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DEPARTMENT OF VETERANS AFFAIRS

Determinations Concerning Illnesses Discussed in National Academy of Sciences

Report: Veterans and Agent Orange: Update 2012

ACTION: Notice.

SUMMARY: As required by law, the Department of Veterans Affairs (VA) hereby gives notice that the Secretary of Veterans Affairs, under the authority granted by the Agent Orange Act of 1991, codified at 38 U.S.C. 1116, has determined that there is no basis to establish a presumption of service connection at this time, based on exposure to herbicide agents, including the substance commonly known as Agent Orange, for several health effects discussed in the December 4, 2013, National Academy of Sciences (NAS) report titled: Veterans and Agent Orange: Update 2012 (hereinafter, "Update 2012"). This determination does not in any way preclude VA from granting service connection for any disease, including those specifically discussed in this notice, nor does it change any existing rights or procedures.

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SUPPLEMENTARY INFORMATION:

I. Statutory Requirements

The Agent Orange Act of 1991, Public Law 102–4 (codified in part at 38 U.S.C. 1116), directed the Secretary to seek to enter into an agreement with the National Academy of Sciences (NAS) to conduct a comprehensive review of scientific and medical literature on potential health effects of exposure to Agent Orange. Congress mandated that NAS determine, to the extent possible: (1) whether there is a statistical association between suspect 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 the herbicides 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 exposure to herbicides and suspect disease.

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.

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

NAS has issued ten previous biennial reports under the Agent Orange Act. Based on those reports and the requirements of the Agent Orange Act, VA has established presumptions of service connection for 14 categories of disease, which are listed at 38 CFR 3.309(e). Additionally, following each prior NAS report, VA has published a notice explaining the Secretary’s determination that presumptions of service connection are not warranted for several diseases discussed in those reports. Those notices are published at: 59 FR 341 (Jan. 4, 1994), 61 FR 41442 (Aug. 8, 1996), 64 FR 59232 (Nov. 2, 1999), 67 FR 42600 (June 4, 2002), 68 FR 27630 (May 30, 2003), 72

FR 32395 (May 20, 2007), 75 FR 32540 (June 8, 2010), 75 FR 81332 (Dec. 27, 2010), and 77 FR 47924 (Aug. 10, 2012). 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 prior NAS reports, as discussed in VA's prior Federal Register notices, and upon the additional information and analysis in Update 2012, as discussed below.

III. Veterans and Agent Orange: Update 2012

On December 4, 2013, NAS publicly released Veterans and Agent Orange: Update 2012, which describes the relevant scientific and medical evidence identified subsequent to the last prior NAS review, Veterans and Agent Orange: Update 2010 (hereinafter, "Update 2010"). NAS reviewed, evaluated, and summarized scientific and medical literature addressing several conditions and the health status of Veterans.

Consistent with its prior reviews, NAS concentrated its review on epidemiologic studies to fulfill its charge of assessing whether specific human health effects are associated with exposure to at least one of the herbicides utilized or to a chemical component of herbicides, such as TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin; referred to as TCDD to represent a single—and the most toxic—congener of the tetrachlorodibenzo-p-dioxins, also commonly referred to as dioxin). NAS also considered controlled laboratory investigations that provided information on whether the association between the chemicals of interest and a given effect is biologically plausible.

In Update 2012, NAS endeavored to emphasize and clarify the relationship among the succession of publications that have provided ever increasing insight into the

health responses of particular exposed populations that have been studied for many years. The information that the present Committee reviewed was identified through a comprehensive search of relevant databases, including databases covering biologic, medical, toxicologic, chemical, historical, and regulatory information. NAS conducted a comprehensive search of all medical and scientific studies on health effects of herbicides used in the Vietnam War, including more than 6,800 potentially relevant studies. Of this group, NAS selected 1,100 studies for careful review. It ultimately identified 61 epidemiologic studies as well as several score of toxicologic studies and exposure evaluations that contributed new information. Relevant animal studies, as with previous biennial “Agent Orange Updates,” were also reviewed to determine biological plausibility and possible mechanisms of action.

