Public Health Goal for
ALUMINUM
In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and publish PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs published by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations

without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR ALUMINUM IN DRINKING WATER

SUMMARY

A PHG of 0.6 mg/L (600 ppb) was derived for aluminum (Al) in drinking water, based on data in a 40-day Al balance study in humans (Greger and Baier, 1983), and exposures of premature infants to Al in their parenteral feeding solution (Bishop et al., 1997). In the Greger and Baier (1983) study, subjects received either 4.6 mg Al per day (control) or 125 mg Al per day (treatment), with treatment and control being exchanged at 20 days so that each subject served as his own control. Treatment at 125 mg Al per day caused a significant increase in serum Al. Assuming a no-observed-adverse-effect-level (NOAEL)/lowest-observed-effect-level (LOEL) of 125 mg/day and an uncertainty factor of 100 for exposure to Al as a bolus dose in water (or juice, in the Greger and Baier study), a health-protective level of 0.6 mg/L was determined based on the pharmacologic effect of increased serum Al. The study of Bishop et al. (1997) showed impaired neurological development in premature infants exposed to Al in parenterally-administered feeding solutions at an Al intake level of 45 µg/kg-d, compared to infants receiving an Al-depleted solution at an Al dose of 4 to 5 µg/kg-d. An uncertainty factor of 100 was applied to the 45 µg/kg-d dose to calculate the health-protective level of 0.6 mg/L from this study for a sensitive subpopulation.

The PHG value of 0.6 mg/L is further supported by the most suitable animal study (Golub et al., 1993) in which mice treated with 200 mg/kg-d Al lactate for six months showed a number of immunological changes. The health protective value calculated from this study was 0.7 mg/L. Other animal studies indicated Al-induced growth retardation, effects on phosphorus metabolism, depressed motor reflex, and immunosuppressive effects including decreased cytokine production. Aluminum exposure via drinking water has been associated with Alzheimer's disease (AD) and other dementia, but no causal link has been established and other factors are likely to be the major causes of AD. The association of Al exposure with various forms of dementia still merits caution and concern. Aluminum is neurotoxic in humans exposed parenterally, via the oral route in those suffering renal disease, and potentially in neonates receiving formulas with excess Al.

Because of the prevalence of Al in foods, consumer products, pharmaceuticals and the environment, it is impossible for humans to avoid exposure to Al compounds. Aluminum in potable drinking water constitutes a small fraction of the total daily intake (<10 percent). The current State maximum contaminant level (MCL) for Al in drinking water is 1.0 mg/L. The U.S. Environmental Protection Agency (U.S. EPA) has not established a primary or health-based MCL for Al although a secondary MCL of 0.05 to 0.2 mg/L has been established based on aesthetic concerns.

INTRODUCTION

This document represents an update of our earlier health risk assessment of Al (DHS, 1988). Prior to 1991, the Office of Environmental Health Hazard Assessment (OEHHA) was a division of the Department of Health Services (DHS).

Aluminum is the most abundant metal and third most abundant of all elements in the earth's crust. Naturally occurring Al compounds have limited solubility in water at neutral pH, but solubility increases markedly with increasing or decreasing pH. Domestic tap water may contain

Al either naturally or because Al has been added as a flocculant in the treatment process. In a U.S. EPA survey of water supplies throughout the United States (U.S.), the maximum Al concentration reported in finished water where an Al compound was used as a coagulant was 5.35 mg/L, whereas the maximum Al level reported in finished water not using an Al coagulant was 1.17 mg/L. The ingestion pathway is the most significant route of transfer of Al from the environment to the healthy animal or human. Results from balance studies in humans demonstrate that the gastrointestinal (GI) absorption of Al is very low (<1 percent). Aluminum is known to react with phosphorus in the GI tract forming insoluble Al phosphate complexes, thus reducing phosphate absorption. Consequently, Al has often been used therapeutically to prevent hyperphosphatemia in uremic patients. Consequences of prolonged Al intake (>1 g Al/day) in these cases may be phosphate depletion, hypercalciuria, bone resorption, and possibly osteomalacia. There is no direct evidence that Al is carcinogenic or mutagenic in humans or animals. Embryotoxic effects have been reported in the offspring of rats and mice injected with doses of 75-200 mg Al/kg on gestational days 9-13 or 14-19 and 20 mg/kg on days 3, 5, 7, 9, 12, 13, and 15 of gestation, respectively. These effects included decreased fetal weight and crown-rump length, and increased number of resorptions. No teratogenic, embryotoxic, or other reproductive effects have been reported in humans.

Aluminum is neurotoxic. There are reports in which tap water has been identified as a significant source of Al in renal dialysis patients, when tap water was misused in hemodialysis. Based on those cases, it has been recommended that the Al concentration not exceed 0.01 ppm (10 ppb) in hemodialysis solutions (Graf et al., 1982). The proposed public health goal (PHG) applies only to water intended for drinking and other domestic purposes, not to solutions administered parenterally during medical procedures. Aluminum from water and other sources has been associated with dialysis encephalopathy (DE) and with similar neurotoxic effects seen in infants receiving total parenteral nutrition. The suggested association of oral Al intake, particularly via drinking water, with Alzheimer's disease or other forms of dementia remains a concern. While the PHG is protective of the general population, there may be sensitive subgroups; e.g., those with impaired renal function, for whom prolonged exposure at the PHG level may not be fully protective. In these cases the safe level of Al in drinking water would depend on a number of factors such as the severity of the disease, prior exposure, and dietary intake. In any event, Al from drinking water would usually constitute a small fraction of the overall Al intake.

CHEMICAL PROFILE

Chemical Identity

Aluminum is a member of group III A of the periodic table, with atomic number 13 and atomic weight 26.98. A number of common Al compounds with formulas and molecular weights are listed in Table 1. The British spelling of "aluminium" can be found in several of the cited references.

Physical and Chemical Properties

Aluminum is a silver-white, malleable, and ductile metal. It is the third most abundant element in the earth's crust, comprising 8.3 percent of its volume (NRC, 1982). Aluminum has a primary hydration number of six and exists in nature only in the trivalent state. The ionic radius is small, only 0.51 angstrom, due to the ion's strong electric charge. The high charge and small size give

Al^{+3} a strong polarizing effect on adjacent atoms (Ganrot, 1986). Aluminum has a high affinity for oxygen and is therefore found predominantly in the oxidized form as alumina, $A1_2O_3$. Pure

$A1_2O_3$ is insoluble in water. Al $(OH)_3$ is amphoteric and at neutral pH has limited solubility, but the solubility increases markedly with increasing or decreasing pH (Elinder and Siogren, 1986). When $Al(OH)_3$ is added to water, a fine flocculate is formed which binds with other suspended particles allowing their removal and precipitation (Elinder and Siogren, 1986). This property is utilized in the treatment of drinking water. Al^{+3} forms an insoluble salt with phosphate and it forms relatively strong complexes with fluoride ion (F^-) (Martin, 1986). In contrast, citrate solubilizes Al and citrate complexation of $A1^{+3}$ provides an effective means for Al absorption into the body from the GI tract. Driscoll & Schecher (1989) have reviewed the aqueous chemistry of Al. Some physical and chemical properties of Al compounds are summarized in Table 1.

Table 1. Selected Physical and Chemical Properties of Aluminum Compounds (Adapted from ATSDR, 1999)

Compound	Molecular Weight	Formula	Physical State	Solubility	Odor
Aluminum	26.98	Al	Crystalline solid	Insoluble, oxidized by water at 180°C; soluble in alkali, acid	Metallic odor when dust is inhaled
Aluminum Chloride	133.24	$AlCl_3$	White crystals	Reacts explosively with water evolving HCl gas; soluble in benzene, chloroform, alcohol and ether	Strong odor of HCl
Aluminum Hydroxide	77.99	$Al(OH)_3$	White powder	Practically insoluble in water, forms gels on prolonged contact; soluble in alkaline aqueous solutions or in HCl, H_2SO_4	No Data
Aluminum Lactate	294.18	$C_9H_{15}AlO_9$	Colorless powder	Freely soluble in water	No Data
Aluminum Nitrate	213.00	$Al(NO_3)_3$	White crystals	Very soluble in water; slightly soluble in acetone	Odorless
Aluminum Oxide	101.94	Al_2O_3	White crystalline powder	Practically insoluble in water (98 µg/100 mL); slowly soluble in aqueous alkaline solution	No Data
Aluminum Phosphate	121.95	$AlPO_4$	White powder	Insoluble in water; very slightly soluble in conc. HCl, HNO_3	No Data
Aluminum Fluoride	83.98	AlF_3	White or colorless crystals	0.56 g/100 mL water at 25°C; sparingly soluble in acids, alkalies, insoluble in acetone or alcohol	No Data
Aluminum Sulfate	342.14	$Al_2(SO_4)_3$	White crystals, granules, powder	Soluble in one part of water, soluble in dilute acids; practically	Odorless

				insoluble in alcohol	

Production and Uses

In nature, Al generally is found combined with silicates, such as bauxite and cryolite (NRC, 1982). Anthropogenic releases are primarily associated with industrial processes like Al reduction (ATSRD, 1999). In 1995, domestic Al production totaled 3.4 million tons (ATSDR, 1999). World production of Al totals approximately 14 million tons per annum (Kaufman, 1983). There are more than 4,000 terminal uses of Al in such fields as electrical engineering and the transport and air traffic industries and in such products as building materials, home furnishings, kitchen appliances, farm implements, containers for packaging material, and building structures. In powder form, Al is a component of paints, pigments, missile fuel, and chemical explosives (NRC, 1982). Medicinally, Al $(OH)_3$ is widely used in non-prescription antacids and buffered aspirins and Al compounds are used to prevent hyperphosphatemia in patients suffering renal failure (Jones and Bennett, 1986). Aluminum compounds are applied in the processing, packaging, and preservation of foods. Finally, Al compounds have been used in cosmetic and antiperspirant preparations.

ENVIRONMENT ALUMINUM OCCURRENCE AND HUMAN EXPOSURE

Air

Ambient air concentrations of Al were reported to range from 0.01 to 0.54 µg/m^3 in Canada. Occupational air concentrations are much higher at 1.0 to 2.0 mg/m^3 (Van Oostdam et al., 1990).

Soil

Aluminum is the third most abundant element of the earth's crust constituting 8.3 percent. It is a major component of a large number of minerals such as alumina-silicates, feldspars, bauxite, and clays (Ganrot, 1986).

Water

At neutral pH, Al minerals are insoluble, but solubility increases at lower pH. Cronan and Schofield (1979) have shown that the acidification of lakes and streams by acid rain mobilized Al from the soil to the aquatic environment. Domestic tap water may contain Al either naturally or because Al has been added as a flocculant in the treatment process. $A1_2(SO_4)_3$ is the most widely used coagulant for clarifying turbid drinking water (Martin, 1986). The levels of dissolved Al in waters are strongly influenced by pH and the presence of other substances in the water. Browne et al. (1990) has studied the speciation of Al in natural water. The fraction of free Al^{+3} and Al OH predicted to occur at pH 5 was about 0.3 for each. At increasing values above pH 5, Al OH species predominate e.g., Al OH^{+2}, Al $(OH)_2$+, Al $(OH)_3$, Al $(OH)_4$. Nieboer et al (1995) and Gardner and Dixon (in Health Canada, 1997, appendix 12) also provide extensive discussions of Al speciation in water. Concentrations of 12-2250 µg/L have been reported for North American rivers (Durum and Haffty, 1963). Miller et al. (1984) surveyed water supplies throughout the U.S., and found that Al was more likely to occur in surface waters than groundwater. Twenty-nine percent of the samples of finished surface water that had not been coagulated had an Al

concentration >0.05 mg/L. Sixty-nine percent of the finished surface waters that had been coagulated with $A1_2(SO_4)_3$ had Al concentrations >0.05 mg/L. Aluminum in finished water in regions of California and Nevada varied (median 0.053 mg/L, range < 0.0014 to 1.167 mg/L). The highest concentration seen in raw waters was 2.5 mg/L. Of 240 finished groundwater samples, only 4 percent had concentrations >0.05 mg/L. Studies in the United Kingdom and Canada have shown that when Al-based coagulants are used in the treatment of water, the level of free Al is increased. Most naturally-occurring Al is bound and not readily bioavailable. Therefore, treating raw water with Al-based coagulants may reduce total Al but increase free bioavailable Al (Health Canada, 1996).

Food

Aluminum is found in the tissues of all plants and animals. The concentration in foods varies widely, depending upon the product, the type of processing, and the geographical origin (Pennington, 1987). The total consumption of Al in a normal diet is believed to be between 1 and 20 mg/day (Sorenson et al., 1974; Alfrey, 1983; Lione, 1983). The richest natural dietary sources of Al are herbs and tea leaves. Tea infusates contain up to 0.5 mg Al/100 g and ingestion of 8 oz of tea with each meal would add 1 to 3 mg Al to the diet (Greger, 1985). Rajwanshi et al. (1997) estimated that 5 cups of tea per day would result in an Al exposure of 5 to 7 mg Al. Koch et al. (1988) found that consumption of 1.2 L tea/day markedly increased urinary excretion of Al. Baxter et al. (1990) found the Al concentration in infant formulas based on cow's milk ranged from 0.03 mg/L to 0.2 mg/L. Higher amounts were present in soya-based formulas: 0.64 mg/L to 1.34 mg/L. Aluminum salts are used as emulsifiers in some processed cheese (700 µg/g), in some baking powders (20-26 mg/g), cake mixes and pickled vegetables (Lione, 1983). There are some indications that the 20 mg/d estimate may be high, as analysis of the Al content of a controlled diet indicated total dietary Al to be only 2.45 mg/day (Gorski et al., 1979). In a Finnish study (Koivistoinen, 1960) daily intake of Al from food was calculated to be 6.7 mg. Pennington et al. (1987) reported that daily intakes of Al, based on analysis of diets, for eight age-sex groups ranged from two to 14 mg/day. Pennington (1987) noted that the major sources of Al in daily diets are probably grain products, processed cheese, tea, herbs, spices, and salt containing Al additives. Aluminum-containing food additives make a significant contribution to Al intake from food. Based on the quantities of Al food additives used daily Al intake was estimated to be 19-20 mg/day, an alternate estimate of Al intake. Greger (1985) assessed the amount of Al present in the diets of Americans. He estimated that Al content of a diet (with salt and herbs, all foods cooked in Al pans) for a 30-year old male was 26.5 mg/day with 1.2 mg from tea.

Other Sources

Much larger amounts (1 g or more per day) are consumed by those taking antacids in which Al $(OH)_3$ is one of the main ingredients (Lione, 1985). Aluminum salts are common buffers in drugs. Buffered aspirin contains up to 50 mg Al per tablet (Crapper McLachlan and Farnell, 1985). Aluminum may comprise 25 percent by weight of antiperspirants, either powders or solutions. While uptake of Al from these products is uncertain, they represent another possible household source. The transfer from cooking utensils or foil of Al to foods on contact, handling, or cooking has been estimated to be less than 0.1 mg/100 g for 47 percent of food items and less than 1 mg/100 g for 85 percent of foods. Acidic foods leach out the largest amounts of Al (Nieboer et al., 1995). Kandiah and Kies (1994) observed that rats fed canned soft drink had significantly higher blood, liver, and bone Al concentrations than rats that were given glass

bottled soft drink. There was 69 percent higher bone Al concentration and 16 percent lower femur weight in rats fed Al-canned soft drink compared to rats fed distilled water.

METABOLISM AND PHARMACOKINETICS

Absorption

Gastrointestinal absorption was evaluated in Wistar rats using ^{26}Al (Jouhanneau et al., 1997). Twenty rats received 3.8 ng of ^{26}Al and 63 ng of ^{27}Al by gavage in water. These authors observed gastrointestinal absorption of 0.1 percent of administered dose. Concomitant intake of citrate led to more rapid, larger, and more variable absorption.

For a long time, it was believed that absorption of Al from the gastrointestinal (GI) tract was negligible. The low Al concentrations consistently found in the tissues of normal, healthy individuals indicate that Al is largely excluded from the body (Jones and Bennett, 1986). In a balance study conducted by Gorsky et al. (1979), six male subjects received oral doses of Al $(OH)_3$ containing between 1 and 3 g of Al/day for four six-day periods. An average positive balance of 23-313 mg Al/day was found from analysis of Al content of diet and medication intake and excretion in urine and feces for the total test period.

Using considerably lower doses of Al, Greger and Baier (1983) performed a 40-day balance study using eight healthy men. During the first 20 days four subjects were given a control diet containing 4.6 mg Al/day while four other subjects received a test diet of 125 mg Al/day (as Al actate). In the second 20 days, the diets were exchanged with each subject acting as his own control. Aluminum levels were determined in food, serum, urine, and feces by atomic absorption spectrometry. Urine and feces were collected daily while blood samples were collected on day 1 and 17 of each 20-day study. The mean serum Al level of all eight subjects before Al treatment and while on the control diet (4.6 mg Al/day) was 4 ± 1 µg/L. This level rose significantly to 7 ± 1µg/L when the subjects were fed the 125 mg Al/day diet. Urinary Al levels also increased from 24-58 µg Al/day for the control diet to 47-212 µg Al/day for the test diet of 125 mg Al/day. The mean fecal loss of Al for both groups of men was ~ 4.6 mg/day during ingestion of the control diet and ~ 125 mg/day when fed the test diet. The fraction of Al intake excreted in urine was 0.78 percent for the control diet and 0.09 percent for the test diet.

Slanina et al. (1986) reported a significant increase in blood Al concentration among ten healthy subjects who received 46.4 mg Al in the form of Al $(OH)_3$. Ten healthy men ingested, twice daily between meals, during each of the seven-day experimental periods: (a) citric acid (as lemon juice), (b) Al $(OH)_3$, or (c) Al $(OH)_3$ plus citric acid. Significant increases in Al concentration in blood as compared with pretreatment values (5 µg/L) were seen after ingestion of either citric acid or Al $(OH)_3$: 9 and 12 µg/L, respectively. Ingestion of both Al $(OH)_3$ and citric acid resulted in a more pronounced, highly significant, increase in Al concentrations in blood, to 23 µg/L.

Clarkson et al. (1972) reported Al absorption in uremic patients who were receiving 1.5, 2.2 or 3.4 g Al/day as Al $(OH)_3$ for 30 days. The investigators found a net GI absorption of Al ranging from 100 to 568 mg/day. Cam et al. (1976) studied the absorption of Al in healthy subjects and uremic patients. Both groups received 100 mL Al $(OH)_3$ gel (approximately 2.5 g of Al) daily for 22-27 days. The absorption of Al ranged from 6-97 mg/day for the healthy subjects and 89-245 mg/day in the two uremic patients. Therefore, it would appear that uremic patients absorb more Al (12 percent of dose) from an oral dose than healthy people (5 percent of dose). Studies concerning GI absorption showed that Al is absorbed through the gut wall, and gastric pH, age and diet affect absorption. Despite the close relationship between Al and iron, recent

evidence suggests that Al uptake via the intestinal tract does not involve iron-specific pathways (Ittel et al., 1996). Aluminum is bound to transferrin in blood and is taken up into cells via transferrin receptors. According to Ganrot (1986), the normal GI absorption would be about 0.1-0.3 percent, assuming that daily intake of Al is 20 mg and normal urinary excretion is 20 to 50 µg per day.

Priest et al. (1998) measured uptake of a single oral dose of 100 Bq ^{26}Al in tap water in two male adults. Gastrointestinal uptake determined by urinary excretion over a seven-day observation period averaged 0.22 percent of dose. Nearly 100 percent of the dose was recovered in the feces. These authors concluded that Al present in most water supplies is unlikely to contribute more than one percent of a typical daily uptake of 10 µg from food.

