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W. Ted Brown, M.D., Ph.D., Director

April 13, 2006

Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
Documents Management Branch
5630 Fishers Lane, Room 1061
Rockville, Maryland, 20857

**RE: Petition to rescind the "generally recognized as safe"
or GRAS status for aluminum based food additives**

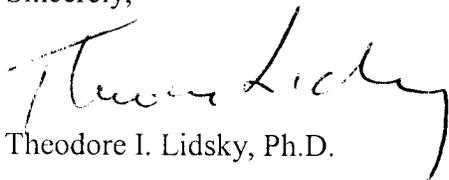
Dear Dr. von Eschenbach:

Enclosed is a document that responds to the petition of 09/14/05 by Mr. Erik Jansson to rescind the FDA's "Generally Recognized As Safe" (GRAS) status for food additives that contain aluminum.

The enclosed was originally sent on February 15, 2006 but was inadvertently dated 2005. The enclosed is the corrected statement.

My apologies for any inconvenience caused by my error.

Sincerely,



Theodore I. Lidsky, Ph.D.

2005P-0377

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CR 1



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W. Ted Brown, M.D., Ph.D., Director

February 15, 2006

Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
Documents Management Branch
5630 Fishers Lane, Room 1061
Rockville, Maryland, 20857

**RE: Petition to rescind the “generally recognized as safe”
or GRAS status for aluminum based food additives**

Dear Dr. von Eschenbach:

This document responds to the petition of 09/14/05 by Mr. Erik Jansson to rescind the FDA’s “Generally Recognized As Safe” (GRAS) status for food additives that contain aluminum. In support of his petition, Mr. Jansson asserts several points based on the scientific literature *viz*:

1. Aluminum is a “neurotoxic metal ‘beyond any doubt.’”
2. Aluminum is specifically elevated in the blood and brain of patients with Alzheimer’s disease
3. Epidemiological studies of water intake show increased risk of Alzheimer’s disease with increased aluminum intake
4. A study of food additives shows increased risk of Alzheimer’s disease with increased aluminum intake
5. Chelation therapy to remove brain aluminum has been found to be an effective way to slow Alzheimer’s disease progression

The first point raised by Mr. Jansson is true but irrelevant. For a neurotoxin to pose a public health risk, it must be able to access the brain at toxic concentrations; aluminum though neurotoxic lacks bioavailability. Mr. Jansson’s other assertions are simply incorrect - aluminum is not specifically elevated in the blood and brain of patients with Alzheimer’s disease and intake, either via drinking water or food additives, has not been shown to be related to increased risk of Alzheimer’s disease. The single study that suggests treating Alzheimer’s by chelating aluminum is so methodologically flawed as to be uninterpretable.

It is my opinion that Mr. Jansson’s petition is based on a review of selected citations of outdated scientific literature, and that erroneous conclusions are advanced based on an incomplete understanding of even those publications. Following is a response that is organized into 2 general sections. The first (pgs. 2 - 6) is a detailed discussion of the specifics of the petition in which the critical points raised by Mr. Jansson are addressed. Following the point by point response is a discussion of Mr. Jansson’s general contention that aluminum has a causative role in Alzheimer’s disease (pgs. 6 - 11).

Discussion of Critical Points Raised in Mr. Jansson's Petition

1. Aluminum is a “neurotoxic metal ‘beyond any doubt.’”

It has been known since 1897 that aluminum (Al) is neurotoxic (Dollken, 1897). Exploration of the mechanisms of aluminum's neurotoxicity have identified a concatenation of adverse effects of aluminum including influences on DNA, apoptosis and necrosis (e.g. Flaten, 2001). Clinical findings have shown that when aluminum enters the brain in sufficiently high concentration in humans it can cause a variety of neurological symptoms and in some cases death (e.g. Alfrey et al, 1976; Bolla et al, 1992).

Thus, Mr. Jansson's assertion that “Aluminum is a ‘neurotoxic metal beyond any doubt’” is not news and is not in any dispute. However, whether or not that neurotoxicity is a potential risk to people depends on its bioavailability particularly to central nervous system tissue. Recent studies (Priest, 2005) show that “...some aluminium is retained in the body-most probably within the skeleton, and that some deposits in the brain. However, most aluminium that enters the blood is excreted in urine within a few days or weeks and **the gastrointestinal tract provides an effective barrier to aluminium uptake.**” [*emphasis added*] The latter is particularly relevant to the present petition since it discusses aluminum that could only enter via the gastrointestinal tract.

