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ALUMINUM TOXICITY IN MITOCHONDRIAL DYSFUNCTION AND ASD

BY NANCY MULLAN, MD, AND AMY YASKO, PHD, AMD, FAAIM

Currently, there is intense interest and discussion surrounding the high incidence of mitochondrial disease and/or dysfunction in children with autism spectrum disorders (ASDs). This interest is fueled at least in part by the 2008 Hannah Poling decision.[1,2] In this landmark case, the federal government's Vaccine Injury Compensation Program (VICP) agreed to award damages to the Poling family when their daughter Hannah, who had an underlying mitochondrial disorder, developed autism-like symptoms after receiving a series of vaccines in a single day. Because Hannah Poling's father is a medical doctor who was in the department of neurology at Johns Hopkins Hospital at the time that his daughter's vaccine injury occurred, her case carried great weight. The Poling case, therefore, served to draw a great deal more attention to mitochondrial disorders within autism than these disorders had previously received.

A carefully executed review and meta-analysis of mitochondrial dysfunction in ASD by Rossignol and Frye discerned that the prevalence of full syndrome mitochondrial disease in children with ASD is significantly higher than it is in children in general.[3] Their analysis also revealed that many children with ASD have findings on laboratory tests that indicate some degree of mitochondrial dysfunction, although not full syndrome mitochondrial disease. Together, these findings indicate a high degree of abnormal mitochondrial function in children with ASD, which other research has corroborated.[2,4-9]

The cause of the high comorbidity between ASD and mitochondrial dysfunction remains obscure. Most ASD patients do not have a genetic abnormality that would explain the association.[4] Nonetheless, there is a great deal of overlap between the symptoms of ASD and the symptoms of genetic mitochondrial diseases, many of which progressively affect multiple body systems. Genetic mitochondrial diseases especially impact organs that have high energy demands, such as the brain and nerves. Because the brain has the highest energy demand of any tissue, mitochondrial disease causes a variety of neurological problems, including intellectual disability, seizures, developmental regression, gastrointestinal problems, and lack of coordination. In addition, because muscles have a high demand for mitochondrial energy, low muscle tone, weakness, and fatigue are features of many mitochondrial diseases. These neurological and muscle-related symptoms are very commonly found in children with ASD as well, though patients who have ASD and biochemical evidence of mitochondrial dysfunction have relatively milder, non-progressive forms of mitochondrial dysfunction when compared with cases of mitochondrial disease caused by genetic aberrations.[10]

SEARCHING FOR EXPLANATIONS

The search continues to identify the reason(s) why so many children with ASD have associated abnormal mitochondrial functioning and biomarkers (as shown by results of laboratory testing). Attention is turning away from genetics toward the environment. As a first line of evidence that environmental factors are involved, there is no question that increased free radicals impair mitochondrial function.[11] This fact may be particularly significant for children with ASD since they have higher levels of oxidative stress and lower levels of glutathione, a major antioxidant that is important for mitochondrial function.[12-14] Children with ASD have been shown to have reduced levels of antioxidants in general when compared with typically developing children.[15-17]

Second, environmental exposure to toxins has come under scrutiny in the search for explanations regarding the link between ASD and mitochondrial dysfunction. Studies have suggested that the mitochondria of children with ASD are more vulnerable to environmental toxicants than the mitochondria of their non-ASD peers.[18] Rossignol and Frye also have looked at this issue, stating the following:

The cause of the high comorbidity between ASD and mitochondrial dysfunction remains obscure. Most ASD patients do not have a genetic abnormality that would explain the association.

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Aluminum offers another plausible explanation as to why the rate of autism did not decline upon the removal of thimerosal from most vaccines. During the highly publicized phase-out period for mercury in 1999-2002, four doses of a new vaccine with high aluminum content were added to the CDC vaccination schedule. During 2005, another two doses of high-aluminum vaccine were added.

