

final action on the application in the **Federal Register**.

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Stephen R. Kratzke,

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DEPARTMENT OF VETERANS AFFAIRS

Health Outcomes 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 authority of the Veterans Education and Benefits Expansion Act of 2001, Public Law 107-103, Section 201(d), has determined that a presumption of service connection is not warranted based on exposure to herbicides used in the Republic of Vietnam during the Vietnam Era for the following health outcomes: Hepatobiliary cancers; oral, nasal, and pharyngeal cancer; bone and joint cancer; skin cancers (melanoma, basal, and squamous cell); breast cancer; female reproductive cancer (cervix, uterus, and ovary); testicular cancer; urinary bladder cancer; renal cancer; leukemia (other than chronic lymphocytic leukemia (CLL)); abnormal sperm characteristics and infertility; spontaneous abortion; neonatal or infant death and stillbirth in offspring of exposed individuals; low birthweight in offspring of exposed individuals; neurobehavioral disorders (cognitive and neuropsychiatric); movement disorders including Parkinson's disease and amyotrophic lateral sclerosis (ALS); chronic peripheral nervous system disorders; respiratory disorders; gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities, ulcers); immune system disorders (immune suppression, autoimmunity); circulatory disorders; amyloid light-chain (AL) amyloidosis; endometriosis; effects on thyroid homeostasis; gastrointestinal tumors (esophagus, stomach, pancreas, colon, rectum; brain tumors; and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

The Secretary's determinations regarding individual diseases are based on all available evidence in a 2004 report of the National Academy of

Sciences (NAS) and prior NAS reports. This notice generally states specific information only with respect to significant additional studies that were first reviewed by NAS in its 2004 report. Information regarding additional relevant studies is stated in VA's prior notices following earlier NAS reports, and will not be repeated here.

FOR FURTHER INFORMATION CONTACT:

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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 health outcome. 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, 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." The Secretary reviews studies that report a positive relative risk and studies that report a negative relative risk of a particular health outcome. He then determines whether the weight of evidence supports a finding that there is or is not a positive association between herbicide exposure and the subsequent health outcome.

The Secretary does this by taking into account the statistical significance, capability of replication, and whether that study will withstand peer review. Because of differences in statistical significance, confidence levels, control for confounding factors, bias, and other pertinent characteristics, some studies are more credible than others. The Secretary gives weight to more credible studies in evaluating the overall evidence concerning specific health outcomes.

Chronology

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. The Secretary also determined that there was no positive association between herbicide exposure and any other health outcome, other than chloracne, non-Hodgkin's lymphoma, and soft-tissue sarcomas, for which presumptions already existed. A notice of the health outcomes that the Secretary determined were not associated with exposure to herbicides 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 update was 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 health outcomes 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 that: "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 conglomeration of scientific evidence, 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 update was the 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 health outcomes that the Secretary determined were not associated with exposure to herbicide agents was published in June 24, 2002 (See 67 FR 42600 (2002)).

NAS issued its fifth report, entitled "Veterans and Agent Orange: Update 2002" (Update 2002) on January 23, 2003. The focus of this update was the new scientific studies published since the release of Update 2000 and review of 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. After NAS issued Update 2002, 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 health outcomes the Secretary determined were not associated with exposure to herbicide agents was published on May 20, 2003 (See 68 FR 27630 (2003)).

Update 2004

NAS issued its sixth report entitled "Veterans and Agent Orange: Update 2004" (Update 2004) on March 4, 2005. Consistent with its prior reports, NAS in Update 2004 found that there was "sufficient evidence of an association" between herbicide exposure and five categories of diseases in veterans and "limited/suggestive evidence" of an association between herbicide exposure and six other categories of diseases in veterans. VA has previously established presumptions of service connection for each of these diseases. NAS, in Update 2004, categorized certain health outcomes to have "inadequate/insufficient" evidence to determine whether an association exists. This category is defined to mean 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. Health

outcomes that met the inadequate/insufficient category include:

Hepatobiliary cancers; oral, nasal, and pharyngeal cancer; bone and joint cancer; skin cancers (melanoma, basal, and squamous cell); breast cancer; female reproductive system cancer (cervix, uterus, ovary); testicular cancer; urinary bladder cancer; renal cancer; leukemia (other than chronic lymphocytic leukemia (CLL)); abnormal sperm characteristics and infertility; spontaneous abortion; neonatal or infant death and stillbirth in offspring of exposed individuals; low birthweight in offspring of exposed individuals; birth defects (other than spina bifida) in offspring of exposed individuals; childhood cancer (including acute myelogenous leukemia) in offspring of exposed individuals; neurobehavioral disorders (cognitive and neuropsychiatric); movement disorders, including Parkinson's disease and amyotrophic lateral sclerosis (ALS); chronic peripheral nervous system disorders; respiratory disorders; gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities, ulcers); immune system disorders (immune suppression, autoimmunity); circulatory disorders; AL amyloidosis; endometriosis; and effects of thyroid homeostasis.

In this same report, NAS found two health outcomes that fell into the "limited or suggestive evidence of no association category. These health outcomes were deemed consistent in not showing a positive association between them and any magnitude of exposure to herbicides. Those health outcomes that met the "no association" category were: gastrointestinal tumors (esophagus, stomach, pancreas, colon, rectum), and brain tumors.

The Secretary's determinations regarding individual diseases are based on all available evidence in Update 2004 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 2004. Information regarding additional relevant studies has 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, which 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 occupational study by Swaen *et al.* (2004) examined cancer mortality in herbicide applicators in the Netherlands, and no deaths from liver or biliary cancer were observed in the cohort.

NAS found that there was no information contained in the research reviewed for Update 2004 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.

Oral, Nasal, and Pharyngeal Cancer

Oral, nasal, and pharyngeal 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 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 oral, nasal, and pharyngeal cancer.

An occupational study by Swaen *et al.* (2004) examined cancer mortality in herbicide applicators in the Netherlands. No deaths from nasal, oral, or pharynx cancers were observed in that cohort.

