

exposure to Alzheimer's disease have been derived from several epidemiological studies of aluminum in drinking water, which represents only a small percentage of the total exposure. They concluded that quantification of the risk of Alzheimer's disease from other sources of aluminum (such as food additives, cosmetics, deodorants, antiperspirants, pharmaceuticals, and respiratory dusts) is needed before the total risk from all environmental sources of aluminum can be fully evaluated.

Despite Graves et al.'s acknowledgment of the limitations of their study (Ref. 37), other authors, e.g., Anane et al. (Ref. 45), report that Graves et al. found an increased risk of Alzheimer's disease with lifetime use of aluminum-containing antiperspirants after an epidemiological study. Anane et al. applied low aqueous concentrations (0.025 to 0.1 micrograms (μ g)/square centimeter) of aluminum chloride ($\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$) to healthy shaved Swiss mouse skin for 130 days. They reported that this led to a significant increase in urine, serum, and whole brain aluminum, especially in the hippocampus area, compared to control animals. They mentioned that this percutaneous uptake and accumulation of aluminum in the brain was greater than that caused by dietary exposure to 2.3 μ g per day in feed and water.

Anane et al. conducted in vitro and in vivo mouse skin studies and showed for the first time that aluminum is absorbed through mouse skin and this contributes to a greater body burden than does oral uptake. They also mentioned that several antiperspirant preparations containing $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ are applied to sensitive regions of the skin, which may increase penetration and could be an important source of body aluminum burden. Anane et al. recommended that an epidemiological study be conducted to ascertain whether use of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ -containing antiperspirants correlates with neurodegenerative disease, because such cannot be excluded based on the results of their study.

Forbes and Agwani (Ref. 46) stated that there is uncertainty about how aluminum-containing substances enter the body, but current information suggests that the skin and/or the lung are important. They mentioned that Priest (Ref. 39) noted that at least some antiperspirant sprays contain aluminum compounds of a particle size of about 1 micrometer (micron) (μ), which is ideally sized for deposition in the deep lung, and that such deposition may also be relevant for skin.

Salib and Hillier (Ref. 47) examined clinically diagnosed Alzheimer's disease patients and controls (other

dementias and nondementias) and collected information to examine the association between Alzheimer's disease and aluminum occupation. They reported that manual work, such as welding, expected to be in direct contact with aluminum dust and fumes does not appear to be significantly associated with the risk of Alzheimer's disease. The authors concluded that no significant association was shown between developing Alzheimer's disease later in life and previous occupational history for all of the occupations in the study. This included both manual workers, who would be expected to have had a higher exposure opportunity to aluminum dust and fumes, and other workers at an aluminum factory. The authors concluded that neither Alzheimer's disease nor dementia in general were shown to be associated with previous aluminum occupation.

Salib and Hillier (Ref. 47), in 1996, repeated Doll's (Ref. 48) conclusions from 1993 that it is generally accepted that the delayed effects of chronic aluminum exposure have not been adequately assessed in man. Factors that govern the bioavailability, neurotoxicity, and the effect of chronic low dose exposure to aluminum compounds remain unclear. Flaten et al. (Ref. 49) stated that the lack of a readily available radioactive isotope of aluminum has been a major obstacle toward elucidating the mechanisms of absorption, distribution, and excretion of the metal.

Both Doll (Ref. 48) and Salib and Hillier (Ref. 47) stated that the possibility of a causal link between aluminum and Alzheimer's disease must be kept open until uncertainty about neuropathological evidence is resolved and the prognosis of humans exposed to aluminum by inhalation is known. Flaten et al. (Ref. 49) stated that multidisciplinary collaborative research efforts, involving scientists from many different specialties, are needed, with emphasis placed on: (1) Increasing knowledge of the chemistry of aluminum in biologic systems and determining the cellular and molecular mechanisms of aluminum toxicity, and (2) variations in neuropathology from long-term, low-level exposure to aluminum.

In summary, the literature shows that at high doses and long-term industrial exposures, aluminum can be associated with recognizable, specific neurologic effects. However, to date, the agency considers the evidence insufficient to link aluminum to Alzheimer's disease, Parkinson's disease, or ALS. Although aluminum uptake and transport by a "nasal-olfactory pathway" has been

suggested in a nonphysiologic study in an animal model (Ref. 36), the agency is not aware of any evidence in humans that supports an olfactory-neuronal transport of aluminum to the brain.

One petition suggested that the agency require that 90 percent of the particles of an aerosol aluminum antiperspirant be greater than 50 μ (currently the requirement is between 10 and 50 μ) to reduce exposure to the upper respiratory tract. The agency notes that both Priest (Ref. 39) and Forbes and Agwani (Ref. 46) discussed a particle size of 1 μ for deposition in the deep lung. Based on current knowledge (no proof in humans of an olfactory neuronal transport of aluminum to the brain) and the lack of information on a minimum particle size to affect the respiratory tract, the agency finds no basis to impose a greater than 50 μ requirement at this time. Flaten et al. (Ref. 49) stated that the possible human toxicity of aluminum has been a matter of controversy for well over 100 years. Despite many investigators looking at this issue, the agency does not find data from topical and inhalation chronic exposure animal and human studies submitted to date sufficient to change the monograph status of aluminum containing antiperspirants. The agency will continue to monitor the scientific literature on aluminum and, if new information appears, will reassess the status of aluminum-containing antiperspirants at such time.

The agency acknowledges that small amounts of aluminum can be absorbed from the gastrointestinal tract and through the skin. Assuming a person has normal renal function, accumulation of aluminum resulting from usual exposures to antiperspirant drug products (application to the underarms once or twice daily) and subsequent absorption is considered minimal. However, people with renal dysfunction have an impairment in normal renal excretion of aluminum.

Flaten et al. (Ref. 49) noted that the first human conditions generally accepted to be causally related to aluminum exposure did not occur until the 1970's, shortly after the introduction of routine dialysis therapy in persons with chronic renal failure. Dialysis encephalopathy was perhaps the first disease recognized in this population (1972, 1976). Later, fracturing osteomalacia (1977, 1978) and a microcytic hypochromic anemia (1980) were related to aluminum exposure in dialysis patients. Flaten et al. indicated that aluminum can cause encephalopathy, bone disease, and anemia in dialysis patients resulting