

VETERANS HEALTH AND AGENT ORANGE

The 1999 Report to the Secretary of Veterans Affairs

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**REPORT TO THE SECRETARY OF VETERANS AFFAIRS
ON
VETERANS AND AGENT ORANGE: UPDATE 1998***

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EXECUTIVE SUMMARY

In February 1999, the Institute of Medicine of the National Academy of Sciences (NAS) released the second update of its 1993 report on the possible health effects of herbicide exposure of U.S. military personnel who served in Vietnam. The latest NAS report, entitled *Veterans and Agent Orange: Update 1998*, contains no major changes in category of association for any disease compared with the 1996 update. In the 1998 document, the NAS finds that for most health outcomes there was "inadequate/insufficient evidence" to determine whether an association between a specified disease and herbicide exposure exists. The initial NAS report as well as the first update reached the same conclusion. The 1998 report classified four health outcomes as having "sufficient evidence of an association." All four conditions were similarly judged by the NAS in 1993 and 1996, and each has been recognized by VA for presumptive service connection. Bladder cancer was moved from the limited/suggestive evidence of no association category to inadequate/insufficient evidence to determine whether an association exists.

The latest NAS report, like the 1996 update, includes six health outcomes in the category of "limited/suggestive evidence" of an association. These conditions are respiratory cancers, multiple myeloma, porphyria cutanea tarda, prostate cancer, acute and subacute peripheral neuropathy, and the birth defect spina bifida in the children of Vietnam veterans. All of these conditions have been recognized for presumptive service connection.

To evaluate the 1998 NAS report, the Secretary of Veterans Affairs appointed a Task Force that was chaired by the Under Secretary for Health. Other Task Force members include key VA officials and policy-makers. The 1999 Agent Orange Task Force established a Working Group of knowledgeable individuals from VA, which consulted with other federal agencies. The 1999 Task Force/Working Group met four times, including one session to solicit input from veterans service organizations and other interested groups.

After careful deliberation, the Task Force recommends:

- ① that the Secretary establish a presumption of service connection for diabetes mellitus based on exposure to an herbicide agent;
- ② that the Secretary seek statutory authority to provide benefits, including health care, to offspring with birth defects born to women Vietnam veterans;
3. that the Secretary of Veterans Affairs request the National Academy of Sciences to carefully review the new investigations of diabetes and ischemic heart disease to determine the strength of an association between exposure to dioxin and the development of these health outcomes experienced by Vietnam veterans;
4. that the Secretary of Veterans Affairs contact the Secretary of Defense to recommend that the investigators in the Air Force Health Study of Ranch Hand personnel develop a fully adjusted, multivariate model, fully controlling for baseline age and obesity (body mass index) and, if possible, for family history of diabetes, central fat distribution, diabetogenic drug exposure, and a measure of obesity at both the time of Vietnam service, and at the time that laboratory testing for diabetes was performed or a diagnosis of diabetes was made (as recommended by the American Diabetes Association in 1997, a fasting plasma glucose

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greater than or equal to 126 mg/dl should be used by this study to define the incidence and prevalence of diabetes);

5. that the Secretary of Veterans Affairs contact the Secretaries of Health and Human Services and Defense to facilitate the combined analysis by researchers of the NIOSH and Ranch Hand studies to further examine the possibility that herbicide or dioxin exposure leads to an increased risk of diabetes;
6. that the Secretary of Veterans Affairs work with the Secretaries of other Executive Departments to promote further research on basal and squamous cell skin cancer incidence among workers exposed to herbicides and Vietnam veteran populations (this research should pay particular attention to the confounding factor of UV exposure) and on the carcinogenicity of organic arsenicals; and
7. that the Secretary of Veterans Affairs request that the NAS in its next report:
 - (a) review both maternal and paternal exposures to dioxin and the risk of adverse reproductive outcomes, including birth defects;
 - (b) review the evidence on biologic plausibility and association of dioxin exposure and diabetes;
 - (c) review the evidence on biologic plausibility and association of dioxin exposure and ischemic heart disease;
 - (d) review neural tube defects in addition to spina bifida;
 - (e) review all cancer ICD-9 codes, including those not discussed in previous reports (for example, cancer of major and minor salivary glands);
 - (f) discuss or clarify criteria used to determine statistical significance (especially when the confidence interval includes 1.0); and
 - (g) continue to assess the scientific literature on latency, including
 - (i) determinants of latency (e.g., factors such as exposure level, duration of exposure, age, and gender); and
 - (ii) whether a minimum or maximum latency period can be determined (particularly if there is a maximum period after which the risk of a disease is no longer elevated due to dioxin/herbicide exposure).

PURPOSE

This report provides the 1999 Agent Orange Task Force's recommendations to the Secretary of Veterans Affairs in response to the National Academy of Sciences (NAS) report, *Veterans and Agent Orange: Update 1998*. This report also describes the requirements of the law that mandates the NAS review, presents highlights of the 1998 update, and details VA actions taken during the past several years in response to NAS reports.

BACKGROUND

Public Law 102-4, the Agent Orange Act of 1991 (Appendix A), directs VA to obtain from the National Academy of Sciences an independent scientific review of the evidence regarding associations between diseases and exposure to herbicides used in support of U.S. and allied military operations in the Republic of Vietnam during the Vietnam era (i.e., February 28, 1961 -- May 7, 1975, inclusive).

Public Law 102-4 indicates that for each disease reviewed, it should be determined: (a) whether there is a statistical association between its occurrence and herbicide exposure; (b) the increased risk of the disease among those exposed to herbicides during service in Vietnam during the Vietnam era; and (c) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease. The NAS is required to include in its report to VA a full discussion of the scientific evidence and reasoning that led to its conclusions.

In its initial report pursuant to Public Law 102-4, released on July 27, 1993, the NAS assigned each of the diseases considered to one of four evidentiary categories. The distinctions between categories were based on the weight of the "statistical association," not on causality, as is more common in scientific reviews. The four evidentiary categories were: (I) sufficient evidence of an association, (II) limited/suggestive evidence of an association, (III) inadequate/insufficient evidence to determine whether an association exists, and (IV) limited/suggestive evidence of no association.