2. Aluminum is specifically elevated in the blood and brain of patients with Alzheimer's disease

Initial reports that the bulk concentration of aluminum was elevated in the brains' of patients with Alzheimer's disease (Crapper & Dalton, 1973) suggested that this metal was involved in the etiology and/or progression of the disorder. However, the studies that followed this initial study were contradictory and led to no unequivocal statement concerning the putative bulk elevation of aluminum. For example while some investigators found elevated aluminum in some regions of the Alzheimer's brain (Trapp et al, 1978; Yoshimasu et al, 1980; Krishnan et al, 1987; Ward and Mason, 1987; Xu et al, 1992, Asndrasi et al, 2005), several studies failed to replicate these findings (McDermott et al, 1979; Markesberry et al, 1981; Traub et al, 1981, Jacobs et al, 1989). In related work, several studies found no specific elevation of aluminum in cerebrospinal fluid of patients with Alzheimer's disease (Hershey et al., 1983; Shore & Wyatt, 1983,; Pailler et al., 1995). The presence of these negative findings has to be given serious consideration for two important reasons. First, negative findings are more difficult to publish and, to make it through editorial review, are typically quite solid methodologically. Second, Bjertness et(1997) have pointed out that measurements made with neutron activation analysis, the technique used to measure aluminum in two of the studies reporting elevated concentrations (Yoshimasu et al, 1980; Ward and Mason, 1987) are subject to contamination by phosphorus. This point is particularly relevant since the authors of these studies (Yoshimasu et al, 1980; Ward and Mason, 1987) did not indicate that they had taken appropriate precautions to ensure accurate measurement.

In general, studies of aluminum concentration in Alzheimer's patients have been criticized for “...methodological problems such as inadequate neuropathological assessment of the AD (*Alzheimer's disease*) and/or control patients, with risks of misclassifications; lack of

appropriately age-matched control patients; too few cases analyzed, leading to risk of type II errors; and lack of geographical homogeneity of the AD and control populations, resulting in a selection bias due to possible differences in aluminum exposure.” (Bjertness et al, 1997). In the most recent investigation of this question, efforts were made to correct the methodological inadequacies of the previous studies concerning selection of controls, sampling bias, aluminum exposure, and Alzheimer’s diagnosis (Bjertness et al, 1997). Aluminum measurements were made with graphite furnace atomic absorption in frontal and temporal cortex, areas most heavily involved in Alzheimer’s pathology. The authors reported that their data “...show conclusively that in AD, bulk aluminum concentration is not increased in two cortical brain regions that are selectively vulnerable to the neuropathological changes associated with this disorder.”

While Alzheimer’s disease does not appear to be reliably associated with bulk aluminum elevations in brain, the picture is less clear concerning more localized accumulations. Although several investigators have reported aluminum concentrated in the neuritic plaques of Alzheimer’s disease (Candy et al, 1986; McLachlan, 1986), the preponderance of reports fail to find such accumulations (reviewed in Kasa et al, 1995). In contrast, there is much more convincing evidence that aluminum is found, along with iron, in Alzheimer’s neurofibrillary tangles (see Perl & Good, 1992).

When increased concentrations of any substance are found in the diseased brain, there is always a question of whether that abnormality is the cause of disease or a consequence. This question is particularly important in Alzheimer’s disease. The normal protection of the brain to neurotoxins, the blood brain barrier, is compromised by amyloid in Alzheimer’s disease (Kalaria, 2003; Zlokovic, 2005). For this reason the presence of aluminum in tangles, plaques or the brain in general does not indicate whether the accumulation is a cause or an effect of the Alzheimer’s disease process. Indeed, the fact that co-concentrations of aluminum and iron are also found in tangles associated with a host of other neurodegenerative diseases, including those in which aluminum clearly plays no etiological role (e.g. dementia pugilistica - Bouras et al, 1997) favors the latter interpretation. Indeed, in dementia pugilistica, the tangles contain higher concentrations of aluminum than do the tangles in the brains of patient’s with Alzheimer’s disease (Bouras et al, 1997). It should be noted that the Alzheimer’s brain also has increased concentrations of copper and zinc (Bush 2003), metals that can also be neurotoxic. Further, iron, copper and zinc concentrations increase in the early phases of Alzheimer’s disease while aluminum increases, when detected, only occur well after the disease process is ongoing (Gupta et al., 2005).

