

By direction of the Secretary.

Denise McLamb,

Program Analyst, Enterprise Records Service.

[FR Doc. 2010-13600 Filed 6-7-10; 8:45 am]

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DEPARTMENT OF VETERANS AFFAIRS

[OMB Control No. 2900-0300]

Agency Information Collection (Veterans Application for Assistance in Acquiring Special Housing Adaptations) Activity Under OMB Review

AGENCY: Veterans Benefits Administration, Department of Veterans Affairs.

ACTION: Notice.

SUMMARY: In compliance with the Paperwork Reduction Act (PRA) of 1995 (44 U.S.C. 3501-3521), this notice announces that the Veterans Benefits Administration, Department of Veterans Affairs, will submit the collection of information abstracted below to the Office of Management and Budget (OMB) for review and comment. The PRA submission describes the nature of the information collection and its expected cost and burden; it includes the actual data collection instrument.

DATES: Comments must be submitted on or before July 8, 2010.

ADDRESSES: Submit written comments on the collection of information through <http://www.Regulations.gov> or to VA's OMB Desk Officer, OMB Human Resources and Housing Branch, New Executive Office Building, Room 10235, Washington, DC 20503 (202) 395-7316. Please refer to "OMB Control No. 2900-0300" in any correspondence.

FOR FURTHER INFORMATION CONTACT: Denise McLamb, Enterprise Records Service (005R1B), Department of Veterans Affairs, 810 Vermont Avenue, NW., Washington, DC 20420, (202) 461-7485, FAX (202) 273-0443 or e-mail denise.mclamb@va.gov. Please refer to "OMB Control No. 2900-0300."

SUPPLEMENTARY INFORMATION:

Title: Veterans Application for Assistance in Acquiring Special Housing Adaptations, VA Form 26-4555d.

OMB Control Number: 2900-0300.

Type of Review: Extension of a currently approved collection.

Abstract: Veterans who are disabled complete VA Form 26-4555d to apply for special housing or modification to their current dwellings. Grants are available to assist the veteran in making adaptations to their current residences

or one they intend to live in as long as the veteran or a member of the veteran's family owns the home.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The **Federal Register** Notice with a 60-day comment period soliciting comments on this collection of information was published on March 29, 2010, at page 15494.

Affected Public: Individuals or households.

Estimated Annual Burden: 25 hours.

Estimated Average Burden per Respondent: 20 minutes.

Frequency of Response: On occasion.

Estimated Number of Respondents: 75.

Dated: June 2, 2010.

By direction of the Secretary.

Denise McLamb,

Program Analyst, Enterprise Records Service.

[FR Doc. 2010-13601 Filed 6-7-10; 8:45 am]

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DEPARTMENT OF VETERANS AFFAIRS

[OMB Control No. 2900-0222]

Agency Information Collection (Application for Standard Government Headstone or Marker for Installation in a Private or State Veterans' Cemetery) Activities Under OMB Review

AGENCY: National Cemetery Administration, Department of Veterans Affairs.

ACTION: Notice.

SUMMARY: In compliance with the Paperwork Reduction Act (PRA) of 1995 (44 U.S.C. 3501-3521), this notice announces that the National Cemetery Administration, Department of Veterans Affairs, will submit the collection of information abstracted below to the Office of Management and Budget (OMB) for review and comment. The PRA submission describes the nature of the information collection and its expected cost and burden; it includes the actual data collection instrument.

DATES: Comments must be submitted on or before July 8, 2010.

ADDRESSES: Submit written comments on the collection of information through <http://www.Regulations.gov>; or to VA's OMB Desk Officer, OMB Human Resources and Housing Branch, New Executive Office Building, Room 10235, Washington, DC 20503, (202) 395-7316. Please refer to "OMB Control No. 2900-0222" in any correspondence.

FOR FURTHER INFORMATION CONTACT:

Denise McLamb, Enterprise Records Service (005R1B), Department of Veterans Affairs, 810 Vermont Avenue, NW., Washington, DC 20420, (202) 461-7485, FAX (202) 273-0443 or e-mail denise.mclamb@va.gov. Please refer to "OMB Control No. 2900-0222."

SUPPLEMENTARY INFORMATION:

Titles:

a. Application for Standard Government Headstone or Marker for Installation in a Private or State Veterans' Cemetery, VA Form 40-1330.

b. Claim for Government Medallion for Installation in a Private Cemetery, VA Form 40-1330M.

OMB Control Number: 2900-0222.

Type of Review: Revision of a currently approved collection.

Abstracts:

a. The next of kin or other responsible parties of deceased veterans complete VA Form 40-1330 to apply for Government provided headstones or markers for unmarked graves.

b. A family member complete VA Form 40-1330M to apply for a Government medallion to be affixed to privately purchased headstone or marker for a deceased veteran buried in a private cemetery.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The **Federal Register** Notice with a 60-day comment period soliciting comments on this collection of information was published on March 29, 2010, at pages 15493-15494.

Affected Public: Individuals or Households.

Estimated Annual Burden: 93,500 hours.

Estimated Average Burden Per Respondent: 15 minutes.

Frequency of Response: One time.

Estimated Number of Respondents: 374,000.

Dated: June 2, 2010.

By direction of the Secretary.

Denise McLamb,

Program Analyst, Enterprise Records Service.

[FR Doc. 2010-13602 Filed 6-7-10; 8:45 am]

BILLING CODE 8320-01-P

DEPARTMENT OF VETERANS AFFAIRS

Health Effects 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 of a May 2008 determination by the Secretary of Veterans Affairs that evidence available at that time did not warrant a presumption of service connection based on exposure to herbicides used in the Republic of Vietnam during the Vietnam era for the following health outcomes: Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses); cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs; esophageal cancer; stomach cancer; colorectal cancer (including small intestine and anus); hepatobiliary cancers (liver, gallbladder and bile ducts); pancreatic cancer; bone and joint cancer; melanoma; non-melanoma skin cancer (basal cell and squamous cell); breast cancer; cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate); urinary bladder cancer; renal cancer; cancers of brain and nervous system (including eye); endocrine cancers (thyroid, thymus, and other endocrine); leukemia (other than chronic lymphocytic leukemia (CLL)); cancers at other and unspecified sites; neurobehavioral disorders (cognitive and neuropsychiatric); and 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, and ulcers); immune system disorders (immune suppression, allergy, and autoimmunity); ischemic heart disease; circulatory disorders (including hypertension); endometriosis; effects on thyroid homeostasis; certain reproductive effects, *i.e.*, infertility, spontaneous abortion, neonatal or infant death and stillbirth in offspring of exposed people, low birth weight in offspring of exposed people, birth defects (other than spina bifida) in offspring of exposed people, childhood cancer (including acute myelogenous leukemia) in offspring of exposed people; 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 2006 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 2006 report. Information regarding additional relevant studies is stated in VA's prior notices following earlier NAS reports, and generally will not be repeated here.

This notice relates only to the Secretary's May 2008 determination based on a 2006 report of the National Academy of Sciences (NAS) and prior NAS reports. Subsequent to the Secretary's May 2008 determination, NAS in 2009 issued a further report discussing additional evidence concerning Veterans and Agent Orange. Based on that 2009 report, VA in March 2010 proposed to establish presumptions of service connection based on herbicide exposure for three conditions (Parkinson's disease, ischemic heart disease, and b-cell leukemias). See 75 FR 14391 (Mar. 25, 2010). The discussion in this notice does not in any way affect those proposed presumptions, but merely explains the basis for the Secretary's prior May 2008 decision, as required by law.

FOR FURTHER INFORMATION CONTACT:

Thomas Kniffen, Chief, Regulations Staff, Compensation and Pension Service, Veterans Benefits Administration, Department of Veterans Affairs, 810 Vermont Avenue, NW., Washington, DC 20420, (202) 461-9725.

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 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 2 years (as measured from the date of the first report) for a 10-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 findings and analyses of the NAS and aspects of the relevant studies, including the magnitude and the statistical significance of the findings, their 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 effects.

Scope of This Notice

NAS issued its seventh report, entitled "Veterans and Agent Orange: Update 2006" (Update 2006), on July 27, 2007. As required by law, this notice explains a determination made by the Secretary in May 2008 that then-existing evidence, as summarized in Update 2006, did not warrant a presumption of service connection for several specific diseases. Among other things, this notice conveys the Secretary's determination that the evidence and analysis in Update 2006 and prior reports did not provide a basis for establishing presumptions of service connection, based on herbicide exposure, for movement disorders (including Parkinson's disease), ischemic heart disease, and leukemia (other than chronic lymphocytic leukemia).

