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For Review Only

Public Health Goal for
ALUMINUM
In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

October 1999

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LIST OF CONTRIBUTORS

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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) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. 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 solely on health effects without regard to cost impacts 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 adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

DRAFT

PHGs adopted 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.

DRAFT

TABLE OF CONTENTS

LIST OF CONTRIBUTORS	II
PREFACE.....	III
TABLE OF CONTENTS	V
PUBLIC HEALTH GOAL FOR ALUMINUM IN DRINKING WATER	1
SUMMARY	1
INTRODUCTION	1
CHEMICAL PROFILE.....	2
Chemical Identity.....	2
Physical and Chemical Properties	2
Production and Uses	3
ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE.....	3
Air	3
Soil.....	3
Water.....	3
Food.....	4
Other Sources.....	4
METABOLISM AND PHARMACOKINETICS.....	5
Absorption	5
Distribution.....	6
Metabolism.....	8
Excretion.....	8
Physiological/Nutritional Role	9
Physiologically Based Kinetic Models.....	9
TOXICOLOGY	10
Toxicological Effects in Animals.....	10
Acute Toxicity.....	10
Subchronic Toxicity.....	11
Genetic Toxicity.....	15
Hematotoxicity.....	16

DRAFT

Developmental and Reproductive Toxicity	16
Immunotoxicity	18
Neurotoxicity.....	18
Chronic Toxicity	19
Carcinogenicity	21
Toxicological Effects in Humans	21
Acute Toxicity.....	21
Subchronic Toxicity	22
Genetic Toxicity.....	23
Hematotoxicity	23
Developmental and Reproductive Toxicity	24
Immunotoxicity	24
Neurotoxicity.....	24
Chronic Toxicity	30
Carcinogenicity	31
Synergy and Antagonism.....	31
DOSE-RESPONSE ASSESSMENT	32
Mode of Action.....	32
Oxidative Injury	33
Membrane Effects	34
Intracellular Calcium Homeostasis	35
Alteration of Neuronal Cytoskeletal Proteins	35
Animal Studies.....	35
Human Studies	38
CALCULATION OF PHG	38
RISK CHARACTERIZATION	42
OTHER REGULATORY STANDARDS	43
REFERENCES.....	45

DRAFT

PUBLIC HEALTH GOAL FOR ALUMINUM IN DRINKING WATER

SUMMARY

A proposed PHG was derived from data in a 40-day aluminum (Al) balance study in humans (Greger and Baier, 1983). In this 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 aluminum. Assuming a NOAEL/LOEL of 125 mg/day and an uncertainty factor of 100 with 10 percent of the ingested total daily Al attributed to water, a PHG of 0.06 mg/L (60 ppb) was determined based on the pharmacologic effect of increased serum Al. Because of the prevalence of aluminum in foods, consumer products, pharmaceuticals and the environment, it is impossible for humans to avoid exposure to aluminum compounds. Aluminum in potable drinking water constitutes a small fraction of the total daily intake (<10 percent). The proposed value of 60 ppb is further supported by an estimated LOAEL of 22.5 mg/kg-d for developmental neurotoxicity in premature infants (Bishop et al., 1997) and a number of animal studies indicating 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, although a causal link has not been established and other factors are likely to be involved in AD. Aluminum is neurotoxic in humans exposed parenterally, via the oral route in those suffering renal disease, or potentially in neonates receiving formulas with excess aluminum.

The current State MCL for aluminum in drinking water is 1.0 mg/L. The U.S. Environmental Protection Agency has not established a primary or health-based MCL for aluminum although a secondary MCL of 0.05 to 0.2 mg/L has been established based on esthetic concerns.

INTRODUCTION

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

Aluminum is the most abundant metal in the earth's crust and third most abundant of all elements. Naturally occurring aluminum compounds have limited solubility in water at neutral pH, but solubility increases markedly with increasing or decreasing pH. Domestic tap water may contain aluminum 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 U.S., the maximum aluminum concentration reported in finished water where an aluminum compound was used as a coagulant was 5.35 mg/L whereas the maximum aluminum level reported in finished water not using an aluminum 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 absorption (GI) of aluminum is very low (<1 percent). Aluminum is known to react with phosphorus in the GI tract forming insoluble aluminum phosphate complexes, thus reducing phosphate absorption. Consequently, aluminum

DRAFT

has often been used therapeutically to prevent hyperphosphatemia in uremic patients. Consequences of prolonged aluminum intake (>1 g Al/day) in these cases may be phosphate depletion, hypercalciuria, bone resorption and possibly osteomalacia. There is no direct evidence that aluminum 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 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 association of oral Al intake, particularly via drinking water, and Alzheimer's disease and related dementia is suggestive but not established. While the proposed PHG is protective of the general population, there may be sensitive subgroups; e.g., those with impaired renal function, for which prolonged exposure at the PHG level may not be fully protective. In these case 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 water aluminum would usually constitute a small fraction of the overall aluminum intake.

