requested. Therefore, in view of the need to allocate and prioritize NHTSA's limited resources to best accomplish the agency's safety mission, the petition is denied.

Authority: 49 U.S.C. 30162(d); delegations of authority at CFR 1.50 and 501.8.

Issued on: June 18, 2002.

Kenneth N. Weinstein,

Associate Administrator for Safety Assurance.

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DEPARTMENT OF VETERANS AFFAIRS

Diseases Not Associated With Exposure to Certain Herbicide Agents

AGENCY: Department of Veterans Affairs.

ACTION: Notice.

SUMMARY: As required by law, the Department of Veterans Affairs (VA) hereby gives notice that the Secretary of Veterans Affairs, under the authority granted by the Agent Orange Act of 1991, has determined that a presumption of service connection based on exposure to herbicides used in the Republic of Vietnam during the Vietnam Era is not warranted for the following conditions: Hepatobiliary cancers, nasal and nasopharyngeal cancer, bone cancers, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia, reproductive effects (abnormal sperm parameters and infertility), Parkinson's disease, chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease (other than diabetes mellitus), immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, gastrointestinal tract tumors, brain tumors, amyloidosis, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

FOR FURTHER INFORMATION CONTACT: John Bisset, Jr., Consultant, Regulations Staff, Compensation and Pension Service, Veterans Benefits Administration, 810 Vermont Avenue, NW., Washington, DC 20420, telephone (202) 273–7213.

SUPPLEMENTARY INFORMATION: Section 3 of the Agent Orange Act of 1991, Public Law 102–4, 105 Stat. 11, directed the Secretary to seek to enter into an agreement with the National Academy of Sciences (NAS) to review and summarize the scientific evidence concerning the association between exposure to herbicides used in support of military operations in the Republic of Vietnam during the Vietnam Era and each disease suspected to be associated with such exposure. Congress mandated that NAS determine, to the extent possible: (1) Whether there is a statistical association between the suspect diseases and herbicide exposure, taking into account the strength of the scientific evidence and the appropriateness of the methods used to detect the association; (2) the increased risk of disease among individuals exposed to herbicides during service in the Republic of Vietnam during the Vietnam Era; and (3) whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the suspect disease. Section 3 of Public Law 102–4 also required that NAS submit reports on its activities every two years (as measured from the date of the first report) for a ten-year period.

Section 2 of Public Law 102–4 provides that whenever the Secretary determines, based on sound medical and scientific evidence, that a positive association (i.e., the credible evidence for the association is equal to or outweighs the credible evidence against the association) exists between exposure of humans to an herbicide agent (i.e., a chemical in an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam Era) and a disease, the Secretary will publish regulations establishing presumptive service connection for that disease. If the Secretary determines that a presumption of service connection is not warranted, he is to publish a notice of that determination, including an explanation of the scientific basis for that determination. The Secretary's determination must be based on consideration of the NAS reports and all other sound medical and scientific information and analysis available to the Secretary.

Although Public Law 102–4 does not define ''credible,'' it does instruct the Secretary to ''take into consideration whether the results [of any study] are statistically significant, are capable of replication, and withstand peer review.'' Simply comparing the number of studies which report a positive relative risk to the number of studies which report a negative relative risk for a particular condition is not a valid method for determining whether the weight of evidence overall supports a finding that there is or is not a positive association between herbicide exposure and the subsequent development of the particular condition. Because of differences in statistical significance, confidence levels, control for confounding factors, bias, and other pertinent characteristics, some studies are clearly more credible than others, and the Secretary has given the more credible studies more weight in evaluating the overall weight of the evidence concerning specific diseases.

NAS issued its initial report, entitled ''Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam,'' (VAO) on July 27, 1993. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of Hodgkin's disease, porphyria cutanea tarda, multiple myeloma, and certain respiratory cancers; and that there was no positive association between herbicide exposure and any other condition, other than chloracne, non-Hodgkin's lymphoma, and soft-tissue sarcomas, for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on January 4, 1994. (See 59 FR 341 (1994).)

NAS issued its second report, entitled ''Veterans and Agent Orange: Update 1996'' (Update 1996), on March 14, 1996. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of prostate cancer and acute and subacute peripheral neuropathy in exposed persons. The Secretary further determined that there was no positive association between herbicide exposure and any other condition, other than those for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on August 8, 1996. (See 61 FR 41442 (1996).)

NAS issued a third report, entitled ''Veterans and Agent Orange: Update 1998'' (Update 1998), on February 11, 1999. The focus of this updated review was on new scientific studies published since the release of Update 1996 and updates of scientific studies previously reviewed. After NAS issued Update 1998, the Secretary determined that there was no positive association between herbicide exposure and any other condition, other than those for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with

exposure to herbicide agents was published on November 2, 1999. (See 64 FR 59232 (1999).)

