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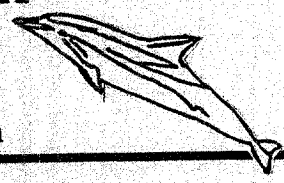

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Dr. Judith Kidwell, HFS-265
5100 Paint Branch Parkway
College Park, MD 20740

February 25, 2006

Re: Docket No.: 2005P-0377/CP 1 (Additional studies.)

Dear Judy,

Some additional supporting studies are enclosed.

Chart 1 presents a schematic relationship of oxidation, inflammation and cytotoxicity produced by toxic substances. In this regard, aluminum produces brain oxidation, inflammation and cytotoxicity - all factors in Alzheimer's and elderly mental impairment. Aluminum is a complete toxin that is kept partially in check by body chemistry, e.g. melatonin, or by dietary items, e.g. curcumin or polyphenols in wine, but these checks start to fade as a person ages, body chemistry changes, and dietary quality deteriorates.

The metal can also damage the brain indirectly, such as through an adverse effect on the availability of heme. Damage to other organs such as the liver has been documented. Exposure to the metal produces higher rates of pneumonia in AD patients, which is the largest source of their death.

Parkinson's Disease Co-Factor: There is growing evidence that aluminum is a co-factor in Parkinson's disease. However, there is presently a sparcity of human epidemiology studies regarding the causation of Parkinson's which is believed to be a largely environmental rather than a genetic condition.

Additional studies are enclosed which further document the concept that inflammation and cytotoxicity, i.e. brain cell death, are the primary issues in the dementia of Alzheimer's, as opposed to brain deposits of the Alzheimer's type such as plaques and tangles.

A very large and rich evidence about the toxicity of aluminum severely conflicts with the FDA characterization of aluminum based food additives as "generally recognized as safe".

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Chart 1

Relationship of Oxidation, Inflammation and Cytotoxicity: (Aluminum Exposure Produces All Three Biological Effects)

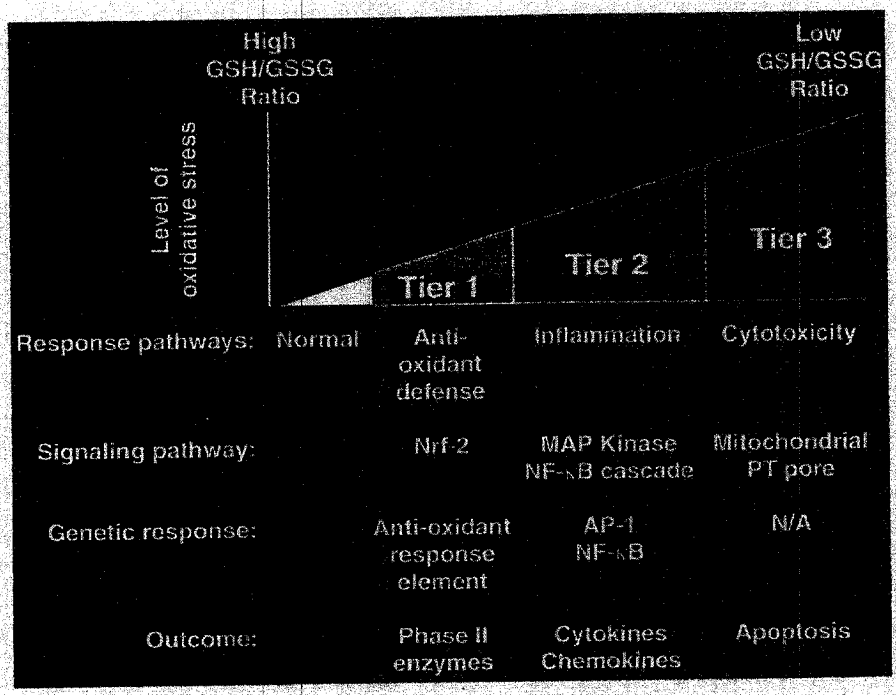

Fig. 3. The hierarchical oxidative stress model. At a lower amount of oxidative stress (tier 1), phase II antioxidant enzymes are induced via transcriptional activation of the antioxidant response element by Nrf-2 to restore cellular redox homeostasis. At an intermediate amount of oxidative stress (tier 2), activation of the MAPK and NF-κB cascades induces pro-inflammatory responses. At a high amount of oxidative stress (tier 3), perturbation of the mitochondrial PT pore and disruption of electron transfer results in cellular apoptosis or necrosis. [Adapted from (*11*)] N/A means not applicable.