CHEMICAL PROFILE

Chemical Identity

Aluminum (Al) is a member of group III A of the periodic table, with atomic number 13 and atomic weight 26.97.

Physical and Chemical Properties

Aluminum is a silver-white, malleable, and ductile metal and 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 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, Al_2O_3 . Pure Al_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 Al^{+3} provides an effective means for Al absorption

DRAFT

into the body from the GI tract. Driscoll & Schecher (1989) have reviewed the aqueous chemistry of aluminum.

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 aluminum reduction (ATSRD, 1997). In 1995, domestic aluminum production totaled 3.4 million tons (ATSDR, 1997). 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.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Ambient air concentrations of aluminum were reported to range from 0.01 to 0.54 µg/m³ in Canada. Occupational air concentrations are much higher at 1.0 to 2.0 mg/m³ (Van Oostdam et al., 1990).

Soil

Aluminum is the third most abundant element of the earth's crust constituting 8.2 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 aluminum either naturally or because Al has been added as a flocculant in the treatment process. Al₂(SO₄)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 aluminum 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

DRAFT

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 Al₂(SO₄)₃ had Al concentrations >0.05 mg/L. Al 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 U.K. 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 aluminum (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/100g and ingestion of 8 oz of tea with each meal would add 1 to 3 mg Al to the diet (Greger, 1985). 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. Al 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 aluminum 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

DRAFT

than 1 mg/100 g for 85 percent of foods. Acidic foods leach out the largest amounts of aluminum (Nieboer et al., 1995). Kandiah and Kies (1994) observed that canned soft drink fed rats 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 6-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 Aluminum lactate). 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 $4 \pm 1 \mu\text{g/L}$. This level rose significantly to $7 \pm 1 \mu\text{g/L}$ when the subjects were fed the 125 mg Al/day diet. Urinary Al levels also increased from 24-58 $\mu\text{g Al/day}$ for the control diet to 47-212 $\mu\text{g Al/day}$ for the test diet of 125 mg Al/day. The mean fecal loss of Al for both groups of men was $\sim 4.6 \text{ mg/day}$ during ingestion of the control diet and $\sim 125 \text{ mg/day}$ 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 10 healthy subjects who received 46.4 mg Al in 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 $\mu\text{g/L}$) were seen after ingestion of either citric acid or Al (OH)₃: 9 and 12 $\mu\text{g/L}$, 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 $\mu\text{g/L}$.

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

DRAFT

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/day.

Priest et al. (1998) measured uptake of a single oral dose of 100 Bq ²⁶Al in tap water in two male adults. Gastro-intestinal uptake determined by urinary excretion over a seven days observation period averaged 0.22 percent of dose. Nearly 100 percent of the dose was recovered in the feces. These authors concluded that aluminum present in most water supplies is unlikely to contribute more than 1 percent of a typical daily uptake of 10 µg from food.

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 no evidence that Al is absorbed through the skin and Al has not been found to penetrate the epidermis (Reller and Luedders, 1977).

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 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 ²⁶Al gavaged rats were a poor measure of GI tract absorption. 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 ²⁶Al 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 1).

DRAFT

Table 1. Concentrations of Aluminum in Human Tissues (mg/g dry weight)

Tissue	USA, Alfrey (1980)	USA, Alfrey et al., (1980) (N = 16)	Australia, Alfrey et al. (1980) (N = 21)
Heart	1.1 ± 0.65 (36)*	1.0 ± 0.8	1.2 ± 0.51
Lung	56.0 ± 63.0 (34)	43.0 ± 43.0	67.0 ± 75.0
Spleen	3.8 ± 5.0 (35)	2.6 ± 2.1	3.3 ± 2.4
Liver	4.0 ± 1.7 (40)	4.1 ± 1.7	4.0 ± 1.8
Muscle	1.2 ± 1.0 (48)	1.2 ± 1.2	1.2 ± 0.7
Bone	3.3 ± 2.9 (8)	3.3 ± 2.9	5.6 ± 2.3
Brain grey matter	2.2 ± 1.3 (10)	2.4 ± 1.3	ND

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

The highest concentrations 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). 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 $3.3 \pm 2.9 \mu\text{g Al/g dry wt.}$ of bone were reported as normal for individuals not on a high Al intake. For those in the high intake group, bone Al of $124.6 \pm 62.9 \mu\text{g Al/g dry wt.}$ was reported for dialysis patients and $24.1 \mu\text{g Al/g dry wt.}$ 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 10 patients with Alzheimer's disease. Of 585 samples, 28 percent had an Al concentration greater than the normal upper limit of $4 \mu\text{g/g}$. 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 $2.7 \mu\text{g/g}$ brain in non-dialyzed uremics, $4.4 \mu\text{g/g}$ in dialyzed uremics and $15.9 \mu\text{g/g}$ 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 $^{26}\text{Al}/^{27}\text{Al}$. 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

DRAFT

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 aluminum 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 aluminum toxicity.