However, after NAS released Update 1998 the National Institute of Occupational Safety and Health (NIOSH) published a report that noted an association, though not a strong association, between Type 2 diabetes and dioxin exposure. The Secretary concluded that the NIOSH study was potentially important enough that it warranted a full review by NAS as soon as possible, and he directed VA to amend its contract with NAS for the third biennial update to require a special report on herbicide exposure and Type 2 diabetes.

In February 2000, before NAS released its report on herbicide exposure and Type 2 diabetes, the U.S. Air Force released data from its study of participants in operation Ranch Hand (the crews assigned to spray Agent Orange from aircraft in Vietnam) (AFHS. 2000a. Air Force Health Study: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. 1997 Follow-up Examination Results. Brook AFB, TX: Air Force Research Laboratory. AFRL–HE–BR–TR–2000–02.) On April 10, 2000, VA asked NAS to include an analysis of the new Ranch Hand data in its report on Type 2 diabetes. NAS agreed to do so.

NAS issued its report, ''Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes'' (VAO: Diabetes) on October 11, 2000. NAS concluded ''there is limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and Type 2 diabetes.'' NAS based its conclusion on the totality of the scientific evidence on this issue, not one particular study. (VAO: Diabetes). After considering all of the evidence, the Secretary determined that there is a positive association between exposure to herbicides and Type 2 diabetes and, therefore, a presumption of service connection was warranted. (See 66 FR 2376 [2001].)

NAS issued a fourth report, entitled ''Veterans and Agent Orange: Update 2000'' (Update 2000), on April 19, 2001. The focus of this updated review was on new scientific studies published since the release of Update 1998 and updates of scientific studies previously reviewed. The Secretary formed a VA task force to review the report and pertinent studies and to make recommendations to assist him in determining whether a positive association exists between herbicide exposure and any condition. The task force has completed that review and submitted its recommendations to the Secretary. This notice, pursuant to Public Law 102–4, summarizes the scientific data reviewed by NAS in its Update 2000 and conveys the Secretary's determination, which is based on the cumulative scientific data reported by NAS, that there is no positive association between herbicide exposure and hepatobiliary cancers, nasal and nasopharyngeal cancer, bone cancers, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia, reproductive effects (abnormal sperm parameters and infertility), Parkinson's disease, chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease (other than diabetes mellitus), immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, gastrointestinal tract tumors, brain tumors, amyloidosis, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

NAS, in Update 2000 and a special additional report, assigns hepatobiliary cancers, nasal and nasopharyngeal cancer, bone cancers, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia, reproductive effects (abnormal sperm parameters and infertility), Parkinson's disease, chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease (except diabetes mellitus), immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, and amyloidosis to a category labeled inadequate/insufficient evidence to determine whether an association exists. This is defined as meaning that the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association with herbicide exposure. In Update 2000, NAS assigned gastrointestinal tract tumors and brain tumors to a category labeled limited or suggestive evidence of no association. This is defined as meaning that the available studies are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure.

Hepatobiliary Cancers

Hepatobiliary cancers are cancers of the liver and intrahepatic bile ducts. There are a variety of known risk factors, including chronic infections with hepatitis B and C, exposure to aflatoxin, vinyl chloride and polychlorinated biphenyl (PCB) and smoking, that should be considered by a credible study.

NAS noted in VAO and subsequent reports that there were relatively few occupational, environmental, or veteran studies of hepatobiliary cancer. It also noted that most of the few existing studies addressing hepatobiliary cancer contain methodological difficulties such as small study size and inadequate control for life-style-related risk factors, or do not support an association with herbicide exposure.

The largest industrial cohort exposed to dioxins is the group of 5,132 U.S. workers known as the NIOSH cohort. This group was assembled from employees of 12 major chemical manufacturers that produced 2,4,5-trichlorophenol, 2,4,5-T, Silvex, Erbon, Ronnel, and hexachlorophene. Workers engaged in production and maintenance were exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a contaminant in these chemicals. The first study of mortality through 1987 among these workers (Fingerhut et al., 1991, (See 59 FR 341 [1994])) found no elevated risk for cancers of the liver or hepatobiliary duct. This cohort has been updated through 1993 (Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Journal of the National Cancer Institute 91(9): 779–786.). In Update 2000, NAS noted that the updated analysis of mortality did not find any elevation in liver cancer mortality. Additionally, NAS noted that this study did not adjust for life-style factors.

NAS reported in Update 2000 that a 1998 study of mortality among Danish paper mill workers (Rix BA, Villadsen E, Engholm G, Lynge E. 1998. Hodgkin's disease, pharyngeal cancer, and soft tissue sarcomas in Danish paper mill workers. Journal of Occupational and Environmental Medicine 40(1):55–62.) did not find any elevation in liver cancer mortality.

