

I Order for U.S. Savings Bonds (PD F 5374); and Series I Order for U.S. Savings Bonds to be Registered in Name of Fiduciary (PD F5374-1).

Description: These forms are completed by the purchaser to issue United States Savings Bonds.

Respondents: Individuals or households.

Estimated Number of Respondents: 10,000,000.

Estimated Burden Hours Per Respondent: 5 minutes per form.

Frequency of Response: On occasion.

Estimated Total Reporting Burden Hours: 830,000 hours.

OMB Number: 1535-0102.

Form Number: PD F 1071.

Type of Review: Extension.

Title: Certificate of Ownership of United States Bearer Securities.

Description: PD F 1071 is used to establish ownership and support a request for payment.

Respondents: Individuals or households, Business or other for-profit.

Estimated Number of Respondents: 1,000.

Estimated Burden Hours Per Respondent: 15 minutes.

Frequency of Response: On occasion.

Estimated Total Reporting Burden Hours: 250 hours.

OMB Number: 1535-0126.

Form Number: PD F 3871.

Type of Review: Extension.

Title: Application for Issue of United States Mortgage Guaranty Insurance Company Tax and Loss Bonds.

Description: PD F 3871 is submitted by companies engaged in the business of writing mortgage guaranty insurance for purpose of purchasing "Tax and Loss" bonds.

Respondents: Business or other for-profit.

Estimated Number of Respondents: 37

Estimated Burden Hours Per Respondent: 15 minutes.

Frequency of Response: On occasion.

Estimated Total Reporting Burden Hours: 20 hours.

Clearance Officer: Vicki S. Thorpe (304) 480-6553, Bureau of the Public Debt, 200 Third Street, Parkersburg, West VA 26106-1328.

OMB Reviewer: Joseph F. Lackey, Jr., Office of Management and Budget, Room 10235, New Executive Office Building, Washington, DC 20503, (202) 395-7316.

Mary A. Able,

Departmental Reports Management Officer. [FR Doc. 03-12676 Filed 5-19-03; 8:45 am]

BILLING CODE 4810-39-P

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 and the Veterans Education and Benefits Expansion Act of 2001, 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, nasopharyngeal cancer, bone and joint cancer, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia (other than chronic lymphocytic leukemia (CLL)), abnormal sperm parameters and infertility, Parkinson's disease and parkinsonism, amyotrophic lateral sclerosis (ALS), chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, gastrointestinal tract tumors, brain tumors, light chain-associated (AL) amyloidosis, endometriosis, adverse effects on thyroid homeostasis, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

FOR FURTHER INFORMATION CONTACT:

Cheryl Konieczny, Consultant, Regulations Staff, Compensation and Pension Service, Veterans Benefits Administration, 810 Vermont Avenue, NW, Washington, DC 20420, telephone (202) 273-6779.

SUPPLEMENTARY INFORMATION: Section 3 of the Agent Orange Act of 1991, Pub. L. 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 Pub. L. 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 Pub. L. 102-4, codified in pertinent part at 38 U.S.C. 1116(b) and (c), 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.

Section 2 of the Agent Orange Act of 1991 provided that the Secretary's authority and duties under that section would expire 10 years after the first day of the fiscal year in which NAS transmitted its first report to VA. The first NAS report was transmitted to VA in July 1993, during the fiscal year that began on October 1, 1992. Accordingly, VA's authority under section 2 of the Agent Orange Act of 1991 expired on September 30, 2002. In December 2001, however, Congress enacted the Veterans Education and Benefits Expansion Act of 2001, Public Law 107-103. Section 201(d) of that Act extended VA's authority under 38 U.S.C. 1116(b)-(d) through September 30, 2015.

Although 38 U.S.C. 1116 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].)

At VA’s request, NAS issued a special interim 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. After NAS issued Update 2000, 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 June 24, 2002 (See 67 FR 42600–608).

NAS issued its fifth report, entitled “Veterans and Agent Orange: Update 2002” (Update 2002) on January 23, 2003. The focus of this updated review was on new scientific studies published since the release of Update 2000, and to review the studies previously reviewed along with the newest scientific evidence. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of chronic lymphocytic leukemia (CLL) in exposed persons. A proposed rule to establish a presumption of service connection for CLL was published in the **Federal Register** of March 26, 2003 (See 68 FR 14567). The Secretary also determined

that there is no positive association between herbicide exposure and hepatobiliary cancers, nasopharyngeal cancer, bone and joint cancer, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia (other than CLL), abnormal sperm parameters and infertility, Parkinson’s disease and parkinsonism, amyotrophic lateral sclerosis (ALS), chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease including liver toxicity, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, gastrointestinal tract tumors, brain tumors, AL amyloidosis, endometriosis, adverse effects on thyroid homeostasis, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted. This notice, pursuant to 38 U.S.C. 1116(c)(1)(B), summarizes the scientific data reviewed by NAS in its Update 2002, and conveys the Secretary’s determination regarding no positive association between herbicide exposure and the above-cited conditions.

NAS, in Update 2002, assigns hepatobiliary cancers, nasopharyngeal cancer, bone and joint cancer, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia (other than CLL), abnormal sperm parameters and infertility, Parkinson’s disease and parkinsonism, chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, AL amyloidosis, endometriosis, and adverse effects on thyroid homeostasis 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 2002, 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.

The Secretary's determinations regarding individual diseases are based on all available evidence in Update 2002 and prior NAS reports. This notice generally states specific information only with respect to significant additional studies that were first reviewed by NAS in Update 2002. Information regarding additional relevant studies has previously been stated in VA's prior notices following earlier NAS reports, and will not be repeated here.

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 or 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.