Stauber et al. (1999) measured the bioavailability of Al in 29 healthy subjects (21 males and eight females, aged 36-76 years). The subjects were given 1.6 L/d of either reconstituted soft water (RSW) of low Al concentration or alum treated water (ATW) from a municipal treatment plant. The Al concentration in RSW was ≤ 1 µg/L compared to 140 µg/L for the ATW. The relative bioavailabilities of Al in food and ATW were determined by measuring Al uptake into blood plasma and excretion in urine of the subjects on a controlled diet. The standard meal contained 1.36 ± 0.05 µg Al/g or 730 µg/542 g meal. The average total intake from food, tea, and water was 3200 µg Al/d. Of this amount, food, and tea contributed about 3000 µg Al/d. ATW contributed 208 to 233 µg Al/d and RSW contributed < 1 µg Al/d. Total Al in blood plasma ranged from 0.24 to 1.25 µg/L. The mean was 0.47 ± 0.12 µg Al/L (excluding outliers). The mean plasma concentration after ingestion of ATW (± citrate) and after ingestion of food were not significantly different ($P > 0.05$). However, in three subjects, plasma Al increased markedly after ingestion of ATW and citrate corresponding to 0.09, 0.12, and 0.13 percent of total Al ingested, or 0.63, 0.81, and 0.86 percent of Al in ATW, respectively. Total Al in urine was 0.68-6.02 µg/L. Daily urinary excretion rates were 1.8-9.3 µg Al/d. Males had significantly higher Al excretion rates than females after ATW was consumed ($P < 0.01$ by ANCOVA) due to a higher Al intake. Citrate had no effect ($P > 0.05$) on the uptake of Al from either ATW or food. Using the urinary excretion data, Al bioavailability (AB) was calculated as follows: AB = (Al in urine/24 hr x 2.2 x 100)/ Al intake. This assumes that Al excreted in the first 24 hr represents 45 percent of the total bioavailable based on a seven day excretion in urine (i.e., 1/2.2 = 0.45). The bioavailability of Al from ATW was thus estimated as 0.39 percent without citrate and 0.36 percent with citrate. The bioavailability of Al from the standard diet and tea was 0.28-0.64 percent. Assuming that only 15 percent of Al in tea is bioavailable, the AB from food would be 0.53 percent. The authors conclude that the bioavailability of Al is quantitatively similar from food and ATW.

Chedid et al. (1991) studied the uptake of Al from antacids in infants. Based on increased blood Al concentration, the estimated absorption was about 0.08 to 0.16 percent. Based on the Chedid et al. (1991) and Priest et al. (1998) studies, the internal absorption of Al is assumed to be 0.2 percent.

There is limited evidence that Al is absorbed through the skin. Aluminum was not found to penetrate the epidermis by Reller and Luedders (1977). Alternatively, Anane et al. (1995) found that the application of low aqueous concentrations of Al chloride ($AlCl_3 \bullet 6H_2O$) (0.025 to 0.1 µg/cm^2) to healthy shaved Swiss mouse skin for 130 days led to a significant increase in urine, serum, and whole brain Al, especially in the hippocampus, compared to controls. A significant dose related uptake was observed when compared to normal control mice and aged controls for doses of 0.1 µg/d and 0.4 µg/d: 292, 524, 654, and 1114 ng/g hippocampus, respectively ($P < 0.05$). Significantly, this percutaneous uptake and accumulation of Al in the brain was greater than that caused by oral exposure to 2.3 µg/d in feed and water.

Inhalation is another route of Al exposure, but is probably a minor pathway. The lungs continually receive Al, mostly as particles of Al, silicates and other poorly soluble compounds. The lungs have a higher concentration of Al than all other organs and the Al concentration increases with age (Alfrey, 1980; Teraoka, 1981).

The ingestion pathway is the most significant route of transfer of Al from the environment to animals and humans; however, at least three authors report instances in which tap water was a significant source of human Al exposure when the water was misused in hemodialysis equipment (Dunea et al., 1978; Kaehny et al., 1977b; Rozas et al., 1978). Based on those reports, the medical community has defined that the Al concentration in water used in hemodialysis solutions must be no greater than 10 µg/L (0.01 ppm) (Berlin, 1982-3; Graf et al., 1982).

Distribution

Jouhanneau et al. (1997) observed that blood measurements in ^{26}Al gavaged rats were a poor measure of GI tract absorption of Al. The amount of Al in the circulatory system never exceeded about 10 percent of that absorbed. About 50 percent of absorbed Al is rapidly (< 2 hr) accumulated in the skeleton of young rats. About 0.0002 and 0.000004 percent of ingested Al was permanently (30 d of observation) deposited in liver and brain respectively. The retention of Al in bone, brain, and liver, relative to that excreted in urine, was indistinguishable in rats exposed to ^{26}Al with or without citrate supplement.

Alfrey (1980) and Alfrey et al. (1980) reported tissue Al levels in 37-48 cases of sudden death from a variety of causes, usually violent (Table 2). Bush et al. (1995) reported the concentrations of five essential and six potentially toxic elements in seven organs collected at autopsy from 30 subjects (Table 2).

Table 2. Concentrations of Aluminum in Human Tissues (µg/g dry weight)

Tissue	USA, Alfrey (1980)	USA, Alfrey et al., (1980) (N = 16)	Australia, Alfrey et al. (1980) (N = 21)	Bush et al. (1995) (N = 30)
Heart	1.1 ± 0.65 (36)*	1.0 ± 0.8	1.2 ± 0.51	0.666 ±0.5 (21)
Lung	56.0 ± 63.0 (34)	43.0 ± 43.0	67.0 ± 75.0	ND
Spleen	3.8 ± 5.0 (35)	2.6 ± 2.1	3.3 ± 2.4	ND
Liver	4.0 ± 1.7 (40)	4.1 ± 1.7	4.0 ± 1.8	1.24 ± 0.72
Muscle	1.2 ± 1.0 (48)	1.2 ± 1.2	1.2 ± 0.7	0.635 ± 0.52
Bone	3.3 ± 2.9 (8)	3.3 ± 2.9	5.6 ± 2.3	1.81 ± 2.58
Kidney cortex	ND	ND	ND	0.78 ± 0.52
Kidney medulla	ND	ND	ND	0.793 ± 0.46
Brain grey matter	2.2 ± 1.3 (10)	2.4 ± 1.3	ND	0.399 ± 0.27
Brain white matter	ND	ND	ND	0.339 ± 0.3

* Means and standard deviation of the mean (number of subjects studied), ND = not determined.

The highest concentrations of Al were found in the lung. Uremic patients, not receiving dialysis, show markedly increased Al concentrations in serum, bone, liver, and spleen, and a slightly increased concentration in brain and skeletal muscle (Alfrey et al., 1980). Bush et al. (1995) concluded that the distributions of most elements in the brain, liver, and kidney are homogeneous except for Al, Mn, the essential elements (Ca, Mg, Cu, Fe, and Zn) in brain, and Cd and Hg in kidney. The blood is responsible for the transport of Al throughout the body and approximately

80 percent of the Al in blood is bound to serum proteins; the remaining 20 percent is diffusible (Graf et al., 1981). Al is bound to serum transferrin, which may play a significant role in the distribution of Al.

Organs of particular interest with regard to Al toxicity are bone and brain. The substitution of Al ions into crystals of calcium-hydroxyapatite has been demonstrated (Iwata, 1979). Levels of 3.3±2.9 μg Al/g dry wt. of bone were reported as normal for individuals not on a high Al intake. For those in the high intake group, bone Al of 124.6 ± 62.9 μg Al/g dry wt. was reported for dialysis patients and 24.1 μg A1/g dry wt. was reported for an ulcer patient with normal renal function (Skalsky and Carchman, 1983). Clearly, increased bone deposition is associated with higher doses of Al (Alfrey, 1980, Alfrey et al., 1980). Increased amounts of Al have been reported in the brain of subjects suffering from Alzheimer's disease and dialysis encephalopathy syndrome. Crapper et al. (1976) examined the Al content in various regions of the brain from ten patients with Alzheimer's disease. Of 585 samples, 28 percent had an Al concentration greater than the normal upper limit of 4 μg/g. In contrast, McDermott et al. (1979) reported no significant difference in brain Al concentration between nine normal brains and ten brains from patients suffering from Alzheimer's disease. An earlier study (McDermott et al., 1978) determined a mean of 2.7 μg/g brain in non-dialyzed uremics, 4.4 μg/g in dialyzed uremics and 15.9 μg/g in patients who died with dialysis encephalopathy.

Walton et al. (1995) studied the uptake of soluble ^{26}Al administered in drinking water into the brains of fasted rats. Eight adult male Wistar rats (510-650 g) were gavaged with 4 mL of purified water containing 70 Bq (0.1 μg) of ^{26}Al and 1.0 μg of ^{27}Al to minimize loss in the syringe and gavage needle. Two control rats received only ^{27}Al. Two weeks after dosing, the animals were sacrificed and their brains analyzed for increased ratio of $^{26}Al/^{27}Al$. Six of the eight brains from the experimental rats had ^{26}Al levels that were substantially higher than the background of the control rats. Four rats showed concentrations of ^{26}Al in the brain 10-20 times higher and two 200-300 times higher than controls. The authors attribute the large variability in uptake into brain to individual differences in Al metabolism including GI tract absorption, timing of peak plasma concentrations of Al, variations in Al-ligand binding, Al excretion values, vascular and cerebral transferrin receptor levels, and overall permeability characteristics of the blood-brain barrier to Al. Ackley and Yokel (1997) studied the mechanism of Al citrate transport across the blood-brain barrier in rats. Using an *in vivo* microdialysis method they concluded that Al uptake into brain was not due to diffusion but more likely involved the monocarboxylic acid transporter. Further, they proposed that the transporter is located at the blood-brain barrier rather than at neuronal or glial cell membranes.

Fosmire et al. (1993) evaluated genetic influences on tissue distribution of Al in mice. Five inbred strains of mice were divided into two groups of eight each. One group received a control diet the other the same diet supplemented with 260 mg Al/kg diet for 28 days. Analysis of brains, livers, and tibias for Al concentrations revealed strain differences with strains DBA/2 and C3H/2 exhibiting higher brain Al and strains A/J, BALB/c, and C57BL/6 exhibiting no differences. The authors suggest that genetic differences in the permeability of the blood brain barrier to Al may be an important variable in Al toxicity.

Minami et al. (1996) have observed an age-dependent accumulation of Al in the aorta and cerebral arteries of 12/23 and 6/23 human cadavers, respectively. In the aorta, Al accumulation occurred mainly in the tunica media. Both phosphorus and calcium appear to enhance Al accumulation.

Metabolism

A serious limitation in the study of Al metabolism and biological studies in general is the lack of suitable radionuclides. One study utilized the short-lived isotope ^{28}Al (half-life 2.3 min) to examine the uptake of Al into cells (Ganrot, 1986). As noted above Jouhanneau et al. (1997) studied the distribution of ^{26}Al (half-life 6.7 seconds) in rats. A number of studies on the intracellular localization of Al^{+3} in the cells of various species have been conducted and they indicate that Al was mainly bound to the cell nucleus and lysosomes (Ganrot, 1986). The behavior of Al^{+3} in cells and biological fluids has been compared to Fe^{+3}. The Al ion is bound to at least one of the two iron-binding sites of serum transferrin. Trapp (1983) calculated the serum-binding capacity for Al at 680 mg/L assuming a Ka of 10^{20} M^{-1} for the reaction: Al^{+3} + apotransferrin $\rightarrow$ Al^{+3}-transferrin. The equilibrium concentration of unbound Al would be about 10^{-12} M. Such ions are thought to exist in four different forms: as free ions; as low molecular weight (MW) complexes; as reversible macromolecular complexes; or as irreversible macromolecular complexes (Ganrot, 1986). Free ions occur in very low concentrations. Low MW complexes with amino acids, nucleotides, phosphates, or carbohydrates may be very stable. Trivalent Al (Al^{+3}) has a very high affinity for proteins, polynucleotides, and glycosaminoglycans, and may exist as reversible complexes with these substances. Some complexes may be so strong as to be practically irreversible. According to Martin (1992), in the blood plasma, citrate is the main small molecule carrier of Al^{+3}, although the recent observation of distinct GI absorption and blood kinetics for co-administered Al and citrate would seem to contradict this (Taylor et al. 1998). In fluids where both transferrin and citrate are low, nucleoside di- and triphosphates become Al^{+3} binders. Al^{+3} will easily displace Mg^{+2} from nucleotides. If nucleotides are also at low concentrations, catecholamines become likely Al^{+3} binders. Double-helical DNA binds Al^{+3} weakly and should not compete with other ligands. In the cell nucleus Al (+3) probably binds to nucleotides or phosphoproteins.

Excretion

Jouhanneau et al. (1997) found that rats excreted about 50 percent of absorbed ^{26}Al in the urine, with 90 percent of this excretion occurring during the first 48 hours after ingestion. Wilhelm et al. (1992) measured single dose toxicokinetics of Al in the rat. Wistar rats were studied after intragastric (i.g.) doses of 1000 and 12,000 µg/ Al/kg and intravenous (i.v.) doses of 10, 100, 1000, and 12,000 µg Al/kg. Serial blood samples, daily samples of urine, and feces as well as brain, liver, kidney, spleen, muscle, and bone samples were collected. Following i.v. doses of 10, and 100 µg/kg, administered Al was recovered completely in urine (94.4 ± 9.9 percent and 98.5 ± 3.2 percent, respectively. Twenty-nine days after the i.v. dose of 1000 µg Al/kg, daily renal excretion decreased to baseline values while only 55.1 ± 8.0 percent of the dose was excreted. Aluminum accumulated in liver and spleen. After a single 1000 µg/kg i.g. dose, no absorption was detected. The i.g. dose of 12,000 µg/kg resulted in a maximum blood Al level of 47.9 ± 12.4 µg/L after 50 min. The blood concentration-time curve fitted a one compartment open model with a half-life of absorption of 28.6 ± 3.6 min. Cumulative renal Al excretion was 0.18 ±0.10 percent of the dose and oral availability was 0.02 percent.

Sutherland and Greger (1998) studied the effect of the size of an oral dose of Al on biliary and urinary Al excretion in rats. Bile was collected from 26 male Sprague Dawley rats following a single gavage dose of 0, 0.25, 0.5, or 1.0 mmol Al/kg in one mL 16 percent citrate solution. Urine was collected from 20 additional rats. Rats given 0.5 or 1.0 mmol Al/kg excreted significantly more Al bile than rats dosed with 0.25 mmol Al/kg or control rats. Urinary Al

excretion was many-fold higher than biliary Al excretion in rats given Al but was less than biliary Al excretion in control rats. The high dose in this study was approximately equal to a scaled human adult equivalent dose of 650 mg Al/kg-d (1 mmol Al/kg x $70^{0.75}$ x 27 mg Al/mmol Al = 653.4 mg Al/kg-d). Although the biliary excretion of Al was saturated at doses of one mmol Al/kg or more, suggesting a carrier mediated process, the mechanism of Al biliary excretion is unknown.

From human dietary balance studies it is clear that most of the ingested Al is unabsorbed. Aluminum levels determined in feces ranged from 76-98 percent of the oral dose (Gorsky et al., 1979). Absorbed Al is excreted in bile and urine. Skalsky and Carchmam (1983) cited studies in their review that reported bile as a major excretory path for Al. In contrast, Kovalchik et al. (1978) reported that the biliary contribution to Al excretion is negligible (less than 0.1 percent of the hemodialysis Al load in dogs). The kidneys appear to be a major excretory organ for Al. Urinary excretion of Al in healthy individuals has been reported to range from less than 3 µg/L to 30 µg/L (Valentin et al., 1976; Kaehny et al., 1977a). Oral doses of Al via antacids can increase the urinary excretion about 50-fold (Kaehny et al., 1977a; Recker et al., 1977).

Williams et al. (1986) compared the excretion of Al via urine and bile in six patients with normal liver and kidney functions. The biliary Al concentration was about twice that of the urine. Since the volumes of bile and urine excreted daily are comparable (1-2 L), biliary excretion of Al may equal or exceed that of the urinary route. However, the studies of Priest et al. (1992) and Priest (1993) with ^{26}Al intravenously administered in a single human volunteer found that only a few percent of the dose was excreted in the feces, indicating probable enterohepatic circulation of biliary Al.

Aluminum Speciation

The anion to which Al is complexed has a significant effect on the intestinal uptake, tissue distribution, and excretion of Al and hence affects the toxicity of the metal. Yokel (1989) ranked different forms of Al for solubility and absorption, and in general the soluble organic and inorganic forms exhibited the greatest potential for intestinal absorption. The rank order was citrate > nitrate > lactate > chloride > hydroxide > glycinate > borate. Priest et al. (1998) observed greater bioavailability with citrate (0.5 to 1 percent) as opposed to hydroxide (0.01 percent) as the counter ion. Aluminum absorption from Al species in municipal tap water was 0.22 percent in human subjects.

Powell et al. (1999) studied the speciation of Al in the gastrointestinal tract. Male Wistar rats (300-350 g) that had been fasted overnight were gavaged three times with either deionized water; deionized water + Al; a liquid diet (Ensure™, Abbott Laboratories), or liquid diet + Al. Gavage times were 60, 20, and 10 minutes before sacrifice (water and water + Al), or 90, 30, and 10 minutes before sacrifice (liquid diet and liquid diet +Al). Aluminum was added as the sulfate, chloride, or phosphate to water at pH 3.0 or the liquid diet at pH ~ 6.5. Immediately following sacrifice, the gut was ligated into three sections: (1) stomach + pre-ampullary duodenum (stomach); (2) first half of the remaining total small bowel (proximal small bowel); (3) second half of the small bowel (distal small bowel). There is no evidence that Al is significantly absorbed from the stomach, but its acidic environment may affect the amount of soluble Al passing into the small bowel. In the bowel 90-95 percent of Al co-ingested with water was found in the 'solid phase' following centrifugation and co-localized with intestinal mucus. Aluminum did not precipitate as particles and similar results were obtained with increased doses of Al under the same conditions.

The Al supernatant along the bowel (5-10 percent of that ingested) was analyzed by ^{1}H NMR but no specific Al-ligand could be identified. Al was presumably bound to soluble endogenous (non NMR detectable) ligands. The authors concluded that the major factor that regulates the absorption of Al in the mammalian gut is intestinal mucus. This is probably a general effect with elements that are well bound to mucus, such as Al and iron (III), that have kinetically slow rates of ligand exchange, being less well absorbed than poorly bound faster-exchanging elements, such as copper (II) and zinc. Strong ligands from the diet could potentially compete with mucus for Al depending upon their concentration. Thus it is possible to promote the absorption of the metal by co-ingestion of a significant quantity of a strong ligand, such as citrate, which could compete with the mucus for Al.

Slanina et al. (1985) treated young male Sprague Dawley rats by gavage for ten weeks (three times weekly) with 100 mg/kg Al in the form of Al hydroxide, Al citrate, Al hydroxide together with citric acid, or with tap water (controls). The rats treated with Al-citrate and especially those treated with Al hydroxide + citric acid showed significant increases in blood (0.014 and 0.039 µg/g), brain cortex (0.048 and 0.092 µg/g), and bone (10.7 and 26.6 µg/g), respectively, compared to controls ($P < 0.005$). Treatment with Al hydroxide alone gave a significant increase in bone versus controls but much less than the other treatments. The authors conclude that the intake of organic Al-ligands in food combined with high oral Al intake from phosphate binding therapeutics may result in elevated levels of Al in the target tissues of brain and bone.

Quartley et al. (1993) studied the short-term tissue distribution of Al in rats after a single oral dose of 0.46 mmol as Al citrate (1:5 molar ratio). Compared with control animals, significantly higher Al concentrations were found at two hour post administration in plasma (539 µg/L), liver (161 ng/g), lung (90 ng/g), spleen (301 ng/g), kidney (682 ng/g), bone (729 ng/g), and duodenum (4140 ng/g). Aluminum concentration in the brain did not change throughout the 24-hour observation period. Unlike the soft tissues, the Al concentration in bone increased over 24-hour to three times the two hour concentration. In animals previously given silicic acid in the drinking water for five days and co-administered Al citrate, the tissue Al distribution pattern at four hours exhibited plasma and soft tissue Al concentrations significantly reduced versus Al citrate alone, with the exception of spleen. The authors speculate that Al retention in the spleen may have been due to aluminosilicate microprecipitates in the reticuloendothelial system.

Domingo et al (1988) evaluated the comparative effects of different chelating agents to affect the distribution and excretion of Al. Acutely toxic i.p. doses of Al nitrate (938, 1688, 2438, and 3188 mg/kg) were administered to male Swiss mice followed 20 minutes later by intra-peritoneal (i.p.) injections of one of six chelating agents (all at ¼ of their respective LD_{50} values). Citric acid, malic acid, and malonic acid resulted in decreased Al levels in liver vs. control mice. Citric acid, malonic acid, and oxalic acid resulted in lower Al levels in spleen. Malic acid also exhibited higher levels in brain and bone ($P < 0.05$). None of the treatments appeared to affect Al levels in the kidneys or heart, although the data are incomplete for these tissues. Malic acid treatment promoted Al urinary excretion while citric acid promoted Al fecal excretion compared to control animals.

