

SUMMARY TABLE

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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 Outcomes¹

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.² 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.

¹ *Herbicides* 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-*p*-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.

² 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).

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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.² 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.

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
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

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