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Aluminum

Operational Guidance Value

There is no consistent, convincing evidence that aluminum in drinking water causes adverse health effects in humans, and aluminum does not affect the acceptance of drinking water by consumers or interfere with practices for supplying good water. Therefore, a health-based guideline or aesthetic objective has not been established for aluminum in drinking water.

In recognition of advancing research into the health effects of aluminum and in an exercise of the precautionary principle, water treatment plants using aluminum-based coagulants should optimize their operations to reduce residual aluminum levels in treated water to the lowest extent possible. For plants using aluminum-based coagulants, operational guidance values of less than 0.1 mg/L (100 µg/L) total aluminum for conventional treatment plants and less than 0.2 mg/L (200 µg/L) total aluminum for other types of treatment systems (e.g., direct or in-line filtration plants, lime softening plants) are recommended. These values are based on a 12-month running average of monthly samples.

Any attempt to minimize aluminum residuals must not compromise the effectiveness of disinfection processes (i.e., microbiological quality) or interfere with the removal of disinfection by-product precursors.

Identity, Use and Sources in the Environment

Aluminum is the most abundant metal on Earth, comprising about 8% of the Earth's crust. It is found in a variety of minerals, such as feldspars and micas, which, with time, weather to clays. Aluminum is chiefly mined as bauxite, a mineral containing 40–60% aluminum oxide (alumina). Aluminum is also found as a normal constituent of soil, plants and animal tissues.

Canada is the world's third largest producer of aluminum; in 1988, national production was estimated at 1.5 million tonnes. The metal is used for the production of a wide variety of articles, including building and construction materials, cans and packaging materials, vehicle parts and aircraft frames.[1] Salts of aluminum are used by the pharmaceutical industry as major ingredients of antacids and antidiarrhoeals. Aluminum is also used extensively as a food additive and as a component of food packaging materials. In addition, substantial amounts of aluminum salts (alum) are commonly added as flocculants during the treatment of drinking water.

Exposure

Because aluminum is ubiquitous in the environment and is used in a variety of products and processes, daily exposure of the general population to aluminum is inevitable.

Varying amounts of aluminum are present naturally in groundwater and surface water, including those used as sources of drinking water. The amount of aluminum in surface water varies, ranging from 0.012 to 2.25 mg/L in North American rivers.[2] Miller *et al*.[3] reported that aluminum is more likely to exist in surface water than in groundwater; only 9% of groundwaters had detectable amounts of aluminum (detection limit 0.014 mg/L), whereas 78% of surface waters had detectable aluminum.

Levels of aluminum in Canadian drinking water vary over a wide range. The highest levels in Canada have been recorded in Alberta, where, during 1987, the mean level in 10 major urban centres was 0.384 mg/L; one water sample attained a level of 6.08 mg/L.[4] In a 1987 survey in Ontario, aluminum levels in treated drinking water ranged from 0.003 to 4.6 mg/L, with a mean of 0.16 mg/L.[5] In Manitoba, aluminum levels of up to 1.79 mg/L have been recorded in the finished water of the distribution system, although the levels were mostly below 0.1 mg/L in the drinking water.[6] In Saskatchewan, the average dissolved aluminum concentration in Regina's drinking water is about 0.035 mg/L, whereas that in Saskatoon's drinking water is about 0.724 mg/L.[7] Thirty-five percent of shallow wells sampled at 17 sites in the Atlantic provinces in the fall of 1993 had high aluminum concentrations, ranging from 0.05 to 0.6 mg/L.[8] The global mean level of aluminum in distributed water in Canada, after treatment, has been reported to be 0.17 mg/L.[9] In a U.S. nationwide survey of 80 surface water treatment plants that used

alum, Letterman and Driscoll[10] reported a mean total aluminum concentration in the finished water of 0.085 mg/L.

Concentrations of aluminum in food range widely (means range from <0.001 to 69.5 mg/100 g), depending on the nature of the foodstuffs.[11] The highest levels are found in nuts, grains and dairy products, particularly processed cheeses. The tea plant accumulates large amounts of aluminum, which can leach from tea leaves[12]; aluminum concentrations in brewed tea tend to be in the range of 2–8 mg/L.[13] There is also potential for exposure from the ingestion of aluminum contained in over-the-counter drugs, including antacids[14,15] and buffered acetylsalicylic acid (aspirin); based on the recommended dose, the range of aluminum exposure from antacids has been given as 840–5000 mg/d[16] and as 120–7200 mg/d,[17] and that from buffered aspirin has been given as 126–728 mg/d[16] and as 200–1000 mg/d.[17] Aluminum leaching from cooking utensils, containers and packaging made of aluminum may also contribute to dietary exposure.[18]

The total intake of aluminum from all food sources (excluding over-the-counter drugs) for an adult is estimated to be 6 mg/d in the United Kingdom[19] and 8–9 and 7 mg/d (adult men and women, respectively) in the United States,[20] although higher daily intakes have been estimated.[21] Estimates of aluminum intakes ranged from 0.7 mg/d for six- to 11-month-old infants to 11.5 mg/d for 14- to 16-year-old males.[20] The 7–9 mg/d estimate is probably a reasonable assessment of Canadian intake, owing to the similar food habits and widespread exchange of food products in North America.

Average levels of aluminum in Canadian ambient air vary over a wide range. In rural locations, the range is from 0.013 µg/m^3 in Igloolik (Arctic)[22] to 1.42 µg/m^3 in Stony Plain, Alberta.[23] In urban locations, the range is from about 0.17 µg/m^3 in Victoria, B.C.[24] to 3.6 µg/m^3 in Edmonton, Alberta.[23] Atmospheric aluminum concentrations in industrial areas are often in the milligram per cubic metre range. The highest levels in ambient air in Canada have been recorded in Edmonton (8.8 µg/m^3).[23] Using a 1981–1983 concentration range in ambient air in Ontario of 0.01–0.54 µg/m^3,[25] Van Oostdam *et al.*[26] calculated a daily exposure range of 0.08–4.2 µg for Canadian adults, assuming daily air intake of 23 m^3 and 35% particle retention in the lungs.

Assuming a daily contribution of 8 mg (average of 7–9 mg/d) from food, 0.0042 mg (maximum daily intake in Ontario) from air and 0.26 mg (global mean level 0.17 mg/L, daily intake 1.5 L) from water, an adult would take in about 8.26 mg of aluminum per day. In other words, approximately 97% of the normal daily intake for an adult is from food and the remainder is from drinking water; the contribution from ambient air is insignificant. This calculation is in agreement with a survey of aluminum in European drinking water, which found that drinking water contributes <5% of most adult daily intakes.[27] However, this average daily intake of 8.26 mg, equivalent to about 0.1 mg/kg bw per day for a 70-kg adult, can be greatly increased in individuals consuming high doses of aluminum-based antacids or buffered aspirin (up to about 70–100 mg/kg bw per day[16,17]).

Aluminum Speciation in Water

The chemical speciation of aluminum in drinking water is of particular interest, as the form of aluminum regulates its solubility, bioavailability and toxicity.

One factor determining the form of aluminum in water is pH. In raw water with low concentrations of dissolved organic compounds such as humic and fulvic acids, the dependence of dissolved aluminum concentration on pH resembles a parabola with a sharp solubility minimum at around pH 6.5.[28] The solubility of aluminum increases at lower pH values owing to the formation of $Al(OH)_2^+$, $Al(OH)^{2+}$ and $Al(H_2O)_6^{3+}$ — often abbreviated as Al^{3+} and sometimes referred to in the literature as free aluminum. The solid $Al(OH)_3$ is the predominant species between pH 5.2 and 8.8, whereas the soluble $Al(OH)_4^-$ predominates above pH 9.[29]

The form in which aluminum is present in drinking water is also dependent on whether the water is fluoridated, as fluoride has a strong affinity for aluminum, particularly under acidic conditions. In unfluoridated water at pH values above 6.5 and with an aluminum concentration of 100 µg/L, the predominant species is $Al(OH)_4^-$. In fluoridated water (typically 53 µmol/L), AlF_2^+ and AlF_3 species are among those that can be found below pH 6.5; above pH 6.5, mixed OH^-/F^- complexes or $Al(OH)_4^-$ may occur.[17]

When alum is added to raw water for treatment, the form of aluminum changes along a number of pathways, depending on the quantity of alum added, the temperature, the pH, the types and concentrations of dissolved materials present as well as the types and surface area of particulate matter present.[30]

In four separate studies, aluminum fractions in raw water and drinking water were analysed.[30–33] Driscoll and Letterman[30] analysed water from Lake Ontario before and after treatment with alum, separating aluminum into three fractions: (1) labile (inorganic) monomeric aluminum, which was considered to include the aquo (Al^{3+}), OH^- (alumino-hydroxide), F^- (alumino-fluoride) and SO_4^{2-} (alumino-sulphate) complexes of monomeric aluminum; (2) non-labile (organic) monomeric aluminum, which was considered to be an estimate of aluminum associated with organic solutes; and (3) acid-soluble aluminum, which was thought to be particulate aluminum or very strongly bound aluminum-organic complexes. A five-fold increase in total aluminum was

evident after coagulant addition and filtration. About 11% of the aluminum (from raw water and alum) was not removed during treatment, and this residual aluminum was transported through the distribution system. A shift in the distribution of aluminum in the three fractions also occurred as a result of water treatment. Before treatment, aluminum was largely present in the acid-soluble (30%) or organic monomeric (70%) fractions, and the concentration of inorganic monomeric aluminum was insignificant. After treatment, only 14% consisted of acid-soluble aluminum; the remaining aluminum was associated with organic matter (24%), was present as monomeric alumino-hydroxide complexes (45%) or was complexed with fluoride (17%). In other words, inorganic monomeric aluminum represented the dominant aluminum fraction after water treatment (62% of total).

