

INSTITUTE FOR BASIC RESEARCH IN DEVELOPMENTAL DISABILITIES

1050 FOREST HILL ROAD
STATEN ISLAND, NEW YORK 10314-6399
(718) 494-0600 / FAX (718) 698-3803

W. TED BROWN., M.D., PH.D., INTERIM DIRECTOR
PETER M. VIETZE, PH.D., DEPUTY DIRECTOR



417
117
April 11, 2002

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

RE: 02P-0013

Dear Hearing Clerk:

This document responds to the petition of 12/03/01 by Dr. Colin Meyer to rescind the FDA's "Generally Recognized As Safe" (GRAS) status for food additives that contain aluminum. In support of his petition, Dr. Meyer asserts several points based on the scientific literature. These are the following, presented in order of their appearance in his petition:¹

1. *"...concentrations of aluminum were identified within the neurofibrillary tangle-bearing neurons of AD victims..."*
2. *"...aluminosilicate deposits were also found at the core of senile plaques..."*
3. *"...intracerebral injections of aluminum salts induced neurofibrillary tangle formation in several species of laboratory animals, notably rabbits...Intravenous injection of aluminum had the same effect."*
4. Based upon epidemiological work, *"...there is now compelling evidence that dietary aluminum in some way contributes to the development of AD.*
5. *"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."*

It is my opinion that Dr. Meyer's petition is based on a review of outdated scientific literature and that erroneous conclusions are advanced based on an incomplete consideration of even the older publications. Each of the points raised by Dr. Meyer is addressed in the discussion that

¹Verbatim citations of Dr. Meyer's statements are italicized and set off in quotes.

02P-0013

CI

follows (*vide infra*).

1. *"...concentrations of aluminum were identified within the neurofibrillary tangle-bearing neurons of AD victims..."*

There have been reports that there are increased concentrations of aluminum (Al) localized in the neurofibrillary tangles of AD patients⁽¹⁾. Although there have been some contradictory findings as well, the weight of current evidence suggests that the association of Al with tangles is a valid finding⁽²⁾. However the presence of Al in tangles does not indicate whether the accumulation is a cause or an effect of neurodegeneration. The blood-brain barrier, that under normal conditions restricts access to the brain from the systemic circulation, breaks down in AD patients. The conclusion that the neurodegenerative process causes Al to collect in neurofibrillary tangles rather than the converse is based on the following. Neurofibrillary tangles are not unique to AD but are found in a host of other neurodegenerative diseases. For example, the brains of patients with dementia pugilistica (punch drunk syndrome) are riddled with neurofibrillary tangles. This disorder is caused by repeated head trauma and variables associated with the "dose" of head injuries (e.g. number of bouts, age at retirement) as well as genetics (APOE status) are the identified risk factors⁽³⁾. Although it would be quite a stretch to suggest that Al plays an etiological role in dementia pugilistica, the neurofibrillary tangles of these patients concentrate Al⁽⁴⁾. It should be noted that neurofibrillary tangles in AD and also other neurodegenerative diseases also concentrate other metals, principally iron and possibly zinc^(5,6).

2. *"...aluminosilicate deposits were also found at the core of senile plaques..."*

Although several investigators have reported Al concentrated in the neuritic plaques of SDAT (7,8), the preponderance of reports fail to find such accumulations (reviewed in 9) including papers authored by investigators who had previously reported Al accumulations in plaques⁽¹⁰⁾.