Under Public Law 102-4, whenever VA determines that a "positive association" exists between exposure to an herbicide agent and the occurrence of a disease in humans, the Secretary of Veterans Affairs shall prescribe regulations providing that a presumption of service connection is warranted for that disease. In making the determination, VA must consider reports received from the NAS and all other sound medical and scientific information available to VA. To be considered a "positive association," the credible evidence in favor of an association must be equal to or greater than credible evidence against an association. In evaluating studies for this purpose, Public Law 102-4 directs VA to consider whether the findings are statistically significant, are capable of replication, and capable of withstanding peer review.

1993 NAS REPORT FINDINGS AND VA RESPONSE

In its initial report, the NAS found "sufficient evidence" to conclude that there is a positive association between herbicides and: (1) soft tissue sarcoma, (2) non-Hodgkin's lymphoma, (3) Hodgkin's disease, (4) chloracne, and (5) porphyria cutanea tarda (in genetically susceptible individuals). The NAS found "limited/suggestive evidence" of an association

between exposure to herbicides used in Vietnam and three other types of cancer: respiratory cancers (including lung, larynx, and trachea), prostate cancer, and multiple myeloma.

For most conditions reviewed, the NAS concluded that there was "inadequate/insufficient evidence" to determine whether an association exists. The NAS Committee included the following diseases and disorders in this third category: hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers (breast, cervical, uterine, ovarian), renal cancer, testicular cancer, leukemia, spontaneous abortion, birth defects, neonatal/infant death and stillbirths, low birthweight, childhood cancer in offspring, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, peripheral nervous system disorders, metabolic and digestive disorders (diabetes, changes in liver enzymes, lipid abnormalities, ulcers), immune system disorders (immune modulation and autoimmunity), circulatory disorders, and respiratory disorders.

For a small group of cancers, the NAS found "limited/suggested evidence" that there is "no association" with herbicides used in Vietnam. This category included skin cancer, gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, rectal cancer), bladder cancer, and brain tumors. The Committee report noted, however, that even for these conditions "the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded."

In addition to these findings, the initial NAS report offered research recommendations and evaluated several specific programs, mentioned in Public Law 102-4, that might be implemented by VA.

On July 27, 1993 (the day the report was released), Secretary Brown announced that VA would recognize Hodgkin's disease and porphyria cutanea tarda for service connection. On September 27, 1993, after further review of the NAS report, Secretary Brown announced that multiple myeloma and respiratory cancers would also be added to the list of conditions presumed for service connection based on exposure to herbicides which contained dioxin. Peripheral neuropathy was not recognized as service connected because Secretary Brown concluded that a presumption was not warranted based on existing scientific evidence.

In making this determination, he gave great weight to the NAS report that indicated that there was inadequate or insufficient evidence to make a determination about the association between herbicides used in Vietnam and the development of this condition. In view of the earlier decision on peripheral neuropathy, Secretary Brown asked the NAS to take a close look at the evidence on this matter during its next review.

Regulations regarding Hodgkin's disease and porphyria cutanea tarda (PCT) were published in the *Federal Register* as proposed rules on September 28, 1993 and in final form on February 3, 1994. Regulations regarding multiple myeloma and respiratory cancers were published in the *Federal Register* as proposed rules in February 3, 1994 and in final on June 9, 1994.

On January 4, 1994, VA published a notice in the *Federal Register* that the Secretary determined that a presumption of service connection based on exposure to herbicides used in Vietnam was not warranted for the following conditions: prostate cancer, peripheral neuropathy, hepatobiliary cancers, bone cancers, female reproductive cancers, renal cancers, testicular cancer, leukemia, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, metabolic and digestive disorders, immune system disorders,

circulatory disorders, respiratory disorders (other than lung cancer), nasal/nasopharyngeal cancer, skin cancer, gastrointestinal tumors, bladder cancer, brain tumors, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

1996 NAS REPORT FINDINGS AND VA RESPONSE

The findings of the 1996 NAS report, released March 14, 1996, were generally similar to those of the 1993 document. The NAS panel used the same schema and the same four categories to classify the various diseases. Most conditions were placed in the same categories as in 1993. Four of the diseases listed in NAS category I in 1993 were again included in this grouping. Porphyria cutanea tarda (PCT) was downgraded to NAS category II (limited/suggestive evidence of an association). No new health outcomes were added to category I.

The number of diseases included in category II doubled from three to six. In addition to PCT, the NAS included acute and subacute peripheral neuropathy and spina bifida in the children of exposed individuals. These latter two conditions were each identified as a "new disease category."

In the 1993 report, the NAS listed peripheral nervous system disorders in category III. The 1996 report split these disorders into either chronic or acute and subacute peripheral neuropathies. Chronic peripheral nervous system disorders remained in the third category, and acute and subacute transient peripheral neuropathy was placed in category II. Similarly, spina bifida was raised to category II, while other birth defects remained in NAS category III. The only other group of conditions that changed categories was skin cancer, moving from category IV to category III.

Following release of the 1996 NAS report, VA's Chief of Staff appointed a Task Force to review the report and make recommendations to the Secretary. The Under Secretary for Health was asked to chair the group. He was joined by several key VA officials (the Under Secretary for Benefits, the General Counsel, and the Director, Environmental Agents Service). Key officials from the Environmental Protection Agency and the Centers for Disease Control and Prevention were included in the Task Force. In addition, the Task Force Chair established a Working Group to support the Task Force. The Working Group included knowledgeable individuals from the Department of Veterans Affairs, National Institutes of Health and the Centers for Disease Control and Prevention.

At one meeting of the Task Force, a wide array of individuals from veterans service organizations and groups concerned about spina bifida were invited to present scientific information and their views. Representatives from the following entities participated in that meeting: Veterans of Foreign Wars of the United States, Vietnam Veterans of America, AMVETS, Paralyzed Veterans of America, American Red Cross, The American Legion, American Ex-Prisoners of War, American G.I. Forum, Non-Commissioned Officers Association, National Veterans Legal Services Program, Spina Bifida Association of America, Agent Orange Class Assistance Program, Presidential Advisory Committee on Gulf War Veterans' Illnesses, Senate Veterans' Affairs Committee, American Association of University Affiliated Programs, Jewish War Veterans, Agent Orange Coordinating Council, staff from the office of Senator Daschle, and the Marine Corps League. Interested parties were also invited to provide written comments by April 30, 1996. Written comments were received from the Vietnam Veterans of America, Spina Bifida Association, and Diversity Associates.

