

# Aluminum exposure and Alzheimer's disease

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The regulatory agencies of the United States and Canada have placed aluminum on priority lists for research designed to fill data gaps relating to neurotoxicity. This is to create a factual basis for the establishment of health standards for drinking water. In this review, we consider evidence for a significant role for aluminum in AD. Aluminum has been implicated as a potential risk factor in Alzheimer's Disease (AD) and for elderly cognitive impairment by epidemiology studies of drinking water and a food study. Most people experience aluminum brain overload in the aging process. Aluminum levels over 20 times higher than those of a middle-aged group were found in a brain autopsy study of elderly persons, roughly correlating over the age period with densities of senile plaques and neurofibrillary tangles. Persons with AD have been found to experience increased absorption of aluminum and higher blood levels. More controversially, the majority of brain studies also show elevated aluminum levels, though there is disagreement over location of metal buildup. Clinical intervention to lower brain aluminum by chelation has slowed the progression of AD.

## 1. Introduction

Aluminum represents about eight percent of the Earth's crust and has no known biological function. It was first recognized as a human neurotoxin in 1886, in a Prussian army study of amputees whose wounds had been treated with alum to staunch bleeding [72]. The first laboratory animal study linking aluminum to brain damage was published in 1937 [52]. Since that time, an extensive literature has accumulated, exploring the metal's role in kidney dialysis encephalopathy [1], cognitive impairment [3,11], childhood learning disabilities [47], damage to the brain function of babies [10],

damage to brain function of workers (eg. welding and smelting) [43,53,67], AD [30,54,70] and elderly mental impairment short of dementia [26,40,41].

In the face of abundant aluminum exposure and its demonstrated toxicity, living organisms have both active and passive mechanisms to exclude aluminum. In the human, this includes gut design that reduces absorption, internal chelation and excretion primarily through the kidney, sequestration in bone and binding by transferrin, the blood based metal shuttle protein, which reduces blood levels. The brain has lower aluminum levels than many other tissues due to partial exclusion by the blood-brain barrier [83], an active efflux mechanism for aluminum from the brain, probably as Al-citrate [83,84], as well as removal by other mechanisms such as by the gastrointestinal peptide YY [6].

While a complete understanding of the mechanism of aluminum toxicity would be ideal before regulatory actions are taken to limit human exposure to aluminum in drinking water, food, drugs and cosmetics, standards of proof in the regulatory area focus generally on the weight of the evidence rather than a complete understanding of a disease process. For example, lead in gasoline, drinking water, and paint was regulated with relatively little information about the biology of action, which while still poorly characterized today have thoroughly lowered lead levels, providing important public health benefits. The essential question is the degree to which the present epidemiology studies linking aluminum to AD and elderly cognitive impairment can be buttressed by the biological literature.

The US Environmental Protection Agency, Health Canada and the US National Institute of Environmental Health Sciences plan to undertake laboratory animal studies of the effects of drinking water aluminum on brain function [36]. In both nations, aluminum has been put on a priority list of drinking water contaminants that need the filling of data gaps to allow establishment of health regulatory standards.

Here we review the epidemiology studies of AD in relation to aluminum exposure; look at studies of blood, bone and brain aluminum and review the capacity of chelation as an AD therapy.

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## 2. Epidemiology, body burdens, and exposure sources

All elderly persons face aluminum exposures putting them at potential risk of injury to health and brain function. Only a portion of elderly people progress to cognitive impairment or dementia, though this proportion doubles every five years after a population reaches 65 years of age. AD is a multi-factor disease with each person bringing to the table a different mix of genetics, exposures, nutrition and lifestyle, as well as a varied capacity to regulate metals including aluminum. Studies of kidney dialysis patients reveal a substantial individual variation in aluminum susceptibility [1]. Some of this stems from the aging process, but there also appears to be some genetic susceptibility to aluminum – such as variations in the genetic structure of transferrin [78].