NAS noted that follow-up reports of the people environmentally exposed to TCDD in Seveso, Italy, (Bertazzi PA, Bernucci I, Brambilla G, Consonni D, Pesatori AC. 1998. The Seveso studies on early and long-term effects of dioxin exposure: a review. Environmental Health Perspectives 106 (Suppl 2):625–

633; Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, Pesatori AC. 2001. Health effects of dioxin exposure: a 20-year mortality study. American Journal of Epidemiology, 153(11): 1031–1044.) did not add any new information concerning hepatobiliary cancer. Additionally, NAS noted that these follow-up reports did not adjust for life-style factors.

NAS reported that a recent study of Air Force personnel (AFHS. 2000b. An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. 1997 Follow-up Examination and Results. Reston, VA: Science Application International Corporation. F41624–96–C1012.) provides a suggestion of an association between herbicide exposure and liver cancer. However, NAS found that, when considered with the overall body of evidence, this finding was not sufficient to a change its conclusion that there is inadequate or insufficient evidence of an association between exposure to herbicides used in Vietnam and hepatobiliary cancer.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and hepatobiliary cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Nasal and Nasopharyngeal Cancer

Nasal and nasopharyngeal cancers are relatively rare in the United States and thus difficult to study epidemiologically. Reported risk factors for nasal cancer include occupational exposure to nickel and chromium compounds, wood dust, and formaldehyde. Studies of nasopharyngeal cancer have reported associations with the consumption of salt-preserved foods, cigarette smoking, and Epstein-Barr virus. NAS noted in VAO and subsequent reports that there was inadequate or insufficient evidence to determine whether an association exists between herbicide exposure and nasal and nasopharyngeal cancer.

NAS reported in Update 2000 that an occupational study (Caplan LS, Hall HI, Levine RS, Zhu K. 2000. Preventable risk factors for nasal cancer. Annals of Epidemiology 10:186–191.) evaluated exposures among cases with nasal cancer identified in population-based cancer registries in five metropolitan areas and three states. The cancers were a mixed group that included mostly nasopharyngeal carcinomas, some sarcomas, and lymphomas. NAS found that this heterogeneity makes attribution of nasopharyngeal carcinoma to particular risk factors difficult.

NAS reported that Bertazzi et al., (2001) did not identify any nasopharyngeal carcinomas in their population of TCDD-exposed residents of Seveso, Italy, and that Ranch Hand participants (AFHS, 2000a) did not show an excess risk of nasopharyngeal cancer.

NAS found that there was no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and nasal and nasopharyngeal cancer. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and nasal and nasopharyngeal cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Bone Cancers

NAS noted that bone cancer is more common in teenagers than adults, and, therefore, the incidence among Vietnam veterans is quite low. Among the risk factors for adults contracting bone and joint cancer are exposure to ionizing radiation from treatment for other cancers and a history of certain noncancerous bone diseases. NAS found in VAO and subsequent reports that there is inadequate or insufficient information to determine whether an association exists between exposure to herbicides and bone cancer.

NAS noted in Update 2000 that Steenland et al.,1999, did not report results for bone cancer, and Rix *et al.,* 1998, found only one case of bone cancer.

NAS found that Bertazzi *et al.,* 1998, did not add any new information to Bertazzi et al., 1997, (See 64 FR 59232 [1999]), and that Bertazzi et al., 2001, did not mention bone cancer mortality. Likewise, NAS noted that in AFHS 2000, bone cancer was not reported as one of the health outcomes of interest.

NAS noted little new information to add to the existing sparse data, and therefore, found there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and bone cancer.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and bone cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Breast Cancer

NAS noted that breast cancer is the single most common cancer among women in the United States, excluding certain skin cancers. Breast cancer incidence generally increases with age. Risk factors other than aging include a personal or family history of breast cancer and certain reproductive characteristics; specifically, early onset of menarche, late onset of menopause, and either no pregnancies or first full-term pregnancy after 30 years of age. NAS noted in VAO and subsequent reports that there is inadequate or insufficient information to determine whether an association exists between exposure to herbicides and breast cancer.

NAS noted in Update 2000, that Bertazzi et al., 1998, and Bertazzi *et al.,* 2001, found no elevations in mortality from breast cancer.

NAS found that, although there appears to be limited evidence to suggest that there is an epidemiologically defined protective effect of exposure to TCDD in reducing the overall incidence of breast cancer, this should be understood as limited to the narrow context of frequency of new disease. NAS noted that the term ''protective'' was used in a narrow technical sense of exposure being associated with a reduction in risk. The effect is not necessarily a benefit as it remains possible that exposure to TCDD and Agent Orange may affect lethality, distribution of tissue type, rate of progression, and invasiveness. NAS found limited evidence that this may be the case for organochlorine exposure in general (Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E. 2000. Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Cancer Epidemiology, Biomarkers and Prevention 9:161–166.), but the data of another study (Hoyer AP, Jorgensen T, Brock JW, Grandjean P. 2000. Organochlorine exposure and breast cancer survival. Journal of Clinical Epidemiology 53(3):323–330.) suggest that the effect is very specific in terms of compound. NAS stated that it is not known whether compounds relevant to Agent Orange exposure have this effect.

