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[Notices]

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DEPARTMENT OF VETERANS AFFAIRS

**Health Outcomes Not Associated With Exposure to Certain Herbicide Agents;
Veterans and Agent Orange: Update 2008**

ACTION: Notice.

SUMMARY: As required by law, the Department of Veterans Affairs (VA) hereby gives notice that the Secretary of Veterans Affairs, under the authority of the Agent Orange Act of 1991, Public Law 102-4 (codified in relevant part at 38 U.S.C. 1116), has determined that a presumption of service connection is not warranted based on exposure to herbicides used in the Republic of Vietnam during the Vietnam Era for any of the diseases, illnesses, or health effects identified in the July 24, 2009, National Academy of Sciences (NAS) report entitled "Veterans and Agent Orange: Update 2008" (Update 2008), except for hairy cell leukemia (HCL) and other chronic b-cell leukemias, Parkinson's disease, and ischemic heart disease. In this regard, the Secretary of Veterans Affairs determined, based upon the NAS report, that there is a positive association between exposure to herbicides and the subsequent development of HCL and other chronic b-cell leukemias, Parkinson's disease, and ischemic heart disease. The Secretary recently published a notice of proposed rulemaking to implement this decision. See 75 FR 14391 (Mar. 25, 2010).

The determination to not establish a presumption of service connection, based on exposure to herbicides used in the Republic of Vietnam during the Vietnam era for any other of the diseases, illnesses, or health effects identified in the July 24, 2009, NAS report, does not in any way preclude VA from granting service connection for these diseases, including those specifically discussed in this notice, nor does it change any existing rights or procedures.

The Secretary's determinations regarding individual diseases are based on all available evidence in the 2008 report of the 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 2008 report. Information regarding additional relevant studies is stated in VA's prior notices following earlier NAS reports, and generally will not be repeated here.

FOR FURTHER INFORMATION CONTACT: Gerald Johnson, Regulations Staff (211D), Compensation and Pension Service, Veterans Benefits Administration, Department of Veterans Affairs, 810 Vermont Avenue, NW., Washington, DC 20420, telephone (202) 461-9727. (This is not a toll-free number.)

SUPPLEMENTARY INFORMATION:

I. Statutory Requirements

Section 3 of the Agent Orange Act of 1991, Public Law 102-4, 105 Stat. 11, directed the Secretary to seek to enter into an agreement with the NAS to review and evaluate the available scientific evidence regarding associations 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 suspected diseases and herbicide exposure, taking into account the strength of the scientific evidence and the appropriateness of the scientific methodology used to detect the association; (2) the increased risk of disease among individuals exposed to herbicide agents during service in the Republic of Vietnam during the Vietnam era; and (3) whether a plausible biological mechanism or other evidence of a causal

relationship exists between herbicide exposure and the health outcome. Section 3 of Public Law 102-4 also requires that NAS submit reports on its activities every 2 years (as measured from the date of the first report) for a 10-year period. The Veterans Education and Benefits Expansion Act of 2001, Public Law 107-103, extended this period until October 1, 2014.

Section 2 of Public Law 102-4, codified in pertinent part at 38 U.S.C. 1116(b) and (c), provides that whenever the Secretary determines, based on sound medical and scientific evidence, that a positive association (i.e., the credible evidence for the association is equal to or outweighs the credible evidence against the association) exists between exposure of humans to an herbicide agent (i.e., a chemical in an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era) and a disease, the Secretary will publish regulations establishing presumptive service connection for that disease. If the Secretary determines that a presumption of service connection is not warranted, he is to publish a notice of that determination, including an explanation of the scientific basis for that determination. The Secretary's determination must be based on consideration of the NAS reports and all other sound medical and scientific information and analysis available to the Secretary.

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

Although 38 U.S.C. 1116 does not define "credible," it does instruct the Secretary to "take into consideration whether the results [of any study] are statistically significant, are capable of replication, and withstand peer review." The Secretary reviews studies that report a positive relative risk and studies that report a negative relative risk of a particular health outcome. He then determines whether the weight of evidence supports a finding that there is or is not a positive association between herbicide exposure and the subsequent health outcome. The Secretary does this by taking into account the statistical significance, capability of replication, and whether that study will withstand peer review. Because of differences in statistical significance, confidence levels, control for confounding factors, bias, and other pertinent characteristics, some studies are more credible than others. The Secretary gives weight to more credible studies in evaluating the overall evidence concerning specific health outcomes.

II. Prior NAS Reports

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 2008 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 (June 12, 2007), and 75 FR 32540 (Jun. 8, 2010).