The 1996 Agent Orange Task Force, in its May 14, 1996 report to the Secretary, made four recommendations:

1. that the Secretary establish a presumption of service connection for prostate cancer based on exposure to an herbicide agent;
2. that the Secretary establish a presumption of service connection for acute and subacute peripheral neuropathy based on exposure to an herbicide agent if manifested within one year of exposure to the agent;
3. that the Secretary support increased research efforts to learn more about the possible relationship between exposure to herbicides and the development of birth defects, including spina bifida, and other health problems in veterans' offspring; and
4. that the Secretary establish a presumption of service connection for spina bifida in the offspring of Vietnam veterans based on exposure to an herbicide agent if statutory authority is enacted granting such authority.

The Secretary approved each of the recommendations. Proposed regulations regarding a presumption of prostate cancer and acute and subacute peripheral neuropathy were published in the *Federal Register* on August 8, 1996, and in final on November 7, 1996.

In July 1996, VA sent to Congress draft legislation that would provide medical care, vocational training, and a monthly allowance for the children of Vietnam veterans. This legislation, with minor modification, was enacted as part of Public Law 104-204 on September 26, 1996.

On November 14, 1996, VA announced that the Louisville VA Medical Center would be the site of a new national research center for epidemiological, clinical, and basic science studies of environmental hazards and their effects on reproductive outcomes.

1998 NAS REPORT FINDINGS

The findings of the 1998 NAS report, released February 11, 1999, were very similar to those of the 1996 document. The NAS panel used the same schema and the same four categories to classify the various diseases. All conditions, except urinary bladder cancer, were placed in the same categories in both 1996 and 1998. Urinary bladder cancer was changed from category IV to category III. The same four outcomes listed in category I in 1996 (soft tissue sarcomas, chloracne, Hodgkin's disease, and non-Hodgkin's lymphoma) were included in this group again in 1998. These four outcomes were also in category I in the 1993 report. No additional health outcomes were added to category I in 1998.

In the 1998 report, there was no change in category II compared with the 1996 document. In the second update, the NAS reported that they found additional scientific support for some previously-identified associations, specifically lung cancer, prostate cancer, and spina bifida.

The NAS report makes several recommendations on research regarding herbicide exposure and diabetes risk. It recommends that a presently unpublished National Institute for Occupational Safety and Health (NIOSH) study of diabetes in dioxin-exposed workers in

chemical plants be documented more completely and published in a peer-reviewed journal. The NAS also recommends further analyses of the Ranch Hand data and suggests that consideration be given to a combined analysis of the Ranch Hand and NIOSH studies to further examine the possibility that herbicide exposure leads to an increased risk of diabetes. The Ranch Hand Study is an Air Force research effort designed to assess the long-term health consequences of herbicide exposure on individuals who served in the unit responsible for most of the serial spraying of herbicides in Vietnam.

Although finding that available evidence is insufficient to determine whether an association exists between herbicide exposure and any forms of skin cancer, the NAS recommends further study of the incidence of basal and squamous cell carcinomas of the skin among exposed workers and Vietnam veterans populations. The NAS suggests that in any future studies, careful attention should be paid to exposure assessment, as well as to controlling for ultraviolet light (UV) exposures.

VA asked the NAS to reassess the classification of soft tissue sarcomas with particular attention to chondrosarcomas of the skull. Pathologists categorize chondrosarcomas of the skull, a type of malignant tumor, with bone cancers even though they sometimes occur outside of bone and may sometimes be histologically complex. Soft tissue sarcomas are recognized by VA for service connection while bone cancers are not. The NAS advises VA that the ICD-9 classification of chondrosarcomas should not be used as a substitute for the expert judgment of pathologists in individual cases.

VA PRELIMINARY RESPONSE TO 1998 NAS REPORT

Following release of the 1998 NAS report, the Secretary appointed a Task Force to review the document and make recommendations for possible VA actions. The Under Secretary for Health, who chaired a similar Task Force that reviewed the 1996 update, was again asked to chair the group. He was joined by several key VA officials (the Under Secretary for Benefits; General Counsel; and Chief Consultant, Occupational and Environmental Health Strategic Health Group). In addition, the Task Force Chair established a Working Group to support the efforts of the Task Force. The Working Group included representatives from Veterans Health Administration (VHA) (headquarters staff, environmental epidemiology, oncology and endocrinology), Veterans Benefits Administration (VBA), and General Counsel staff.

The Task Force/Working Group held three meetings. A Working Group meeting was held on March 8, 1999. At a stakeholders meeting sponsored by the Task Force/Working Group, held March 16, 1999, input was given by representatives of veterans service organizations, and other groups expressed their views on the NAS report.

In addition to considering the NAS reports, studies cited in these reports, and input received from the veterans service organizations, the Task Force was assisted by the VA Headquarters Library, which throughout the year identifies Agent Orange-related publications in "medline" searches for the Environmental Agents Service, and which obtained and provided copies of relevant articles during the Task Force's formal deliberations.

THE LEGAL STANDARD

Both the 1996 and 1999 Task Forces concluded that the legal standard governing the finding of a "positive association" under Public Law 102-4 is an imperfect framework for analyzing the relevant scientific evidence and, further, raises a risk that VA's findings of a "positive association" may be misinterpreted to mean more than they do.

Indeed, almost without exception, the newspapers and other public reports about the 1996 Task Force's conclusions regarding spina bifida were erroneous with regard to VA finding a causal connection between exposure to Agent Orange and the occurrence of this birth defect. Pronouncements by elected officials and media accounts repeatedly either said or implied that the Task Force had determined there to be a causal relationship when, in fact, the Task Force had explicitly said it did not find such a connection and only made the determination it did because of the inoperability of the controlling statutory language in a scientific setting.