Andre Nel, Tian Xia, Lutz Madler, Ning Li, Toxic potential of materials at the nanolevel, Science 311 (2006) 622-7

■ Studies Enclosed

A. Brain Oxidation Produced by Aluminum, Ameliorated by Melatonin (an Aluminum Chelator), and Effect on SOD:

1. S.K. Abd-Elghaffar et al, Aluminum-induced neurotoxicity and oxidative damage in rabbits: Protective effect of melatonin. Neuro Endocrinol Lett 26/5 (2005) 609-16

Melatonin as an Aluminum Chelator: In this study, aluminum administered in drinking water increases brain oxidation, and has a dramatic encephalophathic effect. Melatonin not only reduces oxidation, but also substantially reduces aluminum brain levels, which indicates that it is a chelator.

As noted in the previous package of studies, melatonin levels tend to decrease with aging in humans, which offers one explanation why Alzheimer's occurs only after the age of 60 in most persons.

2. D.V. Micic et al, Superoxide dimutase activitity in the mongolian gerbil brain after acute poisoning with aluminum, J Alzheimers Dis (2005) 49-56

The study finds a biphastic stimulation of brain SOD after aluminum administration, indicative of oxidative stress.

B. Brain Inflammation Produced by Aluminum:

1. L-F Lue et al, Inflammation, AB deposition, and neurofibrillary formation as correlates of Alzheimer's disease neurodegeneration, J Neuropathol Exp Neurol 55/10 (1996) 1083-8

Brain inflammation is a specific characteristic of Alzheimer's disease. As the authors report, what distinguishes high pathology controls, i.e. those with the Alzheimer's type of brain deposits, from those persons with Alzheimer's disease is brain inflammation.

2. A. Becaria et al, Aluminum and copper interact in the promotion of oxidative but not inflammatory events: Implications for Alzheimer's disease, J Alzheimers Dis 5 (2003) 31-38

Aluminum Generates Inflammation Independently: The authors find

that co-exposure of copper and aluminum to human glioblastoma T98G cells enhances oxidation. However, aluminum promotes an independent inflammatory response that does not rely on the oxidative effect of copper.

3. V.J. Johnson and R.P. Sharma, Aluminum disrupts the pro-inflammatory cytokine/neurotrophin balance in primary brain rotation-mediated aggregate cultures: possible role in neurodegeneration, Neurotoxicology, 24 (2003) 261-8

Aluminum maltol (food additive) increases pro-inflammatory gene expression and decreases neurotrophic gene expression - inducing cell death in telencephalon cells removed from Swiss Webster mice.

4. A. Campbell et al, Pro-inflammatory effects of aluminum in human glioblastoma cells, Brain Res 933 (2002) 60-65

In a human glioblastoma cell line, six day exposure to aluminum sulfate enhanced inflammation.

5. A. Becaria et al, Aluminum as a toxicant, Toxicol Ind Health, 18 (2002) 309-20

A partial literature review that considers the effect of aluminum on inflammation, with the conclusion that "both epidemiological and experimental findings described here strengthen the possibility that prolonged exposure to relatively low levels of aluminum may be neurotoxic". (It is difficult to see how a neurotoxic food additive can be considered safe.)

6. A. Campbell, The potential role of aluminum in Alzheimer's disease, Nephrol Dial Transplant 17 (Suppl 2) (2002) 17-20

Another review that includes inflammation, with similar conclusion.

C. Brain Cell Apoptosis by Aluminum Regulated by GDNF and BDNF

1. S-J Yang et al, Opposed regulation of aluminum-induced apoptosis by glial cell line-derived neurotrophic factor and brain-derived neurotrophic factor in rat brains, Mol Brain Res 127 (2004) 146-9

Another laboratory animal study finding that aluminum maltol

produces brain cell apoptosis in rats. This apoptotic effects is prevented by GDNF, consistent with Ghribi's findings. In contrast BDNF accelerates brain cell apoptosis in the presence of aluminum.

D. Additional Studies on Effect of Aluminum on Erythropoietin:

1. D. Vittori et al, The distinct erythropoietin functions that promote cell survival and proliferation are affected by aluminum exposure through mechanisms involving erythropoietin receptor, Biochim Biophys Acta 1743 (2005) 29-36

Aluminum exposure reduces the capacity of cells to resist program cell death in K562 cells but not UT-7 cells. The metal down-modulates EpoR expression. Pathways are different in each cell type, with Epo in K562 cells related to prevention of programmed cell death, and in UT-7 cells related to the stimulation of cell proliferation.

2. D. Vittori et al, Human erythroid cells are affected by aluminum, Alteration of membrane band 3 protein, Biochim Biophys Acts 1558 (2002) 142-150

In vitro results show that aluminum may disturb human erythropoiesis through combined effects on mature erythrocytes and cellular metabolism in late erythroid progenitors.

E. Aluminum As Co-Factor in Parkinson's Disease:

1. P.F. Good et al, Neuromelanin-containing neurons of the substantia nigra accumulate iron and aluminum in Parkinson's disease: a LAMMA study, Brain Res 593 (1992) 343-6

Aluminum accumulated in neuromelanin granules, and the authors propose that the oxidative stress produced aluminum and iron may account for the selective degeneration of neuromelanin-containing neurons in PD.