Van Benschoten and Edzwald[31] determined the aluminum fractions in raw and treated water at two water treatment plants (coagulants used were alum and an aluminum-based product that contains organic polyelectrolytes, respectively) in Danvers, Massachusetts, and Burlington, Vermont: (1) total reactive aluminum (which approximates total aluminum); (2) total dissolved aluminum (using a 0.22-µm filter pore size; fraction includes inorganic aluminum species, e.g., Al^{3+}, $Al(OH)^{2+}$, AlF^{2+} and soluble complexes of aluminum with dissolved organic carbon, or DOC); (3) dissolved monomeric aluminum; (4) dissolved organically bound aluminum; and (5) dissolved organic monomeric aluminum. Aluminum in the raw and treated water at both plants was composed primarily of dissolved species. Inflow concentrations of dissolved aluminum were relatively low and generally increased following treatment; total aluminum concentrations of >0.1 mg/L in treated water at both plants were composed of about 70–80% dissolved aluminum. Because of the low DOC levels in raw water, the organically bound aluminum fraction in the Burlington plant was much smaller than that at the Danvers plant (up to 90% of the dissolved aluminum in the raw water), which uses a water source with high DOC. There was no difference between free and total fluoride concentrations at either plant, suggesting a minimal effect of fluoride on the fate of aluminum, possibly because of the inability of fluoride to compete with hydroxide for aluminum at neutral to alkaline pH. Residual aluminum concentrations were affected by the pH of coagulation, the treated water pH and temperature.

Gardner and Gunn[32] divided aluminum in water into four fractions: (1) total (acid-digestible) aluminum, including most of the particulate species together with the colloidal and dissolved forms; (2) dissolved aluminum, including colloidal and dissolved species and filterable through a 0.45-µm membrane filter; and (3 and 4) low-molecular-weight fractions that were based on equilibrium dialysis through a 1000-MW cut-off membrane and reactivity with 8-hydroxyquinoline; the most chemically labile species (usually the low-molecular-weight forms) react the fastest. In two of three water treatment plants based on coagulation with aluminum, the form of aluminum was changed during treatment to a more chemically labile, low-molecular-weight species. In one raw water sample, most aluminum was in particulate form; the dissolved fraction (including low-molecular-weight and labile forms) was much smaller. After treatment, the total aluminum concentration was reduced by 75%, and all of it was in the form of low-molecular-weight species. The second raw water sample, consisting of relatively acidic upland water, had a relatively high proportion of labile aluminum (about 50% of total aluminum); all aluminum fractions were reduced by treatment, and water passed through the distribution system with little change in aluminum speciation. In the third sample, there was little change in the total aluminum concentration during treatment, but there was a substantial change in speciation: particulate forms were replaced by low-molecular-weight forms.

Health Canada has developed a method for determining the speciation of aluminum in Canadian waters. Bérubé and Brûlé[33] analysed raw surface water before and after treatment with alum from four provinces in Canada. They separated aluminum into (1) total recoverable, (2) total acid leachable and (3) total dissolved aluminum (using 0.45-µm filtering units), as well as (4) dissolved on-column extracted and (5) dissolved non-extracted aluminum. The total recoverable, total dissolved and dissolved on-column extracted aluminum levels (mean values) in four raw water samples from different provinces were approximately 1200 µg/L, 71 µg/L and 7 µg/L (a), 280 µg/L, 7 µg/L and 6 µg/L (b), 1800 µg/L, 20 µg/L and 14 µg/L (c) and 8100 µg/L, 89 µg/L and 25 µg/L (d), respectively. However, after water treatment with alum, the levels of total recoverable aluminum generally decreased, whereas total dissolved and dissolved extractable aluminum levels generally increased. In four finished water samples from the same sites, the total recoverable, total dissolved and dissolved extractable aluminum levels (mean values) were approximately as follows: (a) 110 µg/L, 85 µg/L and 81 µg/L; (b) 970 µg/L, 930 µg/L and 820 µg/L; (c) 320 µg/L, 310 µg/L and 220 µg/L; and (d) 150 µg/L, 130 µg/L and 110 µg/L, respectively. In other words, for raw water, dissolved aluminum is only a small fraction of total aluminum, whereas for treated water, almost all total aluminum is dissolved and completely extractable.

The above four studies thus show that although treatment may reduce the total aluminum concentration in finished drinking water, it also appears to increase the concentration of low-molecular-weight, chemically reactive, dissolved aluminum species.

Analytical Methods

Common methods for determining aluminum in water are described in *Standard Methods for the Examination of Water and Wastewater*.[34] The graphite furnace atomic absorption spectrometric method (detection limit 0.003 mg/L) and inductively coupled plasma atomic emission spectrometric method (detection limit 0.04 mg/L) are free from common interferences and are preferred. The more expensive inductively coupled plasma mass spectrometric method (detection limit 0.1 µg/L) can also be used. Other methods using ultraviolet-visible spectrometry after automated derivatization methods with, for example, Eriochrome cyanine R or pyrocatechol violet are also used for aluminum determination.

A method for determining aluminum species in water has been developed by researchers at the Environmental Health Directorate of Health Canada. This method, which involves on-site speciation followed by measurement in a remote laboratory, has been used for raw and treated surface water[33] and for shallow groundwaters,[8] as well as for treatment/distribution networks.[35] The method is used to measure total recoverable, total acid leachable and total dissolved aluminum, as well as dissolved on-column extracted and non-extracted aluminum.

It should be noted that most aluminum in finished water is in the form of dissolved aluminum species. *Standard Methods for the Examination of Water and Wastewater*[34] defines dissolved aluminum as aluminum that passes through a 0.45-µm filter. However, as only the use of a 0.22-µm filter guarantees that none of the smallest particles remains in solution, it is recommended that dissolved aluminum be defined as aluminum that passes through a 0.22-µm filter.

Treatment Technology

During water purification or treatment processes, aluminum salts (most commonly alum or aluminum sulphate) are frequently used as coagulants to remove colour and turbidity. This results in the reduction of both pathogenic micro-organisms and the particles that protect pathogens from chemical disinfection. Removal of humic substances and other naturally occurring organic matter also reduces the formation of disinfection by-products, including carcinogenic chlorine compounds. The removal of organics that impart colour to water improves the appearance of the water. This is a significant benefit, as appearance is an important factor in maintaining public confidence in the water supply. In addition, removal of colour will promote more efficient chlorination and longer-lasting chlorine residuals.

The most common treatment train using alum is conventional surface water treatment, which involves chemical addition, flocculation, coagulation, sedimentation and filtration. This treatment train and its efficiency in removing contaminants and attaining low levels of residual aluminum are discussed in detail below. There are, however, other processes used in Canada — for example, chemical mixing, coagulation, flocculation and filtration (direct filtration); and chemical mixing, coagulation and filtration (in-line filtration) — that also employ alum as the principal coagulant. The design and operation of each of these processes influence the aluminum concentration in the finished drinking water, which may vary significantly from about 30 µg/L to 200 µg/L or higher. Additional treatment processes, such as lime softening, also influence aluminum levels in finished drinking water.

As a consequence of alum treatment, levels of aluminum in treated water are often higher than those in raw water.[3,30] However, with proper treatment practices in a conventional plant, aluminum levels can be reduced in finished water.[28,32,36] Most of the alum used as a coagulant is changed to insoluble aluminum hydroxide, which either settles out or is removed by filtration. Residual aluminum concentrations in finished waters are a function of the aluminum levels in the source water, the dosing of aluminum-based coagulant, the pH of the water, temperature, DOC levels and the efficiency of filtration.[28,37,38] Gardner and Gunn[32] reported that under optimal conditions, the conventional treatment train is capable of achieving a minimum aluminum concentration in the treated water of around 0.03 mg/L. Higher concentrations may occur in drinking water if the raw water is particularly dirty or if there is inadequate control over pH during treatment[32]; high particulate aluminum residuals may also occur if an insufficient alum dosage has been used.[39] Levels of aluminum in the finished water above 0.3 mg/L usually reflect a lack of optimization in the coagulation, sedimentation or filtration stages of conventional treatment.[40] High residual concentrations of aluminum (above 0.4 mg/L[41]) in some water may result in the deposition of gelatinous aluminum-containing substances in the distribution system, which in turn may result in reductions in flow rate through the system and deterioration of water quality.[38,42,43] High residual aluminum levels in the distribution system may also interfere with the disinfection process, by enmeshing and protecting microorganisms.[44]

Very high concentrations of residual aluminum can be minimized by effective removal of particulate matter, particularly when raw water contains high concentrations of total aluminum.[10,28] The best way to control aluminum is optimization of the coagulation and filtration processes. To achieve optimal coagulation, one should control the coagulant dosage and coagulation pH. Optimizing coagulant dosage may entail increasing or decreasing the amount of alum added, depending on the

specific conditions of the water treatment process. Adjustment of the coagulation pH to 6.0–7.0 provides the best results, as this is the range of minimum solubility of aluminum hydroxide.[10] However, high-alkalinity waters with pH >8 can require significant chemical dosages to reach the optimum pH. Temperature also influences the outcome, because the pH of minimum solubility increases at lower temperatures. Alum coagulation at lower temperatures has been observed to result in slightly higher residual turbidities and may therefore result in higher residual aluminum.[37] Several investigators have found that low turbidity in filtered water (<0.1–0.15 NTU) results in a very low aluminum residual,[10,45] but one should note that this applies only if the pH is in the correct zone. Optimization of coagulation should be accompanied by good mixing, good clarification and good filtration of the treated water.[42,46] A shortfall in any of these can result in increased aluminum residuals as well as other harmful effects.