The correlation between the *in vivo* tissue distribution or the urinary excretion of Al administered with four organic acids and the *in vitro* binding of Al to serum protein in the presence of the organic acids was evaluated by Maitani et al. (1994). Aluminum was administered i.p. to mice at a dose of 20 mg Al/kg (Al**:**ligand ratio = 1**:**1 or 1**:**3). The injection of Al without organic acid resulted in the accumulation of Al in the liver. In both the 1**:**1 and 1**:**3Al-citrate treatments, Al was not accumulated by the liver and kidneys and a large amount of Al was excreted in the

urine. After administration of Al with malate, isocitrate, and tartrate, the hepatic Al concentrations were markedly higher than seen with Al-citrate mixtures though lower than the

control mice. Also the Al concentrations in the kidneys were higher than citrate or the control with malate (1:3), isocitrate, and tartrate. These latter organic acids also promoted greater urinary excretion of Al compared to controls although less than Al-citrate. The chemical state of Al added to control mouse serum as Al-organic acid mixture (1:3) was investigated with a high performance liquid chromatograph equipped with a gel-filtration column and connected to an inductively coupled plasma-atomic emission spectrometer (HPLC-ICP). When Al-citrate mixture was added to the serum, Al was detected only in the low molecular weight (LMW) fraction. With malate, isocitrate, and tartrate, Al was detected in the high molecular weight (HMW), transferrin, and LMW fractions in the Al-organic acid mixtures. Thus in the case where Al in serum was present only in the LMW fraction *in vitro*, hepatic and renal concentrations of Al were low and urinary excretion of Al was very high *in vivo* (Al-citrate). In the case where Al was bound to both HMW and LMW fractions in serum *in vitro*, a considerable amount of Al was transferred to the liver and kidneys and the urinary excretion of Al was still high *in vivo* (Al-other organic acids).

Talbot et al. (1995) studied the intra-subject variability in the metabolism of ^{26}Al-citrate administered intravenously. The clearance of ^{26}Al was evaluated in six healthy male subjects by measuring the tracer in blood and excreta at times up to five to six days. On average only 2 percent of the dose remained in the blood after one day, but 27 ± 7 (SD) percent was retained in the body at five days (range 16 to 36 percent). Fecal excretion was negligible (1 percent in five days). An additional subject who retained 19 percent at five days had a larger dose of ^{26}Al allowing longer-term whole-body counting for more than three years (Priest et al. 1995). Extrapolation from that pattern indicated that lifetime exposure would lead to a deposit of several hundred times the daily systemic uptake.

The bioavailability of ^{26}Al-labelled Al citrate and Al hydroxide was studied in human subjects (Priest et al., 1996). The labeled compounds were administered separately by feeding tube to two male volunteers and blood samples collected at 1, 4, and 24 hours after administration. Their daily output of urine and feces was collected for six days. In addition, the effect of simultaneous citrate ingestion on absorption of Al from its hydroxide was studied. The fractional Al uptake from each of the species was calculated: Al citrate, 5.23×10^{-3}; Al hydroxide, 1.04×10^{-4}; and citrate + Al hydroxide, 1.36×10^{-3}. The co-administration of citrate with the Al hydroxide was found to enhance Al uptake in both volunteers.

The transport and accumulation of Al can be viewed to some extent as a competition among many Al equilibria. The predominance of any one equilibrium system, possibly leading to the redistribution and accumulation of Al in a specific tissue, will depend upon many different factors (Exley et al., 1996). For example, in certain cases of trauma such as following renal transplantation, Al is rapidly mobilized from body stores and redistributed (Davenport et al., 1988). Such redistribution of apparently benign Al stores can result in toxicity.

The rate of reaction of Al with ligands, either mobile as in blood, or fixed as in tissue membranes, will play an important role in the eventual fate of Al. As noted above for example, whether plasma Al is bound by high- or low-molecular-weight ligands determines whether the fate of the bulk of the Al will be in the liver or the urine, respectively (Maitani et al., 1994). The fate and potential toxicity of Al cannot be predicted solely upon the basis of stability constants, which describe Al reactions at equilibrium. The reaction rates or kinetics of formation of various labile Al-complexes are likely to be much more important than the hierarchy of stability constants of such complexes (Exley et al. 1996).

Physiological/Nutritional Role

Aluminum has not been shown to have a definite biological function (Ganrot, 1986).

Physiologically Based Kinetic Models

We were unable to locate any biokinetic models of Al disposition in humans. Such models would appear to be feasible based on those created for other metals (O'Flaherty, 1998; Fisher et al., 1991).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Mortality studies for aqueous solutions of $Al_2(SO_4)_3$ and $AlCl_3$ given orally to mice resulted in LD_{50} values of 6.2 g/kg and 3.85 g/kg, respectively. Additional LD_{50} values for the various routes of exposure for Al compounds are given in Table 3.

Table 3. Acute Toxicity of Aluminum Compounds

Compound	Route	Species	LD_{50} (g/kg)	Reference
$A1_2(SO_4)_3$	Intraperitoneal	Mouse	0.14	Sorenson et al., 1974
	Oral	Mouse	6.2	Sorenson et al., 1974
$AlCl_3$	Oral	Mouse	3.85	Sorenson et al., 1974
	Oral	Rat	0.76	Spector, 1956
	Oral	Rat	0.38	Krasovskii et al., 1979
	Oral	Rabbit	0.4	Krasovskii et al., 1979
	Oral	Guinea pig	0.4	Krasovskii et al., 1979
$Al(NO_3)_3$	Intraperitoneal	Mouse	0.32	Hart et al., 1971
	Intraperitoneal	Rat	0.33	Hart and Adamson., 1971
	Oral	Rat	0.26	Sorenson et al., 1974
	Oral	Rat	4.28	Sorenson et al., 1974

Nephrectomized rats given 374 mg Al/kg as $AlCl_3$ or $A1_2(SO_4)_3$ in their drinking water (Berlyne et al., 1972) died within three days. In a short-term study, Ondreicka et al. (1966) fed rats a diet containing 2665 mg Al/kg (250 mg/kg body weight). A reduced food intake was observed. The fecal elimination of phosphorus was increased as compared to controls. No other effects were reported.

Levine et al. (1992) found that Al administered by intraperitoneal injection to rats produced a local toxic myopathy. Male and female Lewis rats (130-200 g body weight) were given either a single i.p. dose of 1500 mg/kg of the Al compound, 150 mg/kg-d i.p. for 10 days, or 450 mg/kg-d for three days. The role of the anion was determined by studying different compounds including Al lactate, Al citrate, sodium lactate, sodium citrate, sodium acetate, and sodium chloride.

Only Al lactate or Al lactate in combination with Al citrate, sodium chloride, or sodium acetate produced skeletal muscle necrosis of the diaphragm and abdominal wall subjacent to peritoneal surfaces. Deeper muscles were less severely affected. The authors suggest that the myopathy following Al lactate injection was caused by the transient presence of Al ions that diffused into the diaphragm and abdominal wall. Once there, the mechanisms of Al cytotoxicity come into play including potential effects on cell membranes, interactions with phosphate or phosphate containing molecules (ATP, DNA, RNA), or with proteins (calmodulin, transferrin, enzymes, microtubules, and intermediate filaments).

Subchronic Toxicity

A summary of subchronic and chronic toxicity studies is given in Table 4.

Krasovskii et al. (1979) gave male guinea pigs and rats 6, 17, and 50 mg Al/kg-d and rabbits 3, 9, and 27 mg Al/kg as $AlCl_3$ in drinking water for 20-30 days. At the end of the study, ATP, ADP and AMP levels in the blood were significantly depressed in guinea pigs and rabbits receiving 17 and 27 mg Al/kg, respectively. The numbers of animals employed and other experimental details were not given.

Slanina et al. (1985) treated male rats daily by gastric intubation (6 days/week) with 100 mg Al/kg in the form of $Al(OH)_3$ (9 week) or Al citrate (4 week), with citric acid (4 week) or with tap-water (control, 9 week). The cerebral cortex, hippocampus, cerebellum, and samples of bone from each rat were analyzed for Al. No significant increases in tissue Al concentrations were observed after treatment with $Al(OH)_3$. The rats treated with Al citrate showed significantly increased concentrations of Al in all the brain regions studied and in the bone.

Greger et al. (1985) fed male rats diets that contained Al lactate, Al palmitate, Al phosphate, or $A1(OH)_3$ in either reagent grade or desiccated gel forms for 18 days. Rats fed $Al(OH)_3$ and Al lactate tended to accumulate more Al in the brain than rats fed the other Al compounds. The average concentrations of Al in the tibias of rats fed 261-272 µg Al/g diet were 13.0-15.6 µg Al/g and were statistically significantly different from the levels in control animals (1.0-1.9 µg A1/g). These moderate levels of dietary Al did not affect calcium, magnesium, and iron metabolism.

Garbossa et al. (1998) studied the effect of oral Al administration on erythropoiesis in male Wistar rats. Five rats/group were given either Al citrate by gavage in a single daily dose of 1.0 µmol/g (27 mg Al/kg-d) or received no treatment. In a second series, five rats were exposed to 100 mmol Al citrate/L (378 mg Al/kg-d) in drinking water with five controls receiving untreated water. Both treatments were continued for 15 weeks. The gavage administration of 27 mg Al/kg-d caused inhibition of colony forming-units-erythroid (CFU-E) development ($p < 0.05$). However, the other hematological parameters were not significantly affected. The higher exposure in the drinking water series showed significant effects in all parameters measured: CFU-E, ($p < 0.01$); hematocrit, median osmotic fragility, and red blood-cell life-span ($p < 0.05$). In both treatments, serum and bone Al was significantly increased ($p < 0.01$). The results demonstrate that Al can impair erythropoiesis at low doses *in vivo* and at higher doses exhibits toxicity to both CFU-E and mature erythrocytes.

Table 4. Subchronic and Chronic Oral Toxicity of Aluminum Compounds in Animals

Species, sex, number of animals, compound	Dose(s), mg Al/kg-d unless otherwise stated	Duration	Effects	Reference
Guinea pig, NR $AlCl_3$	6, 17, 50, vehicle not stated	20-30 d	Decreased alkaline phosphatase, ATP, ADP, AMP at 17 mg/kg-d	Krasovskii et al., 1979
Rat, NR, $AlCl_3$	6, 17,50 vehicle not stated	20-30 d	As above	As above
Rabbit, NR, $AlCl_3$	3, 9, 27, vehicle not stated	20-30 d	As above but at 9 mg/kg-d	As above
Rat, M, 15/group, $Al_2(SO_4)_3 \bullet 18 H_2O$	0.01 (control), 0.017, 0.022, 0.028, 0.043, 0.085, 0.172, in drinking water	7, 14, 21 d	Dose dependent inhibition of bone marrow cells and increase in chromosome aberrations	Roy et al., 1991
Mouse, M, 5/group, $AlNH_4(SO_4)_2 \bullet 12 H_2O$	0, 5, 25, 125 ppm Al in drinking water ad lib. 0, 0.95, 4.3, 21.3	30 d	Dose dependent increase in expression of Tumor Necrosis Factor α mRNA in cerebrum, $P < 0.05$	Tsunoda and Sharma, 1999
Rat, F, 10/dose $Al(NO_3)_3$	0, 27, 54, 108, in drinking water	30 d	Mild histological changes in spleen and liver at 108 g/kg-d	Gomez et al., 1986
Rat, M, NR, $Al_2(SO_4)_3$	0.3% Al, in drinking water	30 d	Neurobehavioral effects, passive avoidance impairment, increase in muscarinic receptor number	Connor et al., 1988
Mice, F, 10/group, $AlCl_3$	3 (control), 1000 ppm Al in diet with 3.5% sodium citrate	5-7 wk	Reduced grip strength and greater startle responsiveness, no brain lipid or protein oxidative damage evident	Oteiza et al., 1993
Mice, F, 13-14/group' Al lactate	25 (control), 500, 1000 ppm Al in diet	6 wk, 10 d	Higher mortality Al-exposed dams following challenge with Listeria monocytogenes infection ($P < 0.025$)	Yoshida et al., 1989
Mice, F, 7/group, Al lactate	25 (control), 500, 1000 ppm Al in diet + pair fed control	6 wk	Spontaneous motor activity lower in high dose group (vertical < horizontal)	Golub et al., 1989b
Rat, MF, 25 F/group, $Al(NO_3)_3 \bullet 9H_2O$	0, 19, 39, 77 mg/kg-d, vehicle not stated	60 d M 27 d F	Dose-dependent delay in the growth of living offspring, lower offspring survival	Domingo et al. (1987)
Rat, M, 8/group $AlCl_3$	2000 ppm Al in feed	67 d	Decrease in tibia weight, serum triglycerides	Sugawara et al., 1988a
Rat, M, 6-7/group, adult and weanling $Al(OH)_3$, $AlK(SO_4)_2$	2000 ppm Al in feed	67 d	Decrease in serum triglycerides, hepatic glycogen in adults	Sugawara et al., 1988b

Table 4 (continued). Subchronic and Chronic Oral Toxicity of Aluminum Compounds in Animals

Species, sex, number of animals, compound	Dose(s), mg Al/kg-d unless otherwise stated	Duration	Effects	Reference
Mice, F, 6/group, Al lactate	100 (control), 500, 1000 ppm Al in feed	10 wk	Increase in 2-thiobarbituric acid reactive substances in brain but not in liver	Fraga et al., 1990
Mice, M, 8/group, Al lactate	7(control), 500, 1000 ppm in diet	10 wk	Differential reinforcement of high rates and food motivation higher in Al-exposed adults	Golub and Germann, 1998
Rat, M, 4/group, Al lactate	2 (control), 1000 ppm in diet, Ca deficient diet ± Al also evaluated.	10 wk	Normal diet ± Al had no effect, Ca deficient diet +Al showed Al deposition at bone calcification fronts	Konishi et al., 1996
Rat, MF 8/sex/group, $AlCl_3$	0.2% Al, in feed	12 wk	Depressed motor activity	Commissaris et al., 1982
Mice, F, 10-12/group, Al lactate	25 (control), 1000 ppm in diet	90 d	No overt neurotoxicity seen, increased Al in brain and liver, decreased motor activity, grip strength, and startle responsiveness	Golub et al., 1992
Rat, F 10/sex/group, $Al(NO_3)_3$	0, 39, 77, 387, in drinking water	100 d	Decreased weight gain, water consumption, urine volume and plasma glutamic-pyruvic transaminase and increased alkaline phosphatase in the 3600 mg/kg-d group	Domingo et al., 1987
Rat, M 5/group, Al citrate	0, 27mg Al/kg-d by gavage; 0, 378 mg Al/kg-d in drinking water	15 wk	Colony-forming-units-erythroid (CFU-E) inhibited at 27 mg Al/kg-d; reduced hematocrit, hemoglobin conc., median osmotic fragility and red blood-cell life-spans ($p < 0.05$) and inhibited CFU-E ($p < 0.01$) at 378 mg Al/kg-d	Garbossa et al., 1998
Rat, M, 40/group, Al $(NO_3)_3 \bullet 9H_2O$	0, 50, 100 mg/kg-d in drinking water to young (21 days), adult (8 months), and old (16 months) rats	6.5 mo	No effects on behavioral endpoints noted, higher Al concentrations noted in several regions of the brain of young rats	Domingo et al., 1996
Rat, M, 10/ dose group, $Al(NO_3)_3$	0, 50, 100 mg/kg-d in drinking water for groups of young, adult and old rats	6.5 mo	Changes in organ weight/body weight ratios, and in Al tissue concentrations with age	Gomez et al., 1997

Table 4 (continued). Subchronic and Chronic Oral Toxicity of Aluminum Compounds in Animals

Species, sex, number of animals, compound	Dose(s), mg Al/kg-d unless otherwise stated	Duration	Effects	Reference
Mouse, MF, 10/sex/group, Al lactate	6 (control), 1025 ppm in diet	6 mo	Immunosuppression: reduced cytokines production, increased spleen weight; deficiency of $CD4^+$ cells	Golub et al., 1993
Mouse, F, 16-18/dose group. Al lactate	7 (control), 500, 1000 ppm in diet, 1.4, 100, 200 mg/kg-d	Conception to 6 mo	Reduced grip strength at both 500 and 1000 ppm	Golub et al., 1995
Beagle dog MF, 4/sex/dose group, $AlNa_3(PO_4)_2$	0, 3000, 10,000, 30,000 ppm in diet; 4, 10, 27, 75 mg Al/kg-d	26 wk	Decreased food consumption, body weight in high dose males. Decreased testes weight and moderate hepatocyte hypertrophy in high dose males	Pettersen et al., 1990
Rat, M, 10/group, $AlCl_3$	0, 500 mg Al/L in drinking water	26 wk	Decreased spontaneous locomotor activity, acquisition, and retention of learned response. Increased brain lipid peroxidation ($p < 0.01$). Decreased brain Mg-ATPase and NaK-ATPase ($p < 0.05$)	Lal et al., 1993
Rat, M 14/group, $AlCl_3$	0.1 % in feed	11 mo	Neurotoxic effects seen, depressed activity and learning	Commissaris et al., 1982
Rat, NR, $AlCl_3$	0.025, 0.25, 2.5, vehicle not stated	6-12 mo	Depressed motor reflex at 2.5 mg/kg-d. Weak gonadotoxicity. Decreased alkaline phosphatase in serum, transient decrease at 0.25 mg/kg-d	Krasovskii et al., 1979
Mouse, MF 10/sex/group, 3 generations, $AlCl_3$	0, 19.3 in diet or drinking water	Chronic (36-51 wk)	Decreased body weights in later generations. Decreased body weight correlated with duration of exposure	Ondreicka et al., 1966

Table 4 (continued). Subchronic and Chronic Oral Toxicity of Aluminum Compounds in Animals

Species, sex, number of animals, compound	Dose(s), mg Al/kg-d unless otherwise stated	Duration	Effects	Reference
Mice, MF, 60/group, $AlK(SO_4)_2 \bullet 12H_2O$	0, 1.0, 2.5, 5.0, 10.0 % (w/w) in the diet; 0, 85, 213, 425, 850 mg Al/kg-d	20 mo	No significant tumor pathology. Both sexes, increase in absolute kidney and heart weights, decrease in absolute and relative liver weights. NOAEL = 85 mg/kg-d	Oneda et al., 1994
Rat, MF, 53/sex/group, $KAl(SO_4)_2$	0, 5 ppm in drinking water	Lifetime	Increased incidence of gross tumors in males	Schroeder & Mitchener, 1975a
Mouse, MF, 54/sex/group $KAl(SO_4)_2$	0, 5 ppm in drinking water	Lifetime	No adverse effects noted in growth, lifespan, and tumor incidence	Schroeder & Mitchener, 1975b
Rat, M, 27/group AlF_3	0.5 ppm AlF_3 in drinking water vs. 2.1 ppm NaF, and control	52 wk	Brain neuronal injury, reduced neuron density in left hemisphere neocortex; lesser effects in NaF group with same fluoride level	Varner et al., 1998

Note: M = male; F = female; NR = not recorded

Genetic Toxicity

Aluminum compounds are not thought to be mutagenic or otherwise genotoxic (Leonard & Gerber, 1988). However, Al has been reported to interact with DNA and possibly alter gene expression. Effects summarized by Crapper McLachlan et al. (1990) include binding to nuclear DNA phosphate and bases, increasing histone-DNA binding, altering sister chromatid exchange, and decreasing cell division. The accumulation of Al in DNA may alter protein-DNA interactions. Interference by Al with DNA and protein synthesis may play a role in the formation of neural filaments (ATSDR, 1997). Aluminum ions were found the most reactive of 18 metal ions tested on the structure of brain and liver chromatin (Walker et al., 1989). Aluminum precipitated chromatin in the range 100-500 µM Al. In addition, Al significantly inhibited the action of the exogenous nuclease DNase I on brain and liver chromatin. When the chromatin was first exposed to Al, and then, following the removal of Al, exposed to micrococcal nuclease (MNase), brain chromatin was nearly completely resistant to nuclease digestion. The authors concluded that Al ions altered the structure of chromatin. Roy et al. (1991) reported inhibition of bone marrow cells and increased chromosome aberrations in male rats given increasing doses of Al sulfate in drinking water for one to three weeks. The observed decrease in mitotic index was dose dependent but thought to be independent of duration of exposure. The frequency of abnormal cells increased with dose and duration of exposure, except for the lowest dose tested. Most of the aberrations were chromatid breaks. The LOAEL for the study was 0.017 mg Al/kg-d.

