Human exposure to aluminum

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Abstract

Aluminum is the third most abundant element in nature, accounting for nearly 8% of the Earth's crust. Because of its chemical activity, aluminum is not found naturally in its "free", or metallic, state. However, in its ionic or combined forms, aluminum is a truly ubiquitous element.

Because of the widespread use of metallic aluminum in cooking and packaging applications, the Aluminum Association has funded critical reviews of the world's literature on the health effects of aluminum and aluminum compounds for the past 30 years.

More recently, an extensive research and literature surveillance effort was developed to provide information on the neurological implications of aluminum, dietary intakes and body balance, and analytical capabilities. Based on these efforts the following conclusions can presently be drawn: (1) the cause (or causes) of Alzheimer's disease is not known; (2) the biological significance of aluminum found in the brain is not understood; (3) aluminum is poorly absorbed by the body; and (4) the normal ingestion of aluminum from food and water should have no adverse effects on human health.

Introduction

In 1886, the first practical and economic process for producing aluminum metal was discovered. Cookware was the first commercial application for the new metal. Shortly thereafter, claims of various adverse health effects from exposure to aluminum began to appear, but they did not originate from nor were they supported by scientific literature.

The first comprehensive treatise on aluminum compounds in food was published in 1928 (Smith, 1928). The author presented considerable evidence that aluminum is not injurious to health, but added, "Unfortunately, this question has become controversial by reason of conflicting commercial interests."

Starting in 1955, under sponsorship by the Aluminum Association, research teams at the Kettering Laboratory of the University of Cincinnati have periodically searched out and reviewed the world's literature on aluminum and health and published their findings. The first conclusion drawn (Campbell *et al.*, 1957) was that there is no need for concern among the public regarding hazards to human health from exposure to aluminum products. The review was updated in 1974 and the basic conclusions were reaffirmed (Sorenson *et al.*, 1974).

Since 1980, the literature reviews at the University of Cincinnati have been continuous. Recent reports (Krueger *et al.*, 1984; Krueger and Clark, 1988) raise questions about long-time exposure to medicinal doses of aluminum compounds and stress the importance of the ligands with which aluminum is associated since these affect the bioavalability and distribution of aluminum in the body.

When allegations concerning neurological effects of aluminum began appearing about 10 years ago the Association again turned to Kettering Laboratory, this time for an in-depth review of the literature on the neurological implications of aluminum. In addition, discussions began with leading investigators.

The Kettering report (Cooper *et al.*, 1981) concluded that there was no direct clinical or experimental evidence that aluminum is neurotoxic to humans or animals under ordinary conditions of environmental exposure. It was also noted that gaps exist in the knowledge of the significance of aluminum in the human body. This was thought to be principally because aluminum was not generally regarded as posing a health problem and, hence, drew little scientific interest or study.

The need was recognized for basic information on the way aluminum gets into the body, how much typically is absorbed, where it goes, and what effects it may produce. The Association set into place a long-range research program to provide information on these subjects. In addition, literature surveillance and contacts with investigators have been continued.

Occurrence of Aluminum

Aluminum is the third most abundant chemical element, constituting nearly 8% of the mass of the Earth's crust. Only oxygen and silicon are found in greater quantities. It is truly ubiquitous; it is present in soils and clays, in minerals and rocks and in the air and water - but not as the metal.

Because of its chemical activity, and its affinity for oxygen, aluminum was not known in its free, metallic state until about 150 years ago. Instead, aluminum is always found chemically combined with other elements particularly oxygen and silicon. Bauxite, a clay-like substance that is the principal ore of aluminum is a

Table 1 *Estimated daily adult intake of aluminum from various sources.*

Category	*Source*	*mg Al/day*
Food		
	Natural content	2 - 10
	Intentional additives (FDA-approved Al compounds)	20 - 50 +
	Unintentional additives (from metallic Al products)	<3.5[a]
	Total diet: literature values	10 - 100
	Greger	20 - 40
	FDA Study	9 - 14
Water		
	Natural content, alum	<1
Air		
	Dust, smoke, toiletries, sprays	<1
Medications		
	Antacids	50 - 1,000 +
	Buffered Aspirin	10 - 100 +

[a] Maximum value under "worst-case scenario."

combination of alumina (aluminum oxide), silica and iron oxides.

The aluminum industry chemically extracts alumina from bauxite, electrolytically reduces alumina to break the aluminum-oxygen bonds and produces useful metallic products. The industry has only been in existence for the past 100 years, a very short time relative to other metal production, and only an infinitesimally small percentage of the naturally occurring aluminum has been thus converted.