Subsequent to the May 2008 determination that is the subject of this notice, VA in 2009 received another NAS report, entitled "Veterans and Agent Orange: Update 2008." Based on the 2009 report, the Secretary of Veterans Affairs has determined that presumptions of service connection based on herbicide exposure are now warranted for Parkinson's disease, ischemic heart disease, and b-cell leukemias, and VA published a proposed rule in the Federal Register of March 25, 2010 (75 FR 14391) to establish such presumptions. We emphasize that nothing in this notice affects the Secretary's more recent determination, based on additional evidence and analysis by NAS, to establish presumptions of service connection for those three diseases. The Secretary's May 2008 determinations are set forth here merely for the purpose of providing public notice of those determinations as required by statute.

Update 2006

Consistent with its prior reports, NAS in Update 2006 found that there was "sufficient evidence of an association" between herbicide exposure and five categories of diseases in Veterans. VA has previously established presumptions of service connection for each of these diseases. See 38 CFR 3.309(e). NAS, in Update 2006, categorized certain health outcomes to

have "limited or suggestive evidence of an association." This category is defined to mean that evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence. Health outcomes placed in the "limited or suggestive evidence of an association" category are laryngeal cancer; cancer of the lung, bronchus, or trachea; prostate cancer; multiple myeloma; early-onset transient peripheral neuropathy, prophyria cutanea tarda; type 2 diabetes (mellitus); and spina bifida in offspring of exposed people. VA has previously established presumptions of service connection for each of these diseases, see 38 CFR 3.309(e), with the exception of spina bifida, for which VA pays a monetary allowance under 38 CFR 3.814. NAS, in Update 2006, additionally categorized AL amyloidosis and hypertension as having limited or suggestive evidence of an association. VA recently established a presumption of service connection for AL amyloidosis. See 74 FR 21258 (May 7, 2009).

NAS, in Update 2006, categorized certain health outcomes as having inadequate or 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. The health outcomes that met this category are: Cancers of the oral cavity (including tongue), pharynx (including lips and tonsils), or nasal cavity (including ears and sinuses); cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs; esophageal cancer; stomach cancer; colorectal cancer (including small intestine and anus); hepatobiliary cancers (liver, gallbladder, and bile ducts); pancreatic cancer; bone and joint cancer; melanoma; non-melanoma skin cancer (basal cell and squamous cell); breast cancer; cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate); urinary bladder cancer; renal cancer; cancers of brain and nervous system (including eye); endocrine cancers (thyroid, thymus, and other endocrine); leukemia (other than CLL); cancers at other and unspecified sites; neurobehavioral disorders (cognitive and neuropsychiatric); movement disorders (including Parkinson's disease and ALS); chronic peripheral nervous system disorders; respiratory disorders;

gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities, and ulcers); immune system disorders (immune suppression, allergy, and autoimmunity); ischemic heart disease; circulatory disorders (excluding hypertension); endometriosis; effects on thyroid homeostasis; certain reproductive effects, *i.e.*, infertility, spontaneous abortion, neonatal or infant death and stillbirth in offspring of exposed people, low birth weight in offspring of exposed people, birth defects (other than spina bifida) in offspring of exposed people, and childhood cancer (including acute myelogenous leukemia) in offspring of exposed people.

The Secretary's determination that there is not a positive association between herbicide exposure and the diseases addressed in this notice is based upon the NAS's 2006 review and analysis of the relevant scientific evidence as summarized below, the additional analyses provided in this notice, and NAS's and VA's previous analyses of the scientific and medical literature set forth in earlier **Federal Register** notices at: 59 FR 341 (Jan. 4, 1994), 61 FR 41442 (Aug. 8, 1996), 64 FR 59232 (Nov. 2, 1999), 66 FR 2376 (Jan. 11, 2001), 67 FR 42600 (Jun. 4, 2002), 68 FR 27630 (May 30, 2003), 72 FR 32395 (May 20, 2007).

I. Cancer

Cancer of the Oral Cavity, Pharynx, or Nasal Cavity

NAS found that the new occupational studies of cancers of the oral and nasal cavities or pharynx were generally small and so yielded unstable estimates of risk. Integration of the evidence on this set of cancers is challenging because different studies group cases differently. Two studies of agricultural pesticide applicators found significant decreases in certain oral cancers rather than excess risk associated with exposure. Studies on Australian Vietnam Veterans showed some increases in risk, but the results were not adjusted for cigarette-smoking or alcohol use, both of which are known risk factors.

On the basis of its evaluation of the evidence reviewed in Update 2006 and in previous reports, NAS concluded that there was inadequate or insufficient information to determine whether there is an association between herbicide exposure and oral, nasal, and pharyngeal cancers.

Lip Cancer

NAS evaluated lip cancer as a separate entity for the first time in

Update 2006 and found that the available studies suffered from certain limitations. Some studies had very low specificity with respect to exposure to the compounds of interest. NAS noted that these studies defined exposure status almost exclusively in terms of occupation, and even the determination of occupation usually could not be regarded as rigorous.

Other studies used computer techniques to link records in comprehensive databases, such as those matching entries in tumor registries with compendiums of national censuses. NAS noted that these studies amass large samples that may have the effect of inflating power. Such investigations are useful for generating hypotheses, but NAS noted that suggestive findings must be replicated by studies with more refined designs that are capable of gathering more extensive information about the subjects to use in adjusting for confounders.

NAS further noted that the certainty of the diagnostic categories culled directly from death certificates or other databases may be questionable and that diagnoses of lip cancer might overlap with non-melanoma skin cancers in the sources from which the information was gathered for the studies discussed.

NAS also noted the studies in question did not adjust for smoking and sunlight exposure, as would be necessary before inferring that agricultural chemicals played a role in any observed association in an occupational group.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and lip cancer.

Tongue Cancer

NAS also evaluated tongue cancer as a separate category for the first time in Update 2006, and concluded that interpretation of the evidence on tongue cancer is constrained by the grouping of data on them with data on other oral cancers. Most of the studies with information on this specific tumor site observed only a small number of cases and therefore had unstable estimates of risk.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and tongue cancer.

Tonsil Cancer

NAS noted that there is a paucity of findings specifically related to tonsil cancer, because of the extreme rarity of this type of cancer and its occurrence in an anatomic region whose cancers are generally grouped fairly idiosyncratically. That the tissue type developing into a neoplasm at this location might generate a carcinoma, a lymphoma, or a sarcoma has further constrained NAS's ability to assemble a meaningful body of evidence addressing risk factors for this unusual type of cancer. NAS noted that further research, such as a case-control protocol, would be needed to evaluate whether tonsil cancer is associated with exposure to the herbicides used in Vietnam.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and tonsil cancer.

Cancer of the Pleura, Mediastinum, and Other Unspecified Sites Within the Respiratory System and Intrathoracic Organs

NAS's default category for any health outcome for which no epidemiologic research findings have been recovered has always been "inadequate evidence" of association, which in principle is applicable to specific cancers. Cancers of the pleura, mediastinum, and other unspecified respiratory cancers are rarely reported individually and are not as yet seen for the chemicals of interest, reflecting the paucity of information. NAS concluded there is inadequate or insufficient information to categorize such a disease outcome.

Esophageal Cancer

NAS noted that previous updates did not review the risk of esophageal cancer separately. In Update 2006, NAS concluded that the epidemiologic studies of esophageal cancer to date yielded no evidence of an increased risk associated with the compounds of interest, although updates of the health status of the Australian Vietnam Veterans presented an interesting but non-significant pattern of increased risk of esophageal cancer. No toxicologic studies provide evidence of biologic plausibility of an association between the compounds of interest and tumors of the esophagus.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is

an association between herbicide exposure and esophageal cancer.

Stomach Cancer

NAS found that the risk of stomach cancers had not been reviewed separately in previous updates. Among the newly reviewed studies, only one reported a significant relationship, which was between stomach cancer and the rather non-specific exposure of being a forestry worker. The NAS noted some evidence of biologic plausibility in animal models, but concluded that the epidemiologic studies to date do not support an association between exposure to the compounds of interest and stomach cancer.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and stomach cancer.