III. Update 2008

NAS issued Update 2008 on July 24, 2009. The report is available at http://www.nap.edu/catalog.php?record_id=12662. For Update 2008, NAS conducted a search of literature published through September 30, 2008, and identified more than 7,000 potentially relevant citations. About 850 were retained for closer consideration, and about 300 contributed information for the NAS's detailed analysis.

a. Sufficient Evidence of Association

Consistent with its prior reports, NAS in Update 2008 found that there was "sufficient evidence of an association" between herbicide exposure and five categories of diseases in veterans. VA has previously established or proposed presumptions of service connection for each of these diseases. See 38 CFR 3.309(e); 75 FR 14391 (Mar. 25, 2010) (proposing to add HCL and other chronic b-cell leukemias to the category of chronic lymphocytic leukemia (CLL)).

b. Limited/Suggestive Evidence of Association

NAS, in 2008, 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; porphyria cutanea tarda; type 2 diabetes (mellitus); spina bifida in offspring of exposed persons; AL amyloidosis; hypertension; Parkinson's disease; and ischemic heart disease. VA has previously established presumptions of service connection for laryngeal cancer; cancer of the lung, bronchus, or trachea; prostate cancer; multiple myeloma; early-onset transient peripheral neuropathy, porphyria cutanea tarda; type 2 diabetes (mellitus); and AL amyloidosis. See 38 CFR 3.309(e). In instances of spina bifida in offspring of exposed persons, VA pays a monetary allowance under 38 CFR 3.814. VA recently proposed presumptions of service connection for Parkinson's disease and ischemic heart disease. See 75 FR 14391 (Mar. 25, 2010). Hypertension is discussed below.

NAS identified and reviewed information from comprehensive databases covering biologic, medical, toxicologic, chemical, historical and regulatory information to determine whether a statistical association with herbicide exposure exists, whether there is an increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and hypertension. In Update 2006, the NAS changed the category for hypertension from "insufficient evidence" to "limited or suggestive evidence," but clearly could not distinguish the possibility of a small increased risk for hypertension due to herbicide exposure from more prevalent scientifically established risk factors in evaluating the risk to individual Veterans. NAS noted the limitations of the studies regarding hypertension. In the Federal Register of June 8, 2010, VA explained why the studies reviewed in Update 2006 did not, in VA's view, warrant a presumption of service connection for hypertension in veterans exposed to herbicides in service. 75 FR 32540 (Jun. 8, 2010).

In Update 2008, NAS identified six new studies concerning hypertension that the committee found to be generally consistent with its conclusion in Update 2006 that there is "limited/suggestive evidence" of an association between herbicide exposure and hypertension. However NAS also found significant limitations in each of the studies. It noted that a mortality study of a population accidentally exposed to dioxin in Seveso, Italy, had little ability to control for potentially important confounders. Three of the new studies analyzed data from the National Health and Nutrition Examination Survey (NHANES), which the committee characterized as broadly consistent with the Update 2006 conclusion, but also as limited by selection bias that may distort the evidence of association and by the inconsistency of the findings among various exposure categories. NAS noted that a study of 47 exposed people in Florida involved a small survey of a problematic sample, making the data difficult to interpret. Finally, the committee noted that a study of an exposed population in Taiwan found no association between hypertension and being in the exposed population. When the analysis was restricted to persons having chloracne (a skin condition associated with herbicide exposure), the study found an increased incidence of hypertension in women, but not in men, making the findings difficult to interpret.

Relatively few of the positive findings were statistically significant and the findings overall are limited by the inconsistency of the results, the lack of controls, and other methodological

concerns. The inconsistent findings within and across the studies limit the ability to draw any conclusions regarding dose-response relationship. Viewing the new studies published since 2006 in relation to the previously reviewed evidence, VA has determined that the evidence overall does not establish a positive association between herbicide exposure and hypertension. Therefore, a presumption of service connection is not warranted.

c. Inadequate or Insufficient Evidence To Determine Whether an Association Exists

NAS, in Update 2008, categorized certain other health outcomes as having inadequate or insufficient evidence to determine whether an association with herbicide exposure 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 lips and tongue), pharynx (including tonsils), 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 (kidney and renal pelvis); cancers of brain and nervous system (including eye); endocrine cancer (thyroid, thymus, and other endocrine organs); leukemia (other than all chronic B-cell leukemias including chronic lymphocytic leukemia (CLL) and HCL); cancers at other and unspecified sites; neurobehavioral disorders (cognitive and neuropsychiatric); movement disorders (including amyotrophic lateral sclerosis (ALS) but excluding Parkinson's disease); chronic peripheral nervous system disorders; respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disorder, and farmer's lung); gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities and ulcers); immune system disorders (immune suppression, allergy and autoimmunity); circulatory disorders (other than hypertension or ischemic heart disease); endometriosis; effects on thyroid homeostasis and certain reproductive effect 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.