In a Vietnam-veteran study, cancers of the cavity between the jaw and cheek were examined in Operation Ranch Hand veterans who were involved in the aerial spraying of herbicides. No significant difference was reported between Ranch Hand veterans and a comparison group of veterans who did not spray herbicides. (Akhtar *et al.*, 2004).

NAS found there was no information contained in the research reviewed for Update 2004 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and oral, nasal, and pharyngeal 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 oral, nasal, and pharyngeal cancers outweighs the credible evidence for such an association, and has determined that a positive association does not exist.

Bone and Joint Cancer

Primary bone cancers are among the least common malignancies. The bones are a frequent site of secondary tumors of other cancers that have metastasized. NAS studied only primary bone cancer in Update 2004. Bone cancer is most common among teenagers, and is very rare among people in the age groups of most Vietnam veterans. Among the risk factors for adults are exposure to ionizing radiation from treatment for other cancers and a history of certain non-cancerous 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 and joint cancer.

NAS reviewed one occupational study that examined cancer mortality in 1,341 licensed herbicide applicators in the Netherlands. No deaths from bone cancers were observed. (Swaen *et al.*, 2004.) No other relevant environmental or Vietnam-veteran studies were published since Update 2002.

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 has determined that a positive association does not exist.

Skin Cancers—Melanoma, Basal, and Squamous Cell

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 examined two categories of skin cancer: melanoma and nonmelanoma (basal-cell and squamous-cell).

Melanomas occur more frequently in fair-skinned people. Incidence also increases with age, though more so in

males than in females. Other risk factors can include moles on the skin, suppressed immune system, and excessive exposure to ultraviolet radiation, usually from the sun. Family history of melanoma is also a risk factor, though it is unclear whether that is the result of genetic factors or attributable to similarities in skin type and sun exposure.

NAS reviewed an occupational study conducted on licensed herbicide applicators in the Netherlands. No data was available on any risk factor for skin cancer, other than age. Five deaths from skin cancer were recorded for the cohort of 1,341 people. Only 1.4 deaths would be expected. (Swaen *et al.*, 2004). NAS noted that a significant limitation of this study was its inability to discern whether, or to what extent, the increased incidence of skin cancer was attributable to herbicide exposure rather than to exposure to UV radiation, which is a significant and well-known risk factor for skin cancer. NAS concluded that herbicide applicators are likely to have had significant exposure to UV radiation, but that limitations of the study design made it impossible to separate the effect of the two occupational exposures.

No environmental studies of melanoma have been published since Update 2002.

In 2004, a study on the incidence of cancer in Operation Ranch Hand veterans compared with both a group of Air Force veterans not involved in herbicide spraying and a sample of the general population, showed that melanoma was more common among the Ranch Hand veterans and the Air Force veterans than in the general population. NAS noted significant limitations concerning the comparison with the general population, including the lack of control for the confounding factor of sun exposure and the possibility that rates of detection among the study population may be higher than the general population due to the heightened detection methods employed in the study. In the analyses limited to Ranch Hand and comparison Air Force veterans, the associations with melanoma were restricted to the stratum of veterans with no more than 2 years of service in Southeast Asia and to a stratum created by the subset of Ranch Hand veterans who served only in Vietnam and comparison veterans who served elsewhere in Southeast Asia.

NAS found that no satisfactory rationale was given to support why the analysis was limited to veterans with less than 2 years of service or to a definition that confounds Ranch Hand status with service in Vietnam. NAS

stated that, if the classifications employed in the study somehow captured a confounding factor, the proper analysis would have been to combine information from each stratum (more than 2 years of service and 2 years or less) to produce an adjusted relative risk. In view of these limitations, NAS decided that the overall association between exposure to herbicides and the incidence of melanoma in this study was not definitive. (Akhtar *et al.*, 2004).

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

Although some recent studies reported findings suggestive of an association, the weight of those findings is limited by the methodological concerns discussed in the NAS report. Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and melanoma outweighs the credible evidence for such an association, and has determined that a positive association does not exist.

Excessive exposure to ultraviolet radiation is the most important risk factor for non-melanocytic skin cancer, though some skin diseases and exposure to chemicals such as inorganic arsenic have also been identified as possible risk factors.

NAS noted in VAO and subsequent updates that there was inadequate or insufficient information to determine an association between exposure to herbicides and basal-cell or squamous-cell cancers.

There were no relevant environmental or Vietnam-veteran studies published regarding basal-cell and squamous-cell (non melanoma) skin cancers.

NAS concluded that there is no information contained in the research reviewed for Update 2004 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and basal-cell and squamous-cell skin cancers.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and basal-cell and squamous-cell skin cancers 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 U.S. 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.

No studies published since Update 2002 have investigated breast cancer. Previously published studies support the conclusion that the evidence is inadequate or insufficient to determine an association 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.

Female Reproductive Cancer (cervix, uterus, ovary)

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.

No studies published since Update 2002 have investigated cancers of the female reproductive system.

NAS concluded that there is inadequate or insufficient information to determine an association between exposure to herbicides and female reproductive cancers. 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.

Testicular Cancer

Testicular cancer is far more likely in men younger than 40 than in men over the age of 40. Cryptorchidism, or undescended testes, 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.

No relevant occupational, environmental, or Vietnam-veteran studies have been published since Update 2002.

NAS concluded that there is inadequate or insufficient evidence to determine an association 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.

Urinary Bladder Cancer

Urinary bladder cancer is the most common of the urinary 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.

A study of the incidence of urinary bladder cancer in Vietnam veterans who participated in Operation Ranch Hand was published in 2004. The study found no significant difference between the expected and observed incidence of

urinary bladder cancer. (Akhtar *et al.*, 2004).

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. Update 1998 provided additional information that led NAS to change its conclusion to inadequate or insufficient information regarding an association with urinary bladder cancer.

No relevant occupational or environmental studies regarding urinary bladder cancer have been published since Update 2002.

The new evidence presented by Akhtar *et al.*, (2004) did not change the committee's previous findings, which placed urinary bladder cancer in the inadequate or insufficient category.