3. Epidemiological studies of water intake show increased risk of Alzheimer’s disease with increased aluminum intake

Mr. Jansson notes “...that there are 22 drinking water epidemiology studies linking aluminum, and factors affecting aluminum absorption such as water pH, silicon and fluoride, to increased rates of either elderly mental impairment or AD.” However, since this number includes multiple studies of the same cohorts by the same groups of investigators, it is more accurate to note, as pointed out by Flaten (2001), that the number of independent drinking water epidemiology studies is smaller. Flaten discussed 13 investigations in 2001 and an additional study (Gillette-Guyonnet et al., 2005) is discussed below.

Of the 13 sets of studies discussed by Flaten, 9 showed a significant association between aluminum intake and increased risk of Alzheimer's disease while 4 did not. However, among the 9 studies showing increased risk, 1 was in fact not reported as a peer-reviewed paper but was only as a brief note in a letter (Neri & Hewitt, 1991). Further, another of the 9 studies was contradicted by the authors' follow-up research. Martyn et al's first study (1989) concerned the risk of AD as a function of Al concentrations in drinking water. A case-control study was conducted in eight regions of England and Wales as a follow-up of an earlier investigation in which these same authors found that risk varied among populations according to the aluminum concentration in their water supplies. A subsequent confirmatory study was deemed necessary due to weaknesses in the initial investigation including inadequate estimation of aluminum exposure. This second study, improved through the incorporation of important methodological changes, contradicted the earlier report and found no evidence of increased risk of AD according to aluminum concentration in the water supply (Martyn et al., 1997).

Since Flaten's review was published, an additional investigation was published concerning this issue. The authors concluded that their analysis "did not show any evidence for aluminum as a risk factor for AD..." (Gillette-Guyonnet et al., 2005). Thus taken together there are 7 studies indicating a significant association between aluminum intake and increased risk of Alzheimer's disease and 5 that do not show such an association.

In addition to the obvious lack of agreement of the epidemiological studies of aluminum in drinking water and Alzheimer's risk, there are also reasons that negative findings in this context should be given considerable weight in considering aluminum's possible role in Alzheimer's disease. Epidemiologist Sir Richard Doll (1993) has stated: "Not only is it more difficult to get negative results published than positive ones, but negative results are discouraging to the investigators, who may fail to complete the study or to write it up." "...it is possible that preliminary results of long-term studies have been reported when they accorded with an association which would not have been published if they did not."

In evaluating the evidence provided by the epidemiological drinking water studies, the comments of V. Rondeau (2002) are notable. Dr. Rondeau is one of the authors of an 8 year follow-up of a French cohort whose results are counted among those showing a significant association between aluminum intake and increased risk of Alzheimer's disease. Dr. Rondeau concluded "...that not enough epidemiological evidence supports a link between aluminum in drinking water and AD."

4. A study of food additives shows increased risk of Alzheimer's disease with increased aluminum intake

Mr. Jansson relies on a study by Rogers and Simon study in which it was reported that "past consumption of foods containing large amounts of aluminium additives differed between people with Alzheimer's disease and controls, suggesting that dietary intake of aluminium may affect the risk of developing this disease." However, this research has serious methodological and conceptual weaknesses. It is critical that any epidemiological study intended to evaluate the role of an environmentally available agent such as aluminum in the development of Alzheimer's disease accurately determine the extent of exposure and also to focus on the appropriate period of

exposure. The present study suffers from deficiencies in both areas, faults that are so egregious as to render the author's results uninterpretable and their conclusions unsupported.

The first weakness of the Rogers and Simon study concerns the accuracy of the data with respect to the degree of exposure. Rogers and Simon used surrogate informants for exposure information. "Spouses or daughters were interviewed..." and "...asked to recall usual dietary intake for the 5 years before the onset of Alzheimer's disease for cases and for the same 5 year period for the matched control." Long term recall concerning innocuous events in one's own life are well known to be notoriously inaccurate; it can hardly be expected that the precision of memories concerning such events in someone else's life would be any better.