### 2.1. Aluminum accumulates in the aging brain

Aluminum brain overload is experienced by all elderly people, even those who never develop AD. In 1991, it was estimated that Al<sup>3+</sup> accumulated in the human brain at a rate of 6 ug per year of life [21]. An autopsy comparison of the brains of normal elderly people aged 75 to 101, with those of younger persons aged 32 to 46, measured a dramatic increase of bulk aluminum levels [71]. Hippocampus aluminum content averaged 28 times higher in the non-demented elderly than in the younger people, and levels in the frontal cortex averaged 19 times higher. The brains of these elderly people showed hallmark changes typical of AD, such as senile plaques and neurofibrillary tangles, the densities of which correlated roughly with aluminum levels over the age period. Yet they were not demented. Younger adults with much lower aluminum levels showed few of these brain deposits. Compared to this large aluminum buildup over a lifetime, AD patients might experience only another doubling [12,14]. Al<sup>26</sup> studies showed that while aluminum is quickly excreted from most areas of the brain, it is retained for more than 35 days in others [83].

#### 2.1.1. Dietary exposures

An 8.6 fold increased risk of AD among residents of the Loretto Geriatric Center of Syracuse, New York who had consumed food prepared with aluminum additives or food cooked or stored in aluminum containers was reported [69]. The study controlled for body mass, family history of AD, head trauma and other factors.

#### 2.1.2. Drinking water exposures

While there has been considerable debate about the contribution of drinking water aluminum to AD, eighteen drinking water studies have linked aluminum level to elevated risks of AD and elderly cognitive impairment [42]. On the other hand, five epidemiology studies show no effect [31,48,73,81,82]. An additional study cannot be interpreted due to uncertainty about the water contamination measurements [56]. Most of the no-effect studies involved low exposures, small sample populations, and lack of inclusion of significant modifying factors, making a statistical resolution over background variability unlikely. For example, a study from Korea involved average aluminum levels of only 28 ug/liter [73].

A series of multi-factor water studies from Canada, France and Great Britain are of particular interest because they specifically identify aluminum as a key variable in both AD and elderly cognitive impairment risk – not only through levels of the metal itself in the drinking water, but also through the interaction with other water constituents that reduce the absorption of aluminum. Figure 1 summarizes seven studies that have changed our ideas about how to design epidemiology studies relating to aluminum. These and other studies highlight some of the issues relating to drinking water aluminum and AD.

*a. Importance of water pH and other factors in absorption.* Forbes and McLachlan's study of the influence of various drinking water components including aluminum on AD risks in 85 year or older Canadians underscores the potential importance of other water constituents that affect the absorption of aluminum [30]. In this study, aluminum in excess of 250 ug/liter was associated with a 10-fold increase in AD risk, after controlling for six other water factors.

With regard to these water factors, water pH had a large statistically significant effect on AD rates. Residents of water districts consuming drinking water with a pH in excess of 7.85 experienced a 50 percent reduction of AD risk compared to the more acid water districts. This and other epidemiology studies, as well as several studies of the complex aluminum chemistry associated with pH variations suggest that around 7.9 pH, aluminum forms compounds that are more difficult to absorb and of reduced toxicity [7,8].

The study found a 30 percent protective effect for fluoride, in the 0.5–0.98 ppm range. The mechanism by which fluoride acts is not known, but it has been speculated that it reduces aluminum absorption from food or drink, much as is the case with silicon. Fluoride

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### Drinking Water Epidemiology Studies Linking Aluminum And Related Water Constituents to Alzheimer's and Elderly Cognitive Impairment

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Forbes and McLachlan 1996: Aluminum and Alzheimers in 85 Year Olds [30]

- **9.95 Odds Ratio:** After control for six other factors, including ground or surface source, silicic acid, iron, water pH, fluoride and turbidity, water districts with aluminum exceeding 250 ug/liter experienced a 9.95 odds ratio risk for AD, which was statistically significant at the 0.05 level.
- Water pH in excess of 7.85 was associated with about a 50 percent reduction in AD risk; fluoride levels in the range of 0.5 to 0.98 mg/l reduced risk by about 30 percent and; and water turbidity in excess of 33 formazin units reduced risk about 40 percent. All these factors were statistically significant at the 0.05 level.