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 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 Wilms' tumor, which is more likely to appear in children, renal cancer is more common in individuals over age 50. Smoking is a risk factor for renal cancer. Other potential risk factors include diet, weight, and occupational exposure to asbestos, cadmium, and organic solvents. Some people with rare syndromes such as von Hippel-Lindau syndrome and tuberous sclerosis are at higher risk. Firefighters who are exposed to pyrolysis products are also in 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 2004, Swaen *et al.*, published the results on a total of 21 years of follow-up on the mortality experience of an established cohort of 1,341 licensed herbicide applicators in the Netherlands. (Swaen *et al.*, 2004). Four deaths from kidney cancer were reported, and only three were expected. Due to the relatively small study size and lack of exposure information, NAS did not find this study to be sufficiently suggestive of an association.

No relevant environmental or Vietnam-veteran studies have been published since Update 2002.

On the basis of its evaluation of the epidemiologic evidence reviewed and in

previous VAO reports, NAS concluded that there is inadequate or insufficient evidence to determine an association between exposure to herbicides and renal cancer.

Taking account of the available evidence and NAS' analysis, the Secretary has found 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.

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 also 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.

In Update 2004, NAS reviewed two relevant occupational studies. A study of 1,341 licensed herbicide applicators in the Netherlands showed that three deaths from all leukemias were reported when 2.2 deaths were expected. (Swaen *et al.*, 2004).

An occupational population-based, case-control study conducted in 11 agricultural and industrial areas of Italy showed an increased risk of leukemia based on exposure to phenoxy

herbicides. (Miligi *et al.* 2003.) NAS noted that the small number of cases and other limitations prevented adequate analysis of the increased risk based on the study data.

No environmental studies have been published since those reviewed in Update 2002.

A study of Operation Ranch Hand veterans and a cohort of other Air Force veterans who were not involved in the spraying of herbicides was published in 2004. In this study, all leukemias were combined with multiple myeloma and the lymphomas to form the category of lymphopoietic cancers. No excess of such cancers was reported in the Operation Ranch Hand veterans. These results did not change when the analyses were restricted to veterans whose tours of duty ended between 1966 and 1970, the years when Agent Orange was the predominant herbicide in use in Vietnam. (Akhtar *et al.*, 2004).

On the basis of its evaluation of the epidemiologic evidence reviewed and in previous VAO reports, NAS concluded that there was inadequate or insufficient evidence to determine an association between exposure to herbicides and leukemias 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 Characteristics 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.

A study examined factors possibly associated with infertility in a group of women living in an agricultural region of Wisconsin. For the study, a woman was considered infertile if she had 12 months of unprotected intercourse without conceiving a pregnancy that ended in live birth. Nine case subjects and 11 control subjects reported being exposed to 2,4,5-T and four case subjects and four control subjects reported being exposed to 2,4-D. This study was limited because the sample sizes were small presenting an inability to examine the effects of specific herbicides. Moreover, information on risk factors were obtained from self-reports, which can be subject to recall bias. (Greenlee *et al.*, 2003).

A study examined whether previously poor semen quality in men from rural and urban areas was attributable to use of pesticides including herbicides, fungicides, and other substances. None of the subjects from Minnesota had detectable 2,4-D metabolites in their urine. The subjects from Missouri had 2,4-D metabolite levels that were only of borderline statistical significance. The study showed that 2,4-D was not associated with sperm mobility or concentration, but showed a weak association with sperm morphology. (Swaen *et al.*, 2003).

A study was conducted to determine whether there was an association between TCDD exposures and the menstrual characteristics of women exposed to it for the next 20 years. The study used women who lived near the site of an industrial explosion in 1976 at Seveso, Italy. The main conclusion from the study was that serum TCDD concentration was associated with some menstrual cycle characteristics, with possible effect modification by menarchial status. (Eskenazi *et al.*, 2002).

No relevant Vietnam-veteran studies have been published since Update 2002.

NAS concluded that there is inadequate or insufficient evidence to determine an association between exposure to herbicides and infertility, subfertility, sperm quality or count, or altered hormone concentrations.

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

Spontaneous Abortion

Spontaneous abortion is the expulsion of a nonviable fetus, usually before 20 weeks of gestation. The background risk of a spontaneous abortion is generally 7–15%, but this does not include the many more pregnancies that terminate before the woman becomes aware of the pregnancy.

NAS concluded in VAO and subsequent updates that there was inadequate or insufficient information to determine an association between exposure to herbicides and spontaneous abortion.

No relevant occupational or Vietnam-veteran studies have been published since Update 2002.

Eskenazi *et al.* (2003) evaluated data from the Seveso Women's Health Study of women who lived near the site of an

industrial explosion in 1976 at Seveso, Italy for an association between individual serum TCDD concentrations and birth outcomes in women who resided near the accident. No association was revealed by the Eskenazi study. Because the spontaneous abortions were self-reported, a truly unexposed control population could not be used in the study. Therefore, it could be hypothesized that the study does not rule out the possibility of a TCDD effect during the earliest period of pregnancy.

NAS concluded that there is insufficient information available to determine whether an association exists between the risk of spontaneous abortion and maternal exposure to herbicides.

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

Neonatal or Infant Death and Stillbirth in Offspring of Exposed Individuals

Stillbirth, or late fetal death, typically refers to the delivery at or after 20 weeks of gestation of a fetus that shows no signs of life. Neonatal death refers to the death of a liveborn infant within 28 days of birth. Typically, causes of stillbirth and neonatal death overlap considerably and are commonly analyzed together in a category called perinatal mortality. The most common causes of perinatal mortality among low-birthweight liveborn and stillborn infants are placental and delivery complications. Among infants weighing more than 2,500 grams at birth, the most common causes are complications of the cord, placenta, and membranes and lethal congenital malformations. (Kallen, 1988).

NAS concluded in VAO and subsequent updates that there was inadequate or insufficient information to determine an association between exposures to herbicides and stillbirth, neonatal death, or infant death.

No relevant occupational, environmental, or Vietnam-veteran studies have been published since Update 2002.

NAS concluded that there is inadequate or insufficient evidence to determine an association between exposure to herbicides and stillbirth, neonatal death, or infant death in offspring of exposed individuals.