Colorectal Cancer

NAS found that previous updates had not reviewed the risk of colorectal cancers separately. In Update 2006, NAS found no evidence to suggest an association between the compounds of interest and colorectal cancer in the epidemiologic studies reviewed to date. The only significant increase in intestinal cancers noted in Update 2006 was a reported result concerning cancer of the small intestine based on cases in two exposed people. NAS explained that this is a very uncommon tumor and was reported in Update 2006 with the more common cancers of the large intestine and rectum for completeness of coverage. NAS found no evidence of biologic plausibility of an association between exposure to any of the compounds of interest and the development of tumors of the colon or rectum. NAS concluded that the available evidence does not support an association between the compounds of interest and colorectal cancer.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and colorectal cancer.

Hepatobiliary Cancers

For Update 2006, NAS found that no new reports of a definitive link between exposure to the compounds of interest and hepatobiliary tumors were found. One study suggested a reduced risk of hepatic cancers in Veteran populations, and one suggested an increased risk of cancer of the gallbladder among forestry

workers. However, given the relatively low incidence of hepatobiliary cancers in Western populations, NAS concluded that the evidence from epidemiologic studies remains inadequate to link the compounds of interest with hepatobiliary cancer.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and hepatobiliary cancer.

Pancreatic Cancer

NAS noted that one study reported increased rates of pancreatic cancer among Australian Vietnam National Service Veterans, but that the findings could be associated with increased rates of smoking and cannot be attributed to exposure to the compounds of interest. NAS noted that other reports have been largely negative.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and pancreatic cancer.

Bone and Joint Cancer

NAS reviewed results of several pertinent studies published since the previous update. The studies either reported a non-significant increase in risk of bone and joint cancer, observed too few events to estimate relative risk (RR) adequately, or did not present data that sufficiently linked observed results to specific compounds of interest to this report. NAS concluded that the new results add little to the previous body of results that, taken together, do not indicate an association between exposure to the compounds of interest and bone cancer.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and bone and joint cancer.

Skin Cancer—Melanoma

NAS found that new occupational studies were small and could not provide stable estimates of RR associated with herbicide exposure. NAS stated that the evidence from a number of studies of occupational and environmental populations is inconsistent, but that significant associations have been demonstrated in some studies of populations with well-characterized exposures to the

compounds of interest. NAS noted, however, that the evidence of an association with melanoma in these studies may be limited by the possibility of bias or chance. Further, NAS noted that positive findings of a study of Australian Vietnam Veterans are limited by internal inconsistency, and that an increase in mortality reported by the Centers for Disease Control and Prevention Vietnam Experience Study is consistent but too small to be considered significant.

NAS stated that the results of the Air Force Health Study (AFHS) have long been anticipated as the most directly pertinent to the experience of US Vietnam Veterans, so NAS was impressed by recent reports of a strong dose-response relationship between serum TCDD concentrations and melanoma in this population. Some members of the committee were concerned, however, that the findings of the AFHS have not been presented in a complete and systematic fashion. Further, NAS noted that the two recent Ranch Hand studies are based on diagnoses rendered up to 1999 and 2003, respectively, but that there is some indication that more recent melanoma diagnoses among the control subjects greatly exceeds that of the Ranch Hands, which might produce quite different results. NAS therefore endorses further evaluation and longitudinal analysis of the entire data set on cancer outcomes generated in the important AFHS population. NAS noted that, despite the findings in the AFHS study, there was a persisting concern that there was little suggestion of an association in other relevant populations.

After extensive deliberation concerning new evidence and the results of studies reviewed in previous updates, NAS was unable to reach consensus as to whether the evidence concerning an association between herbicide exposure and melanoma met the criteria for being considered limited or suggestive or whether this health outcome should remain in the inadequate or insufficient classification primarily because the suggestive findings are almost exclusively from the AFHS, whose final data on both the Ranch Hand and comparison subjects have not yet been analyzed in a satisfactory and uniform manner.

As indicated in prior NAS reports and reiterated in Update 2006, occupational and environmental studies generally have not found a significant increase in the risk of melanoma associated with herbicide exposure, and the few significant findings are limited by methodological concerns. In its 2004

report, NAS noted that a 2004 study by Swaen *et al.* of herbicide applicators in the Netherlands reported a significantly increased incidence of all skin cancers, but the data were limited because they could not distinguish the effects of herbicide exposure from the significant confounding factor of sun exposure, which was likely to be common among herbicide applicators. In its 1996 update, NAS also noted that one occupational study of Danish herbicide-production workers reported a significant increased incidence of melanoma, but because of the small number of cases (4) and the lack of adequate information in the study, it was not considered to provide evidence of an association.

Although recent analyses of the Ranch Hand Veterans provides some evidence of an association, as noted in Update 2006, the evidence overall continues to weigh against an association. Occupational exposures, particularly among herbicide-production workers are ordinarily expected to exceed in duration and magnitude the types of exposures that would be seen in Vietnam Veteran populations. As NAS noted in Update 2006, the general lack of significant findings in occupational studies is a relevant consideration in interpreting the more recent findings concerning the Ranch Hand Veterans. Additionally, based on the indications in Update 2006 that more recent data concerning the Ranch Hand population could affect the findings of the recent studies suggests that further inquiry is needed before definitive conclusions can be drawn regarding the significance of those findings.

Skin Cancer—Basal-Cell and Squamous-Cell Cancer (Non-Melanoma)

NAS found that the new results demonstrate only a small RR that is not statistically significant, and the dose-response relationship also is not statistically significant.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and basal-cell or squamous-cell cancer.

Breast Cancer

NAS reviewed several new studies concerning breast cancer in Update 2006 and, with one exception, found that they did not provide evidence supporting an association between breast cancer and herbicide exposure. NAS found that recent results from the Agricultural Health Study (AHS) cohort

generally do not support the hypothesis that exposure to the compounds in Agent Orange increases breast-cancer incidence or mortality in women, although exposure to the specific compounds of interest was not specified. NAS noted that recent studies of environmental exposure found null associations, but that the exposures in some cases were of questionable relevance. NAS further noted that two studies of organochlorine concentrations in adipose tissue failed to find any evidence of increased risk in association with higher adipose concentrations; in fact, the more relevant study found the risk in the highest tercile of dioxin concentrations in breast fat was lower than in the lowest tercile of dioxin concentrations, although not significantly so.

NAS found that one study published since the last update does provide some evidence of an association between exposure to 2,4-D and breast-cancer risk in female farm workers in California. The study is limited by lack of detailed information on potential confounding factors and lack of evidence of a dose-response relationship, but it is large and the investigators were able to estimate individual exposures by linking work histories to an extensive database on pesticide use.

NAS considered the new information in the context of the cumulative data from studies reviewed in previous updates. NAS found that the results of four prior studies lend support to the hypothesis that there is an association between breast cancer and exposure to the compounds of interest. However, each study has limitations or weaknesses that keep its conclusions about the association in question from being definitive.

NAS noted that the recent data from a 2005 study by Mills and Yang, although not persuasive in themselves, lend additional weight to an association between the relevant herbicide exposures and breast-cancer risk. This study has reasonable size and relatively specific exposure information but is limited chiefly by the data available to control for confounding. Some members of the committee considered the body of evidence as a whole to be suggestive of an association; for others, the few modestly positive results associated with a diversity of exposures suggested chance findings rather than a coherent picture. Further laboratory and epidemiologic work on this association should be pursued.

The main reason for the unresolved division in the NAS opinion concerning the adequacy of the available evidence to support an association between breast

cancer and exposure to the components of the herbicides sprayed in Vietnam was differing individual views about the specificity and relevance of the studied exposures for the population of primary concern to the committee, Vietnam Veterans. Overall, the committee was impressed by the positive results from earlier studies reviewed, but several members considered this a very small sample upon which to anchor an association. The degree to which the profile of chemicals contributing to total toxicity equivalency in the more positive epidemiologic studies differed from that of Vietnam Veterans diminished the conviction of some members that these results constituted fully relevant evidence.

After extensive deliberation concerning the new evidence and the results of studies reviewed in previous updates, NAS was unable to reach consensus as to whether the evidence of an association between exposure to the compounds of interest and breast cancer met the criteria for being considered limited or suggestive or whether concerns about chance, bias, and confounding remained so substantial that breast cancer should remain in the inadequate or insufficient classification.