The epidemiologic information evaluated in Update 2012 was integrated with that previously assembled including Veterans studies, occupational studies, and environmental studies. NAS noted that few studies concerning the health of Vietnam Veterans were identified as having been published since the studies evaluated in Update 2010, and almost all addressed mental health issues that are not within the scope of its report. There were no new studies of Vietnam Veterans and only a single case-control study on Vietnam era South Korean Veterans with cardiac disease, some of whom had served in Vietnam. This study examined whether a history of Vietnam service is associated with the clinical course of coronary disease, not with the occurrence of coronary disease itself.

Since Update 2010, several occupational studies have been published which may show potential health effects of herbicide exposure. For instance, studies focused

on cancer mortality in pentachlorophenol (PCP) workers who are part of the National Institute for Occupational Safety and Health (NIOSH) cohort, and cancer incidence in a NIOSH subcohort of chemical workers in a Dow Chemical Company plant in Michigan. Another study investigated plasma dioxin concentrations and cause-specific mortality in German production workers in a plant included in the International Agency for Research on Cancer (IARC) cohort in Hamburg, Germany. Three new studies of IARC subcohorts in the Netherlands that collectively reported on cancer mortality, ischemic heart disease, humoral immunity, atopic disease, and immune suppression in herbicide workers. The incidence of gliomas in pesticide applicators in participants in the Upper Midwest Health Study was reviewed. Also, eight reports from the Agricultural Health Study (AHS) examined cancer incidence, body-mass index, amyotrophic lateral sclerosis, and mortality in private pesticide applicators (farmers), their spouses, and commercial pesticide applicators in Iowa and North Carolina.

Since Update 2010, numerous studies on environmental exposures to chemicals of interest have been published. Researchers reported on cancer incidence and reproductive factors in people who lived near the site of the industrial accident in Seveso, Italy. Five new studies published by the Prospective Investigations of the Vasculature in Uppsala Seniors (PIVUS) group reported on stroke, atherosclerosis, diabetes, and obesity. Several new studies from Taiwan examined hypertension, cardiovascular disease, and insulin resistance in people who lived in the vicinity of a closed PCP factory. Other studies looked at hypertension, bone mineral density, and environmental exposures via the National Health and Nutrition Examination Survey, and diabetes and hypertension in the Anniston (Alabama) Community Health Survey.

Another study focused on reproductive outcomes in mother–infant pairs exposed to TCDD and other chemicals that have dioxin-like biologic activity in Japan, Finland, the Netherlands, United States, and Vietnam. New case-control studies examined environmental exposures to the chemicals of interest and several types of cancer, myelodysplastic syndromes, endometriosis, menstrual cycles, and Parkinson's disease.

As in its prior reports, NAS placed each health outcome it reviewed in one of four categories based on the strength of the evidence of association between herbicide exposure and the health outcome. The four categories are: Sufficient Evidence of Association; Limited or Suggestive Evidence of Association; Inadequate or Insufficient Evidence to Determine Whether an Association Exists; and Limited or Suggestive Evidence of No Association. VA has established presumptions of service connection for all diseases NAS placed in the first category and for most of the diseases NAS placed in the second category. However, VA will not establish a presumption of service connection for a condition solely on the basis that NAS has placed the condition in one of the two highest categories of association used by NAS. Rather, each condition is considered individually, based on available evidence, and informed by conclusions and recommendations of NAS. The “limited or suggestive evidence” category used by NAS may encompass a potentially wide range of evidentiary circumstances, and NAS’ placement of a disease in that category is not intended to express any view on policy matters or on the outcome of VA’s application of the “positive association” standard prescribed by 38 U.S.C. 1116(b). This notice explains the basis for VA’s determination that no new presumptions of service connection are warranted for the diseases discussed in Update 2012.

Limited or Suggestive Evidence of an Association

NAS has defined this category of association to mean that the “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.”