Taking account of the available evidence and NAS' analysis, the

Secretary has found that the credible evidence against an association between herbicide exposure and stillbirth, neonatal death, and infant death in offspring of exposed individuals outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Low Birthweight in Offspring of Exposed Individuals

The World Health Organization (WHO) recommends 2,500 grams as the threshold determination for low birthweight. Low birthweight is among the important predictors of neonatal mortality and morbidity, and preterm delivery is a significant cause. Factors most strongly associated with reduced birthweight are maternal tobacco use during pregnancy, multiple births, and race or ethnicity. Other potential risk factors are socioeconomic status, maternal weight, birth order, maternal complications during pregnancy, and obstetric history. Established risk factors for preterm delivery include race, marital status, low socioeconomic status, tobacco use, and cervical, uterine, or placental abnormalities. (Berkowitz and Papiernik, 1993).

A case-control study examined birthweight in the offspring of women who were involved in farming for seven (7) or more days during their pregnancies. In total, the study included 117 women who delivered low birthweight infants (cases) and 377 women who delivered infants weighing at least 2,500 grams (controls). No significant differences were exhibited in the birthweights in the exposed and non-exposed groups. Pregnancy duration was also the same time, with a mean of 38 weeks in cases and controls. NAS determined the study was limited by its retrospective nature. (Dabrowski *et al.*, 2003).

An environmental study examined the association between TCDD exposure and reproductive outcomes among 510 women exposed to TCDD who had complete pregnancies within 20 years of their exposure. The study showed a small non-significant association between maternal dioxin concentrations and decreased birthweight and prematurity. NAS determined that there were flaws in the study, such as the fact that information was obtained by self-report, and that there was no control group or a measurement of background dioxin. (Eskenazi *et al.*, 2003).

No relevant Vietnam-veteran studies were published since Update 2002.

NAS concluded that there is inadequate or insufficient evidence to determine an association between

exposure to herbicides and low birthweight and preterm delivery in offspring of exposed individuals.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and low birthweight and preterm delivery in offspring of exposed individuals outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Birth Defects (Other Than Spina Bifida) in Offspring of Exposed Individuals

The March of Dimes defines a birth defect as "an abnormality of structure, function, or metabolism, whether genetically determined or as a result of an environmental influence during embryonic or fetal life." (Bloom, 1981). Major birth defects, which occur in 2–3% of live births, are severe enough to interfere with viability or physical well-being. Birth defects are detected in another 5% of babies through their first year of life.

The causes of most birth defects are unknown. Known causes include genetic factors, exposure to some medications, environmental contaminants, occupational hazards, and lifestyle factors.

In 1994, NAS found in VAO that there was inadequate or insufficient information to determine an association between exposure to herbicides and birth defects among offspring. But in Update 1996 and subsequent studies, NAS concluded that there was limited or suggestive evidence of an association between at least one of the compounds of interest and spina bifida in the children of exposed veterans. There was no change in the conclusions about other birth defects.

An environmental study examined the impact of exposure to emissions from municipal solid waste incinerators on birth defects in a region of France over a ten-year period. Congenital anomalies were not significantly associated with exposure overall, but some specific anomalies (facial clefts, renal dysplasia, obstructive uropathies, cardiac anomalies) showed significant dose-response relationships. The exposure indicator in this study could not differentiate exposure to dioxins from exposure to metals. (Cordier *et al.*, 2004).

An ecologic study compared rates of adverse birth outcomes in U.S. agricultural states. The use of herbicides on the fields during the times when certain babies were conceived showed a possible increased risk for some defects, such as musculoskeletal and

integumental anomalies. However, this study did not directly measure herbicide exposure; instead, it measured by acreage. (Schreinemachers, 2003).

No relevant occupational studies have been published since Update 2002.

Data from the Centers for Disease Control and Prevention (CDC) regarding birth defects in the past 25 years showed that there was no greater risk among Vietnam veterans for fathering babies with serious birth defects. (Correa-Villasenor *et al.*, 2003).

Excluding spina bifida, NAS concludes that there is inadequate or insufficient evidence to determine an association between exposure to herbicides and all other birth defects in offspring of exposed individuals.

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

Childhood Cancer (Including Acute Myelogenous Leukemia) in Offspring of Exposed Individuals

Cancer remains the leading cause of death from disease in children under the age of 15. Leukemia is the most common cancer in children. The second most common group of cancers in children is that of the central nervous system.

NAS concluded in VAO and subsequent studies that there was inadequate or insufficient information to determine an association between exposure to herbicides and childhood cancers.

An agricultural health study examined childhood cancer in the offspring of male pesticide applicators in Iowa. Incidence was compared with the Iowa Surveillance, Epidemiology and End Result data. Potential associations between pesticide exposure and individual types of cancer were not examined. There was a higher rate of childhood cancers for paternal exposure to herbicides than for maternal exposure. (Flower *et al.*, 2004).

No relevant environmental or Vietnam-veteran studies have been published since Update 2002.

The only new study reviewed for this update (Flower *et al.*, 2004), did not show any significant association between the relevant exposures and childhood cancer in offspring of exposed individuals.

On the basis of its evaluation of the epidemiologic evidence reviewed here

and in previous VAO reports, NAS concluded that there is inadequate or insufficient evidence to determine an association between exposure to herbicides and childhood cancer in offspring of exposed individuals.

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

Neurobehavioral Disorders (Cognitive or Neuropsychiatric)

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.

Since Update 2002, five reports have investigated associations between neurobehavioral disorders and possible exposure to herbicides. The five reports are: (1) An update of the Air Force Health Study (AFHS) (Barrett *et al.*, 2003), (2) a cross-sectional study of a cohort of Korean veterans who served in Vietnam (Kim *et al.*, 2003), (3) an update of an occupational cohort from the Czech Republic (Pelclova *et al.*, 2002), (4) a cohort study from the Bordeaux region of France (Baldi *et al.*, 2003) and (5) a semi-ecological study from a community adjacent to a wood treatment plant (Dahlgren *et al.*, 2003).