An environmental study of the residents of Chapaevsk, Russia, an industrial community with documented contamination by dioxins and other chemicals of the food and water supply, revealed a higher incidence of liver cancer than in Russia as a whole or the Samara region of Russia, in which Chapaevsk is located, although no information was provided on exposed cases or estimated relative risk for morbidity. (Revich B, Aksel E, Ushakova T, Ivanova I, Zuchenko N, Lyuev N, Brodsky B, Sotsov Y. 2001. Dioxin exposure and public health in Chapaevsk, Russia. *Chemosphere* 43:951-966) In Update 2002, NAS determined that this study cannot be taken as strong evidence for an association between dioxins and liver cancer because the study failed to adjust for confounding by socioeconomic, lifestyle, comorbidity and other factors, and because of the likelihood of multiple exposures and concerns regarding the study design.

NAS found that there was no information contained in the research reviewed for Update 2002 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between

exposure to herbicides 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.

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.

An environmental study of the residents of Chapaevsk, Russia, revealed a higher incidence of pharyngeal cancer in females than in Russia as a whole, although no information was provided on exposed cases or estimated relative risk for morbidity. (Revich et al., 2001.) Male residents of Chapaevsk did not show a higher incidence of pharyngeal cancer. NAS reported, in Update 2002, that the usefulness of these data is restricted because of factors such as lack of adjustment for confounding, the likelihood of multiple exposures, concern regarding the study design, and the absence of information on the completeness and accuracy of cancer incidence data.

NAS found that there was no information contained in the research reviewed for Update 2002 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides 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 nasopharyngeal cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Bone and Joint Cancer

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.

An environmental study of the residents of Chapaevsk, Russia, revealed seven deaths in male residents and seven deaths in female residents due to cancer of the bones or soft tissues. (Revich et al., 2001.) In Update 2002, NAS reported that these results cannot be taken as evidence for an association between bone cancer and dioxins, because cancers of the bone and soft tissue were combined in the analysis. Further, the increased risk for death due to bone cancer and soft-tissue cancer combined was not statistically significant.

NAS found that there was no information contained in the research reviewed for Update 2002 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and bone and joint 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 and joint 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 second most common cancer among women in the United States. 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 age 30. 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.

In its prior reports, NAS reviewed several studies finding no increased risk of breast cancer associated with herbicide exposure or Vietnam service, and possibly even showing a limited protective effect for new incidence of breast cancer

NAS reviewed a number of new studies for Update 2002. A follow up to an occupational study reviewed in Update 2000 published results on the reproducibility of the self-reported data on farm exposures to potentially hazardous agents such as pesticides. (Duell EJ, Millikan RC, Savitz DA, Schell MJ, Newman B, Tse CJ, Sandler DP. 2001. Reproducibility of reported farming activities and pesticide use among breast cancer cases and controls: A comparison of two modes of data collection. *Annals of Epidemiology* 11(3):178–185) It was found that the farming-exposure information was generally reproducible, which provided some assurance that the prior conclusion of no overall excess risk of breast cancer was not due to measurement error in the exposure assessment.

An environmental study of the joint effects of all congeners of polychlorinated biphenyls (PCBs) (Holford TR, Zheng T, Mayne ST, Zahm SH, Tessari JD, Boyle P. 2000. Joint effects of nine polychlorinated biphenyl (PCB) congeners on breast cancer risk. *International Journal of Epidemiology* 29 (6):975–82) showed that total PCB was not significantly associated with breast cancer risk. NAS noted, however, that significant protective effects were detected for potential antiestrogens and a dioxin-like congener. This study was consistent with results of previously reported studies. General population controls were not used, which limited the external validity of the results.

The relationship between the relatively high dioxin concentrations in Chapaevsk, Russia and breast cancer incidence and related mortality was studied in Revich *et al.* (2001). The incidence rate of female breast cancer, age-adjusted to the Russian standard population, was higher in Chapaevsk in all age groups than in Russia and the Samara region. NAS noted that the lack of adjustment for such risk factors as family size, breastfeeding, alcohol use, body-mass index and fat consumption was one of the main weakness of this study.

Two environmental studies provided evidence of a relationship between the development of breast cancer and increased concentrations of PCB congeners that have dioxin-like activity. (Aronson KJ, Miller AB, Woolcott CG, Sterns EE, McCready DR, Lickley LA, Fish EB, Hiraki GY, Holloway C, Ross T, Hanna WM, SenGupta SK, Weber J-P. 2000. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. *Cancer Epidemiology, Biomarkers and*

Prevention 9(1):53–63; Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E. 2002. Plasma concentrations of polychlorinated biphenyls and the risk of breast cancer: A congener-specific analysis. *American Journal of Epidemiology* 155(7):629–635) NAS noted that the external validity of one of the studies (Aronson *et al.*) was limited by the lack of general-population controls. NAS found that the other study (Demers *et al.*) was well conducted and appears to have used appropriate statistical methods. NAS also noted, however, that PCB congeners also have non-dioxin-like components, and that the observed effects may be attributable to those components.

Another study found further evidence of increased breast cancer risk associated with increased serum TCDD. (Warner M, Eskenazi B, Mocarelli P, Gerthoux PM, Samuels S, Needham L, Patterson D, Brambilla P. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environmental Health Perspectives* 2002; 110(7) 625–628) NAS found that this study adjusted for risk factors and was apparently free from potential bias. NAS also noted, however, that the findings were potentially limited because they were based on only 15 cases.

In a Vietnam veteran study that included 4,140 female Vietnam veterans and 4,140 veteran controls that did not service in Vietnam, it was concluded that Vietnam veterans did not experience a significantly higher prevalence of breast cancer. (Kang HK, Mahan CM, Lee KY, Magee CA, Selvin S. 2000. Prevalence of gynecologic cancers among female Vietnam veterans. *Journal of Occupational & Environmental Medicine* 42(11):1121–1127.) Although the prevalence of breast cancer was higher in female Vietnam veterans than in non-Vietnam veterans, the difference was not considered statistically significant. This study, also, was considered by NAS to be well designed, have adequate power, and be highly relevant for the assessment of the effect of Agent Orange and other herbicides on breast cancer risk in Vietnam veterans. NAS also noted, however, that the study's usefulness may be limited because questions on exposure focused on the Vietnam experience as a whole instead of on exposures to Agent Orange, other herbicides or their contaminants.