The second difficulty concerns the period of exposure upon which Rogers and Simon focused their attention. If, as in the present study, a putative role in etiology is at issue, it is critical to have accurate exposure data for the period preceding the onset of the disease; effects of exposure after disease onset may be relevant to questions of disease progression but are immaterial to conclusions about causality. The authors state that efforts were made to determine "...usual dietary intake for the 5 years before the onset of Alzheimer's disease for cases and for the same 5 year period for the matched control." However, onset of disease was defined as date on which the definitive diagnosis of Alzheimer's disease was made. It is therefore noteworthy that the appearance of symptoms sufficient to warrant a diagnosis of Alzheimer's disease occur long after the beginning of the disease process and at a much earlier time point than 5 years before symptoms are noticed. The most authoritative work has been done by Braak and Braak (1998) who concluded that "...decades elapse between the beginning of histologically verifiable lesions and phases of the disorder in which the damage is extensive enough for clinical symptoms to become apparent..." Accordingly, the period of exposure studied in the Rogers and Simon study corresponded to a point well after the onset of Alzheimer's disease in the study group cases. Thus, even if the serious concerns regarding accuracy could be addressed, the results of this study provide no information whatsoever concerning aluminum's putative role in the initiation of Alzheimer's disease.

5. Chelation therapy to remove brain aluminum has been found to be an effective way to slow Alzheimer's disease progression

Mr. Jansson asserts that chelation therapy to remove brain aluminum has been found to be an effective way to slow Alzheimer's disease progression. If this was true, one wonders why this treatment is not routinely administered to the millions of patients with Alzheimer's disease. Indeed, the study on which Mr. Jansson relies for his optimistic view was published 15 years ago. Clearly, if chelation therapy was shown to be an effective treatment, one would think that by now chelation would be the treatment of choice; the fact that it is not an approved treatment is telling.

In 1991, McLachlan and associates reported that desferrioxamine (DFO), a trivalent chelating agent, significantly slowed the progression of AD. Since the analysis of the brains of DFO-treated patients who died during the study indicated that chelation lowered cortical aluminum concentrations without affecting iron, manganese, and copper, the authors opined that the "...therapeutic effect of DFO is likely due to the lowering of aluminum concentration in brain

rather than some other effect.” (McLachlan et al., 1993) However, a number of methodological and interpretational difficulties render the implications of this study much less clear than is implied by the McLachlan et al’s sanguine conclusion.

Although DFO was administered to patients in a trial that was described as both single-blind and also placebo controlled, examination of the methodology reveals that the study was neither. DFO was injected intramuscularly twice daily while controls received either oral lecithin once daily or no treatment. Clearly, neither non-DFO group was comparable to the treatment group and therefore there was no acceptable control group to evaluate possible placebo effects. Moreover, if placebo effects reflect the degree of patient manipulation, such influences would be greater with the twice daily injection received by patients in the treatment group. Furthermore, the likelihood of a placebo effect was also increased since the DFO-treated patients (and their care givers) were told about the nature of their treatment. The unblinding of the treated patients, in addition to increasing the possibility of non-specific effects, also destroyed the single blind design of the trial. Specifically, the administrators of the behavioral assessment (the primary outcome measure of the trial) were testing individuals who knew if they were being treated with DFO. Thus, the test administrator may well have known the nature of the treatment of the subject who was being assessed.

In addition, it is unclear if DFO’s actions were confined to effects on aluminum, the post-mortem findings notwithstanding. DFO removes other trivalent cations including physiologically important iron. Iron mediates the formation of neurotoxic hydroxyl radicals; DFO’s lack of effect on bulk iron levels does not preclude redistribution on a cellular or subcellular level. DFO also has anti-inflammatory effects, both through influences on iron and also via other biological pathways (Hirschelmann et al., 1986; Morgan et al., 1986) Anti-inflammatory agents have been demonstrated to have a beneficial effect on persons with AD. That chelation can have positive effects on the brain apart from any influences on aluminum is illustrated in a recent experiment assessing recovery from traumatic brain injury in rats (Long et al., 1996). Those animals submitted to a controlled cortical impact that also received DFO showed significantly better spatial memory performance than similarly injured animals that received only saline injection.

Does Aluminum Have a Causative Role in Alzheimer’s Disease?

In 1965 Sir Austin Bradford Hill proposed criteria for determining whether there was persuasive scientific evidence that influences from occupation and lifestyle have a causative role in a variety of diseases. Since then, these criteria have been widely accepted as the standard for determining causation particularly with respect to epidemiological findings. Although Dr. Hill outlined 9 criteria, the following subset has been identified as “necessary criteria” to establish causation with respect to neurocognitive disorders such as Alzheimer’s disease (van Reeekum et al., 2001): 1) a strong association between the causative agent and the outcome, 2) consistency of findings, 3) appropriate temporal sequence of exposure to agent and outcome and 4) biological plausibility. Each of these criteria are discussed with respect to aluminum’s putative causative role in Alzheimer’s disease.