Psychological functioning was compared in Ranch Hand veterans and other Vietnam veterans (Barrett *et al.*, 2003). The characteristics of the study groups indicated that those with high exposure were more likely to be younger enlisted personnel; those with background or low exposure were older officers. Two standard psychological test instruments were administered: The Minnesota Multiphasic Personality Inventory (MMPI) and the Millon Clinical Multiaxial Inventory (MCMI). MMPI results were inconsistent and showed no significant associations with exposure. The conclusions from the studies were limited by the possibility of misclassification of exposure, selection bias, and uncontrolled confounding. The authors concluded that there were few consistent differences in psychological functioning between groups based on serum dioxin concentrations.

A study published results of a cross-sectional study of Korean veterans who served in Vietnam. Health outcomes were assessed by a group of four family

practitioners, blinded to subjects' exposure status, using a "standardized comprehensive clinical investigation." There was a significantly higher prevalence of post-traumatic stress disorder (PTSD) and mood disorder in Vietnam veterans than in the non-Vietnam comparison group; although the association was not significant after controlling for multiple potential confounders, and it did not differ by exposure in Vietnam veterans. The study was limited because of the possibility of selection bias and a chance of residual confounding because of the demographic difference between groups. (Kim *et al.*, 2003).

The Bordeaux study (Baldi *et al.*, 2003) examined a cohort of 2,792 persons over age 65, enrolled in 1987 for the purposes of studying normal and pathological cerebral aging and loss of independence in the elderly. Exposures were categorized into quartiles by the likelihood of occupational use of chemical pesticides on the basis of self-reports, which introduced the possibility of recall bias. The high drop-out rate raises concerns of selection bias. The authors of the study could not identify exposure to specific compounds. The study offered no evidence that would implicate the compounds of interest because the exposures were not comparable to herbicide exposures in Vietnam.

Dahlgren *et al.* used a semi-ecological design to assess the possibility that self-reported symptoms suggesting neurobehavioral disorders in a group of people from eastern Mississippi were related to residence near a creosote treatment plant. (Dahlgren *et al.*, 2003). The study suffered from design weaknesses, including selection and ascertainment bias, lack of objective exposure data, and lack of physician-confirmed diagnoses.

NAS concluded that there is no consistent evidence for any association between neurobehavioral disorders and herbicide exposure.

On the basis of its evaluation of the epidemiological evidence reviewed here and on previous VAO reports, NAS concludes that there is still inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and neurobehavioral disorders (cognitive or neuropsychiatric).

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and neurobehavioral disorders (cognitive or neuropsychiatric) outweighs the credible evidence for such an

association, and he has determined that a positive association does not exist.

Movement Disorders, Including Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS)

• Parkinson's Disease

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that affects millions of people worldwide. Its primary clinical manifestations are bradykinesia, resting tremor, cogwheel rigidity, and gait instability. These signs were first described in 1817 as a single entity by James Parkinson, who believed that severe fright from a traumatic experience was a probable cause.

Because of the increasing concern that a link exists between 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 non-exposed individuals.

In the Bordeaux cohort study, new cases at the 8- and 10-year follow-up were identified by self-report in response to the question, "Do you have Parkinson's disease?" The incidence for exposed and unexposed subjects, respectively, was estimated at 8.9 and 4.1 cases per 1,000 person-years. The results do suggest increased risk to men with occupational exposure to pesticides, but the use of fungicides in vineyards predominated, rather than any of the compounds of interest. The case-control study from Bordeaux compared 84 subjects over age 70 with PD who had been recruited from hospital-based specialty clinic practices with a control group of 252 subjects without PD, identified from the previously described cohort. There is no evidence from that study to implicate herbicides to Vietnam veterans. (Baldi *et al.*, 2003).

On the basis of its evaluation of the epidemiologic evidence reviewed here and in previous VAO reports, NAS concluded that there is inadequate or insufficient information to determine whether an association exists 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.

No relevant epidemiologic studies have been published since Update 2002.

On the basis of its evaluation of the epidemiologic evidence reviewed here and in previous VAO reports, 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 Peripheral Nervous System Disorders

Peripheral neuropathy consists of disorders of the peripheral nervous system. Manifestations of this syndrome can include a combination of sensory changes, motor weakness, or autonomic instability.

NAS noted in VAO and subsequent reports that there was inadequate or insufficient evidence of an association between exposure to herbicides and peripheral neuropathy.

Peripheral neuropathy was one outcome considered in a study of Korean Vietnam veterans (Kim *et al.*, 2003). It was significantly more common in Vietnam veterans than in non-Vietnam veterans, with a 2.4-fold risk even after controlling for alcohol use and age, although there were no differences based on estimated TCDD exposure within subgroups of Vietnam veterans. Diabetes was also more common in Vietnam veterans. The authors of the study concluded that there was an excess frequency of peripheral neuropathy in Vietnam veterans. The report distinguishes between "peripheral neuropathy" and "neuropathy with diabetes," which was not significantly different between the groups. The possibility of selection bias was a concern in this study, only 28% of eligible Vietnam veterans participated in the study and participation may have been related to health status. Therefore,

the study provides some evidence of an association between service in Vietnam and peripheral neuropathy. However, the study does not provide evidence for an association between specific exposure to the compounds of interest and chronic persistent neuropathy.

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.

Respiratory Disorders

Non-malignant respiratory disorders comprise acute and chronic lung diseases other than Cancer. Acute respiratory disorders include pneumonia and other respiratory infections. Those disorders can be increased in frequency and severity when the normal defense mechanisms of the lower respiratory tract are compromised.

The major risk factor for many non-malignant respiratory disorders is cigarette smoking. Cigarette smoking is the major cause of many airway disorders, and makes almost every respiratory disorder more severe and symptomatic than would otherwise be the case. Vietnam veterans are reported to smoke more heavily than are non-Vietnam veterans (McKinney *et al.*, 1997).

NAS noted in VAO and subsequent updates that there was inadequate or insufficient information to determine an association between exposure to herbicides and respiratory disorders.

A cross-sectional environmental study used questionnaires to gather information on potential adverse health effects among residents near a wood treatment plant. Exposed residents reported greater frequency of chronic bronchitis by history and asthma by history. Selection bias and recall bias limit the utility of the results. It is unclear whether the authors adequately controlled for history of tobacco use. In addition, multiple environmental exposures occurred in the neighborhood near the plant, and the authors could not determine which exposures were responsible for the reported adverse health effects. (Dahlgren *et al.*, 2003).