NAS concluded that there is still inadequate or insufficient evidence to determine whether there is an association between exposure to herbicides and breast cancer.

As noted above, studies reviewed in prior NAS reports predominately showed no association between breast cancer and herbicide exposure, or possibly a limited protective association. The additional evidence reviewed in Update 2002 includes evidence consistent with those prior studies, as well as some studies providing evidence of an association, subject to the limitations discussed above.

Taking account of the available evidence and NAS's 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.

In Update 2002, NAS reported that the environmental study involving Chapaevsk, Russia (Revich *et al.*, 2001) appeared to show an increased risk of cervical cancer, but noted that the number of cases on which the rates were calculated was not provided and may have been small, and further noted that the potential for confounding by socioeconomic factors was not addressed.

NAS noted that the Kang *et al.* (2000) environmental study on gynecologic cancers among female Vietnam veterans provided some evidence that service in Vietnam does not substantially increase the risk of uterine, ovarian or cervical cancer, but the report made no attempt to examine exposures to herbicides or TCDD in Vietnam.

NAS found that no strong studies addressing female reproductive cancers

in relation to herbicides or their contaminants had been conducted since Update 2000. They concluded that there was no information contained in the research reviewed for Update 2002 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 over 40 years. 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*. Exposure to inorganic arsenic is also a risk factor for bladder cancer, and cacodylic acid is a metabolite of inorganic arsenic. The data remain insufficient to conclude that studies of inorganic arsenic exposure are directly relevant to exposure to cacodylic acid. Therefore, NAS did not consider the literature on inorganic arsenic.

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, beginning with Update 1998, changed that conclusion to inadequate or insufficient information regarding an association.

In Update 2002, NAS reviewed an updated occupational study of mortality in Dow chemical workers potentially exposed to herbicides (Burns CJ, Beard KK, Cartmill JB. 2001. Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945–1994: an update. *Occupational and Environmental Medicine* 58(1):24–30), which found no increased risk of mortality due to bladder cancer.

NAS also reviewed Revich *et al.* (2001), in which an increase in age-adjusted bladder cancer incidence was shown in Chapaevsk compared to the Samara Region of the Russian Republic. NAS noted, however, that the study did not control for occupation and smoking history, and there was no information on the number of cases included in the analysis or the completeness of surveillance for cancer in Chapaevsk and the Samara region.

In Update 2002, NAS concluded that there is no evidence to support changing the "inadequate or insufficient" categorization for 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 over age 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.

In Update 2002, NAS reviewed an updated occupational study of mortality in Dow chemical workers potentially exposed to herbicides (Burns *et al.*, 2001), which concluded that there was no evidence of an association between exposure to 2,4-D and mortality due to renal cancer. NAS noted that this study has low precision due to the small number of deaths from renal cancer.

NAS also reviewed the results of Revich *et al.* (2001), which found age-adjusted incidence of renal cancer to be similar between Chapaevsk and the Samara region. Incidence rates of renal cancer in all of Russia was slightly lower. However, NAS noted that no information was given on the number of cases in the calculation of those incidence rates or the stability of those rates in previous years, and does not consider confounders other than age.

NAS stated that there is no information contained in the research reviewed for Update 2002 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.

In Update 2002, NAS reviewed an update of an occupational study of mortality in chemical workers at Dow Chemical Company (Burns *et al.*, 2001). One death from testicular cancer was identified among 1,517 male Dow employees. The study concluded that there is no significant risk of testicular cancer in this cohort. NAS concluded that the updated study analysis provided no evidence to suggest that chronic herbicide exposure increases the risk of 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 (Other than chronic lymphocytic leukemia (CLL))

There are four primary types of leukemia: The acute and chronic forms of lymphocytic leukemia and the acute and chronic forms of myeloid (or granulocytic) 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.

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 that abnormality.

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. Because CLL, the most common form of leukemia, shares many traits with lymphomas, NAS reviewed it separately from the other leukemias in Update 2002.

In Update 2002, NAS reviewed one new occupational study (Burns *et al.*, (2001)) which reported data on a cohort male workers involved in the manufacture or formulation of 2,4-D. Mortality from leukemia in the entire cohort was similar to rates in all U.S. males. Similar results were obtained in an analysis based on a 20-year induction period. In the comparison with nonexposed workers, an excess in lymphopietic mortality was noted in workers with high-cumulative-dose exposure to 2,4-D. NAS noted, however, that at least some of the deaths may have been due to Hodgkin's disease or multiple myeloma.

In another occupational study, cancer incidence and mortality were assessed in a cohort of 504 forestry workers in Sweden who were characterized by presence or absence of exposure to phenoxy herbicides in 1954-1967 (Thorn A, Gustavsson P, Sadigh J, Westerlund-Hannerstrand B, Hogstedt C 2000. Mortality and cancer incidence among Swedish lumberjacks exposed to phenoxy herbicides. Occupational and Environmental Medicine 57:718-720). No cases of leukemia occurred in the exposed members of this cohort.

In an environmental study, Revich *et al.* (2001) analyzed data on cancer incidence and mortality in Chapaevsk, Russia. Mortality due to leukemia during the years 1995-1998 was compared with mortality in the Samara

region as a whole. Age-adjusted incidences during 1998 were reported for leukemia and lymphoma combined. The rates in Chapaevsk were lower than in the Samara region in men but higher in women. NAS noted a number of weaknesses contained in this study, including failure to report the actual number of cases, failure to calculate confidence intervals, and lack of adjustment for factors other than age.