3. *"...intracerebral injections of aluminum salts induced neurofibrillary tangle formation in several species of laboratory animals, notable rabbits...Intravenous injection of aluminum had the same effect."*

In 1965, Wisniewski and colleagues demonstrated AD-like neurofibrillary pathology induced by injection of Al salts into the rabbit brain⁽¹¹⁾. However subsequent work, some by these very same investigators, showed that the similarities between Al-induced tangles and those of AD were more apparent than real. As reviewed in Wisniewski and Wen⁽¹²⁾, under light microscopy with silver staining, Al-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. Al-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 Al-induced pathology is also found in the spinal cord. Indeed, with Al-induced tangles, the spinal burden appears to exceed that of the brain itself. Within single neurons, Al-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. Al-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 Al-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 Al-induced tangles of rabbits^(13,14), it should be noted that the majority of investigators fail to confirm the presence of tau^(e.g. 15,16,17,18) and that those who do find this protein report that it is primarily in unphosphorylated form⁽¹⁴⁾. Accordingly, Al-induced tangles fail to react with the 5-25 monoclonal antibody to AD tangles⁽¹⁹⁾. The marked qualitative differences between Al-induced tangles in rabbits and the neurofibrillary lesions of AD are summarized in Table 1.

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.

- Based upon epidemiological work, "*...there is now compelling evidence that dietary aluminum in some way contributes to the development of AD.*"

Although there has been considerable epidemiological work investigating the risk of AD associated with Al exposures in the workplace and through drinking water, Dr. Meyer does not address the occupational studies (that have been largely negative - e.g. Iregren et al, Letzel et al^(20,21)) and justifiably dismisses the drinking water studies because "*...they defy logic.*" Rather, Dr. Meyer bases much of his opinion on a study of aluminum exposure through antiperspirant use by Graves et al⁽²²⁾ and via food additives by Rogers and Simon⁽²³⁾.

The study by Graves et al reported an association between the use antiperspirants that contain Al and the development of AD. However, this study has been carefully evaluated by the noted epidemiologist Sir Richard Doll⁽²⁴⁾ who pointed out a number of methodological problems including use of surrogate informants for exposure information, poor agreement between informants, and missing data on antiperspirant exposure for either the case or the control in over

half the case-control pairs. As a result of these methodological weaknesses it is difficult to draw any conclusions from this work. Doll (1993) noted that "...information about the use of antiperspirants that was sought...was so difficult to obtain that it was missing for either the case or the control in half the case-control pairs and when it was obtained concordance between the histories given by the controls and their surrogates was poor..." "The evidence is,...in the case of antiperspirants, very weak and the results show principally the difficulty of obtaining reliable information about the aetiology of the disease by the case-control method."

The Rogers and Simon study 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 study is as flawed as the Graves et al investigation. 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. Similar to Graves et al, 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 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..."⁽²⁵⁾. 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.

Perhaps more germane to the issue of Al and AD are studies of people who clearly have

abnormally high concentrations of Al in their brain. Do such people exhibit AD-like pathology? As a result of disease, certain patients will accumulate high concentrations of Al in the brain. Since the primary route for eliminating ingested Al is through the kidneys, some patients with renal insufficiency who are exposed to high levels of dietary Al and Al-containing phosphate binders, accumulate this metal in their brains. Since the brain Al concentration of these patients is well above normal and remains elevated over a long time span (i.e. years), consideration of the neuropathological sequelae in such patients is very relevant to the question of Al'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 Al intake show more AD pathology than age matched controls? The brains of 50 such patients were evaluated in a recent study⁽²⁶⁾. 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 Al exposure were "...lysosome-derived intracytoplasmic, Al-containing, pathognomonic, argyrophilic inclusions in choroid plexus, epithelia, cortical glia and neurons." The degree of morphological change increased with increasing Al intake. In contrast, AD-like lesions were not associated with Al exposure and the authors concluded that, in their "experience, Al does not cause an increase in AD morphology, at least not in terms of bioavailable Al in drugs or as a result of long-term..." hemodialysis.

5. *"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."*

Alois Alzheimer's first description of a patient with the disease that eventually came to bear his name was in 1906. Dr. Meyer noted that *"...aluminum-containing leavening agents became commercially available after the Civil War and came into common usage by the end of the nineteenth century... 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."* However, based on this form of deduction, one could also reason that the ice cream cone, invented in 1896, or, given the long prodromal period of AD, the potato chip, invented in 1853, are the real causes of AD.