Minami et al. (1996) have observed an age-dependent accumulation of aluminum 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 K_a of 10^{20} M^{-1} for the reaction: $\text{Al}^{+3} + \text{apotransferrin} \rightarrow \text{Al}^{+3}\text{-transferrin}$. 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 aluminum (Al^{+3}) has a very high affinity for proteins, polynucleotides, 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} . 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 hr 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 $\mu\text{g}/\text{Al}/\text{kg}$ and intravenous (i.v.) doses of 10, 100,

DRAFT

1000, and 12,000 $\mu\text{g Al/kg}$. 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 $\mu\text{g/kg}$ 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 $\mu\text{g Al/kg}$, 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 $\mu\text{g/kg}$ i.g. dose no absorption was detected. The i.g. dose of 12,000 $\mu\text{g/kg}$ resulted in a maximum blood Al level of 47.9 ± 12.4 $\mu\text{g/L}$ 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.

From human dietary balance studies it is clear that most of the ingested Al is unabsorbed. Al 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 $\mu\text{g/L}$ to 30 $\mu\text{g/L}$ (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 (1-2L), 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.

Physiological/Nutritional Role

Aluminum has not been shown to have a definite biological function. Overall the properties of Al^{+3} make it incompatible with fundamental life processes (Ganrot, 1986).

Physiologically Based Kinetic Models

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

DRAFT

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Mortality studies for aqueous solutions of $\text{Al}_2(\text{SO}_4)_3$ 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 2.

Table 2. Acute Toxicity of Aluminum Compounds

Compound	Route	Species	LD_{50} (g/kg)	Reference
$\text{Al}_2(\text{SO}_4)_3$	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
	$\text{Al}(\text{NO}_3)_3$	Intraperitoneal	Mouse	0.32
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 $\text{Al}_2(\text{SO}_4)_3$ in their drinking water (Berlyne et al., 1972) died within 3 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

DRAFT

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 aluminum lactate, aluminum citrate, sodium lactate, sodium citrate, sodium acetate, and sodium chloride. Only Aluminum lactate or aluminum lactate in combination with aluminum 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 Aluminum 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, intermediate filaments).

Subchronic Toxicity

A summary of subchronic and chronic toxicity studies is given in Table 3.

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 bw 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 bw, 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/wk) with 100 mg Al/kg bw in the form of $\text{Al}(\text{OH})_3$ (9 wk) or aluminum citrate (4 wk), with citric acid (4 wk) or with tap-water (control, 9 wk). 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 $\text{Al}(\text{OH})_3$. 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 aluminum lactate, aluminum palmitate, aluminum phosphate or $\text{Al}(\text{OH})_3$ in either reagent grade or desiccated gel forms for 18 days. Rats fed $\text{Al}(\text{OH})_3$ 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 tibiae 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 Al/g). These moderate levels of dietary aluminum 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 aluminum citrate by gavage in a single daily dose of 1.0 $\mu\text{mol/g}$ bw (27 mg Al/kg-d) or received no treatment. In a second series, five rats were exposed to 100 mmol aluminum 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 ($p < 0.0$). 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.

DRAFT

Table 3. 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 •18 H ₂ O	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
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	30d	Neurobehavioral effects, passive avoidance impairment, increase in muscarinic receptor number	Connor et al., 1988
Rat, M, 8/group AlCl ₃	2000 ppm Al in feed	67d	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	67d	Decrease in serum triglycerides, hepatic glycogen in adults	Sugawara et al., 1988b
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.
Rat, MF 8/sex/group, AlCl ₃	0.2% Al, in feed	12 wk	Depressed motor activity	Commissaris et al., 1982

DRAFT

Table 3 (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
Rat, F 10/sex/group, Al(NO ₃) ₃	0, 360, 720, 3600, 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 concn., 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, 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
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

DRAFT

Table 3 (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
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 and 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 lipid peroxidation in brain ($p < 0.01$). 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	Significantly depressed motor reflex at 2.5 mg/kg-d. Weak gonadotoxic effects. Decreased alkaline phosphatase in serum, transient decrease at 0.25mg/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
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