Practicable, large-scale water treatment technology is not available at every water system for reducing aluminum levels in finished water. Alternative coagulants, such as iron chloride,[47] polyaluminum chloride and polyaluminum sulphate,[48] may be useful as replacements for aluminum sulphate and will result in lower aluminum residuals. Alternative coagulants should be used only following a thorough on-site evaluation of their performance.[43]

Health Considerations

Absorption and Bioavailability

Quantitative data on the pharmacokinetics of aluminum are not reliable owing to the lack of a suitable radioactive isotope and difficulties in controlling contamination during chemical analysis. As well, collection and analysis of faecal samples do not provide data sensitive enough to monitor aluminum absorption when absorption is less than 1%.[49] In most studies, aluminum absorption is measured by changes in urinary and plasma levels. Ganrot[50] suggested that urinary aluminum excretion could be assumed to represent the minimal amount of aluminum absorption.

Greger and Powers[51] estimated that weanling Sprague-Dawley rats fed aluminum (as aluminum hydroxide) at a concentration of 1–3 g/kg diet absorbed 0.011–0.036% of the aluminum, based on tissue accumulation of aluminum in relation to dose. Absorption decreased with higher aluminum doses. Estimates of absorption based on urinary excretion of aluminum in the same rats were slightly lower, ranging from 0.006% to 0.013%. Moreover, rats excreted a higher percentage of aluminum with increased dose.

In general, the proportion of aluminum absorbed by humans following oral intake is small, with most estimates ranging between 0.2% and 1.5%. The percentage absorbed appears to depend on the size of the dose. The percentage of aluminum absorbed in humans was 10- to 100-fold greater with small aluminum doses (5 mg/d) than with pharmaceutical doses (i.e., 1–3 g/d).[21] Weberg and Berstad[52] also found that the fractional absorption of aluminum decreases with increasing dose in healthy human subjects.

Factors Affecting Absorption

The degree of aluminum absorption in animals depends on a number of parameters, including pH, aluminum speciation and dietary factors.[38,53–56] More aluminum is absorbed at low pH than at neutral or high pH.[57] Aluminum absorption does not appear to occur in the stomach,[58] where most aluminum is converted to soluble monomolecular species at low pH. However, in the intestine, at near-neutral pH, most of the aluminum changes into insoluble form and is not available for uptake. The small portion that remains available for transport is the fraction that has been complexed with organic molecules in the stomach, allowing it to remain soluble at the higher pH of the small intestine.[59]

The solubility and speciation of the aluminum compounds administered are also important factors affecting absorption. Kaehny *et al.*[60] found that subjects had a greater increase in serum and urine aluminum when they were given aluminum as aluminum hydroxide, aluminum carbonate or dihydroxy aluminum aminoacetate rather than as aluminum phosphate. Yokel and McNamara[61] reported that the increases in serum aluminum concentrations in rabbits fed similar doses of aluminum as borate, hydroxide, chloride, glycinate or acetate were significantly smaller than those observed after doses of aluminum citrate or nitrate.

Although aluminum concentrations in brewed tea are 10–100 times those in drinking water,[62] aluminum in tea is present almost exclusively (91–100%) in the form of high-molecular-weight organic complexes, which are not readily absorbed.[32,63] Koch *et al.*[12] and Gardner and Gunn[32] reported increased levels of aluminum in urine after tea drinking; however, Gardner and Gunn[32] noted that the increase was small with respect to the quantity of aluminum ingested, suggesting relatively low bioavailability from this source. Other investigators have confirmed the low bioavailability of aluminum in tea.[62,64,65] Although drinking tea with milk or lemon juice over a short period does not contribute significantly to the total aluminum burden,[66–68] absorption of aluminum in heavy tea drinkers, particularly those with enhanced absorption, may not be insignificant because of the relatively high aluminum content of tea.[17]

The composition of the food eaten in conjunction with drinking water that contains aluminum has a strong effect on the absorption of aluminum. In rats given

aluminum in water in combination with lemon juice, orange juice, coffee or wine, aluminum absorption increased by 1800%, 1700%, 250% and 188%, respectively.[56,69] In the case of the lemon and orange juices, this increase was probably due to the formation of non-ionized aluminum citrate, which is expected to readily cross the gastrointestinal barrier.[70] In fact, in the human diet, citric acid may be the most important factor determining the absorption of aluminum. Several studies have found that the presence of citrate in food or beverages significantly increases the absorption of aluminum from dietary sources,[51,71–73] although Gardner and Gunn[32] did not observe a significant increase in aluminum excretion in human volunteers who had ingested aluminum-spiked orange juice compared with spiked water, and Jouhanneau *et al.*[74] reported no change in the intestinal absorption of aluminum from a normal diet in rats in the presence of citrate.

Studies in rabbits suggest that maltol also enhances the gastrointestinal absorption of aluminum.[75] Ascorbic and lactic acids have been shown to promote aluminum uptake in mice[76] and rats.[77] Partridge *et al.*[53] suggested that several compounds in the diet, including ascorbic acid, citric acid, lactic acid and malic acid, may increase aluminum absorption in the intestine by elevating the pH of aluminum hydroxide precipitation. Although absorption has been reported to be elevated in patients with low ferritin levels[78,79] and divalent iron has been reported to decrease aluminum absorption in an *in situ* perfusion system of rat small intestine,[80] the actual role that iron plays in aluminum uptake, if any, is uncertain.[17]

Phosphate is also an important dietary factor, forming complexes even at low pH[81] and making aluminum less available for absorption. It has been suggested that the presence of phosphates in the diet is probably the chief "natural" mechanism whereby aluminum is prevented from entering the circulation.[82] Wicklund Glynn *et al.*[83] hypothesized that the intake of acidic, aluminum-rich drinking water with meals containing phosphorus-rich compounds (e.g., phytate and casein) may result in a low absorption of aluminum.

Silica may act like phosphate, as studies with human volunteers suggest that dissolved silica suppresses gastrointestinal aluminum uptake, possibly by promoting the formation of insoluble aluminosilicate species in the gastrointestinal tract.[84] As aluminum has been found to reduce the absorption of fluoride,[85] the reverse may also be true,[86] although it has not been specifically examined.

A critical review of the scientific literature suggests that certain diseases enhance the gastrointestinal absorption of aluminum. For example, there is some evidence that patients suffering from chronic renal insufficiency or uraemia absorb aluminum more readily than normal individuals.[79,87–90] Aluminum absorption may also be increased through alterations in the permeability of the intestinal wall, affecting those with more permeable guts,[91] infants[92] and those with enteropathy.[93]

Age may also be an important factor in determining aluminum absorption. The concurrent oral administration of aluminum hydroxide and citric acid quickly enhanced aluminum absorption in 10 healthy individuals 77–88 years of age compared with 10 younger volunteers (69–76 years). There was a significant correlation between age and blood aluminum in these two control groups. In a group of 10 patients with Alzheimer's disease (AD) (65–76 years), aluminum absorption was significantly raised compared with 10 age-matched controls. Although the increase in aluminum absorption in older (79–89 years) AD patients was substantial, it was not significant when compared with age-matched controls.[72] Bjertness *et al.*,[94] on the other hand, found no difference in the concentration of aluminum in the liver and head of femur between AD and control groups, suggesting that a significant increase in absorption under normal conditions is unlikely.

Individual variability in aluminum absorption has been found in human subjects.[56,72] Nieboer[95] assessed the increase in serum aluminum levels after oral administration of aluminum hydroxide and citrate in diluted lemonade in 20 healthy volunteers (age 15–59), 10 probable AD patients (age 64–84) and seven healthy age-matched controls. About 20% of all subjects (including one of the probable AD patients) were high absorbers (serum aluminum increased from 1–6 µg/L to >150 µg/L), and this was independent of age. Intraspecies genetic differences in aluminum absorption are also reported in animals, although the mechanisms responsible have not been determined. In a study in which five inbred strains of mice were exposed to aluminum in the diet for 28 days, strains DBA/2 and C3H/2 demonstrated elevated aluminum concentrations in the brains, whereas A/J, BALB/c and C57BL/6 strains demonstrated no difference from control mice in brain aluminum concentrations.[96] These findings suggest that there are genetic differences in the permeability of the blood–brain barrier.

