Department of the Planet Earth

701 E Street, SE - Suite 200, Washington, DC 20003

(301) 475-8366 - planetearth@erols.com; www.deptplanetearth.com

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

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Re: Interaction of Aluminum With Melatonin and With Erythropoietin in Aging and Alzheimer's: Relevance to the Safety of Aluminum Food Additives.

Dear Judy,

Enclosed is another study, Rajan et al, of aluminum brain levels in normal persons of 50-60 years of age, in this case from India. Aluminum levels averaged 58 to 196 ug/g "wet weight" which makes them comparable to the levels measured by Shumizu among non-demented younger and elderly persons from China. Put these on a chart, and there is almost a smooth curve of increased aluminum brain concentration by age group in normal people.

Furthermore, a high ratio of aluminum to iron was found in the temporal cerebrum and hippocampus: i.e. two brain regions significantly involved in Alzheimer's.

Alzheimer's rates in India are very low compared to those of the United States. It is believed that curcumin (yellow part of the spice turmeric used in yellow curry) in the diet and very high fluoride (4 ppm or over) in the drinking water may be largely responsible. Both bond with aluminum (1-2). Curcumin is also a potent anti-oxidant. The US diet lacks similarly high levels of curcumin types of anti-oxidants and high levels of aluminum bonder agents that could counteract the high aluminum food levels.

Brain defenses against the toxicity of aluminum become depleted in the aging process: i.e. a big issue with regard to the safety of aluminum food additives for anyone over the age of 60. Melatonin is one of several brain defenses against aluminum that can become depleted.

A. Melatonin Partly Defends Against Brain Aluminum, But Is Reduced in Aging and Alzheimer's.

There is a substantial scientific literature analyzing the effects of aluminum on the brain of laboratory animals, and the countering effect of

melatonin. Enclosed are some relatively new studies, others, and summaries:

1. Abd-Elghaffer et al, (2005): This study is still not on the National Library of Medicine shelf. I'll send a copy when it appears.

   Chronic exposure of laboratory rabbits to aluminum in drinking water produced atrophy and apoptosis of neurons in the cerebral cortex and hippocampus, neurofibrillary degeneration, schwan cell degeneration, demyelination, and reduction of SOD - all of which mimic Alzheimer's. Co-administration of melatonin substantially reduced these effects.

2. Gomez et al (2005): Administration of aluminum to rats increased oxidation in the hippocampus. Co-administration of melatonin substantially reduced these effects.

3. Esparza et al (2005): Administration of aluminum to male rats increased oxidative stress and increased gene expression in cerebral cortex and cerebellum. Brain levels doubled for the cortex and increased five fold in the cerebellum with this treatment - quite similar the the human situation in aging. Co-administration of melatonin substantially quenched this oxidative stress.

4. Daniels et al (1998): In human blood platelets, both B-amyloid and aluminum dose-dependently increased lipid peroxidation, with the metal more potent. Co-administration of melatonin inhibited this effect in a dose-dependent way.

Depletion of MT Receptor in AD and Melatonin Levels in Aging and AD

5. Savaskan et al (2005): Reduced hippocampal MT2 melatonin receptor expression is found in Alzheimer's patients.

6. Zhou et al (2003): Early neuropathological AD changes in aged persons is accompanied by decreased cerebrospinal fluid melatonin levels.

7. Ozcankaya and Delibas (2002): Melatonin blood levels were significantly decreased in AD but not controls, and iron and malondialehyde increased in AD.

8. Kin et al (2004): 24 hour secretion of melatonin declined significantly with age in women in the age bracket from 42 to 83 years in Canada but not in men.

9. Graham and McLachlan (2004): Melatonin levels decreased with age in Australia: i.e. significantly lower in the oldest (over 75) population versus the youngest (56-65).

10. Editorial (2005): Melatonin levels are orders of magnitude higher in some body compartments such as the cerebrospinal fluid and bile than in blood.

