

from Centers for Disease Control and Prevention's (CDC's) National Health and Nutrition Examination Surveys and NIH's Longitudinal Investigation of Fertility and the Environment study cohorts. The large body of international work examined included the Danish Fetal Origins 1988–1989 Cohort, Duisburg (Germany) Birth Cohort Study, Hokkaido Study on Environment and Children's Health and its Sapporo companion study, the (Chapaevsk) Russian Children's Study, the Seveso (Italy) Woman's Health Study, and publications concerning populations in Belgium, Brazil, Canada, China, Finland, France, Greece, Hong Kong, Italy, Korea, Nicaragua, Norway, Spain, and Taiwan. Ten newly published studies of birth and other health outcomes in the Vietnamese population were also identified and reviewed.

Case-Control Studies

Several new publications using case-control methodology from the CDC's National Birth Defects Prevention Study were identified for the current update. These included studies of parental exposure to the COIs and spina bifida, congenital heart defects, gastroschisis, and a series of defects including anotia/microtia, anorectal atresia/stenosis, transverse limb deficiency, craniosynostosis, and diaphragmatic hernia in offspring.

A number of case-control studies in various other populations that examined forms of cancer (including cutaneous melanoma, female breast cancer, hepatocellular carcinoma, infiltrating ductal carcinomas, non-Hodgkin lymphoma, pancreatic cancer, prostate cancer, soft tissue sarcoma, and testicular cancer) and other health outcomes including Parkinson disease, amyotrophic lateral sclerosis, and kidney and urinary disorders were also reviewed.

THE COMMITTEE'S CONCLUSIONS

General Observations Regarding Findings

VAO committees classify the evidence regarding exposure to the COIs and health outcomes into four categories: sufficient, limited or suggestive, inadequate or insufficient, and no association. Table S-1 sets forth the criteria for assigning categorizations and summarizes the committee's conclusions, with the changes in classification made since the previous volume (*Update 2014*) indicated in bold-face. The classifications are based on the committee's evaluation of the epidemiologic literature and reflect the committee members' judgement of the relative certainty of the association between the outcome and exposure to the herbicides that were used in Vietnam or to any of their components or contaminants (with no intention of specifying particular chemicals).

The changes and the decisions not to modify other findings from earlier VAO committees were made after the present committee weighed the strengths and

TABLE S-1 Summary of the *Eleventh Biennial Update* Findings on Vietnam-Veteran, Occupational, and Environmental Studies Regarding Scientifically Relevant Associations Between Exposure to Herbicides and Specific Health Outcomes

Sufficient Evidence of an Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.^b For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

- Soft-tissue sarcoma (including heart)
- * Non-Hodgkin lymphoma
- * Chronic lymphocytic leukemia (including hairy cell leukemia and other chronic B-cell leukemias)
- * Hodgkin lymphoma
- Chloracne
- Hypertension** (category change from Limited or Suggestive in *Update 2014*)
- Monoclonal gammopathy of undetermined significance (MGUS)** (newly considered condition)

The committee did not reach consensus on whether the evidence regarding type 2 diabetes (mellitus) was more properly classified as *Sufficient* or *Limited or Suggestive*.

Limited or Suggestive Evidence of an Association

Epidemiologic 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.^b For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

- Laryngeal cancer
- Cancer of the lung, bronchus, or trachea
- Prostate cancer
- Cancer of the urinary bladder
- * Multiple myeloma
- * AL amyloidosis
- Early-onset peripheral neuropathy
- Parkinson disease (including Parkinsonism and Parkinson-like syndromes)
- Porphyria cutanea tarda
- Ischemic heart disease
- Stroke
- Hypothyroidism

The committee did not reach consensus on whether the evidence regarding type 2 diabetes (mellitus) was more properly classified as *Sufficient* or *Limited or Suggestive*.

continued

TABLE S-1 Continued**Inadequate or Insufficient Evidence to Determine an Association**

The 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, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes that were explicitly reviewed:

- 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 in 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 cancers
- Melanoma
- Non-melanoma skin cancer (basal-cell and squamous-cell)
- Breast cancer
- Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
- Renal cancer (kidney and renal pelvis)
- Cancers of brain and nervous system (including eye)
- Endocrine cancers (thyroid, thymus, and other endocrine organs)
- Leukemia (other than chronic lymphocytic leukemia, including hairy-cell leukemia and other chronic B-cell leukemias)
- Other myeloid diseases (including myeloproliferative neoplasms)
- Cancers at other and unspecified sites
- Infertility
- Spontaneous abortion (other than after paternal exposure to TCDD, which appears not to be associated)
- Neonatal or infant death and stillbirth in offspring of exposed people
- Low birth weight in offspring of exposed people
- Birth defects in offspring of exposed people, including spina bifida
- Childhood cancer (including acute myeloid leukemia) or other adverse health outcomes in offspring of exposed people
- Neurobehavioral disorders (cognitive and neuropsychiatric)
- Neurodegenerative diseases, excluding Parkinson disease
- Chronic peripheral nervous system disorders
- Hearing loss
- Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
- Gastrointestinal, metabolic, and digestive disorders (changes in hepatic enzymes, liver disorders including cirrhosis, lipid abnormalities, and ulcers)
- Immune system disorders (immune suppression, allergy, and autoimmunity)
- Circulatory disorders (other than hypertension, ischemic heart disease, and stroke)
- Endometriosis

