical exam and agreed to provide serum samples for the dioxin assay. A total of 872 Ranch Hands (79 percent of original cohort, 88 percent of 1987 cohort) and 1,036 comparison subjects (67 percent of original group, 80 percent of 1987 cohort) were available for analysis, after exclusion of samples that were unreliable because of laboratory error or that had dioxin levels below the level of detection or above an upper threshold for background (10 parts per trillion [ppt]) for comparison subjects. Of the 872 Ranch Hands, 454 had 1,006 self-reported conceptions and 419 fathered 792 liveborn infants during their service in Vietnam or until January 1990. Of the 1,036 comparison veterans, 570 had 1,235 conceptions and 531 fathered 981 liveborn infants during this period.

The initial dioxin level was estimated from the current level using a first-

order decay rate model with a fixed 7.1-year half-life estimate. The referent group for the Ranch Hands included the conceptions and offspring of comparison men with "background" levels (≤10 ppt, $N = 570$, mean = 3.9 ppt). Ranch Hands with levels at background were analyzed as a separate stratum ($N = 179$), since the authors felt this group included a mixture of exposed and unexposed veterans, given their mean level of 6.1 ppt and uncertainties in dioxin elimination. The other strata used in the analysis included Ranch Hand "low" (current ≤10 ppt and initial ≤ 110 ppt, $N = 119$) and Ranch Hand "high" (current ≤10 ppt and initial >110 ppt, $N = 156$). The 110 ppt level was chosen because it is the median estimated initial dioxin level at the time of conception of the Ranch Hands with levels greater than 10 ppt. As the authors point out, this cutoff is arbitrary, with no assumed biologic meaning. Reproductive outcomes of comparison veterans with a current dioxin levels of greater than 10 ppt were not analyzed, because the investigators suspected that these may reflect dioxin exposure after service in Vietnam.

The reproductive and developmental outcomes included in the analyses included spontaneous abortion (miscarriage, fetal death less than 20 weeks gestation), stillbirth (fetal death 20 weeks or greater gestation), and birth defects. All conceptions reported by the men, their wives, or their partners were verified through medical records and vital statistics review. The proportion of adverse outcomes verified by specific sources was not stated. This may be important, given the known limitations of vital statistics records for the identification and classification of certain pregnancy outcomes.

Stratified analyses were performed, adjusting for six covariates, including father's race, mother's smoking and drinking during pregnancy, mother's and father's age at birth or conception, and father's military occupation (officer, enlisted flyer, enlisted nonflyer). In addition, adjustment was made for history of spontaneous abortion prior to service in Southeast Asia. The authors noted that the adjustment of father's military occupation was performed because it may serve as a proxy for education and occupation is associated with dioxin level. Adjustment for occupation may, in fact, lead to some degree of "overadjustment" owing to the high correlation between occupation and exposure potential. Comparison of the adjusted estimates with the unadjusted risk ratio estimates derived from the data provided in the paper showed little difference, indicating that the adjustment for military occupation did not materially affect the results.

The validation of self-reported birth defects in this study was systematic and of high quality. Although the etiology of most birth defects remains unknown, the study accounted for an array of factors controlled for in most previous studies of birth defects. Considering all birth defects combined, there was a slightly higher proportion of defects among Ranch Hand children than among comparison children (22.3 percent versus 20.8 percent). No general pattern of increasing risk with increasing dioxin levels was found. A small increased RR of 1.3 (CI 1.0-1.6) was found for the low-dioxin category. There was a slightly higher

prevalence of major birth defects among Ranch Hand children compared to comparison children (7.4 percent versus 5.7 percent). There was an elevated risk ratio for the low-level category (RR = 1.7; CI 1.1-2.7), although a dose-response gradient was not evident, with an RR of 1.1 for background (0.6-1.8) and 1.2 (CI 0.8-2.1) for the high-level category. The analysis of birth defect groups yielded a total of 11 increased and five decreased risk ratios for the low- and high-level comparisons with the referent category. For example, the analysis of circulatory system and heart defects found risk ratios of 2.3 for low and 0.9 for high levels. Genital defects had risk ratios of 1.8 for low and 1.2 for high; urinary system defects had risk ratios of 2.0 for low and 2.1 for high. Examination of specific defects included in this larger defect grouping did not show any specific associations or patterns. Interestingly, neural tube defects (spina bifida, anencephaly) were in excess among offspring of Ranch Hands, with four total (rate of five per 1,000), in contrast to none among the comparison infants (exact p = .04). The four cases were distributed as two spina bifida in the high-level category, one anencephaly and one spina bifida in the low-dioxin category. There was no clear pattern of association with developmental disabilities in terms of specific delays in development or hyperkinetic syndrome, although the low-level stratum for specific delays in development had a risk ratio of 1.5 (CI 1.0-2.3).