Hematotoxicity

Oral exposure of female Wistar rats to 100 mg $AlCl_3$/kg-d for 21 days caused normocytic anemia (Chmielnicka et al., 1994a). In a subsequent study, female Wistar rats were given 4 mg/kg-d i.p. for three weeks (Chmielnicka et al., 1996). A significant decrease was seen in serum iron concentration ($p < 0.05$) after each week and an increase in platelet count ($p < 0.05$) after the first week of exposure. Significant decreases were also seen in hemoglobin, hematocrit, mean corpuscular hemoglobin mass, and mean corpuscular hemoglobin concentration after three weeks of exposure, and increases in white blood cells after two and three weeks. Heme oxygenase (H.O.) activity was significantly elevated in liver versus controls at 7, 14, and 21 days ($p <0.01$). Heme oxygenase in kidney was not significantly affected by treatment with $AlCl_3$. δ-Aminolevulinic acid synthase (ALA-S) activities were significantly elevated in liver ($p < 0.05$) and kidney ($p < 0.01$) of Al-treated animals. δ-Aminolevulinic acid dehydratase (ALA-D) activity in the blood, liver, and kidney of treated rats was not significantly different than in control animals. This latter result contrasts with earlier findings (Chmielnicka et al., 1994b). Chmielnicka et al. (1996) compared the responses and sequence of effects with earlier oral studies (Chmielnicka and Nasiadek, 1991) and found that effect on examined parameters was dependent on the concentration of Al in the tissue and the route of administration. When total doses were expressed as log mM Al/kg body weight, increases in H.O. (liver) were seen at 0.015 i.p. versus 1.05 p.o. and decreases in serum Fe were seen at 0.015 i.p. versus 1.40 p.o. Increases in ALA-S (liver, kidneys) were seen at 0.3 i.p. vs. 1.05 (liver) p.o., and decreases in hemoglobin at 0.5 i.p. versus 1.90 p.o. These differences are mainly due to limited uptake of Al by the gastrointestinal tract and the most sensitive indicators were decreases in iron in the serum and increases in H.O. in liver. The authors speculate that Al-induced anemia is caused by a change in the activity of the enzymes of heme biosynthesis (ALA-S) and catabolism (H.O.) in rats.

Developmental and Reproductive Toxicity

Golub and Domingo (1996) have reviewed the developmental toxicity of Al in experimental animals and humans. Aluminum exposure during gestation can cause *in utero* death, malformation, growth restriction, and developmental delay. High Al exposures via intravenous or intraperitoneal administrations result in death and resorption, skeletal and soft tissue abnormalities, and growth retardation (Benett et al., 1975; Wide, 1984). Aluminum exposures by gavage may also produce growth retardation, delayed ossification, and increased incidence of gross, internal and skeletal abnormalities (Domingo, 1995).

McCormack et al. (1979) added $AlCl_3$ to the diet of pregnant Sprague-Dawley rats to give 500 or 1,000 ppm Al from day 6 to day 19 of gestation, when the fetuses were removed by Cesarean section and examined. Al in the diet did not affect the embryo or fetal mortality rate, litter size, fetal body weight, or body length. However, in parallel groups of pregnant rats that received subcutaneous injections of parathyroid hormone (PTH, 68 units/kg) on days 6, 9, 12, 15, or 18 of gestation, there was a significant increase ($p < 0.05$) in the resorption rate in those animals receiving Al at 1,000 ppm. $AlCl_3$ injections (3-18 mg) in eggs are embryolethal and cause malformations in chick embryos (Gilani and Chatzinoff, 1981); however, the chick embryo response is not necessarily relevant to a possible human response because there is no maternal absorption, distribution, excretion, detoxification, or toxication and because high concentrations of the metal are placed in direct contact with embryonic tissues by injection.

Golub et al. (1987) have shown developmental retardation in offspring of mice following oral exposure to Al during gestation, parturition, and lactation. Female mice fed Al lactate at levels of 500- or 1000-ppm in their diet from the beginning of gestation to day 21 postpartum were compared to mice which received a 100-ppm Al diet ad libitum. Dams receiving the 500- and 1000-ppm Al diets showed signs of neurotoxicity beginning at days 12-15 postpartum with significant weight loss. The signs considered indicative of Al-induced neurotoxicity included the Wahlsteen neurobehavioral test battery in mouse pups. Offspring showed dose-dependent decreases in body weight, crown-rump length, and ponderal index at birth and preweaning. Absolute and relative liver and spleen weights were lower in pups from the high Al groups compared to controls. In addition to showing oral toxicity of excess Al during development, dose dependent toxic effects of parenteral Al exposure were demonstrated in pregnant mice which were injected subcutaneously with Al lactate solution at 10, 20 or 40 mg Al/kg on days 3, 5, 7, 9, 12, 13 and 15 of gestation. Fetal crown-rump lengths were significantly reduced in the 20 mg/kg Al group. There was no establishment of a no-observed-adverse effect level in the Golub et al. (1987) study.

Teratogenic effects of $Al(NO_3)_3$ in the rat were shown after oral administration (Paternain et al., 1988). Three groups of ten pregnant rats were given intragastrically a daily dose of 180, 360 or 720 mg/kg of $Al(NO_3)_3 \bullet 9H_2O$ on days 6-14 of gestation. Fetal examinations were performed on day 20 and embryotoxicity of Al (as measured by percent dead and resorbed fetuses) was not found. However, 180 mg/kg-day caused a decrease in the weight and development of the fetuses and a marked increase in the incidence of skeletal malformations (delayed ossification). The disinfectant $AlCl_3$ increased the frequency of congenital abnormalities when injected into rats (Benett et al., 1974). Fetal deaths and resorption were also increased (Benett et al., 1975).

Other reproductive effects include decreased spermatozoa counts and motility in rats administered 2.5 mg/kg $AlCl_3$ (0.5 mg Al) by gavage daily for six months (Krasovskii et al., 1979), decreased testicular weights in rats and mice, and seminiferous tubule necrosis in rats injected s.c. for 30 days with 2.67 nmol (0.14 µg Al)/kg-d $A1_2(SO_4)_3$ (Kamboj and Kar, 1964). Exposure to 500 mg Al/L as $AlCl_3$ in drinking water for 30-90 days, however, did not adversely affect the reproductive capacity of male rats (Dixon et al., 1979).

Rabbits received 20 s.c. Al lactate injections of 0 or 400 µmol (10.8 mg) Al/kg during the first month postpartum or 0, 25, 100, or 400 µmol Al/kg during the second month postpartum (Yokel, 1987). Results were compared to studies in which pregnant, lactating, or adult rabbits received comparable Al injections. Aluminum injections to neonatal rabbits decreased milk consumption, but not as severely as seen in neonates of does receiving Al during gestation or lactation. Reduction in body weight gain was greater in adult rabbits than in any group of rabbits exposed to Al at a younger age. Increased carpal joint width, suggestive of poor bone calcification, was observed in rabbits receiving 400 µmol Al injections during the second postnatal month, but not in any other Al-exposed group. Learning and memory changes were not observed after Al treatment of neonatal and immature rabbits, compared to the biphasic effect enhancement after low doses, attenuation after high doses seen in gestationally exposed rabbits, and the attenuation observed in adult rabbits.

In a review of 14 studies (eight in mice, five in rats, one in rabbit) including four different Al compounds (Al chloride, Al hydroxide, Al citrate, Al lactate) by four routes of administration (diet, gavage, i.p. injection, s.c. injection) at doses from 13.5 to 8,400 mg/kg, Borak and Wise (1998) concluded that dietary Al exposures were unlikely to pose risks of Al accumulation to pregnant animals or their fetuses (see comments on this review by Golub and Domingo, 1998). The accumulation of Al as a result of exposure is thought to be essential for Al-induced disease

(Ganrot, 1986). There was little evidence of Al accumulation by mothers or their offspring in gestation-only studies. In gestation-plus studies, organ-specific Al levels of pups were not increased when measured at weaning, even when mothers were exposed throughout lactation. Accumulation of Al in maternal organs was reported in three gestation-plus studies. Elevated Al was found in bone and liver (Donald, et al., 1989), plasma (Muller et al., 1990), and liver, bone and kidney (Yokel, 1985). Elevated Al was found in placental tissue in three of seven studies. Borak and Wise note that toxicologically significant Al accumulation might occur in specific cells or subcellular structures despite normal total body burdens and normal target organ levels. Such micro-accumulation is difficult to demonstrate as evidenced by much of the recent research on the brains of Alzheimer's disease (AD) patients (see below).

Studies in rats, mice, and dogs indicate that Al does not affect reproduction (ATSDR, 1997). However, Bataineh et al. (1998) reported adverse effects of subchronic administration of Al in drinking water on the sexual behavior of male rats. Ten adult male Sprague Dawley rats (300 g) were administered $AlCl_3$ in drinking water at 1000 ppm for 12 weeks. Ten rats receiving normal tap water served as controls. Male sexual behavior of the Al-treated rats was suppressed as indicated by prolonged intromission, ejaculation latencies and reduced copulatory efficiency. Male aggression was also affected with markedly suppressed lateralizations, boxing bouts, and fights with stud male and ventral presenting postures. Fertility was not affected. However, body weight, absolute testis weight, and absolute seminal vesicles weight were all significantly reduced relative to controls ($p < 0.001$).

Immunotoxicity

Gomez et al. (1986) observed that 54 mg Al/kg-d administered to female Sprague Dawley rats for one month in drinking water caused hyperemia in the red pulp of the spleen. Alternatively, Domingo et al. (1987) found that 259 mg Al/kg-d for 100 days in drinking water had no effect on spleens of female Sprague Dawley rats. Golub et al. (1993) found that 24.4 mg Al/kg-d as Al lactate in the diet of pregnant Swiss Webster mice exposed through gestation and lactation led to effects in the offspring including increased spleen weights, and decreased spleen concentrations of interleukin-2, interferon-γ, and tumor necrosis factor-α. A deficiency of CD4+ cells in T cell populations was also seen in the offspring.

Aluminum may cause peripheral inflammation. Cherroret et al. (1995) treated young rats (postnatal days 5 to 14) with Al chloride (100 mg Al/kg-d) or Al lactate (100 or 200 mg Al/kg-d) by gastric intubation. The treatment lead to decreased body weight gain and decreased plasma concentrations of total proteins and albumin. However, the $\alpha 1$ globulin levels were observed to increase in all treated groups ($P < 0.01$) indicating the presence of an inflammation process. The $\alpha 2$ globulin levels showed no significant differences in any of the treatment groups. The level of β globulin + fibrinogen was decreased in the $AlCl_3$ group ($P < 0.01$) and in the 200 mg Al lactate/kg-d group ($P < 0.001$).

Demircan et al. (1998) reported that Al in total parenteral nutrition (TPN) solutions caused portal inflammation in rats. Sixty albino rats were divided into six groups of ten rats receiving the following treatments: (1), 0.9 percent saline i.p. 14 d; (2), TPN i.p. 7 d; (3), TPN i.p. 7 d + 0.9 percent saline i.p. 7 d; (4), $AlCl_3$ i.p. 7 d; (5), $AlCl_3$ i.p. 14 d; (6), TPN i.p. 7 d + $AlCl_3$ i.p. 7 d. The TPN formula and the $AlCl_3$ solutions used both had 300 g Al/L. Hepatic Al accumulation was higher in the TPN and $AlCl_3$ groups than it was in the control group and was dependent on dose and duration of exposure to TPN and $AlCl_3$ ($P < 0.05$). Portal inflammation was observed in all groups except the control group. The number of rats determined to have portal inflammation were: Group (1), zero; (2), three; (3), two; (4), one;

(5), four; and (6), seven. The hepatic Al contents correlated positively with the morphologic inflammation index (MPII) in all groups ($r = 0.58$, $P < 0.05$), but was more significant in both $AlCl_3$ (4 and 5) and TPN groups (2 and 6) ($r = 9.99$, $P < 0.05$ for each). In all groups, the correlation between serum bile acid concentrations and hepatic Al contents were significant ($r = 0.68$, $P < 0.05$). The mechanism of Al-induced portal inflammation is unknown.

Chary-Valckenaere et al. (1994) studied the articular toxicity of Al compounds *in vivo*. Two rabbits per group were given an intraarticular injection of 0.25 mL of either sterile saline (control), Al lactate or Al hydroxide (300 mg Al/mL, pH 7.3) into their right knee under sterile conditions. After injection Al lactate was distributed within the animal while Al hydroxide remained locally. However, Al lactate resulted in perivascular edema, sparse infiltration of inflammatory cells in the synovium and a hemorrhagic effusion. Al hydroxide did not affect joint structures. The inflammatory effect of Al compounds was further investigated in the air pouch model. Twenty mL of sterile air were injected under light anesthesia into the subcutaneous tissue of the back. The pouch was then injected with 5 mL of sterile saline, Al lactate, Al hydroxide, or sodium lactate solution (10 mg/L) and was monitored at various intervals up to 72 hours. Aluminum lactate increased prostaglandin E_2 (PGE_2) levels from three to ten hours after its injection and less intensively leukotriene B_4 (LTB_4) levels after six hours, in the absence of leukocytes migration into the cavity. In contrast, Al hydroxide increased leukocytes count in pouch-washout fluid from three to 24 hours after its injection when PGE_2 and LTB_4 levels were unchanged. The authors note that the inflammatory effect of soluble Al may have relevance in patients with severe Al intoxication who develop joint disorders.

Wicklund Glynn et al. (1999) exposed three groups of 12 male Sprague Dawley rats to 0, 50, or 500 mg Al/L in drinking water for seven to nine weeks. Exposure of four 13-week old rats to 500 mg Al/L caused an increased number of splenocytes, whereas exposure of nine 16 weeks old rats to 500 mg Al/L caused increased number of thymocytes. Moreover, the proliferative response of splenocytes to the mitogen Con A (2 µg/mL) was increased in the 500 mg Al/L rats compared with controls. The results indicate that Al exposure caused slight stimulation of immune function in the rat at Al plasma concentrations normally found in the human population (< 10 µg Al/L).

Neurotoxicity

Golub and Domingo (1996) have reviewed studies of developmental neurotoxicity.
Earlier studies involving dosing of dams with 100-400 mg Al/kg-d (usually as Al lactate) during gestation and lactation or directly to pups caused adverse effects on neuromotor development (Bernuzzi et al., 1986; Golub et al., 1987; Bernuzzi et al., 1989a, 1989b; Muller et al., 1993). Toxic effects were seen in mother and infant (Bernuzzi et al., 1989a, 1989b; Muller et al., 1990). Other studies have shown similar effects on the offspring without maternal toxicity or growth retardation (Donald et al., 1989; Muller et al., 1990; Golub et al., 1992, 1993, 1994). The most frequently reported effects in rats and mice were negative geotaxis and the grip, or grasp reflex. Effects on righting, limb withdrawal, landing footsplay, startle response, and locomotor coordination were also seen. Both prenatal only and postnatal (lactation) only exposure to Al also caused effects in rats and mice (Muller et al., 1990; Golub et al., 1992).
Neurodevelopmental toxicity resulting from pre- and postnatal Al exposure can persist after the period of Al exposure in rats and mice (Muller et al., 1990; Cherroret et al., 1992; Golub et al., 1995). While relatively little is known about the mechanism of Al neurotoxicity, in both developing and adult brains Al exposure appears to result in decreased choline acetyltransferase activity (Clayton, 1992).

Alleva et al. (1998) report a number of behavioral and neurochemical effects in offspring of Al-exposed mouse dams during gestation. Two strains of mice (CBA/T6 and C57BL/6J) were exposed to Al sulfate during gestation and were followed from birth to adulthood. Exposure routes were either by i.p. injection (200 mg/kg $Al_2(SO_4)_3$) on days 10-13 of gestation or orally via drinking water (750, 1000, 1250 mg/L) during days 10-17 of gestation. Control animals were injected with saline or supplied with drinking water at the same pH as the Al sulfate doses. Aluminum exposure resulted in alterations in the pattern of ultrasonic vocalizations (1000 and 1250 mg/L) and a marked reduction in central nervous system (CNS) choline acetyltransferase activity. Prenatal Al also affected CNS cholinergic functions under Nerve Growth Factor (NGF) control. NGF levels were observed to be 35 percent higher in Al-treated mice compared to controls. Impaired performance in a maze learning test was specifically related to increased NGF in the hippocampal area. Strain differences in the maze learning test may be the result of impairments in motor rather than cognitive abilities.

Bielarczyk et al. (1998) studied the ability of $AlCl_3$ to affect cholinergic transmission on synaptosomal fractions of rat brain *in vitro*. Addition of 1 mM Ca caused a 266 percent increase in the acetylcholine (ACh) release. Under these conditions 0.25 mM Al raised mitochondrial and decreased synaptoplasmic acetyl-Coenzyme A (CoA). Simultaneously, a 61 percent inhibition of Ca-evoked ACh release was observed at 0.25 mM (6.7 ppm) Al, with a significant decrease seen at 0.05 mM (0.67 ppm) Al ($p < 0.05$). This can be compared to increases of 0.05 or 0.09 ppm Al in brain cortex observed by Slanina et al. (1985) after ten weeks of three times weekly treatments of rats with 100 mg/kg of Al citrate or Al hydroxide, respectively. Omission of inorganic phosphate from the medium abolished the suppressive effects of Al on acetyl-CoA content and Ca-evoked ACh release. It seems likely that the $Al(PO_4)OH^-$ complex may be the active form of Al. According to Bielarczyk et al.(1998), the accumulation of Al in the brain, by activation on nonquantal ACh release and simultaneous inhibition of Ca-evoked acetyl-CoA transport to synaptoplasm, may lead to severe impairment of the release of the functionally important quantal transmitter pool. It would be useful to confirm these findings with a more soluble salt of Al than the chloride, and evaluate the same parameters after *in vivo* treatments.

Llansola et al. (1999) studied the effect of prenatal exposure to Al on glutamatergic neurotransmission in rat cerebellum. Female Wistar rats were administered 3 percent (30,000 ppm) Al sulfate in the drinking water starting from the first day of pregnancy. Primary cultures of neurons were prepared from cerebella of seven-day-old pups. The body weight of the control pups was 12.7 ± 1.3 g, whereas for pups prenatally exposed to Al, the weight was 8.9 ± 1.5 g. These values are the means of 14 litters for each group with a total of 193 control pups and 105 Al-treated pups. With primary neuronal cell cultures, the number of cells per cerebellum obtained from the Al-treated group was significantly lower than for control pups (7.3 ± 2.9 versus 12.8 ± 2.9 million cells). Glutamate-induced neuronal death was significantly reduced in neurons from Al-treated pups (LC_{50} of 60 μM in controls vs. 1.0 mM in Al-treated). Prenatal exposure to Al prevented glutamate-induced proteolysis of the microtubule-associated protein-2 and disaggregation of microtubules. The effects noted indicate Al-induced impairment of *N*-methyl-D-aspartate (NMDA) receptor-associated signal transduction pathways. Prenatal exposure to Al also reduced the content of nitric oxide synthase and guanylate cyclase and increased calmodulin in both cultured neurons and the whole cerebellum. The effect was selective for proteins of the glutamate-nitric oxide-cGMP pathway, suggesting a possible mechanism for the neurotoxic effects of Al. The authors note that the activity of guanylate cyclase is decreased about 50 percent in the superior temporal cortex of Alzheimer's disease patients (Bonkale et al., 1995).

Tsunoda and Sharma (1999) observed modulation of tumor necrosis factor α (TNFα) expression in mouse brain after exposure to Al in drinking water. Groups of male BALB/c mice (five/group) were administered Al ammonium sulfate in drinking water ad libitum at 0, 5, 25, and 125 ppm Al for one month. An additional group received 250 ppm ammonium as ammonium sulfate. After treatment, the cerebrum, splenic macrophages, and lymphocytes were collected. The expression of TNFα mRNA, determined by measurement of polymerized chain reaction amplified products, was significantly increased among Al-treated groups compared to control, in a somewhat dose dependent manner. Other cytokines did not show Al-related effects. Increased TNFα mRNA expression by Al in cerebrum may reflect activation of microglia, a major source of TNFα in this region of the brain. The authors suggest that Al-induced modulation of mRNA and protein synthesis may be one of the mechanisms of Al neurotoxicity. Specifically cytokines such as interleukin-1β, TNFα, and interferon γ have been previously observed to be involved in neurotoxic mechanisms (see references in Tsunoda and Sharma, 1999) and effects on cytokines in splenic lymphocytes have been observed after chronic administration of Al lactate to mice (Golub et al., 1993).

Chronic Toxicity

Ondreika et al. (1966) administered $AlCl_3$ to groups of ten mice in drinking water at average doses of zero and 19.3 mg Al/kg-d in a three-generation study. The parental generation was treated for 180-390 days and unspecified numbers of weanlings were similarly treated from four weeks of age. Decreased body weight in the second and third generations was the only treatment-related effect seen. Feed consumption was not reported. Decreased feed consumption was seen in other parts of the study. No changes were seen in erythrocyte counts or hemoglobin levels in blood or in histology of liver, spleen, or kidneys of treated mice versus controls.