The medical and scientific evidence reviewed by the NAS and the Task Force does not easily lend itself to analysis under the statutory standard requiring weighing of the evidence "for" an association and the evidence "against" an association. Generally, in accordance with longstanding scientific literature convention, studies with positive findings and statistically significant findings are much more likely to be published than studies with negative or inconclusive findings. Accordingly, although the available studies concerning a particular health outcome may entail a proportionately greater amount of "positive" evidence, the prevalence of such "positive" evidence tends to overemphasize the likelihood that an association between herbicide exposure and the health outcome actually exists.

Additionally, the Task Force believes that it is difficult in many cases to characterize epidemiological study findings as evidence either "for" or "against" an association. Studies showing a weak or statistically insignificant association may be viewed either as evidence "for" an association, in the sense that the data reflect a slightly increased risk or rate of occurrence, or conversely they could be viewed as evidence "against" an association, in the sense that the absence of a strong or statistically significant increased risk tends to suggest that an association does not exist. Moreover, methodological questions may be raised about some statistically significant studies. Also, the mandated standard is difficult to apply in a meaningful way to medical conditions for which research data are very limited.

In particular, as noted above, the Task Force is concerned that VA's finding of a "positive" association under the very liberal standard of Public Law 102-4 may be misconstrued as reflecting a scientific judgment that a causal association exists between herbicide exposure and a particular disease. The Task Force emphasizes that its conclusions made for the limited purposes of Public Law 102-4 do not reflect a judgment that a particular health outcome has been shown to be caused by, or in some cases even definitely associated with, herbicide exposure under the standards ordinarily governing such conclusions for purposes of scientific inquiry and medical care.

Notwithstanding these difficulties with the statutory standard mandated by Public Law 102-4, the Task Force recognized its charge to examine whether the credible evidence for an association is equal to or outweighs the credible evidence against an association and has endeavored to conduct its review and analysis in a manner consistent with the statute. In determining the credibility of studies, the Task Force considered the extent to which they have withstood peer review, such as by publication in peer-reviewed scientific or biomedical journals;

the extent to which the findings are statistically significant; and whether the methodologies have been sufficiently described so that the studies could be replicated.

Recognizing that the evidence with respect to most of the health outcomes is insufficient to support any conclusion of causality from a scientific standpoint, the Task Force has nevertheless focused on whether the evidence is sufficient to establish a "positive association" within the meaning of Public Law 102-4. In making that determination, the Task Force focused on the quality, applicability, and relative strength of the findings stated in individual epidemiologic and other studies, and on the relative weight of the total credible evidence for and against an association.

Further, both in evaluating individual studies and in weighing the evidence as a whole, the Task Force concluded that it was appropriate to accord great weight to the conclusions of the NAS, although the Task Force did not in all instances entirely agree with the NAS' characterizations of particular studies and findings, nor did it accept unquestioningly the NAS' conclusions.

TASK FORCE DELIBERATIONS

The deliberations of the 1999 Task Force are described below using the evidentiary categories employed by the NAS.

Category I - Health Outcomes with Sufficient Evidence of an Association

The Task Force reviewed the reassessments of conditions that the NAS included in this category in the 1998 update (i.e., soft tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease and chloracne). Each of these conditions was classified by NAS in category I in 1993 and 1996, and each has been presumptively recognized as service connected based on exposure to an herbicide agent. The Task Force was not aware of other pertinent studies besides those considered by the NAS.

The Task Force concluded that the credible evidence for an association between exposure to herbicides and development of any of these conditions continues to be equal to or to outweigh the credible evidence against such an association.

Category II - Health Outcomes with Limited/Suggestive Evidence of an Association

Porphyria Cutanea Tarda

The Task Force carefully reviewed the NAS reassessment of porphyria cutanea tarda (PCT). This condition was moved from category I to this category in the 1996 NAS report and remained there in the 1998 update. PCT is a rare disorder of porphyrin metabolism caused by a hereditary or acquired deficiency of uroporphyrinogen decarboxylase. Uroporphyrins and coproporphyrins are excreted in the urine of affected individuals. Few new studies were available for review in 1998.

After review of the scientific information regarding PCT and herbicide exposure, the Task Force came to the following conclusions: The association of herbicide exposure and development of PCT shortly after that exposure is biologically plausible. Multiple investigations

have demonstrated elevations of porphyrins in the acute exposure period of human subjects to TCDD and related compounds. The failure of PCT studies which utilize small sample size to demonstrate a positive association may relate to the lack of statistical power to detect real differences if they exist. While these studies fail to support a positive association between herbicide exposure and PCT, no conclusions regarding lack of an association can be drawn. Case studies demonstrate acute development of PCT in genetically susceptible individuals.

Since no credible evidence of lack of association exists and case studies show acute cases of PCT in genetically susceptible individuals, the weight of evidence for an association is at least equal to the evidence against an association. TCDD-associated PCT would become manifest during military service and improve with time following termination of exposure.

Prostate Cancer

In the 1996 report, the NAS concluded that there was limited/suggestive evidence of an association between herbicide exposure and prostate cancer.

The 1998 update noted that several additional studies have been published, examining prostate cancer mortality, incidence, or both, in populations with possible or documented exposures to TCDD. Too few cases were seen among Ranch Hand study participants to provide, if any, useful information about prostate cancer.

In a larger study of deaths among U.S. Vietnam veterans, those who had last served in Vietnam more than sixteen years earlier had a weakly elevated proportionate mortality ratio (PMR) of 1.1. The NAS report cautioned that PMR studies should not be given much weight because they include only deaths. In this type of study, findings for any single outcome are strongly influenced by associations between the exposure of interest and other causes of death, especially the most common ones.

The NAS was particularly interested in a detailed analysis of an Australian male Vietnam veteran cohort study (Crane et al., 1997). In this study, which the NAS noted had a much stronger design, an elevated rate of prostate cancer mortality was observed among those who served in Vietnam. The 1999 Task Force concludes that the credible evidence for an association was at least equal to the credible evidence against an association.