Summary

The recently published results of the analysis of birth defects among the offspring of Ranch Hands suggest the possibility of an association between dioxin exposure and risk of neural tube defects. These findings require a consideration of the current evidence for an association between herbicides and neural tube defects and an increased risk among Vietnam veterans exposed to herbicides. Table 2.1 includes a summary of the studies that have reported results specifically for neural tube defects (typically anencephaly and/or spina bifida), including studies in *VAO* and more recent publications. Unfortunately, some studies (e.g., Seveso), particularly the occupational and environmental studies, do not have results specific for individual birth defects, usually because of the small number of cases. A number of studies of veterans appear to show an elevated relative risk for either service in Vietnam or estimated exposure to herbicides or dioxin and neural tube defects (anencephaly and/or spina bifida) in their offspring. Many of the estimates are imprecise, and chance cannot be ruled out. Nonetheless, the pattern of association warrants further evaluation. The CDC Birth Defects Study (Centers for Disease Control, 1988), the CDC Vietnam Experience Study (Centers for Disease Control, 1989), and the Ranch Hand Study (Wolfe et al., 1992) are of the highest overall quality. The CDC VES cohort study found that more Vietnam veterans reported that their children had a central nervous system anomaly (OR = 2.3; 95 percent CI 1.2-4.5) than did non-Vietnam veterans (Centers for Disease Control, 1989). The odds ratio for spina

bifida was 1.7 (CI 0.6-5.0). A substudy was conducted in an attempt to validate the reported cerebrospinal defects (spina bifida, anencephaly, hydrocephalus) by examination of hospital records. A difference was detected, but its interpretation was limited by differential participation between the veteran groups and failure to validate negative reported—that is, the veterans not reporting their children having a birth defect. Thus, the issue of a recall bias remains a major concern with this study.

The CDC Birth Defects Study utilized the population-based birth defects registry system in the metropolitan Atlanta area (Centers for Disease Control, 1988). There was no association between overall Vietnam veteran status and the risk of spina bifida (OR = 1.1, CI 0.6-1.7) or anencephaly (OR = 0.9, CI 0.5-1.7). However, the exposure opportunity index based on interview data was associated with an increased risk of spina bifida; for the highest estimated level of exposure (EOI-5), the OR was 2.7 (CI 1.2-6.2). There was no similar pattern of association for anencephaly. This study has a number of strengths, including the use of a population-based birth defects registry system and adjustment for a number of potentially confounding factors. Two study limitations include the relatively low response proportions among the case and control subjects (approximately 56 percent) and the lag between birth and interview for some cases and controls.

Thus, all three epidemiologic studies (Ranch Hand, VES, CDC Birth Defects Study) suggest an association between herbicide exposure and an increased risk of spina bifida in offspring. Although the studies were judged to be of relatively high quality, they suffer from methodologic limitations, including possible recall bias, nonresponse bias, small sample size, and misclassification of exposure. In addition, the failure to find a similar association with anencephaly, an embryologically related defect, is of concern.

Conclusions

Strength of Evidence in Epidemiologic Studies

There is limited/suggestive evidence of an association between exposure to the herbicides considered in this report and spina bifida. There is inadequate or insufficient evidence to determine whether an association exists between exposure to the herbicides and all other birth defects. The evidence regarding association is drawn from occupation and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

Biologic Plausibility

Laboratory studies of the potential developmental toxicity, specifically birth defects, of TCDD and herbicides as a result of exposure to adult male animals are too limited to permit conclusions. Chapter 3 of the full report examines these