Relative Bioavailability Studies

Because aluminum in drinking water constitutes only a small fraction (about 3%) of the total oral intake of aluminum, it is important to determine the relative bioavailability of aluminum from drinking water and food. Some research has been conducted in this area, but much more needs to be done before definitive conclusions can be drawn with respect to the bioavailability of aluminum from both sources.

Wicklund Glynn *et al.*[83] tested their hypothesis that labile aluminum in drinking water is more available for absorption in the gastrointestinal tract than aluminum complexed in rat feed by exposing rats for 10 weeks to

aluminum at a concentration of 4 mg/L (controls exposed to 0.5 mg/L; concentration in feed 4–5 mg/kg) in acidic drinking water; almost all of the aluminum in the drinking water was present as labile aluminum. Rats exposed to labile aluminum in acidic drinking water did not show a greater retention of aluminum in bone, liver or brain compared with the control animals exposed to aluminum through food. However, urinary excretion was not measured, so it is possible that excess aluminum absorbed from the water was excreted by the kidney. The authors suggested that labile aluminum forms complexes with ligands in the stomach, thus lowering its bioavailability to the same level as that of aluminum in the feed.[83] It has also been suggested that the highly acid conditions of the stomach convert a large fraction of aluminum, regardless of how it is ingested, to the same chemical form. As the stomach contents pass into the intestines, the acid content is immediately neutralized, which causes most of the aluminum to precipitate and become unavailable for absorption.[97]

To test their hypothesis that low-molecular-weight, chemically labile forms of aluminum might be absorbed more readily by the body than higher-molecular-weight aluminum complexes, Gardner and Gunn[32] measured urinary aluminum concentrations in human volunteers following consumption of aluminum-spiked mineral water and tea. The slight increase in urinary aluminum concentrations that was observed after consumption of both beverages suggested to the authors that the bioavailability of aluminum from both sources is relatively low. However, it should be noted that the mineral water used had a relatively high silicate concentration, which may have reduced the aluminum bioavailability.

Distribution and Accumulation

Once absorbed into the bloodstream, aluminum binds to certain plasma proteins, in particular albumin and transferrin.[98,99] In the tissues, aluminum is nearly always found in association with iron. Approximately 60% binds to transferrin, 34% to albumin and the remainder to citrate in normal human blood serum.[99] Transferrin may be a means of transporting aluminum to different organs, as the regional distribution of gallium-67, a marker for aluminum, in the brain is very similar to that of transferrin receptors.[100]

The highest levels of aluminum in mammalian tissues are found in the skeleton, lungs, kidneys, spleen, thyroid and parathyroid glands. Experience with dialysis patients has shown that aluminum has the potential to accumulate in the skeleton and brain.[101,102] The normal blood aluminum levels in humans are reported to be between about 1 and 16 µg/L.[52,103] Following the administration of aluminum hydroxide in drinking water to male mice for 105 days, aluminum concentrations increased by 30% in the kidney (18.13 ± 4.75 vs. 14.28 ± 5.41 µmol/g), by 60% in the liver (28.63 ± 6.37 vs. 17.69 ± 4.51 µmol/g) and by 340% in the brain (1.41 ± 0.40 vs. 0.32 ± 0.16 µmol/g).[104]

Aluminum accumulation in the tissues varies with the aluminum salt administered, the species studied and the route of administration,[61] as well as with age, kidney function, disease status and dietary factors.[21] In the brain, aluminum levels increase with age, and the highest levels of aluminum are found in the grey matter. Even in persons with normal renal function, the ingestion of aluminum-containing antacids can cause an elevation of the brain aluminum levels from 0.6 µg/g wet weight to 1.1 µg/g wet weight.[102] Dollinger and colleagues[105] found high levels of aluminum in the brains (1.05 µg/g wet weight or 5.25 µg/g dry weight) of 10 patients who were given 70 mL of a high-aluminum-content antacid per day (dose not reported) for 10 days, compared with 10 patients (aluminum in brain 0.412 µg/g wet weight or 2.60 µg/g dry weight) who were given an equal amount of low-aluminum-content antacid for 10 days. The mean aluminum level in brain tissue from 20 controls was 0.583 µg/g wet weight.

Even moderate reductions in kidney function in rats have been correlated with increased aluminum accumulation in bone.[21] Suboptimal dietary zinc increases aluminum accumulation in the brain.[106]

Excretion

In humans, absorbed aluminum is excreted from the body via the kidneys.[107] Renal excretion is inefficient owing to the significant reabsorption of aluminum in the proximal tubules. In individuals with healthy kidneys, any aluminum absorbed is eliminated from the body before deleterious effects can occur. In patients with kidney dysfunction or in normal persons under high aluminum load, the buildup of aluminum can lead to toxic effects.[108]

The bulk of ingested aluminum from all sources is unabsorbed and excreted primarily in the faeces. A population fed a diet high in aluminum for an extended period excreted approximately 99.9% of the intake in the faeces; the rest was accounted for in the urine.[109] Although intravenous injection with the radioisotope tracer ^{26}Al in a human volunteer showed that only a small percentage of the aluminum was excreted in the faeces,[110] rats excreted 60% of an intravenous dose of aluminum in urine and 40% in faeces[111]; this suggests that the route of excretion varies with the route of administration of aluminum in humans and that there may be a difference in the route of excretion in humans and other species.

Gardner and Gunn[32] found inter-individual differences in excretion rates of aluminum in a study in which four subjects drank various beverages spiked with aluminum. The excretion rates for one subject

were consistently higher than for the other three subjects. Inter-subject variability in the metabolism of aluminum following intravenous injection of ^{26}Al as citrate in six healthy male volunteers has also been reported.[112]

Toxicity in Humans

On acute exposure, aluminum is of low toxicity. In humans, oral doses up to 7200 mg/d (100 mg/kg bw per day) are routinely tolerated without any signs of harmful short-term effects. However, two healthy individuals who drank water accidentally contaminated with an aluminum sulphate solution (aluminum concentrations ranged from 30 to 620 mg/L[113]) experienced ulceration of the lips and mouth.[114]

Intake of large amounts of aluminum can lead to a wide range of toxic effects, including microcytic anaemia,[115,116] osteomalacia,[117,118] glucose intolerance of uraemia[119] and cardiac arrest.[118] Elderly persons with elevated serum aluminum levels exhibit impaired complex visual-motor co-ordination and poor long-term memory.[120] In addition, aluminum has been shown to inhibit a number of enzyme activities, including those of key enzymes involved in catecholamine synthesis, such as dihydropteridine reductase.[103]

Dialysis Encephalopathy

There is extensive literature on the impairment of various aspects of central nervous system function in humans following inadvertent parenteral exposure to aluminum. The most studied aluminum-related syndrome is dialysis encephalopathy, chronic symptoms of which include speech disorders, neuropsychiatric abnormalities and multifocal myoclonus.[121] More subtle symptoms of the condition include disturbances to tetrahydrobiopterin metabolism and abnormalities in a number of psycho-motor functions (e.g., visual spatial recognition memory), all occurring at mildly elevated serum aluminum levels (59 µg/L) and in the absence of chronic dementia.[122] Patients with dialysis dementia were shown to have markedly elevated serum aluminum levels with increased concentrations in many tissues, including the cerebral cortex.[117,123] Investigators reported a correlation between the aluminum concentration in water used to prepare the dialysate fluid and the incidence of dialysis dementia.[124] The mechanism of neurotoxicity in dialysis dementia has not been established. However, mild cases have been reported to respond to chelation therapy with desferrioxamine to lower serum aluminum.[125]

Amyotrophic Lateral Sclerosis (ALS) and Parkinson's Dementia (PD)

It has been postulated that aluminum plays a role in the aetiology of two severe neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and Parkinson's dementia (PD). ALS and PD, which are observed at very high incidence among the Chamorro people on Guam, are both characterized by the loss of motor neuron function and the presence of neurofibrillary tangles in the brain.[126] A high incidence of ALS is also found in two other areas, western New Guinea and the Kii Peninsula of Japan. The soils and drinking water of Guam and the two other affected areas are very low in calcium and magnesium but very high in aluminum, iron and silicon.[127] Intraneuronal deposition of calcium and aluminum in post-mortem brains of patients with ALS has been reported.[128] Garruto and Yase[129] suggested that chronic nutritional deficiencies of calcium and magnesium may lead to increased absorption of aluminum (and other metals), resulting in the deposition of aluminum in neurons. These deposits could interfere with the structure of neurons and eventually result in neurofibrillary tangles.[130] The dramatic decrease in the incidence of ALS and PD on Guam with a change in dietary habits and local water supplies has given support to this theory.[126] However, as the diet of the Guam population is known to include the seeds of the false sago palm,[50,131] which contain the toxic amino acid beta-*n*-methylamino-L-alanine — an amino acid that caused a degenerative disease with similarities to ALS when given repeatedly by mouth to two cynomolgus monkeys — the contribution of these seeds to Guam's high incidence of neurological disorders should be examined more closely.[131] As well, non-native persons who had lived for long periods on Guam did not exhibit an increased incidence of dementia, which suggests the dementia may have a genetic rather than an environmental cause.[132]

Alzheimer's Disease (AD)

Aluminum has also been suggested as having a causal role in the onset of AD. Memory lapses, disorientation, confusion and frequent depression are the first recognizable symptoms that mark the beginning of progressive mental deterioration in patients with AD. Numerous other causes have been suggested for AD, including genetic and environmental factors, but none of them has been proven.