NAS noted that there is a possibility that TCDD exposure could adversely affect the natural history of tumors that do arise. NAS cited a finding from Demers et al., 2000, that higher organochlorine exposure is associated with more invasive and progressive

disease, once a cancer does develop. NAS noted that Hoyer et al., 2000, found that higher levels of one organochlorine were associated with poorer prognosis of breast cancer. NAS stated that the relevance to women exposed to Agent Orange is uncertain. Importantly, NAS found no evidence from which to evaluate the possibility that exposure to organochlorine may modify the natural history if exposure takes place at certain sensitive periods during the development of breast tissue, such as puberty and pregnancy.

NAS found no information in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and breast cancer. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and breast cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Cancers of the Female Reproductive System

NAS noted that the cancers of the female reproductive system include cancers of the cervix, endometrium (also referred to as the corpus uteri), and ovaries. Cervical cancers occur more often in African-American women than in white women, whereas white women are more likely to develop endometrial and ovarian cancers. The incidence of endometrial and ovarian cancer also depends on age, with older women at greater risk. Human papillomavirus infection is the most important risk factor for cervical cancer. Diet, a family history of the disease, and breast cancer are among the risk factors for endometrial and ovarian cancers. NAS noted in VAO and subsequent reports that there is inadequate or insufficient information to determine whether an association exists between exposure to herbicides and cancers of the female reproductive system.

NAS stated in Update 2000 that the evidence from the reviewed studies is inconclusive because most of the published studies include a small number of cases and/or have poor exposure characterization or too short a follow-up period.

NAS noted that Bertazzi et al., 1998 and 2001, found no increases in female reproductive cancers.

NAS found that a case-control study of endometrial cancer in Sweden (Weiderpass E, Adami HO, Baron JA, Wicklund-Glynn A, Aune M, Atuma S, Persson I. 2000. Organochlorines and endometrial cancer risk. Cancer Epidemiology, Biomarkers and Prevention 9:487–493.), after adjustment for age and body mass index, reported no pesticides were associated with endometrial cancer.

NAS reported that a study of female Vietnam veterans from Australia (Commonwealth Department of Veterans' Affairs (CDVA). 1998b. Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Community. Volume 2: Female Vietnam Veterans Survey and Community Comparison Outcomes. Canberra: Department of Veterans' Affairs.) found an excess of all cancers combined. However, NAS noted that the numbers were small, and since the authors did not stratify or adjust for marital status, the findings may be confounded.

NAS found that there was no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and cancers of the female reproductive system. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and cancers of the female reproductive system outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Urinary Bladder Cancer

Urinary bladder cancer is the most common of the genitourinary tract cancers. Bladder cancer incidence increases greatly with age for individuals older than 40. The most important known risk factor for bladder cancer is smoking. Occupational exposures to aromatic amines (also called arylamines), polycyclic aromatic hydrocarbons (PAHs), and certain other organic chemicals used in the rubber, leather, textile, paint products, and printing industries are also associated with higher incidence of bladder cancer. High-fat diets have been implicated as risk factors, along with exposure to the parasite Schistosoma haematobium.

NAS noted in VAO and Update 1996 that there was limited or suggestive evidence of no association between exposure to herbicides used in Vietnam or the contaminant dioxin and urinary bladder cancer. NAS in Update 1998 changed that conclusion to inadequate or insufficient information regarding an association.

NAS noted in Update 2000 that coexposure to TCDD and the known bladder carcinogen 4-aminobiphenyl in the Steenland *et al.,* 1999, study makes it very difficult to determine whether dioxin exposure affected the observed incidence of bladder cancer.

NAS reported that the overall results concerning bladder cancer from Bertazzi et al., 1998, and Bertazzi et al., 2001, were statistically indistinguishable from the expected number of bladder cancer cases.

NAS noted that AFHS (2000) combined bladder and kidney cancers for analysis. Since both these cancers have a common association with smoking but are otherwise etiologically distinct diseases, NAS reported that the AFHS results were weakened.

NAS found no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and urinary bladder cancer. Taking account of the available evidence and NAS'' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and urinary bladder cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Renal Cancer

Renal cancer is twice as common in men as in women. With the exception of Wilm's tumor, which is more likely to occur in children, renal cancer is more common in individuals older than 50. Smoking is a well-established risk factor for renal cancer. Other potential risk factors include diet, weight, and occupational exposure to asbestos and cadmium. Firefighters, who are routinely exposed to the decomposition of organic substances caused by a rise in temperature, are a known higher-risk group.

NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and renal cancer.