DRAFT

Table 3 (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, 54/sex/group KAl(SO ₄) ₂	0, 5ppm 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	Neuronal injury in brain, reduction in neuronal density in the neocortex of the left hemisphere; lesser effects seen 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, Aluminum 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 μ M 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 aluminum 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 AlCl₃/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 vs controls at 7, 14, and 21 days ($p < 0.01$). Heme oxygenase in kidney was not significantly affected by treatment with AlCl₃. 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 the occurrence of 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. vs. 1.05 p.o. and decreases in serum Fe were seen at 0.015 i.p. vs. 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. vs. 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 aluminum 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 AlCl₃ 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. Aluminum 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. AlCl₃ injections (3-18 mg) in eggs are embryo-lethal and cause malformations in chick embryos (Gilani and Chatzinoff, 1981); however, the relevance of the chick embryo response is not necessarily related to the 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.

DRAFT

Golub et al. (1987) have shown developmental retardation in offspring of mice following oral exposure to aluminum during gestation, parturition and lactation. Female mice fed aluminum 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 aluminum lactate solution at 10, 20 or 40 mg Al/kg bw 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 $\text{Al}(\text{NO}_3)_3$ 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 $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ 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 each day for 6 months (Krasovskii et al., 1979), decreased testicular weights (in rats and mice) and seminiferous tubule necrosis in rats injected subcutaneously for 30 days with 2.67 nmol (0.14 μg Al)/kg-d $\text{Al}_2(\text{SO}_4)_3$ (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. aluminum 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 neonatal rabbits 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 (8 in mice, 5 in rats, 1 in rabbit) including four different Al compounds (aluminum chloride, aluminum hydroxide, aluminum citrate, aluminum 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

DRAFT

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 aluminum does not affect reproduction (ATSDR, 1997). However, Bataineh et al. (1998) report adverse effects of subchronic administration of aluminum in drinking water on the sexual behavior of male rats. Ten adult male Sprague-Dawley rats (300 g) were administered AlCl₃ 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 and 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 aluminum 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.

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 aluminum 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

DRAFT

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 aluminum sulfate during gestation and were followed from birth to adulthood. Exposure routes were either by i.p. injection (200 mg/kg $\text{Al}_2(\text{SO}_4)_3$) 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 aluminum sulfate doses. Al 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 synaptosomal acetyl-CoenzymeA (CoA). Simultaneously, a 61 percent inhibition of Ca-evoked ACh release was observed at 0.25 mM Al, with a significant decrease seen at 0.05 mM Al ($p < 0.05$). Omission of inorganic phosphate from the medium abolished the suppressive effects of aluminum on acetyl-CoA content and Ca-evoked ACh release. It seems likely that the $\text{Al}(\text{PO}_4)\text{OH}^-$ complex may be the active form of Al. 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 functionally important quantal transmitter pool (Bielarczyk et al., 1998). It would be useful to confirm these findings with a more soluble salt of Al than the chloride.

Chronic Toxicity

Ondreika et al. (1966) administered AlCl_3 to groups of 10 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 vs. 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 of months 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

DRAFT

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 aluminum sulfate ($\text{KAl}(\text{SO}_4)_2$) in concentrations of 0 and 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 that 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 exposed to 0 or 5 mg Al/L as $\text{KAl}(\text{SO}_4)_2$ 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 aluminum 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 aluminum 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 aluminum 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 $500 \mu\text{g AlF}_3/\text{L}$ 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 aluminum 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. Aluminum increased

DRAFT

the ratio of the maximum tubular transport of phosphate to glomerular filtration rate (TRPi/GFR, $\mu\text{g}/\text{mL}$): 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 aluminum 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/m³ aluminum chlorhydrate (Al₂(OH)₅Cl) for 6 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/m³ and in 100 percent of animals at 25 mg Al/m³. 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/m³ 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 lymphnode. 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/m³ as alumina fibers (Al₂O₃) for 86 weeks (35 hr/wk). In a parallel exposure group with 50 rats exposed to 4.57 mg/m³ chrysotile asbestos for 77 weeks, both benign and malignant pulmonary neoplasms were seen.

Schroeder and Mitchner (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.

Toxicological Effects in Humans

Acute Toxicity

Despite widespread human exposure to aluminum 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, aluminum 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 $\mu\text{mol}/\text{L}$ on therapy vs. 0.64 ± 0.33 $\mu\text{mol}/\text{L}$ 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.