Crapper McLachlan and Farnell[133] found that the average aluminum content of control human brains (1.9 ± 0.7 mg/kg dry weight) was less than that of AD-affected brains (3.8 mg/kg dry weight), and Xu *et al.*[134] reported small but significant increases of aluminum in brain tissues of AD patients compared with age-matched controls. However, Bjertness *et al.*[94] found no increase in the bulk content of aluminum in the two brain regions most severely affected by neuropathological changes in AD (i.e., frontal and temporal cortex). The presence of neurofibrillary tangles and senile plaques in the brain and amyloid deposits around cerebral blood vessels are

characteristics of Alzheimer's patients.[135] Large numbers of neurofibrillary tangles are reported in the regions of brain showing elevated aluminum levels.[136] The presence of neurofibrillary tangles is a common feature of AD, ALS and PD. Aluminum has been shown to coexist with silicon in an aluminosilicate form in the amyloid core of senile plaques and neurofibrillary tangles of AD brains.[135] The presence of aluminum at the plaque cores has led to the theory that it might be involved in initiating events leading to plaque formation and that the aluminosilicate complex provides a backbone for the protein precipitation seen in plaques.[137] Calcium-mediated cell death and neurofibrillary tangles are thought to accelerate AD progression. Another hypothesis that has been advanced is that mutations in the ß-amyloid precursor protein gene itself may be responsible for the abnormal cleavage of the protein, resulting in AD.[138,139]

There have been many attempts to study the relationship between AD and exposure to aluminum from an epidemiological point of view. Most of the published epidemiological studies (nearly 20) have been ecological in nature and have examined whether there was any link between exposure to aluminum in drinking water and the incidence of AD. However, none of these studies has produced convincing evidence for a role for aluminum in the aetiology of the disease.

An ecological study in Newfoundland found an excess of dementia mortality (diagnosis of dementia of unknown form and severity obtained from death certificates, which may not be entirely reliable with regard to diagnosis) from the north shore of Bonavista Bay in 1985 and 1986 that could not be explained by differences in sex, age or other parameters. The area on the northern tip of the bay was reported to have a high aluminum concentration in the drinking water (165 µg/L) and low pH (5.2).[140] Two other areas on the southern part of the bay with high aluminum levels in drinking water (125 and 128 µg/L) and higher pH (5.9) had lower rates of dementia mortality. No adjustments were made for confounding factors. Frecker[141] has pointed out that the first area had a low silica concentration (0.8 mg/L) and might have more bioavailable aluminum, whereas the two areas with few dementia deaths and high aluminum concentrations had high silica concentrations (1.7 and 2.2 mg/L) and potentially less bioavailable aluminum.

In a Canadian case–control study, Neri and Hewitt[142] and Neri *et al.*[143] reported a dose–response relationship between the aluminum content of finished drinking water and risk of AD, as estimated by hospital discharges with a diagnosis of dementia or presenile dementia in Ontario in 1986–1987. The relative risks associated with the consumption of drinking water containing aluminum concentrations of <0.01, 0.01–0.1, 0.1–0.199 and ≥0.200 mg/L were estimated to be 1.00, 1.13, 1.26 and 1.46, respectively.[142] In a subsequent re-analysis, the dose–response relationship held more strongly for those over 75 years of age, and the results thus suggest that there may be a stronger influence of aluminum in water (in the 10 years before diagnosis) in the older age group.[144] The aluminum concentration in water was taken as the average for a 12-month period, as provided by the Ontario Ministry of the Environment. It appears that no adjustment for confounding factors other than age and sex was made.

A longitudinal study of aging correlated exposure to high and low levels of aluminum and fluoride in the water supply in Ontario with the absence of any mental impairment.[145,146] Using data provided by the Ontario Ministry of the Environment, the investigators estimated exposure to aluminum and fluoride for 485 76-year-old men, 280 of whom showed no signs of cognitive impairment (cases). Although men living in areas where the aluminum concentration in water was low (i.e., below 85 µg/L, the 50th percentile) showed no signs of mental impairment slightly more often, the difference was not significant (odds ratios of 1.00 and 0.93, respectively). However, the data also showed that men living in areas where aluminum concentrations in drinking water were high and fluoride concentrations were low were about three times more likely to have some form of mental impairment than those living in areas where aluminum concentrations were low and fluoride concentrations were high (odds ratios of 1.00 and 0.37, respectively). In a further analysis, Forbes *et al.*[147] published preliminary results suggesting that neutral pH, relatively low aluminum concentrations and relatively high fluoride concentrations in drinking water decrease the odds of showing indications of cognitive impairment by a factor of about five. In a case–control study performed in South Carolina, Still and Kelley[148] showed that the annual incidence of primary degenerative dementia was significantly lower (3.6/100 000) in a region where the water fluoride level was high (4.18 mg/L) than in another district where it was low (0.49 mg/L) (incidence 20.8/100 000); the authors suggested that high fluoride levels may protect against the development of AD by attenuating the neurotoxicity of aluminum.

In a recent autopsy-verified case–control study in which the case–control odds ratio was used as an estimate of relative risk and the aluminum concentration in the public drinking water at the last residence before death (annual 12-month average from 1981 to 1989) was used as the measure of exposure, the estimated relative risk associated with aluminum levels above 100 µg/L was 1.7 (95% confidence interval [CI] = 1.2–2.5) when all AD cases were compared with all non-AD controls. Based on weighted 10-year residential histories, the odds ratio increased to 2.5 (95% CI = 1.2–5.3). Cases

(296) were based on the presence of clinical history of dementia and strict neuropathological criteria (presence of both neuritic plaques and neurofibrillary tangles in middle temporal cortex and inferior parietal lobule in brains of cases, in the absence of any other degenerative process).[149] However, as the authors point out, the potential contributions of confounding and mitigating factors were not examined in this study; for example, confounding factors such as fluoride, silica and pH were not taken into consideration, and the ages of the cases and controls were not reported.

Wood *et al.*[150] examined the relationship between aluminum in drinking water in 386 hip fracture patients over 55 years of age in England and dementia. No relationship was found between mental score, bone density or aluminum in their drinking water.

In a controversial cross-sectional epidemiological study purporting to demonstrate an increased incidence of AD in areas of England and Wales where the aluminum levels in drinking water were high,[151] mean aluminum levels in water over the previous 10 years were obtained from waterworks agencies and were stratified in five groups by concentration, from 0.01 to 0.2 mg/L. Rates of AD were estimated from records of computerized tomographic scanning units. Four hundred and forty-five patients were classified as having probable AD. Districts in which aluminum concentrations in drinking water exceeded 110 µg/L were found to have a 50% increased risk of AD compared with districts that had aluminum concentrations below 10 µg/L. This study can be criticized on a number of points, including (1) lack of knowledge of actual exposure, (2) the lack of control of important potential confounding variables, (3) uncertainties in the diagnosis of AD and (4) the lack of a clear dose–response effect. It has also been pointed out by the authors that it is difficult to reconcile such a large effect when the contribution made by drinking water to the total daily intake of aluminum is so small. In order to explain this discrepancy, it becomes necessary to assume that aluminum in drinking water is more readily taken up than that from food.[151] In a further case–control study to investigate the relationship between aluminum and silicon in drinking water and the risk of AD, Martyn *et al.*[152] found no evidence that risk of AD is increased by aluminum in drinking water at average concentrations up to about 0.2 mg/L or that concentrations of silicon in drinking water above 6 mg molybdate-reactive silica/L exert a protective effect.

Vogt[153] investigated the relationship between aluminum levels in water and the frequency of Alzheimer's and Alzheimer-like diseases in southern Norway, where surface waters provide drinking water for 85% of the population and aluminum is added in only 4% of the waterworks. Rates of mortality associated with age-related dementia (from death certificates) were found to correlate positively with concentrations of aluminum in water. The risk of death from dementia was 1.48 times higher in the zone with the highest concentration of aluminum in water (>0.2 mg/L) than in the zone with the lowest aluminum level (<0.02 mg/L). However, this study has a number of weaknesses: the use of water data for aluminum concentrations is based on raw water rather than on distributed supplies, and there is some uncertainty over the link between the true prevalence of AD and clinical reporting of dementia as a cause of death. Flaten[154] also reported a highly significant correlation between aluminum in processed drinking water and mortality from dementia between 1974 and 1983 in Norway. The cause of death was found from registered death certificates. Age-adjusted death rates per 100 000 population grouped by aluminum concentrations in water (<0.05 mg/L; 0.05–0.2 mg/L; >0.2 mg/L) showed relative risks for dementia in males of 1.0, 1.15 and 1.32, respectively; for females, the corresponding values were 1.0, 1.19 and 1.42. Flaten[154] cautioned that ecological studies like this are useful in the generation of hypotheses but not for inferring causality and that differences in the diagnosing and reporting of dementia may be responsible for the observed geographical association between aluminum and dementia.