Peripheral Neuropathy

Peripheral neuropathy has been of concern to Vietnam veterans for many years. On May 23, 1991, the VA's Advisory Committee on Environmental Hazards concluded that there is a significant statistical association between peripheral neuropathy and exposure to dioxin. On July 1, 1991, the Secretary of Veterans Affairs announced that VA would propose rules granting service connected disability status to certain veterans with peripheral neuropathy. Proposed regulations implementing this decision were published in the *Federal Register* on January 21, 1992. When the initial NAS report, released on July 27, 1993, placed "peripheral nervous system disorders" in category III, VA reversed plans to recognize peripheral neuropathy as service connected. VA subsequently asked that the NAS reconsider in detail the relationship between exposure to herbicides and the development of acute and subacute effects of peripheral neuropathy versus chronic neuropathy. Upon consideration of the available evidence, the 1996 Task Force concluded that the credible evidence for an association was at least equal to the evidence against such an association. It is expected that acute or subacute peripheral neuropathy associated with herbicides would manifest within one year of exposure.

The 1998 NAS update found no new publications that bear on this issue. After re-examining the studies reviewed by the 1996 Task Force, the 1999 Task Force agrees with the previous findings and concludes that the credible evidence for an association for acute and subacute transient peripheral neuropathy is equal to or greater than evidence against such an association, and the credible evidence for an association for chronic persistent peripheral neuropathy is not greater than or equal to the evidence against such an association. These conclusions are consistent with the 1996 Task Force findings.

Other conditions

The Task Force reviewed the reassessments in the 1998 NAS report regarding respiratory cancers and multiple myeloma which the earlier Task Forces had discussed at length. The 1998 NAS update reports that new occupational studies (Kogevinas et al., 1997; Ott and Zober 1996) show a dose-response relationship between TCDD exposure and lung cancer. Recent Australian and U.S. veterans' studies also indicate an association for lung cancer, but the confounding risk factor of smoking was present.

The Task Force was not aware of pertinent studies other than those considered by the NAS. The Task Force concluded that the credible evidence for an association between exposure to herbicides and the development of either of these conditions continues to be equal to or to outweigh the credible evidence against such an association.

Spina bifida, which the NAS also included in category II in both the 1996 and 1999 updates, is discussed separately below.

Category III - Health Outcomes with Inadequate/Insufficient Evidence to Determine Whether an Association Exists, and

Category IV - Health Conditions with Limited/Suggestive Evidence of No Association

The following health outcomes were included in these categories: hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers (cervical, uterine, ovarian), breast cancer, renal cancer, testicular cancer, leukemia, spontaneous abortion, birth defects (other than spina bifida), neonatal/infant death and stillbirths, low birth weight, 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, ulcer), immune system disorders (immune suppression and autoimmunity), circulatory disorders, respiratory disorders, skin cancer, gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, rectal cancer), urinary bladder cancer, and brain tumors.

Appendix B lists the evidence reviewed in the 1998 NAS report and by the Task Force for each of the conditions included in categories III and IV for which the Secretary has authority to regulate. This excludes health outcomes (except for the birth defect spina bifida) in the children of Vietnam veterans. Following a thorough analysis of the scientific basis of the 1993, 1996, 1998 NAS reports and all other available information, the current Task Force agreed that each condition contained within categories III and IV does not individually meet the statutory

standard of credible evidence for an association which is equal to or greater than the credible evidence against an association.

Many Vietnam veterans are suffering from or have expressed particular concerns about the possible relationship between herbicide exposure and two relatively common adverse medical conditions: diabetes mellitus and skin cancers. The NAS carefully reviewed these matters in the 1998 update. The following sections discuss the NAS conclusions and the Task Force analyses.

Diabetes

Primary diabetes mellitus is a heterogeneous metabolic disorder characterized by hyperglycemia and quantitative and/or qualitative deficiency of insulin action. Two main types have been recognized: insulin-dependent diabetes mellitus (Type I) and non-insulin-dependent diabetes mellitus (Type II).

Type I is generally thought to result from beta-cell dysfunction, caused by a genetically based autoimmune destruction. Type II accounts for about 90 % of cases of primary diabetes. It is rare before age 30, but increase steadily with age thereafter. The etiology of Type II is unclear, but the condition frequently is associated with obesity.

In the 1996 report, the NAS Committee concluded that there was inadequate or insufficient evidence to determine whether an association exists between exposure to the herbicides considered and diabetes.

In its current report, the NAS concluded that the *scientific* evidence regarding an association between herbicide exposure and diabetes risk is "equivocal." Early reports did not consistently find an association between herbicide exposure and diabetes; however, the two recent studies reviewed in the NAS report (Heariksen et al., 1997; and Sweeney et al., 1996, 1997) using serum TCDD levels appear to have consistency. Although the majority of earlier reports on humans suggest little association, the 1997 report from the Ranch Hand study raises the possibility that Vietnam veterans in the highest herbicide exposure category may be at increased risk.

Bertazzi et al. (1989) published results of a 10-year mortality follow-up on those living in the area of Seveso, Italy, at the time of the incident in 1976. The relative risk of diabetes mortality was 1.3 (95% CI 0.7-2.3) for men and 1.5 (95% CI 0.9-2.5) for women.

Occupational studies of exposed workers have given inconsistent results. Pazderova-Vejlupkova et al. (1981) reported on the 10-year follow-up of 55 workers exposed to TCP and 2,4,5-T. Ninety-five percent of these individuals developed chloracne and 8% had diabetes at onset of exposure. In a 10-year follow-up study, 20% were reported to have an abnormal glucose tolerance test. Moses et al. (1984) studied 117 2,4,5-T production workers with chloracne compared to 109 without chloracne and found no increase in diabetes 10-20+ years after accidental and chronic exposures. In a study which used serum TCDD as the exposure measure, Ott et al. (1994) reported on 138 BASF employees exposed to TCDD in a 1953 industrial accident. The study found a borderline significant ($p=0.06$) positive association for increased fasting blood glucose levels, approximately 37 years later. The authors noted that this finding appeared to be linked with obesity and suggested that the TCDD-glucose association was secondary to a link between diabetes and obesity. In a follow-up of 158 TCDD-exposed BASF workers, a group which had substantial overlap with the workers reported by Ott, Zober et al.