Krasovskii et al. (1979) administered 0.025, 0.25, and 2.5 mg Al/kg-d to rats in drinking water for 6-12 months. The numbers of animals employed and other experimental details were not given. At the 2.5 mg/kg-d dose, changes in serum, alkaline phosphatase and decreased development of conditioned reflexes were seen after six months of exposure. Animals exposed to 0.25 mg Al/kg-d showed a change (direction not stated) in alkaline phosphatase activity in blood serum only during the first month of dosage. The gonadotoxic effect of Al was weak. Changes in the number of spermatozoa and their motility were seen only at the 2.5 mg Al/kg-d dose (154 ± 17 in exposed rats vs. 208 ± 10 in controls, $p < 0.05$). The authors identified 0.025 mg Al/kg-d as a NOAEL for the study.

Schroeder and Mitchener (1975a) exposed weanling male and female rats to potassium Al sulfate ($KAl(SO_4)_2$) at 0 or 5 mg/L in drinking water over the lifetime of the animals. The treated males gained significantly more weight than controls, but the weights of the females were similar to those of the controls. Al treatment did not alter life span or the level of glucose or protein in the urine. Groups of 54 weanling mice/sex were also exposed to 0 or 5 mg Al/L as $KAl(SO_4)_2$ over the lifetime of the animals (Schroeder and Mitchener, 1975b). No treatment-related effects were seen on body weight, survival, edema, blanching of the incisor teeth, or tissues as indicated by gross and limited histological examination (heart, lung, kidney, and liver). Assuming water consumption of 17 percent body weight, the dose was 0.85 mg/kg-d (U.S. EPA, 1987).

Pettersen et al. (1990) conducted a 26-week toxicity study with basic sodium Al phosphate (KASAL) in beagle dogs. Groups of four male and four female dogs were fed dietary concentrations of 0, 3,000, 10,000, or 30,000 ppm KASAL. The doses of elemental Al were 4, 10, 27, 75 mg Al/kg-d in males and 3, 10, 22, 80 mg Al/kg-d in females. There were no mortalities during the study. Toxicity was limited to a sharp, transient decrease in food

consumption, and concomitant decrease in body weight in high dose males. No effects were seen in females. Postmortem findings were limited to a decrease in testes weight and microscopic changes including mild to moderate hepatocyte vacuolation accompanied by hepatocyte hypertrophy and mild bile stasis involving bile canaliculi in three of four animals. Two high dose males showed moderate seminiferous tubule germinal epithelial cell degeneration and atrophy. These data would support a study NOAEL of 27 mg/kg-d in males. Since the study duration was less than that of a chronic study duration of one year or greater, an uncertainty factor of three will be used to adjust to a chronic NOAEL.

Varner et al. (1998) studied alterations in the nervous system resulting from chronic administration of Al fluoride (AlF_3) or equivalent levels of fluoride as sodium fluoride (NaF). Twenty male Long-Evans rats were administered either 0.5 ppm AlF_3, 2.1 ppm NaF, or a control of double distilled drinking water for 52 weeks. The Al levels in samples of brain and kidney were higher in both the AlF_3 and NaF groups relative to the control. The AlF_3 group also had greater mortality than in the control group. The effects of AlF_3 and NaF treatments on cerebrovascular and neuronal integrity were different. The alterations, including a reduction in neuronal density in the neocortex of the left hemisphere, were more prominent in the AlF_3 group than in the NaF group or the controls. Cellular abnormalities in the form of chromatin clumping, pyknosis, vacuolation, and ghost-like cells were also more common in the AlF_3 group. The effects were similar to those previously reported for cats administered intracerebroventricular $AlCl_3$ (Crapper and Dalton, 1973). Vascular Al-fluorescence was more pronounced throughout most structures of the left hemisphere of the AlF_3 group. The hippocampus was an exception with abnormalities found only in areas of the right hemisphere of both treatment groups. The authors concluded that chronic administration of AlF_3 or NaF in drinking water of rats resulted in distinct morphological changes in the brain, including effects on neurons and cerebrovasculature. The LOAEL for AlF_3 in this study was about 500 µg AlF_3/L of drinking water.

Mahieu and Calvo (1998) studied the effect of chronic Al administration on the renal handling of phosphate in the rat. The rats were given Al hydroxide (80 mg/kg, i.p.), three times per week for six months. Phosphate renal tubular transport capacity was evaluated during the infusion of phosphate solutions with increasing phosphate concentrations. Al increased the ratio of the maximum tubular transport of phosphate to glomerular filtration rate (TRPi/GFR, µg/mL): 76 ± 4 for Al-treated rats vs. 57 ± 7 for controls. In addition, the calcemia recovery following a hypocalcemic stimulus and the nephrogenic excretion of cAMP (Al-treated 44 ± 4, control 91 ± 7 pmol/min) were diminished. The authors conclude that Al exposure interferes with Pi excretion either by decreasing parathyroid hormone (PTH) levels or by diminishing its affinity for their receptors at the renal tubule level. This effect may be associated with a decrease in the cAMP excretion. It is known that Al is a potent inhibitor of PTH secretion (Morrisey et al., 1983; Morrisey and Slatopolsky, 1986; Balsan et al., 1987).

Carcinogenicity

Granulomas were present in the lungs of Fischer 344 rats and Hartley guinea pigs inhaling 2.5 or 25 mg/m^3 Al chlorhydrate ($Al_2(OH)_5Cl$) for six months (10 animals/sex/dose, 6 hr/day, 5 days/week) (Steinhagen et al., 1978). Exposure related lung lesions were seen in 50 percent of the animals at 2.5 mg Al/m^3 and in 100 percent of animals at 25 mg Al/m^3. The multifocal granulomatous pneumonia was characterized by proliferation and/or infiltration of mononuclear

inflammatory cells and large macrophages in alveoli around the termination of air passageways. The changes fit the classical description of granuloma. It should be noted that at the lowest dose tested of 0.25 mg Al/m^3, 3/20 guinea pigs had slight exposure related effects characterized by increased alveolar macrophages and 1/20 rats showed an indication of granulomatous change in the peribronchial lymph node. However, Pigott et al. (1981) found no increase in tumors in male or female Wistar-derived rats (25/sex) exposed via inhalation to 2.18 or 2.45 mg /m^3 as alumina fibers (Al_2O_3) for 86 weeks (35 hr/wk). In a parallel exposure group with 50 rats exposed to 4.57 mg/m^3 chrysotile asbestos for 77 weeks, both benign and malignant pulmonary neoplasms were seen.

Schroeder and Mitchener (1975b) exposed mice (54/sex) to 5 ppm Al in drinking water in a lifetime exposure study. Aluminum was not considered by these authors as tumorigenic. Only half of Al-treated and control animals were autopsied and the number of treated versus control animals judged to have malignant tumors was not statistically significant.

Oneda et al. (1994) evaluated the chronic toxicity and oncogenicity of Al potassium sulfate (APS) in $B6C3F_1$ mice. APS was administered in the diet at 0, 1.0, 2.5, 5.0, and 10.0 percent (w/w) (0, 10,000, 25,000, 50,000, and 100,000 ppm, yielding approximate doses of 0, 85, 213, 425, and 850 mg/kg-d, respectively) to 60 animals/sex/dose group for 20 months. The survival rates at the end of the dosing period were 73 percent (male) and 78 percent (female) in the control group and 87 to 95 percent (male) and 87 to 92 percent (female) in the APS treatment groups. The were no significant increases in tumor pathology. The incidence of hepatocellular carcinoma was significantly decreased in females in all groups including the control. A significant increase in the absolute organ weight was observed in the kidneys and heart in both sexes in the 1.0, 2.5, and 5.0 percent APS dose groups, in the pituitary in males in the 2.5 percent APS group, and the brain in females in the 1.0 percent APS group. Also there were significant decreases in absolute organ weight of the liver in both sexes in the 5.0 and 10.0 percent APS groups, the heart and brain in both sexes in the 10.0 percent APS group, and lungs (males) and spleen (females) in the 10.0 percent APS group compared to the control group. There were also significant decreases in relative liver weight in males at 2.5, 5.0, and 10.0 percent APS and in females in all APS dose groups ($P < 0.01$). The small increases in organ weight at 1 percent (85 mg/kg-d) dietary Al are not judged to be an adverse effect, and therefore the NOAEL is 85 mg/kg-d in this study.

Toxicological Effects in Humans

Acute Toxicity

Despite widespread human exposure to Al compounds via food, drinking water, and antacids, there is little indication that they are acutely toxic by the oral route in healthy adult individuals (ATSDR, 1997). For example, Al hydroxide is insoluble and essentially harmless by oral administration. It has been used as a gastric antacid and is known to cause constipation. Administration of Al antacids to infants has raised the concern of Al toxicity. Chedid et al. (1991) measured plasma and urinary levels of Al in seven infants (36 weeks mean gestational age, 11 days mean postnatal age) before and after antacid therapy (0.4 - 0.8 mmol Al) for two days. Plasma levels increased on therapy and reached potentially toxic levels (3.48 ± 2.86 µmol/L on therapy vs. 0.64 ± 0.33 µmol/L before therapy, $p = 0.03$). Urinary Al to creatinine ratio also increased. Hawkins et al. (1994) concluded that infants receiving formula with > 300 µg Al/L, particularly casein hydrolysate formulas, were at risk of Al toxicity. Aluminum oxide or finely powdered Al metal reacts slowly to form $Al(OH)_3$. Workers exposed to Al-containing dusts for various periods have developed severe pulmonary reactions including

granulomatosis, fibrosis, emphysema, and pneumothorax, presumably due to inhalation exposure (Chen et al., 1978; De Vuyst et al., 1987; Gaffuri et al., 1985; Musk et al., 1980).

Subchronic Toxicity

German, Swedish, and British occupational studies have shown that inhalation of a specific type of Al dust (i.e., stamped Al powder) causes pulmonary fibrosis (Elinder and Sjogren, 1986). Two case reports (Vallyathan et al., 1982) suggest that pulmonary fibrosis might be associated with long-term exposure to Al welding fumes. On the other hand, no signs of pulmonary fibrosis were found in a cross-sectional study of 64 Al welders in Sweden (Elinder and Sjogren, 1986).

Al salts are available to the public as food additives as well as components of non-prescription drugs (Lione, 1985). Al-containing antacids are widely used in over-the-counter and prescription treatment of peptic ulcers and as phosphate-binding gels, particularly in cases of renal failure. Excess Al can cause a variety of adverse effects in humans. These effects can be divided into three major categories: (1) the effect in the gastrointestinal tract, (2) neurological effects, and (3) skeletal effects.

Gastrointestinal effects

When Al compounds are ingested in excessive amounts they can affect GI tract motility, delay gastric emptying and thus cause chronic constipation (Hurwitz et al., 1976). Al compounds such as Al hydroxide can reduce absorption of iron, fluoride, phosphorus and calcium in the GI tract (Alfrey, 1983). The binding of phosphate in the GI tract can lead to phosphate depletion and osteomalacia (Lotz, 1968).

Skeletal effects

Aluminum has been recognized for many years as a cause of low-turnover osteomalacic bone disease and encephalopathy in patients with uremia (Kerr et al., 1986). Hodsman et al. (1982) studied 59 patients on hemodialysis. Bone biopsies were obtained and analyzed for Al content in relation to Al body burden. Among 23 patients diagnosed as having osteomalacia, the average Al content of bone was 175 mg/kg dry weight (dw), ranging from 50 to >400 mg/kg dw. In the other patients on hemodialysis the Al concentration was 46-81 mg/kg dw. Normal concentration was on an average 2.4 mg/kg dw.

Aluminum-related osteomalacia has been observed in non-dialyzed patients receiving Al-containing antacids (Andreoli et al., 1984). Kaye (1983) described a patient with chronic renal failure who developed toxic levels of Al in bone (324 mg/kg dw in the iliac crest) after one year of oral $Al(OH)_3$ ingestion with a total dose of 711 g (ca. 30 mg/kg-d). The effects seen were a general joint discomfort and a decreased rate of mineralization of new bone. Woodson (1998) described a case of osteomalacia in a woman who took the maximum allowable daily dose of an antacid containing Al and magnesium hydroxide over an eight-year period. The calculated dosage of elemental Al was about 120 mg/kg-d. Studies on Al loading and Al intoxication in infants and children with chronic renal failure indicate that orally administered Al-containing phosphate-binding gels are probably the source of the excess Al burden (Andreoli et al., 1984; Sedman et al., 1985). Infants, children, and adults with chronic renal failure who are not receiving dialysis have been shown to be at risk for Al intoxication from oral administration of Al-containing phosphate binders.

Low-turnover osteomalacia and bone pain, but not encephalopathy, has also been seen in adult patients with normal renal function who were receiving total parenteral nutrition (TPN) (Klein et al., 1980). Aluminum contamination of TPN solutions was associated with casein hydrolysate used as a protein source (Klein et al., 1982). In both uremic and TPN patients the Al concentration at the mineralization front of bone was inversely correlated with the rate of bone formation. Sedman et al. (1985) studied Al loading in serum, urine and bone of pre-term infants receiving TPN for three weeks. Sources of Al were calcium and phosphate salts, albumin, heparin, and infant formula. Koo et al. (1986a,b, 1988) found that Al accumulated at the mineralization front in the bones of premature infants. Bishop et al. (1997) observed that pre-term infants given 45 μg Al/kg-d via TPN had a lower score on the Bayley Mental Development Index at age 18 mo (92 ± 20) than did age-matched infants who received TPN with 4-5 μg Al/kg-d (102 ± 17). Bougle et al. (1998) found that lumbar spine bone mineral density and content were negatively correlated with serum Al concentrations in healthy premature infants. Pre-term infants are more likely to retain Al administered intravenously since 95 percent of Al is bound to circulating plasma proteins, mainly transferrin, and only about 5 percent of circulating Al is ultrafilterable (Klein et al., 1982, 1998). The U.S. Food and Drug Administration (FDA) has proposed a maximum Al concentration of 25 μg/L for large-volume parenteral solutions (Klein et al. 1998). FDA also suggests 4-5 μg Al/kg-d as a possible safe upper limit for Al intake from TPN solutions in uremic patients.

Genetic Toxicity

Aluminum compounds are not thought to be mutagenic or otherwise genotoxic. However, animal and human data indicate that Al may interact with neuronal DNA resulting in altered gene expression and protein formation (Crapper McLachlan et al., 1990).

Hematotoxicity

Persons suffering chronic renal failure and receiving dialysis treatment often exhibit normochromic anemia (Jeffery et al., 1996). This anemia can be controlled by administration of exogenous erythropoietin, suggesting that the impaired kidney is not producing sufficient endogenous erythropoietin (Winearls et al., 1986). Fewer patients exhibit a hypochromic microcytic anemia, which is not controlled by erythropoietin therapy. This anemia correlates with plasma and red blood cell Al concentrations and can be reversed by stopping Al exposure or by Al chelation therapy with desferrioxamine (Cannata et al., 1983; Touam et al., 1983; Abreo et al, 1989). A similar Al-induced anemia has been observed in animals (Touam et al., 1983; Fulton and Jeffery, 1994). The cause of the hypochromic microcytic anemia is thought to be decreased hemoglobin synthesis. Aluminum was observed to inhibit hemoglobin in synthesis in Friend erythroleukemia cells and in bone marrow cells (Abreo et al., 1990). Altmann et al. (1987) found reduced levels of erythrocyte dihydropteridine reductase (DHPR) associated with increased serum Al in 38 hemodialysis patients who had no clinical evidence of encephalopathy ($r = -0.61$, $p < 0.001$). The authors suggest that Al inhibition of DHPR may also occur in the brain and could play a role in Al neurotoxicity since DHPR and tetrahydrobiopterin are involved in the synthesis of neurotransmitters.

Developmental and Reproductive Toxicity

Golub and Domingo (1996) have reviewed studies of developmental aluminum toxicity in humans and animals. They found no link between cognitive function and Al exposure in

children. However, they also noted that no adequate study of long-term effects of Al exposure on brain development has been performed in children. Similarly, there were no studies of long-term effects of Al on skeletal maturation or hematopoiesis. Bishop et al. (1997) studied 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g who required intravenous feeding. The infants received standard or special Al-depleted intravenous-feeding solutions. Neurologic development was tested at 10 months of age in 182 surviving infants. The 90 infants who received the standard feeding solutions had a mean (± SD) Bayley Mental Development Index (BMDI) of 95 ± 22, as compared with 98 ± 20 for 92 infants who received Al-depleted feeding solutions ($p = 0.39$). An analysis subgroup of infants in whom duration of i.v. feeding exceeded the median and who did not exhibit neuromotor impairment, had BMDI values of 92 ± 20 ($n = 41$) for the standard solution and 102 ± 17 ($n = 39$) for Al-depleted solution ($p = 0.02$). For all 157 infants without neuromotor impairment, increasing Al exposure was associated with a reduction in the BMDI ($p = 0.03$), with an adjusted loss of one index point per day of i.v. feeding of infants receiving the standard solutions (ca. 45 µg Al/kg-d). Gilbert-Barness et al. (1998) report a case study of a female child who suffered a neurodegenerative disorder with profound mental retardation and died at age nine. Following autopsy, the mother disclosed that she had consumed 75 Maalox tablets per day during the entire pregnancy. Each tablet contained 200 mg $Al(OH)_3$. The total dose of Al would be about 5.2 g/day or 83 mg/kg-d for a 62 kg female. The authors postulate that the anemia and poor bone mineralization of the acetabula observed in the child at four months of age may have been due to Al toxicity. The authors further caution against the consumption of high doses of Al-containing compounds during pregnancy. There are no human studies that indicate that Al or Al compounds affect reproduction.

Immunotoxicity

No studies were located that evaluated the effect of Al or Al compounds on the human immune system. There is some evidence of a positive correlation between Al deposition and focal lung inflammation. Schwarz et al. (1998) evaluated workers exposed to dust containing hard metals and Al oxide. Six heavily exposed workers were examined by bronchoscopy and bronchoalveolar lavage and five underwent transbronchial biopsy. Microchemical analysis of the biopsies showed a high lung burden of exogenous particles, especially metals. Three workers exhibited at biopsy diffuse interstitial inflammatory changes, two of these were asymptomatic and the third had clinically evident disease. Two other workers showed focal inflammation. The worker with clinical disease and one asymptomatic worker with interstitial inflammatory changes had elevated bronchoalveolar lavage fluid-eosinophilia counts. The authors suggest that the observed eosinophilia may be an early, subclinical marker indicating risk of developing hard metal- and Al-induced lung disease.

A few reports indicate a possible link between Al in vaccines and hypersensitivity in children (Boehler-Sommeregger and Lindemayer, 1986; Veien et al., 1986). The use of triple vaccines for childhood immunization may induce sensitization to the Al hydroxide added to the vaccine (Al-precipitated antigen extracts). Typical clinical features include pruritic plaques and persistent nodules at the injection site. Persistent subcutaneous nodules were also seen in patients hyposensitized with Al-precipitated antigen extracts (Lopez et al., 1994). In addition, contact dermatitis was observed to be aggravated by systemic Al from toothpaste (Veien et al., 1993). As noted above, Al affects cytokines in mice exposed orally to Al.

Neurotoxicity

Aluminum has been implicated as an etiological factor in dialysis encephalopathy, a progressive syndrome in uremic patients. Dialysis encephalopathy (DE) may occur not only in patients on hemodialysis treatment, but also in those on peritoneal dialysis and in some patients who have not been dialyzed (Wills and Savory, 1983). The non-dialyzed patients were children with renal failure who were given oral $Al(OH)_3$ (Griswold et al., 1983).

Altmann et al. (1989) observed psychomotor function in 27 long-term hemodialysis patients with apparently normal cerebral function, who had only mildly raised serum Al (59 ± 9 µg/L). They concluded that the "patients psychological function was impaired, that they had abnormal flash-stimulated visual evoked response, and that changes in their erythrocyte DHPR activity after desferrioxamine treatment were accompanied by similar changes in symbol digit coding test response times." The mean duration of individual patient dialysis was 7.2 ± 0.6 years. The hemodialysis patients showed significant deficits versus matched controls in visual spatial ability accuracy ($p = 0.003$); visual perceptual analysis time ($p = 0.003$); visual spatial recognition memory accuracy and time ($p \leq 0.001$); and increased errors in the Bexley Maudsley category sorting test ($p = 0.004$). A subset of ten patients with mean serum Al of 72 ± 12 µg/L showed a significant delay in flash-stimulated visual evoked potential ($p = 0.0001$). The mean difference between the flash and pattern potentials (F-P difference) was also greater in the patients than in matched controls ($p = 0.012$). The authors conclude that mild to moderate Al accumulation inhibits erythrocyte DHPR activity, erythrocyte DHPR is likely to reflect intracerebral DHPR activity, inhibition of brain DHPR is associated with impairment of psychomotor function, and that short term desferrioxamine can improve erythrocyte and probably brain DHPR activity.