Strong association between the causative agent and the outcome: Examination of the neuropathological and neuropsychological findings from patients with longstanding abnormal elevations of brain aluminum indicates that there is no strong association between aluminum exposure and Alzheimer's risk. Since the primary route for eliminating ingested aluminum is through the kidneys, some patients with renal insufficiency who are exposed to high levels of dietary aluminum and aluminum-containing phosphate binders, accumulate this metal in their brains. Since the brain aluminum concentration of these patients is well above normal and remains elevated over a long time span (i.e. years), consideration of the neuropathological sequelae and clinical sequelae in such patients is very relevant to the question of aluminum's involvement in AD.

The neuropathological hallmarks of AD are intraneuronal neurofibrillary tangles, extracellular β -amyloid plaques, amyloid angiopathy and neuronal loss. Do patients with long standing renal insufficiency and increased aluminum intake show more AD pathology than age matched controls? The brains of 50 such patients were evaluated in a recent study (Reusche et al., 2001). The median duration of chronic renal failure was 9.8 years (range 7 months to 30 years) and that treatment via hemodialysis, 3.2 years (range 1 months to 14.9 years). Changes characteristic of aluminum exposure were "...lysosome-derived intracytoplasmic, aluminum-containing, pathognomonic, argyrophilic inclusions in choroid plexus, epithelia, cortical glia and neurons." The degree of morphological change increased with increasing aluminum intake. In contrast, AD-like lesions were not associated with aluminum exposure and the authors concluded that, in their "experience, aluminum does not cause an increase in AD morphology, at least not in terms of bioavailable aluminum in drugs or as a result of long-term..." hemodialysis.

Bolla and her colleagues evaluated the neurocognitive functioning of dialysis patients with increased body burden of aluminum but without symptoms of dialysis encephalopathy (Bolla et al., 1992). Increasing aluminum levels were associated with increasing impairment of visual memory. In addition, in those patients with lower premorbid levels of intellectual functioning, attention/concentration functioning also declined with increasing aluminum levels while these cognitive functions were unaffected in patients with higher premorbid levels of intellectual functioning. A clinical picture similar to that of AD was not observed.

Consistency of findings: A hallmark of the epidemiological literature concerning aluminum exposure and risk of Alzheimer's is inconsistency. Not only is there lack of agreement between studies conducted by different investigators, there is also lack of consistency between findings reported by the same investigators. In addition to the contradictory results reported by Martyn et al (1989, 1997) already discussed, another important series of epidemiological papers shows similar inconsistency. Rifat et al studied miners from northern Ontario who were exposed to aluminum as part of a prophylactic program against silicotic lung disease. These individuals inhaled air containing a dust (McIntyre Powder) said to be composed of 15% elemental aluminum and 85% aluminum oxide (20,000-34,000 ppm) for 10 minutes preceding each work shift. This program began in 1944 and was ended in 1979 based on the conclusion of a medical panel that the conditions in mines had changed such that silicosis risk had declined to the extent that prophylaxis was no longer necessary. The Ontario Ministry of Labor, in 1987, commissioned studies of miners who had been exposed to McIntyre Powder to determine if there was any long-

term negative impact on health. In their initial study, Rifat et al (1990) reported that, although there was no increased incidence of neurological disorders in exposed miners, a higher proportion showed cognitive impairment than did the control group of unexposed miners. However, there were significant methodological concerns that were prompted by the cross-sectional design of the study, sampling procedures and statistical analysis. Consequently, the investigators designed a more comprehensive assessment incorporating methodological changes that corrected the weaknesses of the initial study. In contrast to their earlier findings, this follow-up investigation revealed no statistically significant differences between exposed and non-exposed miners with respect to neurological disease or cognitive impairment.

Appropriate temporal sequence of exposure to agent and outcome: It is critical that an epidemiological study intended to evaluate the role of an environmentally available agent such as aluminum in the development of Alzheimer's disease focus on the exposure of the study group during a time period appropriate to the established natural history of the disease. If, as in the Mr. Jansson's petition, a putative role in etiology is at issue, it is critical to have accurate exposure data for the period preceding the onset of the disease; effects of exposure after disease onset may be relevant to questions of disease progression but are immaterial to conclusions about causality.