(1994) found that significantly fewer of the exposed workers had medical insurance diagnoses of diabetes mellitus.

Among four mortality studies of TCDD-exposed cohorts that reported risk of death for diabetes, only the Seveso study found a significant elevation of risk (Pesatori et al., 1998). However, it should be noted that vital statistics data are known to be unreliable in terms of ascertainment of diabetes-related deaths. Diabetes is under-reported on death certificates; therefore the Task Force found it significant that the Pesatori mortality study showed a positive association.

Calvert et al. recently published the NIOSH morbidity study of two U.S. plants with TCDD-exposed production workers. The NAS committee did not review this paper when drafting its report. In this just published investigation, TCDD levels were used as the exposure measure. 568 workers from the two plants were eligible for the study. Four hundred individuals (68.3%) were alive and could be located; 281 (70%) were examined including serum lipid-adjusted TCDD levels, fasting serum glucose concentration and thyroid function. Diabetes was found in 60% (6 of 10) of workers with current TCDD concentration exceeding 1,500 pg/gm lipid. This study suggests that workers with very high TCDD body burdens may have an increased risk of diabetes mellitus. The strength body mass index (BMI) was significantly higher among the six diabetics compared to all other workers and to other diabetic workers. However, no overall differences were found in BMI between these three groups of workers. The investigators stated that the higher BMIs did not explain the high proportion of diabetes in their heavily exposure group. This well-conducted study supports an association between high levels of TCDD exposure and diabetes mellitus.

In addition to the associations described in occupational studies, research investigations examining the association between TCDD exposure and the risk of diabetes in veterans have been positive. The recent Ranch Hand report is described by the NAS as potentially important and well conducted. In this study, Henrikson et al. (1997) compared 989 dioxin-exposed Ranch Hand veterans to 1,276 unexposed veterans serving in the military during the same period. Exposure was classified on the basis of original exposure calculated from serum dioxin levels determined in 1987 and 1992. The prevalence of diabetes mellitus by 1995 was 13.2% in the comparison group and increased from 9.5% to 17.2% to 20.1 % with increasing Ranch Hand exposure category. The investigators found a modest but statistically significant increase in prevalence of the highest-exposure category relative to the comparison group (RR 1.5, 95% CI 1.2-2.0). The strength of the findings in this study is decreased by residual questions about the case definition used for diabetes and adequate control of confounders such as obesity. The NAS suggested that the data from this study undergo more rigorous statistical analyses to address the issue of residual confounding, including the application of a fully adjusted multivariate model that fully controls for obesity.

Likewise, a study of 641 Australian Vietnam veterans (O'Toole 1996) found a 60% increased risk (RR 1.6; 99% CI 0.4-2.7) of diabetes when compared to Australian population rates. This scientific strength of this study's findings is limited by lack of verification of the health outcomes and use of a non-comparable control population.

Animal studies provide potential biologically plausible mechanisms for an association between herbicide exposure and diabetes risk. In addition, the Task Force is aware of unpublished data from a study of a TCDD-exposed cohort near the Vertac/Hercules Super Fund site in which high TCDD levels were associated with hyperinsulinemia and possibly with insulin resistance.

The current NAS report concluded that there is inadequate/insufficient evidence to determine whether an association exists between herbicides or dioxin exposure and increased risk of diabetes. However, in their synthesis of the literature regarding the evidence for a connection between herbicide exposure and diabetes risk they describe their findings as "equivocal". The Task Force agrees with both of these NAS conclusions. Importantly, the studies to date do not support a causal relationship between dioxin exposure and diabetes mellitus. In addition, the literature does not provide a clear, unequivocal scientific basis to determine that TCDD exposure is associated with an increased risk of diabetes. However, the Task Force finds that the available scientific evidence for an association is equal to the evidence against such an association. Based on a literal application of the standards set forth in Public Law 102-4, the Task Force finds that the evidence is indicative of a "positive association" between herbicide exposure and diabetes mellitus and recommends that the Secretary create a presumption of service connection for diabetes on this basis. However, the Task Force emphasizes and reiterates that its conclusions made for the limited purposes of Public Law 102-4 do not reflect a judgment that diabetes has been shown to be caused by, or even definitely associated with, herbicide exposure under the standards ordinarily governing such conclusions for purposes of scientific inquiry and medical care. This finding of positive association between diabetes and herbicide exposure in Vietnam veterans is solely a function of applying the standards required by Public Law 102-4 and should not affect diagnostic evaluations, medical decisions or treatment guidelines in any circumstance.

Future Studies of Diabetes

The NAS report further recommended that consideration be given to a combined analysis of the Ranch Hand and NIOSH studies to further examine the possibility that herbicide or dioxin exposure leads to an increased risk of diabetes. The NAS report also recommends that the RANCH HAND data be reanalyzed with a fully controlled multivariate model. The 1997 American Diabetes Association (ADA) definition of diabetes (that is, a fasting plasma glucose greater than or equal to 126 mg/dl) should be employed in these studies. The ADA does not consider impaired glucose tolerance or impaired fasting plasma glucose clinical conditions.

The Task Force agrees with these conclusions and recommendations. The Task Force recommends that the Ranch Hand Study fully control for baseline age and obesity (body mass index) and, if possible, for family history of diabetes, central fat distribution, diabetogenic drug exposure, and a measure of obesity at both the time of Vietnam service, and at the time that diagnostic testing is performed or a diagnosis of diabetes made.

The Task Force also recommends that the Secretary of Veterans Affairs contact the Secretaries of Health and Human Services and Defense to facilitate the combined analysis by researchers of the NIOSH and Ranch Hand studies to further examine the possibility that herbicide or dioxin exposure leads to an increased risk of diabetes. The Task Force agrees that VA should work with the Ranch Hand Study group and NIOSH to facilitate an expanded investigation of the effects of herbicide exposure on the development of diabetes through a pooled analysis of the data from these two studies.