In addition, Dr. Meyer's contention, that AD was unknown prior to the end of the 19th century, is probably wrong. The following history is quoted verbatim⁽²⁷⁾:

"Though the idea of Alzheimer's disease is a fairly modern concept, there is evidence its symptoms were familiar in antiquity.

Many diseases that have acquired modern names were well-known before the twentieth century. Before we begin our discussion of modern-day Alzheimer's disease, it might be useful to answer a history question: Was Alzheimer's a disease familiar to people before its "discovery" in the twentieth century? The answer to this question is not easy to determine. The rigorous scientific standards required of medical investigators are really phenomena of the last hundred years or so. It has only been in the twentieth century that human life expectancy has increased sufficiently for researchers to examine meaningfully the diseases of old age. Despite these obstacles, scholars believe archeological evidence exists indicating that long-term age-related

forgetfulness was known to the ancient world.

NINTH CENTURY B.C., EGYPT

One of the earliest known records of chronic forgetfulness in older populations occurred in Egypt. Historical texts indicate that in the ninth century B.C., a form of Alzheimer's was described in the Maxims of the Ptah Holy.

THIRD-CENTURY ROME

What some historians claim to be the first physical descriptions of Alzheimer's appear in the writings of Claudius Galen, where he recounts symptoms of age-related forgetfulness. A Roman physician who lived between A.D. 130 and 200, Galen was a skilled surgeon whose primary clientele were Roman gladiators. For centuries, he deeply influenced the medical practices of Western physicians.

FOURTEENTH-CENTURY ENGLAND

A form of Alzheimer's also appears to have been known in the medieval era. A verbal exam that seems to screen for a kind of forgetfulness has even been uncovered.”

Dr. Meyer's opinion concerning the role of Al in AD, once considered to be at least credible, has come to be held by a diminishingly tiny minority of scientists. The decreasing interest in the role of Al 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.”⁽²⁸⁾ 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 Al's role in AD indicates that this research area is widely considered to be without merit.

Sincerely,



Theodore I. Lidsky, Ph.D.

Center for Trace Element Studies and Environmental Neurotoxicology

References

1. Perl D.P., Brody, A.R. Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. *Science*, 1980, 208: 297-299.
2. Wisniewski, H.M., Lidsky, T.I. The role of aluminum in Alzheimer's disease. in *Health in the Aluminum Industry*. N.D. Priest & T.V. O'Donnell (Eds.), Middlesex University Press, London, 1999, 263-273.
3. Jordan, B.D. Chronic traumatic brain injury associated with boxing. *Seminars in Neurology*, 2000, 20: 179-185.
4. Bouras C., Giannakopoulos, P., Good, P.F., Hsu, A., Hof, P.R., Perl, D.P. A laser microprobe mass analysis of brain aluminum and iron in dementia pugilistica. *European Neurology*, 1997, 38: 53-58.
5. Sayre LM, Perry G, Atwood CS, Smith MA The role of metals in neurodegenerative diseases. *Cellular and Molecular Biology*, 2000, 46: 731-741.
6. Suh SW, Jensen KB, Jensen MS, Silva DS, Kesslak PJ, Danscher G, Frederickson CJ Histochemically -reactive zinc in amyloid plaques, angiopathy, and degenerating neurons of Alzheimer's diseased brains. *Brain Research*, 2000, 852: 274-278.
7. Candy, J.M., Klimowski, J., Perry, R.H., Perry, E.K., Fiarbairn, A., Oakley, A.E., Carpenter, T.A., Atack, J.R., Blessed, G., Edwardson, J.A. Aluminosilicates and senile plaque formation in Alzheimer's disease. *Lancet*, 1986, 1: 354-356.
8. McLachlan, D.R. C. Aluminum and Alzheimer's disease. *Neurobiol. Aging*, 1986, 7: 525-532.
9. Kasa, P., Szerdahelyi, Wisniewski, H.M. Lack of topographical relationship between sites of aluminum deposition and senile plaques in the Alzheimer's disease brain. *Acta Neuropathol.*, 1995, 90: 526-531.
10. Candy, J.M., McArthur, F.K., Oakley, A.E., Taylor, G.A., Chen, C.P.L.-H., Mountfort, S.A., Thompson, J.E., Chalker, P.R., Bishop, H.E., Beyreuther, K., Perry, G., Ward, M.K., Martyn, C.N., Edwardson, J.A. Aluminum accumulation in relation to senile plaque and neurofibrillary tangle formation in the brains of patients with renal failure. *J. Neurol. Sci.*, 1992, 107: 210-218.
11. Wisniewski, H.M., Terry, R.D., Peña, C., Streicher, E., Klatzo, I. Experimental production of neurofibrillary degeneration. *J. Neuropath. & Exp. Neurol.*, 1965, 24: 139
12. Wisniewski, H.M., Wen, G.Y. Aluminum and Alzheimer's disease. *Aluminum in biology and medicine*. Wiley, Chichester (Ciba Foundation Symposium 169), 1992, pp. 142-164.