TABLE S-1 Continued

Disruption of thyroid homeostasis (other than hypothyroidism)
Eye problems
Bone conditions
Kidney and urinary disorders (including chronic kidney disorder, differences in kidney function, nephropathy, and end stage renal disorder)
Chronic skin disorders (including skin infections and changes in skin pigmentation)

The committee used a classification that spans the full array of cancers. However, reviews for non-malignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. By default, any health outcome on which no epidemiologic information has been found falls into this category.

Limited or Suggestive Evidence of No Association

Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to a component of the herbicides of interest and the outcome. A conclusion of “no association” is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. In addition, the possibility of a very small increase in risk at the exposure studied can never be excluded. There is limited or suggestive evidence of no association between exposure to the herbicide components of interest and the following health outcome:

Spontaneous abortion after paternal exposure to TCDD
^a <i>Herbicides</i> indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin (TCDD or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from veteran, occupational, and environmental cohort studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.
^b Evidence of an association is strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.
[*] The committee notes the consistency of these findings with the biologic understanding of the clonal derivation of lymphohematopoietic cancers that is the basis of the World Health Organization classification system (Campo et al., 2011; see table here: www.ncbi.nlm.nih.gov/pmc/articles/PMC3109529/table/T1 , accessed May 17, 2018).

limitations of the epidemiologic evidence reviewed in this report and in previous VAO reports. Although the studies published since *Update 2014* are the subject of detailed evaluation in this report, the committee drew its conclusions in the context of the entire body of literature, and the committee did not weigh new findings more heavily than past research.

As mandated by PL 102-4, the distinctions among categories are based on statistical association and not on strict causality. The committee was directed to review the scientific data, not to recommend VA policy; therefore, the conclusions reported in Table S-1 are not intended to imply or suggest policy decisions. The conclusions are related to the associations between exposure and outcomes in

human populations, not to the likelihood that any individual's health problem is associated with or caused by the herbicides in question.

Hypertension

The committee concluded that the information now assembled constitutes sufficient evidence of an association between exposure to at least one of the COIs and hypertension. The decision to change the classification from limited or suggestive evidence of an association was motivated in large part by the work of Cypel and colleagues (2016). These investigators conducted a study on the population of interest, U.S. Vietnam veterans (specifically, the Army Chemical Corps), that was characterized by a large sample size, appropriate controls, and validated health endpoints. The statistical analyses conducted were robust, used state-of-the-art methods, and adjusted for relevant confounders. The study clearly showed that self-reported hypertension rates were the highest among those military personnel with the greatest opportunity for exposure to the COIs. Among Vietnam-deployed veterans, there was a statistically significantly elevated association between the odds of hypertension for sprayers versus nonsprayers that remained after an adjustment for potential confounders. Similarly, for those veterans who did not deploy to Vietnam, self-reported hypertension was significantly elevated among sprayers compared with nonsprayers. Earlier studies reviewed in previous updates consistently reported increased hypertension with increasing levels of serum dioxin in Vietnam veterans as well as increased prevalence in veterans with higher presumed exposure to the COIs. When considered in light of other new research and earlier studies that demonstrated a consistency in the direction and magnitude of this effect, the committee found that this body of literature constitutes sufficient evidence of an association.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

The committee also concluded that there was sufficient evidence of an association between exposure to at least one of the COIs and MGUS. MGUS is a precursor to multiple myeloma, although only an estimated 1% of MGUS cases progress to multiple myeloma each year. It is a clinically silent condition defined by the presence of a monoclonal antibody, antibody heavy chain, or antibody light chain in the blood or urine of a person lacking symptoms or signs of a more serious plasma cell dyscrasia. The foundation of this finding was a well-conducted study by Landgren and colleagues (2015) that examined data and biospecimens from a population of veterans that included participants with known exposure to herbicides in Vietnam: the Air Force Health Study cohort. The study used previously measured serum levels of TCDD and performed a new assay of serum samples to detect MGUS. Known confounders including age, race, body mass index, smoking and drinking history, and a history of radiation therapy or