Hypertension

NAS placed hypertension in the “Limited or Suggestive Evidence of Association” category. Hypertension affects more than 70 million adult Americans and is a major risk factor for coronary artery disease, myocardial infarction, stroke, and heart and renal failure. A recent study of the Framingham cohort (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2004) showed that in both 55 and 65-year-old participants, the cumulative lifetime risk for the development of hypertension (at or above 140/90 mm Hg, regardless of treatment) was 90 percent. The lifetime risk statistic is the probability that an individual will develop a disease over a lifetime. Major risk factors are well established and include tobacco use, diet, physical inactivity, obesity, diabetes mellitus, alcohol, and heredity.

In its reports prior to 2006, NAS placed hypertension in the “Inadequate or Insufficient Evidence” category. In Veterans and Agent Orange: Update 2006 (hereinafter, “Update 2006”), Update 2008, and Update 2010, NAS elevated hypertension to the “Limited or Suggestive Evidence” category, but could not clearly 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, December 27, 2010, and August 10, 2012, VA explained why the studies reviewed in Update 2006, Update 2008, and Update 2010 did not, in VA's view, warrant a presumption of service connection for hypertension in Veterans exposed to herbicides in service. 75 FR 32540 (June 8, 2010), 75 FR 81332 (Dec. 27, 2010), and 77 FR 47924 (Aug. 10, 2012).

NAS identified no Vietnam Veteran studies addressing exposure to the chemicals of interest and hypertension published since Update 2010. One group of researchers performed a retrospective study of outcomes of Vietnam-era South Korean Veterans undergoing coronary angiography because of acute coronary syndrome according to whether they served or did not serve in Vietnam. This study examined whether a history of Vietnam service is associated with the clinical course of coronary disease, not with the occurrence of coronary disease itself. NAS concluded that this study was not helpful in assessing whether herbicide exposure was a factor in the development of hypertension.

Medical research studies related to Agent Orange generally fall into one of three categories – environmental studies, occupational studies, and case-control studies. Environmental studies focus on exposure outside of the workplace (i.e., in the surrounding environment), usually due to an industrial incident or accidental release of Agent Orange or other related chemicals of interest. Occupational studies focus on workplace exposure to Agent Orange or related chemicals of interest. Case-control studies identify individuals with the health outcome of interest (cases) and individuals

without the health outcome (controls), then compare the exposure experience (often self-reported) of the two groups.

NAS did not identify any occupational studies or case-control studies of exposure to chemicals of interest and hypertension published since Update 2010.

In Update 2012, NAS identified three environmental studies published since Update 2010 focusing on environmental exposure to chemicals of interest and hypertension. Researchers reported findings from the cross-sectional sample of residents of Taiwan living in an area with a high level of industrial contamination from various compounds including dioxins, furans, and mercury. This study updated and extended an earlier report discussed in Update 2010. The updated report extended the survey period for an additional 7 months increasing the number of surveyed residents from 1,478 to 1,812. Data were reviewed using factor analysis and multivariate models. Factor analysis was used to determine which components of metabolic syndrome appeared to be most strongly associated with dioxin toxic equivalency concentrations, based on serum dioxin and furan levels. The authors of the study concluded that dioxin toxic equivalencies were more strongly associated with blood pressure than other syndrome components. Based on multivariate analysis, the researchers concluded that there was a highly statistically significant association between toxic equivalency concentrations and diastolic blood pressure but not systolic blood pressure after adjustment for age, sex, obesity, smoking status, alcohol use, and family history of hypertension or diabetes.

NAS considered the strengths and weaknesses of the study. It stated that the strengths of the study are the large number of potential confounding variables

addressed and the clear exposure to the chemicals of interest. The weaknesses are that it is a cross-sectional survey which precludes making a strong causal inference since the temporal relationship between exposure and the outcome is unknown. Additionally, NAS noted that surveys are prone to selection factors that may bias relationships between exposures and outcomes.

Another study examined data on 394 residents of Anniston, Alabama, who were living in an area with high levels of polychlorinated biphenyls (PCB). The purpose of the study was to determine the relationship between blood pressure and serum concentrations of 35 PCBs and nine chlorinated pesticides. Individuals taking antihypertensive medications were excluded from the study. The authors concluded that, other than age, total serum PCB concentrations were the strongest correlate of blood pressure after adjustment for age, body mass index, sex, race, smoking status, and exercise. They saw a weak, not statistically significant, association between blood pressure and mono-ortho PCBs. PCBs with more potent dioxin-like activity were not measurable within the limits of the assay used. NAS concluded that this study shares strengths and weaknesses with the Taiwanese survey, but exposures to chemicals of interest and specifically TCDD were lower in the Alabama sample.