Neurotoxicity has also been observed in premature infants receiving intravenous-feeding solutions (Bishop et al., 1997). These authors found impaired neurologic development associated with parenteral administration of standard feeding solutions resulting in Al intake of 45 µg/kg-d compared to Al-depleted solutions giving only 4.0 – 5.0 µg/kg-d. Feeding durations ranged from 6 to 16 days and for 157 infants on study, Al exposure to the standard solutions was associated with a reduction in the Bayley Mental Development Index ($p = 0.03$) of one point per day of Al exposure.

Nieboer et al. (1995) have summarized brain and bone Al concentrations in a number of studies of DE patients and control subjects (Table 5). The data allow several conclusions. First, background levels of Al in bone are about 1-3 µg/g dry weight based on the lowest levels consistently observed. Second, bone Al becomes elevated compared to controls in patients with renal failure who were treated with $Al(OH)_3$ as a phosphate scavenger or in individuals on total parenteral nutrition. Third, the highest bone Al concentrations were seen in patients on hemodialysis using dialysates contaminated with Al. Fourth, background levels of Al in brain (mostly gray matter) are about 1-3 µg/g dry weight (< 0.5 µg/g wet weight), based on the lowest levels seen. Fifth, brain Al was clearly elevated in subjects who had died of chronic renal failure, with or without dialysis but with $Al(OH)_3$ treatment.

Table 5. Aluminum Levels in Brain and Bone in Renal Failure Patients and Controls[a]

Tissue	Al Level mean ± SD µg/g (range) dry weight	Number of Subjects	Health Status	Reference
Brain	66 (36-96)	2	Dementia	Flendrig et al., 1976
	12 (6.1-18)	**2**	**Controls**	
Bone	273 (215-330)	2	Dementia	
	11 (7.5-15)	**4**	**Controls**	
Brain (gray matter)	12.4 ± 4.9	4	Dementia	Arieff et al., 1979
	6.6 ± 1.5	8	Renal failure without dialysis	
	3.8 ± 0.8	5	Renal failure with dialysis	
	4.1 ± 0.8	12	Acute renal failure	
	0.9 ± 0.2	**19**	**Controls**	
Brain (gray matter)	25 ± 9	6	Dementia	Alfrey et al., 1976
	6.5 ± 2.9	7	Uremia with dialysis	
	2.2 ± 0.7	**5**	**Controls**	
Bone (trabecular)	98 ± 60	16	Uremia with dialysis	
	37	3	Uremia without dialysis	
	2.4 ± 1.2	**9**	**Controls**	
Brain	16 ± 11	16	Dementia	McDermott et al., 1978
	4.4 ± 2.7	11	Uremia with dialysis	
	2.7 ± 1.4	2	Uremia without dialysis	
Bone	12-130*	11	Histologic osteomalacia	Cournot-Witmer et al., 1981
	4-112*	10	Osteitis fibrosa	
	< 8*		**Normal value**	
Bone	14-265	11	Total parenteral nutrition	Klein et al., 1982a,b
	< 10		**Normal value**	
Brain (gray matter)	6.4 and 4.7	2 (infants)	Uremia	Freundlich et al., 1985
	< 0.1	**40**	**Controls**	
Bone	22 and 16	2 (infants)	Uremia	
	18 ± 6	**40**	**Controls**	

Table 5 (continued). Aluminum Levels in Brain and Bone in Renal Failure Patients and Controls[a]

Tissue	Al Level mean ± SD µg/g (range) dry weight	Number of Subjects	Health Status	Reference
Bone	20 ± 13	6	Premature infants on i.v. > 3 wk	Sedman et al., 1985
	2.0 ± 1.4	**17**	**Controls with limited or no i.v.**	
Bone	2.7 ± 2.0 (0.5-7.9)	15	Renal failure without dialysis	Van de Vyver et al., 1986
	35 ± 29 (3.2-85)	27	Renal failure with dialysis	
	2.0 ± 0.4	**10**	**Controls**	
Bone	22 ± 11	15	Hemodialysis patients	Sebert et al., 1986
	14 ± 5	12	Hemofiltration patients	
	2 ± 1	**7**	**Non uremic corpses**	
Bone	8.0 (1.5-33)	97	Predialysis	Ellis et al., 1988
	22 (1.9-113)	107	Renal replacement treatments	
	7.6 (1.5-13)	**27**	**Death from non-renal causes**	
Bone	20 (4-91)*	69	Chronic hemodialysis	Leflon et al., 1990
	2.4 ± 1.1*	**24**	**Controls**	
Bone	2.5, 5.3	2	Controls who drank Al-contaminated water for 6-7 months	Eastwood et al., 1990

[a]Note: Adapted from Nieboer et al., 1995; all values are dry weight basis except those marked with an asterisk (*) which are wet weights.

It has been suggested that two neurological diseases, Alzheimer's disease (AD) and Guam and Ku peninsula amyotrophic lateral sclerosis (ALS) might result from Al intoxication (McLachlan and De Boni, 1980). Whole brain tissue Al concentration have been reported to be increased in these two diseases (Crapper et al., 1976; Trapp et al., 1978). However, more recent analyses using a multi-technique approach found only slight elevations in Al in small bulk AD brain samples and in some AD brain cellular and subcellular components (Ehmann and Markesbery, 1994). Another study of 92 diagnosed AD patients and normal elderly subjects found no differences in frontal or temporal cortex, liver or head of femur Al concentrations (Bjertness et al. (1996). Patients with AD and ALS develop characteristic neurofibrillary tangles which lead to the

degeneration of the affected neurons (Jones and Bennett, 1986). However, the microscopic changes in the brain seen in AD patients are absent in patients suffering from dialysis dementia. In cases of dialysis dementia, Al is located mainly in the cytoplasm of the brain cells while in AD the Al is located in the nucleus. This suggests that Al metabolism in AD is different from that which occurs in encephalopathy.

In Table 6, the results of several epidemiological studies of AD and related dementia and exposure to Al in drinking water are summarized. Five of the eight studies listed show some evidence of a dose-response trend, albeit marginal in a few cases. Also in Table 6, adapted from Nieboer et al. (1995), are listed calculated odds ratios based on logistic regressions for nominal Al concentrations of 0.01, 0.05, and 0.10 mg/L to facilitate comparison of the different studies. Rate ratios of AD from multivariate Poisson regressions of AD versus Al concentration and other factors from Forbes and Gentleman (1998) are also summarized. Both odds ratios and rate ratios are relative risks used to express and quantify the relative differences observed in populations with and without the given level of exposure. An alternative risk measure is the absolute risk, e.g. the annual individual risk of mortality from smoking ten cigarettes/day is estimated at $5x10^{-3}$ (Forbes and Thompson, 1989).

Table 6. Epidemiological Studies of Exposure to Aluminum in Drinking Water

Principal study author, location, design	Health Effect	Al, mg/L, Measured; Calculated*	Odds Ratio, O. R.	95% Confidence Interval	Mantel-Haenzel Trend Test
Wettstein, 1991, Switzerland, cross-sectional	Dementia	0.004; 0.098. 0.01* 0.05* 0.10*	0.92 0.43* 0.01* 0.00*	0.66-1.29; 0.01-12.47* 0.0 > 99.99* 0.0- > 99.99*	Not determined, only two levels
Michel, 1990, 1991, France, cross-sectional	Probable Alzheimer's disease	≤ 0.01; 0.02-0.04; 0.05-0.07; ≥ 0.08. 0.01* 0.05* 0.10*	4.59 1.16* 2.10* 4.41*	0.46-9.60 1.13-1.20* 1.84-2.49* 3.39-6.19*	Positive
Martyn, 1989,1990, U.K., ecological	Probable Alzheimer's disease	< 0.01; 0.02-0.04; 0.05-0.07; 0.08-0.11; > 0.11 0.01* 0.05* 0.10*	1.42 2.89* > 99.99* > 99.99*	1.19-1.70 0.65-12.83* 0.12-> 99.99* 0.01-> 99.99*	Negative
Neri,1991, Canada, case control	Alzheimer's disease or presenile dementia	< 0.01; 0.01-0.099; 0.1-0.199; ≥ 0.2. 0.01* 0.05* 0.10*	1.33 1.02* 1.11* 1.22*	1.10-1.63 1.02-1.03* 1.08-1.14* 1.16-1.29*	Positive

Table 6 (continued). Epidemiological Studies of Exposure to Aluminum in Drinking Water

Principal study author, location, design	Health Effect	Al, mg/L, Measured; Calculated*	Odds Ratio, O.R.	95% Confidence Interval	Mantel-Haenzel Trend Test
Flaten, 1987, 1990, Norway, ecological	Senile or presenile dementia	< 0.05; 0.05-0.2; >0.2. 0.01* 0.05* 0.10*	1.21 1.04* 1.19* 1.42*	1.16-1.25 1.03-1.04* 1.18-1.22* 1.38-1.48*	Positive
McLachlan, 1995, Canada, case-control	Alzheimer's disease, autopsy verified	0.05; 0.075; 0.100; 0.125; 0.150; 0.175.	1.2 1.4 0.5 4.56 5.05 8.14	0.28-5.3 0.36-5.1 0.19-1.4 1.28-16.2 1.11-22.9 1.03-64.0	Not determined
Martyn, 1997, U.K., case-control	Alzheimer's disease	< 0.015 vs. 0.015-0.044 0.045-0.109 ≥ 0.110	[1.00] 0.90 0.72 1.11	 0.35-2.28 0.28-1.87 0.35-3.51	Not determined
Forbes, 1998, Canada, death certificates, multiple regression **	Alzheimer's disease	≤ 0.067 vs. 0.068-0.250 > 0.250	[1.00] 0.73-0.91 4.76-9.90	Not determined	Not determined

Note: Adapted from Nieboer et al., (1995); values marked with asterisks (*) are calculated O.R.s and C.I.s for three levels of exposure based on logistic regression coefficient if calculable, or O.R./(difference in concentration). (**) Multiple Poisson regressions of rate ratios of AD versus Al, source of water, silica, iron, fluoride, pH, and turbidity. Ratios ranged from 4.76 for Al only analysis to 9.90 for analysis with all seven variables. Rate ratios for analyses with two to six variables increased regularly between these respective values.

Studies in humans and animals with the ^{26}Al radioisotope and accelerator mass spectrometric detection have shown that Al can enter the central nervous system following ingestion via drinking water (Walton et al., 1995). Among the major components of the AD neurodegenerative lesions are the microtubule-associated protein tau, β-amyloid, and to a lesser extent, neurofilament proteins (Savory and Garruto, 1998). Tau is one of six isoforms of a family of highly conserved proteins that is common in neural tissue. In AD, there is a high concentration of the insoluble highly phosphorylated form of tau that comprises the hydrophobic neurofibrillary tangles (NFTs). Two hypotheses invoke either the peptide Aβ derived from amyloid precursor protein or tau as central to the development of AD. However, there is yet no well-substantiated mechanism for AD.

While early experimental studies of Al-induced neurotoxicity indicated a limited value of an animal model of AD (Katsetos et al., 1990), followup work with immunohistochemical and monoclonal antibody techniques has demonstrated that Al-induced protein aggregates in animals contain abnormal tau similar to that seen in NFTs of AD (Savory et al., 1995). Amyloid precursor protein, ubiquitin, and α_1-antichymotrypsin also show increased immunohistochemical staining intensities in neurons containing Al-induced NFTs in animals, like that seen in AD (Savory et al., 1996). An association of Al, tau, and AD was additionally strengthened by studies showing that Al intoxication is greater in aged (4-5 years old) than in young adult rabbits demonstrated by more severe neurologic symptoms and more extensive formation of intraneuronal argyrophilic aggregates (Savory, et al., 1996).

Epidemiologic data suggest that Al exposure via drinking water is associated with an increased incidence of AD (McLachlan, 1995). The data are problematic with respect to duration of exposure and show an association rather than causality, although some indication of a dose trend was seen in a number of studies as noted above (Nieboer et al., 1995) (Table 5). On the basis of the experimental database, McLachlan (1995) has recommended lowering Al exposure in municipal drinking water to below 50 µg/L, at least in the province of Ontario, Canada. Alternatively, Nieboer et al., (1995) support strict enforcement of a 100 µg/L drinking water guideline. The devastating nature of the disease, the lack of an effective treatment or prevention, and the high cost to the health care system were cited as factors weighing against the moderate cost of reducing Al in drinking water (McLachlan, 1995).

Another observation linking Al neurotoxicity to AD is that of a clinical trial involving the treatment of AD with the Al and iron chelator desferrioxamine (McLachlan et al., 1991; Savory et al., 1998). While the beneficial effects noted on AD could have been due to reducing oxidative stress-induced neuronal damage (Miranda et al. 2000, Rottkamp et al., 2000) or other beneficial effects of desferrioxamine (Long et al., 1996), a relationship with Al removal remains a possibility. As noted above, there is no substantiated mechanism for AD, however the possible role of Al as one of several factors in the tau-AD disease link, including oxidative and inflammatory processes, should not be ignored (Savory and Garruto, 1998; Campbell and Bondy, 2000).

Although it has not been established that AD is a result of Al intoxication, there is considerable evidence that Al is neurotoxic in man. Perl et al. (1982) showed prominent accumulation of Al within the nuclear region and perikaryal cytoplasm of neurofibrillary tangle-bearing neurons in patients with ALS and Parkinsonism-dementia of Guam. High levels of Al and unusually low levels of calcium and magnesium have been found in samples of drinking water and garden soils from Guam. Studies measuring trace elements in subcellular compartments demonstrated increased Al and Fe concentrations in Lewy bodies (Hirsch et al., 1991), which are a hallmark of Parkinson's disease (PD), and in the neuromelanin granules of neurons in the substantia nigra of patients with PD (Good et al., 1992a,b). Thus, Al, in conjunction with different modes of action in each disease, could contribute to the cascade of events which eventually results in neuron death in AD, PD, and the Guam PD/ALS syndrome (McLachlan, 1995).

Altmann et al. (1999) conducted a retrospective study of neurological effects in a population accidentally exposed to Al sulfate in the drinking water. In 1988 20 tons of Al sulfate were accidentally emptied into a treated water reservoir that served 20,000 residents of the Camelford area of Cornwall in the United Kingdom (U.K.). Early health complaints included rashes and gastrointestinal disturbances within days and later musculoskeletal pains, malaise, and impaired concentration and memory. Two years later 400 people were suffering from symptoms attributed to the incident. The retrospective survey involved 55 exposed adults three years after the incident

and 15 unexposed siblings of similar age. The study included an assessment of premorbid IQ with the national adult reading test, a computerized battery of psychomotor testing, and

measurement of the difference in latencies between the flash and pattern visual evoked potentials. The mean IQ was above average, 114.4, siblings, 116.3. The most sensitive of the psychomotor tests for organic brain disease was the symbol digit coding test which has a normal score of 100, with abnormal less than 85. Exposed subjects performed badly: 51.8 ± 16.6 (SE) vs. 87.5 ± 4.9 (SE) for the unexposed siblings ($p = 0.03$). The flash-pattern differences in the Al-exposed group were greater than in 42 unrelated control subjects of similar age ($p = 0.0002$). The authors concluded that the Al sulfate water contamination incident probably led to long term cerebral impairment in some of the exposed people in Camelford. Although no additional followup studies have been conducted, anecdotally, some affected individuals still have symptoms 11 years later.

Chronic Toxicity

The chronic toxicity of Al is limited almost exclusively to individuals who appear to be uniquely susceptible to its toxicity because of impaired kidney function (Nieboer et al., 1995). Patients on dialysis for chronic renal failure tend to develop osteomalacia (OM) or aplastic bone disease probably because of Al exposure. Patients undergoing chronic hemodialysis are also subject to dialysis encephalopathy (DE) also known as dialysis dementia due to Al neurotoxicity. Symptoms of DE progress from intermittent alteration of speech due to disordered muscle action (dysarthria) and difficulty in swallowing (dysphagia) to myoclonic jerks, grand mal seizures, inhalation pneumonia, and death. Autopsy results confirm high levels of Al in brain and other tissues such as liver, spleen, and bone (Nieboer et al., 1995). The association of chronic Al exposure via drinking water and AD is suggestive albeit controversial and has been discussed above.

Carcinogenicity

There is evidence that workers engaged in primary Al production have an increased risk of developing lung cancer. There were 57 cases of lung cancer (7,410 male employees) compared to an expected figure of 35.9, as estimated from the National Statistics in Norway (Andersen et al., 1982). In an American study which included 2,100 workers, an increase in cancer of the pancreas (standardized mortality ratio, SMR = 180) was observed, in addition to a moderate increase in lung cancer (SMR = 117), as well as in tumors originating from lymphatic and hemopoietic tissues (SMR = 184). Only the latter observation was significant ($p < 0.05$) (Milham, 1976). Smoking habits have not been considered in any of the studies, and in the electrolysis of Al, tar oils, fluorides, and polyaromatic hydrocarbons are formed.
Most researchers consider the effect to be the result of a simultaneous exposure to different types of tar oils during the electrochemical process and not to Al itself (Elinder and Sjogren, 1986). There are no epidemiological data available on workers exposed solely to Al or its compounds and it is not possible to conclude from the available data whether Al poses a carcinogenic hazard for humans.

Synergy and Antagonism

Fluoride (F) exerts a protective effect against the toxic effects of Al, as does SiO_2, but the effects of SiO_2 only become important at higher SiO_2 concentrations. The effects of fluoride appear to be based on mutual antagonism in competing for intestinal absorption (Kraus and Forbes, 1992). Canadian investigators studying the toxicity of Al observed that relatively high risks of a measure of mental impairment was frequently associated with relatively low SiO_2 and F in the drinking

water in different parts of Ontario (Forbes and Agwani, 1994). These authors suggest that the biotoxic effects of Al at low concentrations involve membrane interactions, which are less likely to occur in the presence of higher SiO_2 or F concentrations. Jacqmin-Gadda et al. (1996) studied cognitive impairment in 3,777 French subjects age 65 years and older. They evaluated the potential relationship of silica, Al, pH, calcium, magnesium, fluoride, zinc, copper, and iron in drinking water and cognitive impairment. An inverse relation was found between calcium concentration and cognitive impairment. No important associations were found between cognitive impairment and F, Mg, Fe, Cu, or Zn. An association between cognitive impairment and Al depended on pH and the silica level. High concentrations of Al appeared to have an adverse effect when the silica concentration was low, but there was an apparent protective effect when the pH and silica levels were high. Adverse relationships to Al were seen at low concentrations as well as high, with a threshold value as low as 3.5 µg Al/L.

Fluoride has also been observed to have synergistic interactions with the toxicity of Al. As noted above, Varner et al. (1998) found greater neuronal brain injury in rats treated with AlF_3 as opposed to equimolar NaF. While the animals were not exposed to Al without F, these effects occurred at levels far lower than those at which toxic effects were seen in other studies with various Al compounds, suggesting a synergistic effect (Table 3). In cultured rat hippocampal neurons *in vitro*, van der Voet et al. (1999) observed a potentiation of Al interference with neuronal cytoskeleton metabolism by F. In this study, effects were seen with 50 µM NaF and 12.5 µM $AlCl_3$.

The influence of Al on bone formation, which may be either inhibitory, leading to osteomalacia, or stimulatory (Gomez-Alonso et al., 1999), can also be affected by interaction with fluoride. Susa et al. (1997) observed that F action on osteoblasts and bone was potentiated by Al, which can form a complex with F (fluoroaluminate, AlFx) and activate heteromeric G proteins. They studied signaling pathways activated by AlFx in MC3T3-E1 osteoblastic and NIH3T3 fibroblastic cells. In MC3T3-E1 cells, AlFx induced a decrease in cAMP levels and an increase in MAP and p70 S6 kinase phosphorylations. These responses were partially or completely prevented by pertussis toxin, an inhibitor of GαI proteins. Caverzasio et al. (1997) extended these observations with the finding that the mitogenic effect of AlFx in MC3T3-E1 osteoblast-like cells is mediated by the activation of a pertussis toxin-sensitive Gi/o protein.