> *...In vitro exposure to diesel exhaust particles (DEP) has been shown to inhibit mitochondrial function, and elevated environmental concentrations of DEP have been associated with ASD. Other environmental toxicants that inhibit mitochondrial function and have been associated with ASD include mercury, lead, cadmium, PCBs, and pesticides.*[19] *(p. 26)*

Toxicants such as those listed by Rossignol and Frye have attracted the attention of researchers and clinicians looking for the causes of the current epidemic of autism for some time. Due to public outcry and insistence, thimerosal (a mercury-containing preservative) was phased out of most vaccines from 1999 through 2002. Thimerosal-laden vaccines were not recalled outright, however, meaning that the many doses remaining in doctors' offices and pharmaceutical distributors' warehouses continued to be administered. During this "phase-out" period, moreover, the Centers for Disease Control and Prevention (CDC) actually added flu shots containing thimerosal to the vaccines recommended for all babies from 6 to 23 months. The CDC also extended the list of recommended flu shot recipients to include first-trimester pregnant women, which is tantamount to giving mercury to the fetus. As a rule, the younger the organism, the more damaging is the toxicant. The persistence of thimerosal in flu shots may, in part, explain why the incidence of autism did not decline after the reported thimerosal phase-out. Ironically, the absence of a decline in autism after the phase-out has been used by the proponents of vaccines as they are currently formulated and scheduled to support their contention that vaccines are safe.[20,21]

THE ROLE OF ALUMINUM

Aluminum added to childhood vaccines functions as an adjuvant to potentiate the impact of the vaccine, although the mechanisms by which aluminum enhances immune response are poorly understood.[22] Aluminum offers another plausible explanation as to why the rate of autism did not decline upon the removal of thimerosal from most vaccines. During the highly publicized phase-out period for mercury in 1999-2002, four doses of a new vaccine with high aluminum content were added to the CDC vaccination schedule. During 2005, another two doses of high-aluminum vaccine were added. Infants who follow the CDC schedule now receive repeat doses of aluminum in their vaccines as shown in Table 1.

In all, infants are injected with 250 mcg of aluminum at birth; an additional 1,225 mcg of aluminum at 2 months; another 975 to 1,000 mcg at 4 and 6 months, respectively; and 1,475 mcg from 12 to 18 months. *The resulting grand total of parenteral (injected through the skin) aluminum received in the first 18 months of life is almost 5 milligrams (or 5,000 mcg).*

The US Food and Drug Administration (FDA) is aware that aluminum is dangerous. The FDA recommends that patients with impaired kidney function, including premature neonates, be limited to 4 to 5 mcg per

The US Food and Drug Administration (FDA) is aware that aluminum is dangerous.

Table 1.
Aluminum in childhood vaccines, birth to 18 months

Vaccine	Schedule	Total doses	Aluminum per dose (micrograms)	Total aluminum per vaccine (micrograms)
Hepatitis B (Engerix-B)	Birth and 2 and 6 months	3	250 mcg	750 mcg
DTaP (Infanrix)*	2, 4, 6, 15 months	4	625 mcg	2,500 mcg
Hib (Pedvax)†	2, 4, 12 months	3	225 mcg	675 mcg
PCV (Prevnar)‡	2, 4, 6, 12 months	4	125 mcg	500 mcg
Hepatitis A (Havrix)	12 and 18 months	2	250 mcg	500 mcg
TOTAL:	**By 18 months**	**16**	**n/a**	**4,925 mcg**

* Diphtheria, tetanus, and acellular pertussis † Haemophilus B conjugate ‡ Pneumococcal conjugate vaccine

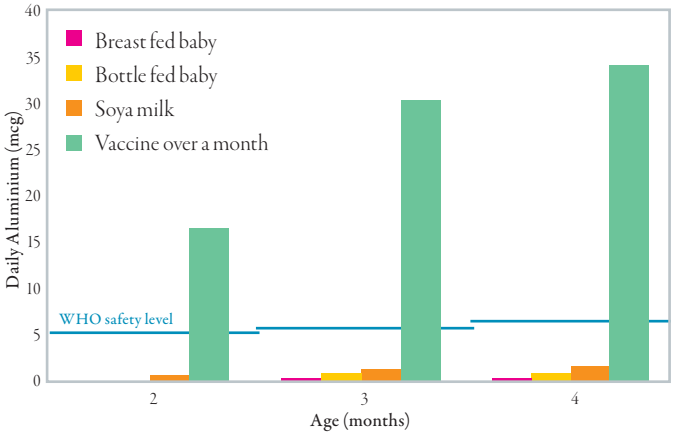
kilogram of body weight of parenteral aluminum per day.[23] Over this limit, patients will accumulate aluminum in their tissues at levels associated with central nervous system and bone toxicity. Aluminum retention and tissue loading may occur at even lower levels depending upon the patient's kidney function.