Even in its metallic form aluminum remains a chemically active element. What makes aluminum usable as a metal, in contrast to sodium for example, is that it reacts instantly with oxygen in the air to form a thin, invisible oxide coating (Epstein, 1984). The oxide adheres tightly to the metal surface and protects it from further oxidation and from attack by many substances. However, the oxide is only stable in a pH range of about 4.5 to 9 which means that aluminum is subject to chemical attack by both acids and alkalies.

Exposure to Aluminum

Figure 1 graphically illustrates how aluminum in the soil is acted upon by natural forces, carried into the air and bodies of water, and enters the food chain. Virtually all foods, water and air contain measurable amounts of the element. Thus it is practically impossible to avoid exposure to aluminum, but the human body appears to have adjusted well to its everyday exposures.

Table 1 lists the sources of aluminum which might be normally ingested. Estimates are given for the daily amounts of aluminum typically expected from those sources where data are available. The adult body content has been estimated at 295 mg (Skalsky and Carchman, 1983).

Food

The Food and Drug Administration (FDA) publishes a *Total Diet Study* which lists 234 foods commonly eaten in the US. Using one such list (Pennington, 1983), Greger

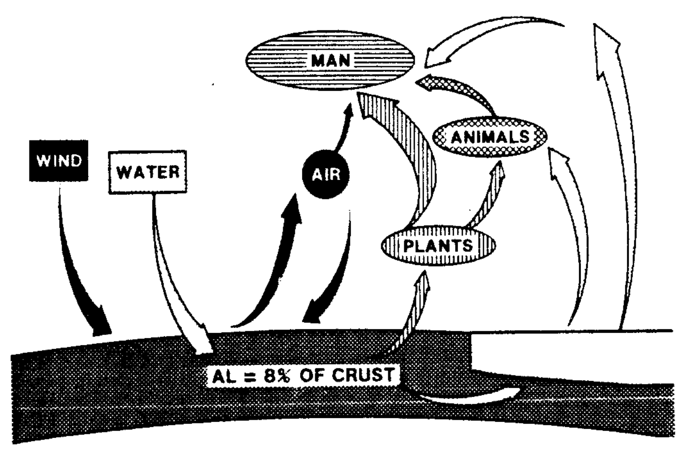

Figure 1 *The aluminum cycle.*

(1985) estimated the aluminum content of typical American diets to be from three to over 100 mg of aluminum daily, with most adults probably consuming between 20 to 40 mg/day. Amounts from earlier studies were estimated in the range of 10 to 100 mg/day. Researchers at FDA have recently analyzed the aluminum content of a large number of foods and Pennington (1988), using the 1984 Total Diet Study, estimated daily intakes of 9 mg/day for teenage and adult females and 12 - 14 mg/day for teenage and adult males.

Aluminum in the diet comes from several sources:

Natural content Because of the omnipresence of aluminum in soils and waters, virtually all foods contain measurable amounts of natural aluminum. The average adult American probably takes in between 2 and 10 mg of aluminum per day as "natural" content of the foods eaten. Pennington (1988) expects a minimum adult intake of 2 - 7 mg/day even if all additives and aluminum-rich foods were avoided.

Intentional additives The major source of aluminum in the typical US diet are foods with aluminum additives. These are FDA-approved aluminum compounds used as preservatives, coloring agents, leavening agents, *etc.*, in a wide variety of foods. According to Greger (1985) the amount of aluminum ingested in these compounds can range from about 20 to over 50 mg, but can vary widely depending on the dietary preferences. Pennington (1988) concurs that this represents the largest contribution of aluminum to the diet; estimates based on production data indicate intakes of 19 - 20 mg/day.

Unintentional additives The third source of aluminum in food comes from unintentional additives, *i.e.*, that which is added to the food through cooking, packaging and handling in metallic aluminum products. Based on a comprehensive study involving a variety of foods and analyses by state-of-the-art atomic absorption techniques (Greger *et al.*, 1985), Greger (1985) estimated that about 3.5 mg of aluminum per day could be added to the diet from this source if *all* cooking and handling is done with uncoated aluminum products. This represents only a small percentage of the average dietary intake of aluminum, even under conditions of highest use. Pennington (1988) concludes that aluminum that may migrate from aluminum containers, cookware, utensils or wrapping is probably not a major or consistent source of this element in the diet.

Water

Virtually all water contains small amounts of aluminum. Most aluminum compounds are relatively insoluble in neutral water, and there is usually less than 1 mg/L of aluminum in these waters although the levels were found to vary widely depending primarily on pH (Miller *et al.*, 1984). At this level, a typical intake of 1 to 2 L of water daily will contribute less than 1 mg aluminum to the diet.