After considering the NAS report, the Secretary has determined that presumptions of service connection are not warranted for any of the diseases listed above. As noted above, VA has previously explained, in a series of Federal Register notices, its analysis of prior NAS reports concerning these diseases. The additional evidence and analysis addressed in Update 2008 with respect to these conditions is summarized below.

In Update 2008, NAS identified no additional studies relevant to the possible association between herbicide exposure and cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs; esophageal cancer; bone and joint cancer; cancers of the male reproductive organs (other than prostate cancer), endocrine cancer, movement disorders (including ALS but excluding Parkinson's disease); endometriosis; effects on thyroid homeostasis; and certain reproductive effects. Accordingly, the NAS's conclusions regarding those conditions were unchanged from Update 2006.

In Update 2008, NAS found that the relevant new studies it identified did not include any statistically significant findings of association between herbicide exposure and the following diseases: oral, nasal, and pharyngeal cancers; colorectal cancer; hepatobiliary cancer, melanoma, non-melanoma skin cancer; cancers of the female reproductive organs; urinary bladder cancer; renal cancer; chronic peripheral nervous system disorders; gastrointestinal, metabolic, and digestive disorders (including changes in liver enzymes, lipid abnormalities, and ulcers); and endometriosis. Accordingly, NAS found that the additional evidence generally did not support an association between herbicide exposure and those health outcomes.

With respect to several other health outcomes, NAS in Update 2008 found that, although the new studies included some statistically significant positive findings, those findings did not warrant a change in the conclusion that the evidence overall is inadequate or insufficient to determine whether the health outcome is associated with herbicide exposure, as explained below.

NAS discussed two new studies regarding stomach cancer. One of the studies found no increased mortality from stomach cancer in the exposed population. The other study found a statistically significant increased risk of stomach cancer among farm workers who used pesticides. NAS noted that this study was consistent with findings of a previously-reviewed occupational study finding evidence of an association between exposure to phenoxy herbicides (but not other types of herbicides) and stomach cancer. However, NAS noted that several other significant studies it had previously reviewed--including studies of Vietnam veteran cohorts, studies of the International Agency for Research on Cancer (IARC) cohort, and the U.S. Agricultural Health Study--had provided no evidence suggestive of an association between herbicide exposure and stomach cancers. Accordingly, NAS in Update 2008 concluded that the overall evidence does not support an association between exposure to the herbicides of interest and stomach cancer.

NAS discussed two new studies regarding pancreatic cancer. One of the studies found no increased mortality from pancreatic cancer in the exposed population. The other study found a statistically significant increase in pancreatic cancer among deployed U.S. female Vietnam veterans in comparison to their nondeployed counterparts. NAS noted that a previously reviewed study also found evidence of an increased risk of pancreatic cancer in deployed Australian Vietnam veterans. NAS noted that no increase in risk has been detected to date in U.S. male Vietnam veterans or in agricultural cohorts or IARC follow-up studies. It further noted that the Vietnam veteran studies were limited due to lack of control for smoking and lack of supportive evidence from occupational or environmental studies. NAS found that the overall evidence remained insufficient or inadequate to determine whether an association exists.

NAS discussed four new studies concerning breast cancer. Three of the studies, including a Vietnam veteran study, found no increased risk of breast cancer in exposed populations. One study found an increased risk of breast cancer associated with self-reported use of household pesticides. NAS concluded that the new evidence tended to weigh against an association and that the one positive study was limited by potential recall bias and the lack of information regarding specific exposures.

NAS discussed four new studies regarding cancers of the brain and nervous system (including the eye). It found that the new studies were consistent in finding no association between herbicide exposure and the development of gliomas (the most common type of brain cancer). NAS noted that one of the new studies provided evidence of a possible relationship between herbicide exposure and meningiomas (a type of nervous system cancer) in women, but that the lack of identification of specific chemicals of interest makes interpretation of that result uncertain. NAS concluded that the overall evidence remained inadequate or insufficient to determine whether and association exists.

NAS discussed three new studies addressing whether all forms of leukemia are associated with herbicide exposure. One of the studies found no evidence of an association between herbicide exposure and leukemias, while the other two found evidence of such an association. However, NAS found that one of the positive studies was limited by concern over possible misclassification of causes of death for the few people whose deaths were attributed to forms of leukemia other than those already considered to be associated with herbicide exposure (i.e., b-cell leukemias). Viewing the new evidence in relation to the previously reviewed evidence, NAS found that the overall evidence was inadequate or insufficient to determine whether an association exists. NAS's finding that the evidence does not establish an association between herbicide exposure and all forms of leukemia does not affect its independent finding that there is sufficient evidence

of a causal association between herbicide exposure and specific forms of leukemia (i.e., CLL and other chronic b-cell leukemias).