Wettstein *et al.*[155] evaluated the mnestic (subtest of the Mini Mental Status Test) and naming skills of 800 residents aged 81–85 years and living for more than 15 years in districts of Zurich, Switzerland, with high (98 µg/L) or low (4 µg/L) aluminum concentrations in the drinking water. The mnestic and naming performance of the octogenarians did not differ between the high- and low-concentration areas, even though 73% of dementia cases are of the AD category or type in the area examined. Furthermore, no significant difference was found in the serum aluminum, urinary aluminum or urinary aluminum/creatinine ratio of clinically diagnosed AD patients and controls (10 per group) in both areas. According to the authors, it is highly probable that aluminum in drinking water is not an essential factor in the pathogenesis of senile dementia. However, McLachlan[156] points out that the higher risk associated with elevated aluminum concentrations may not be discerned at these relatively low aluminum concentrations and that failure to detect a relationship may represent geochemical differences in the drinking water supplies.

Michel *et al.*[157] examined the cognitive function of 2792 elderly aged 65 years or more in a community in southwestern France and related this to the level of aluminum in the drinking water. The diagnosis of AD was based on psychologists' assessments and neurologists' criteria; 40 probable AD cases were identified. The concentrations of aluminum in drinking water were obtained from the water distribution companies. The investigators found a relationship between aluminum

in drinking water and AD after adjustment for urban or rural residence and education level. The relative risk was 1.16 for 0.01 mg/L and 4.53 for 0.1 mg/L. However, Smith[144] states that the authors have since modified their conclusions, as the potential inaccuracy of the historical information on the chemical analysis of aluminum in drinking water considerably changes the exposure classification of the subjects and therefore the results. Jacqmin *et al.*,[158] using data collected in 1988–1989, further studied the relationship between the risk of cognitive impairment (score lower than 24 on the Mini-Mental State Examination) in 3777 French elderly (65 and older) and levels of aluminum in drinking water. Adjustment for confounders such as age, sex, education and occupation of the participants was made. No significant effect of aluminum was found when pH was not included in the model, but there was a positive association between aluminum in drinking water and cognitive impairment at pH <7.3 and a negative association at pH >7.3. The authors also demonstrated an inverse relationship between cognitive impairment and calcium concentrations in drinking water. In a later study of the same population, Jacqmin-Gadda *et al.*[159] determined that high concentrations of aluminum in drinking water appeared to have a deleterious effect on cognitive status when the silica concentration in the drinking water was low, possibly because of a change in the bioavailability of aluminum in the presence of silica; however, there was also a protective effect of aluminum when the pH and silica level were both high, a finding that the authors found difficult to explain.

In a case–control study in northern England, Forster *et al.*[62] investigated the relationship between "presenile dementia of the Alzheimer type" (PDAT) in patients who had been clinically diagnosed as having dementia before the age of 65 years during the period 1981–1989 and exposure to aluminum in the diet (as well as family history, medical history and cigarette smoking). One hundred and nine cases of PDAT and 109 controls matched for age and sex were compared for exposure to the risk factors. No significant relationship (odds ratios) between exposure to aluminum (water supplies containing mean aluminum concentrations of <50 µg/L, >50 µg/L, >99 µg/L or >149 µg/L at the place of residence for at least 10 years before dementia onset, prolonged antacid use or high levels of tea drinking) and PDAT was observed. Limitations of the study included the inability to verify the consumption of aluminum-containing antacids and the need to use mean levels of aluminum in drinking water over a specific time period. In a follow-up study, Taylor *et al.*[160] collected water samples and the places of residence for at least 10 years before dementia onset for these cases and controls and reported an inverse relationship between dissolved aluminum and dissolved silicon. As silicon helps determine the bioavailability of aluminum, this suggests a possible preventive role of silicon in PDAT.

Graves *et al.*[14] examined, in a case–control study of 130 matched pairs, the association between AD and lifelong exposure to aluminum in antiperspirants and antacids. A statistically significant dose–response relationship between AD and antacids was demonstrated, with a very strong increasing trend in risk observed with increasing number of years of using antacids of any type. There was not, however, a significant association between aluminum-containing antacids and AD, and there was only a weak association between aluminum-containing antiperspirants and AD. Graves *et al.*[14] concluded that the results for antacids did not support their aluminum hypothesis; however, they cautioned that their findings should be considered preliminary as a result of methodological limitations, including the use of surrogate respondents and the small sample numbers used in sub-analyses. In a Canadian population-based case–control study in which 258 cases clinically diagnosed with probable AD were matched with 535 controls, no association was found between the use of aluminum-containing antacids and AD. For antiperspirants containing aluminum, the OR was 1.33 (not significant); the OR for tea consumption at 1.40 was also not significantly elevated.[161] Flaten *et al.*[15] found no association between antacid use and mortality from AD including dementia among 4179 gastroduodenal ulcer patients in Norway. The investigators suggested that they may not have covered a long enough period after exposure. In a case–control study, Heyman *et al.*[162] found no indication that the regular use of aluminum-containing antacids for at least three months is more frequent in patients with AD than in unaffected individuals; in fact, such antacids had been taken for this period of time by a slightly higher proportion of controls than of patients.

Occupational Exposure

Rifat and co-workers[163] examined the effect of prolonged exposure to respirable aluminum dust in miners in northern Ontario. The miners performed significantly more poorly on cognitive tests than an age-matched unexposed group of miners; these differences persisted with adjustment for factors that influenced the effect measure, such as years of underground mining, education and immigrant status. However, there were no significant differences between exposed and non-exposed miners in reported diagnoses of neurological disorder. The authors suggested that follow-up studies should be conducted to determine whether this was due to missed diagnoses, to the fact that Alzheimer-type dementia and other related conditions may be an extreme and atypical manifestation of aluminum intoxication or to some other factor.

In a cross-sectional study, Bast-Pettersen *et al.*[164] reported signs of nervous system impairment (suggestion of an increased risk of impaired visual-spatial organization and a tendency to a decline in psychomotor tempo) in 14 Norwegian potroom workers following at least 10 years of occupational exposure to aluminum in a primary aluminum plant when compared with control group workers who were not exposed to aluminum. These symptoms were not observed in eight less-exposed foundry workers.

Two studies have examined the incidence of cancer in aluminum plant workers — one in an aluminum reduction plant in France[165] and the other in an aluminum smelter in Quebec.[166] In the first study, there was not a statistically significant increase in cancer mortality compared with the French male population; however, the authors pointed out that the numbers of cancers of individual sites were not sufficiently numerous for thorough analysis, and they recommended that monitoring of the incidence of cancer among workers employed in the aluminum industry be continued. The Quebec study showed an increased incidence of bladder cancer in aluminum smelter workers, particularly workers in Soderberg potrooms; however, the authors concluded that the cancers were probably due to benzo(a)pyrene exposure and cigarette smoking and not to aluminum.

Toxicity in Animals

Short-term Exposure

Male Sprague-Dawley rats (25 per group) were fed for 28 days on a diet containing basic sodium aluminum phosphate or aluminum hydroxide or a control diet. Mean daily aluminum doses were calculated by the authors to be 5 mg/kg bw per day for the control animals and 67–302 mg/kg bw per day for the test animals. No aluminum-related effects were observed on body weight, organ weights, haematology, clinical chemistry or histopathology of tissues. There was no evidence for increased aluminum accumulation in bone. The no-observed-effect levels (NOELs) can be considered to be 288 and 302 mg Al/kg bw per day for sodium aluminum phosphate and aluminum hydroxide, respectively, the highest doses tested.[167]

Female Sprague-Dawley rats (10 per group) received drinking water containing aluminum nitrate at doses of 0, 375, 750 or 1500 mg/kg bw per day (equivalent to 0, 27, 54 and 108 mg Al/kg bw per day) for one month. No significant effects on appearance, behaviour, food and water consumption or growth of treated rats were observed during the study. Increased aluminum levels were reported in the heart (highest dose) and spleen (two highest doses), and mild histological changes (hyperaemia) were apparent in the liver (highest dose) and spleen (two highest doses). No effects were reported at the lowest dose level of 27 mg Al/kg bw per day.[168]

Male Sprague-Dawley rats fed diets containing aluminum hydroxide at either 257 or 1075 mg Al/kg diet for 67 days (approximately 13 and 54 mg Al/kg bw per day) showed increased levels of aluminum in the tibias, liver and kidneys (levels were similar for both doses). No change in the breaking strength or elasticity of the bones was observed at the low dose level, but significantly reduced bone strength was noted at the high dose level.[169] Oral administration of aluminum (as aluminum hydroxide) to rats at levels of 261 and 268 mg Al/kg diet for 18 days (controls given 5 mg/kg diet) resulted in a statistically significant increase in the levels of aluminum in the kidneys.[170]

Groups of female Sprague-Dawley rats (10 per group) received aluminum nitrate in their drinking water at doses of 0, 360, 720 or 3600 mg/kg bw per day (equivalent to 0, 26, 52 and 260 mg Al/kg bw per day) for 100 days. Body weight, organ weights (brain, heart, lungs, kidneys, liver, spleen), histopathology of heart, liver, spleen, brain and kidney, haematology and clinical chemistry parameters were examined. The treated animals drank significantly less water than the controls. Lower body weight gain associated with lower water and food intake was reported at the highest dose level. The other two groups did not show any significant difference in body weight. Although concentrations of aluminum were higher in tissues of exposed rats than in control animals, no significant relationship between dose and accumulation of aluminum could be observed. No histological changes were reported. According to the authors, the possibility of intoxication in humans from ingestion of aluminum would be very low.[171]

Pettersen *et al.*[172] fed dogs (four per sex per group) diets containing basic sodium aluminum phosphate at 0, 3000, 10 000 or 30 000 ppm for 26 weeks. The mean daily doses of aluminum were 4, 10, 27 and 75 mg/kg bw for males and 3, 10, 22 and 80 mg/kg bw for females. Mild histopathological changes were observed in the kidney, liver and testes of high-dose males; changes in the liver and testes were attributed to body weight reductions caused by reduced food intake, whereas changes in the kidney may have been secondary to the effect on body weight. No effects on body weight or food consumption were observed in females. Brain aluminum concentrations were slightly elevated in high-dose females. No effects were observed at the lower dose levels. The no-observed-adverse-effect level (NOAEL) was 10 000 ppm, equivalent to 22 mg/kg bw per day in females and 27 mg/kg bw per day in males.