A study examining urinary arsenic concentrations and hypertension in the 2003–2008 National Health and Nutrition Examination Survey showed no statistically significant association. NAS stated that it did not consider this study because the relationship between urinary arsenic and the arsenic-containing chemical that the Veterans were exposed to, cacodylic acid, is unclear.

Based on its analysis of these studies published since Update 2010, NAS concluded that the new relevant data are consistent with a relationship between the chemicals of interest and blood pressure, and continued its placement of hypertension in the limited or suggestive category.

VA has reviewed this additional information in relation to the information in prior NAS reports analyzing studies concerning hypertension. Based on this review, the Secretary has determined that the available evidence is not sufficient to establish a new presumption of service connection for hypertension in Veterans exposed to herbicides. As noted in VA's evaluation of prior NAS reports, 75 FR 32540 (June 8, 2010), 75 FR 81332 (Dec. 27, 2010), and 77 FR 47924 (Aug. 10, 2012), the evidence overall includes a wide variety of results. While some Veteran studies have reported increased incidence of hypertension, others have found no increase. Similarly, numerous environmental and occupational studies have found no significant increased risk of hypertension. Two environmental studies published since Update 2010 examining environmental exposures in Taiwan and Alabama suggested a possible association between serum concentration of dioxin-like compounds and elevated blood pressure. Based on this limited amount of new information, NAS reaffirmed its decision to place hypertension in "limited or suggestive evidence of an association" category. The two studies that provide evidence of an increased risk are limited by the design of the study or the type of assay used to measure exposure. Accordingly, the Secretary has determined that the available evidence does not at this time establish a positive association between herbicide exposure and hypertension that would warrant a presumption of service connection.

Stroke

NAS placed stroke in the “Limited or Suggestive Evidence of Association” category. Stroke is the third leading cause of death and the second leading cause of disability among adults in the United States. The incidence of stroke increases with age and varies according to ethnicity and gender. The cumulative lifetime risk for development of stroke is about 1 in 6 for men and 1 in 5 for women. Black and Latino men are at the highest risk for stroke. The incidence of stroke for people over 75 years of age is more than twice that of people 55-65 years old. Other factors that increase the risk of stroke include: smoking, diabetes, hypertension, and obesity. Based on these factors alone, some members of the aging Vietnam Veteran cohort can be expected to experience stroke in their lifetime. A recently completed 25-year follow up of the National Vietnam Veterans Readjustment Study cohort found a 0.6 percent mortality rate from stroke, a rate which is comparable to that of the U.S. general population experience.

In prior reports NAS placed stroke in the “Inadequate or Insufficient Evidence” category. This determination was made based on its analysis of relevant studies. In Update 2012, NAS identified three new occupational studies and one environmental study addressing exposure to chemicals of interest and stroke.

No Vietnam Veteran studies addressing exposure to the chemicals of interest and cerebrovascular disease and stroke have been published since Update 2010. No case-control studies of exposure to the chemicals of interest and cerebrovascular disease or stroke have been published since Update 2010.

One study reported findings on mortality in 2,122 production workers engaged in the manufacture of PCP in four midwestern plants. PCP contains dioxin and furan contaminants that do not include the most toxic 2,3,7,8-TCDD congener. The cohort was partitioned into a subcohort of 1,402 workers (PCP-only group) who were employed only in production of PCP and a separate subcohort of 720 workers (PCP-plus-TCDD group) who also worked in PCP production and were exposed to TCDD. The cohort was followed through the end of 2005. The authors did not observe an increase in cerebrovascular deaths among the workers compared to the general population. NAS noted that the researchers used the U.S. population as a referent group, which would tend to understate associations because of confounding by the healthy-worker effect.