Air

Aluminum compounds are present in air coming from various sources, such as dry soil, coal combustion and cigarette smoke. They are in household and workplace environments, particularly as aluminum oxide dust. Although amounts present vary from location to location, they are relatively small. The American Conference of Governmental Industrial Hygienists recommends a threshold limit value for aluminum and aluminum oxide in air of 10 mg/m^3, the same level as for other nuisance dusts. There are few environments where this level is exceeded. At ambient levels of aluminum in air, typically a few micrograms per cubic meter, intake from this source is far less than 1 mg/day based on inhalation of about 20 m^3 of air per day. A study of occupational exposures to aluminum is in progress.

Medications

Most antacids contain aluminum compounds, and one antacid tablet may contain 50 mg or more of aluminum. It is not unusual for a person with a stomach disorder to consume more than 1,000 mg of aluminum per day. Those with chronic stomach conditions, such as peptic ulcers, may take multiples of such doses over a considerable length of time. A buffered aspirin tablet may contain about 10 to 20 mg of aluminum. Aluminum compounds are also in many vaccines as adjuvants and carriers. Indeed, the World Health Orgnization and the Food and Drug Administration recognize aluminum's value in injectable drugs, and define permissible levels with full knowledge that the aluminum is going directly into the blood stream. Clearly, the amount of aluminum taken into the body through medications can dwarf the amount from normal ingestion and inhalation.

Absorption and Distribution in the Body

The gastrointestinal tract is only very slightly permeable to aluminum and provides a relatively effective barrier to its absorption (Skalsky and Carchman, 1983). Very little is known about human absorption and metabolism of aluminum. Such studies have been hampered by the lack of a useful aluminum radio-isotope for tracer studies and the difficulties in determining the trace levels of chemical aluminum present in the blood and body tissues (Savory and Wills, 1983). In particular, contamination from the ever-present aluminum in the environment makes analysis even more difficult and can lead to falsely elevated measurements (Brown *et al.*, 1983).

In a recent review an attempt was made to compensate for the lack of knowledge regarding aluminum in the body by substituting data for other, but chemically similar, metallic ions (Ganrot, 1986). By these comparisons, a more detailed picture of the behavior of aluminum in the body was simulated.

Homeostatic processes strive to maintain an equilibrium between the body and its environment. Most, if not all, of the aluminum that is ingested from whatever source is excreted. This was demonstrated in a study at the University of Wisconsin (Greger and Baier, 1983) in which eight adult males were fed 125 mg of aluminum per day by supplementing their controlled dietary intake with soluble aluminum lactate. On the average, no retention of aluminum was detected. Earlier studies had shown some retention of aluminum at daily intakes exceeding 1,000 mg/day (Skalsky and Carchman, 1983). Thus, apparently at some level of exposure between 125 and 1,000 mg/day, the body may absorb aluminum faster than it can excrete it

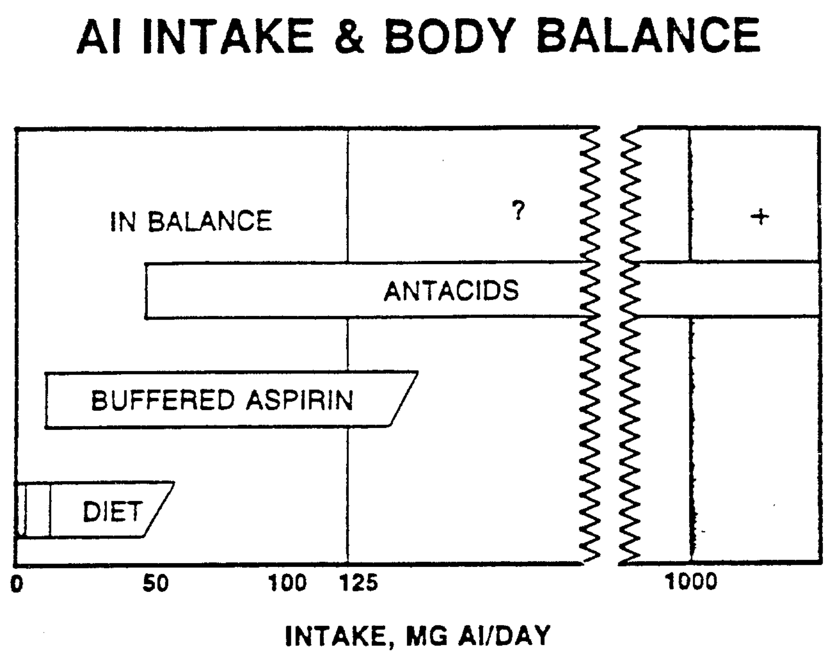

Figure 2 *Typical aluminum intakes and body balance.*

and aluminum may begin to accumulate. A comparison of intake levels and body balance is shown in Figure 2.

