

Secretary has found that the credible evidence against an association between herbicide exposure and chronic persistent peripheral neuropathy outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Lipid and Lipoprotein Disorders

Plasma lipid (notably cholesterol) concentrations have been shown to predict cardiovascular disease and are considered fundamental to the underlying atherosclerotic process. The two major types of lipids, cholesterol and triglycerides, are carried in the blood attached to proteins to form lipoproteins. NAS in VAO and subsequent reports found there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and lipid and lipoprotein disorders.

An occupational study of 92 workers at a municipal waste incinerator in Japan included measures of serum polychlorinated dibenzo-p-dioxins (PCDD) and self-reported history of a number of diseases and health-related conditions. (Kitamura K, Kikuchi Y, Watanabe S, *et al.* Health effects of chronic exposure to polychlorinated dibenzo-p-dioxins (PCDD), dibenzofurans (PCDF) and coplanar PCB (Co-PCB) of municipal waste incinerator workers. *Journal of Epidemiology* 2000;10:262–270.) Eight of the 92 subjects reported having been diagnosed with high cholesterol.

NAS noted that this study's contribution to the literature is limited for a number of reasons: the study is cross-sectional, so there is no opportunity to establish that the exposure clearly preceded the outcome; the sample is small; the exposure is an aggregate measure of PCDD (with TCDD as only one component); and the measure of high cholesterol is based solely on self-report. NAS stated that, because of those limitations, the study does not change the inconclusive status of the epidemiologic evidence on the relationship between exposure to herbicides and high serum lipids.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and lipid and lipoprotein disorders outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Gastrointestinal and Digestive Disease, Including Liver Toxicity

Gastrointestinal and digestive disease includes diseases of the esophagus, stomach, intestines, rectum, liver, and pancreas. NAS, in VAO and subsequent reports, found there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and gastrointestinal and digestive disease, including liver toxicity.

An occupational study reported on two cases of heavy TCDD intoxication, and presented a 2-year follow-up. (Geusau A, Abraham K, Geissler K, Sator MO, Stingl G, Tschachler E. 2001. Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication: clinical and laboratory effects. *Environmental Health Perspectives* 109(8):865–869.) One patient, a 30-year-old woman, presented with chloracne and had the highest TCDD concentration ever recorded in a human. The other patient was a 27-year-old woman who worked in the same room as the first patient. Both patients experienced gastrointestinal symptoms, including nausea, vomiting, epigastric pain, and loss of appetite, which lasted about 4 months. Liver function studies were within the normal limits, except for one value in the first patient of alkaline phosphatase at 1.5 times the upper limit of normal. Apart from the chloracne and gastrointestinal symptoms, few clinical signs or symptoms were observed in the acute phase of the intoxication.

In a report evaluating hepatic abnormalities in Vietnam veterans of Operation Ranch Hand, the authors examined exposure to TCDD and the prevalence of liver disease and hepatomegaly through March 1993 in relation to tests of liver function at the 1992 physical examination. (Michalek JE, Ketchum NS, Longnecker MP. 2001. Serum dioxin and hepatic abnormalities in veterans of Operation Ranch Hand. *Annals of Epidemiology* 11(5):304–311.) Hepatomegaly among veterans in the high-exposure category was slightly higher than that in nonexposed veterans in the comparison category. The prevalence of nonspecific liver disorders increased across categories of TCDD exposure and among Ranch Hands in the high-exposure category. The study authors and NAS noted that the significance of those findings may be limited because heightened levels of the enzyme GGT, an abnormality sometimes reported in association with TCDD exposure, may also be caused by alcohol consumption, and the mean GGT in the high-exposure group was significantly increased among veterans

with history of light to moderate drinking. The authors concluded that evidence of clinically significant liver disease was limited to the increase in hepatomegaly, and that the increased GGT could have been due to confounding.

NAS stated that the evaluation of the effects of herbicide exposure on noncancer gastrointestinal ailments is very difficult, due to limitations of medical history and physical examination in diagnosing such ailments and the strong interdependence between individual characteristics of a person and the body burden of TCDD.

NAS concluded that there was no information contained in the research reviewed for Update 2002 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and gastrointestinal and digestive diseases.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and gastrointestinal and digestive disease outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Immune System Disorders

The immune system is responsible for protecting the body against invasion by infectious microorganisms. NAS noted in VAO and subsequent reports that there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and immune system disorders.

No relevant occupational, environmental, or Vietnam-veteran studies were published subsequent to Update 2000.

NAS concluded that there was no information reviewed for Update 2002 to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and immune system disorders.

Taking account of the available evidence and NAS' analysis, the Secretary has found that the credible evidence against an association between immune system disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Circulatory Disorders

NAS noted in VAO and subsequent reports that there was inadequate or