The 250 mcg of aluminum contained in the hepatitis B vaccine given at birth is significantly higher than the FDA-advised limit for the typical 6-10 pound neonate (10-20 mcg). At two months of age, when babies typically weigh 15 to 20 pounds, they receive 1,225 mcg of aluminum from their combined vaccines, which again is significantly higher than the recommended safe levels. Although infants also take in some aluminum in their food, Figure 1 shows that the aluminum load from vaccines (shown in green) is far greater than that from any ingested substance (only just visible on the chart) and also well above the safety levels put forth by the World Health Organization (WHO). Chapter 21 of the US Code of Federal Regulations [610.15(a)] limits the amount of aluminum in biological products, including vaccines, to 0.85 mg/dose or 850 mcg.[24] Clearly, the cumulative amount of parenteral aluminum in multiple doses of aluminum-containing vaccines given simultaneously well exceeds 0.85 mg.

Figure 1

The aluminum load from vaccines is well above the World Health Organization safety level

Infant's body load of aluminium from diet and vaccines over a month (assumes 0.7% absorption; range 1%-0.01%)



Source: Halvorsen R. How much aluminium does a baby receive in routine vaccinations? Available online at: http://web.mac.com/richardhalvorsen1/aluminium_over_month.html

The CDC's Agency for Toxic Substances and Disease Registry (ATSDR) released its updated *Toxicological Profile for Aluminum* in 2008 (see selected excerpts in sidebar).[25] This 357-page CDC report, signed by Dr. Julie Gerberding (former CDC director and ATSDR administrator and current president of Merck's vaccine division), details the many routes of possible exposure to aluminum and its impact on the different systems of the body. The profile notes that aluminum is a toxic substance, but that it can be found in consumer products including antacids, astringents, buffered aspirin, food additives, antiperspirants, and cosmetics (p. 2). Aluminum compounds also may be added during the processing of foods such as flour, baking powder, coloring agents, and anticaking agents (p. 3).

Overall, the CDC would like us to be very relaxed about aluminum. While the report provides a great detail of information about inhalation, oral, and dermal exposures, nowhere does the *Toxicological Profile for Aluminum* contain information about the impact of parenteral exposure, which is the most potent route for introducing any substance into the body. Although the ATSDR profile notes that there is aluminum in vaccines, the document asserts that it is a small amount. The document also reasserts that vaccines may contain no greater than 0.85 mg of aluminum per dose (p. 4) but says nothing about the recommended vaccination schedule that allows multiple aluminum-containing vaccines to be given at the same time.

ALUMINUM TOXICITY IN NEONATES AND INFANTS

There is no scientific evidence that injected aluminum is safe. In their article titled "Aluminum vaccine adjuvants: are they safe?," Tomljenovic and Shaw state the following:

> *Experimental research...clearly shows that aluminum adjuvants have a potential to induce serious immunological disorders in humans. In particular, aluminum in adjuvant form carries a risk for autoimmunity, long-term brain inflammation and associated neurological complications and may thus have profound and widespread adverse health consequences.*[26]

A 1996 American Academy of Pediatrics (AAP) position paper on aluminum toxicity in infants and children drawn up by its Committee on Nutrition begins its discussion by noting that aluminum "has no known useful biological function." The AAP goes on to state that aluminum's "toxic effect on living organisms has become clear," adding that "Aluminum is now being implicated as interfering with a variety of cellular and metabolic processes in the nervous system and in other tissues."[27]

Adult humans have a variety of mechanisms to reduce the impact of inhaled or ingested aluminum. Even so, aluminum can accumulate in adult bone, urine, and plasma. In adults, aluminum also can displace iron from its protective proteins, thereby increasing iron-related diseases such as breast cancer, liver degeneration, neurodegenerative disease, diabetes, heart failure, and atherosclerosis.[28]

In healthy infants, elevated plasma aluminum levels have been reported when the infants are given aluminum-containing antacids.[29] Evidence suggests that tissue distribution of aluminum may be age-dependent. This is not surprising, given that neonates and infants do not have the same protective mechanisms in place as adults. Aluminum can be transferred to offspring through both the placenta and milk. Thus, fetuses, premature babies, and nursing infants are at particular risk for aluminum toxicity. Aluminum competes with essential trace elements needed for rapid growth and development. When aluminum crosses the placenta, it accumulates in fetal tissue, causing *in utero* death, malformations, delayed ossification, delayed growth, and developmental retardation.