Forbes et al, 1994: Aluminum and Elderly Impaired Mental Functioning – Longitudinal Study of 75 Year Old Men [26]

- **1.72 Odds Ratio:** After control for nine other factors, including fluoride, water pH, ground or surface source, education, health and income and number of moves, drinking water aluminum equal or in excess of .0847 mg/liter was associated with a 1.72 odds ratio of risk for elderly impaired mental functioning.
- Fluoride equal to or in excess of 0.88 mg/l was associated with a 36 percent reduction of risk, water pH in the band between 7.85 and 8.05 was associated with a 60 percent reduced risk compared to more acid water and about a 30 percent reduced risk compared to more alkaline water. It was an U shaped curve. Finally, ground water was associated with about a 70 percent reduction of risk. (This water is not treated with Alum.)

Forbes, 1995: Aluminum and Alzheimer's From Death Certificates [28]

- **3.54 Odds Ratio:** After control for five variables, drinking water aluminum equal or in excess of 0.336 mg/liter was associated with an odds ratio of 3.54 for AD.
- Water pH in the range of 7.85 to 7.95 was associated with a 30 percent reduction of AD rates, compared to both more acid and alkaline waters. It was a U shaped curve. Silicon dioxide levels equal or in excess of 1.5 mg/liter were associated with a 6 percent reduction in risk.

Fig. 1.

appears to be effective over a fairly wide pH range [26]. There was also a 42 percent reduction in AD risk in water districts with high water turbidity – evidence that the utility had not used alum as a coagulant and but also an indication of possible preventative effects of other constituents of turbid water.

*b. Skin, lung and nose absorption.* The substantial effect of a more alkaline water pH in reducing both AD and elderly cognitive impairment risks at any given aluminum level is consistent with the idea that absorption of aluminum from drinking water takes place primarily through the more alkaline skin, lung and nose surfaces, as in taking a shower or bath, rather than through the highly acid stomach and the remainder of the gut [29].

The significant correlations shown by seven studies between reduced AD and elderly cognitive impairment risk and higher water pH would not be possible if the gut was the primary surface of absorption, because stomach acid would instantly acidify the water.

There is striking evidence from laboratory and worker studies that these more alkaline body surfaces can be relatively efficient in absorbing aluminum. For example, Anane found that aluminum applied to the skin of laboratory animals penetrated to the brain [4,5]. Likewise, Perl and Good found that aluminum injected into the nose of laboratory rabbits went directly into the brain through the olfactory bulb [66]. And Gitelman finds the presence of a sensitive uptake process for alu-

McLachlan, 1995: Alzheimer's Identified From the Canadian Brain Tissue Bank and Compared to Drinking Water Aluminum in Ontario [53][54]

- 2.5 Odds Ratio: Drinking water aluminum in excess of 100 ug/liter carried an odds ratio for AD of 2.5, equivalent to the increased risk of developing AD among those with the APOEε4 allele.
- 6.7-8.14 Odds Ratio: Depending on how the AD patients were grouped, drinking water containing 175 ug/liter of aluminum was associated with an odds ratio of developing AD of 6.7 to 8.14.

Rondeau et al, 2000: Drinking Water Aluminum and Alzheimer's in France – An Eight Year Follow-Up Study [70]

- 2.14 Odds Ratio: The best fit model (#5) found drinking water aluminum in excess of 0.10 mg/liter associated with a 2.14 odds ratio for AD.
- Silica in excess of 11.25 mg/liter was associated with about a 27 percent reduction of risk.
- Control factors included age, gender, education, place of residence and wine consumption.

Jacqmin-Gadda et al, 1996: Silica and Aluminum in Drinking Water and Elderly Cognitive Impairment [41]

- The threshold for an effect of aluminum on elderly cognitive impairment was very low at 3.5 ug/liter.
- 1.30 Odds Ratio: Water districts with high aluminum but low silica and low pH experienced a 1.30 odds ratio for elderly mental impairment.
- 0.75 Odds Ratio: But high aluminum combined with high silica and high pH (in excess of 7.35) showed an odds ratio of only 0.75. French water silica levels range from 4.2 to 22.4 mg/liter, and the threshold for effects on elderly mental impairment was found to be 10.4 mg/liter.