NAS found no compelling or consistent evidence of an association with exposure to herbicides contained in the new reports reviewed for Update 2002 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and leukemia (other than CLL).

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 (other than CLL) outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Abnormal Sperm Parameters 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.

In Update 2002, NAS reviewed the results of an environmental study which assessed whether exposure to heavy metals, PCBs, volatile organic compounds, and polycyclic aromatic hydrocarbons is related to early reproductive effects. (Staessen JA, Nawrot T, Hond ED, Thijs L, Fagard R, Hoppenbrouwers K, Koppen G, Nelen V, Schoeters G, Vanderschueren D, Van Hecke E, Verschaeve L, Vlietinck R, Roels HA. 2001. Renal function, cytogenetic measurements, and sexual development in adolescents in relation to environmental pollutants: a feasibility study of biomarkers. *Lancet* 357(9269):1660-1669. [Comment in *Lancet* 2001. 358(9295):1816-1817.]) The study compared 100 17-year-old lifetime residents of two highly exposed suburbs of Antwerp, Belgium, with 100 17-year-old lifetime residents of a rural control community. Concentrations of several environmental agents, including dioxin-like compounds in serum samples, were found to be higher in the two suburban locations than in the control community, after adjustment for sex, body-mass index (BMI), weeks of breastfeeding, parental social class, and dietary fat intake. NAS noted that the

results indicate that children in the two suburban locations experienced substantial and statistically significant delays in sexual maturation and lower testicular volume. NAS further noted that the results of this study support a potential effect on male reproductive capacity, but that the implication for Vietnam veterans remains unclear, inasmuch as most veterans were past their pubertal development during their tours of duty.

NAS also discussed a review of medical literature (Figá-Talamance I, Traina ME, Urbani E. 2001. Occupational exposures to metals, solvents, and pesticides: recent evidence on male reproductive effects and biological markers. *Occupational Medicine* 51(3): 174-88.), the authors of which concluded that there is insufficient evidence to conclude that the use of pesticides leads to significantly higher risk to human reproduction.

NAS stated that there is no information in the research reviewed for Update 2002 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 and Parkinsonism

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

In Update 2002, NAS reviewed an occupational study in which 238 subjects exposed to pesticides in an occupational setting and 72 nonexposed controls were examined for the presence of parkinsonism. (Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WT, Scott KC, Hudnell K, Anger WK, Camicioli R. 2001. Parkinsonism and occupational exposure to pesticides.

Occupational and Environmental Medicine 58:582–589.) NAS stated that the overall results of this study are similar to those of many other studies reviewed in Update 2000, in which an association with many years of occupational exposure is associated with parkinsonism but no association is found with any individual pesticide or class of pesticides.

NAS also reviewed a prospective cohort study with 30 years of follow up on 7,986 Japanese-American men (Honolulu Heart Program) who worked on sugar cane and pineapple plantations in Hawaii to determine whether working on a plantation or exposure to pesticides is associated with an increased risk of PD. (Petrovich *et al.* (2002, in press).) The study showed that as the duration of work increased, pesticide exposure increased significantly. NAS stated that even though age-adjusted incidence of PD increased with increasing pesticide exposure, the trend was not significant. Those with over 20 years of plantation work had twice the risk of PD of those with no plantation work. With 10 years of plantation work or less, there was no increase in risk of PD, but a significant trend of increased risk occurred with further years of exposure.

NAS noted that an association of PD with exposure to 2,4-D, 2,4,5-T, or TCDD is not reported in any of the studies.

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.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive motor neuron disease with adult onset that presents with muscle atrophy, weaknesses, and fasciculations. The incidence of ALS peaks between the ages of 55 to 75 years. Known risk factors for ALS are age and a family history of ALS. Interest in the role of occupational or environmental exposure originated in cases of motor neuron disease associated with exposure to heavy metals, chemical plants, animal carcasses, heavy manual labor, work with electricity, pneumatic tools, work in the plastic industry, and work as a truck driver.

In Update 2002, NAS summarized the results of five epidemiologic studies of pesticide exposure and ALS. One study found the association between pesticides and ALS was not statistically significant but was positive. (Deapen DM, Henderson BE. 1986. A case-control study of amyotrophic lateral sclerosis. *American Journal of Epidemiology* 123:790–799.) In another study, no statistically significant associations were found between ALS and several risk factors, including agricultural chemicals and organic solvents, although there was a positive association between ALS and agricultural chemicals. (Savettieri G, Salemi G, Arcara A, Cassata M, Castiglione MG, Fierro B. 1991. A case-control study of amyotrophic lateral sclerosis. *Neuroepidemiology* 10:242–245.)

A case-control epidemiologic study in Scotland of 103 ALS cases from a Scottish motor neuron disease register and 103 age- and sex-matched controls identified risk factors for development of the disease. (Chancellor AM, Slattery JM, Fraser H. 1993. Risk factors for motor neuron disease: A case-control study based on patients from the Scottish motor neuron disease register. *Journal of Neurology, Neurosurgery, and Psychiatry* 56:1200–1206.) Significant differences with increased exposure in cases were found for occupational exposure to lead and “solvent/chemicals.” NAS noted that occupational pesticide exposure was not significantly different but did have a positive association.

The results of a mortality study of male employees of the Dow Chemical Company (Burns *et al.*, 2001) showed three deaths due to ALS. The study found a significantly increased relative risk of death due to ALS. All three died more than 20 years after their first exposure; duration of employment was 1.3, 1.8, and 12.5 years.