Melatonin Bonds With Aluminum

11. List of Literature: In the enclosed list of literature on the interaction of aluminum and melatonin, #13, Lack et al (2001); #17, Limson et al (1998); #18, van Rensburg (1997), demonstrate that melatonin and its precursors bond with aluminum. Indeed, the later authors propose that the lack of indoor lighting in South Africa, thus increasing melatonin exposure, may be partly responsible for the very low incidence of AD in the rural areas.

B. Anti-oxidant and Anti-inflammatory Herbal Medicine Dipsacus asper Wall Counteracts Effects of Aluminum

12. Zhang et al (2003): Confirming the previous findings of Pratico (copy you already have), these authors found that feeding rats 0.3 percent aluminum chloride in drinking water for 90 days increased cognitive deficits and overexpression of B-amyloid.

    The Dipsacus asper extract was more effective than vitamin E in reversal of these aluminum effects.

❑ Summary - Aluminum Food Additives Not Safe for Aging

Pratico et al in the enclosed study found that 74 to 76 year old persons with mild cognitive impairment have increased lipid peroxidation in cerebrospinal fluid, plasma and urine compared to cognitively normal persons aged 72. The authors propose that oxidative monitoring may identify those who will progress to AD. Inflammation was not reviewed in this study. Clearly, a food supply rich in aluminum is not safe for the older populations because they tend to be depleted in protective anti-oxidants like melatonin.

C. New Literature on Erythopoietin (EPO) and Neuron Protection: i.e. a Likely Indirect Way That Aluminum Kills Brain Cells.

The Alzheimer's Research Forum has recently published the enclosed literature review on new thinking about the role of EPO in protection of neurons in neurodegenerative diseases and brain injury - including Alzheimer's. As you can see, Wendy Camana from the University of California - San Diego has recently found that the EPO receptor mRNA is downregulated in the AD brain, particularly in late stage disease: i.e. 30 percent less expression. EPO levels are also lower in AD patents.

I have already sent you studies concerning the adverse effect of aluminum on the red blood cell process and erythropoietin:

a. Florence (1994) who proposed that the depletion of heme by aluminum acting on the bone marrow may be responsible for the brain cell death in laboratory rats;
b. Garabossa (1998) who found that oral aluminum administration who found that the metal interfered with red blood cell production, and;
c. Drueke (2001) who summarized the literature on factors that produce hyporesponsiveness to recombinant human erythropoietin including aluminum.

Additionally, Altamna (2002) reported that heme deficiency may be a factor in the mitochondrial and neuronal decay of aging (3). And Barzan (2002) reported that brain hypoxia such as might be produced by anaemia produces pro-inflammatory gene expression (4). (See enclosed abstract) Reduction of heme is likely to be one mechanism of several by which aluminum kills brain cells and contributes to the atrophy of the brain in Alzheimer's which accounts for the dementia.

Obviously, more information is needed. However, the evidence is increasingly pointing to the depletion of heme as one way that aluminum exposure kills brain cells in an indirect fashion. It is difficult to see how aluminum food additives can be considered safe under the circumstances. Hope this material is helpful.

With best regards,

Erik Jansson, Exec. Dir.

(1) A.R. Llorente et al, Aluminum binding to chromatin DNA as revealed by formation of fluorescent complexes with 8-hydroxyquinoline and other ligands, J Microsc 155 (Pt. 2) (1989) 227-30
(2) C.N. Still, Aluminum neurotoxicity and Alzheimer's disease, J South Carolina Medical Association (Nov. 1994) 560-4
(3) H. Altamna et al, Heme deficiency may be a factor in the mitochondrial and neuronal decay of aging, Proc Nat Acad Sci USA 99 (2002) 14807-12
(4) N.G. Bazan et al, Hypoxia signaling to genes: significance for Alzheimer's disease, Mol Neurobiol 26 (2-3)(2002) 283-98