Taylor et al, 1995: Early Onset Alzheimer's and Drinking Water Aluminum and "Soluble" Silicon in Great Britain [75]

- At about 3.5 mg/liter of "soluble" silicon, "soluble" aluminum fell to less than 25 ug/liter in all districts.
- 0.8 Odds Ratio: For this population of less than 65 years of age, the odds ratio of having AD where drinking water soluble silicon exceeded 3 mg/liter was 0.8 – suggestive a 20 percent reduction of risk. But the sample size was very small, and the results not statistically significant.

Fig. 1. continued.

minum through airway exposure [32]. Davenport and Goodall point out one exception to the suggestion that drinking water aluminum may be primarily absorbed through skin, lung and nose exposure [16]. Reconstitution of orange juice using city water containing aluminum created an elevated aluminum level, and complexed with citrate could present a much greater uptake of aluminum than a similar volume of tap water.

*c. Sensitive drinking water epidemiology requires multi-factor analysis.* Forbes' series of multi-factor studies from Ontario, indicate that water districts with drinking water aluminum below 100 ug/liter, with wa-

ter pH close to 7.9 and with about 1 ppm of fluoride can achieve a 70 percent reduction of elderly mental impairment and large reduction of AD risks [26,28]. The failure of any epidemiology study to control for water pH, with its 50 percent effect, would sharply reduce its likelihood of discovering an effect of aluminum on AD or elderly cognitive impairment risk. That is also true of other active water variables like fluoride, silicon, turbidity and calcium.

Two studies conclude that drinking water silicon in excess of 10 ppm completely neutralizes the effects of higher aluminum contamination on both AD and

elderly cognitive impairment risk [41,70]. As Jacquemin-Gadda summarized:

“... The association between cognitive impairment and aluminum depended on the pH and concentration of silica: high levels of aluminum appeared to have a deleterious effect when silica concentration was low, but there was a protective effect when the pH and the silica level were high. The threshold for an aluminum effect, however, was very low (3.5 ug per liter) and did not support the hypothesis of a deleterious effect for only high levels of aluminum” [41].

Silicon bonds with aluminum, and can protect fish from death in waters enriched with aluminum [9]. Similarly, a study of early onset AD in the UK found that when “soluble” silicon in the drinking water exceeded about 3.5 ppm, soluble aluminum fell to very low levels [75]. While the sample size was too small to allow statistical significance, water districts where soluble silicon levels exceeded 3 ppm experienced a 20 percent reduction of early onset AD risk. Silicon is a safer alternative for high aluminum refractory waters than fluoride, which has been demonstrated to have worrisome biological effects [46,80].

*d. Better definition of AD improves epidemiology results.* Today, it is still difficult to identify all of the AD cases during life with existing testing methods, which will reduce the sensitivity of any epidemiology study. Unlike Canada, neither death certificates nor methods for measuring aluminum in drinking water are standardized in the United States. As a result, it would be difficult to replicate the Ontario epidemiology studies on drinking water aluminum in the United States. McLachlan's study from Ontario confirmed the presence of AD in his drinking water study population based on the Canadian Brain Tissue Bank rather than from death certificates [53,54]. He found that drinking water in excess of 100 ug/liter of aluminum carries an AD risk equivalent to carrying the APOE $\epsilon$ 4 allele. The effects of aluminum were dose related. The odds ratio of having AD was 2.6 at 100 ug/liter of water aluminum and increased to 7.6 at 175 ug/liter. It should also be noted that an unpublished study by William Forbes found that these odds ratios were increased when fluoride was added as a second variable to McLachlan's study.

An accidental spillage of aluminum sulfate into the water supply of Camelford, UK produced damage to cerebral function that persisted three years among persons aged in their early 40's, although the high exposure period took place over only a few weeks [2]. While the

analysis of this spill is controversial because the sample was self-chosen as part of a court case, it employed a very sensitive neurological test method, and the results are similar to findings for dialysis patients, exposed to aluminum but without overt aluminum toxicity [3].