Relatively few studies provide evidence of a positive association between herbicide exposure and breast cancer. As NAS noted, most of the recent studies do not support an association, although some of the studies are of questionable relevance and thus would not provide strong evidence against an association. Of the five positive studies identified by NAS, two are limited by potential confounding factors. As noted above, the 2005 study by Mills and Yang lacked data to control for confounding. A 2001 study by Revich *et al.* found an increased mortality from breast cancer among persons exposed to dioxins from working in or residing near a chemical plant, but the potential for confounding exists because the subjects were exposed to a number of other toxic chemicals. One of the positive studies, a 2000 Vietnam Veteran study by Kang *et al.*, reported an increase in breast cancer among female Vietnam Veterans, but the result was not statistically significant. The other two studies showed positive results, although the NAS noted some limitations related to study size and relevance of exposures. Although those studies provide some supportive evidence, the overall weight of the current evidence does not support an association between herbicide exposure and breast cancer.

Cancers of the Female Reproductive System

NAS found that two analyses of the same cohort found increased incidence of and mortality from ovarian cancer in women who had been engaged in pesticide application. The weight of those studies for the present purposes is limited by the lack of detail on chemical exposures and the absence of data that would allow for control of confounding. Future studies of ovarian cancer should be watched carefully, particularly studies that use biomarkers of exposure or more detailed chemical-exposure histories.

On the basis of its evaluation of the evidence in Update 2006 and in previous reports, NAS has concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and uterine, ovarian, or cervical cancer.

Testicular Cancer

NAS found that the evidence from epidemiologic studies is inadequate to link herbicide exposure and testicular cancer. The relative rarity of this cancer makes it difficult to develop risk estimates with any precision. Most cases occur in men 25–35 years old, and men who have received such a diagnosis could be excluded from military service; this could explain the slight reduction in risk observed in some Veteran studies.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and testicular cancer.

Bladder Cancer

NAS found that available analyses of an association between exposure to the compounds of interest and bladder-cancer risk are characterized by low precision because of the small numbers, low exposure specificity, and lack of ability to control for confounding. No new data have emerged since Update 2004 to alter the conclusion that the cumulative evidence of such an association is inadequate or insufficient.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and bladder cancer.

Renal Cancer

NAS found that available analyses of an association between exposure to the

compounds of interest and renal-cancer risk are limited by the small number of cases and lack of exposure specificity. No new data have emerged since Update 2004 to alter the committee's conclusion that the evidence is inadequate or insufficient to determine whether there is an association.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and renal cancer.

Cancer of the Eye and Orbit

NAS found that most of the epidemiologic studies of findings on eye cancer alone reported few or no cases, were of low power, and had statistically non-significant results. The studies with the largest numbers of cases did not indicate significant increases in risk associated with herbicide exposure. Some analyses of the Australian Vietnam Veterans showed excess risk, but it was probably due to excess exposure to UV radiation, which was not adjusted for. It should be noted that eye cancer is sometimes reported in a combined category with brain cancers.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and eye cancer. Any future findings for this cancer site will be tracked with results on brain cancer.

Brain Cancer

NAS found that since Update 2004, several relevant studies have been identified, including cohort and case-control designs. Many studies rely on surrogate indicators of exposure, such as occupational titles, but several studies estimated exposure to one or more of the compounds of interest on the basis of a job-exposure matrix or self-reported exposure history. Most used cancer-registry data with a high degree of diagnostic certainty. However, each study has limitations or weaknesses that keep its conclusions about the association in question from being definitive.

Most of the relevant prior cohort studies do not show substantial risk differences from the null hypothesis, but this may reflect the limited power of the cohort method to identify risk differences in rare diseases, such as brain cancer. However, with the accumulation of findings that deviate from consistency with the null hypothesis, the present committee can

no longer retain the original VAO committee's conclusion that the available evidence is suggestive of no association.

On the basis of detailed evaluation of the epidemiologic evidence from new and previously reported studies of populations with potential herbicide exposure, NAS concluded that the categorization in prior updates (limited or suggestive evidence of no association) should be revised to inadequate or insufficient to determine whether there is an association between herbicide exposure and brain cancer and other nervous system cancers.

Endocrine Cancers

Update 2006 is the first to consider endocrine cancers as constituting a separate cancer type. NAS found several relevant studies that show low thyroid-cancer incidence and cancer mortality in various populations. The studies assessed exposure to one or more of the compounds of interest although the metrics often were based on surrogate indicators or self-reported exposure. Some of the cohort studies used cancer-registry data with a high degree of diagnostic certainty. Several of the studies show somewhat increased risks of thyroid or other endocrine cancers in association with the compounds of interest. The two studies with any indication of statistical significance both had mixed results. The authors were conducting analyses on large samples whose exposure was no better characterized than "agricultural worker" on a death certificate or census response, whereas in a third study, the risks of endocrine cancers were lower in phenoxy herbicide workers who also had exposure to TCDD. Most showed no substantial risk differences in association with the compounds of interest. Many of the studies had very small numbers of cases, and their limitations preclude risk estimation. There were no significant findings in Vietnam-Veteran studies. Thus, the studies reviewed do not provide sufficient evidence to determine whether there is an association between exposure to the compounds of interest and thyroid cancer.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and thyroid or other endocrine cancers.

Leukemia (Other Than CLL)

NAS found that the new studies did not provide any new evidence of an

association between exposure to the compounds of interest and leukemia.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that, at the time of Update 2006, there was inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and leukemias other than CLL.

Acute Myelogenous Leukemia

NAS found that taken together, the occupational, environmental, and Veteran studies are limited by the paucity of reports related to the types of leukemia and to acute myelogenous leukemia (AML) in particular. In concluding its review of the available findings related to the occurrence of AML in Veterans exposed to the herbicides sprayed in Vietnam, NAS notes the finding in Update 2000 of limited or suggestive evidence of an association between exposure to the compounds of interest and AML in the children of Vietnam Veterans and the reversal of the finding in the report on AML. The recognition of an error in a key publication and new information on the illness resulted in reclassification of AML in children to inadequate evidence to determine whether there is an association.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and AML.

Cancers at Other and Unspecified Sites

NAS' default category for any health outcome for which no epidemiologic research findings have been recovered has always been "inadequate evidence" of association, which in principle is applicable to specific cancers. Cancers at other and unspecified sites are rarely reported individually and not as yet seen for the chemicals of interest, reflecting the paucity of information. NAS concluded there is inadequate or insufficient information to categorize such a disease outcome.

II. Reproductive and Developmental Effects

Fertility

NAS found that although there is much evidence of the biologic plausibility of disruption of male and female fertility by exposure to the chemicals of interest, there continues to be a lack of substantive epidemiologic data that demonstrate any association in human populations.

On the basis of its evaluation of the evidence reviewed in Update 2006, NAS concluded that there is inadequate or insufficient evidence of an association between herbicide exposure and altered hormone concentrations, menstrual-cycle abnormalities, decreased sperm counts or sperm quality, and sub-fertility or infertility.

Spontaneous Abortion

NAS found that no additional information was available to the committee responsible for Update 2006 to motivate changing the assessment of the last two committees. Given the age of the Vietnam-Veteran cohort, it is highly unlikely that additional information on this outcome among the population will appear.

In Update 2006, NAS concluded that paternal exposure to TCDD is not associated with risk of spontaneous abortion and that insufficient information is available to determine whether an association exists between the risk of spontaneous abortion and maternal exposure to TCDD or either maternal or paternal exposure to 2,4-D, 2,4,5-T, picloram, or cacodylic acid.

Stillbirth, Neonatal Death, and Infant Death

NAS found that the study reviewed for Update 2006 did not find significant associations between the relevant exposures and rates of infant or fetal deaths. The study was limited in that exposure was based on environmental concentrations of dioxin and individual exposure data were not obtained. Furthermore, several risk factors that could confound associations between exposure and outcome were not assessed.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and stillbirth, neonatal death, or infant death in offspring of exposed people.

Low Birth Weight and Preterm Delivery

NAS found that the three studies reviewed in Update 2006 did not find an association between exposure to the compounds of interest and the risk of low birth weight or prematurity. The two new weakly significant findings may simply be spurious results arising among many comparisons; a modest increase in average birth weight would not be construed as an adverse effect, and the small decrease in average gestation is of questionable biologic importance. Although the results overall

suggest a lack of an association, they should be interpreted with caution because of some methodologic limitations, such as a long recall period in the cohort study and exposure misclassification in the environmental studies.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and low birth weight or preterm delivery in offspring of exposed people.