Li et al. (1990) observed an antagonistic effect of Al on acute F toxicity in male Wistar rats. The optimum ratios of Al:F for antagonism ranged from 0.3:0.7 to 0.1:0.9. In a follow up study with the perfused rat small intestine *in vivo* (Li et al., 1991), the authors observed that F absorption was not significant over 40 minutes perfusion with solutions of high (23:1) or low (4:1) Al:F ratios. However, the high Al:F ratio solution resulted in much higher Al absorption than the low Al:F solution. The authors concluded that Al inhibits F absorption and toxicity by formation of an Al fluoride complex.

Levine et al. (1990) studied the effects of diabetes mellitus and Al toxicity on myocardial calcium transport. Diabetics have an increased risk of developing renal disease, as well as congestive heart failure independent of atherosclerosis or hypertension. Al toxicity is being recognized increasingly in patients with impaired renal function and Al accumulates to a greater degree in tissues of patients with diabetes. Studies in patients with end stage renal disease have implicated excess Al as a possible cause of reduced cardiac function. In studies with rats Al alone had no effect on (Ca + Mg)-ATPase, an essential enzyme involved in myocardial calcium transport. Enzyme activities in both diabetic and diabetic + Al groups were significantly lower than controls. The calcium regulatory protein calmodulin was also significantly reduced in the diabetic and diabetic + Al groups but was not affected by Al alone. The authors concluded that diabetes mellitus is associated with decreased myocardial calmodulin activity which may

contribute to reduced sarcoplasmic reticulum (Ca + Mg)-ATPase and calcium transport activities. Aluminum toxicity decreases sarcoplasmic reticulum calcium uptake potentiating the adverse effects of diabetes.

Nielsen et al. (1988) studied the effects of dietary magnesium, manganese, and boron on rats exposed to high dietary Al. Four experiments of seven weeks duration were conducted with weanling Sprague-Dawley male rats. The dietary supplements in ppm were boron (0 and 3), $AlCl_3$ (0 and 1000), magnesium acetate (100 and 400 or 100, 200, and 400), and manganese acetate (20 and 50). High dietary Al seemed the most toxic when dietary magnesium was low enough to cause growth depression (100 ppm). High dietary Al elevated the spleen weight/body weight and liver weight/body weight ratios in magnesium deficient rats, but not in rats with adequate Mg. In contrast to the findings with magnesium, Al more markedly depressed growth in boron-supplemented than in boron-deprived rats. In the boron-deprived rats fed 400 ppm Mg, hematocrit and hemoglobin were normalized by Al. Plasma Mg was significantly depressed by high Al when the Mn supplement was 50 ppm but not when it was 20 ppm. The results indicate that magnesium, manganese, and boron influence the toxic responses to high dietary Al.

Golub et al. (1991, 1993) observed that excess dietary Al exacerbated the adverse effects of manganese in developing mice but not in adult mice. Compared to controls, Mn deficiency led to growth retardation and lower forelimb and hindlimb grip strength at 24 days postnatal. Weight was reduced 10 percent by a Mn-deficient diet ($^{-}$Mn) and 15 percent by a Mn-deficient, Al-excess diet ($^{-}$Mn $^{+}$Al). Grip strength was reduced by 28 and 42 percent, respectively. Female mice (10-12/group) were fed $^{-}$Mn or $^{-}$Mn $^{+}$Al diets over a 90-day period. The Mn deficient diet led to tissue Mn depletion but no effects on growth or behavior. Excess Al led to tissue accumulation of Al, slight increase in growth, decreased grip strength, and attenuated startle response. No interactive effects were observed.

Xie et al. (1996) found that intraneuronal Al potentiated iron-induced oxidative stress in cultured rat hippocampal neurons. The hippocampal cell cultures were established from 18-day old Sprague-Dawley rat embryos. All experiments were conducted on seven to ten-day-old cultures. The cultures were treated with 500 µM Al ± 1 µM A23187, an ionophore. Cellular Al uptake was facilitated by A23187 with intraneuronal Al concentration, determined by laser microprobe mass spectrometry, of ca. 750 µM vs. ca. 200 µM without the ionophore. In the presence of A23187, iron induced oxidative stress and Al potentiated the oxidative stress. In the absence of the ionophore, oxidative stress was only slightly greater with Al and Fe than with Fe alone, indicating that intraneuronal Al, not extracellular Al, was responsible for the potentiating effect. Aluminum alone did not significantly induce oxidative stress.

DOSE-RESPONSE ASSESSMENT

Mode of Action

Although detailed mechanisms of the toxic actions of Al are unknown, a number of possible mechanisms have been suggested. Aluminum competes with cations such as magnesium, calcium, and iron and binds to anions such as phosphate and fluoride. Such interactions can affect the uptake, distribution, and excretion of biologically important ions (Spencer and Lender, 1979; Spencer et al., 1980). Aluminum's effect on bone formation involves inhibition of parathyroid hormone secretion and possibly direct inhibition of osteoblast formation. The developmental toxicity of Al including impairments of mobility and geotaxis may result from Al

competition for essential elements uptake during development of the nervous system. The mechanisms of Al neurotoxicity have received considerable research attention. Many mechanisms have been proposed including deposition of neurofilament aggregates, alteration of cyclic nucleotide levels, altered cholinergic activity, effects on glucose metabolism via inhibition of hexokinase and glucose-6-phosphate dehydrogenase, inhibition of brain dihydropteridine reductase (DHPR), effects on signal transduction pathways, and lipid peroxidation (Strong et al., 1996). Some of these and other recent potential mechanisms are described in more detail below. At this time, it is uncertain which of these or other unknown mechanisms may be operative in Al toxicity but it seems likely that more than a single mechanism is involved.

Oxidative Injury

As noted above, the molecular mechanisms by which Al^{+3} causes neurotoxic effects are unclear. However, lipid peroxidation may play an important role. Fraga et al. (1990) evaluated brain and liver peroxidation in mice fed Al lactate at 100 (control), 500, and 1,000 ppm Al in the diet for six weeks. The highest dose produced a significant increase in brain 2-thiobarbituric acid reactive substances (TBARS) but not in liver TBARS. The results indicate a higher rate of *in vivo* production of oxidative reactions occurring in the brains of Al-treated mice. Abd El-Fattah et al. (1998) using similar methods found that brain glutathione (GSH) contents were significantly reduced in mice fed Al acetate at 6,000 ppm in the diet for two weeks. Co--administration of α-tocopherol (Vitamin E, TH) at 500 ppm diet significantly preserved the GSH content of the brain and decreased the rate of lipid peroxidation. TH terminates the chain reaction of lipid peroxidation by scavenging the propagating free radicals such as peroxy ($RO_2\bullet$) and alkoxy ($RO\bullet$) radicals of polyunsaturated fatty acids according to the following equations:

$$RO_2\bullet + TH \rightarrow RO_2H + T\bullet$$

$$RO\bullet + TH \rightarrow ROH + T\bullet$$

The tocopherol radicals ($T\bullet$) produced in these reactions are insufficiently reactive to abstract H atoms from the polyunsaturated fatty acids of membrane lipids (Abd El-Fattah et al., 1998). In rats fed 250 mg $AlCl_3$/kg-d for six weeks significant decreases in brain thiols, glutathione reductase, and adenosine triphosphatase (ATPase) were seen without an increase in lipid peroxidation (Katyal et al., 1997). Bondy et al. (1998) found increased nitric oxide synthase (NOS) in the brains of rats administered Al gluconate (3 mg Al, i.p, every third day) for 21 days. The cerebral NOS increases were not significantly affected by co-administration of iron. Although NO can act as a neuroprotective agent by virtue of its vasodilator and glutamate receptor blocking properties, excess NO levels are capable of causing damage to CNS tissue. The authors concluded that the increased NOS was largely due to the inducible glial rather than neuronal enzyme.

Swain and Chainy (1998) observed that oral administration of Al sulfate (200 and 400 mg/kg-d) to developing male White Leghorn chicks for 30 days inhibited the activity of cytosolic total and CN^- insensitive superoxide dismutase (SOD) in the cerebral hemisphere and liver. The effect was seen in the 400 mg/kg-d dose group treated for 7 or 30 days and in the 200 and 400 mg Al/kg-d groups co-administered citric acid (62 mg/kg-d) for 15 days. Significantly, no effect on either tissue lipid peroxidation was observed.

Neiva et al. (1997) observed Al^{+3} –induced human blood platelet aggregation *in vitro* and have postulated a mechanism based on lipid peroxidation. Using chemiluminescence (CL) of luminol as an index of total lipid peroxidation capacity, they established a correlation between lipid

peroxidation capacity and platelet aggregation. Al^{+3} (20-100 μM) stimulated CL production by platelets as well as their aggregation. Incubation with the antioxidants nor-dihydroguaiaretic acid (NDGA) and n-propyl gallate (NPG), which inhibit the lipoxygenase pathway, completely prevented CL and platelet aggregation. The findings suggest that Al stimulates lipid peroxidation and the lipoxygenase pathway in human blood platelets, thereby causing their aggregation.

Membrane Effects

The action of Al^{+3} in the form of Al acetylacetonate [$Al(acac)_3$] causes osmotic fragility and echino-acanthocytes formation on erythrocytes. Zatta et al. (1997) used electron spin resonance (ESR) measurements in rabbit and human erythrocyte ghosts after treating with spin probes or labels. They observed that $Al(acac)_3$ caused a reduction in membrane fluidity in rabbit erythrocytes and a reduction of rotational mobility of cell-surface sialic acid of human erythrocytes. Jones and Kochian (1997) studied Al interaction with plasma membrane lipids and enzyme metal binding sites in microsomes from wheat (*Triticum aestivum*) and liposomes from lipids of various sources including dog and bovine brains. The binding of Al to microsomes and liposomes was lipid dependent with phosphatidylinositol-4, 5-bisphosphate having the highest affinity for Al with an Al:lipid stoichiometry of 1:1. Al binding was reduced by high concentrations of Ca^{+2} (> 1 mM). The results indicate that the toxic mode of Al action is not through interaction with enzymatic catalytic metal binding sites but more likely via interaction with specific membrane lipids.

Mammalian cells take up iron via transferrin (Tf) receptor-mediated endocytosis and the Tf-independent iron uptake system (Tf-IU). Golub et al. (1996) studied the effect of Al-transferrin (Al-Tf) on transferrin receptor regulation in primary rat oligodendrocyte cultures derived from newborn rat brain. The effects of Al-Tf on ^{54}Mn and ^{59}Fe uptake were compared to those of apo-, Fe-, or Mn-Tf. Al-Tf but not equal concentrations of $AlCl_3$ or Al citrate resulted in dose-dependent increases in cellular Al. Incubation with Al- or Fe-Tf decreased ^{59}Fe uptake and incubation with Al- or Mn-Tf decreased ^{54}Mn uptake. The authors conclude that Al-Tf down regulates surface Tf receptors thereby limiting Fe and Mn uptake by this mechanism.

Tf-IU is involved in the accumulation of transition metals in a variety of cultured cells. Oshiro et al. (1998) observed that Al accumulated in primary cultures of rat brain cerebral cortical cells upregulated the Tf-IU for iron. Physiological Al levels of 20 to 200 μM were effective and Al was more effective than other metals tested (Cu, Zn, Mn, Cd, Ni, or Fe at 200 μM). The Al-induced increase was more than 2-fold over Tf-IU of Fe-loaded cells. When this experiment was repeated on human fibroblasts Al did not strongly upregulate the Tf-IU for iron and was the least effective of the metals tested. This indicates the specificity of the Al effect on the neural cells. By studying the kinetics of ^{55}Fe uptake it was found that Al increased the apparent V_{max} of iron uptake without affecting the K_m. This strongly suggests that Al is transported by the same or a similar mechanism as observed in human fibroblasts. Overall, the data support the idea that Al accumulates in the cortical cells via the Tf-IU system, which is upregulated by Al at physiological concentrations of ca. 20 μM.

Intracellular Calcium Homeostasis

Gandolfi et al. (1998) found that Al^{+3} (10-100 μM) modified Ca^{+2} uptake in the endoplasmic reticulum of rat liver cells, accelerated the release of Ca^{+2} from rat liver mitochondria, and inhibited the Ca^{+2}-ATPase pump. Further, Al was reported as activating the Na^+/K^+-ATPase and inhibiting Ca^{+2} accumulation in the ER of myometrial cells, thus interfering with the Ca^{+2} pump. Aluminum has a pH-dependent effect on the voltage-activated calcium channel current of

cultured rat dorsal root ganglion neurons (see papers cited in Gandolfi et al., 1998). Overall, the results suggest that Al^{+3} neurotoxicity may be due to a disruption of the intracellular calcium regulatory system.

Alteration of Neuronal Cytoskeletal Proteins

Perturbations of the neuronal cytoskeletal proteins (tau and/or neurofilaments) are commonly seen in several neurodegenerative diseases including AD, Parkinson's disease, diffuse Lewy body disease, Lewy body variant of AD, and amylotrophic lateral sclerosis. Wisniewski et al. (1980) demonstrated that $AlCl_3$ injected into the brains of developing rabbits produced profound neurofibrillary changes in neurons of spinal cord and cerebrum. Singer et al. (1997) demonstrated that tau is present in Al-induced neurofibrillary tangles (Al-NFT) in a rabbit model using immunocytochemical and immunoblotting techniques. The tau-immunoreactive Al-NFTs were seen in both young and mature rabbits, with both low and high doses of Al lactate. The data suggest that as the Al-NFTs in the neuron become larger, more tau is incorporated into the Al-NFTs and less tau is seen in the perikarya of the neuron (outside the Al-NFT). In a separate study in rabbits, Chambers and Muma (1997) observed that Al might have produced a transient but direct effect on neuronal gene expression. This resulted in a down-regulation of high molecular weight neurofilaments (NFH) by an inhibitory feedback mechanism induced by perikaryal accumulations of NFs. Aluminum binds directly to phosphate groups so the phosphoproteins tau and neurofilaments are likely Al binding targets. Possible metal binding sites have been located in tau by Himmler (1989). Aluminum levels are elevated in NFTs in AD and Guamanian Parkinsonism/amylotrophic lateral sclerosis. Studies in AD brain tissue and chelation studies in rat brain indicate that Al may bind directly to phosphorylated regions of tau (Shin et al., 1994). However, Singer et al. (1997) did not observe similar Al binding in rabbits. While the details of the mechanism(s) of Al-induced neurofibrillary pathology are not fully understood, they appear to involve interactions between tau and neurofilaments, their phosphorylation, and their deposition into pathological inclusions.

Animal Studies

Table 7 lists a number of animal studies considered in the dose-response for chronic Al toxicity. Most of the studies used soluble and bioavailable forms of Al with chloride, sulfate or lactate counter ions. The bioavailability of Al in the Pettersen et al. (1990) dog study may have been affected by administration of the phosphate, although there were apparent dose-dependent increases of Al in trabecular bone and brain (high dose only) in males, but not in females. Since these studies varied in duration, design, test species, and target organs, it is impossible to make any meaningful conclusions regarding speciation and toxic dose-response. AlF_3 clearly appeared to be the most toxic, with a LOAEL for brain effects of only 0.5 ppm (0.16 ppm Al) in drinking water for the rat. This finding is complicated by the fact that equivalent NaF also caused some brain effects. The chloride appeared to be next in toxicity with LOAELs in the 2 to 20 mg Al/kg-d range for rats and mice, respectively. The lactate appeared less toxic than the chloride with LOAELs in the 100 to 200 mg Al/kg-d range in mice. In general, organic carboxylic acid forms like citrate or lactate are more toxic than inorganic forms. Similarly the phosphate had a NOAEL of 27 mg Al/kg-d in the dog and appeared less toxic than the chloride, probably due to lower bioavailability. Also the studies by Schroeder and Mitchener with Al-sulfate had NOAELs of 5 ppm in water in rats and mice. The rat value is identical to the chloride NOAEL but the sulfate was administered for a longer period than the chloride (10 to 18 months versus 6 to

12 months). In order to make informative comparisons of speciation and dose-response the chronic studies would need to be done under identical dosing and evaluation protocols.

Relatively few of the chronic studies of Al toxicity in animals have employed multiple doses. The most relevant studies for chronic dose response assessment are summarized in Table 7. The most recent study by Varner et al. (1998) found that a high mortality rate resulted from chronic administration of 0.5 ppm AlF_3 to rats in drinking water. A parallel dose group receiving NaF at an equivalent F concentration did not exhibit similar mortality. However F was found to exhibit neurotoxic effects albeit less prominent than those seen with AlF_3. While an important study for indicating the potential neurotoxic hazard of Al, particularly in the AlF_3 form, the difficulty of separating effects due to Al, AlF_3, and F makes this study problematic as the basis of a PHG. Also, technical limitations make this study difficult to use. Apparently, some of the animals in both groups died from illness before their brains were fixed for histological analysis, raising doubts about the strength of the findings noted. Additionally, the amount of Al in the rat chow was not taken into account and the method of Al analysis was not standard. The study really needs to be repeated with many of these shortcomings taken into account in the study design.

The two multiple dose studies with clearly defined NOAELs, Krasovskii et al. (1979) in rats and Pettersen et al. (1990) in dogs, gave values varying by 100-fold. The mouse studies of Ondreika et al. (1966) and Golub et al. (1993) gave LOAELs of approximately 20 mg/kg-d and 200 mg/kg-d, respectively. The best single study value is the chronic LOAEL of Golub et al. (1993) of 200 mg/kg-d for immunotoxicity in mice as indicated by altered cytokines production in spleen. This study had a control Al diet level of 1.1 mg Al/kg-d, was reasonably well reported, and identified a new toxic endpoint for Al, namely immunotoxicity. Also, a recent report by Tsunoda and Sharma (1999) indicates a possible role of altered brain cytokines in the mechanism of Al neurotoxicity.

A recent workshop co-sponsored by Health Canada and U.S. EPA (Health Canada, 1997) evaluated the possibility of designing a drinking water study in animals to use as the basis of a drinking water standard. There was some disagreement that an animal study was the best course of action and that more relevant information might be obtained from the existing human database. With respect to animal studies, agreement could not be reached on a single species and, if funding were limited, the priority recommended was mice > rabbits > transgenic mice carrying risk factors for Alzheimer's disease. For the latter, three studies were suggested: transgenic mice with presenilin 1; transgenic mice with the human amyloid mutation, AB 1-48; and transgenic mice with both factors. Unfortunately, normal mice are resistant to Al-induced encephalopathy and Al uptake into the brain varies among strains. Rabbits have the advantage of being susceptible to Al intoxication and, unlike rodents, they develop Al-induced neurofibrillary pathology. It was also noted that all currently available human and animal studies had methodological shortcomings, resulting in the absence of national or international health-related guidelines for Al in drinking water.

Table 7. Chronic Animal Studies of Aluminum Toxicity for Dose-Response Assessment, applying representative uncertainty factors

Study	Species, Duration	Critical Effect	NOAEL(N), LOAEL (L)	Uncertainty factor	C, mg/L*
Ondreika et al., 1966	Mouse, 36-52 wk, 3 generations	Growth retardation, possible effect on P metabolism	19.3 mg Al/kg-d as $AlCl_3$ (L)	1,000	0.068
Krasovskii et al., 1979	Rat, 6-12 mo.	Depressed motor reflex, weak gonadotoxicity, decreased alkaline phosphatase in serum	0.25 mg Al/kg-d as $AlCl_3$ (N)	100	0.009
Schroeder and Mitchener, 1975a	Rat, 160 wk	No adverse effects, increase in total tumors probably not biologically significant	5 ppm in drinking water as $KAl(SO_4)_2$ (N)	100	0.005
Schroeder and Mitchener, 1975b	Mouse, lifetime	No adverse effects	5 ppm in drinking water as $KAl(SO_4)_2$ (N)	100	0.005
Pettersen et al., 1990	Dog, 26 wk	Decreased body weight, testis weight, hepatocyte hypertrophy	27 mg Al/kg-d as $AlNa_3(PO_4)_2$ (N)	300	0.32
Varner et al., 1998	Rat, 52 wk	Mortality, brain neuronal injury, F also neurotoxicity in separate test with NaF	0.5 ppm AlF_3 in drinking water (L)	1,000	2.5×10^{-5}
Oneda et al., 1994	Mouse, 20 mo	No tumor or other pathology; organ weight effects at all doses	85 mg/kg-d as $AlK(SO_4)_2$, (N)	100	3.0
Golub et al., 1995	Mouse, 6 mo	Reduced grip strength	100 mg Al/kg-d as Al lactate (L)	1,000	0.35
Golub et al., 1993	Mouse, 6 mo	Increased absolute and relative spleen weights, decreased spleen cell interleukin-2, interferon-g, tumor necrosis factor-a, deficiency of CD4+ T-cell populations.	200 mg Al/kg-d as Al lactate (L)	1,000	0.70

* Note: C is the calculated health protective concentration of Al in drinking water using default exposure and uncertainty factors (including 10-fold for animal to human extrapolation), and an RSC of 0.1 (see next section).