13. Savory, J., Huang, Y., Herman, M.M. Reyes, M.R., Wills, M.R. Tau immunoreactivity associated with aluminum maltolate-induced neurofibrillary degeneration in rabbits. *Brain Res.*, 1995, 669: 325-329.
14. Singer, S.M., Chambers, C.B., Newfry, G.A., Norlund, M.A., Muma, N.A. Tau in aluminum-induced neurofibrillary tangles. *NeuroToxicology*, 1997, 18: 63-76.
15. Bergholf, R.L., Herman, M.M., Savory, J., Carpenter, R.M., Sturgill, B.C., Katsetos, C.D., Vandenberg, S.R., Wills, M.R. A long-term intravenous model of aluminum maltol toxicity in rabbits: tissue distribution, hepatic, renal, and neuronal cytoskeletal changes associated with systemic exposure. *Toxicol. Appl. Pharmacol.*, 1989, 98: 58-74.
16. Kowall, N.W., Szendrei, G.E., Lee, V.M., Otvos, L., Jr. Aluminum induced neurofibrillary degeneration affects a subset of neurons in rabbit cerebral cortex, basal forebrain, and upper brainstem. *Neuroscience* 1989, 29: 329-337.
17. Johnson, G.V.W., Watson, A.L. Lartius, R., Uemera, E. Jope, R.S. Dietary aluminum selectively decreases MAP-2 in brains of developing and adult rats. *Neurotoxicol.*, 1992, 13: 463-474.
18. Strong, M.J., Wolff, A.V., Wakayama, I., Garruto, R.M. Aluminum induced chronic myelopathy in rabbits. *Neurotoxicology*, 1991, 12: 9-22.
19. Grundke-Iqbal, I., Wang, G.P., Iqbal, K., Wisniewski, H.M. Alzheimer paired helical filaments: identification of polypeptides with monoclonal antibodies. *Acta Neuropath.*, 1985, 68: 279-283
20. Iregren A, Sjogren B, Gustafsson K, Hagman M, Nysten L, Frech W, Andersson M, Ljunggren KG, Wennberg A. Effects on the nervous system in different groups of workers exposed to aluminium. *Occup Environ Med* 2001 Jul;58(7):453-460
21. Letzel S, Lang CJ, Schaller KH, Angerer J, Fuchs S, Neundorfer B, Lehnert G, Longitudinal study of neurotoxicity with occupational exposure to aluminum dust. *Neurology* 2000 Feb 22;54(4):997-1000
22. Graves, A.B., White, E., Koepsell, T.D., Reiffler, B.V., Van Bele, G., Larson, E.B. The association between aluminum containing products and Alzheimer's disease. *J. Clin. Epidemiol.*, 1990, 43: 35-44.
23. Rogers MA, Simon. A preliminary study of dietary aluminium intake and risk of Alzheimer's disease. *Age and Ageing*, 1999, 28: 205-209
24. Doll, R. Review: Alzheimer's disease and environmental aluminum. *Age and Ageing*, 1993, 22: 138-153.