Birth Defects (Other Than Spina Bifida)

NAS found only one new occupational study of birth defects and exposures to the chemicals of interest, and the information generated was too sparse to provide additional insights into the risks of birth defects. Birth defects were addressed indirectly by a new environmental study, which found an association between residence in the areas with the highest soil dioxin concentrations and deaths before the first birthday due to any congenital abnormality, but this relationship did not carry over to deaths occurring in the first month or in the first week of life.

Only one study addressed birth defects among the offspring of female Vietnam War Veterans, who overall constitute fewer than 10,000 of the roughly 3 million U.S. Vietnam Veterans. NAS noted that, in general, the relatively small number of offspring among Vietnam Veterans seriously restricts the ability to detect statistically significant increases in specific birth defects. In addition, as the offspring of Veterans become older, the risk of diseases stemming from congenitally transmitted defects that alter normal physiologic function, such as endocrine and reproductive function, merits increasing attention.

Another study reported a substantially greater strength of association between exposure to Agent Orange and birth defects in the studies of Vietnamese populations than in those of non-Vietnamese populations. The non-Vietnamese study populations consisted of Vietnam Veterans, who were almost exclusively men, whereas the Vietnamese populations had a much greater likelihood of maternal exposure. This study also conducted subgroup meta-analyses based on presumed exposure intensity. Meta-analytic methods are the best approach to assessing the overall import of the studies of exposures to the chemicals of interest and the risk of specific birth defects. However, the numbers of cases

reported were too small to allow meta-analysis of specific types of birth defects.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and birth defects (other than spina bifida) in offspring of exposed people.

Childhood Cancer

NAS found that the studies reviewed for this update did not find significant associations between the relevant exposures and childhood cancers. As with other outcomes in the offspring of Vietnam Veterans, the small number of these rare childhood cancers expected among the circumscribed number of Vietnam Veterans would seriously hinder detection of any actual increases. NAS reviewed newly available occupational and environmental studies but found the value of these studies to be limited by the questionable reliability of self-reported exposures or other factors.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and childhood cancers in offspring of exposed people.

III. Neurologic Disorders

Neurobehavioral (Cognitive and Neuropsychiatric) Disorders

NAS found that there is not consistent epidemiologic evidence of an association between neurobehavioral disorders (cognitive or neuropsychiatric) and Agent Orange exposure. Difficulties in case identification and diagnosis, misclassification of exposures because of a lack of contemporaneous measures, subject ascertainment and selection bias, and uncontrolled confounding from many comorbid conditions are common weaknesses in the studies reviewed. The variability of the test results over time, the weak and inconsistent associations, and a lack of consistent dose-response relationships also detract from evidence of an association between the compounds of interest and neurobehavioral disorders.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide

exposure and neurobehavioral disorders (cognitive or neuropsychiatric).

Movement Disorders, Including Parkinson's Disease

NAS found that epidemiologic studies have pursued various occupational exposures as potential risk factors for Parkinson's disease; pesticide use is among those receiving the most attention, but it has rarely been possible to isolate the effects of selected chemical herbicides, because exposures often are mixed and assessments usually are retrospective, relying on such broad categories as "ever exposed to any pesticide," which is not considered informative for this report. In addition, reported associations have been inconsistent, and only rarely has evidence supported dose-response relationships. Thus, the data are weakened for the committee's purposes by persistent methodologic limitations and by the lack of specificity for the compounds of interest.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that, at the time of Update 2006, there was inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and Parkinson's disease.

Peripheral Neuropathy

NAS found that epidemiologic studies that used appropriate comparison groups and standard techniques for diagnosis and assessment of exposure have not demonstrated consistent associations between exposure to the compounds of interest and the development of peripheral neuropathy. Several reports have shown no significant association, and in the reports that did indicate an association, chance, bias, or confounding could not be ruled out with confidence. In particular, diabetes might confound the results, inasmuch as many of the subjects with neuropathy also had diabetes, which is a known cause of neuropathy. Controlling for the effects of diabetes is a technical challenge because there is evidence of an association between diabetes and exposure to at least one of the compounds of interest; in many cases, diabetes could be in the causal pathway that links exposure and peripheral neuropathy.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide

exposure and delayed or persistent peripheral neuropathy.

IV. Other Health Effects

Respiratory Disorders

NAS found that results of the new studies of mortality from nonmalignant respiratory diseases do not support the hypothesis that herbicides increase mortality from them. The results of one study showed a positive association, although it is based on only nine deaths in the high-exposure area, and this finding could have been due to chance or misclassification of causes of death. More important, although it recognizes that mortality studies are limited by small numbers of events and misclassification of causes of death, especially respiratory conditions, NAS does not believe that scientific conclusions can be based on health outcomes that are defined vaguely, for example, by combining a wide array of disparate respiratory health outcomes into one large category.

Two new cross-sectional studies have reported positive associations between exposure and the prevalence of various chest conditions. The nonspecificity of the types of respiratory conditions reported in one of the two studies makes it exceedingly difficult to draw any conclusions regarding specific respiratory conditions, and the lack of observed association with serum TCDD concentrations also argues against the existence of an association. The issue of nonspecificity is key to interpreting this study. The results of a second study were weakened by a definition of "wheeze" that was very broad and included any episode in the year before administration of the questionnaire. Further, only 28 percent of subjects reporting this symptom also reported having asthma or atopic conditions.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and the respiratory disorders specified.

Immune-System Disorders (Immune Suppression, Allergy, and Autoimmunity)

NAS found that TCDD is a well-known immunosuppressive agent in laboratory animals. Therefore, one would expect that exposure of humans to sufficiently high doses would result in immune suppression. However, several studies of various measures of human immune function have failed to reveal consistent correlations with

TCDD exposure, and no detectable pattern of increased infectious disease has been documented in Veterans exposed to 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.

Epidemiologic studies have been inconsistent with regard to TCDD's influence on IgE production in humans (Update 2004). No animal or human studies have specifically addressed the influence of TCDD on autoimmune disease. One study of post-service mortality associated with various causes showed no increase in deaths of Vietnam Veterans that could be attributed to immune-system disorders.

Few effects of phenoxy herbicide exposure on the immune system have been reported in animals or humans, and clear association between phenoxy herbicide exposure and autoimmune or allergic disease has not been found.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and immune suppression, allergy, or autoimmune disease.

Lipid and Lipoprotein Disorders

NAS found that previously reviewed literature showed inconsistent changes in serum lipids or lipoproteins after exposure to the compounds of interest, and in most cases the sample sizes were insufficient to support any conclusions. The recent report on Ranch Hand Veterans shows that serum TCDD concentrations are positively associated with serum triglycerides; however, even in Ranch Hand Veterans with the highest TCDD exposure, the mean serum triglyceride concentration (130 mg/dL) is well below that considered to be abnormal (250 mg/dL). It is notable that the Ranch Hand Veterans with abnormally high serum triglycerides tend to be those with the highest TCDD exposure.

Hypertriglyceridemia is considered to be a major risk factor for acute pancreatitis when serum triglyceride concentrations exceed 1,000 mg/dL, and there is some evidence that it is an independent but weak risk factor for ischemic heart disease at concentrations over 150 mg/dL. More commonly, however, high serum triglyceride concentrations (150–500 mg/dL) are considered to be a consequence of other underlying diseases, particularly diabetes mellitus and metabolic syndrome, and hypertriglyceridemia is a

well recognized marker of these diseases, especially when associated with low high-density lipid (HDL) concentrations.

The VAO committee responsible for type 2 diabetes concluded that there was limited or suggestive evidence of an association between type 2 diabetes mellitus and exposure to herbicides in Vietnam. Although the latest Ranch Hand study adjusted the RR of hypertriglyceridemia for smoking and body-mass index (BMI), it failed to account for the presence of diabetes mellitus. Diabetes mellitus is strongly associated with hypertriglyceridemia, as discussed above, so it is plausible that the increased percentage of Ranch Hand Veterans with abnormally high serum triglycerides may be a consequence of diabetes mellitus. In that regard, the percentage of all Ranch Hand Veterans with a diagnosis of diabetes mellitus (about 23 percent) could include the percentage with hypertriglyceridemia (about 13 percent).