Another study reported an updated mortality analysis of workers exposed to TCDD at two Dutch chlorophenoxy-herbicide production facilities. Results of that cohort have been included in previous NAS Updates. Workers in plant A were exposed to high concentrations of dioxin both as a contaminant of 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) production and through accidental exposure after the explosion of a kiln. Plant B was involved in 2,4-Dichlorophenoxyacetic acid (2,4-D) production, but TCDD exposure was assumed to be minimal. The study followed all male employees of either factory during their years of operation, which lasted until 1985 for plant A and 1986 for plant B. Mortality was ascertained through the end of 2006. The authors did not observe an increase in cerebrovascular deaths among the workers compared to the general population. NAS concluded that the study has good exposure measurement, using non-exposed workers in the same plants as the referent population, and 39 total

stroke deaths were observed; but no association with cerebrovascular death was observed.

Researchers reported on a 23-year follow up of workers exposed to dioxins in a chemical plant in Hamburg, Germany, that manufactured herbicides and pesticides, including 2,4,5-T. Results on that cohort have been included in previous NAS Updates. The study included 1,191 men and 398 women who were employed full-time at the plant for at least 3 months during 1952–1984. Individual cumulative exposure was estimated from work history on the basis of company records, and the intensity of TCDD exposure in workplaces was based on previous analyses of serum and fat-tissue dioxin concentrations. The authors found a statistically significant higher risk of cerebrovascular-disease mortality than expected in men, but not in women.

NAS relied primarily on the results of research on the PIVUS study in placing stroke in the limited or suggestive category. The PIVUS study recruited participants, within 2 months after their 70th birthdays, randomly from the registry of residents of the community of Uppsala, Sweden, from April 2001 to June 2004. The primary aim was to investigate cardiovascular disease in an elderly population with adjustment for sex. All participants answered a questionnaire about medical history, medication, diet, and smoking habits. The burden of persistent organic pollutants (POPs) including several dioxin-like PCBs, was assessed from blood serum or plasma. The investigators examined the relationship between POPs in 898 70-year-old residents of Uppsala, Sweden, and their incidence of stroke 5 years later. The investigators measured 16 PCBs, Octachlorodibenzodioxin (OCDD), and four other pollutants. Thirty-five participants developed stroke; stroke subtype was not determined. All odds ratios

discussed below were adjusted for gender, body mass index, cigarette smoking, exercise, alcohol consumption, hypertension, diabetes, triglycerides, and serum cholesterol. Plasma concentrations of OCDD and of most PCBs with fewer than seven chlorine atoms were positively related to stroke risk. A total of 35 study participants suffered strokes. Participants in the highest 25th percentile of OCDD had 3.5 times the odds of developing stroke compared with those in the lowest 25th percentile. Both chemicals that had dioxin-like properties and ones that did not were positively associated with stroke. Total toxic equivalencies, however, were strongly associated with stroke risk. Those with toxic equivalencies at or above the 90th percentile had 4.2 times the odds of developing stroke. Stroke risk was also greater in participants that had higher concentrations of chlorine-containing pesticides.

NAS also summarized relevant previous studies that addressed stroke or cerebrovascular disease. It noted that two existing studies found an increased incidence of cerebrovascular mortality in Vietnam Veterans, but neither achieved statistical significance, and one of the studies failed to control for important potential confounders.

NAS discussed an environmental study published in 2008, in which researchers reported on the 25-year mortality experience of residents exposed to dioxin through an accidental industrial release in Seveso, Italy. The mortality from cerebrovascular disease was assessed in residents of areas of high, medium, and low exposure to TCDD compared with residents of non-exposed areas in this region of Italy. Because of the relatively small number of residents in the high-exposure zone and the rarity of stroke, NAS noted that the precision of the estimate for that zone was quite low.

However, the study did show an increase in stroke mortality in medium-exposure and low-exposure zones. NAS concluded that the strengths of the study are the documented exposure to a chemical of interest and measured TCDD concentrations that support the geographic exposure classification. The associations were adjusted for age, sex, and time but were not adjusted for other stroke risk factors.

NAS also discussed a 1998 IARC study, in which researchers pooled data on 36 populations of workers involved in the manufacture of chemicals associated with dioxin contamination. There were 263 stroke deaths among the 21,863 included phenoxy herbicide or chlorophenol workers. Workers who were exposed to dioxin had 54 percent higher cerebrovascular-disease mortality than workers who were not. However, the study's finding was not statistically significant at the 95 percent confidence interval.