NAS discussed three new studies regarding neurobehavioral effects. Two of the studies found an increased reporting of neurobehavioral symptoms with self-reported pesticide exposure, but no associations specific to herbicide exposure. The third study found an increased incidence of abnormalities on neurobehavioral testing among persons chronically exposed to herbicides, but NAS found this study limited by the small sample size, the lack of information on methodology, and the possibility that many other environmental and age-related factors may have affected the results. Further, the data do not clearly relate the increased symptoms or abnormal test results to specific neurobehavioral diseases or diagnoses. NAS concluded that the overall evidence remained inadequate or insufficient to detect an association.

NAS noted that several previously reviewed studies failed to support the hypothesis that herbicide exposure is associated with respiratory mortality from non-cancer diseases. In Update 2008, NAS identified one new study showing increased respiratory mortality, but determined that no conclusions could be drawn from the study due to lack of specificity regarding the health outcomes and due to other methodological concerns. In Update 2008, NAS also discussed new and previously reviewed studies relating to three specific categories of respiratory effects: chronic obstructive pulmonary disease (COPD), "wheeze" and asthma, and farmer's lung. NAS concluded that most prevalence studies found no association between herbicide exposure and COPD, and the two that did find evidence of such association were limited by methodological concerns. NAS found that the relevant studies did not detect an association between herbicide exposure and "wheeze" or asthma after adjusting for known confounders, and that the sole relevant study on farmer's lung was inconclusive.

NAS discussed two new studies regarding immune system disorders. One study found no evidence of immune system disorders in persons highly exposed to dioxin. The other study found an increase in self-reported arthritis (thought to be an autoimmune disorder) among exposed women, but not men. NAS concluded that the positive finding was unsupported by experimental evidence and that the overall evidence remained inadequate or insufficient to determine whether an association exists.

NAS identified one study finding evidence of an increased risk of mortality from rheumatic heart disease in an exposed population, but concluded that the basis for the observed association was unclear and that the data were limited by the lack of control for significant confounders and other methodological concerns. NAS found that the overall evidence was inadequate or insufficient to determine whether herbicide exposure is associated with any circulatory disorders other than ischemic heart disease or hypertension.

NAS discussed four new studies regarding thyroid homeostasis. It found that the new studies were generally consistent with previously reviewed studies suggesting that herbicides may exert some effect on thyroid function. However, NAS concluded that the significance of the observed effects is unclear because the body's adaptive capacity should be sufficient to accommodate them. **NAS concluded that there was inadequate or insufficient evidence to determine whether herbicide exposure is associated with clinical or overt adverse effects on thyroid homeostasis.**

NAS noted that previous Veterans and Agent Orange (VAO) committee findings did not find any significant association between the relevant exposure and several reproductive outcomes. In Update 2008, **NAS determined that there is inadequate or insufficient evidence of an association between herbicide exposure and endometriosis; semen quality; infertility; spontaneous abortion; late fetal, neonatal, or infant death; low birth weight or preterm delivery; birth defects other than spina bifida; and childhood cancers (including acute myelogenous leukemia) in offspring of exposed people.**

Among three new studies on endometriosis, two found no significant evidence of association and the third found a decreased risk among the most highly exposed persons. NAS found that several new studies regarding the effects of herbicide exposure on semen quality and female infertility provided little evidence of any adverse impact. NAS found that two new studies regarding spontaneous abortion provided conflicting results and that the overall evidence indicates that paternal exposure is not associated with spontaneous abortion and that there is inadequate or insufficient evidence to determine whether maternal exposure is associated with such outcomes. NAS concluded that one new study regarding the effect of dioxin-like substances on stillbirth, neonatal, death, or spontaneous abortion, did not provide primary evidence for an association between dioxin and such outcomes. NAS discussed four new studies concerning low birth weight or preterm delivery and found that the evidence overall suggests no association between herbicide exposure and those outcomes. **NAS concluded that two new studies provided no evidence of an association between herbicide exposure and birth defects other than spina bifida.** NAS concluded that the four new studies of childhood cancer in the offspring of exposed individuals contained conflicting findings, but that the positive findings in two studies were limited by broad exposure classifications.

Conclusion:

After careful review of the findings of the NAS Report, Veterans and Agent Orange Update 2008, the Secretary has determined that the scientific evidence presented in the 2008 NAS report and other information available to the Secretary indicates that **no new presumption of service connection is warranted at this time for any disease other than HCL and other chronic b-cell leukemias, Parkinson's disease, and ischemic heart disease.**

Signing Authority

The Secretary of Veterans Affairs, or designee, approved this document and authorized the undersigned to sign and submit the document to the Office of the Federal Register for publication electronically as an official document of the Department of Veterans Affairs. John R. Gingrich, Chief of Staff, Department of Veterans Affairs, approved this document on December 20, 2010, for publication.

Dated: December 20, 2010.

Robert C. McFetridge,

Director, Regulations Policy and Management, Department of Veterans Affairs.

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