Long-term Exposure

No effects on life span, body weight, heart weight, serum glucose, cholesterol and uric acid, or urinary protein and glucose content were observed when two groups of Long-Evans rats (52 of each sex) were given aluminum (as potassium aluminum sulphate) in drinking water at a concentration of 0 or 5 mg/L over their lifetime.[173] Similarly, no adverse effects on body weight or longevity were observed in Charles River mice (54 per sex per group) given 0 or 5 mg Al/kg of diet (as potassium aluminum sulphate) during their lifetime.[174]

Mutagenicity and Related End-points

The rec assay using *Bacillus subtilis* strains failed to show mutagenic activity for aluminum oxide, aluminum chloride and aluminum sulphate at concentrations ranging from 0.001 to 10 M.[175,176] No reverse mutations were observed in the Ames test using *Salmonella typhimurium* strain TA102 with aluminum chloride at concentrations ranging from 10 to 100 nM per plate.[177] Leonard and Leonard[178] reviewed the data on the mutagenicity of aluminum and found negative results in most short-term mutagenic assays. According to these authors, however, some aluminum compounds appear able to produce chromosomal anomalies in plant material, probably as a result of an interference with microtubule polymerisation.

Crapper McLachlan[179] summarized the genotoxic and subcellular effects of aluminum on DNA in neurons and other cells, including nuclear effects such as binding to DNA phosphate and bases, increased histone–DNA binding, altered sister chromatid exchange and a decrease in cell division. Chromosomal aberrations were induced in human leukocyte cultures by aluminum.[180]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

No evidence for impaired reproductive performance — pregnancy rate, implantation efficiency, incidence of live or dead implants — was observed for male Sprague-Dawley albino rats receiving drinking water containing up to 500 ppm aluminum as aluminum chloride (approximately 0.5, 5 and 50 mg Al/kg bw per day) for up to 90 days prior to breeding. The histopathology and plasma gonadotropin levels of exposed and control animals were also not significantly different.[181]

In a study in which pregnant Sprague-Dawley rats were fed aluminum chloride (500 or 1000 mg Al/kg diet) in their diet on days 6–18 of gestation, there were no effects on foetal resorption rate, litter size, foetal body weight or foetal crown-rump length.[182]

Groups of 10 pregnant Sprague-Dawley rats administered oral (by gavage) aluminum nitrate doses of 0, 180, 360 or 720 mg/kg bw per day (equivalent to 0, 13, 26 and 52 mg Al/kg bw per day) from day 14 of gestation through to day 21 of lactation did not exhibit overt foetotoxic effects. However, offspring from treated dams (particularly at the higher doses) showed depressed body weight gain.[183]

No significant maternal or developmental toxicity was observed when aluminum hydroxide was given by gavage at dose levels of 192, 384 or 768 mg/kg bw per day to pregnant Wistar rats on days 6 through 15 of gestation.[184] When aluminum (133 mg/kg bw per day) as aluminum hydroxide, aluminum citrate or aluminum hydroxide concurrent with citric acid was administered by gavage to pregnant Sprague-Dawley rats on gestational days 6 through 15, the group treated with aluminum hydroxide and citric acid exhibited significantly reduced maternal body weight gain, a significant decrease in foetal body weight and a significantly increased incidence of skeletal variations. As aluminum was not detected in whole foetuses of treated groups, the authors recommended that further investigations evaluate the possible developmental toxicity of oral citric acid.[185]

Pregnant Swiss albino (CD-1) mice were given daily aluminum doses of 57.5 mg/kg bw per day by gavage, as aluminum hydroxide, aluminum lactate or aluminum hydroxide concurrent with lactic acid, on gestational days 6–15. Foetal body weight was significantly reduced in the aluminum lactate group, and foetal morphological changes, including cleft palate and skeletal variations, were observed. Maternal toxicity was also observed in this group and in the aluminum hydroxide/lactic acid group.[186] No signs of maternal or developmental toxicity were observed when pregnant Swiss mice were given by gavage daily doses of aluminum (104 mg/kg bw per day, as aluminum hydroxide) with or without ascorbic acid on gestational days 6–15.[187] Domingo *et al.*[188] found no evidence of maternal toxicity, embryo/foetal toxicity or teratogenicity when aluminum hydroxide was administered by gavage to pregnant Swiss mice at daily doses of 0, 66.5, 133 or 266 mg/kg bw on gestational days 6 through 15.

In a three-generation study, 10 mice received aluminum chloride in their drinking water at an average dose of 19.3 mg Al/kg bw per day for 180–390 days. Treated mice as well as 10 controls were fed a diet containing 170 ppm aluminum (approximately equivalent to the daily drinking water dose). The weanlings were treated like their parents from four weeks of age. There were no significant differences in the numbers of litters or offspring between the treated and control mice. A decrease in growth was observed in the second and third generations of mice. However, no significant differences in the erythrocyte counts and haemoglobin levels in the first and third generations and in the controls were reported, and no pathological changes could be found in the liver, spleen or kidney.[189]

A significant increase in aluminum concentration of the placenta and foetuses was reported when pregnant BALB/c mice were given oral (by gavage) aluminum chloride doses of 200 or 300 mg/kg bw (equivalent to 40 and 60 mg Al/kg bw) on days 7–16 of gestation.[190] Colomina *et al*.[186] also noted a significantly elevated aluminum concentration in whole foetuses of mice given aluminum lactate (57.5 mg/kg bw per day by gavage) during organogenesis (gestational days 6–15). In contrast, most reproductive studies have shown that oral aluminum administration does not result in aluminum accumulation in foetuses or pups.[182,184,191–194]

Many reproductive studies have examined the effects of aluminum administration on neurobehavioural development. These studies are discussed in detail in the next section.

Special Studies on Neurotoxicity and Neurobehavioural Development

Several studies have examined the neurotoxicity of aluminum in animals. Following single oral doses of aluminum hydroxide (100 or 200 mg/kg) in fasted mice, transient dose-related electroencephalographic alterations in the 7.5–12 Hz frequency band were observed in mice; changes were seen as early as 45 minutes after dosing and were strongly correlated to brain aluminum levels.[195]

In another study, male Sprague-Dawley rats (11 per group) had access *ad libitum* to drinking water that had been supplemented with 0 or 100 µM aluminum chloride (three times the aluminum concentration found in commercial beverages) over a one-year period. At the end of this period, when the animals were tested in a T-maze for learning and recall, treated animals showed a tendency to take more time to reach the food source and made more errors, but statistically there was only a marginally significant difference between exposed and control animals. There was no significant difference in brain weight between the two groups, but the brains of the experimental group contained more aluminum.[196]

In a different study, the diet of male Sprague-Dawley rats was supplemented with aluminum (0.1% as aluminum chloride) for an 11-month period, following which the locomotor response was decreased and the shuttle-box avoidance behaviour was adversely affected. There was no effect when 0.2% dietary aluminum chloride was administered to female Sprague-Dawley rats or to male Fischer rats for 12 weeks.[197]

Young Wistar rats were treated with aluminum lactate (0, 100 or 200 mg Al/kg bw per day) from postnatal day 5 to 14 by gastric intubation. At the high dose, cerebral aluminum concentrations increased and brain choline acetyltransferase activity was reduced. At 50 and 100 days of age, the treated rats did not differ in their learning abilities in an avoidance test and a radial maze test, but a slight reduction in general activity was observed in high-dose rats.[198]

CD-1 mice were given 1.0% aluminum (as aluminum chlorhydrate) in their drinking water from day 1 to eight weeks of age, and another group was similarly treated from one to four months of age; controls received tap water. All mice were trained for conditioned avoidance response (CAR) at two months. The CAR of the first group of mice was 26% less than that of the control group, but CAR values of the second group of mice did not differ from those of its control. The authors concluded that oral ingestion of aluminum induced neurotoxicity in mice during the weaning period; tissue aluminum levels were not measured, so a relationship between CAR changes and aluminum content in the brain could not be determined.[199]