Skin Cancer

Skin cancers are generally divided into two broad categories: those cancers that develop from melanocytes (malignant melanoma) and those that do not. The most common nonmelanocytic skin cancers, include basal cell and squamous cell carcinomas, are much more common than malignant melanoma and are less aggressive and more treatable. In the initial two

NAS reports, released in 1993 and 1996, all skin cancers were combined. In the latest report, the NAS considered these two types separately.

Known etiologic agents associated with melanoma include ultraviolet (UV) radiation or sunlight and polycyclic aromatic hydrocarbons (PAHs). Cytochrome P4501A1 (CYP1A1), a P450 isozyme, under the control of the aryl hydrocarbon receptor (AhR), is expressed in the skin. It has been linked to the development of skin cancer. Since TCDD toxicity is also mediated by the AhR, it is plausible that exposure to TCDD could be associated with increased risk of melanoma.

The NAS found that the epidemiologic data are not strong in this area. Only three studies show statistically significant increases in melanoma mortality. None of these studies controlled for the greatest known risk factor for melanoma, sunlight exposure. Therefore, the NAS recommended future studies of the melanoma risk of occupational and Vietnam veteran populations to make an effort to control confounding from UV (sunlight) exposures. The Task Force agrees with this recommendation.

The NAS noted conflicting findings of a significant elevated risk of basal cell, but not squamous cell, carcinoma in the Ranch Hand study. The NAS recommended further study of basal and squamous cell skin cancer incidence among working and Vietnam veteran populations. The NAS further recommended that careful attention be paid to exposure assessment, as well as to controlling for confounding from UV exposure.

Cacodylic acid, an organic arsenic herbicide widely used in Vietnam as Agent Blue, has been linked to the development of skin cancers and skin sensitization by PAHs. According to military records, more than 1.1 million gallons of Agent Blue were dispensed in the Department of Defense herbicide program in Vietnam. The NAS recommended that efforts to examine the carcinogenicity of organic arsenicals be encouraged.

The Task Force agrees with these recommendations.

Chondrosarcomas of the Skull

At VA's request, the NAS did an in-depth review of the literature regarding chondrosarcomas of the skull, including pathologic classification and evidence of association with herbicide exposure. Chondrosarcomas are malignant tumors derived from cartilage cells or their precursors. If they arise in the skull, mandible, or vertebral column, they are classified under the ICD codes used for bone cancers at these sites. Certain rare chondrosarcomas involve soft tissue.

For purposes of compensation under 38 CFR 3.309(e), which implements 38 U.S.C. § 1116, VA defines soft tissue sarcomas according to tumor type rather than tumor location. To be recognized as soft tissue sarcomas, tumors must be malignant and arise from tissue of mesenchymal origin, including muscle, fat, blood, and lymph vessels, but not including cartilage or bone. Chondrosarcomas do not fit this definition of soft tissue sarcomas. Moreover, the statute governing presumptive service connections based on herbicide exposure (38 U.S.C. § 1116(a)(2)(B)) expressly excludes chondrosarcomas from the category of soft-tissue sarcomas for which presumptive service-connection was established by Congress. This is consistent with the conclusion that chondrosarcomas are not within the ordinary definition of soft-tissue sarcomas as used in the medical and scientific literature suggesting a relationship between soft-tissue sarcomas and exposure to herbicide agents. Accordingly, VA does not consider chondrosarcomas

to be soft tissue sarcomas for the purpose of presumptive service connection under 38 U.S.C. § 1116.

NAS did not recommend that VA reconsider its division of chondrosarcomas and soft tissue sarcomas. Inasmuch as NAS found no scientific literature that suggested an association of chondrosarcomas with exposure to herbicides, the Task Force finds that there is no basis to change existing policy or request new legislation. The expert judgment of pathologists will continue to be used in developing individual cases and providing a histologic diagnosis when necessary.

VA does have the authority to create a presumption if the evidence establishes a positive association between chondrosarcomas and exposure to herbicide agents. In its 1998 report, the NAS did not identify any studies that specifically addressed the issue of chondrosarcomas and exposure to herbicide agents. Such associations would be grouped with bone cancers. The NAS assigned bone cancers to the category of health outcomes with limited/suggestive evidence of no association with exposure to herbicide agents. The Task Force was not aware of any other pertinent studies on this issue.

Birth Defects in Offspring of Women Vietnam Veterans

Most epidemiologic studies completed to date provide information on the health consequences of Vietnam Service for male veterans. Women veterans were excluded from many studies because of problems arising from their small numbers. The studies of birth defects among male Vietnam veterans have been mostly negative in that service in Vietnam was not associated with a general increase in the risk of fathering a child with birth defects, spontaneous abortions, stillbirths or neonatal deaths.

The Department of Veterans Affairs Environmental Epidemiology Service recently completed an investigation entitled "Women Vietnam Veterans Reproductive Outcomes Health Study" (Kang et al., 1998). This study was not finalized prior to the completion of the 1998 NAS report and therefore was not reviewed by the NAS committee.

In the study, a total of 4,410 women Vietnam veterans surviving as of January 1, 1992, and an equal number of women Vietnam era veterans were contacted for a telephone interview. Overall, 92% of these women were located and 90% completed the structured telephone interview. The two groups were similar in annual household income and education levels after controlling for nursing occupational status. Eight percent of Vietnam veterans and 7.1% of Vietnam era veterans reported a cancer of the reproductive organs however the differences were not statistically significant. Furthermore, multivariate analysis found no difference in reported rates of miscarriage, stillbirth, low birthweight, pre-term births or infant deaths.

The study identified a statistically significant increase in the risk of birth defects in women Vietnam veterans (10.5% vs. 7.0%) and with severe birth defects (7.7% vs. 5.8%). The risk of having a child with birth defects was significantly elevated even after adjustment for age, demographic variables, military characteristics, smoking and alcohol consumption of the mothers (OR 1.66, 95% CI 1.24-2.22). Similarly the risk of having a child with a severe birth defects was significantly elevated among women Vietnam veterans (OR 1.46, 95% CI 1.06-2.02).

Based on these findings, the Task Force recommends that the Secretary seek statutory authority to provide benefits, including health care, to the offspring of women Vietnam veterans with birth defects.