There is no scientific evidence that injected aluminum is safe.

Numerous animal studies have shown that aluminum administered to pregnant or lactating females is transferred to the brain of their offspring.[30] A study that administered radioisotopic aluminum to pregnant or lactating rats showed that considerable amounts of this element transferred to the offspring's brains.[31] Specifically, aluminum injected into pregnant rats not only transferred transplacentally to the fetuses but was 30% higher in the fetal brain than in the liver; in comparison, the mothers' brains contained only 1% of the amount of aluminum found in the liver.[32] This suggests that the fetal brain may act as a sink for aluminum.[32] Aluminum exposure during gestation also leads to the impairment of neuromotor maturation and learning ability in fetal animals and young offspring.[33-35]

Aluminum is thought to cause neurotoxicity through a number of mechanisms. It has been postulated, for example, that the neurotoxic effects of aluminum might be relevant to a disturbance of the global recruiting action response and synchronization, which are responsible for wide networks of cortical activity in the frontal cortex.[36] In addition, in animal studies the activity of the neurotransmitter acetylcholine was increased or decreased depending on the duration of exposure to aluminum in the striatum, the hypothalamus, and the olfactory bulb of the rat brain.[37]

ALUMINUM AND MITOCHONDRIAL DYSFUNCTION

Aluminum has pro-oxidant activity, in part related to its ability to free iron from its bound form in other molecules.[38] It produces free radicals that put the organism under oxidative stress and, as already mentioned, impair mitochondrial function.[11] Because children with ASD have higher levels of oxidative stress and lower levels of antioxidants, especially glutathione,[12-17] their mitochondria are, therefore, particularly vulnerable to oxidative damage. Aluminum directly inhibits specific enzymes in the mitochondria as well as having indirect effects on mitochondrial oxidation.

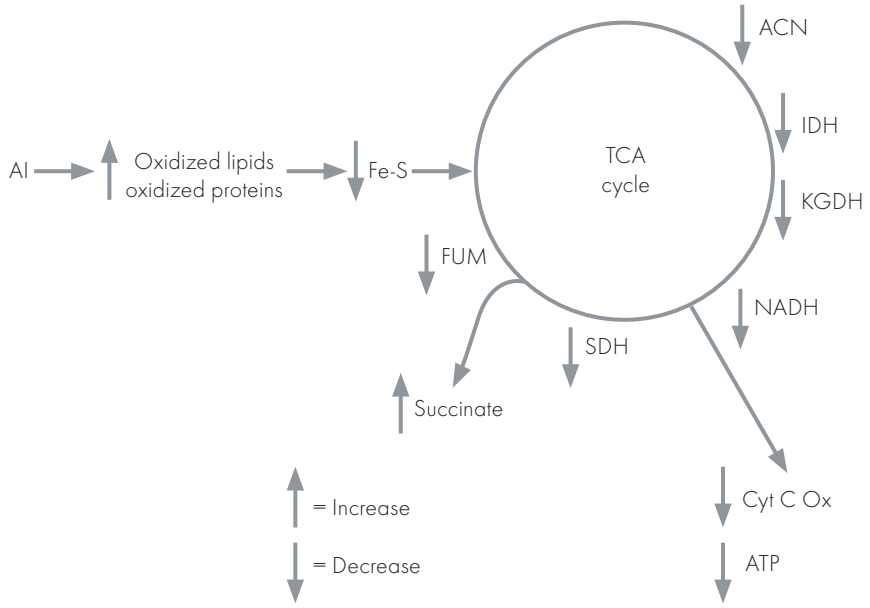
Investigators who exposed rats to soluble salt of aluminum (AlCl3) and checked its influence on mitochondrial respiratory activity in the liver, brain, and heart found that aluminum had a negative impact on mitochondrial activity in all three organs.[39] In another animal study, investigators examined the impact of aluminum on rat liver and found that it impaired the energy production cycle in liver mitochondria.[40] Specifically, this research group demonstrated that the activity and expression of six mitochondrial enzymes were decreased in activity and function following exposure to aluminum (Figure 2). These six enzymes are part of the cycle in the mitochondria that generates energy that can later be used by cells for a wide range of activities, many of which are compromised by mitochondrial dysfunction. The six affected mitochondrial enzymes were:

- succinate dehydrogenase (SDH)
- alpha ketoglutarate dehydrogenase (alpha-KGDH)
- isocitrate dehydrogenase (IDH)
- fumarase (FUM)
- aconitase (ACN)
- cytochrome C oxidase (Cyt C Ox)

To put the study's results another way, the study found that aluminum decreased the activity of 5 out of 10 key enzymes that the mitochondria use to generate energy via the tricarboxylic acid (TCA) cycle (also called the Krebs cycle) in addition to affecting an enzyme in the respiratory chain.[40] Other researchers[41] demonstrated that the inhibitory impact of aluminum on mitochondrial enzymes could also be extended to studies on the heart. Using porcine heart, the researchers were able to demonstrate inhibition of the enzyme IDH by aluminum, leading to the conclusion that "The inhibition of NADP isocitrate dehydrogenase by two forms of aluminum ions may explain aluminum toxicity in various tissues and organs."[41]

Figure 2

The tricarboxcyclic acid cycle in the mitochondria (Krebs cycle) that generates energy is impaired by aluminum



Mailloux RJ, Hamel R, Appanna VD. Aluminum toxicity elicits a dysfunctional TCA cycle and succinate accumulation in hepatocytes. *J Biochem Mol Toxicol.* 2006;20(4):198-208.

Specific research is needed, of course, to extend these findings to individuals with autism. However, given the known toxicity of aluminum and its impact on mitochondria, it seems likely that in time aluminum will be added to the list of environmental toxicants that produce mitochondrial dysfunction in patients with ASD. If confirmed, the role of aluminum in mitochondrial dysfunction would point to a need to heed the words of Redhead and colleagues from the National Institute of Biological Standards and Control in the United Kingdom, who studied the accumulation of aluminum in the brain of test animals following vaccines containing aluminum as adjuvant back in 1992.[30] Twenty years ago, these authors recommended looking for alternatives to aluminum as adjuvants in compromised populations:

> *Alternatives to aluminum adjuvants, such as calcium phosphate, have been developed as potential adjuvants for DTP vaccines and it would seem prudent to explore the use of such alternatives in children with suspected impaired renal function.*[30]

Excerpts from the CDC's Toxicological Profile of Aluminum[25]

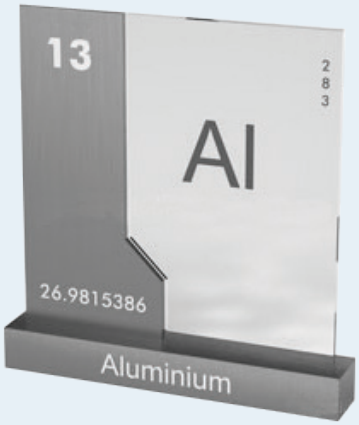
An average adult in the United States eats about 7-9 mg of aluminum per day in their food. If you are exposed to aluminum, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it.

COMMENTS ON ROUTES OF EXPOSURE AND PRESUMED SAFETY:

A small amount of the aluminum you breathe will enter your body through your lungs. A very small amount of the aluminum in food or water will enter your body through the digestive tract. An extremely small amount of the aluminum found in antacids will be absorbed.

A very small amount may enter through your skin when you come into contact with aluminum. Most aluminum in food, water, and medicines leaves your body quickly in the feces. Much of the small amount of aluminum that does enter the bloodstream will quickly leave your body in the urine.

Oral exposure to aluminum is usually not harmful. Some studies show that people exposed to high levels of aluminum may develop Alzheimer's disease, but other studies have not found this to be true. We do not know for certain that aluminum causes Alzheimer's disease.