NAS stated in Update 2000 that the results of a study of male Dutch production and contract workers (Hooiveld M, Heederik DJ, Kogevinas M, Boffetta P, Needham LL, Patterson DG Jr, Bueno de Mesquita HB. 1998. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. American Journal of Epidemiology 147(9):891–901.) are limited by the lack of control for smoking.

NAS reported that, because cigarette smoking covaried with the indicators of

herbicide exposure used by AFHS (2000a) researchers, the analysis was confounded. NAS noted that the elevated incidence of renal cancer was seen in AFHS, 2000a, in the low-dioxin category but not the high-dioxin category, which would not be expected if an association existed between exposure and renal cancer.

NAS stated that there is no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and renal cancer. Taking account of the available evidence and NAS'' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and renal cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Testicular Cancer

Testicular cancer is far more likely in men younger than 40 than in those who are older. Undescended testicles is a major risk factor for testicular cancer. Family history of the disease also appears to be a risk factor for testicular cancer.

NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and testicular cancer.

NAS noted in Update 2000 that, among the studies reviewed, only one (Fleming LE, Bean JA, Rudolph M, Hamilton K. 1999b. Cancer incidence in a cohort of licensed pesticide applicators in Florida. Journal of Occupational and Environmental Medicine 41(4):279–288.) reported a statistically significant difference between the observed and expected number of cases of testicular cancer. NAS stated that the pesticide appliers studied by these researchers were likely exposed to a wide variety of chemicals, making it difficult to ascribe any effect to a particular compound.

NAS reported that Bertazzi *et al.,* 1998, did not report testicular cancer separately, but instead included it into a category called ''genitourinary cancers.'' However, NAS noted, no increased risk was reported. Bertazzi et al., 2001, similarly did not report an increased risk for this category.

NAS reported that the government of Australia conducted a mail survey of male veterans (CDVA, 1998a. Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community. Volume 1: Male Vietnam Veterans Survey and Community Comparison Outcomes. Canberra: Department of Veterans' Affairs.). A follow-up study was conducted to medically confirm selected conditions (Australian Institute of Health and Welfare (AIHW). 1999. Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community: Volume 3, Validation Study. Canberra: AIHW.). NAS noted that the authors found no elevated risk for testicular cancer.

Noting that studies with either large numbers of cases or known TCDD exposures do not show an increased risk for testicular cancer, NAS stated that there is no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and testicular cancer. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and testicular cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Leukemia

Acute lymphocytic leukemia (ALL) is a disease of the young and of individuals older than 70, and plays a small role in the age groups that characterize most Vietnam veterans. Exposure to high doses of ionizing radiation is a known risk factor. Acute myeloid leukemia (AML) is the most common leukemia among adults. Risk factors for AML include high doses of ionizing radiation, occupational exposure to benzene, and some medications used in cancer chemotherapy. Genetic disorders including Fanconi's anemia and Down's syndrome are associated with an increased risk for AML. Tobacco smoking has been suggested as a risk factor.

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in men. It is largely a disease of individuals older than 40, and incidence doubles every 5 years for individuals in the age groups that characterize most Vietnam veterans. Some occupational groups, such as farmers, appear to have a higher incidence of CLL. A family history of the disease and a compromised immune system are additional suspected risk factors. Exposure to ionizing radiation does not appear to be associated with increased incidence of CLL.

The incidence of chronic myeloid leukemia (CML) increases with age for individuals over 30. For individuals in the age groups that characterize most Vietnam Veterans, CML accounts for about one in five leukemias. CML is associated with an acquired chromosomal abnormality known as the ''Philadelphia chromosome.'' Exposure to high doses of ionizing radiation is a known risk factor for CML.

NAS noted in VAO and subsequent reports that there is inadequate or insufficient information to determine whether an association exists between exposure to herbicides and leukemia.

NAS, in Update 2000, reported that Hooiveld *et al.,* 1998, Rix *et al.,* 1998, Steenland *et al.,* 1999, showed no increase risk for leukemia. NAS stated that CDVA, 1998a and 1998b, validated by AIHW, 1999, found no increased risk for leukemia.

NAS stated that the small number of cases found by AFHS (2000a/b) led to nonsignificant results.

NAS reported that there was no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether as association exists between exposure to herbicides and leukemia. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and leukemia outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Reproductive Effects

Reproductive effects on veterans may include sperm quality and infertility.

NAS noted in VAO and subsequent reports that there is inadequate or insufficient information to determine whether an association exists between exposure to herbicides and altered sperm parameters or infertility.

NAS, in Update 2000, reported that studies of Danish farmers (Larsen SB, Joffe M, Bonde JP. 1998. Time to pregnancy and exposure to pesticides in Danish farmers. Occupational and Environmental Medicine 55(4): 278–283.) and greenhouse workers (Abell A, Juul S, Bonde JP. 2000. Time to pregnancy among female greenhouse workers. Scandinavian Journal of Work, Environment, and Health 26(2):131–136.) lacked information on TCDD level as a contaminant of the pesticides investigated. NAS also noted that studies limited to couples who achieve a pregnancy can be biased, because cases of infertility are excluded

(Sallmen M, Lindbohm ML, Nurminen M. 2000. Paternal exposure to lead and infertility. Epidemiology 11(2): 148–152.).