A population-based case-control epidemiologic study was conducted to examine the relationship between ALS and occupational exposures to metals, solvents, and agricultural chemicals. (McGuire V, Longstreth WT, Nelson LM, Koepsell TD, Checkoway H, Morgan MS, van Belle G. 1997. Occupational exposure and amyotrophic lateral sclerosis: A population-based case-control study. *American Journal of Epidemiology* 145:1076–1088.) Exposure to metals and solvents was not associated with ALS. Association between exposure to agricultural chemicals and ALS was observed in men. Exposure to specific agricultural chemicals, such as herbicides, did not pose a significantly increased risk of

ALS. Excess exposure to agricultural chemicals from accidents or spills was associated with ALS, but this accounted for six cases and only three controls. NAS noted that the careful attention to exposure assessment in this study makes the association between agricultural chemicals and ALS intriguing, but that there are few exposed subjects and further studies are needed.

NAS concluded that there is inadequate or insufficient evidence of an association between exposure to herbicides and motor neuron disease or ALS.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and ALS 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.

A publication relating serum TCDD and peripheral neuropathy from the 1982, 1985, 1987, 1992, and 1997 examinations of the Ranch Hand study found significantly increased risk of peripheral neuropathy among Ranch Hand veterans in the high-exposure category in 1997. (Michalek JE, Akhtar FZ, Arezzo JC, Garabrant DH, Albers JW. 2001. Serum dioxin and peripheral neuropathy in veterans of operation ranch hand. *Neurotoxicology* 22:479–490.) NAS noted a major problem in the interpretation of TCDD effects on the peripheral nerves in light of the presence of diabetes and preclinical diabetes in the majority of the cases identified. NAS also noted that the cases of probable and possible peripheral neuropathy were identified for the first time in 1992 and 1997, with prior examinations being normal. NAS determined that these findings weakened the ability to implicate TCDD exposure as the etiologic agent given that the peripheral nerve is known to repair itself after cessation of exposure or after diminution of the body burden of the responsible toxicant.

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 (notably cholesterol) concentrations have been shown to predict cardiovascular disease and are considered fundamental to the underlying atherosclerotic process. The two major types of 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.

An occupational study of 92 workers at a municipal waste incinerator in Japan included measures of serum polychlorinated dibenzo-p-dioxins (PCDD) and self-reported history of a number of diseases and health-related conditions. (Kitamura K, Kikuchi Y, Watanabe S, *et al.* Health effects of chronic exposure to polychlorinated dibenzo-p-dioxins (PCDD), dibenzofurans (PCDF) and coplanar PCB (Co-PCB) of municipal waste incinerator workers. *Journal of Epidemiology* 2000;10:262–270.) Eight of the 92 subjects reported having been diagnosed with high cholesterol.

NAS noted that this study's contribution to the literature is limited for a number of reasons: the study is cross-sectional, so there is no opportunity to establish that the exposure clearly preceded the outcome; the sample is small; the exposure is an aggregate measure of PCDD (with TCDD as only one component); and the measure of high cholesterol is based solely on self-report. NAS stated that, because of those limitations, the study does not change the inconclusive status of the epidemiologic evidence on the relationship between exposure to herbicides and high serum lipids.

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, Including Liver Toxicity

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, including liver toxicity.

An occupational study reported on two cases of heavy TCDD intoxication, and presented a 2-year follow-up. (Geusau A, Abraham K, Geissler K, Sator MO, Stingl G, Tschachler E. 2001. Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication: clinical and laboratory effects. *Environmental Health Perspectives* 109(8):865–869.) One patient, a 30-year-old woman, presented with chloracne and had the highest TCDD concentration ever recorded in a human. The other patient was a 27-year-old woman who worked in the same room as the first patient. Both patients experienced gastrointestinal symptoms, including nausea, vomiting, epigastric pain, and loss of appetite, which lasted about 4 months. Liver function studies were within the normal limits, except for one value in the first patient of alkaline phosphatase at 1.5 times the upper limit of normal. Apart from the chloracne and gastrointestinal symptoms, few clinical signs or symptoms were observed in the acute phase of the intoxication.

In a report evaluating hepatic abnormalities in Vietnam veterans of Operation Ranch Hand, the authors examined exposure to TCDD and the prevalence of liver disease and hepatomegaly through March 1993 in relation to tests of liver function at the 1992 physical examination. (Michalek JE, Ketchum NS, Longnecker MP. 2001. Serum dioxin and hepatic abnormalities in veterans of Operation Ranch Hand. *Annals of Epidemiology* 11(5):304–311.) Hepatomegaly among veterans in the high-exposure category was slightly higher than that in nonexposed veterans in the comparison category. The prevalence of nonspecific liver disorders increased across categories of TCDD exposure and among Ranch Hands in the high-exposure category. The study authors and NAS noted that the significance of those findings may be limited because heightened levels of the enzyme GGT, an abnormality sometimes reported in association with TCDD exposure, may also be caused by alcohol consumption, and the mean GGT in the high-exposure group was significantly increased among veterans

with history of light to moderate drinking. The authors concluded that evidence of clinically significant liver disease was limited to the increase in hepatomegaly, and that the increased GGT could have been due to confounding.

NAS stated that the evaluation of the effects of herbicide exposure on noncancer gastrointestinal ailments is very difficult, due to limitations of medical history and physical examination in diagnosing such ailments and the strong interdependence between individual characteristics of a person and the body burden of TCDD.

NAS concluded that there was no information contained in the research reviewed for Update 2002 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

The immune system is responsible for protecting the body against invasion by infectious microorganisms. 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.

No relevant occupational, environmental, or Vietnam-veteran studies were published subsequent to Update 2000.

NAS concluded that there was no information reviewed for Update 2002 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 2002, NAS noted that there is growing evidence that exposure to inorganic arsenic is a risk factor for cardiovascular disease, and cacodylic acid (DMA) is a metabolite of inorganic arsenic. However, the data remain insufficient to conclude that studies of inorganic arsenic exposure are directly relevant to exposure to cacodylic acid. Therefore, the literature on inorganic arsenic was not considered by NAS.