2. E.C. Hirsch et al, Iron and aluminum increase in the substantia nigra of patients with Parkinson's disease: an X-ray microanalysis, J Neurochem 56 (1991) 446-51

Aluminum was found in the Lewy bodies. The authors conclude that the higher substantia nigra levels of iron and aluminum was not a product of neuronal degeneration.

3. C. Andre et al, Effect of metals on herbicides - alpha synuclein association: a possible factor in neurodegenerative disease studied by capillary electrophoresis, Electrophoresis 26 (2005) 3256-64

Occupational herbicide and metal exposures have been found to be possible environmental factors in Parkinson's causation. In contrast to Alzheimer's, alpha-synuclein is the characteristic protein that is abnormally folded in Parkinson's. Here the authors find that aluminum most potently interacts with herbicides to produce this folding. Other potential metals involved are cadmium, manganese, copper and zinc. Magnesium, on the other hand, decreases the folding. (Aluminum is competitive with magnesium in biology.)

4. V.N. Uversky et al, Metal-triggered structural transformations, aggregation, and fibrillation of human alpha-synuclein, J Biol Chem 276/47 (2001) 44284-96

Aluminum was found to be the most effective metal in producing the characteristic folding of alpha-synuclein: i.e. the primary folded protein in Parkinson's.

5. L. Meglio and P.I. Oteiza, Aluminum enhances melanin-induced lipid peroxidation, Neurochem Res 24/8 (1999) 1001-8

The authors speculate that aluminum "contributes to neuromelanin-mediated oxidative damage in dopaminergic neurons and subsequent neuronal degeneration and death in Pakinson's disease.

6. K. Oyanagi, The nature of the parkinsonism-dementia complex and amylotrophic lateral sclerosis of Guam and magnesium deficiency, Parkinsonism and Related Disorders 11 (2005) S17-23

Depleting rats of magnesium in the diet for two generations produced exclusive loss of dopamiergic neurons. (Aluminum competes with mangnesium in biology.)

Obviously, more research needs to be done with regard to aluminum as a co-factor in Parkinson's. As with Alzheimer's, it is likely that the brain deposits are not the key issue, but rather brain cell death.

F. Possible Impact of Aluminum on Pneumonia in AD:

1. J. Attems et al, Cause of death in demented and non-demented elderly inpatients; an autopys study of 308 cases, J Alzheimers Dis 8 (2005) 57-62

49.6 percent of Alzheimer's patients died of pneumonia, compared to 38 percent of all patients, and 28 percent of non-demented patients.

The McLachlan successful human clinical trial of aluminum chelation with desferrioxamine as a therapy for Alzheimer's slowed the disease process by 50 percent. It also reduced deaths, mostly from pneumonia, from 9 in the untreated controls to only 1 in the treatment group. (DRC McLachlan et al, Aluminum and the pathogenesis of Alzheimer's disease: a summary of the evidence, Ciba Foundaton Symposium 160, Aluminum in Biology and Medicine, John Wiley & Sons, New York 1992, pp. 87-108) Chronic elevation of aluminum may impair immune response.

G. Further Evidence That Brain Atrophy Is the Key Factor in Alzheimer's Disease Dementia Rather Than Brain Deposits:

While aluminum exposure can generate amyloid, contribute to amyloid folding, and neurofibrillary tangle folding, the loss of brain cells (and previous inflammation) are the key issues in dementia of Alzheimer's. Aluminum kills brain cells, which indicates that it cannot be considered a safe food additive for persons over the age of 60 or even earlier.

1. L.A. van de Pol et al, Hippocampal atrophy in Alzheimer's: Age matters, Neurology 66 (2006) 236-238

2. D. Erten-Lyons et al, Brain volume loss in MCI predicts dementia, Neurology 66 (2006) 233-5

3. T. den Heijer et al, Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly persons, Arch Gen Psychiatry 63 (2006) 57-62

"Atrophy of the hippocampus and amygdala on MRI in cognitively intact elderly people predicts dementia during a 6-year follow-up."

4. J.A. Kaye et al, Asynchronous regional brain volume losses in presymptomatic to moderate AD, J Alzheimers Dis 8 (2005) 51-6

"In contrast to the hippocampal rates of change, the annualized rates of atrophy of total brain volume or CSF spaces (ventricles) during the transition to dementia are 3 to 4 times greater...than the stable control group. This is very consistent with rates of total brain atrophy reported in other studies of established AD (2.1-5.2%/year) and control subjects (0.2-0.9%/year)."

In summary, the enclosed studies provide further evidence in support of the petition to FDA to rescind the present "generally recognized as safe" status for aluminum based food additives. The published evidence severely conflicts with that designation.

Hope this is helpful.

With best regards,

Erik Jansson, Exec. Dir.

c.