Aluminum is present in the body - in all organs, tissues and fluids - from birth. Because of this, some investigators have suspected that aluminum may be an essential element but have been unable to produce the aluminum-free environment needed to substantiate this supposition. This has also made it difficult to ascertain the biological significance of aluminum in the body.

Figure 3 graphically depicts the distribution of aluminum among the organs of the human body (Skalsky and Carchman, 1983). The graph is constructed as the logarithm of the ratio of the percent aluminum in the organ to the organ weight as a percent of the body weight, which has the effect of "normalizing" the values. The majority of the organs and tissues are shown to contain aluminum in relative proportion to their masses. Blood, brain and adipose contain significantly less aluminum than would be expected based on tissue mass, whereas bone and lung tissue contain more aluminum than expected based on their relative masses. This can be interpreted as an indication that aluminum does not accumulate in blood, brain and adipose to any great extent but does accumulate in bone and in the lung, with the data suggesting that bone may offer a major reservoir for aluminum absorbed into the body.

Discussion

During the past few years, several excellent reviews on possible causes of Alzheimer's disease have been published. Symposia have been held, and more are planned, on the possible role of environmental aluminum in this disease.

A Conference on Aluminum Analysis in Biological Materials, cosponsored by the Aluminum Association and the University of Virginia, was held in June 1983. Researchers in attendance agreed on two points: (1) the cause (or causes) of Alzheimer's disease is not known and (2) the biological significance of aluminum in the brain is not understood.

In a review article on Alzheimer's disease, Wurtman (1985) wrote "No one knows its cause or how to stay its inexorable course." Six models which now underline most research on Alzheimer's disease were presented and discussed: (1) faulty genes, (2) abnormal proteins, (3) an infectious agent, (4) an environmental toxin, (5) inadequate blood flow and (6) a neurotransmitter deficiency.

The search for the cause of Alzheimer's disease was further discussed by Katzman (1986). Regarding aluminum, Katzman concluded, "There is no evidence that exposure to such sources of exogenous aluminum as aluminum antacids, antiperspirants, or even the large amount used in renal dialysis increase the risks of Alzheimer's disease. Thus, a direct relation between exogenous aluminum and aluminum deposits in the brains of persons with Alzheimer's disease has not been established."

In September 1986 the National Institute on Aging (NIA) and the American Association of Retired Persons (AARP) jointly sponsored a research conference on Trace Metals, Aging and Alzheimer's Disease. Khachaturian (1986), the conference organizer, later wrote, "At the conference there was a general consensus on the following