NAS reviewed data that updated results from several of the populations included in the IARC report. In addition to the Dutch and Hamburg chemical-worker studies, two articles published before Update 2010 provided updated information on stroke mortality in cohorts that had been included in the IARC analysis. Neither publication reported a significant increase in stroke mortality in exposed workers compared with the general population. None of the studies could adjust for relevant risk factors, such as smoking and body mass index.

VA has reviewed this additional information in relation to the information in prior NAS reports analyzing studies concerning stroke. Based on this review, the Secretary has determined that the available evidence is not sufficient to establish a new presumption of service connection for stroke in Veterans exposed to herbicides. In prior reports NAS placed stroke in the Inadequate or Insufficient Evidence to Determine

Whether an Association Exists category. It moved stroke to the “limited or suggestive” category based largely on the results of the PIVUS study. Although VA agrees with NAS that the PIVUS study is generally well designed, it also has a number of limitations for purposes of evaluating the potential health effects of exposure to herbicides used in Vietnam. As noted by the authors of the study, there were only 35 cases of strokes documented and the confidence intervals were wide, so interpretation of the results should be cautious and associations might be chance findings. NAS noted that follow up for the incidence of stroke was incomplete (about 80 percent), which potentially could bias the results. NAS also noted that the study methodology theoretically could have led to some exposure misclassification. Additionally, the study analyzed nearly 60 data comparisons and, with that large number of comparisons, one would expect at least three to reach statistical significance at the 95 percent confidence level by chance alone.

Conclusions based on the PIVUS study are further limited because the chemicals being measured in the serum levels of PIVUS study participants are not those found in Agent Orange, and there is significant uncertainty as to whether the associations found for the chemicals studied can support any conclusions regarding the health effects of dioxin or other chemicals in herbicides used in Vietnam. The assumption underlying comparison of those chemicals (primarily PCBs) to dioxin is that both are capable of binding to the “Ah” receptor found on the surface of vascular endothelial cells and that this binding can be measured in the form of a total Toxic Equivalency. However, the authors of the PIVUS study noted that their data indicated that the associations found were not clearly related to this dioxin-like activity of the chemicals studied. Thus,

because the associations detected in the PIVUS study were not clearly related to the dioxin-like properties of the chemicals studied, the study has limited value for determining the extent to which dioxin may be associated with stroke.

On consideration of the available scientific and medical evidence, including the PIVUS study, VA has determined that the evidence does not currently establish a positive association between herbicide exposure and stroke. Of the five studies previously identified by NAS relating to stroke or cerebrovascular disease in Vietnam Veterans, only one study published in 1985 showed a statistically significant increase in risk for stroke mortality. However, that study did not control for important potential confounders. Of the 12 relevant occupational studies identified by NAS, only one showed a statistically significant higher risk of cerebrovascular-disease mortality and that finding is limited somewhat by the fact that the increased risk was observed only in exposed men, while no increased risk was observed in exposed women. Thus, most of the relevant studies do not provide statistically significant evidence of an association between exposure to chemicals of interest and stroke, and the few studies that provide such evidence are limited by methodological concerns and other factors as discussed above. Accordingly, the Secretary has determined that the available evidence does not at this time establish a positive association between herbicide exposure and stroke that would warrant a presumption of service connection.

Inadequate or Insufficient Evidence To Determine an Association

NAS has defined this category of association to mean that available epidemiologic studies are of insufficient quality, consistency, or statistical power to

permit a conclusion regarding the presence or absence of an association. For example, these studies may fail to control for confounding factors, have inadequate exposure assessment, or fail to address latency.