NAS stated that there is no information in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and altered sperm parameters or infertility.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and reproductive effects in veterans outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Parkinson's Disease

Because of the increasing concern that a link exists between Parkinson's disease (PD) and various chemicals used in herbicides, NAS, in VAO and subsequent reports, suggested that as Vietnam veterans move into the age groups when PD is more prevalent, attention be given to the frequency and character of new cases of PD in exposed versus nonexposed individuals.

NAS, in Update 2000, stated that of the 30 studies summarized, only eight provide an estimate of relative risk of PD based on exposure to herbicides. Five of these studies found a significant association between herbicide exposure and PD (Butterfield *et al.,* 1993 (See 61 FR 41442 [1996]); Gorrell *et al.,* 1998 (See 64 FR 59232 [1998]); Liou *et al.,* 1997 (See 64 FR 59232 [1998]); Seidler *et al.,* 1996 (See 64 FR 59232 [1998]); Semchuk *et al.,* 1992 (See 61 FR 41442 [1996])). One study found no association between herbicide exposure and PD (Taylor CA, Saint-Hilaire MH, Cupples LA, Thomas CA, Burchard AE, Feldman RG, Myers RH. 1999. Environmental, medical, and family history risk factors for Parkinson's disease: a New England-based case control study. American Journal of Medical Genetics (Neuropsychiatric Genetics) 88: 742–749.). The two remaining studies found a negative association between herbicide exposure and PD (Kuopio A, Marttila RJ, Helenius H, Rinne UK. 1999. Environmental risk factors in Parkinson's disease. Movement Disorders 14: 928–939; Stern *et al.,* 1991 (See 61 FR 41442 [1996])). Based on the totality of the evidence, NAS concluded that there remains inadequate or insufficient evidence of an association between exposure to herbicides and PD.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and PD outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Chronic Persistent Peripheral Neuropathy

NAS noted in VAO and subsequent reports that there was inadequate or insufficient evidence of an association between exposure to herbicides and chronic persistent peripheral neuropathy. Data from the Air Force Health Studies, in a large measure, accounted for this conclusion.

In Update 2000, NAS reported that AFHS, 2000, found five cases of peripheral neuropathy in the Ranch Hand ground crew. NAS stated that this finding was consistent with the expected prevalence for peripheral neuropathy in the general population and prevalence increases with age. NAS noted that the development of a peripheral neuropathy associated with a toxic exposure begins when the exposure is occurring or shortly after cessation of the exposure. Furthermore, the peripheral nervous system has the ability to repair itself when the exposure ceases. Therefore, NAS stated that it is not biologically plausible that peripheral neuropathies found for the first time were caused by an exposure to herbicides that occurred 30 years earlier.

NAS concluded that there remains inadequate or insufficient evidence of an association between exposure to herbicides and chronic persistent peripheral neuropathy. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and chronic persistent peripheral neuropathy outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Lipid and Lipoprotein Disorders

Plasma lipid concentrations (notably cholesterol) have been shown to predict cardiovascular disease and are considered fundamental to the underlying atherosclerotic process. The two major lipids, cholesterol and triglycerides, are carried in the blood attached to proteins to form lipoproteins. NAS in VAO and subsequent reports found there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and lipid and lipoprotein disorders.

NAS, in Update 2000, stated that AFHS, 2000a/b, provided incomplete and inconsistent evidence on a possible association between dioxin exposure and lipid abnormalities and noted the failure to evaluate the role of obesity. NAS noted that there were no other new studies for it to evaluate on this subject. NAS concluded that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and lipid and lipoprotein disorders.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and lipid and lipoprotein disorders outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Gastrointestinal and Digestive Disease

Gastrointestinal and digestive disease includes diseases of the esophagus, stomach, intestines, rectum, liver, and pancreas. NAS, in VAO and subsequent reports, found there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and gastrointestinal and digestive disease.

NAS, in Update 2000, stated that most of the studies reviewed for the first time had insufficient numbers of cases to draw confident conclusions. NAS noted that one study with a relatively large number of observations (Vena J, Boffeta P, Becher H, Benn T, Bueno de Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Pesatori AC, Saracci R, Steenland K, Kogevinas M. 1998. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. Environmental Health Perspectives 106 (Suppl. 2): 645–653.) found lower digestive system disease and liver cirrhosis mortality among exposed workers than unexposed controls.

NAS reported that studies of Australian veterans (CDVA 1998a and 1998b) suggested a higher incidence of stomach and duodenal ulcers in both men and women, but information was self-reported and the analyses were not controlled for confounding influences.