Hypertriglyceridemia itself was not considered a health outcome for Update 2006, but it was recognized that its presence may indicate the emergence of a more significant health concern, metabolic syndrome. Metabolic syndrome is characterized by obesity, high triglycerides (over 150 mg/dL), low HDL (under 40 mg/dL), hypertension (over 130/85 mm Hg), and high fasting plasma glucose or diagnosed diabetes mellitus. As noted above, NAS previously concluded that there is suggestive evidence of a link between exposure to herbicides in Vietnam and type 2 diabetes mellitus, whereas the Update 2006 has concluded that there is suggestive evidence of a link between exposure to herbicides in Vietnam and hypertension. Thus, an increasing number of Vietnam Veterans may be exhibiting at least three of the diagnostic criteria for metabolic syndrome: Hypertriglyceridemia, diabetes mellitus, and hypertension. It will be important to analyze the incidence of those individual outcomes as potential components of a larger disease syndrome.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and lipid or lipoprotein disorders.

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

In Update 2006, NAS noted there is no evidence that Vietnam Veterans are at greatly increased risk for serious liver disease, and reports of increased risk of abnormal liver-function tests have been mixed. Although increased rates of gastrointestinal disease have not been reported, the possibility of a relationship between dioxin exposure and subtle alterations in the liver and in lipid metabolism cannot be ruled out.

On the basis of its evaluation of the evidence reviewed in Update 2006 and in previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and gastrointestinal and digestive diseases.

Hypertension

In Update 2006, NAS concluded that there was “limited or suggestive evidence of an association between exposure to the compounds of interest and hypertension.” Prior NAS reports concluded that there was inadequate or insufficient evidence to determine whether there was an association between exposure to herbicides and any cardiovascular diseases, including hypertension. Because Update 2006 suggests that the evidence for an association between herbicide exposure and hypertension is stronger than at the time of prior reports, hypertension warrants close consideration.

As an initial matter, it must be noted that the NAS finding of “limited or suggestive evidence of an association” does not imply any view by NAS as to whether the scientific evidence establishes a “positive association” between herbicide exposure and hypertension within the meaning of 38 U.S.C. 1116(b). The NAS category of “limited or suggestive evidence” is defined to mean that “[e]vidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.” Update 2006, at 11. NAS has explained that, “[f]or example, a well-conducted study with strong findings in accord with less compelling results from populations with similar exposures could constitute such evidence.” *Id.* In contrast, the “positive association” standard in 38 U.S.C. 1116(b)(1) and (3) directs VA to determine whether “the credible evidence for the association is equal to or outweighs the credible evidence

against the association.” In making that determination, VA must consider the NAS reports and any other available evidence and must consider, with respect to scientific studies, “whether the results are statistically significant, are capable of replication, and withstand peer review.” 38 U.S.C. 1116(b)(2). As NAS noted in a 2007 report, “the IOM limited/suggestive category covers a broad range of epidemiological evidence from relatively weak to strongly suggestive,” and the NAS characterization thus cannot be viewed as determinative of the “positive association” determination VA is required to make. Institute of Medicine, *Improving the Presumptive Disability Decision-Making Process for Veterans*, at 98 (National Academies Press 2007).

VA has carefully reviewed the NAS findings and analyses in Update 2006 and prior reports. For the reasons explained below, VA has determined that a positive association does not currently exist between herbicide exposure and hypertension, but that Update 2006 does identify significant new evidence that warrants careful consideration of hypertension on an ongoing basis.

The finding in Update 2006 of “limited or suggestive evidence” for hypertension is based primarily upon one new Vietnam Veteran study, which NAS found to be significant and consistent with results of other lower quality studies. NAS also noted, however, that findings in other studies suggested that hypertension is not associated with herbicide exposure.

NAS found that a 2006 study by Kang *et al.* supported an association between herbicide exposure and hypertension. That study assessed the incidence of hypertension among 1,499 U.S. Army Chemical Corps (ACC) Veterans who handled or sprayed Agent Orange in Vietnam and a control group of 1,428 Veterans from the same era who did not serve in Vietnam. The study found no significant difference in the rates of hypertension between the two groups. However, when analysis was restricted to ACC Veterans who served in Vietnam, Veterans who reported having sprayed herbicides had a higher incidence of hypertension than those who did not report spraying herbicides. Because there is some evidence that type 2 diabetes, a condition that may cause hypertension, is associated with herbicide exposure, the researchers separately evaluated the risk of hypertension in only non-diabetic ACC Veterans and found that hypertension was associated with herbicide spraying in non-diabetic Veterans.

NAS found that this study had several strengths, including its focus on one of the most highly exposed Vietnam Veteran cohorts. NAS noted that exposure to TCDD was directly measured in one subset of the ACC cohort. It also concluded that the study had the merit of controlling for established risk factors for hypertension. NAS further stated that, although the increased incidence of hypertension among ACC sprayers was not large, it was consistent with the existence of several other well-established contributors to the development of hypertension.

NAS noted that one limitation of this study is the potential for information bias, inasmuch as the data on hypertension and on herbicide spraying were self-reported. The study relied upon information provided in telephone interviews in which the Veterans were asked whether a physician had ever diagnosed them with hypertension and also requested information as to whether they had sprayed or handled herbicides in service. NAS felt that the potential information bias was diminished, in part, because a patient is more likely to report accurately a chronic disorder that requires continuing management, including hypertension and diabetes. NAS noted that the researchers did not attempt to verify self-reported hypertension by medical-record review, but that they did seek to verify self-reports of diabetes and found the self-reports verified in 79 percent of cases. NAS also noted the potential for misclassification among exposure groups and the possible recall bias that could lead to over-reporting of herbicide spraying among men who have serious health conditions. NAS noted that, although there is evidence that ex-sprayers were more likely to report several health conditions besides hypertension, comparison within the ex-sprayer subgroup according to serum TCDD concentration suggests that recall bias does not fully explain the associations.

NAS noted that selection bias could arise from the cross-sectional nature of the study, which accounts for disease prevalence only among people in the original deployed and non-deployed ACC cohorts who were still alive and participated. NAS concluded, however, that concern for that type of selection bias is tempered by the high and nearly equal rates of participation by deployed Veterans (72 percent) and non-deployed Veterans (69 percent), and by the fact that the prevalence of hypertension among the non-deployed Veterans (30 percent) was similar to that among U.S. men of comparable age (32 percent).

NAS stated that, despite those data, it remains unknown whether the observed relationship of spraying to the prevalence of hypertension is equivalent to what one would have observed if the cohort had been followed longitudinally. Nonetheless, because the primary population of concern to VA is the current living cohort of Vietnam Veterans, the findings from the study are particularly relevant.

NAS stated that the results of the Kang study are consistent with those of other studies of Vietnam Veterans, including the other most highly exposed cohort composed of Vietnam Veterans who served in Operation Ranch Hand. NAS stated that multiple examination cycles of the Air Force Health Study (AFHS) of those Veterans have consistently reported an increase in the prevalence of hypertension with a doubling of serum dioxin concentration. NAS stated that the analyses controlled for the major risk factors for hypertension, and diagnosis was confirmed with medical-record review. NAS noted that limitations of the AFHS studies include the potential for selection bias and the variation in the comparison group over examination cycles, but that selection bias is reduced, in part, by the relatively high participation rates across certain cycles. NAS stated that the Kang study is also consistent with three other Veteran studies—a 1996 study of Australian Veterans by O'Toole *et al.*, a 1988 study of American Legion Vietnam Veterans by Stellman *et al.*, and a 1988 Vietnam experience study (VES) by the Centers for Disease Control (CDC)—which NAS characterized as reporting “significant increases” in the incidence of hypertension. NAS noted, however, that only the Kang study controlled for potential confounding variables and used an index of herbicide-related exposure.

NAS noted that there was also evidence weighing against an association between herbicide exposure and hypertension. Specifically, NAS noted that the key Vietnam Veteran ACC study was not consistent with a previous study of herbicide factory workers exposed to TCDD that failed to identify a significant association between measured TCDD and hypertension after controlling for hypertension risk factors. NAS stated that “[t]he negative findings argue against an association between TCDD exposure and hypertension,” although it noted some limitations in the study. Similarly, NAS noted that the ACC study was not consistent with another recent environmental study examining the prevalence of hypertension in

relation to serum concentrations of PCDDs and PCDFs in persons residing near a municipal waste dump. NAS stated that this study “showed that serum concentrations of dioxin-like PCDDs and PCDFs are not associated with an increased incidence of hypertension when major risk factors are adjusted for,” although NAS again noted certain limitations in the study. Accordingly, the report identifies significant evidence both for and against an association between herbicide exposure and hypertension.