Consistent with its findings in Update 2010, NAS in Update 2012, found inadequate or insufficient evidence to determine whether an association exists between herbicide exposure and the following conditions: (1) Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), and nasal cavity (including ears and sinuses); (2) cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs; (3) cancers of the digestive organs (esophageal cancer; stomach cancer; colorectal cancer (including small intestine and anus), hepatobiliary cancers (liver, gallbladder, and bile ducts), and pancreatic cancer); (4) bone and joint cancer; (5) melanoma; (6) nonmelanoma skin cancer (basal cell and squamous cell); (7) breast cancer; (8) cancers of the reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate); (9) urinary bladder cancer; (10) renal cancer (kidney and renal pelvis); (11) cancers of the brain and nervous system (including eye); (12) endocrine cancers (including thyroid and thymus); (13) leukemia (other than all chronic B-cell leukemias including chronic lymphocytic leukemia and hairy cell leukemia); (14) cancers at other and unspecified sites (other than those as to which the Secretary has already established a presumption); (15) reproductive effects (including infertility; spontaneous abortion other than after paternal exposure to TCDD; and—in offspring of exposed people—neonatal death, infant death, stillborn, low birth weight, birth defects [other than spina bifida], and childhood cancer [including acute myeloid leukemia]); (16) neurobehavioral disorders (cognitive and neuropsychiatric);

(17) neurodegenerative diseases (including amyotrophic lateral sclerosis (ALS) but excluding Parkinson's disease); (18) chronic peripheral nervous system disorders (other than early-onset peripheral neuropathy); (19) respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung); (20) gastrointestinal, metabolic, and digestive disorders (including changes in liver enzymes, lipid abnormalities, and ulcers); (21) immune system disorders (immune suppression, allergy, and autoimmunity); (22) circulatory disorders (other than hypertension, ischemic heart disease, and stroke); (23) endometriosis; (24) effects on thyroid homeostasis; (25) hearing loss; (26) eye problems; and (27) bone conditions.

With respect to the 27 categories of disease considered in its prior reports, NAS identified no new Vietnam Veteran studies, occupational studies, environmental studies, or case studies published since Update 2010 addressing the potential relationship between the chemicals of interest and basal cell carcinoma, squamous cell carcinoma, and chronic lymphocytic leukemia. It identified 31 studies published since Update 2010 that addressed the relationship between the chemicals of interest and at least one of the remaining types of cancer listed above. It identified no new Vietnam Veteran studies, occupational studies, environmental studies, or case studies published since Update 2010 addressing the potential relationship between the chemicals of interest and thyroid homeostasis, eye problems, hearing loss, or chronic peripheral nervous system disorders. A total of 27 studies were published since Update 2010 that addressed the relationship between the chemicals of interest and the remaining non-cancer conditions list above. After analyzing the results of research published since the last update, NAS found that the studies published since Update 2010 generally did not contain statistically

significant findings or other significant evidence of association between herbicide exposures and those health outcomes.

In notices following prior NAS reports, cited in section II above, VA has explained the basis for the Secretary's determination that a positive association does not exist between herbicide exposure and the health conditions identified in Update 2012 in the "inadequate or insufficient evidence" category. For the reasons explained above, VA has determined that the additional studies discussed in Update 2012 do not change the Secretary's determination that a positive association does not currently exist between herbicide exposure and those health conditions.

Limited or Suggestive Evidence of No Association

NAS has previously concluded that there is limited or suggestive evidence of no association between paternal herbicide exposure and spontaneous abortion. In Update 2012, NAS identified no new studies relevant to that health outcome. Accordingly, the Secretary has determined that there is no positive association between paternal herbicide exposure and spontaneous abortion.

Detailed information on NAS' findings may be found at <http://www.iom.edu/Reports/2013/Veterans-and-Agent-Orange-Update-2012.aspx>. After selecting the link titled: "Read Report Online for Free," report findings, organized by category, may be found under the heading, "Table of Contents."

Conclusion

After careful review of the findings of the 2012 NAS report, Veterans and Agent Orange: Update 2012, the Secretary has determined that based on the scientific evidence presented in this report and prior NAS reports, no new presumptions of service connection are warranted at this time for any of the conditions discussed in this notice.

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. Jose D. Riojas, Chief of Staff, Department of Veteran Affairs, approved this document on March 25, 2014, for publication.

Dated: April 4, 2014

William F. Russo, Deputy Director
Regulation Policy and Management
Office the General Counsel
Department of Veterans Affairs.

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