NAS noted that AFHS, 2000a, found a significantly higher percentage of liver disorders among Ranch Hands in the high-dioxin category than among comparisons. NAS found that this data was consistent with an interpretation of a dose-response relationship, but that

other explanations were also plausible. NAS noted that the authors of AFHS, 2000a/b, are preparing a separate report examining the relationship between liver disorders and herbicide exposure in greater detail.

NAS concluded that there was no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and gastrointestinal and digestive diseases. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and gastrointestinal and digestive disease outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Immune System Disorders

NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and immune system disorders.

In Update 2000, NAS noted that the immune effects described in humans exposed to TCDD have been marginal and have varied from study to study. Some studies showed increased risk, others decreased risk, and others no effect. Further, workers exposed to high levels of TCDD for several years with body burdens at least ten times higher than the general population had no significant risk for immune system disorders.

NAS reported that immune parameters were measured in veterans of Operation Ranch Hand (Michalek JE, Ketchum NS, Check IL. 1999a Serum dioxin and immunologic response in veterans of Operation Ranch Hand. American Journal of Epidemiology 149: 1038–1046; AFHS, 2000a/b). NAS noted that there was no evidence of a consistent relationship between dioxin exposure and immune system alteration.

NAS reported in Update 2000 that there is no information contained in the research reviewed for this report to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and immune system disorders. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between immune system disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Circulatory Disorders

NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and circulatory disorders.

In Update 2000, NAS stated that new studies from occupational epidemiology contain the key limitations recognized in Update 1998: reliance on mortality as an outcome, the unassessed validity of assigned cause of death, and the inability to address potential confounding by other causes of cardiovascular and cerebrovascular disease.

NAS reported that the evidence of increased circulatory disease mortality exists in the follow-up of the Seveso, Italy, population (Bertazzi et al., 2001), but the pattern is somewhat inconsistent across levels of exposure and the statistical power of the study remains limited, particularly for women.

NAS reported that the findings on circulatory conditions from AFHS 2000 tend to be inconsistent and inconclusive. Excess mortality is reported for enlisted ground personnel from Operation Ranch Hand, but this finding is not supported in subsequent analyses of cardiovascular and cerebrovascular morbidity. NAS noted that AFHS 2000 shows no dioxin-related increased risk for myocardial infarction and the combination of stroke and transient ischemic attack.

NAS noted that elevated rates of heart disease were reported in the Australian veterans studies (CDVA, 1998a and 1998b). However, NAS stated that there was some uncertainty in the numbers of cases due to possible misreporting.

NAS concluded that there is no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and circulatory disorders. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and circulatory disorders outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Respiratory Disorders

Cigarette smoking is a major, often overwhelming, confounding factor that dominates as a risk for respiratory disorders and may obscure weaker risks. NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and respiratory disorders.

NAS noted in Update 2000 that new evidence (cited below) suggests that there may be an increased risk for respiratory disorders among individuals exposed to TCDD. However, NAS stated that this association is based on small numbers, is not adjusted for smoking, and is not internally consistent. Other studies of occupationally exposed subjects do not show this association, although some of these studies are large enough to have revealed this association if it were present.

NAS reported that Steenland *et al.,* 1999, showed no risk for respiratory disorders. NAS noted that this study was large enough to have the statistical power to demonstrate such a risk. Also, NAS found that AFHS 2000 showed no increased risk for respiratory disorders.

NAS concluded that there is no information contained in the research reviewed for Update 2000 to change the conclusion that, except for respiratory cancers, there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and respiratory disorders. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and respiratory disorders other than respiratory cancers outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Skin Cancer

NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and skin cancer.

NAS stated that studies reviewed for the first time in Update 2000 provide additional morbidity data and mortality analyses to account for factors that confound the evaluation of melanoma incidence in groups with exposure to chemical agents. NAS reported that Bertazzi *et al.,* 2001, has too few cases of melanoma to be informative. NAS noted that CDVA, 1998a and b, and AFHS 2000 provided some new important data. However, NAS also reported that AFHS 2000 had too few cases of melanoma to be informative. NAS noted that CDVA, 1998a and b, included the use of self-reported cases with no validation through medical record reviews or other means.

According to NAS, CDVA, 1998a and b, did not control for confounders and used a nonmilitary control group.

NAS reported that there are relatively few studies that examine nonmelanomas and fewer that separate basal and squamous cell carcinomas. NAS stated that CDVA, 1998a and 1998b, and AFHS, 2000a/b, provide new morbidity data for these outcomes. However, NAS reported that the small number of cases in AFHS 2000 limited the results. NAS noted that CDVA, 1998a and 1998b, used self-reported cases and failed to control for important confounders. Also, NAS noted that the results for females were based on a very small number of subjects.