25. Braak, H., Braak, E. Evolution of neuronal changes in the course of Alzheimer's disease. *J Neural Transm Suppl.* 1998;53:127-40
26. Reusche, E., Koch, V., Lindner, B., Harrison, A.P., Friedrich, H.J. Alzheimer morphology is not increased in dialysis-associated encephalopathy and long-term hemodialysis. *Acta Neuropath.*, 2001, 101: 211-216.
27. Medina J. *What You Need to Know About Alzheimer's*. New Harbinger Publ., 1999 (quoted passage available at www.mhsource.com/catalog/alzpreview.html)
28. Munoz, D.G. Is exposure to aluminum a risk factor for the development of Alzheimer Disease? - No. *Arch. Neurol.*, 1998, 55: 737-739.

32

100

FedEx USA Airbill
Express

FedEx
Tracking
Number

8258 5197 3101

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records

Date 4-12-02 FedEx Tracking Number 825851973101

Sender's Name Theodore T. Lidsky, Ph.D. Phone 718 494 5140

Company MYS INSTITUTION FOR POLYMER RESEARCH

Address 1000 FOREST HILL RD Dept./Floor/Suite/Room

City STATEN ISLAND State NY ZIP 10314

2 Your Internal Billing Reference

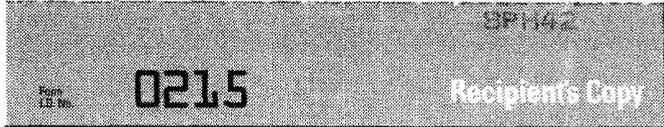
3 To

Recipient's Name _____ Phone _____

Company Dockets Management Branch
HFA-305, Room 1061

Address 5630 Fishers Lane We cannot deliver to P.O. boxes or P.O. ZIP codes.

City Rockville State MD ZIP 20852



4a Express Package Service

FedEx Priority Overnight Next business morning
 FedEx Standard Overnight Next business afternoon
 FedEx First Overnight Earliest next business morning delivery to select locations
 FedEx 2Day* Second business day
 FedEx Express Saver* Third business day
*FedEx Envelope/Letter Rate not available Minimum charge: One-pound rate

4b Express Freight Service

FedEx 1Day Freight* Next business day
 FedEx 2Day Freight Second business day
 FedEx 3Day Freight Third business day
*Call for Confirmation. Packages up to 150 lbs. Delivery commitment may be later in some areas.

5 Packaging

FedEx Envelope/Letter*
 FedEx Pak*
 Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.
*Declared value limit \$500

6 Special Handling

SATURDAY Delivery Available only for FedEx Priority Overnight and FedEx 2Day
 SUNDAY Delivery Available only for FedEx Priority Overnight to select ZIP codes
 HOLD Weekday at FedEx Location Not available with FedEx First Overnight
 HOLD Saturday at FedEx Location Available only for FedEx Priority Overnight and FedEx 2Day to select locations
Include FedEx address in Section 3.

Does this shipment contain dangerous goods?
One box must be checked.
 No Yes As per attached Shipper's Declaration
 Yes Shipper's Declaration not required
 Dry Ice Dry Ice 9, UN 1845 x kg
Dangerous Goods cannot be shipped in FedEx packaging. Cargo Aircraft Only

7 Payment Bill to:

Enter FedEx Acct. No. or Credit Card No. below.
 Sender Acct. No. in Section 1 will be billed.
 Recipient Third Party Credit Card Cash/Check
 Obtain Recip. Acct No.

Total Packages	Total Weight	Total Charges
		Credit Card Auth.

*Our liability is limited to \$100 unless you declare a higher value. See the FedEx Service Guide for details.

8 Release Signature Sign to authorize delivery without obtaining signature.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.
Questions? Visit our Web site at www.fedex.com
or call 1-800-Go-FedEx (800)463-3339.
SFS 1100 • Rev. Date 7/00 • Part #1559125 • ©1994-2000 FedEx • PRINTED IN U.S.A.

402