Spina Bifida

Because the 1996 NAS report placed spina bifida in offspring in category II, for purposes of advising the Secretary, the 1996 Task Force devoted considerable effort to evaluating available evidence regarding the association between spina bifida and parental exposures to herbicides of the type used in Vietnam.

Several studies of Vietnam veterans suggest apparent increases in the risk for spina bifida offspring of Vietnam veterans. These include studies conducted by the Centers for Disease Control and Prevention and, recently, a study of offspring of Air Force Ranch Hand personnel. These were discussed at length by the VA review panel in 1996. Questions were raised about biological plausibility, including limited scientific evidence for a male mediated cause for malformations following dioxin exposure in animals. It was also noted that there was no parallel increase in anencephaly, a neural tube defect related to spina bifida. Furthermore, most of the studies cited did not show statistically significant differences.

Notwithstanding these scientific questions, the 1996 Task Force concluded that sufficient data exist of a possible association and that spina bifida meets the liberal standards set forth in Public Law 102-4. As noted earlier, Public Law 104-204, established certain benefits and services for the Vietnam veterans' children with birth defects.

The 1998 NAS update reports that several new occupational studies (Dinich-Ward et al., 1996; Blatter et al., 1997; and Kristensen et al., 1997) provide additional support for the association of herbicide exposure with spina bifida. The NAS notes that concerns remain, including the control of confounding exposure determination and isolation of exposure to specific herbicides and TCDD.

The Task Force concluded that the evidence for an association between exposure to herbicides and development of spina bifida continues to be equal to or outweighs the evidence against such an association.

The Task Force noted that the 1998 report states, "The previous reports and this update have limited their reviews to studies of paternal exposures." It also states that "most of the etiologic research has focused on maternal and fetal exposures." In view of the 7,000 women who served in the U.S. military in Vietnam it is recommended that VA request that the NAS review maternal exposures, as well, in their next report.

The Task Force suggested that the NAS, in its next review, re-examine the literature on birth defects, specifically regarding neural tube defects. Legislation would be required for VA to provide benefits and services for Vietnam veterans' children with neural tube defects other than spina bifida. At present, there is a lack of scientific evidence relating these conditions to exposure to herbicides.

Other Issues

In its discussion of cancers, the Task Force observed that some cancers that Vietnam veterans have experienced and attributed to their Agent Orange exposure have not been discussed in any of the three NAS reports. An example of this is cancer of major and minor salivary glands. Consequently, the Task Force recommended that the NAS, in its next report, review all cancer ICD-9 codes, including those not previously reported.

Task Force members were troubled by the inconsistent use of the term "statistically significant" in the NAS report. The Task Force recommended that the NAS in its next report discuss and clarify criteria use to determine statistical significance, especially when the confidence interval includes 1.0.

The Task Force also suggested that NAS provide an expanded discussion of latency, particularly whether there is a maximum period after which the risk of a disease is no longer elevated due to dioxin/herbicide exposure.

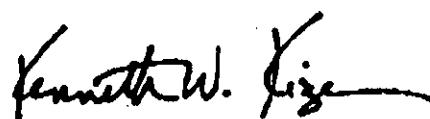
TASK FORCE RECOMMENDATIONS

After careful review of the findings of National Academy of Sciences' *Veterans and Agent Orange: Update 1998*, and other pertinent information, the 1999 Agent Orange Task Force recommends, pursuant to Public Law 102-4:

1. that the Secretary establish a presumption of service connection for diabetes mellitus based on exposure to an herbicide agent;
2. that the Secretary seek statutory authority to provide benefits, including health care, to offspring with birth defects born to women Vietnam veterans;
3. that the Secretary of Veterans Affairs request the National Academy of Sciences to carefully review the new investigations of diabetes and ischemic heart disease to determine the strength of an association between exposure to dioxin and the development of these health outcomes experienced by Vietnam veterans;
4. that the Secretary of Veterans Affairs contact the Secretary of Defense to recommend that the investigators in the Air Force Health Study of Ranch Hand personnel develop a fully adjusted, multivariate model, fully controlling for baseline age and obesity (body mass index) and, if possible, for family history of diabetes, central fat distribution, diabetogenic drug exposure, and a measure of obesity at both the time of Vietnam service, and at the time that laboratory testing for diabetes was performed or a diagnosis of diabetes was made (as recommended by the American Diabetes Association in 1997, a fasting plasma glucose greater than or equal to 126 mg/dl should be used by this study to define the incidence and prevalence of diabetes);
5. that the Secretary of Veterans Affairs contact the Secretaries of Health and Human Services and Defense to facilitate the combined analysis by researchers of the NIOSH and Ranch Hand studies to further examine the possibility that herbicide or dioxin exposure leads to an increased risk of diabetes;
6. that the Secretary of Veterans Affairs work with the Secretaries of other Executive Departments to promote further research on basal and squamous cell skin cancer incidence among workers exposed to herbicides and Vietnam veteran populations (this research should pay particular attention to the confounding factor of UV exposure) and on the carcinogenicity of organic arsenicals; and

7. that the Secretary of Veterans Affairs request that the NAS in its next report:
 - (a) review both maternal and paternal exposures to dioxin and the risk of adverse reproductive outcomes, including birth defects;
 - (b) review the evidence on biologic plausibility and association of dioxin exposure and diabetes;
 - (c) review the evidence on biologic plausibility and association of dioxin exposure and ischemic heart disease;
 - (d) review neural tube defects in addition to spina bifida;
 - (e) review all cancer ICD-9 codes, including those not discussed in previous reports (for example, cancer of major and minor salivary glands);
 - (f) discuss or clarify criteria used to determine statistical significance (especially when the confidence interval includes 1.0); and
 - (g) continue to assess the scientific literature on latency, including:
 - (i) determinants of latency (e.g., factors such as exposure level, duration of exposure, age, and gender); and
 - (ii) whether a minimum or maximum latency period can be determined (particularly if there is a maximum period after which the risk of a disease is no longer elevated due to dioxin/herbicide exposure).

Submitted on behalf of the 1999 Agent Orange Task Force.



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