ALUMINUM TOXICITY

Occurrence

Aluminum (Al) is a widely dispersed metal being found in igneous rocks, shales, clays and most soils. Al is absorbed by many plants and occurs in plant products in the diet. The daily ingestion of Al by humans is estimated to be 30 to 50 mg (National Library of Medicine 2000). The general population is also exposed to Al from its widespread use in water treatment, as a food additive, from various Al-based pharmaceuticals, from occupational dusts, and from Al containers and cooking utensils (Harris, Berthon et al. 1996). The leaching of Al from the soils by acid rain is increasing free Al in the environment and in the surface waters. The increase in Al exposure of the general population becomes of increasing concern with studies that suggest possible association between exposure and neurological diseases (Harris, Berthon et al. 1996; van Landeghem, D'Haese et al. 1997; Altmann, Cunningham et al. 1999).

The amount of Al in drinking water is small compared to the amount in food (Priest, Talbot et al. 1998). The species of Al found in drinking water are different from the Al species most abundant in food. The occurrence of Al is highly variable in water and in finished drinking water. Concentrations of 12 to 2,250 µg/L have been reported for North American rivers (Durum and Haffty 1963). Al is more likely to occur in surface water and is increased in finished drinking water when Al is added as coagulant in the treatment process. Where Al sulfate was used as a coagulant in treating a surface water supply, the amount of Al found in the finished water ranged from 14 to 2,670 µg/L with an average of 100 µg/L (Orme and Ohanian 1990). In one New York facility, Al concentration was 10 µg/L in the raw water and 49 µg/L with alum treatment. In this water 52% was simple Al-OH species, 19% was Al-F complexes and 29% was organically bound. The Al concentration in the drinking water in California and Nevada varied from 1.4 to 1,167 µg/L with a median of 53 µg/L (Miller, Kopfler et al. 1984). In an epidemiology study from Southern France, the average values reported were 33 µg/L for more than 3,000 water samples (Jacqmin, Commenges et al. 1994). In the United Kingdom, the Northumbrian Water Authority produces water with 120 µg/L Al in alum-using plants and 70 µg/L in non-alum-using plants (National Library of Medicine 2000). At neutral pH Al exists primarily as hydroxide complexes, but under slightly acidic conditions, approximately 50 % occurs as organic complexes and Al-F complexes.

Toxicity of Al in humans

Toxicity of Al in humans is known to occur in at least two specific situations. Dementia in dialysis patients is related to Al exposure (van Landeghem, D'Haese et al. 1997; Suarez-Fernandez, Soldado et al. 1999). The Al intoxication in patients can be controlled by control of Al levels in the dialysis fluids (Mazzaferro, Perruzza et al. 1997). Chronic renal failure may lead to decreased Al excretion and enhances Al toxicity (Flaten, Alfrey et al. 1996). The pathogenesis of Al toxicity is complex and may be related to other factors such as impaired parathyroid function which affects Al absorption and/or distribution (National Library of Medicine 2000). A second prominent Al toxicity found in dialysis patients is osteomalacia or metabolic bone disease (Kausz, Antonsen et al. 1999) (Klein 1998).

Preterm infants with parenteral administration of nutritional solutions are also at risk for Al-induced neurotoxicity (Hawkins, Coffey et al. 1994; Driscoll, Cummings et al. 1997). Al inhalation, especially in workers, may be associated with increased incidence of asthma (Sorgdrager, de Looff et al. 1998; Vandenplas, Delwiche et al. 1998). Pre-term infants are also at risk for Al-induced metabolic bone disease (Klein 1995; Klein 1998).

Toxicity of Al in animal studies

A low calcium high Al diet in *Macaca Fasicularis* monkeys caused neurological disease compatible with those of amyotrophic lateral sclerosis and Parkinsonism (Garruto, Shankar et al. 1989). Swiss Webster female mice fed diets containing 1000 µg Al/g diet for 6 months were reported to have deficit in immune effector cell function (Golub, Takeuchi et al. 1993). Swiss Webster female mice fed diets containing 1000 µg Al/g diet plus sodium citrate for 5 to 7 weeks were reported to have lower grip strength and increased startle response compared to controls (Oteiza, Keen et al. 1993). Offspring of mice given Al lactate in the diet at 1000 µg Al/g diet during gestation and lactation showed post-weaning neurobehavioral changes (Donald, Golub et al. 1989).

Two studies in rats report enhanced mortality in rats exposed to 0.5 ppm AlF3 complexes in the drinking water (Varner, Horvath et al. 1994; Varner, Jensen et al. 1998). Several committees that investigated this finding suggested that further studies were warranted.

Neurotoxicity of Al

Al is clearly neurotoxic causing degeneration of astrocytes (Suarez-Fernandez, Soldado et al. 1999) and interferes with the metabolism of the neuronal cytoskeleton (van der Voet, Schijns et al. 1999). Al causes encephalopathy in patients undergoing renal dialysis (Morris, Candy et al. 1989; Ogborn, Dorcas et al. 1991; van Landeghem, D'Haese et al. 1997). Cerebral disfunction was reported in people exposed to drinking water that had been contaminated with Al sulphate (Altmann, Cunningham et al. 1999). Al has been implicated in a series of neurological diseases including amyotrophic lateral sclerosis, dementia associated with Parkinson's disease and suggested for Alzheimer's disease although this link is quite tenuous (van der Voet, Schijns et al. 1999). Animal studies indicate that oral exposure to Al leads to accumulation in the brain, bone, muscle, kidney and other organs.