No relevant occupational or Vietnam-veteran studies have been published

since Update 2002. No new studies provide evidence of a direct risk of non-malignant respiratory disorders in adults since those reviewed in Update 2002.

On the basis of its evaluation of the epidemiologic evidence reviewed in Update 2004 and in previous VAO reports, NAS concluded that there is inadequate or insufficient evidence to determine an association between exposure to herbicides and non-malignant acute or chronic 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 outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Gastrointestinal, Metabolic, and Digestive Disorders (Changes in Liver Enzymes, Lipid Abnormalities, Ulcers)

Gastrointestinal and digestive disease includes diseases of the esophagus, stomach, intestines, rectum, liver, and pancreas. The two conditions most often discussed in the literature reviewed are peptic ulcer disease and liver disease. The symptoms and signs of gastrointestinal disease and liver toxicity are highly varied and often vague.

The most convenient way to categorize diseases that affect the gastrointestinal system is by the affected anatomic segment.

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.

No relevant environmental or Vietnam-veteran studies have been published since Update 2002.

NAS concluded that there was no information contained in the research reviewed for Update 2004 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.

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.

No relevant environmental or Vietnam-veteran studies of lipid and lipoprotein disorders have been published since those reviewed in Update 2002.

An occupational study conducted measured cholesterol and triglyceride concentrations in 12 men who were exposed to extremely high concentrations of TCDD in the late 1960s while they were employed in herbicide production at a chemical factory in the former Czechoslovakia. The correlation between TCDD in 1996 and highest recorded measurement of triglyceride or cholesterol at any point between 1968 and 2001 was 0.66 for triglyceride and 0.78 for cholesterol. No information was given about follow up measures of lipids collected in standard or periodic fashion for participants and there is no discussion of how individual differences in treatment of elevated cholesterol could influence the highest recorded value for total cholesterol. (Pelclová *et al.*, 2002).

Hu *et al.* (2003) conducted a cross-sectional study of dioxin-furan exposures and lipids in workers at municipal-waste incinerator plants in Taipei City, Taiwan. A total of 133 workers were randomly sampled from 3 plants; the workers had to have been employed for at least 6 months in the operation and control or maintenance departments. Seventeen (17) congeners were measured, including TCDD. Workers with TCDD above the median had higher average cholesterol and were more likely to have cholesterol above 220 mg/dL. The relationship between TCDD and cholesterol was not statistically significant when TCDD was measured by tertiles, quartiles, or as a continuous variable. TCDD was not associated with triglyceride as a continuous or categorical measure.

The study by Pelclová *et al.* has some shortcomings, including the small sample (12 men). The study by Hu *et al.* successfully recruited a cross-section of workers and did show significant variation in cholesterol by a dichotomous measure of TCDD. The loss of statistical significance with more detailed categories or along the full continuum of TCDD values suggests that

the findings from the initial analysis are not robust or consistent. Several individual congeners other than TCDD were identified as statistically significant correlates of elevated cholesterol. The study did not allow for isolation of the effect of any single exposure. The relationship between herbicide exposure and lipid remains uncertain.

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.

Immune System Disorders (Immune Suppression, Autoimmunity)

The immune system defends the body against infection by viruses, bacteria, and other disease-producing microorganisms (pathogens). The immune system's cells arise from stem cells in the bone marrow; they are found throughout the body's lymphoid tissues, and they circulate in the blood as white blood cells. The immune system also operates in cancer surveillance, destroying cells that have transformed and might otherwise develop into tumors.

Autoimmune disease is an example of the immune system's causing rather than preventing disease. In this case, the immune system mistakenly attacks the body's own cells and tissues as if they were foreign.

In new studies from Seveso, Italy, plasma immunoglobulin (Ig) and complement concentrations were measured in a random sample of the population. This was conducted in highly exposed zones and in the surrounding uncontaminated areas. The concentrations of one plasma immunoglobulin (IgG), significantly decreased with increasing TCDD concentration. The association was present after adjusting for age, sex, tobacco use, and computation of domestic livestock and poultry. (Baccarelli *et al.*, 2002).

Two studies have evaluated the influence of exposure to TCDD-like compounds on immune response in children. One study characterized the immune status of adolescent boys and girls in Flanders, Belgium, in relation to their blood concentrations of PCBs and dioxin like compounds. The results

found in the adolescents might suggest a dioxin-induced suppression of the immune response, consistent with the findings in the laboratory animals exposed to TCDD. (Van Den Heuvel *et al.*, 2002).

In a follow up study of 8 year-old Dutch children perinatally exposed to dioxin, researchers found a decrease in allergy in relation to increasing dioxin exposure. The study found an increased percentage of naïve versus activated T cells, which is consistent with a generalized decrease in immune responsiveness associated with dioxin exposure. (Tusscher *et al.* 2003).

One study examined Korean Vietnam War veterans for evidence of immune system changes in relation to their operation in various areas of Vietnam. A significant increase in plasma IgE was found in both groups of veterans compared with control subjects. The patient group also had significantly decreased plasma IgG1. Those changes correlated with decreased production of interferon gamma in the patient group and with increased production of interleukin 4 in both veterans' groups when the T cells from the subjects were cultured in vitro. No changes in the plasma concentrations of antibodies against double-stranded DNA or extractable nuclear antigens, both markers of autoimmune disease, were found in the veterans, nor were changes found in frequency distribution of peripheral blood leukocyte subpopulations. (Kim H-A *et al.*, 2003).

TCDD is a well known immunosuppressive agent in laboratory animals; it is among the most potent immunotoxicants in the environment. Therefore, one would expect that exposure of humans to sufficiently high doses of TCDD would result in immune suppression. However, several studies of various parameters of human immune function have failed to reveal consistent correlations with TCDD exposure, and no detectable pattern of increased infectious diseases has developed in veterans exposed to high concentrations of TCDD or other herbicides used in Vietnam. Although suppression of the immune response by TCDD could increase the risk of some cancers in Vietnam veterans, there is no evidence to support that connection.