We agree with NAS that the recent Kang study is a significant addition to the scientific literature concerning herbicide exposure and hypertension. However, we also note that a number of factors relating to that and other positive studies cited by NAS limit the strength of the evidence. The Kang study is limited in part because it is based on unconfirmed self-reports of hypertension diagnoses. In other reports provided to VA, NAS has noted the inherent limitations of studies based on self-reports. For example, in a 2007 study of health effects of deployment-related stress, NAS noted that some studies had found an increase in hypertension related to deployment but that “because most are based on self-reports, not much reliance can be placed on them.” Institute of Medicine, *Gulf War and Health, Volume 6, Deployment-Related Stress and Health Outcomes*, at 193 (National Academies Press 2007).

In Update 2006, NAS noted that the potential bias of self-reports was tempered because people are more likely to accurately recall and report a chronic disease requiring continuous management, such as hypertension and diabetes, and because the researchers had verified the accuracy of 79 percent of the self-reported diagnoses of diabetes. The seemingly conflicting views concerning the reliability of self-reported hypertension present some difficulty in interpreting the evidence. We note that there is some reason to believe that the potential error rate in self-reported hypertension may be significant enough to impact the study's findings. In its 1994 report on Veterans and Agent Orange, NAS explained that in the CDC's 1988 VES study comparing hypertension incidence in Vietnam Veterans and non-deployed Vietnam-era Veterans “[a] significant difference in self-reported hypertension between the groups was reported,” but that “there was no significant difference in hypertension measured as part of a physical examination in the study.” Institute of Medicine, *Veterans and Agent Orange; Health Effects of*

Herbicides Used in Vietnam, at 702 (National Academies Press 1994).

As noted above, the Kang study did find that 79 percent of self-reported diabetes diagnoses were confirmed by medical record research, and it is reasonable to believe that a similar verification rate would exist for self-reported hypertension. That finding suggests that most self-reports are accurate, but also acknowledges a potentially significant margin of misreported diagnoses. The NAS report does not address the potential impact that such misreported diagnoses could have on the study.

We note also that the Kang study found no significant difference in hypertension between Veterans who served in Vietnam and non-deployed Vietnam era Veterans. This factor does not undermine the study's finding of an increased risk of hypertension in the most highly exposed group, although it might suggest that any association between herbicide exposure and hypertension would be limited to certain high levels of exposure.

The other Vietnam Veteran studies cited as consistent with the Kang study also have a number of limitations. As noted above, NAS noted that several cycles of the AFHS study have consistently reported an increase in the prevalence of hypertension with a doubling of serum dioxin concentration. However, the AFHS findings as reported in Update 2006 report increased risks that are relatively small and in most instances are not statistically significant. Although the consistent findings of increased risk may weigh in favor of an association, the low magnitude of the findings and the general lack of statistical significance may argue against an association or at least may be viewed as indeterminate.

NAS indicated that the CDC's 1988 VES study found a significant increase in the incidence of hypertension in Vietnam Veterans. As noted above, however, that finding existed only with respect to self-reported hypertension diagnoses, and was not supported by physical examinations. Accordingly, in another recent report, NAS characterized the CDC study as finding that the prevalence of hypertension was "not significantly higher" in Vietnam Veterans as compared to non-deployed Vietnam-era Veterans. Institute of Medicine, *Gulf War and Health, Volume 6, Deployment-Related Stress and Health Outcomes* at 185 (National Academies Press 2007).

NAS discussed the 1996 O'Toole study in *Veterans and Agent Orange: Update 1998*. The study involved a simple random sample of Australian

Vietnam Veterans' self-reported health status information in relation to the Australian public. The study found a significant increase in self-reported hypertension among the Vietnam Veterans. Because the study was based on self-reports, it is subject to some of the same concerns discussed above in relation to the Kang study. More significantly, the results apparently do not control for confounding factors. In fact, the study found that the Veterans were significantly more likely than the control population to be current or former smokers and to report high alcohol consumption. The lack of controls for potentially significant risk factors known to exist in the study population significantly limits the weight of this study for present purposes.

NAS discussed the 1988 Stellman study in its 1994 *Veterans and Agent Orange* report. That study was also based on self-reports of hypertension diagnoses. The report found no significant differences in the prevalence of hypertension in Vietnam Veterans and non-deployed Vietnam-era Veterans. It did, however, find a significant increase in self-reported hypertension in Vietnam Veterans who handled herbicides as compared to Vietnam Veterans who did not. NAS noted that the conclusions to be drawn from the study are limited by the potential for misclassification of exposure and the lack of validation of self-reported diagnoses. As noted above, the potential for misreporting of hypertension diagnoses limits the strength of the reported data on association.

Further, in update 2006, NAS acknowledged that the CDC, O'Toole, and Stellman studies did not control for potentially confounding variables. These variables may include alcohol or tobacco use, body mass index or obesity, and type 2 diabetes. The failure to control for confounding factors renders it difficult to draw significant conclusions from the reported data. In Update 2006, for example, NAS noted that a 2006 environmental study by Chen *et al.* based on self-reported data initially found a more than five-fold increase in the risk of hypertension associated with elevated serum PCDD and PCDF concentrations in persons who lived near municipal-waste incinerators; however, when the results were controlled for age, sex, smoking status, and body mass index, the results showed that the study population actually had a decreased risk of hypertension.

NAS identified a number of studies finding no association between

herbicide exposure and hypertension. Among Vietnam Veteran studies, a 2005 study by Ketchum and Michalek of mortality of Ranch Hand Veterans found no significant increase in mortality from hypertension. As noted above, although the CDC's 1988 Vietnam Experience Study found a significant increase in self-reports of hypertension, physical examinations did not show any differences in increased blood pressures, which argues against an association.

The two environmental studies cited by NAS showed no increased risk of hypertension. As noted above, the 2006 study by Chen *et al.* found that persons residing for at least 5 years near a municipal-waste incinerator and who had elevated serum PCDD and PCDF concentrations did not have any increased risk of hypertension. This study has the strength of controlling for confounding factors, although NAS noted a potential limitation in the lack of information on the criteria for diagnosing hypertension. A 2001 study by Bertazzi *et al.* of mortality among persons exposed to TCDD as the result of an accident in Seveso, Italy, found no increased mortality due to hypertension.

Occupational studies identified by NAS generally found no increased risk of hypertension in exposed populations. A 2005 study by 't Mannetje *et al.* of mortality rates among New Zealand workers exposed to phenoxy herbicides and dioxins found no increased mortality due to hypertension. A 1998 study by Calvert *et al.* of workers exposed at two U.S. herbicide factories did not find any significant increase in the risk of hypertension. This study controlled for risk factors and included exposure information based on serum TCDD levels, although NAS noted potential limitations in that some of the information on hypertension was based on self-reports and the overall response rate was low, which could contribute to selection bias. A 1984 study by Suskind and Hertzberg of circulatory disorders among workers at an herbicide production plant found no significant differences in rates of self-reported hypertension associated with exposure. A 2000 study by Kitamura *et al.* of workers at a municipal-waste incinerator found no significant increase in self-reported hypertension associated with elevated serum PCDD levels. Several other studies found no significant increase in circulatory disorders, including hypertension, in persons occupationally exposed to herbicides, but these studies are less helpful because they do not specifically isolate findings concerning hypertension.

The consistently negative findings in the occupational studies identified to date is of interest because, as NAS has noted (Update 2006 at 38), at least in studies of chemical-production workers, the magnitude and duration of exposures in occupational studies generally would be greater than in Vietnam Veteran studies. Accordingly, if the increase in self-reported hypertension observed in the recent Kang study is attributable to herbicide exposure, one would expect similar findings in occupational studies of herbicide-production workers.