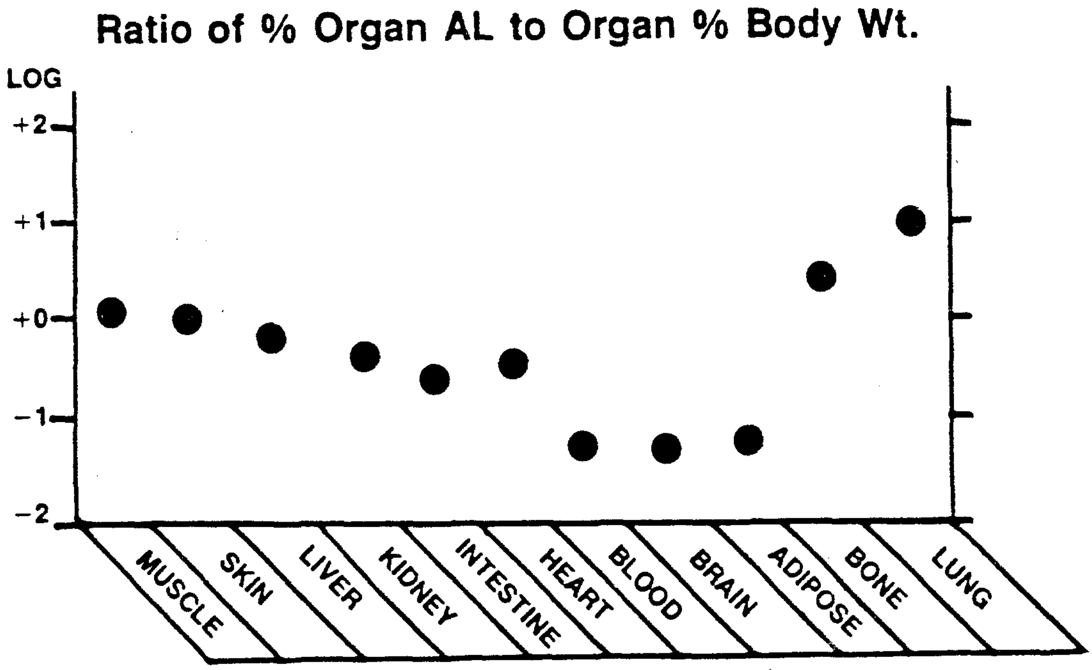

Figure 3 *Aluminum distribution in body organs.*

four points: (a) the nature of the materials in the classic morphological lesions of Alzheimer's disease are becoming increasingly clear; (b) there is clear evidence that aluminum can be a neurotoxin; (c) there is agreement that aluminum does accumulate in at least specific regions of Alzheimer's disease brains and that the chemistry of aluminum is so complex as to make the interpretation of data difficult just from the molecular level; and (d) there is no clear evidence that the removal of aluminum or the prevention of its accumulation would alter the course of Alzheimer's disease, which is the question with which we ultimately have to wrestle." Proceedings of the conference have not been published.

The November/December 1986 issue of *Neurobiology of Aging* was a special issue devoted to "Controversial Topics on Alzheimer's Disease: Intersecting Crossroads." In one of two review articles on aluminum, Crapper McLachlan (1986) concluded that the evidence does not support an etiological role for aluminum in Alzheimer's disease. He cited two opposing points of view on the functional significance of aluminum in Alzheimer's disease: (1) aluminum merely accumulates passively in neurons compromised by the Alzheimer degenerative process and the accumulation is of no significance to the mechanisms of the disease; or alternatively, (2) aluminum is a plausible candidate for a neurotoxic environmental factor acting in the pathogenesis of the degenerative processes.

The commentaries on the review ranged widely. One paper (Wisniewski, Moretz and Iqbal, 1986) maintained there is no evidence for aluminum in the etiology and pathogenesis of Alzheimer's disease.

The second review involving aluminum presented a novel hypothesis that Alzheimer's disease may begin in the nose and may be caused by aluminosilicates (Roberts, 1986). Terry (1986) commenting on the hypothesis wrote that it stands on two fragile legs. However, in a letter to *The Lancet*, Perl (1987) reported finding evidence of direct uptake into the brain of rabbits via nasal-olfactory pathways. No neurofibrillary changes were observed, and experiments with long-term exposures are reportedly underway.

A one-day session of Aluminum and Alzheimer's Disease was held in London in April 1987 as part of the Second International Symposium on Geochemistry and Health supported by the Royal Society. The major issues were reviewed; considerable controversy arose regarding studies purporting to show a link between aluminum in drinking water and death rates from dementia particularly in Norway and the United Kingdom. Proceedings of the Symposium have not yet been published.

Considerable attention has been given to new findings that strengthen the evidence of a genetic role in Alzheimer's disease and a demonstrated link with Down's Syndrome (Grundke-Iqbal, *et al.*, 1986; Kosik, Joachim and Selkoe, 1986; Robakis *et al.*, 1986; Robakis, Wisniewski *et al.*, 1987). However, in a recent paper on etiology of the disease, the authors contend that present evidence is sufficiently impressive to justify the provisional conclusion that a virus is responsible for Alzheimer's disease (Mozar, Dileep and Howard, 1987). In either case, the door is kept open that environmental factors, such as aluminum, may play a role in the development of the disease.

One final comment: in the last few years, three case-control studies were performed to assess the possible roles of various factors in the development of Alzheimer's disease (Heymann *et al.*, 1984; French *et al.*, 1985; Amaducci *et al.*, 1986). Included in the studies were occupational exposures and exposures to aluminum-containing antacids. There were no indications that such exposures increased the risk of the disease in the populations studied.

Conclusion

Through research efforts, through continuing surveillance of the world's scientific literature, and through personal contacts and discussions with leading researchers in the field, several conclusions have been drawn concerning the present state of knowledge regarding the relationship between aluminum and Alzheimer's disease (Epstein, 1985). These, listed below, continue to appear valid.

- The cause (or causes) of Alzheimer's disease is not known.
- The biological significance of aluminum in the brain is not understood.
- Aluminum is poorly absorbed by the body.
- Ordinary environmental exposure to aluminum is safe.

The Aluminum Association continues to fund research into the role of aluminum if any, in the human body. The scientific and medical literature on the health effects of aluminum is continually reviewed and discussions are held periodically with investigators at universities and research institutions to remain at the forefront of this subject. A comprehensive monograph on all aspects of aluminum and health has been recently published.

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