NAS concluded that there is no information contained in the research reviewed for Update 2000 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and skin cancer. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and skin cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Cognitive and Neuropsychiatric Effects

NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and cognitive and neuropsychiatric effects.

NAS noted in Update 2000 that AFHS 2000 found an association between dioxin exposure and only one of five disease categories studied, ''other'' neuroses, which included more than 100 clinically dissimilar classifications of diseases. NAS reported that the biological plausibility for such an association is lacking. NAS noted that, in cases where verified psychological diagnoses from AFHS 2000 were combined with verified psychological diagnoses from previous AFHS studies, it is not clear whether the past diagnoses were active at the time of the AFHS 2000 report. NAS questioned the criteria used for these psychological diagnoses. Also, NAS stated that if these other neuroses were associated with dioxin exposure, the onset of symptoms of specific conditions would have occurred at a much earlier time, when they would be more closely related to actual exposure.

NAS concluded that there is still inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and cognitive and neuropsychiatric effects. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and cognitive and neuropsychiatric effects outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Gastrointestinal Tract Tumors

The incidence of stomach, colon, rectal, and pancreatic cancers increases with age for individuals between 45 and 59. Other risk factors vary for these cancers but always include family history of the same form of cancer, certain diseases of the affected organ, and dietary factors.

NAS noted in VAO and subsequent reports that there was limited or suggestive evidence of no association between exposure to herbicides and gastrointestinal (GI) tract tumors.

NAS stated in Update 2000 that, with only rare exceptions, studies on GI tract cancers and exposure to herbicides in production, from agricultural use, from environmental sources, and among veteran populations provided no evidence of any increase in risk. NAS noted that Steenland *et al.,* 1999, did not report site-specific GI cancers, and there was a nonsignificantly elevated excess risk for GI cancers in the highest-exposed subgroups. NAS noted that Rix *et al.,* 1998, found some nonsignificant elevations of GI cancers, but the possible link with dioxin exposure was not well established. NAS noted that Hooiveld *et al.,* 1998, found no significant risk of GI cancer. NAS noted that Bertazzi *et al.,* 2001, found some statistically excess risks, but these were based on relatively small numbers of cases and do not seem to occur with any consistency. Also, NAS noted that among studies of Vietnam veterans (AFHS, 2000a/b; CDVA, 1998a and 1998b; AIHW, 1999) there was no significant evidence of an association between herbicide exposure and any GI cancer.

NAS concluded that there was no new evidence to change the previous determination that there is limited or suggestive evidence of no association between exposure to herbicides and gastrointestinal tract cancer. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and gastrointestinal tract cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Brain Tumors

NAS noted in VAO and subsequent reports that there was limited or suggestive evidence of no association between exposure to herbicides and brain tumors.

NAS reported in Update 2000 that the studies reviewed for the first time found small numbers of cases of brain tumors and no excess risk. NAS noted that Hooiveld *et al.,* 1998, found no deaths due to brain cancer. NAS noted that Bertazzi *et al.,* 2001, found no new deaths from brain cancers. NAS noted that AFHS 2000 reported only one case of brain cancer and, consequently, the authors performed no statistical analysis.

NAS concluded that there was no new evidence to change the previous determination that there is limited or suggestive evidence of no association between exposure to herbicides and brain tumors. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and brain tumors outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Amyloidosis

Amyloidosis is a group of bone marrow diseases, poorly understood and relatively rare, characterized by accumulation of insoluble fibrillar proteins (amyloid) in various organs and tissues of the body such that vital function is compromised. Systemic amyloidosis is a complication that occurs in approximately 15–20 percent of patients with multiple myeloma, which is also a bone marrow disease.

VA asked NAS to address the possible association between exposure to herbicides and amyloidosis, a condition not examined in its prior reports.

In Update 2000, NAS identified a single report that addressed exposure to the herbicides and amyloidosis. This report (Tóth K, Somfai-Relle S, Sugár J, Bence J. 1979. Carcinogenicity testing of herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. Nature 278(5704):548–549.) described the results of carcinogenicity tests of the herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. NAS reported that the mice developed amyloidosis secondary to skin lesions caused by the chemical exposure. NAS did not identify any literature addressing primary (in

absence of a discernible preceding disease) amyloidosis in animals or people exposed to herbicides or dioxin.

NAS concluded that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and amyloidosis. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and amyloidosis outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS reviewed scientific and medical articles published since the publication of its first report as an integral part of the process that resulted in ''Veterans and Agent Orange: Update 2000.'' The comprehensive review and evaluation of the available literature which NAS conducted in conjunction with its report has permitted VA to identify all conditions for which the current body of knowledge supports a finding of an association with herbicide exposure. Accordingly, the Secretary has determined that there is no positive association between exposure to herbicides and any other condition for which he has not specifically determined that a presumption of service connection is warranted.

Approved: June 11, 2002.

Anthony J. Principi,

Secretary of Veterans Affairs.

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