In summary, the available occupational and environmental studies to date have consistently failed to detect a significant association between herbicide exposure and hypertension. The available Vietnam Veteran studies have produced a mixture of positive and negative findings, as well as findings that are essentially indeterminate in that they report low-magnitude increases that are not statistically significant. The primary evidence in favor of an association is the recent study by Kang *et al.* Other Vietnam Veteran studies reporting a significant increased risk of hypertension are limited primarily by concern of control for confounding factors. Viewing the evidence as a whole and taking into account the considerations discussed above, the Secretary has determined that the credible evidence for an association between hypertension and herbicide exposure is not equal to nor does it outweigh the credible evidence against an association. Therefore, he has determined that a positive association does not exist. In view of the suggestive findings in the recent Kang study, VA will continue to closely monitor further developments regarding the possible association between herbicide exposure and hypertension.

Circulatory Disorders

NAS found that circulatory diseases constitute a group of diverse conditions, of which hypertension (addressed above), coronary heart disease, and stroke are the most prevalent, that account for 75 percent of mortality from circulatory diseases in the United States. The major quantifiable risk factors for circulatory diseases are similar to those for hypertension and include age, race, smoking, serum cholesterol, BMI or percentage of body fat, and diabetes.

NAS found that reported results of new morbidity and mortality studies of the most highly exposed Vietnam-Veteran cohorts (ACC and Operation Ranch Hand) were not entirely consistent. NAS noted that ACC

Veterans who sprayed Agent Orange reported a significant increase in the prevalence of heart disease, primarily ischemic heart disease, but that the AFHS did not find the prevalence of heart disease, myocardial infarction, or stroke to be significantly associated with either current or back-extrapolated serum TCDD concentrations in Ranch Hand Veterans. NAS stated that one study found a significant increase in mortality due to atherosclerotic heart disease in Ranch Hand ground crew personnel, but the increase in mortality from circulatory disease among all Ranch Hand Veterans based on back-extrapolated serum TCDD was not significant.

NAS also noted that several new occupational studies reported no significant increase in risk of circulatory disorders, including ischemic heart disease, associated with herbicide exposure; in fact, two new studies found that the risk of certain circulatory disorders was significantly lower in the exposed populations.

NAS noted that some previously reviewed studies of herbicide factory workers occupationally exposed to TCDD reported findings supporting an association between herbicide exposure and heart disease. Those findings came primarily from mortality studies in which the researchers did not have access to information concerning the impact of potentially confounding risk factors. NAS noted that, in the studies that did have information on potential confounders, the cardiovascular health endpoints were described imprecisely and did not clearly distinguish ischemic heart disease from other conditions. Viewing those prior studies in relation to the new findings from the studies of ACC and Ranch Hand Veterans, some members of the NAS committee felt that there was limited/suggestive evidence of an association between herbicide exposure and ischemic heart disease. Other members of the committee, however, felt that the lack of information on potential confounders limited the strength of many of the studies and that the evidence remained inadequate or insufficient to determine whether an association exists between herbicide exposure and ischemic heart disease. For all other types of circulatory disease, the committee agreed that the evidence is inadequate or insufficient to determine whether there is an association with exposure to the compounds of interest.

Upon consideration of Update 2006 and prior NAS reports, the Secretary in May 2008 determined that the then-existing credible evidence for an association between circulatory

disorders and herbicide exposure was not equal to nor did it outweigh the credible evidence against an association. Therefore, he determined that a positive association was not established at that time. Although Update 2006 found some evidence supporting an association between herbicide exposure and ischemic heart disease, there was also significant evidence against an association, including several studies that found no significant increased risk of the disease and at least one that found a significantly decreased risk. Further, a number of the studies reporting a significant increase in mortality due to ischemic heart disease were unable to consider potential confounding factors, a concern that limits the strength of the reported data.

As stated previously, based upon the NAS report "Veterans and Agent Orange: Update 2008," the Secretary, on October 13, 2009, announced his decision to establish a presumption of service connection between exposure to herbicides and the subsequent development of hairy cell leukemia (HCL) and other chronic B cell leukemias, Parkinson's disease, and ischemic heart disease. See 75 FR 14391 (Mar. 25, 2010).

Endometriosis

In prior reports, NAS evaluated five studies relevant to endometriosis. It found that three environmental studies reported no increased incidence of endometriosis associated with herbicide exposure and that two case-control studies reported elevated odds ratios but had very wide confidence intervals that precluded statistical significance. In Update 2006, NAS identified two new environmental studies, both of which reported significant increases in the incidence of endometriosis in the populations exposed to dioxin-like PCBs. NAS noted, however, that one of the studies was limited because it was unable to differentiate the effects of the dioxin-like PCBs and non-dioxin-like PCBs to which the subjects were exposed.

On the basis of its evaluation of the evidence reviewed in Update 2006 and previous reports, NAS concluded that there is inadequate or insufficient evidence to determine whether there is an association between herbicide exposure and endometriosis.

Effects on Thyroid Homeostasis

NAS noted that numerous animal experiments and several epidemiologic studies have shown that TCDD and dioxin-like compounds appear to exert an influence on thyroid homeostasis. Specifically, those compounds may

affect the secretion of thyroid-stimulating hormone (TSH), which governs the function of the thyroid gland in secreting the hormones T3 and T4. In prior reports, NAS noted that several human studies observed an increase in TSH levels associated with TCDD exposure, but without a corresponding increase in T4 levels, suggesting that the human body was able to adapt to any effect on TSH production. In Update 2006, NAS noted that, in the newly identified studies of adults, there was lack of correlation between dioxin-like compounds and TSH concentrations. Likewise, NAS noted that, in the newly identified studies of changes in thyroid homeostasis in relation to fetal and infant development, there were not significant associations between magnitude of exposure to dioxin or dioxin-like compounds and measures of thyroid function. NAS concluded that the studies continue to suggest that people were able to adapt to changes in thyroid status that might have been induced by exposure to TCDD and other dioxin-like compounds.

NAS concluded that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and clinical or overt adverse effects on thyroid homeostasis. Although some effects have been observed in humans, the functional importance of the changes reported in the studies reviewed remains unclear, because adaptive capacity could be adequate to accommodate them.

AL Amyloidosis

In Update 2006, the NAS found there was limited or suggestive evidence of an association between herbicide exposure and AL amyloidosis. We are not addressing AL amyloidosis in this Notice because a presumption of service connection has been established for this disease. VA published a final rule

providing a presumption of service connection for AL amyloidosis for any Veteran exposed in service to an herbicide agent who develops the disease at any time after separation from service in the **Federal Register** on May 7, 2009, at 74 FR 21258.

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 2006." 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 a positive association with herbicide exposure. The Secretary's determinations regarding the diseases discussed in Update 2006 are based upon the NAS's identification and analysis of the relevant scientific and medical literature in Update 2006, as summarized above, and the additional analyses set forth in this notice, viewed in relation to prior relevant NAS reports and VA's prior notices addressing these matters.

Taking account of the available evidence and NAS's analysis, the Secretary in May 2008 found that the evidence and analysis available to VA at that time did not warrant a presumption of service connection for cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses); cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs; esophageal cancer; stomach cancer; colorectal cancer (including small intestine and anus); hepatobiliary cancers (liver, gallbladder, and bile ducts); pancreatic cancer; bone and joint cancer; melanoma; non-melanoma skin cancer (basal cell and squamous cell);

breast cancer; cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate); urinary bladder cancer; renal cancer; cancers of brain and nervous system (including eye); endocrine cancers (thyroid, thymus, and other endocrine); leukemia (other than CLL); cancers at other and unspecified sites; neurobehavioral disorders (cognitive and neuropsychiatric); movement disorders (including Parkinson's disease and ALS); chronic peripheral nervous system disorders; respiratory disorders; gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities and ulcers); immune system disorders (immune suppression, allergy and autoimmunity); ischemic heart disease; circulatory disorders (including hypertension); endometriosis; effects on thyroid homeostasis; certain reproductive effects, *i.e.*, infertility, spontaneous abortion, neonatal or infant death and stillbirth in offspring of exposed people, low birth weight in offspring of exposed people, birth defects (other than spina bifida) in offspring of exposed people, childhood cancer (including acute myelogenous leukemia) in offspring of exposed people; and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted. That determination was based on a finding that the then-existing credible evidence against an association between herbicide exposure and the cited conditions outweighed the credible evidence for such an association and that a positive association therefore did not exist.

Approved: May 28, 2010.

John R. Gingrich,

Chief of Staff, Department of Veterans Affairs.

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