

Theodorou, and Kilroe-Smith (Ref. 36) in which rabbits were exposed to aluminum oxide dust for 8 hours a day, 5 days a week, for 5 months. The authors of the study found that the brains of these rabbits had a significant increase in aluminum at the end of the study. The first petition contended that this study showed that the inhalation of aluminum antiperspirants poses a special risk because this route of delivery bypasses the blood-brain barrier. The comment calculated that this study would be equivalent to a person using spray antiperspirants for approximately 10 seconds daily for 789 years to experience the same toxicity. The second petition contended that this 10-seconds-exposure assumption was incorrect because the aluminum particles in an antiperspirant aerosol remain suspended in the air for a long period of time, and the exposure will be more than the comment calculated.

The agency finds this study has a number of limitations: (1) The extraordinary high concentrations of aluminum oxide exposure in the animals, (2) the small sample size (eight animals in each group), and (3) an overlap in the standard deviations of the results obtained decreases the power and generalizability of the study. While the study shows an accumulation of aluminum in the rabbits' body tissues under certain exposure conditions, the agency does not consider the study as providing evidence of a direct nasal-olfactory pathway or that normal use of aluminum-containing antiperspirants would provide comparable results. Further, the second petition's position includes a number of assumptions, which might not occur: (1) That the place where the product is used is a confined, poor-ventilated airspace, and (2) that the user remains in the vicinity of the dispersed aerosol for a period of time during which significant inhalation would occur.

One petition claimed that an epidemiology study by Graves et al. (Ref. 37) has shown that Alzheimer's disease was associated with the use of aluminum antiperspirants and that a high incidence of amyotrophic lateral sclerosis (ALS) and Parkinson's disease in Chamorro natives of Guam, as reported by Garruto (Ref. 38), may be related to high environmental aluminum. The agency has looked closely at the Graves et al. study (Ref. 37) because it explored the association between exposure to aluminum through the lifetime use of antiperspirants and antacids and Alzheimer's disease. This was a case-control study of 130 matched pairs, where the controls were friends or nonblood relatives of the case. Subjects

(cases and controls) were matched by age, sex, and the relationship between the case/control and his or her surrogate (spouse or child).

The authors mentioned that, in general, antiperspirants contain aluminum and deodorants do not, except for some deodorants marketed for women. The authors reported that there was no association between the use of "any" antiperspirant/deodorant and Alzheimer's disease. However, when the data were stratified by aluminum-containing antiperspirants the overall odds ratio showed a modest increase in risk and a statistically significant trend emerged between increasing lifetime use of aluminum-containing antiperspirants and the estimated relative risk of Alzheimer's disease.

The authors commented that, to their knowledge, this was the first epidemiological study of this association between antiperspirants and Alzheimer's disease, and there were several methodologic limitations that made interpretation of their results difficult. First, there were missing data because the case surrogate and the control surrogate could only recall all variables (frequency and duration of use, and product brand name) in about one-half of the matched pairs. Second, there might have been some misclassification because the analyses were based on the most common brand provided, while some subjects may have used multiple brands. Third, the authors considered the validity of the data, resulting from difficulty in learning the subjects' exposure using telephone interview methods, to be a critical limitation. Despite these limitations, the authors considered an association between aluminum-containing antiperspirants and Alzheimer's disease as biologically plausible, but concluded that their findings are provocative and, due to methodologic problems, should be considered preliminary.

Garruto (Ref. 38) described efforts to establish models of chronic motor neuron degeneration in a long-term effort to understand the cellular and molecular mechanisms of aluminum neurotoxicity. He studied foci of dementia (ALS and Parkinson's disease) in western Pacific populations. He mentioned experimental models in rabbits and cell culture as demonstrating that chronic, rather than acute, toxicity is the cause of human neurodegenerative disorders with a long latency and slow progression. However, Garruto stated that he and his colleagues had been most deficient in the design and implementation of good epidemiological studies, particularly of

Alzheimer's disease and the epidemiology of aluminum intoxication per se, and described what he felt was needed for future well-designed studies.

The petitions/comment also discussed environmental exposure to aluminum, percutaneous absorption after topical use, inhaled absorption after aerosol use, aluminum neurotoxicity (and a possible relationship to Alzheimer's disease), and possible mechanisms of action. Numerous references were provided. The agency has reviewed these references and other literature published on aluminum since the petitions were submitted. Many early references were simply hypotheses and different theories that have not been adequately substantiated in humans or any animal models. A number of studies were pilot projects in a few animals, and the agency is unable to draw any definite conclusions based on the small sample sizes.

The agency notes Priest's (Ref. 39) statement that most investigators now agree that aluminum is unlikely to be implicated in causing Alzheimer's disease, whereas Rowan (Ref. 40) contended it would be considerably more correct to state that the issue is controversial. More recently, Savory et al. (Ref. 41) stated that the question whether aluminum presents a health hazard to humans as a contributing factor to Alzheimer's disease is still subject to debate.

The agency finds the literature shows the issue of aluminum toxicity and Alzheimer's disease remains controversial and is not resolved. Scott et al. (Ref. 42) reported that aluminum has been detected in Alzheimer neurofibrillary tangles, but the significance of its presence is unknown. Kasa, Szerdahelyi, and Wisniewski (Ref. 43) reported that histochemical staining showed that aluminum was present in brain samples from Alzheimer's disease victims, but the structural localization indicated that it is not primarily involved in the etiology of the disease. Candy et al. (Ref. 44) reported that data from post mortem brain examinations of patients with chronic renal failure who did not have dialysis encephalopathy suggest that it is unlikely that aluminum plays any major role in neurofibrillary tangle formation and that its role in senile plaque formation is likely to be only part of a complex cascade of changes. Savory et al. (Ref. 41) stated that the lack of agreement on the question whether the brain content of aluminum is increased in Alzheimer's disease attests to the complexity of the issue.

Savory et al. (Ref. 41) indicated that most of the data linking aluminum