Some people who have kidney disease store a lot of aluminum in their bodies. The kidney disease causes less aluminum to be removed from the body in the urine. Sometimes these people developed bone or brain diseases that doctors think were caused by the excess aluminum. Although aluminum-containing over the counter oral products are considered safe in healthy individuals at recommended doses, some adverse effects have been observed following long-term use in some individuals (p. 4).

Eating large amounts of processed food containing aluminum additives or frequently cooking acidic foods in aluminum pots may expose a person to higher levels of aluminum than a person who generally consumes unprocessed foods and uses pots made of other materials (e.g., stainless steel or glass). However, aluminum levels found in processed foods and foods cooked in aluminum pots are generally considered to be safe (p. 6).

COMMENTS ON TOXICITY IN ANIMALS AND HUMANS:

Some workers who breathe aluminum-containing dusts or aluminum fumes have decreased performance in some tests that measure functions of the nervous system. **Studies in animals show that the nervous system is a sensitive target of aluminum toxicity** (p. 5, emphasis added).

Very young animals appeared weaker and less active in their cages and some movements appeared less coordinated when their mothers were exposed to large amounts of aluminum during pregnancy and while nursing. In addition, aluminum also affected the animal's memory. These effects are similar to those that have been seen in adults (p. 6).

Occupational exposure studies and animal studies suggest that the lungs and nervous system may be the most sensitive targets of toxicity following inhalation exposure. … There may be a relationship between chronic aluminum exposure and subclinical neurological effects such as impairment on neurobehavioral tests for psychomotor and cognitive performance and an increased incidence of subjective neurological symptoms (p. 12).

There is a rather extensive database on the oral toxicity of aluminum in animals. These studies clearly identify the nervous system as the most sensitive target of aluminum toxicity and most of the animal studies have focused on neurotoxicity and neuro developmental toxicity (p. 13). Neurodegenerative changes in the brain manifested as intraneuronal hyperphosphorylated neurofilamentous aggregates, is a characteristic response to aluminum in certain species (p. 14).

Significant alterations in motor function, sensory function, and cognitive function have been detected following exposure to adult or weanling rats and mice or following gestation and/or lactation exposure of rats and mice to aluminum lactate, aluminum nitrate, and aluminum chloride. The most consistently affected performance tests were forelimb and/or hind limb grip strength, spontaneous motor activity, thermal sensitivity, and startle responsiveness. Significant impairments in cognitive function have been observed in some studies (p. 14).

Studies in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum contaminated dialysate and the use of aluminum-containing phosphate binding agents provide evidence that aluminum is an important etiologic factor in dialysis-related health disorders, particularly the neurological syndrome dialysis encephalopathy (p. 16).

Immunological alterations (decreased spleen concentrations of interleukin-2, interferon g, and tumor necrosis factor and a decrease in CD4+ cells) were observed in mice exposed to 200 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through postnatal day 180 (p. 17).

Memory loss, fatigue, depression, behavioral changes, and learning impairment were reported in five children who, over a 5-day period, consumed drinking water containing unknown levels of aluminum sulfate, which was accidentally placed in a water-treatment facility in England (Ward 1989). The water also contained elevated levels of copper and lead, a highly neurotoxic element, which leached from the plumbing systems due to the greater acidity of the water. Thus, the role of aluminum in the onset of the neurological symptoms is unclear. Acute-duration oral exposure to aluminum phosphide (19–157 mg Al/kg) caused altered sensorium in 4 of 16 persons who ingested it either accidentally or in suicide attempts (Khosla et al. 1988). Restlessness and loss of consciousness were observed in 10 of 15 people who ingested unknown amounts of aluminum phosphide (Chopra et al. 1986). The toxicity associated with aluminum phosphide ingestion was probably due to the formation of highly toxic phosphine gas rather than the aluminum exposure (p. 76).

Prolonged dialysis with aluminum-containing dialysates, possibly combined with oral treatment with aluminum hydroxide to control hyperphosphatemia, has produced a characteristic neurotoxicity syndrome which has been referred to as "dialysis dementia." The onset of neurotoxicity is rapid and marked by confusion, muscle twitching, grand mal seizures, coma, and death (p. 76).

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