TABLE 2-1 Epidemiologic Studies—Neural Tube Defects

Reference	Description	*N*	OR/RR (95% CI)
Occupational			
No specific results for neural tube defects			
Environmental			
Hanify et al., 1981	Anencephaly	10	1.4 (0.6-3.3)
	Spina bifida	13	1.1 (0.6-2.3)
Stockbauer et al., 1988	TCDD soil contamination in Missouri		
	Central nervous system defects	3	3.0 (0.3-35.9)
Vietnam veterans			
Erickson, 1984a,b	Birth Defects Study		
	Vietnam veteran: spina bifida	19	1.1 (0.6-1.7)
	Vietnam veteran: anencephaly	12	0.9 (0.5-1.7)
	EOI-5: spina bifida	19[a]	2.7 (1.2-6.2)
	EOI-5: anencephaly	7[a]	0.7 (0.2-2.8)
CDC, 1989	Vietnam Experience Study		
	Interview study		
	Spina bifida	9	1.7 (0.6-5.0) among Vietnam veterans
		5	among non-Vietnam veterans
	Anencephaly	3	among Vietnam veterans
		0	among non-Vietnam veterans
Australian veterans	Birth defects and father's Vietnam service (Australia)		
Health Studies, 1983	Neural tube defects	16	0.9
AFHS, 1995	Follow-up of Air Force Ranch Hands		
	Neural tube defects		4 among Ranch Hand[b]
			0 among comparison

NOTE: *N* = number of exposed cases; OR/RR = Odds Ratio/Relative Risk; CI = Confidence Interval; SIR = Standardized Incidence Ratio.

[a]Number of Vietnam veterans fathering a child with a neural tube defect given any exposure opportunity index score.

[b]Four neural tube defects among Ranch Hand offspring include 2 spina bifida (high dioxin level), 1 spina bifida (low dioxin), and 1 anencephaly (low dioxin). Denominator for Ranch Hand group is 792 liveborn infants.

experimental studies at greater length, as well as others focusing on developmental toxicity.

Risk in Vietnam Veterans

Since the strongest associations are from studies of Vietnam veterans and there are some data suggesting that the highest risks were for those veterans estimated to have had exposure to Agent Orange (e.g., Ranch Hands), it therefore follows that there is limited/suggestive evidence for an increased risk in Vietnam veterans of spina bifida in offspring.

PERIPHERAL NEUROPATHY

Introduction

This section taken from Chapter 10 of the full report summarizes published scientific literature on exposure to herbicides and acute and subacute transient peripheral neuropathy. At the specific request of the Department of Veterans Affairs (DVA), earlier data in *VAO* relating to chronic persistent and transient acute or subacute peripheral neuropathy were reclassified and reexamined in the *Update 1996* report.

Although some of the case reports reviewed in *VAO* suggested that an acute or subacute peripheral neuropathy can develop with exposure to TCDD and related products, other reports with comparison groups did not offer clear evidence that TCDD exposure is associated with chronic peripheral neuropathy. The most rigorously conducted studies argued against a relationship between TCDD or herbicides and chronic persistent neuropathy.

The current report places chronic persistent peripheral neuropathies and acute or subacute peripheral neuropathies into distinct disease categories. The committee found there is inadequate or insufficient evidence of an association between exposure to the herbicides considered in this report and chronic persistent peripheral neuropathy.

The methodology used to establish associations between putative causal agents and persistent chronic neurological deficits relies heavily on epidemiological studies with adequate control or comparison populations. Such methodology can rarely be set in motion with sufficient speed to assess relationships between unexpected chemical exposure and the development of acute or subacute transient neurological disturbance. Because of the very transient nature of the conditions, documenting signs and symptoms in association with documented exposures can be difficult to accomplish in a systematic manner. In such instances, greater reliance must be placed on isolated case histories and less well controlled studies. This section reviews the data from such sources regarding occupational, environmental, and Vietnam herbicide exposure. Because this

disorder is of special interest to the DVA, this discussion integrates the studies reviewed in *VAO* with those published more recently.

The following text reviews the data from such sources regarding occupational, environmental, and Vietnam herbicide exposure and acute and subacute transient peripheral neuropathy. Because this disorder is of special interest to the DVA, this discussion integrates the studies reviewed in *VAO* with those published more recently. Chapter 6 of the full report expounds on many of these studies.

Review of the Scientific Literature on Acute and Subacute Transient Peripheral Neuropathy

Occupational Studies A number of reports have suggested that acute or subacute peripheral neuropathies can be associated with occupational exposure to herbicides (Ashe and Suskind, 1950; Baader and Bauer, 1951; Goldstein et al., 1959; Todd, 1962; Berkley and Magee, 1963; Poland et al., 1971; Jirasek et al., 1974). However, only a very limited number of studies on the PNS provide any control or comparison group data. Since peripheral neuropathies can be induced by such common medical and environmental conditions as diabetes and poor nutrition, especially in alcoholics, the presence of neuropathy in an herbicide-exposed population cannot be attributed necessarily to the herbicide without consideration of these other factors. Rigorously defined and examined comparison groups, although especially important in the analysis of peripheral neuropathies, are not available for the topic of acute and subacute neuropathies. The studies cited below provide suggestive but limited evidence of the concept that acute or subacute peripheral neuropathy can develop after exposure to dioxin or related compounds.