NAS reviewed an occupational study of mortality in male workers at a Dow chemical plant (Burns *et al.*, 2001). NAS stated that mortality due to circulatory conditions among the workers was similar to that experienced by U.S. white males in general. NAS noted that mortality analyses of other occupational cohorts have tended to find cardiovascular effects among the more highly exposed workers, but that a dose-specific analysis of the data on this outcome was not reported.

A cross-sectional occupational study was conducted in 1998 to assess the association between serum PCDD and a variety of health conditions in a sample of workers employed at a municipal waste incinerator in Japan (Kitamura *et al.*, 2000). Fourteen of the 92 workers participating in the study reported a history of hypertension. No information was provided on the date of this diagnosis relative to dates of employment at the plant. The coefficients for the categories of PCDD were reported as not statistically significant, but the values of the coefficients and their standard errors were not given.

In an environmental study, a survey was administered to 727 adult residents of farming households and 262 residents of nonfarming households. (Masley ML, Semchuk KM, Senthilselvan A, *et al.* Health and environment of rural families: results of a community canvass survey in the Prairie Ecosystem Study. *Journal of Agricultural Safety and Health* 2000;6:103–115.) The survey included questions about the use of pesticides and fertilizers and a number of health conditions and symptoms that might be associated with agricultural exposures. Physician-diagnosed hypertension and heart disease were reported by 154 and 44 survey respondents, respectively. Neither condition was associated with residing on a farm. No information was provided on the validity of measurement of the self-reported health conditions, and the report did not examine more specific

associations with pesticide or fertilizer use.

NAS noted that neither Kitamura *et al.* (2000) nor Masley *et al.* (2000) provided data on validation from medical records or direct measurement of blood pressure, that some misclassification is likely (with false negatives being more common than false positives), and that both studies used nonspecific assessment of exposure. NAS further noted the possibility that the null findings on hypertension in these studies reflect the influence of misclassification that led to bias toward the null.

Mortality from cardiovascular diseases was examined by Revich *et al.* (2001) in their study of multiple health outcomes among the residents of Chapaevsk. The authors reported that mortality from cardiovascular diseases in men was 1.14 times greater than the mortality rate for Russia as a whole, and that the difference in mortality was especially pronounced in men 30 to 49 years old. The authors also noted, however, that trends in mortality were directly related to trends in unemployment, which NAS noted suggests the simultaneous effects of other aspects of the environment in the area.

NAS concluded that there is no information contained in the research reviewed for Update 2002 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

The major risk factor for both acute and chronic respiratory disorders is cigarette smoking. Cigarette smoking is a major confounding factor in interpreting the literature on risk factors for respiratory disease. 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 nonmalignant respiratory disorders.

In Update 2002, NAS reviewed an occupational study of a cohort of male employees of the Dow Chemical Company (Burns *et al.*, 2001). No excess

mortality from nonmalignant respiratory disorders was demonstrated.

NAS concluded that there is no information contained in the research reviewed for Update 2002 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 discussed the evidence concerning two categories of skin cancer: Melanoma and nonmelanoma (basal-cell and squamous-cell).

In Update 2002, NAS reviewed an occupational study of mortality in a cohort of male Dow Chemical Company workers (Burns *et al.*, 2001). No deaths due to skin cancer of any type were reported in the study.

NAS also reviewed an occupational study which analyzed cancer incidence and mortality in a cohort of forestry workers in Sweden (Thorn *et al.*, 2000). The observed frequency of cancer was compared with expected values on the basis of data on the population of Sweden. One case of melanocytic skin cancer was recorded in an exposed female worker. Nonmelanocytic skin cancer was diagnosed in one exposed foreman, and in three nonexposed workers. The report found increased risks for both types of skin cancer, but the findings were not statistically significant and were limited by the small number of cases.

An environmental study analyzed cancer incidence and mortality in Chapaevsk, Russia (Revich *et al.*, 2001). Mortality data were not reported for skin cancer. The age-adjusted incidence of melanoma in Chapaevsk relative to the Samara region during 1998 was somewhat lower in men but notably higher in women. The age-adjusted incidence of skin cancers other than melanoma was similar in men and somewhat higher in women. NAS noted that the number of cases was not given, hypothesis testing and interval

estimation were not performed, and no confounding factors were considered besides age. NAS noted that the lack of complete information prevented conclusions based on the study.

NAS stated that the new studies add little information on the association between exposure to herbicides and the incidence of skin cancer.

NAS concluded that there is no information contained in the research reviewed for Update 2002 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.

Results of a Vietnam veteran study of cognitive functioning from an Air Force Health Study (AFHS) examination in 1982 were reviewed by NAS in Update 2002. (Barrett DH, Morris RD, Akhtar FZ, Michalek JE. 2001. Serum dioxin and cognitive functioning among veterans of operation ranch hand. *Neurotoxicology* 22:491–502.) NAS noted that cognitive functioning in the Ranch Hand veterans evaluated with about 33 measures assessed through a variety of tests found eight significant group differences that did not support a dose-effect relationship with TCDD; that is, worse performance was seen in the background or low-TCDD groups. Ranch Hand veterans with the highest TCDD exposure had significantly lower scores on Logical Memory (Wechsler Memory Scale Form 1 (WMS)). NAS stated that finding could be attributed to chance alone and was not in agreement with other administered tests of verbal memory. NAS further stated that overall, the significant weaknesses in the study design, analyses, and interpretation of the results in the examination of serum TCDD and cognitive functioning in the Ranch Hand veterans prevent an association between exposure and neuropsychologic effects from being established.