The effects of prolonged aluminum exposure on behaviour were assessed in young (21 days), adult (eight months) and old (16 months) male Sprague-Dawley rats given aluminum nitrate nonahydrate in drinking water at doses of 0, 50 or 100 mg Al/kg bw per day together with citric acid for 6.5 months. There were no effects of aluminum exposure on horizontal and vertical activity in an open field in any age group, and there were no significant differences among dose groups in passive-avoidance conditioning in the young rats; adult and old rats showed low passive-avoidance conditioning regardless of aluminum dose.[200]

Several reproductive studies have examined neurobehavioural changes in the offspring of dams exposed to aluminum in the diet. When Swiss-Webster mice were fed aluminum as aluminum lactate in a purified diet (25, 500 or 1000 µg Al/g diet; 5, 100 and 200 mg/kg bw per day at the beginning of pregnancy and 10.5, 210 and 420 mg/kg bw per day near the end of lactation) from conception to weaning, weanlings whose dams had been fed high-aluminum diets generally exhibited greater foot splay, decreased sensitivity to heat and greater forelimb and hindlimb grip strength.[191]

Swiss Webster mice were exposed to 7 (controls), 500 or 1000 µg Al/g diet as aluminum lactate (equivalent to an average adult mouse intake of 1.4, 100 and 200 mg Al/kg bw per day) from conception until weaning or from conception through adulthood. Enhanced cagemate aggression in offspring as adults was observed at 1000 µg Al/g diet, and both treatment diets led to faster attainment of criterion during the training phase of the operant studies and reduced grip strength; however, there was no effect on performance of cognitive tasks (delayed spatial alternation or discrimination reversal testing). The authors identified 500 µg Al/g diet, equivalent to about 100 mg Al/kg bw per day, as the lowest-observed-adverse-effect level (LOAEL). According to the authors, the similar behavioural effects in mice

exposed to both diets suggest that accumulated body burden rather than daily intake may be related to neurobehavioural effects.[201]

Golub *et al.*[192] fed Swiss Webster mice either 25 (control) or 1000 (high Al) µg Al/g diet (as aluminum lactate) (about 5 and 250 mg/kg bw per day) from conception through lactation; litters were fostered either between or within groups. Neurobehavioural tests administered at weaning showed effects of high aluminum exposure during gestation and/or lactation on forelimb grasp strength, negative geotaxis, hindlimb grasp and temperature sensitivity.

When pregnant Wistar rats were treated orally with aluminum (400 mg Al/kg bw per day) as aluminum lactate during three periods of gestation (day 1 to day 7, day 1 to day 14, and day 1 to parturition), no effects on litter size, mortality rate or weight gain of pups were observed. However, significant effects in the negative geotaxis test (second and third gestational groups) and in the locomotor coordination and operant conditioning tests (all three treatment groups) were observed.[202]

An increase in pre-weaning mortality and a delay in weight gain and neuromotor development in surviving pups were reported in the offspring of albino Wistar rats given oral doses (in the diet) of aluminum chloride (equivalent to about 155 and 192 mg Al/kg bw per day) from day 8 of gestation through parturition.[203] Neurotoxicity and weight loss were also reported in mouse dams fed a diet containing aluminum lactate at 500 or 1000 ppm from day 0 of gestation to day 21 postpartum. Offspring showed growth retardation and somewhat delayed neurobehavioural development, which was consistent with maternal toxicity.[204] Donald *et al.*[191] suggested that the effects observed in this experiment may have been attributable to the low trace metal content in the diet to which the aluminum was added.

In a study in which pregnant rats were exposed to a 20% solution of Maalox (a stomach antacid) in tap water (approximately 3.2 mg Al/mL) from the second day of gestation, Anderson *et al.*[205] found that offspring of aluminum-exposed dams showed significantly more aggressive responses, although the time spent on each aggressive response was less than in controls. Furthermore, the offspring of aluminum-exposed mothers showed a significantly longer latency period in the escape-training phase following a three-day period of exposure to non-avoidable shocks.

Classification and Assessment

Aluminum occurs naturally in water. During surface water treatment, alum (aluminum sulphate) is normally added as a coagulant to assist in the removal of turbidity, which results in the reduction of pathogenic micro-organisms, such as viruses and *Giardia*; coagulation also reduces the formation of disinfection by-products by removing organic material prior to disinfection. However, high residual aluminum levels in some waters can result in deposition of gelatinous aluminum-containing substances in the distribution system and subsequent flow rate reductions.[41,42] High residual aluminum levels can also interfere with the disinfection process by enmeshing and protecting micro-organisms.[44] Residual aluminum concentrations in finished waters are a function of a variety of factors, including the aluminum levels in the source water, the amount of alum used as coagulant, pH, temperature and the processes used to treat the surface water. Under optimal conditions, the conventional surface water treatment process can achieve a minimum aluminum concentration in the finished drinking water of around 30 µg/L[32]; the concentration may be higher — up to 200 µg/L or more — with direct or in-line filtration.

Aluminum has no known beneficial effect in humans. There is evidence that aluminum is neurotoxic in animals at higher doses. High levels of aluminum in the blood and tissues of patients with chronic renal disease and undergoing dialysis caused acute dementia[123] resulting from iatrogenic exposure to aluminum.[117] Aluminum may be a contributory factor in certain neurodegenerative diseases, such as AD, ALS and PD. Aluminum has been found in the neurofibrillary tangles in brains of AD patients examined post-mortem, but whether it is a cause or a result of the condition is unknown. The role of aluminum in ALS and PD is not clear either.

Several epidemiological studies have reported a small increased relative risk of AD associated with high aluminum concentrations in drinking water.[140,142,145,151,154,157] All these studies have methodological weaknesses, but a true association between high aluminum concentrations in drinking water and dementia (including AD) cannot be ruled out, especially for the most elderly (e.g., over 75).[17,144] According to a review by Doll,[131] the evidence from several epidemiological, clinical and experimental studies suggests that aluminum is neurotoxic in humans but does not suggest that it causes AD. However, Doll[131] stressed that the possibility that aluminum does cause AD must be kept open until the uncertainty about the neuropathological evidence is resolved.

Food is the main source of aluminum intake; drinking water contributes only about 3% of total daily intake. The relative bioavailability of aluminum from the two sources is not known. Experimental studies have shown that the actual amount of aluminum absorbed from water depends on a number of factors, including the presence of other dietary constituents in the gastrointestinal tract that can either enhance (e.g., citrate) or suppress (e.g., phosphate) its uptake. Aluminum in finished water is largely in the form of dissolved species,

including soluble organic species, which appear to be the most readily absorbed. Little is known about the bioavailability of aluminum in food, although it is known that aluminum in tea is highly complexed and thus insoluble. The possibility must be considered that the uptake of aluminum in drinking water is not insignificant,[17,144] even though it is low. This is particularly true in the elderly, as absorption may be higher in that population traditionally considered at greatest risk for AD.[72,156]

Rationale

To minimize any potential risk from residual aluminum in water treated with aluminum-based coagulants, water treatment processes should be optimized in order to reduce residual aluminum levels to the lowest extent possible. A specific operational guidance value will depend on water characteristics and the treatment process used. An operational guidance value of less than 100 µg/L total aluminum is recommended for conventional treatment plants using aluminum-based coagulants. For direct or in-line filtration plants or for plants with lime softening, an operational guidance value of less than 200 µg/L should be considered. These values are based on a 12-month running average of monthly samples. For certain water supplies and types of treatment systems, this value must be determined for individual plants by considering the ability of the plants' processes to reduce aluminum. It is recognized that the possible health effects are not well defined and that the contribution of drinking water to any health effect is unknown; thus, there are insufficient data at present to support setting a health-based guideline.

For conventional surface water treatment plants using aluminum-based coagulants, optimization of the clarification process (coagulant dose optimization, pH control and good mixing, flocculation, sedimentation and filtration) can minimize aluminum levels in the finished water. From a plant operational point of view, it is important to reduce both total and dissolved aluminum — dissolved as a measure of optimization of coagulant, and total as a measure of particulate removal through filtration. Dissolved aluminum is defined as aluminum that passes through a 0.22-µm filter. Aluminum concentrations should be expressed as a running annual average of monthly samples, because aluminum concentrations in drinking water can vary quite rapidly with changes in raw water quality or with operational changes.

Optimization of pH prior to clarification is a recognized means of reducing residual aluminum levels in the finished water. However, any measures taken to lower pH in order to reduce residual aluminum must be accompanied by an evaluation of the effect of such changes on the chemical corrosiveness of the finished water. Remedial actions for the production of corrosive water include the addition of an alkali following filtration to raise pH or the use of phosphate corrosion inhibitors. The use of alternative coagulants or alternative treatment processes may also be considered, although the substitution of one coagulant or treatment process for another should be undertaken only after the safety and effectiveness of the substitute have been thoroughly studied.

It is not expected that all water supplies using aluminum-based coagulants will be able to reduce their dissolved and total aluminum concentrations immediately. When water systems are expanded or upgraded, every effort should be made to reduce residual aluminum concentrations in the finished drinking water to as low a level as possible. However, attempts to minimize aluminum residuals must not compromise either the effectiveness of disinfection processes (i.e., microbiological quality) or the performance of coagulation/sedimentation/filtration processes in the removal of disinfection by-product precursors.

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