Rationale for consideration of testing Al in the drinking water

Historically, high levels of Al have not engendered concern since it appears little of ingested Al is absorbed and what is absorbed is rapidly excreted. The absorption of Al is poorly understood but both soluble and mucosally associated luminal metal-binding ligands may regulate the initial uptake (Powell, Whitehead et al. 1999). Several recent studies have demonstrated that co-administration of Al with citrate, lactate or acetate increases Al levels in a variety of organs including the brain. Organic Al-complexes that do not undergo hydrolysis, such as Al-maltolate, are also associated with increased uptake of Al. Diets with suboptimal levels of copper also result in increased deposition of Al in the tissues (Lui and Stemmer 1990; Lui and Stemmer 1990). In many, but not all, experiments demonstrating increased uptake of Al, there is also evidence of neurotoxicity. Recently, evidence of increased absorption of Al has also been demonstrated with an inorganic Al-complex, AlF_3. Fluoride also enhances the neurotoxicity of Al (van der Voet, Schijns et al. 1999). The potential relevance of such Al- complexes derives from the observation that under slightly acidic source water conditions organic Al-complexes and Al-F complexes predominate, and these can persist to a significant degree through drinking water treatment. The absorption and toxicity vary by species of Al.

Al occurs naturally in the sources for drinking water. Acid rain is further increasing Al in surface waters by the release of Al from soils and rocks (Harris, Berthon et al. 1996). In fresh waters acidified by acid rain, Al toxicity has led to fish extinction (Flaten, Alfrey et al. 1996). A diversity of coagulants containing Al sulfate, Al chloride, polyAl chloride or Al chlorohydrate used in the drinking water treatment process cause a further increase in the concentrations of Al in the finished drinking water.

Fluoridation of water is another factor resulting in Al-fluoride complexes. Reports suggests that fluoride enhances Al uptake in rabbits (Ahn, Fulton et al. 1995), increases the toxicity of Al on the neuronal cytoskeleton (van der Voet, Schijns et al. 1999) and amplifies Al inhibition of enzyme activity (Husaini, Rai et al. 1996). While Al is widely found in the diet, Al species found in the drinking water vary significantly from those found in the diet and may have different absorption and toxicity.

There is clear evidence that unless Al levels in dialysis fluid are carefully controlled, patients will suffer from neurotoxicity and metabolic bone disease (Flaten, Alfrey et al. 1996; van Landeghem, D'Haese et al. 1997; Klein 1998; van Landeghem, De Broe et al. 1998). Clear evidence also exists that Al can be neurotoxic and and cause metabolic disease in pre-term infants with parenteral nutrition (Klein 1995; Klein 1998). Limited evidence exists that Al can be neurotoxic in experimental animals under certain conditions. Most water treatment processes result in increased levels of Al in the finished drinking water. Further there is evidence that fluoridation will result in Al fluoride complexes with enhanced neurotoxicity or that fluoride itself will enhance uptake and toxicity of the Al. Almost no data exists on the potential neurotoxic effect of chronic exposure to the Al species that exist in the drinking water. It is important to include cognitive function in the neurotoxicological examination.

Proposed Studies

A primary interest to the EPA Office of Water is the extent to which various Al-complexes influence Al body burdens. Therefore, the effect of Al citrate and Al fluoride complexes in the drinking water on the body burdens of Al including the brain need to be evaluated as part of the toxicokinetic studies. It is recommended that F344 rats and B6C3F1 mice be exposed to long-term

(6 to 12 months) to Al fluoride complexes as part of a comprehensive neurotoxicology examination. Consideration should be given to also including an organoAl (perhaps citrate) as a representative compound.

Documenting the mineral characteristics of the drinking water and the rodent diet used in these studies will be crucial to the interpretation. Further, other ions in the diet, for example calcium and magnesium and other metals such as zinc and copper need to be documented. The parathyroid function in the rodent models also needs to be evaluated. Since cancer is not considered a high priority, the emphasis needs to be on neurobehavioral and cognitive function evaluation at multiple time points. A detailed neuropathological examination of the nervous system should be conducted with a traditional examination of other organs and tissues.

Short-term studies and developmental studies should included animals for EPA NHEERL investigators to investigate sensitive indicators of neuronal damage. It is recommended that the dosing be done under NTP conditions with the animals or tissues provided to EPA investigators who will assist in the evaluation of the potential neurotoxicity of Al species found in the drinking water.

Bone is a site of Al deposition and osteomalacia is associated with Al toxicity in dialysis patients and pre-term infants with parenteral nutrition. Therefore, research needs should include further studies about the possible role of the Al species found on drinking water on bone development and metabolic bone disease.

There are several new transgenic mouse models for degenerative neuropathologies. This study offers the opportunity to evaluate the potential role of Al in enhancing the onset of disease in these models. This offers both the opportunity for evaluation of the Al species found in the drinking water but just importantly may lead to the development of useful animal models for neurotoxicity evaluation.

The EPA Office of Water has also expressed interest in potential effects in offspring that may result from exposure to Al during pregnancy and lactation. Therefore Al developmental reproductive toxicity studies need to also be considered.

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