DRAFT

Aluminum oxide or finely powered Al metal reacts slowly to form $\text{Al}(\text{OH})_3$. 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 aluminum 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 aluminum 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 $\text{Al}(\text{OH})_3$ 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 aluminum 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

DRAFT

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 aluminum 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 parenterals (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 aluminum 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 synthesis in Friend erythroleukemia cells and in bone marrow cells (Abreo et al., 1990).

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 feed 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 (\pm 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. $45 \mu\text{g Al/kg-d}$). 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 aluminum 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 aluminum or aluminum compounds affect reproduction.

Immunotoxicity

No studies were located that evaluated the effect of aluminum or aluminum compounds on the human immune system. A few reports indicate a possible link between aluminum 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 aluminum hydroxide added to the vaccine (aluminum-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 aluminum-precipitated antigen extracts (Lopez et al., 1994). In addition, contact dermatitis was observed to be aggravated by systemic aluminum from toothpaste (Veien et al., 1993). As noted above aluminum affects cytokines in mice exposed orally to aluminum.

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

DRAFT

failure who were given oral Al (OH)₃ (Griswold et al., 1983). Neurotoxicity has also been observed in premature infants receiving intravenous-feeding solutions (Bishop et al., 1997).

Nieboer et al. (1995) have summarized brain and bone Al concentrations in a number of studies of DE patients and control subjects (Table 4). 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 aluminum. 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 4. Aluminum Levels in Brain and Bone in Renal Failure Patients and Controls^a.

Tissue	Al Level mean ± SD mg/g (range)	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	

DRAFT

Table 4 (continued). Aluminum Levels in Brain and Bone in Renal Failure Patients and Controls^a.

Tissue	Al Level mean \pm SD mg/g (range)	Number of Subjects	Health Status	Reference
Bone (trabecular)	98 \pm 60	16	Uremia with dialysis	
	37	3	Uremia without dialysis	
	2.4 \pm 1.2	9	Controls	
Brain	16 \pm 11	16	Dementia	McDermott et al., 1978
	4.4 \pm 2.7	11	Uremia with dialysis	
	2.7 \pm 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 \pm 6	40	Controls	
Bone	20 \pm 13	6	Premature infants on i.v. > 3 wk	Sedman et al., 1985
	2.0 \pm 1.4	17	Controls with limited or no i.v.	
Bone	2.7 \pm 2.0 (0.5- 7.9)	15	Renal failure without dialysis	Van de Vyver et al., 1986
	35 \pm 29 (3.2-85)	27	Renal failure with dialysis	
	2.0 \pm 0.4	10	Controls	
Bone	22 \pm 11	15	Hemodialysis patients	Sebert et al., 1986
	14 \pm 5	12	Hemofiltration patients	
	2 \pm 1	7	Non uremic corpses	

DRAFT

Table 4 (continued). Aluminum Levels in Brain and Bone in Renal Failure Patients and Controls^a.

Tissue	Al Level mean \pm SD mg/g (range)	Number of Subjects	Health Status	Reference
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 \pm 1.1*	24	Controls	
Bone	2.5, 5.3	2	Controls who drank Al- contaminated water for 6-7 mo	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 (Crappier et al., 1976; Trapp et al., 1978). 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 5 the results of several epidemiological studies of AD and related dementia and exposure to aluminum 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 5, 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 10 cigarettes/day is estimated at 5×10^{-3} (Forbes and Thompson, 1989).

DRAFT

Table 5. 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 determin-ed ,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
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

Table 5 (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
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 vs. 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 ²⁶Al 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), follow up work with immunohistochemical and monoclonal antibody techniques has demonstrated that Al-induced protein aggregates in animals

DRAFT

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). The association of Al, tau, and AD is additionally strengthened by studies showing that Al intoxication is greater in aged (4-5 yr 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 five of eight studies as noted above (Nieboer et al., 1995)(Table 5). On the basis of the experimental database, McLachlan (1995) has recommended a lowering aluminum exposure in municipal drinking water to below 50 $\mu\text{g/L}$, at least in the province of Ontario, Canada. Alternatively, Nieboer et al. (1995) support strict enforcement of a 100 $\mu\text{g/L}$ 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 aluminum 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 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, it seems more likely to have been related to Al removal. 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 should not be ignored (Savory and Garruto, 1998).

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, aluminum, in conjunction with different modes of action in each disease, may contribute to the cascade of events which eventually results in neuron death in AD, PD, and the Guam PD/ALS syndrome (McLachlan, 1995).