In Update 2002, NAS reviewed a 30-year follow-up occupational study of 13

men in Czechoslovakia with TCDD exposure during the production of 2,4,5-T. (Pelcova D, Fenclova Z, Dlaskova Z, Urban P, Lukas E, Prochazka B, Rappe C. 2001. Biochemical, neuropsychological, and neurological abnormalities following 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. *Archives of Environmental Health* 56:493–500.) TCDD was correlated significantly with the memory quotient from WMS, the verbal IQ from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and the Benton test of visual memory. Age-corrected norms were used to determine abnormal performance. Education did not affect the results, but no demographic data on education were presented. Ten of 13 subjects drank alcohol daily, but this was not taken into account in the analyses. NAS reported that the low-voltage electroencephalogram with increased beta activity seen in 7 subjects could be related to the daily alcohol consumption. NAS further noted that it is not possible to determine the relationship between TCDD and cognitive functioning without attention to confounding.

An environmental study (Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gauvreau D. 2001. Environmental pesticide exposure as a risk factor for Alzheimer's disease: A case-control study. *Environmental Research Section A* 86:37–45) found that long-term exposure to herbicides and insecticides was not significantly related to the development of Alzheimer's disease. Occupational exposure to neurotoxic substances, including pesticides, was also not significantly related to Alzheimer's disease.

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 years old. 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.

An occupational study (Burns *et al.*, 2001) of mortality of male employees of the Dow Chemical Company found fewer deaths than expected from all malignant neoplasms and specifically cancers of the digestive organs and peritoneum.

An environmental study of residents of Chapaevsk, Russia (Revich *et al.*, 2001) showed a higher incidence of colon cancer in males than Russia as a whole or the Samara region of Russia. Female residents of Chapaevsk did not have a higher incidence. However, female residents of Chapaevsk did have a higher incidence of stomach cancer than Russia or Samara. Male residents of Chapaevsk had a lower incidence of stomach cancer than Russia, but higher than Samara. Both male and female residents of Chapaevsk had a lower incidence of rectal cancer than Russia or Samara. NAS stated that, because of the lack of adjustment for confounding, the likelihood of multiple exposures, the absence of information on the completeness and accuracy of cancer diagnoses, and the ecologic study design, this study provides little evidence for associations with gastrointestinal cancers.

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

Exposure to ionizing radiation is an established risk factor for brain cancer. Several other potential factors have been examined, but most brain cancers are not associated with any known risk factors. Brain cancer occurs relatively infrequently.

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

Two occupational studies published since Update 2000 were reviewed by

NAS in Update 2002. Both studies (Burns *et al.*, 2001; Thorn *et al.*, 2000) demonstrated no excess mortality from brain cancer. NAS noted, however, that both studies were small and had limited power to detect an increase in an uncommon outcome.

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.

AL Amyloidosis

Amyloidosis refers to a group of diseases in which insoluble fibrillar proteins (amyloid) accumulate in tissues to a point that causes organs to malfunction. NAS reviewed AL amyloidosis (also sometimes referred to as primary amyloidosis), in which the light chain of immunoglobulin molecules is the aberrant protein. AL amyloidosis is the most common form of amyloidosis in the United States.

NAS in Update 2000 found there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and AL amyloidosis.

No relevant occupational, environmental, or Vietnam-veteran studies have been published since Update 2000.

NAS concluded that there is no information to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and AL 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.

Endometriosis

NAS reviewed endometriosis for the first time in Update 2002.

Endometrium is the tissue that lines the inside of the uterus. In endometriosis, endometrium is found outside the uterus, usually in other parts of the reproductive system, the abdomen, or the tissues near the

reproductive organs, and results in inflammation, internal bleeding, and degeneration of blood and tissue which can cause scarring, pain, infertility, adhesions, and intestinal problems. The cause of endometriosis is unknown.

Suspicion that TCDD is involved in the etiology of endometriosis began after the observation that the incidence of endometriosis was higher in monkeys treated with low doses of TCDD than in control monkeys.

In Update 2002, NAS reviewed a study which analyzed blood TCDD concentrations in 79 women who were being evaluated for infertility, 44 of whom were diagnosed with endometriosis by laparoscopy. (Mayani A, Barel S, Soback S, and Almagor M. 1997. Dioxin concentration in women with endometriosis. *Human Reproduction*. 12:373-375.) Eight of the 44 women with endometriosis were positive for TCDD compared with one of the 35 controls. NAS noted that the number of subjects in this study is small, the ethnic distribution differed, and the limit of TCDD detection was not clear. Although the study reported an increased risk, the confidence interval was very wide and the finding was not statistically significant.

Another study assessed whether TCDD toxic equivalents (TEQs) in serum are associated with endometriosis in an infertile population of women who enrolled in fertility treatment. (Pauwels A, Schepens PJ, D'Hooghe T, Delbeke L, Dhont M, Brouwer A, Weyler J. 2001. The risk of endometriosis and exposure to dioxins and polychlorinated biphenyls: A case-control study of infertile women. *Human Reproduction*. 16:2050-5.) The case-control study evaluated 42 women with endometriosis and 27 controls without endometriosis, but with infertility related to other causes. The authors reported no association between median total TEQs and endometriosis in infertile women.

NAS concluded that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and endometriosis.

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

Thyroid Homeostasis

NAS reviewed the thyrotoxic potential of herbicides for the first time in Update 2002.

The thyroid gland secretes hormones (T4 and T3) which stimulate metabolic rate. Secretion of T4 and T3 is under the control of thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary gland. The thyroid also secretes calcitonin, a hormone that controls calcium concentration in the blood and storage of calcium in bones. Chemical-induced alterations in thyroid homeostasis can adversely affect the development of many organ systems, including the nervous and reproductive systems. Most adverse effects are caused by lack of thyroid hormone alone rather than by increases in TSH. TCDD affects the concentrations of thyroid hormones; the effects appear to be species-dependent and may reflect both the dose and the duration of exposure. TCDD influences the metabolism of thyroid hormones and TSH. Studies of environmental exposure have emphasized thyroid alterations in prenatal and early childhood development rather than in adults.

