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UNITED STATES ARMY VETERINARY COMMAND
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REPLY TO:
ATTENTION OF:
MCVS-LAB

December 18, 2001

Dockets Management Branch
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

Dear FDA:

I am submitting this cover letter to provide additional information for the petition that I forwarded to your office on December, 3rd, 2001. The following is provided IAW CFR Section 10.30 (b).

- A. *Action Requested.* Stated in manuscript.
- B. *Statement of Grounds.* Stated in manuscript.
- C. *Environmental Impact.* None anticipated.
- D. *Economic Impact.* This issue is addressed within the manuscript. No significant adverse economic impact is anticipated.
- E. *Certification.* The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

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MCVS-LAB

December 3, 2001

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Dear FDA:

I am writing to petition the FDA to rescind the Generally Recognized As Safe (GRAS) status for aluminum-containing food additives, specifically sodium aluminum sulfates, sodium aluminum phosphates and aluminum sulfates. The grounds for this petition are the series of epidemiological studies linking dietary aluminum with risk of Alzheimer's disease (AD) plus numerous pathological findings of concentrations of aluminum within the lesions of Alzheimer's victims. These studies are described below.

Alzheimer's victims have pathological changes in the brain termed neurofibrillary tangles and senile plaques. The fine filaments of neuronal cells literally become tangled like mats of hair and deposits of a strange protein named beta amyloid form into plaques. These lesions are pathognomonic for AD. If an elderly person has symptoms of dementia and is subsequently found to have tangles and plaques upon histopathological examination, the diagnosis is AD.

In 1980, concentrations of aluminum were identified within the neurofibrillary tangle-bearing neurons of AD victims (reference 1). A few years later, aluminosilicate deposits were also found at the cores of senile plaques (ref 2). The location of these aluminosilicate aggregates at the centers of the plaques suggested that they may be the initiating factors. Further, quantification of aluminum levels in whole brains of AD patients indicated that they had 10x the amount of unaffected controls (ref 3).

It was known at the time that intracerebral injections of aluminum salts induced neurofibrillary tangle formation in several species of laboratory animals, notably rabbits (ref 4). Intravenous injection of aluminum had the same effect (ref 5).

In light of these findings, numerous investigators initiated studies to seek an association between aluminum exposure and incidence of AD in people. Most of these focused upon retrospective comparisons of AD risk between those who consumed aluminum-containing antacids versus cohorts who did not. Superficially, this appeared to be an ideal model for assessment of aluminum exposure because those who frequently ingested aluminum-containing antacids would consume hundreds of times more of the element than those who did not. Dozens of such studies were conducted throughout the

1980s but no association between aluminum-containing antacid use and AD risk could be found.

Concurrently, the initial reports of aluminum concentrations within tangle-bearing neurons and senile plaques were also being challenged. Several follow-up studies failed to find aluminum deposits within plaques or tangles. Others suggested that the aluminum in the lesions were attributable to aluminosilicate contaminants in the staining materials used to prepare the samples. In response to this, additional studies were done using methods that did not employ staining materials. Several investigators again identified aluminum aggregates within AD lesions using these methods while others could not.

In light of all of this, the NIH and the Alzheimer's Assn decided that the negative findings of the epidemiological studies and the inconsistent results of the bioassay research were sufficient evidence to conclude that aluminum was not a causal factor for AD. Many investigators felt that the aluminum concentrations within AD brains were indeed present but were the result of Alzheimer's degenerative process rather than an initiating factor. This line of reasoning implies that the damaged membranes and devitalized tissues within a diseased brain allowed aluminum to accumulate but that its presence had no significance in the pathogenesis of AD. Accordingly, circa 1990 the NIH and AA decided to discontinue funding for all aluminum-AD research. This policy currently remains in effect.