Chronic Toxicity

The chronic toxicity of aluminum 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 aluminum exposure. Patients undergoing chronic hemodialysis are also subject to dialysis encephalopathy (DE) also known as dialysis dementia due to aluminum 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

DRAFT

chronic Al exposure via drinking water and Alzheimer's disease 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 (7410 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 2100 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 SiO₂, but the effects of SiO₂ only become important at higher SiO₂ concentrations. Canadian investigators studying the toxicity of aluminum observed that relatively high risks of a measure of mental impairment was frequently associated with relatively low SiO₂ 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 SiO₂ or F concentrations. Jacqmin-Gadda et al. (1996) studied cognitive impairment in 3777 French subjects age 65 years and older. They evaluated the effects of silica, aluminum, 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 a protective effect when the pH and silica levels were high. Adverse effects of Al were seen at low concentrations as well as high, with a threshold value as low as 3.5 µg Al/L.

Levine et al. (1990) studied the effects of diabetes mellitus and aluminum 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. Aluminum 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 aluminum 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 in by Al alone.

DRAFT

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 aluminum. Four experiments of seven weeks duration were conducted with weanling Sprague-Dawley male rats. The dietary supplements in ppm were boron (0 and 3), AlCl₃ (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 aluminum.

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 lead to growth retardation and lower forelimb and hindlimb grip strength at 24 days postnatal. Weight was reduced 10 percent by Mn deficient diet (Mn) and 15 percent by 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, slight increase in growth, decreased grip strength, and attenuated startle response. No interactive effects were observed.

Xie et al. (1996) found that intraneuronal aluminum potentiated iron-induced oxidative stress in cultured rat hippocampal neurons. The cell cultures of hippocampus were established from 18-day old Sprague-Dawley rat embryos. All experiments were conducted on 7-10 -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

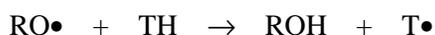
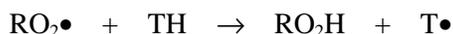
Although detailed mechanisms of the toxic actions of aluminum are unknown, a number of possible mechanisms have been suggested. Aluminum competes with cations such as magnesium, calcium, and iron and binds to anions such as phosphate and fluoride. Such interactions can affect the uptake, distribution, and excretion of biologically important ions (Spencer and Lender, 1979; Spencer et al., 1980). Aluminum's effect on bone formation

DRAFT

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, 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 aluminum lactate at 100 (control), 500, and 1000 μg Al/g 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 aluminum acetate at 6000 μg /g diet for two weeks. Co-administration of α -tocopherol (Vitamin E, TH) at 500 μg /g 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:



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 Aluminum 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 the neuronal enzyme.

Swain and Chainy (1998) observed that oral administration of aluminum 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.

DRAFT

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 aluminum acetylacetonate ($\text{Al}(\text{acac})_3$) 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 $\text{Al}(\text{acac})_3$ 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 aluminum 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. Aluminum binding was reduced by high concentrations of Ca^{+2} ($> 1 \text{ mM}$). 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 aluminum 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 up regulated 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 up regulate 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 up regulated 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 $\text{Na}^{+}/\text{K}^{+}$ -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 amyotrophic 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 aluminum 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 aluminum 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). Al levels are elevated in NFTs in AD and Guamanian Parkinsonism/amyotrophic 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

Relatively few of the chronic studies of aluminum toxicity in animals have employed multiple doses. The most relevant studies for chronic dose response assessment are summarized in Table 6. 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

DRAFT

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 aluminum in the rat chow was not taken into account and the method of aluminum 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 comparable LOAELs of approximately 20 mg/kg-d. The geometric mean of the rat and dog NOAELs of 2.3 mg/kg-d is similar to the projected NOAELs from the mouse studies (22 mg/kg-d/10 UF = 2.2 mg/kg-d). The best single study value is the chronic LOAEL of Golub et al. (1993) of 24.4 mg/kg-d for immunotoxicity in mice. 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 aluminum, namely immunotoxicity. However in general animal toxicity studies may be of limited value in assessing risks of human exposure to aluminum.

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.

DRAFT

Table 6. Chronic Animal Studies of Aluminum Toxicity for Dose-Response Assessment

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/kg-d (L)	1000	0.068
Krasovskii et al., 1979	Rat, 6-12 mo.	Depressed motor reflex, weak gonadotoxicity, decreased alkaline phosphatase in serum	0.25 mg/kg-d (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 (N)	100	0.005
Schroeder and Mitchener, 1975b	Mouse, lifetime	No adverse effects	5 ppm in drinking water (N)	100	0.005
Pettersen et al., 1990	Dog, 26 wk	Decreased body weight, testis weight, hepatocyte hypertrophy	27 mg/kg-d (N)	300	0.32
Varner et al., 1998	Rat, 52 wk	Mortality, brain neuronal injury, F also exhibited neurotoxicity in separate test with NaF	0.5 ppm AlF ₃ in drinking water (L)	1000	2.5 x 10 ⁻⁵
Golub et al., 1995	Mouse, 6 mo	Reduced grip strength	100 mg/kg-d (L)	1000	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+ cells in T-cell populations.	24.4 mg/kg-d (L)	1000	0.085