One environmental study reviewed by NAS evaluated 38 mother-infant pairs, selected for normal birth weight and no complications. (Pluim HJ, Koppe JG, Olie K, Vd Slikke JW, Kok JH, Vulsma T, Van Tijn D, De Vijlder JJ. 1992. Effects of dioxins on thyroid function in newborn babies. *Lancet*. 339:1303.) In cord blood, the concentrations of total T4 and thyroxine-binding globulin (TBG) were suggestively higher in the high exposure group, but no other measurements approached significance. At 1 week, total T4 and the ratio of total T4 to TBG were significantly greater in the high-exposure than the low-exposure group, and the same was true at 11 weeks. TSH concentrations were also significantly higher at 11 weeks. When only infants who were breastfed for the full 11 weeks were considered, only the ratio of total T4 to TBG remained significantly different. In a subset of the births for which values were obtained in both the cord and 1-week samples, the increases in total T4 and in TBG were substantially higher in the high-exposure group. NAS stated that concerns about those results are related to the size of the study sample and the loss of nearly one-fourth of the maternal-blood samples and five of the cord-blood samples for all thyroid measurements. Several more samples were insufficient for some of the analyses.

A larger study of 105 mother-infant pairs conducted similar analyses. (Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschipholt IJ, Van der Paauw CG, Tuinstra LG, Brouwer A, Sauer PJ. 1994. Effects of dioxins and polychlorinated biphenyls

on thyroid hormone status of pregnant women and their infants. *Pediatric Research*. 36:468–73.) TEQ correlated negatively with maternal pregnancy total T3 and maternal postdelivery total T3 and total T4; similar associations were seen for planar PCB TEQ and total PCB and TEQ, and the associations with total T3 were also observed for nonplanar PCB TEQ. In addition, all four TEQ measurements correlated positively with infant 2-week TSH, and all except the nonplanar PCB TEQ were positively associated with the infant 3-month TSH.

Another environmental study examined PCB concentrations in breast-milk specimens, without adjustment for lipids, in relation to thyroid hormones in cord serum in a population with background exposure. (Longnecker MP, Gladen BC, Patterson DG, Rogan WJ. 2000. Polychlorinated biphenyl (PCB) exposure in relation to thyroid hormone levels in neonates. *Epidemiology* 11:249–254.) They found little evidence of an association, although the direction of the coefficient for TSH in multiple-regression analysis was consistent with findings in other studies: increases in TSH with increases in PCBs. NAS stated that because non-dioxin-like PCBs are the most abundant, and PCBs are contaminated with furans, this study is not very informative for the effects of TCDD or the herbicides used in Vietnam.

Another environmental study examined TCDD-exposed workers at two plants who were engaged in the production of 2,4,5-T or one of its derivatives. (Calvert GM, Sweeney MH, Deddens J, Wall DK. 1999. Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Occupational and Environmental Medicine* 56(4):270–276.) Referents were residents in the neighborhood of each worker, matched by age, race, and sex. Serum specimens were analyzed for TCDD, total T4, TSH, and thyroid hormone binding resin, and the free T4 index was calculated. The results showed that workers had a significantly higher adjusted mean free T4 index than referents, and the highest index was among those with the highest half-life extrapolated TCDD, but a clear dose-response relationship was not observed.

A Vietnam veteran study examined thyroid-hormone status in the AFHS

cohort. (Pavuk M, Schecter AJ, Akhtar FZ, Michalek JE. Serum 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Levels and Thyroid Function in Air Force Veterans of the Vietnam War (in press).) At each of the 1982, 1985, 1987, 1992, and 1997 examinations, there was a trend toward an increasing concentration of TSH, which was not accompanied by changes in circulating T4 or in the percentage uptake of T3 (measured only in the earlier years). In a repeated-measures linear regression adjusted for age, race, and military occupation, the low-exposure and high-exposure Ranch Hands had TSH significantly higher than the comparison population. There was no evidence of changes in clinical thyroid disease. The percentage with abnormally high TSH was higher at each examination in the high-exposure group than in the comparison population, but these findings were not very precise.

After reviewing the relevant literature, NAS stated that although some effects on thyroid homeostasis have been observed, mainly in the perinatal period (the period shortly before and after birth), the functional importance of those changes is unclear because adaptive capacity may be adequate to accommodate them. NAS noted that the AFHS study demonstrated biologic changes in TSH levels, but without any accompanying effect on the health of the Ranch Hand veterans. NAS further stated that the evidence indicates that both infants and Ranch Hand personnel were able to adapt to the changes that may have been induced by higher body burdens of TCDD.

NAS concluded that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and adverse effects on thyroid homeostasis.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and adverse effects on thyroid homeostasis 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 2002." 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: May 8, 2003.

Anthony J. Principi,

Secretary of Veterans Affairs.

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DEPARTMENT OF VETERANS AFFAIRS

National Commission on VA Nursing; Notice of Meeting

The Department of Veterans Affairs (VA) gives notice under Public Law 92–463 (Federal Advisory Committee Act) that the National Commission on VA Nursing will hold its fifth meeting on June 11–12, 2003, at the Hyatt Regency Crystal City, 2799 Jefferson Davis Highway, Arlington, VA 22202. On Wednesday, June 11, the meeting will begin with registration at 8:30 a.m. and adjourn at 5 p.m. On Thursday, June 12, the meeting will begin at 8 a.m. and adjourn at 2 p.m. The meeting is open to the public.

The purpose of the Commission is to provide advice and make recommendations to Congress and the Secretary of Veterans Affairs regarding legislative and organizational policy changes to enhance the recruitment and retention of nurses and other nursing personnel in VA. The Commission is required to submit to Congress and the Secretary of Veterans Affairs a report, not later than two years from May 8, 2002, on its findings and recommendations.

On June 11, the Commission will discuss the findings of several recent surveys on nurse turnover and work environment, and will review testimony from Commission hearings held during April. On June 12, the Commission will focus most of its work on finalizing its interim report.