*e. Iron coagulants can substitute for alum.* Much of the biologically active aluminum exposure from the public water supply comes from alum, aluminum sulfate, added by the water utility as a coagulant [18,57]. The replacement of alum with iron coagulants not only reduced aluminum contamination, but also reduced iron levels in the finished water which addresses concerns that iron coagulants might pose a risk of iron overload in elderly people [57]. Furthermore, the Framingham Study demonstrated that inorganic iron presented in food and drink is not a significant source of iron overload to the elderly, suggesting that iron coagulants do not pose the health risk associated with heme iron and vitamin pills [24]. Further, iron coagulants are equally effective if not more so than alum in purifying drinking water [15,20,37,57,76] while presenting no additional cost [49,76]. As is the case with substitution of aluminum based baking powder or aluminum based antacids with alternatives constituted with calcium, cost is not the major basis of decision.

*f. Control of drinking water pH is an inexpensive method to reduce aluminum toxicity:* The Canadian studies by Forbes and McLachlan indicated that the maintenance of drinking water in a pH band close to 7.9 can reduce AD rates by 50 percent. This is an inexpensive program conferring other benefits for water utilities. More alkaline water does reduce corrosion, water main breaks, and leaching of lead and copper into the finished water [45].

### 2.1.3. Other aluminum exposure sources

A range of drugs like antacids, buffered aspirin, cosmetics like deodorants, vaccines [65] and the leaching of aluminum from cola cans present a significant chronic exposure to the population [19]. Graves found that the use of aluminum based deodorants increased risk for AD by 60 percent, whereas use of antacids based on aluminum resulted in a 30 percent reduction of AD risk [35]. Her study raises the question of how it is possible that low levels of aluminum intake from drinking water or deodorants generate higher rates of AD, while very high aluminum intake from antacids will sharply reduce incidence? The answer may lie in the sensitivity of some individuals to aluminum overload due to genetics [78] or possibly to individual variations in transferrin abundance [23] or the efficiency of

the various mechanisms of metal regulation including individual variation in kidney function which is known to decline with age. It is well documented that high aluminum exposure can kill kidney dialysis patients with marked differential in susceptibility [1].

The key issue is that the published antacid studies are retrospective rather than longitudinal. What is called "mortality bias" in epidemiology may be a controlling factor. The evidence is consistent with the idea that the high dosage of aluminum from antacids may represent a slow cumulative lethal dose [26] for elderly individuals who absorb and retain the metal better, as do many AD patients [74]. Antacids are known to significantly increase aluminum blood loadings. Roberts compared aluminum serum levels and urine output of AD patients with patients on regular aluminum hydroxide therapy, and concluded that the "increased absorption of aluminum in dementia patients is equivalent to the intestinal loading of Aludrox therapy" [68].

## 2.2. Aluminum in blood, bone and brain in AD

Numerous studies demonstrate that Alzheimer's patients experience elevations of blood, bone and brain aluminum, though there is individual variation.

*Blood levels in AD.* One study found mean serum Al levels in AD patients to be about 60 percent greater than serum levels of matched controls, and that blood levels also tended to rise with the aging process [85]. Others confirm elevated serum Al levels in AD and an increased absorption in dementia [60,68]. In AD patients younger than 76 years, aluminum absorption was measured at three times faster than controls, though that was not true of the older AD cases compared to their age-matched controls [74]. And the curve of aluminum absorption turned up sharply after the age of 65 to resemble the rate of increase of dementia in this same age group – doubling every five years. Down's Syndrome patients – most of whom develop the pathological changes of AD before the age of 50 – absorbed aluminum six times faster over a 60 minute period than controls of the same age [59].

*Bone levels in AD.* While some studies of patients found AD patients to have higher aluminum bone levels than age and sex matched controls [58] other studies found no elevation [39]. But, it is difficult to reconcile higher blood levels without higher bone levels, given that bone is the primary storage area for the metal.

*Brain levels in AD.* Most but not all studies of the brain of AD patients find elevated aluminum [53]. An early study of neocortical gray matter found aluminum

levels in normal people averaging 0 to 4 ppm of dry weight, compared to 0 to 8 ppm for AD patients [14]. More recently, the LAMMA method found roughly twice the level of aluminum and iron in the neurofibrillary tangles, the nuclei of neurons and neuropils in relevant brain sections in cases of AD and dementia pugilistica (DP) patients [12].