* Note: C is the calculated health protective concentration of Al in drinking water (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 aluminum 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<0.001). 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 aluminum 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 of 125 mg Al/day (1.8 mg/kg-d) can be derived based on increased serum Al. Increased blood aluminum is the only route by which ingested Al can bioaccumulate in the human central nervous system (Graf et al. 1981; Walton et al., 1995). 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 6 the safe levels of Al in drinking water, C, in mg/L can be calculated according to the following equation:

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

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;

DRAFT

- RSC is the relative source contribution, either defaults of 20, 40 or 80 percent, or other values if supported by data. In the case of aluminum several studies (e.g., Greger, 1985) indicate that waterborne intake represents less than 10 percent of total Al intake so an RSC of 10 percent is employed, as 0.1 in the equation above;
- UF the product of uncertainty factors. Those employed here are 10 for LOAEL to NOAEL, 10 for interindividual differences, and 10 for interspecies differences.
- W is the daily water intake of 2L/day for an adult or 1 L/day for a child.

As can be seen in Table 6, with exception of the Varner et al. (1998) study with AlF_3 , the calculated values of C range from 0.005 to 0.32 mg/L or 5 to 320 ppb. The most suitable study of Golub et al. (1993) gives a value of 85 ppb:

$$C = \frac{24.4 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.1}{1000 \times 2\text{L/d}} = 0.085 \text{ mg/L}$$

For comparison, the geometric mean of the animal studies, without the Varner et al. value, is 0.039 mg/L.

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 upon which to base a calculation of the PHG. The route of administration (oral) is directly applicable to the problem of Al in drinking water. The dosimetry is good since each subject served as his own control. The effect observed, increased circulating Al concentrations, is a pharmacologic rather than toxicologic response and did not persist when the Al intake was reduced to the 4.6 mg/d control level. It is plausible the increased blood aluminum is a precursor to increased aluminum in the human central nervous system.

A value of 0.10 is incorporated into the calculation to adjust for the relative contribution of Al in California drinking water to the total daily oral intake:

$$\text{NOAEL/LOEL} = 125 \text{ mg/day};$$

10 percent relative source contribution of total daily Al from drinking water;

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.

$$C = \frac{125\text{mg/d} \times 0.10}{100 \times 2\text{L/d}} = 0.0625 \text{ mg/L} = 60 \text{ ppb (rounded)}$$

DRAFT

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 alternative calculation could be based on the study of Bishop et al. (1997) that 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 6-16 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. 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 0.08-0.16 percent. These values are similar to those seen in adults using more quantitative methods.

For a premature infant the health protective water concentration would be calculated as follows:

$$C = \frac{45 \mu\text{g/kg-d} \times 1.3 \text{ kg} \times 0.1}{300 \times 0.5 \text{ L/d} \times 0.002} = 20 \mu\text{g/L}$$

For a larger child (toddler) the calculation would be:

$$C = \frac{45 \mu\text{g/kg-d} \times 10 \text{ kg} \times 0.1}{300 \times 1.0 \text{ L/d} \times 0.002} = 75 \mu\text{g/L}$$

In these calculations the parenteral LOAEL for neurodevelopmental toxicity is 45 µg/kg-d (oral LOAEL estimate 0.045 mg/kg-d/0.002 = 22.5 mg/kg-d), the child body weights are 1.3 kg (Bishop et al., 1997) or 10 kg, the Relative Source Contribution is 10 percent (0.1), the uncertainty factors are 10 for LOAEL to NOAEL, three for short term (6-16 d) to longer term exposure, and ten for interindividual variation, water intake is assumed to be either 0.5 L/d for the premature infant or 1.0 L/d for a larger child, and intestinal absorption of Al from drinking water is assumed to be 0.2 percent (0.002). The use of a three fold uncertainty factor for longer-term exposure is justified because little is known about the influence of duration of aluminum exposure on the early human post natal development. Similarly even though the Bishop et al. study involved 157 infants an uncertainty factor of 10 seems appropriate for interindividual variation in view of the potentially greater sensitivity and variation in sensitivity of developing children. The calculated intestinal absorption value for the normal infant is not significantly different from the adult value based on increased blood Al from 20 days oral intake of aluminum lactate (above). These studies and the health protective drinking water values derived from them are summarized in Table 7.