Studies that examined the influence of TCDD on IgE production have generated additional conflicting data. Two studies revealed a significant reduction in IgE production and associated allergic responses correlated with increasing exposure to TCDD and related compounds among children in Belgium and the Netherlands (Tusscher *et al.*, 2003; Van Den Heuvel *et al.*,

2002). In contrast, Korean Vietnam veterans had increased rather than decreased IgE concentrations in plasma—independent of health status. (Kim H-A *et al.*, 2003).

No relevant occupational studies were published since those reviewed in Update 2002.

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.

NAS concluded that there was no information reviewed for Update 2004 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

The term circulatory disorder includes hypertension, heart failure, arteriosclerotic heart disease, peripheral vascular disease, and cerebrovascular 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 circulatory disorders.

An occupational study presented results for a 21-year-old follow up of mortality in a cohort of 1,341 licensed herbicide applicators working for government agencies in the Netherlands. The workers had relatively low cardiovascular mortality. (Swaen *et al.*, 2004).

An ecological study reported no association between measure of dioxin emissions and cardiovascular or cerebrovascular mortality after adjustment for socioeconomic correlates of dioxin emissions. However, the study design precludes inferences about the relationship between exposure and disease among individuals. This study cannot be interpreted as important evidence of no association. (Fukuda *et al.*, 2003).

A Vietnam-veteran study reported the results of a cross-sectional study of exposure to Agent Orange and the prevalence of large number of health outcomes in Korean veterans who had served in Vietnam. The study shows an elevated prevalence of hypertension in

Vietnam veterans compared with that for veterans who served elsewhere. However, some of the weaknesses included in this study include no information on the measurement of disease, and therefore no opportunity to comment on the quality of measurement. There is also the possibility of selection bias in the formation of the study population due to a law in Korea to support medical care and compensation for herbicide victims. (Kim J-S *et al.*, 2003).

The new occupational and environmental studies of circulatory conditions do not support an association for exposure to herbicides, but they also do not represent compelling evidence for the lack of an association.

On the basis of its evaluation of the epidemiologic evidence reviewed here and in previous VAO reports, NAS concluded that there is no information contained in Update 2004 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and specific circulatory disorders (coronary artery disease, myocardial infarction, stroke, hypertension) or circulatory conditions in general.

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.

AL Amyloidosis

Amyloidosis refers to a group of related disorders that share the common feature of the deposition of insoluble, fibrous amyloid protein, mainly in the extracellular spaces of organs and 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.

VA identified AL amyloidosis as a concern in Update 1998. It was examined specifically by the committees responsible for Updates 2000 and 2002. In Update 2002, NAS 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 2002.

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

The endometrium is the tissue that lines the inside of the uterus. In endometriosis, the endometrium is found outside the uterus, usually in other parts of the reproductive system, the abdomen, or the tissues near the reproductive organs. The tissue develops into growths or lesions that respond to hormonal changes in the body, and break down and bleed each month in concert with a woman's menstrual cycle. It results in inflammation, internal bleeding, and degeneration of blood and tissue, which can cause scarring, pain, infertility, adhesions, and intestinal problems. The exact cause of endometriosis is unknown, though genetics is a possible etiology.

NAS reviewed endometriosis for the first time in Update 2002. Since Update 2002, three environmental studies have been conducted that examined the relationship between exposures to some of the compounds of interest and endometriosis. One such study investigated the development of endometriosis among participants of the Seveso Women's Health Study. The cohort consisted of women who had lived in proximity to the Seveso accident site in 1976 and had TCDD serum measurements in blood collected between 1976 and 1980. Women in the highest exposure group showed a doubling in the risk of endometriosis compared with the lowest exposure group, although the increase was not statically significant, possibly because of the small number of confirmed cases. A major limitation of the study was the inability to confirm with laparoscopy the disease state of the largest group, those with an uncertain diagnosis. No truly unexposed control group was included in the study. (Eskenazi *et al.*, 2002).

The second study completed a population-based cross-sectional study of residents in several Belgian towns in

the vicinity of industrial sites or municipal solid waste incinerators and a control group with no known exposures to dioxins or PCBs. There was no difference in the mean TEQ (toxicity equivalent) concentrations between the 10 cases and 132 controls. The study's usefulness is compromised because of reliance on self-reports and because of the small number of cases. (Fierens *et al.*, 2003).

The third study conducted a pilot case-control study of women of reproductive age in Italy and Belgium to determine whether there is a correlation between blood concentrations of dioxin-like compounds and endometriosis. Controls were patients suspected of having a benign adnexal mass; cases were suspected of having endometriosis. The data did not indicate that the concentration of 2,3,7,8-TCDD was elevated in women with endometriosis. Overall, the study did not show that women with endometriosis had higher 2,3,7,8-TCDD or total TEQ than did controls. The study was limited in its ability to detect differences, however, by the small number of subjects. The selection criteria, which allowed all women with suspected gynecological abnormality, also introduced bias. (De Felip *et al.*, 2004).

No relevant occupational or Vietnam-veteran studies have been published since Update 2002.

None of the three studies demonstrated an increased risk for endometriosis with exposure to dioxin or dioxin-like compounds. 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.

Effects on Thyroid Homeostasis

The thyroid gland secretes hormones (T4 and T3) that stimulate metabolism. 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.

NAS reviewed the thyrotoxic potential of herbicides for the first time in Update 2002 and concluded that there was inadequate or insufficient information to determine an association between exposure to herbicides and adverse effects on thyroid homeostasis.

An occupational study measured serum hormone and TCDD concentration in 37 men who had sprayed 2, 4,5-T. In correlation analysis, TCDD concentrations were inversely related to T3 and TSH. The association was strongest when historical, but not current, serum TCDD concentrations were considered. (Johnson *et al.*, 2001).

No relevant environmental studies were published since Update 2002.

A Vietnam-veterans study examined thyroid hormone status in the AFHS cohort. At each examination 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. Ranch Hand veterans had TSH significantly higher than did the comparison population. No changes in microsomal or antithyroid antibodies were observed, nor was there any evidence of changes in clinical thyroid disease. (Pavuk *et al.*, 2003).

NAS determined the lack of data on the association between exposure to the chemicals of interest and adverse effects on thyroid homeostasis, coupled with the lack of exposure information on Vietnam veterans precludes quantification of any possible increase in their risk.