However, at about that same time some epidemiologists began evaluating AD risk to types of aluminum exposure other than antacids. Graves et al (abstract is enclosure A) sought to identify an association between AD risk and lifetime use of aluminum-containing antiperspirants or aluminum-containing antacids. The antacid findings were negative, but for antiperspirants they found an odds ratio of 1.6: 1 (95% confidence interval) with a trend for higher disease risk with increased use. For the tertile of the population with the history of highest usage, the odds ratio was 3.2: 1. These findings were quite provocative, but no follow-up study was done. Graves et al is the only epidemiological study that has been performed that assesses AD risk among users of aluminum-containing antiperspirants

From the period of 1989-2000, a series of epidemiological studies identified correlations between aluminum levels in community drinking water supplies and AD risk in the local populations (examples are ref 6 and enclosures B thru F). Summarizing their findings, nine out of 13 published studies identified statically significant positive associations (encl G). Collectively these studies make a compelling case that waterborne aluminum induces or actively contributes to the development of AD.

The problem with these drinking water studies is that they defy logic. In developed societies, two-thirds of dietary aluminum is from food additives and most of the remainder is attributable to natural levels of aluminum in foods. Thus even in those areas with the highest levels of aluminum in the water supply the contribution of waterborne aluminum to total intake is trivial, e.g., 0.5 mg/day via water versus 7-9 mg/day in foods (ref 7).

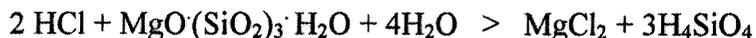
Since the majority of dietary aluminum is from food additives, the most appropriate epidemiological model would seem to be a study of foodborne aluminum intake and risk of AD. A preliminary study of this type was published by Rogers and Simon in 1999 (the entire publication is enclosure H). This investigation was small in scope – 23 cohort pairs – and was intended to determine if a trend was apparent rather than attain statistical significance.

Rogers and Simon found an odds ratio of 8.6: 1 (81% confidence interval) for intake of foods with high levels of aluminum among AD cases versus controls. This trend was most pronounced for the food group that contains the highest level of aluminum per serving, that being pancakes, biscuits, cornbread and other grain products that contain aluminum leavening agents. The trend for AD risk was so pronounced for this food group that statistical significance was obtained despite the small sample size (odds ratio infinite, 97.5% confidence interval). This preliminary study is the only epidemiological study of aluminum levels in food and AD risk that has been performed.

Overall, these aluminum-AD studies appear to be contradictory and mutual resolution seems impossible. The dozens of consistently negative antacid studies make a strong case that aluminum is not causal for AD. While most of the drinking water studies yield positive findings, their credibility is suspect due to the low dietary contribution of waterborne aluminum. The two studies suggesting that aluminum in antiperspirants and in food additives will predispose AD are provocative but neither has had any follow-up work to corroborate or refute their initial findings.

I believe that this paradox can be explained by considering the role of silicon in aluminum-containing antacid products and in drinking water. I'll address antacids first.

During the 1960-1980 era, most aluminum-containing antacid products were formulated using both aluminum hydroxide and magnesium trisilicate. This combination was popular because the laxative properties of the former countered the constipating tendencies of the latter and both compounds neutralized stomach acid. When magnesium trisilicate reacts with stomach acid it is converted to silicic acid, H_4SiO_4 :



Silicic acid is water soluble (it is the only water-soluble form of silicon) and it combines aggressively with solubilized aluminum. Aluminum absorption from the gut virtually ceases in the presence of silicic acid because these two compounds readily combine to form insoluble aluminosilicates. The propensity with which aluminosilicates form under these conditions is remarkable. These reactants bond with greater affinity than any other chemical reaction in all on inorganic chemistry (ref 8). Once formed into aluminosilicates, neither the aluminum nor the silicon is bioavailable. Studies have confirmed that the absorption of aluminum is greatly diminished when silicon coexists in the gut (refs 9, enclosure I).