The cognitive symptoms that result in a diagnosis of Alzheimer's disease occur long after the beginning of the disease process. The most authoritative work has been done by Braak and Braak (1998) who concluded that "...decades elapse between the beginning of histologically verifiable lesions and phases of the disorder in which the damage is extensive enough for clinical symptoms to become apparent..." Accordingly, the period of exposure studied in the majority of epidemiological studies of drinking water, ≤ 10 years preceding diagnosis, corresponds to a point in time well after the onset of the disease. Thus, the results of these studies are irrelevant to any questions concerning aluminum's putative role in the initiation of Alzheimer's disease.

Biological plausibility: In order for any agent to be considered to have a role in the cause of a disease, there must be evidence of its involvement in that disorder's pathological mechanisms. In the case of Alzheimer's disease, the pathognomonic features are neurofibrillary tangles and amyloid plaques. The latter are particularly important and it is widely thought that an error in the processing of amyloid precursor protein (the amyloid cascade hypothesis) is one of the initiating steps in the etiology of this disorder (e.g. Munoz & Feldman, 2000; Mattson, 2004; Rosenberg, 2005; Churcher & Behr 2005; Lemper 2005). Although there certainly has been no shortage of *in vitro* and *in vivo* studies of aluminum's neurotoxic mechanisms, **there is not a single extant paper showing that aluminum causes or contributes to the production of either neurofibrillary tangles or amyloid plaques of the type seen in Alzheimer's disease.**

Although aluminum does produce neurofibrillary changes in the brain of the rabbit, these tangles are unequivocally qualitatively different from those associated with Alzheimer's disease. As reviewed in Wisniewski and Wen (1992) under light microscopy with silver staining, aluminum-induced tangles and AD pathology appear similar. However, only AD tangles show strong fluorescence when stained with thioflavin-S and bi-refringence associated with a β -pleated sheet after staining with Congo red. Aluminum-induced tangles differ from those of AD in their distribution on both gross and ultrastructural levels. While both types of tangle are found in the

cortex and hippocampus, only aluminum-induced pathology is also found in the spinal cord. Indeed, with aluminum-induced tangles, the spinal burden appears to exceed that of the brain itself. Within single neurons, aluminum-induced tangles are found in the perikaryon and the proximal parts of the dendrites and axon. In contrast, AD tangles are found throughout the neuron including the entire length of the dendrites and throughout the axons including the terminals. Aluminum-induced tangles are made up of straight 10nm diameter neurofilaments while AD tangles are 20-24 nm paired helical filaments. The protofilament building blocks of aluminum-tangles also differ from those of AD with the diameter of the former $\approx 20\text{\AA}$ and the latter $\approx 32\text{\AA}$. The peptide composition of Al-induced tangles is chiefly neurofilament protein while AD paired helical filaments are composed primarily of hyperphosphorylated tau, a microtubule associated protein, and ubiquitin. Although a few investigators have reported that tau is also found in the aluminum-induced tangles of rabbits (Savory et al., 1995; Singer et al., 1996), it should be noted that the majority of investigators fail to confirm the presence of tau (Bergholf et al., 1989; Kowall et al., 1989; Johnson et al., 1992, Strong et al., 1992) and that those who do find this protein report that it is primarily in unphosphorylated form (Singer et al., 1997). Accordingly, aluminum-induced tangles fail to react with the 5-25 monoclonal antibody to AD tangles (Grundke-Iqbal et al., 1985). The similarities and differences between Al-induced tangles in rabbits and the neurofibrillary lesions of AD are summarized in Table 1.

Alzheimer's plaques are neuritic and composed of extracellular deposits of fibrils and amorphous aggregates of amyloid β -peptide resulting from aberrant processing of amyloid precursor protein (Mattson, 2004). "Starting in the 5th decade of life progressively greater proportions of individuals develop cortical senile plaques, until the 8th decade when approximately 75% of the population is so affected. The fact that the density of senile plaques does not increase with age suggests that brains switch from plaque-free to plaque-bearing status in a short period of time; the mechanism responsible for this change is unknown. Plaques start as innocuous deposits of nonaggregated, putatively non-neurotoxic β -amyloid (diffuse plaques). However, in some individuals they undergo an orderly sequential transformation into the mature senile neuritic plaques that are associated with the development of AD." (Munoz & Feldman, 2000). It has never been demonstrated that aluminum can initiate or even potentiate the formation of Alzheimer's-like plaques (e.g. neuritic, fibrillar plaques with β -pleated sheet configuration).