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.

Gastrointestinal Tumors (Esophagus, Stomach, Pancreas, Colon, Rectum)

Gastrointestinal Tract tumors are among the most common of cancers. NAS reviewed data on esophageal cancer, stomach cancer, pancreatic cancer, colon cancer, and rectal cancer. Colon cancer makes up about 40% of gastrointestinal tract cancer diagnoses and deaths.

The incidence of stomach, colon, rectal, and pancreatic cancers increase with age in people 50–64 years old. In general, the incidence is higher in men than women, and is higher in blacks than in whites. Other risk factors for those cancers vary but always include family history of the same form of cancer, some 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 examined two occupational studies. One study showed that male chemical production workers previously exposed to substantial amounts of dioxin experienced no increased risk from death from gastric cancer. (Bodner *et al.*, 2003).

In another study of licensed herbicide applicators in the Netherlands, a lower than expected number of deaths due to esophagus and stomach cancer was reported. (Swaen *et al.*, 2004).

An environmental study of 590 municipalities in Japan examined the relationships between indexes of dioxin emissions from incineration plants and cause-specific mortality among nearby residents. When the analysis was restricted to municipalities with incineration plants, there was a positive and statistically significant correlation in men for stomach cancer for one dioxin index and a statistically significant negative correlation for three dioxin indexes. (Fukuda *et al.*, 2003).

The Vietnam-veteran study reported on cancer incidence and mortality in Air Force veterans of the Vietnam War. Index cases were Operation Ranch Hand veterans who sprayed dioxin-contaminated herbicides in Vietnam. Comparison subjects served in Southeast Asia during the same period but did not spray herbicides. The group reported that the incidence of cancer of the digestive system was significantly lower than expected, compared with national incidence rates, in white Ranch Hand veterans. There were insufficient numbers of non-white Ranch Hand veterans to make estimates. (Akhtar *et al.*, 2004).

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.

The evidence that suggests that there is no association between exposure to herbicides and gastrointestinal tumors also implies that Vietnam-veterans are not at increased risk of gastrointestinal tumors resulting from herbicide exposure.

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 tumors outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Brain Tumors

The only well-established environmental risk factor for brain tumors is exposure to high doses of ionizing radiation. (American Cancer Society, 2004a; Wrensch *et al.*, 2002). Several other potential risk factors have been examined, but most brain cancers are not associated with any known risk factors. Brain cancer occurs fairly 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.

An occupational study conducted in 2003 updated cancer mortality among Dow Chemical Company workers who were likely to have been exposed to high concentrations of dioxins. Cancers of the brain and nervous system were not elevated. (Bodner *et al.*, 2003).

A 2004 study of the mortality of a cohort of 1,341 licensed herbicide applicators in the Netherlands showed an insignificant increase in brain cancer, but the study was limited by the small number of cases and by potential confounders that could not be evaluated. (Swaen *et al.*, 2004).

No relevant environmental studies were published since Update 2002.

A Vietnam-veteran study describes cancer incidence and mortality in a prospective cohort study of Air Force Operation Ranch Hand veterans who sprayed Agent Orange while serving in Southeast Asia. The Ranch Hand cohort was compared to a group of veterans who did not serve in Southeast Asia as well as U.S. national cancer rates. There was a non-significant increase in the incidence of cancer of the brain and nervous system compared with national rates, and a non-significant increase in Ranch Hand veterans who served during the heaviest use of Agent Orange. There

was no increase in mortality attributable to cancer of the brain and nervous system. This study was limited by the small number of cases. (Akhtar *et al.*, 2004).

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.

Conclusion

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 2004." The comprehensive review and evaluation of the available literature that 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.

After careful review of the NAS findings in Update 2004 and other pertinent information, the Secretary has determined that no new presumptions

of service connection are warranted for any illnesses based on exposure to herbicides used during the Vietnam War or to dioxin.

Approved: June 5, 2007.

Gordon H. Mansfield,

Deputy Secretary of Veterans Affairs.

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DEPARTMENT OF VETERANS AFFAIRS

Advisory Committee on OIF/OEF Veterans and Families; Notice of Meeting

The Department of Veterans Affairs (VA) gives notice under Public Law 92-463 (Federal Advisory Committee Act) that a subcommittee of the Advisory Committee on OIF/OEF Veterans and Families will conduct a site visit in the Las Vegas, Nevada area on June 26-28, 2007. The site visit will include a town hall meeting, tours and briefings at various VA facilities, and a tour of Nellis AFB medical facilities. The town hall meeting will be open to the public.

The purpose of the Committee is to advise the Secretary of Veterans Affairs on the full spectrum of health care, benefits delivery and related family support issues that confront servicemembers during their transition from active duty to veteran status and during their post-service years. The Committee focuses on the concerns of all men and women with active military service in Operation Iraqi Freedom and/or Operation Enduring Freedom, but pays particular attention to severely disabled veterans and their families.

On June 26, the subcommittee will attend a veterans small business conference at the Caesars Palace Hotel and will receive afternoon briefings by Nellis AFB officials. On June 27, the subcommittee will tour several VA medical clinics and will receive briefings by Veterans Health Administration and Veterans Benefits Administration personnel on issues of particular relevance to OIF/OEF veterans and their families. The subcommittee will conduct a two hour town hall meeting beginning at 7 p.m. in the Jewel Box Theater at the Clark County Library, 1401 E. Flamingo Road, Las Vegas, Nevada. On June 28, the subcommittee will hold a wrap up session to review and analyze the previous days' briefings. That session will be held at the MGM Grand, 3799 Las Vegas Boulevard South, Las Vegas, Nevada.

Public comments will be received by the subcommittee at the town hall meeting on June 27. Individuals wishing to make oral statements at the meeting should contact the Committee at oifoeef@va.gov. Just prior to the town hall meeting, there will also be a sign up sheet for people to register their interest in making public statements. Oral statements by the public will be limited to five minutes each.

Anyone seeking additional information should contact Ronald Thomas, Esq., Designated Federal Officer, at (202) 273-5182.

Dated: June 6, 2007.

By direction of the Secretary.

E. Philip Riggins,

Committee Management Officer.

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