Human Studies

The most important route of human exposure to Al is oral. Results from several balance studies in humans demonstrate that the GI absorption in humans of ingested Al is low (<1 percent). Slanina et al. (1985) reported a human study in which ten healthy men consumed 23.2 mg Al twice daily during seven days where Al hydroxide was administered as 10 mL of an antacid suspension. Blood was sampled at the beginning and end of the study period. Supplementation of the diet with $Al(OH)_3$ resulted in a pronounced increase in the Al concentration in the blood. The mean of the individual differences before and after the treatment was highly significant ($p<0.00l$). Although there are no reported clinical effects due to the intake 46.4 mg Al/day, it is clear that GI absorption occurred. Excretion of Al by subjects in this study was not monitored.

Greger and Baier (1983) studied mineral metabolism in eight adult males given either 4.6 mg Al/day (control) or 125 mg Al/day (treatment) as Al lactate in the diet. Exposure continued for 20 days after which the controls and treatments were exchanged and continued for another 20 days. Each subject served as his own control. Blood samples were collected from subjects on day one of the study and on day 17 of treatment period. Feces and urine were collected. The amount of Al excreted in the urine per day, expressed as a percentage of the intake level, was 0.09 percent during 125 mg Al/day intake with diet. The apparent retention of Al by each subject was calculated by subtracting fecal and urinary losses from the measured intake of Al for each subject. The apparent average retention of Al by subjects in this study was undetectable by the balance technique. Although apparent retention was undetectable, subjects had higher ($p < 0.05$) concentrations of Al in their sera when fed the diet containing 125 mg Al than when fed the control diet containing 4.6 mg Al/day. No toxic effects were reported in the study. From this study a subchronic NOAEL/LOEL of 125 mg Al/day (1.8 mg/kg-d) can be derived based on increased serum Al. Increased blood Al is the only route by which ingested Al can bioaccumulate in the human central nervous system (Graf et al. 1981; Walton et al., 1995). The increased serum Al levels observed by Greger and Baier of 7±1 µg/L (vs. 4±1 µg/L in controls) is consistent with the mean level of 59 ± 9 µg/L serum Al for the disturbance of cerebral function in hemodialysis patients observed by Altmann et al. (1989). While the lower dose of 23.2 mg Al/d from Slanina et al. (1985) discussed above also caused a significant increase in circulating blood Al, the duration of exposure was only seven days.

CALCULATION OF PHG

From the chronic animal studies noted in Table 7, the health protective concentration of Al in drinking water, C, in mg/L can be calculated according to the following equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times W} = mg/L$$

Where:

- NOAEL/LOAEL is the no-observed-adverse-effect-level or lowest-observed-adverse-effect-level in mg/kg-d;
- BW is the average adult human body weight of 70 kg or the child weight of 10 kg;

- RSC is the relative source contribution, either defaults of 20, 40 or 80 percent, or other values if supported by data or relevant to the exposure in the critical study. In the case of Al, several studies (e.g., Greger, 1985) indicate that waterborne intake normally represents far less than 10 percent of total Al intake;
- UF -- the product of uncertainty factors. Common factors are 10 for LOAEL to NOAEL, 10 for interindividual differences, and 10 for interspecies differences;
- W is the daily water intake, a default of 2 L/day for an adult or 1 L/day for a child.

A health-protective concentration has been calculated from the animal study judged to be most suitable for risk assessment evaluation (Golub et al., 1993). In this calculation, the daily dose of 200 mg/kg-d in mice is utilized with the general default values described above. A minimal RSC of 0.1 is used for this calculation, although actual Al intake from water is likely to be less, as a fraction of total intake. The resulting calculation is:

$$C = \frac{200 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.1}{1000 \times 2 \text{ L/d}} = 0.70 \text{ mg/L}$$

As can be seen in Table 7, the calculated values of C from the animal studies range from 0.005 to 3.0 mg/L or 5 to 3,000 ppb, excluding the questionable Varner et al. value. The geometric mean of estimated health protective values from the animal studies, without the Varner et al. value, is 0.088 mg/L. All of these animal studies are judged to be less relevant for PHG calculation than the available human data.

The study of Greger and Baier (1983), discussed in both the Metabolism and Pharmacokinetics and the Dose-Response Assessment sections above, is an appropriate human investigation to utilize in derivation of the PHG. The route of administration (oral) is directly applicable to the ingestion of Al in drinking water. The dosimetry is good since each subject served as his own control. The effect observed, increased circulating Al concentrations, did not persist when the Al intake was reduced to the 4.6 mg/d control level. It is plausible that the increased blood Al is a precursor to increased Al in the human central nervous system.

No correction for relative source contribution is used in this calculation (i.e., an RSC of 1.0), since the response is based upon a bolus dose of Al in water, ignoring possible contributions from dietary or other sources of Al. The calculation uses a NOAEL/LOEL = 125 mg/d, and uncertainty factors of 10 to account for the short duration of the study (40 days including 20 days at the 125 mg Al/d level) and 10 for interindividual variation and sensitive subgroups. Therefore,

$$C = \frac{125 \text{ mg/d}}{100 \times 2 \text{ L/d}} = 0.625 \text{ mg/L} = 0.60 \text{ mg/L (rounded)} = 600 \text{ ppb}$$

where C is the concentration in water estimated to have no effect assuming an average 70-kg human ingests two liters of water per day for a lifetime.

An additional basis for the PHG is the study of Bishop et al. (1997) of Al effects in premature infants. This study found impaired neurologic development associated with parenteral administration of standard feeding solutions that provided an Al intake of 45 µg/kg-d, compared to Al-depleted solutions giving only 4.0 to 5.0 µg/kg-d. Feeding durations ranged from 6 to

16 days. For 157 infants on study, Al exposure to the standard solutions was associated with a reduction in the Bayley Mental Development Index ($p = 0.03$) of one point per day of Al exposure. Chedid et al. (1991) studied uptake of Al from antacids in similar infants and, based on increased blood Al concentration following antacid administration, estimated intestinal intake was about 0.08 to 0.16 percent. These values are similar to those seen in adults using more quantitative methods.

The health protective water concentration is calculated from this study without a relative source contribution (equivalent to an RSC of 1.0), because the parenteral solution provides the entire diet for these premature infants. A body weight value of 1.3 kg for a premature infant is used from the Bishop et al. (1997) study. The uncertainty factors are 10 for extrapolation from a LOAEL to a NOAEL, three for short-term (6 to 16 days) to longer-term exposure, and three for interindividual variation, for a total of 100. Three is chosen for interindividual variation in sensitivity (rather than the default value of 10) because the measured effect is based on: a) a sensitive subpopulation, and b) average values within that population. Fluid intake is not well characterized for premature infants, because it depends partly on composition on the feeding formula; we have selected 0.5 L as an upper-end estimate of volume consumed. A value for intestinal absorption of aluminum in water of 0.2 percent is assumed. The resulting water concentration is:

$$C = \frac{45\ \mu g/kg\text{-}d \times 1.3\ kg}{100 \times 0.5\ L/d \times 0.002} = 585\ \mu g/L = 0.6\ mg/L\ (rounded) = 600\ ppb$$

A similar toxic effect from exposure to formula would not necessarily be expected in a larger infant, because of more competent renal function in normal-term infants. However, to address potential exposure to this additional sensitive population, the corresponding health protective concentration is also estimated. For a toddler, the calculation uses a body weight of 10 kg and a default RSC of 0.2 (actual contribution would vary by age, as the infant progresses from liquid to solid foods). The uncertainty factor and assumed percent absorption of Al are left the same as in the premature infant, while the fluid consumption is assumed to be 1.0 L/day. The resulting water concentration would be:

$$C = \frac{45\ \mu g/kg\text{-}d \times 10\ kg \times 0.2}{100 \times 1.0\ L/d \times 0.002} = 450\ \mu g/L$$

The applicability of this calculation, which adds a relative source contribution, and assumes equivalent sensitivity to the premature infant population, is not clear. These human and animal studies and the health protective drinking water values derived from them are summarized in Table 8.

Table 8. Principal Studies Used in the Derivation of the Health Protective Concentration of Aluminum in Drinking Water

Study Authors	LOAEL/ NOAEL	Uncertainty Factors Product	Effect	C, mg/L
Golub et al., 1993	200 mg/kg-d LOAEL	1000	Immunotoxicity	0.700
Eight animal studies*	Various see Table 7	100 to 1000	Various - see Table 7	0.088 (geometric mean)
Greger and Baier, 1983	125 mg/d LOEL	100	Increased serum Al in adults	0.625
Bishop et al., 1997	22.5 mg/kg-d est. LOAEL	100	Neurodevelopmental toxicity for 1.3 kg infant	0.585
Bishop et al., 1997	22.5 mg/kg-d est. LOAEL	100	Neurodevelopmental toxicity for a 10 kg child	0.450

*Note: The eight studies from Table 7 are Golub et al. (1993, 1995); Pettersen et al., 1990; Ondreika et al., 1986; Krasovskii et al., 1979; Oneda et al., 1994; and Schroeder and Mitchener, 1975 a,b. Varner et al., 1998 was excluded for reasons given in the text.

Based on the human NOAEL/LOEL of 125 mg/d for increased serum Al, and an estimated LOAEL of 22.5 mg/kg-d for developmental neurotoxicity in premature infants, a PHG of 0.60 mg/L (600 ppb) was derived for Al.

The value of 0.60 mg/L derived from both the Greger and Baier (1983) study and the Bishop et al. (1997) study is similar to two other estimates noted above, for a normal child (0.45 mg/L) and the best single animal study (0.70 mg/L). It is well above the geometric mean of eight animal studies (0.088 mg/L), which are judged overall to be of less relevance than the human data. However, the estimates based on animal data incorporate a 10-fold factor for extrapolation from animals to humans; it should not be inferred that animals are more sensitive to the effects of Al than are humans. Thus, the 0.60 mg/L value can be considered representative of the values and toxic endpoints in the table. OEHHA believes this value provides a sufficient margin of safety for the large majority of the population who may be exposed to residual Al in drinking water. Premature infants are administered special formulas as described above, and are not directly exposed to tap water.

The large number of studies in experimental animals exhibiting a variety of toxic effects including growth retardation, depressed motor reflex, effects on phosphorus metabolism including decreased serum alkaline phosphatase, and immunosuppression including decreased production of cytokines, support the development of a toxicity based standard for aluminum in drinking water, although we have not based the PHG on an extrapolation from these endpoints in the animal studies.

It should be noted that the Greger and Baier (1983) study is the basis of the current California primary drinking water standard (MCL) for Al of 1.0 mg/L established in 1989. That value was derived using a relative source contribution of 17 percent and an uncertainty factor of 10 for short-term to lifetime extrapolation and interindividual variation. Since the 1989 MCL, two state drinking water statutes have been enacted which increase the level of protection of the California

public with respect to chemical contaminants in drinking water. These statutes are the Safe Drinking Water Act of 1989 and the Calderon-Sher Safe Drinking Water Act of 1996, which superceded the earlier law. Both measures require OEHHA to consider the existence of groups in the population that are more susceptible to the adverse effects of the contaminants than a normal healthy adult. The studies reviewed in this document, many published since 1988, make it clear that there are subgroups more susceptible to Al in drinking water than the average population. Susceptible subgroups may include infants, children and adults who are not receiving parenteral Al or dialysis but are at increased risk from oral Al exposure due to altered Al absorption or impaired renal clearance.

Also the concern about a causal or contributory role of chronic Al intake in healthy adults and the incidence of neurodegenerative diseases, while not conclusive, is nevertheless a possibility that cannot be wholly discounted. The law requires OEHHA to use criteria protective of public health with an adequate margin of safety in cases where the scientific evidence is unclear. For these reasons, OEHHA has chosen to reevaluate and recalculate the exposure estimate of the earlier (1988) assessment to account for lifetime exposure and variability of response within the human population (i.e., a UF of 100 overall versus 10). The decision not to use a relative source contribution for both of the critical studies (Greger and Baier, 1983; Bishop et al., 1997), reflects the design of these studies. The responses are associated with the indicated dose consumed either as a bolus or as total parenteral nutrition, independent of other Al sources. The actual contribution of Al from drinking water to total daily Al exposure at a drinking water concentration below 0.6 mg/L would be less than 10 percent, based on a total Al ingestion of 20 mg/day. However, the uncertainty in bioavailability estimates from food versus drinking water makes relative source contributions difficult to estimate. The moderate decrease in recommended safe level, compared to the 1988 Al evaluation, provides an additional margin of safety.

RISK CHARACTERIZATION

- Aluminum is neurotoxic in humans exposed via kidney dialysis, via total parenteral nutrition solutions, or in patients with renal failure. Aluminum administered orally to neonatal infants as antacids or in formulas with high Al may also be of concern with respect to Al toxicity.
- Aluminum also causes bone effects, osteomalacia, and microcytic anemia in patients exposed parenterally or suffering renal failure.
- Miners exposed to powdered Al showed cognitive deficits without other signs of toxicity (Rifat et al., 1990). However, dust-exposed workers at a German Al powder plant exhibited no cognitive deficits (Letzel et al., 2000).
- Workers in Al remelting plants exhibited neurobehavioral impairment and symptoms of pulmonary toxicity (Kilburn, 1998). Norwegian Al welders exhibited a decrease in hand steadiness with increased years of exposure (Bast-Pettersen et al., 2000).
- In animals intracerebral or subcutaneous injection of Al salts results in encephalopathy.
- Aluminum is generally poorly absorbed by the gastrointestinal tract, much less than one percent in humans (Priest et al., 1998). However since the chemical species of Al, age, renal disease, and the presence of natural chelating agents can significantly affect bioavailability of Al, in some cases, the contribution of Al via drinking water may be significant (Nieboer et al., 1995).
- High dietary exposure to Al during gestation and/or lactation causes neurodevelopmental effects in mice and rats.
- Oral administration of Al to rats has caused hematotoxicity to both mature and developing red blood cells. Severe Al intoxication is associated with anemia in humans.

- A single case report was found of high Al intake during a human pregnancy possibly resulting in severe neurodegenerative disease in the offspring.
- Toxic effects seen in subchronic and chronic oral toxicity studies in experimental animals include effects on phosphorus metabolism, decrease in serum alkaline phosphatase, neurobehavioral effects such as passive avoidance impairment, depressed motor activity, decreased body weight, immunosuppressive effects including decreased cytokine production, and brain neuronal damage.
- The bioavailability of Al can be increased by certain counter ions such as fluoride, citrate, and lactate. Al may potentiate adverse effects in certain disease states such as diabetes and magnesium deficiency. Al may also potentiate iron-induced intracellular oxidative stress.
- An epidemiology study conducted in France found that a low concentration of Al in drinking water was associated with cognitive impairment in the elderly. When the protective effects of silica were accounted for, a significant odds ratio of 3.94 (95 percent C.I. = 1.39-11.2) was obtained for an Al concentration of only 3.5 µg/L. However, when the level of silica and the pH were both high, subjects exposed to Al were less likely to be cognitively impaired than unexposed subjects (OR = 3.94 x 0.58 x 0.31 = 0.71). While this study is indicative of a low level chronic effect of Al in drinking water, the limited dosimetry makes it difficult to use in risk assessment.
- A number of epidemiological studies have observed an association of low levels of Al in drinking water and the incidence of Alzheimer's disease (AD) or other senile dementia. While a causal relation is plausible and suggested by other findings, it is inconclusive. Aluminum may be only one of many factors figuring in the causation of AD and perhaps similar diseases. A few authors have suggested that a concentration of 0.1 mg Al/L drinking water would be necessary to provide sufficient protection from AD and related effects observed in various epidemiological studies (OMH, 1993). In the absence of a conclusive causal Al/AD link it is argued by these authors that the cost of Al reduction is low compared to the high cost of the disease even if Al is only a minor factor in the disease process. However, OEHHA concludes that the evidence is insufficient to support this recommendation.
- The uncertainty factor (UF) of 100 used in calculating the PHG is thought to be sufficiently health protective based on the NOAEL/LOEL of the Greger and Baier (1983) study. In that study healthy, young male subjects were administered Al lactate in fruit juices with their meals for 20 days. Administration of Al in water between meals would have been a more useful protocol for assessing the effects of Al in drinking water. It is possible that a 100 UF is insufficient to extrapolate from 20 days exposure in healthy young men to much longer exposure periods in Al-sensitive subpopulations such as infants and adults with impaired renal function and possibly other disease states, and the elderly. Alternatively it might be argued that increased serum Al, since it is not an adverse effect per se, would not lead to increased uptake by brain or other target tissues even if the increase was maintained for years or decades. The 20-day exposure in the Greger and Baier study represents less than 0.1 percent of a human lifetime.
- A UF of 100 is also used in the evaluation of the toxicity of aluminum parenterally administered to premature infants (Bishop et al., 1997). This study shows a decrease in a sensitive indicator (the Bayley Mental Development Index) in a sensitive population, over a short exposure duration (6-16 days). It could be argued that the UF is too high (because of

the sensitive measure of effect, and a sensitive population), or too low, based on the very short exposure time. OEHHA concludes that the extrapolation from a LOAEL to a NOAEL, plus the potential for variation among infants and short exposure time, requires a UF of this magnitude. A UF of 100 and a PHG of 0.6 mg/L is judged adequate to protect infants from neurodevelopmental effects of Al.

- When an RSC of 0.2 is incorporated into a calculation for non-premature infants, the potential health-protective concentration is somewhat lower, although not significantly different from the PHG value of 0.60 mg/L. OEHHA concludes that the small contribution of Al in drinking water to total daily dose of Al makes calculations using typical RSCs of 0.1 to 0.8 to be of dubious relevance.
- An RSC of 0.1 was used in an earlier draft of this PHG, but was eliminated from the final calculation based on considerations of the design of the critical study versus normal Al intake patterns. The wide range of estimates of relative Al bioavailability from water compared to food makes specific RSC estimates tenuous. However, based on an estimated Al intake of 20 mg/day, ingestion of water containing 0.6 mg/L Al would provide less than 10 percent of the daily Al exposure. Elimination of the RSC resulted in an increase in the PHG from 0.06 mg/L in the draft to 0.60 mg/L for the final value.

OTHER REGULATORY STANDARDS

The U.S. EPA has not established a primary drinking water standard for Al. A secondary standard of 0.05 to 0.2 mg/L has been established (40 CFR 60.4, 1990).

The California Department of Health Services in 1988 established a primary MCL of 1.0 mg/L and a secondary MCL of 0.2 mg/L for Al in drinking water (California Health and Safety Code Sections 64431 and 64449).

Health Canada has adopted an operational guidance value for Al in drinking water of less than 0.1 or 0.2 mg/L. The former value applies to water treatment plants using Al-based coagulants and the latter value for other types of treatment systems. (See Health Canada, 1996 for proposal, final document in press.)

The Province of Ontario, Canada has established the operational drinking water guidance value of 0.1 mg/L.

The WHO has established a drinking water guideline of 0.2 mg/L Al for aesthetic quality.

OSHA has set limits for Al inhalation based on an eight hour time weighted average exposure of 15 mg/m^3 for total Al dust and 5 mg/m^3 for respirable fraction (29 CFR 1910.1000, 1974).

The State of Arizona has established a drinking water guideline of 0.073 mg/L for Al (ATSDR, 1999).

The State of Maine has established a drinking water guideline of 1.43 mg/L for Al (ATSDR, 1999).

ATSDR has derived an intermediate duration oral exposure minimum risk level (MRL) of 2.0 mg/kg-d for Al.

ATSDR has determined no minimum risk levels (MRLs) for any exposure duration for inhalation of Al (ATSDR, 1999).

U.S. EPA has not classified Al for human carcinogenicity (IRIS, 1997).

The American Conference of Governmental and Industrial Hygienists has determined that Al is not classifiable with respect to carcinogenicity, Group A4 (ACGIH, 1996).

The International Agency for Research on Cancer has classified Al production as Group 1 indicating that there is a causal relationship between human exposures (via inhalation) and cancer (IARC, 1984, 1987b).

U.S. EPA regulates Al and Al compounds under the Clean Air Act, but these agents are not designated as hazardous air pollutants.

U.S. EPA regulates Al under the Clean Water Act. The acute ambient water quality criterion for fresh water is 0.75 mg/L; the chronic criterion is 0.087 mg/L.

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