In recognition of this problem, Mr Jansson suggests that it is wrong to focus on plaques in Alzheimer's disease and further reports that "There is a open and growing vocal dispute in the scientific community about the importance of plaque deposits in AD..." Perhaps Mr. Jansson should share this insight with the numerous investigators who are actually researching the causes and possible treatment for Alzheimer's disease, the federal government that funds research projects in these areas and the drug companies that have invested considerable resources in developing treatments based on the central role that abnormal processing of amyloid precursor protein plays in Alzheimer's disease. A Medline search for articles in which the keywords amyloid and Alzheimer appear reveals a total of 8,801 with more than 700 such papers in the last 12 months alone. It is also noteworthy that if the keyword aluminum is added to the search, there were only 2 such papers in the last 12 months.

Mr. Jansson avers that such reactions as oxidative stress with cell loss are a far better focus than

plaque formation apparently unaware that these pathologic effects are in fact caused by abnormal amyloid processing. "Central to the disease is altered proteolytic processing of the amyloid precursor protein...resulting in the production and aggregation of neurotoxic forms of A β . Neurons that degenerate in AD exhibit oxidative damage, impaired energy metabolism and perturbed cellular calcium homeostasis; A β appears to be an important instigator of these abnormalities." (Mattson, 2004)

Tangle Characteristics	Aluminum-Induced	AD
Protein Composition	Neurofilament	Tau
Configuration	Single, Straight Filaments	Paired Helical Filaments
Diameter	10nM	20-24nM
Building Blocks	2.0 nM Protofilaments	3.2 nM Protofilaments
Intraneuronal Localization	Cell Body, Proximal Portion of Dendrites and Axons	Entire Neuron
Regional Localization	Forebrain, Spinal Cord	Forebrain
Reaction to Congo Red	No Reaction	Bi-Refringence
Reaction to Thioflavin-S	No Reaction	Fluorescence

Table 1: Characteristics of tangles associated with Al in rabbits and AD.

In summary, consideration of the published research concerning aluminum's role in Alzheimer's disease indicates that not 1 of the 4 Bradford Hill criteria deemed necessary to establish causation with respect to neurocognitive disorders such as Alzheimer's disease (van Reeekum et al., 2001) has been satisfied.

Mr. Jansson's concerns about the dangers of dietary aluminum are heavily grounded in the aluminum hypothesis of Alzheimer's disease. Although never a major theory of Alzheimer's disease, the aluminum hypothesis was initially deemed worthy of investigation and it has received a fair and thorough evaluation by scientists. Consideration of the research findings in this area indicate that the scientific community, with the exception of a diminishingly tiny minority of researchers, has found the aluminum hypothesis to be wanting and have relegated it to the scientific pale. The decreasing interest in the role of aluminum in Alzheimer's disease is based on a large body of solid scientific investigation that simply does not support the hypothesis. "Mainstream science has long ago left behind the Aluminum Hypothesis, which is generally considered to be a fringe theory. It is noteworthy that papers supporting the Aluminum Hypothesis are conspicuously absent at meetings of the Society for Neuroscience or American Association of Neuropathologists, and likewise constitute a marginal fraction of peer-reviewed publications." (Munoz, 1998) Just how few scientists have any interest in aluminum with respect

to Alzheimer's disease or any other aspect of brain function is illustrated by Table 2 which lists the number of presentations at the Society for Neuroscience Meetings since 2000 that investigated Alzheimer's disease, amyloid and aluminum.

Table 2 Abstracts at Society for Neuroscience Meetings

KEYWORD	2000	2001	2002	2003	2004	2005
Alzheimer	588	631	516	659	635	683
Amyloid	275	429	341	463	400	486
Aluminum	4	6	2	3	1	3

These numbers have meaning; researchers choose to work in areas where the existing scientific literature suggests that their efforts have a reasonable probability of bearing fruit. The lack of scientific interest in aluminum's role in AD indicates that this research area is widely considered to be without merit. It is my opinion that Mr. Jansson's petition is similarly without merit.

Sincerely,



Theodore I. Lidsky, Ph.D.

Center for Trace Element Studies and Environmental Neurotoxicology

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