

Occupational and Environmental Medicine 58:582–589.) NAS stated that the overall results of this study are similar to those of many other studies reviewed in Update 2000, in which an association with many years of occupational exposure is associated with parkinsonism but no association is found with any individual pesticide or class of pesticides.

NAS also reviewed a prospective cohort study with 30 years of follow up on 7,986 Japanese-American men (Honolulu Heart Program) who worked on sugar cane and pineapple plantations in Hawaii to determine whether working on a plantation or exposure to pesticides is associated with an increased risk of PD. (Petrovich *et al.* (2002, in press).) The study showed that as the duration of work increased, pesticide exposure increased significantly. NAS stated that even though age-adjusted incidence of PD increased with increasing pesticide exposure, the trend was not significant. Those with over 20 years of plantation work had twice the risk of PD of those with no plantation work. With 10 years of plantation work or less, there was no increase in risk of PD, but a significant trend of increased risk occurred with further years of exposure.

NAS noted that an association of PD with exposure to 2,4-D, 2,4,5-T, or TCDD is not reported in any of the studies.

Based on the totality of the evidence, NAS concluded that there remains inadequate or insufficient evidence of an association between exposure to herbicides and PD.

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

Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive motor neuron disease with adult onset that presents with muscle atrophy, weaknesses, and fasciculations. The incidence of ALS peaks between the ages of 55 to 75 years. Known risk factors for ALS are age and a family history of ALS. Interest in the role of occupational or environmental exposure originated in cases of motor neuron disease associated with exposure to heavy metals, chemical plants, animal carcasses, heavy manual labor, work with electricity, pneumatic tools, work in the plastic industry, and work as a truck driver.

In Update 2002, NAS summarized the results of five epidemiologic studies of pesticide exposure and ALS. One study found the association between pesticides and ALS was not statistically significant but was positive. (Deapen DM, Henderson BE. 1986. A case-control study of amyotrophic lateral sclerosis. *American Journal of Epidemiology* 123:790–799.) In another study, no statistically significant associations were found between ALS and several risk factors, including agricultural chemicals and organic solvents, although there was a positive association between ALS and agricultural chemicals. (Savettieri G, Salemi G, Arcara A, Cassata M, Castiglione MG, Fierro B. 1991. A case-control study of amyotrophic lateral sclerosis. *Neuroepidemiology* 10:242–245.)

A case-control epidemiologic study in Scotland of 103 ALS cases from a Scottish motor neuron disease register and 103 age- and sex-matched controls identified risk factors for development of the disease. (Chancellor AM, Slattery JM, Fraser H. 1993. Risk factors for motor neuron disease: A case-control study based on patients from the Scottish motor neuron disease register. *Journal of Neurology, Neurosurgery, and Psychiatry* 56:1200–1206.) Significant differences with increased exposure in cases were found for occupational exposure to lead and "solvent/chemicals." NAS noted that occupational pesticide exposure was not significantly different but did have a positive association.

The results of a mortality study of male employees of the Dow Chemical Company (Burns *et al.*, 2001) showed three deaths due to ALS. The study found a significantly increased relative risk of death due to ALS. All three died more than 20 years after their first exposure; duration of employment was 1.3, 1.8, and 12.5 years.

A population-based case-control epidemiologic study was conducted to examine the relationship between ALS and occupational exposures to metals, solvents, and agricultural chemicals. (McGuire V, Longstreth WT, Nelson LM, Koepsell TD, Checkoway H, Morgan MS, van Belle G. 1997. Occupational exposure and amyotrophic lateral sclerosis: A population-based case-control study. *American Journal of Epidemiology* 145:1076–1088.) Exposure to metals and solvents was not associated with ALS. Association between exposure to agricultural chemicals and ALS was observed in men. Exposure to specific agricultural chemicals, such as herbicides, did not pose a significantly increased risk of

ALS. Excess exposure to agricultural chemicals from accidents or spills was associated with ALS, but this accounted for six cases and only three controls. NAS noted that the careful attention to exposure assessment in this study makes the association between agricultural chemicals and ALS intriguing, but that there are few exposed subjects and further studies are needed.

NAS concluded that there is inadequate or insufficient evidence of an association between exposure to herbicides and motor neuron disease or ALS.

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

Chronic Persistent Peripheral Neuropathy

NAS noted in VAO and subsequent reports that there was inadequate or insufficient evidence of an association between exposure to herbicides and chronic persistent peripheral neuropathy.

A publication relating serum TCDD and peripheral neuropathy from the 1982, 1985, 1987, 1992, and 1997 examinations of the Ranch Hand study found significantly increased risk of peripheral neuropathy among Ranch Hand veterans in the high-exposure category in 1997. (Michalek JE, Akhtar FZ, Arezzo JC, Garabrant DH, Albers JW. 2001. Serum dioxin and peripheral neuropathy in veterans of operation ranch hand. *Neurotoxicology* 22:479–490.) NAS noted a major problem in the interpretation of TCDD effects on the peripheral nerves in light of the presence of diabetes and preclinical diabetes in the majority of the cases identified. NAS also noted that the cases of probable and possible peripheral neuropathy were identified for the first time in 1992 and 1997, with prior examinations being normal. NAS determined that these findings weakened the ability to implicate TCDD exposure as the etiologic agent given that the peripheral nerve is known to repair itself after cessation of exposure or after diminution of the body burden of the responsible toxicant.

NAS concluded that there remains inadequate or insufficient evidence of an association between exposure to herbicides and chronic persistent peripheral neuropathy.

Taking account of the available evidence and NAS' analysis, the