

where it remains and accumulates. The petition cited a study by Perl and Good (Ref. 33) that suggested that inhaled aluminum compounds could have a direct nasal-olfactory pathway to the brain. The other petition contended that two inhalation studies (Refs. 34 and 35) provided by industry showed aluminum absorption in the peribronchial lymph nodes, brain, and adrenal glands of the animals after 12 and 24 months. Both petitions expressed concern about the potential neurotoxicity of aluminum upon chronic use, especially a possible link to Alzheimer's disease.

The comment that disagreed with one petition contended that the majority of the petitioner's references described findings from in vitro studies that did not consider the blood-brain barrier, which is the brain's main defense against potentially toxic substances such as aluminum. The comment contended that extraordinarily high concentrations of aluminum were used in these studies, and that aluminum from antiperspirants would never reach a biologically significant level to be of concern. The comment stated that the majority of researchers investigating the etiology of Alzheimer's disease would consider current evidence insufficient to link aluminum to Alzheimer's disease. The comment concluded that current scientific information does not support the need to reclassify the safety of aluminum-containing antiperspirants.

The agency does not find the current evidence sufficient to conclude that aluminum from antiperspirant use results in Alzheimer's disease. Both petitions mention the widely quoted study by Perl and Good (Ref. 33) as showing that inhaled aluminum compounds may get directly into the brain by a nasal-olfactory pathway. The agency does not consider this animal study (published as a one-page Letter to the Editor in *Lancet*) as adequate to establish a direct nasal-olfactory pathway for aluminum. This study was only a small pilot animal study, about which the agency has a number of concerns.

First, the method of introducing the aluminum to these animals was not physiologically relevant. Two strips of Gelfoam (absorbable gelatin sponge, USP) saturated with high concentrations of aluminum salts (15 percent aluminum lactate or 5 percent aluminum chloride) were inserted into rabbits' left nasal recess through a hole drilled into the frontal bone. While the authors attempted to demonstrate the accessibility of aluminum from the nasal recess to the brain, the agency questions whether the normal use of antiperspirant aerosols would ever

produce a high aluminum concentration in this relatively distant anatomic site. Second, the size of this study was very small (only three rabbits in each group). The agency is concerned that any error in this complicated surgical procedure to introduce the aluminum salts or in preparing the specimens for analysis could have caused a major difference in the final results. Third, the results were not consistent. Of the three animals exposed to aluminum lactate, besides the involvement of the left olfactory bulb and the cerebral cortex, only one rabbit had a lesion in the hippocampus while the other two rabbits had granulomas found in the pyriform cortex. In the group exposed to aluminum chloride, only one rabbit had a granuloma in the olfactory bulb while the other two rabbits were free of lesions. The distribution of lesions in this study was fairly random. If a nasal-olfactory pathway exists for neuronal aluminum transport, the agency believes that the distribution of these lesions should follow a more persistent anatomical pattern. In addition, the authors were unable to explain why two of the six rabbits were free of lesions. Finally, although some of the rabbits had granulomas, these lesions did not resemble the plaques or neurofibrillary tangles found in Alzheimer's disease, and none of the rabbits had any symptomatic neurologic deficit. While this study implied that access to the brain via the nasal recess may be possible under nonphysiological conditions, a direct nasal-olfactory pathway and any relationship to Alzheimer's disease cannot be established. Several other studies, which were not done with aluminum, are of no value in establishing a direct nasal-central nervous system pathway for aluminum antiperspirants.

Aluminum lactate, one aluminum salt used in this study (Ref. 33), is not included in this final monograph. Sodium aluminum lactate has been used as a buffer for aluminum sulfate in a nonaerosol dosage form, but that product is nonmonograph.

In one of the inhalation studies (Ref. 34), the life-span of the male hamsters exposed to the aluminum chlorhydrate aerosol was shorter (583 days) than that of the controls (661 days). The female hamsters exposed to aluminum chlorhydrate had a slightly longer life-span (489 days) than the controls (481 days). Male hamsters exposed to aluminum chlorhydrate coated with a high concentration of isopropyl myristate, an emollient frequently used to increase the retention on the skin of the aluminum salts used in antiperspirant products, had a life-span

(646 days) comparable to the controls (661 days). Overall, these numbers do not follow a consistent pattern and could be affected by other experimental conditions.

The same petition criticized the other inhalation study (Ref. 35), contending that the results showed that the animals had suffered significant weight loss and increased terminal brain-to-body weight ratios, results it considered consistent with clinical aluminum toxicity, and that the increase in brain weight was possibly due to cerebral edema. The petition claimed that because aluminum was found to be deposited in the animals' brains, peribronchial lymph nodes, and adrenal glands, this proved that systemic absorption of aluminum had occurred and that aluminum had been transported to the brain. Other comments disagreed with the petition's argument that the rats in this study were found to have detectable aluminum levels in their brains after 12 months, contending that this finding may only be artificial considering the analytical methods used. The comments added that if aluminum did accumulate in the rats' brains, those rats should have had symptoms of neurotoxicity, which they did not have. The comments concluded that the artificial finding should be ignored.

The agency does not concur with the petition's extrapolations. The weight loss occurred only in rats and not in guinea pigs that were similarly treated. The increase in terminal brain-to-body weight ratio occurred only in the female rats at 12 months in the low- and high-dose groups. The female rats in the middle-dose group and all the males were not affected. At 24 months, this same ratio was found to increase only in the high-dose groups of both sexes; however, the increase in the female high-dose group was not statistically significant. The agency notes that all of these findings did not follow any predictable pattern or a pattern that would be expected from a dose-related or cumulative toxin exposure.

The pattern of deposition was not consistent. In the guinea pigs, aluminum was found in the peribronchial lymph nodes, but not in the adrenal glands and brains (as occurred in the rats). The agency finds it possible that aluminum absorption and deposition may be animal dependent. If this were the case, then even if the rat data were evidence of a problem, the same situation may not apply to humans. The agency is not aware of other investigators having similar results.

The petitions and the comment had different views on a study by Rollin,