

insufficient information to determine whether an association exists between exposure to herbicides and circulatory disorders.

In Update 2002, NAS noted that there is growing evidence that exposure to inorganic arsenic is a risk factor for cardiovascular disease, and cacodylic acid (DMA) is a metabolite of inorganic arsenic. However, the data remain insufficient to conclude that studies of inorganic arsenic exposure are directly relevant to exposure to cacodylic acid. Therefore, the literature on inorganic arsenic was not considered by NAS.

NAS reviewed an occupational study of mortality in male workers at a Dow chemical plant (Burns *et al.*, 2001). NAS stated that mortality due to circulatory conditions among the workers was similar to that experienced by U.S. white males in general. NAS noted that mortality analyses of other occupational cohorts have tended to find cardiovascular effects among the more highly exposed workers, but that a dose-specific analysis of the data on this outcome was not reported.

A cross-sectional occupational study was conducted in 1998 to assess the association between serum PCDD and a variety of health conditions in a sample of workers employed at a municipal waste incinerator in Japan (Kitamura *et al.*, 2000). Fourteen of the 92 workers participating in the study reported a history of hypertension. No information was provided on the date of this diagnosis relative to dates of employment at the plant. The coefficients for the categories of PCDD were reported as not statistically significant, but the values of the coefficients and their standard errors were not given.

In an environmental study, a survey was administered to 727 adult residents of farming households and 262 residents of nonfarming households. (Masley ML, Semchuk KM, Senthilselvan A, *et al.* Health and environment of rural families: results of a community canvass survey in the Prairie Ecosystem Study. *Journal of Agricultural Safety and Health* 2000;6:103–115.) The survey included questions about the use of pesticides and fertilizers and a number of health conditions and symptoms that might be associated with agricultural exposures. Physician-diagnosed hypertension and heart disease were reported by 154 and 44 survey respondents, respectively. Neither condition was associated with residing on a farm. No information was provided on the validity of measurement of the self-reported health conditions, and the report did not examine more specific

associations with pesticide or fertilizer use.

NAS noted that neither Kitamura *et al.* (2000) nor Masley *et al.* (2000) provided data on validation from medical records or direct measurement of blood pressure, that some misclassification is likely (with false negatives being more common than false positives), and that both studies used nonspecific assessment of exposure. NAS further noted the possibility that the null findings on hypertension in these studies reflect the influence of misclassification that led to bias toward the null.

Mortality from cardiovascular diseases was examined by Revich *et al.* (2001) in their study of multiple health outcomes among the residents of Chapaevsk. The authors reported that mortality from cardiovascular diseases in men was 1.14 times greater than the mortality rate for Russia as a whole, and that the difference in mortality was especially pronounced in men 30 to 49 years old. The authors also noted, however, that trends in mortality were directly related to trends in unemployment, which NAS noted suggests the simultaneous effects of other aspects of the environment in the area.

NAS concluded that there is 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 circulatory disorders.

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

### Respiratory Disorders

The major risk factor for both acute and chronic respiratory disorders is cigarette smoking. Cigarette smoking is a major confounding factor in interpreting the literature on risk factors for respiratory disease. 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 nonmalignant respiratory disorders.

In Update 2002, NAS reviewed an occupational study of a cohort of male employees of the Dow Chemical Company (Burns *et al.*, 2001). No excess

mortality from nonmalignant respiratory disorders was demonstrated.

NAS concluded that there is no information contained in the research reviewed for Update 2002 to change the conclusion that, except for respiratory cancers, there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and respiratory disorders.

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

### Skin Cancer

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 skin cancer. NAS discussed the evidence concerning two categories of skin cancer: Melanoma and nonmelanoma (basal-cell and squamous-cell).

In Update 2002, NAS reviewed an occupational study of mortality in a cohort of male Dow Chemical Company workers (Burns *et al.*, 2001). No deaths due to skin cancer of any type were reported in the study.

NAS also reviewed an occupational study which analyzed cancer incidence and mortality in a cohort of forestry workers in Sweden (Thorn *et al.*, 2000). The observed frequency of cancer was compared with expected values on the basis of data on the population of Sweden. One case of melanocytic skin cancer was recorded in an exposed female worker. Nonmelanocytic skin cancer was diagnosed in one exposed foreman, and in three nonexposed workers. The report found increased risks for both types of skin cancer, but the findings were not statistically significant and were limited by the small number of cases.

An environmental study analyzed cancer incidence and mortality in Chapaevsk, Russia (Revich *et al.*, 2001). Mortality data were not reported for skin cancer. The age-adjusted incidence of melanoma in Chapaevsk relative to the Samara region during 1998 was somewhat lower in men but notably higher in women. The age-adjusted incidence of skin cancers other than melanoma was similar in men and somewhat higher in women. NAS noted that the number of cases was not given, hypothesis testing and interval