Landsberg, on the other hand, concluded in their 1992 study that any aluminum found in senile plaques was an artifact of the stains [44]. To answer the claim that stains were responsible for the elevated aluminum in AD brains, the LAMMA method was used to analyze tissue processed in parallel, stained and unstained. Selective accumulation of Al was attained in all 10 subjects with AD. Probe sites directed to neurons identified in snap-frozen cryostat sections from 2 subjects with Alzheimer's disease revealed similar spectra with prominent aluminum-related peaks, suggests that elevated aluminum is not related to exogenous contamination through fixation, embedding, or other procedures prior to analysis [34]. Use of a chelating autoclave method with desferrioxamine on AD brain sections prior to Morin histochemistry attenuated the positive fluorescence of NFT, indicating Al removal from them [61].

## 2.3. Metal dysregulation in Alzheimer's disease

The increased aluminum and iron levels in AD may be due to global dysregulation of metal transport in AD [12]. Lower levels of serum transferrin (iron transport protein) with no difference in serum ferritin (iron storage protein) were noted in AD [23]. Transferrin binding to Al is a primary sequestration mechanism for aluminum, and with other factors maintains reduced blood levels. Further, ferritin from the cerebral cortex in AD cases does not accumulate aluminum despite high blood levels, implying that ferritin does not buffer aluminum as it does iron [17]. It has been found that the iron shuttle protein, transferrin, in AD patients has variant genetic structures that was in some cases associated with less efficient binding to aluminum or gallium serving as a surrogate [22,38]. An increased frequency of the transferrin C2 subtype was found in AD patients [62,77,78], with an average 6.7 year earlier onset of AD among patients having both the transferrin C2 subtype and the APOE $\epsilon$ 4 allele [79].

*Transferrin independent systems.* How aluminum crosses the blood-brain barrier is not fully understood. It has been found that the transferrin-independent uptake system (Tf-IU) may be involved in the accumulation of metals like aluminum in brain cells, particularly in the glial cells [63,64].

#### 2.4. Aluminum chelation therapy

The potential therapeutic capacity of chelation of aluminum for AD was demonstrated [50]. A low dose of the injectable desferrioxamine was used to remove about a third of the aluminum (from 4.09 ug/g to 2.69 ug/g) from the brains of elderly AD patients over two years. The trial slowed the disease process for the entire group by an average of 50 percent. Some good responder patients were benefited for up to five years [51]. Deaths mostly from pneumonia were dramatically reduced from 9 in the untreated group to only 1 in the treatment group.

Oral chelator drugs offer a great advantage to AD therapy because they simplify compliance. Most iron chelators are effective in removal of aluminum [25]. Gomez surveys the effectiveness of desferrioxamine and four orally administered 3- hydroxypyrid-4-ones [33]. Of the later, deferiprone (Li) has become the first commercially available oral chelator for iron overload, and it is also one of the better aluminum chelators. A multi-center human clinical trial of the oral iron chelator deferiprone (Li) in Europe has found the drug to be relatively safe even at the high levels required for iron control [13]. The European Commission in late 1999, approved the use of deferiprone for iron overload.

Peptide YY offers another opportunity for inexpensive and relatively safe removal of brain aluminum. Experiments with the Down Syndrome mouse model Ts65Dn found that infusion of these animals with recombinant human PYY over three days removed 73 percent of brain aluminum in three days. An 86 percent removal of brain aluminum in the diploid control mice was achieved with the same procedure [6].

### 3. Conclusion

In this article we have meshed the epidemiology studies with some of the findings about the biochemistry of how aluminum may participate in AD. Metal chelation therapy may offer AD patients a substantial slowing of disease progression. These observations support the view that minimizing aluminum exposure may provide significant public health benefits. Furthermore, a substantial reduction of aluminum exposure to the population from food, drinking water, drugs and cosmetics is possible at low or equivalent costs.

### Acknowledgement of Support

The Department of the Planet Earth is a non-profit citizen group, with board members from the United States and Canada. The author, the organization, and the board members have not received any financial support in preparation of this article. We have received valued technical assistance from a number of experts, particularly Dr. William Forbes of Ottawa, now deceased. He was a pioneer of drinking water epidemiology.

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