Hence not only was the aluminum contained within the antacids unavailable for absorption but the silicic acid would also bind aluminum from food in the gut. It is quite likely that those who consumed aluminum-containing antacids during this era actually had a good deal less bioavailable aluminum than non-users due to the frequent co-formulation with magnesium trisilicate. Indeed, the Graves et al study (encl A) found that those who consumed aluminum-containing antacids had a lesser risk of AD than non-users (odds ratio 0.7:1, 95% confidence interval).

Another consideration regarding the antacid studies is that aluminum is absorbed only through the gastric mucosa and only in the completely ionized Al^{+++} form. This completely ionized ion can exist only when the pH of the solution is 3 or lower. However, a single dose of any commercial antacid product typically raises the pH of the gastric contents to the 4-5 range, thereby immediately creating an environment in which the aluminum cannot be absorbed. Thus the bioavailability of aluminum in antacid products is inversely proportional to dosage: The more that is consumed, the higher the pH and the bioavailability of gastric aluminum diminishes accordingly.

Thus there are two well established physio-pharmacological rationales why these antacid-Alzheimer's epidemiological studies are hopelessly confounded. The methodology of these studies was fundamentally flawed and their findings are meaningless.

Regarding the drinking water studies, in water there is a highly significant inverse relationship between aluminum levels and silicon levels (enclosure J). As discussed in enclosures I and J, this provides the most logical explanation for the link between aluminum levels in water and risk of AD. Water is a trivial source of aluminum but is the primary source of soluble silicon. Therefore high levels of waterborne silicon will diminish the bioavailability of aluminum from not only drinking water but also from all other dietary sources.

There is a study that appears to confirm that waterborne silica is indeed protective against AD. Published in 2000, an epidemiological study by Rondeau et al (the entire publication is encl K) identified not only a direct relationship between waterborne aluminum and AD (odds ratio 2.14:1, 95% confidence interval) but also found an inverse correlation between silica levels in drinking water and AD risk (odds ratio 0.74:1, 95% confidence interval). This finding also supports the thesis that silicon compounds formulated into antacid products were responsible for the inverse association between use of aluminum-containing antacids and AD incidence.

Historically, aluminum-containing leavening agents became commercially available after the Civil War and came into common usage by the end of the nineteenth century (ref 11). The appearance of these additives in the food supply coincides well with the first report of AD in 1906 and this may not be a coincidence. The symptoms of the disease are so distinct that we have little difficulty diagnosing it in millions of Americans, including celebrity figures such as Ronald Reagan, Rita Hayworth, Barry Goldwater, Burgess Meredith and Sugar Ray Robinson. AD is now the third leading

cause of death in our society behind cardiovascular disease and cancer. However, there is not a single presumptive case of AD known prior to the twentieth century. We know the circumstances surrounding the deaths of many people throughout history before 1900, not only through historical records about numerous kings, queens, popes, presidents, generals, authors, artists and other notables, but also through letters, diaries, family records and hospital records of countless millions of common people. In the entire history of mankind, we cannot identify even one person with symptoms that were suggestive of AD prior to the introduction of aluminum-containing food additives.

In light of this, the potential for aluminum-containing food additives to be causal or contributory factors for AD clearly deserves further examination. Aluminum-containing additives were in common usage before there was an FDA and the GRAS status of these agents is a result of "grandfathering". And even if toxicity testing were to be performed on these aluminum compounds, the types of routine studies required by the FDA to approve food additives would clearly not be appropriate for the unique pathology of AD.

The information that I am presenting in this correspondence is not intended to establish proof that aluminum exposure is the cause of AD. The etiology of this disease remains unknown. But there is now compelling evidence that dietary aluminum in some way contributes to the development of AD. In consideration that AD is now nearly epidemic in America and its incidence continues to climb, the GRAS status of aluminum-containing food additives begs reconsideration. It is obviously in the best interests of the public's health to err on the side of caution until biomedical research can confidently demonstrate that these food additives pose no significant risk.

Respectfully submitted,

A handwritten signature in cursive script that reads "Colin C Meyer". The signature is written in black ink and is positioned above the typed name and title.

Colin Meyer, DVM, PhD
Colonel, US Army
Director

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