Todd (1962) reported a sprayer of 2,4-D weedkiller who developed a gastrointestinal disturbance and, within days, a severe sensory/motor polyneuropathy after contact with the chemical. Recovery occurred gradually over the ensuing months. Berkley and Magee (1963) reported another patient who developed a polyneuropathy four days after exposure to a liquid solution of 2,4-D, which was being sprayed in a cornfield. The neuropathy was purely sensory in type. His symptoms gradually resolved over months. Goldstein et al. (1959) described three patients who had sensory/motor polyneuropathies that developed over several days and progressed over several weeks after exposure to 2,4-D. All had incomplete recovery after several years. Although these patients were not examined neurologically before their exposure, the temporal relationship between the development of their clinical problem and the herbicide exposure was clearly documented. Nonetheless, the possibility that their occurrence was unrelated to the herbicide exposure and represented examples of other disorders, such as idiopathic Guillain-Barre syndrome, cannot be entirely excluded.

Environmental Studies After the Seveso, Italy, chemical explosion, inhabitants from the high-exposure zone were evaluated for signs and symptoms of peripheral nerve disease and compared with inhabitants of a lower-exposure zone. No information is available on acute transient neuropathic effects, since the first reports documented findings in patients evaluated more than six months after the disaster. Boeri et al. (1978) conducted clinical and neurophysiological examination of the peripheral nerves 7 to 11 months after the explosion and reported descriptive differences between 470 volunteer subjects in Zone A (high-exposure group) and 152 volunteer residents of Zone R (low-exposure group). Peripheral nerve problems were frequent in both groups, suggesting to the authors that undefined neuropathic factors predating the explosion may well have been responsible for their findings. Although cranial and peripheral nerve problems were generally more prevalent among the highly exposed group, no statistical analyses were performed on the prevalence data. The electrophysiological studies failed to show any significant abnormalities in either group.

As a complement to the above screening in the first year after exposure, Pocchiari et al. (1979) echoed the observation that neuropathic symptoms were more prevalent in the high-exposure group. No new data were provided. Reporting on symptoms and signs in patients examined eight or more months after the accident, Filippini et al. (1981) compared 308 Seveso residents with 305 non-exposed residents from nearby towns. They examined patients clinically and electrophysiologically, using strict physiological criteria for defining peripheral neuropathy. The authors found no increased risk of "acute" peripheral neuropathy among the exposed residents. However, within the subgroup of exposed subjects who showed clinical signs of significant exposure (chloracne or elevated hepatic enzymes), the risk ratio was 2.8 (CI = 1.2-6.5). Similarly, for Seveso residents with other risk factors for peripheral neuropathy (alcoholism, diabetes, and inflammatory diseases), an elevated risk ratio was also observed (2.6, CI = 1.2-5.6). The authors argued that heavy exposure to dioxin was associated with mild peripheral neuropathy in this two-year follow-up report. Subsequent follow-up studies suggested that there was no increased prevalence of peripheral neuropathy several years after the accident among the high-risk Seveso group (Barbieri et al., 1988; Assennato et al., 1989).

Vietnam Veterans Studies The committee has identified no data on acute or subacute neuropathies related to herbicide exposure in Vietnam. All published data concern chronic effects.

Summary of Acute and Subacute Transient Peripheral Neuropathy

There is some evidence to suggest that neuropathy of acute or subacute onset may be associated with herbicide exposure. This is based primarily on case

histories from occupational exposure and the descriptive reports following the Seveso accident. The trend to recovery in the individual cases reported and the negative findings of many long-term follow-up studies of peripheral neuropathy (see section on Chronic Persistent Peripheral Neuropathy in the full report) suggest that if a neuropathy indeed develops, it resolves with time.

Conclusions

Strength of Evidence in Epidemiologic Studies

There is limited/suggestive evidence of an association between exposure to the herbicides considered in this report and acute and subacute transient peripheral neuropathy. The evidence regarding association is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

New data from animals (Grehl et al., 1993; Grahmann et al., 1993) suggest biological plausibility for an association between TCDD and peripheral neuropathy. Chapter 3 of the full report discusses the toxicologic studies in greater detail.

Increased Risk of Disease among Vietnam Veterans

If TCDD is associated with the development of transient acute and subacute peripheral neuropathy, the disorder would become evident shortly after exposure; therefore, there is no evidence that new cases that develop long after service in Vietnam are associated with herbicide exposure that occurred there.

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