Table 7. Principal Studies Used in the Calculation of the Health Protective Concentration of Aluminum in Drinking Water

Study Authors	LOAEL/NOAEL	Uncertainty Factors	Effect	C, mg/L
Golub et al., 1993	24.4 mg/kg-d LOAEL	1000	Immunotoxicity	0.085
Bishop et al., 1997	22.5 mg/kg-d est. LOAEL	300	Neurodevelopmental toxicity for a 10 kg child	0.075
Greger and Baier, 1985	125 mg/d LOEL	100	Increased serum Al in adults	0.0625
Seven animal studies geometric mean*	Various see Table 6	Various see Table 6	Various see Table 6	0.039
Bishop et al., 1997	22.5 mg/kg-d est. LOAEL	300	Neurodevelopmental toxicity for 1.3 kg infant	0.020

*Note: The seven studies from Table 6 are Golub et al. (1993, 1995); Pettersen et al., 1990; Ondreika et al., 1986; Krasovskii et al., 1979; 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 aluminum, and an estimated LOAEL of 22.5 mg/kg-d for developmental neurotoxicity in premature infants, a PHG of 0.06 mg/L (60 ppb) is proposed for aluminum. The value of 60 ppb also falls midway between four other estimates noted above: premature infants (20 ppb); geometric mean of seven animal studies (39 ppb); normal child (75 ppb); and best animal study (85 ppb). OEHHHA believes this value provides a sufficient margin of safety for the large majority of the population who may be exposed to residual aluminum in drinking water. This value is further supported by a number of studies in experimental animals exhibiting a variety of toxic effects including growth retardation, depressed motor reflex, and effects on phosphorus metabolism including decreased serum alkaline phosphatase, and immunosuppression including decreased production of cytokines.

It should be noted that the Greger and Baier (1983) study is the basis of the current California primary drinking water standard (MCL) for aluminum of 1.0 mg/L established in 1988. 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 1988 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, namely 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 OEHHHA 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

DRAFT

subgroups more susceptible to Al in drinking water, namely infants, children and adults who are not receiving parenteral Al or dialysis but are at increased risk from oral Al exposure. Also the concern about a causal or contributory role of chronic Al intake in healthy adults and the incidence of neurodegenerative disease including Alzheimer's disease, while not conclusive, is nevertheless a real uncertainty that cannot be wholly discounted. The law requires OEHHA to use criteria most protective of public health in cases where the scientific evidence is unclear. For these reasons, OEHHA has chosen to use a higher uncertainty factor than in the earlier (1988) assessment to account for lifetime exposure and variability of response within the human population (i.e., 100 overall vs. 10). The use of a more realistic relative source contribution of 10 percent (0.1) also provides an additional margin of safety over the earlier assessment.

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 aluminum 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).
- Workers in aluminum remelting plants exhibited neurobehavioral impairment and symptoms of pulmonary toxicity (Kilburn, 1998).
- In animals intracerebral or subcutaneous injection of Al salts results in encephalopathy.
- Aluminum is generally poorly absorbed by the gastrointestinal tract, much less than 1 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.

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- 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.
- 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 not yet conclusive. Aluminum may only be one of many factors figuring in the mode of action of AD and perhaps similar diseases. Several authors have suggested that a concentration of 0.1 mg Al/L drinking water (i.e., 100 ppb) appears 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.
- 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, 70 kg male subjects were administered Al lactate in fruit juices with their meals for 20 days. Administration of aluminum 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 aluminum, 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 relative source contribution (RSC) for Al in drinking water of 10 percent is employed in the calculation of the PHG. It could be argued that this value is either too low or too high. In the case of individuals consuming Al-based antacids, the Al RSC would be very low even at the maximum allowable California water concentration of 1.0 mg/L. Alternatively, it could be argued that bound forms of aluminum in food and antacids are much less bioavailable than soluble or "free" Al in finished drinking water and that a higher RSC should be used. Unfortunately, the speciation of aluminum in drinking water is so complex with interactions of pH and various counter ions that at present it is not possible to consider measures other than total aluminum and intake from typical diets.

OTHER REGULATORY STANDARDS

The U.S. EPA has **not** established a primary drinking water standard for aluminum. A secondary standard of 0.05 to 0.2 mg/L has been established (40CFR 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 aluminum in drinking water (California Health and Safety Code Sections 64431 and 64449).

Health Canada has adopted an operational guidance value for aluminum in drinking water of less than 0.1 or 0.2 mg/L. The former value applies to water treatment plants using aluminum-based

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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 aluminum for aesthetic quality.

OSHA has set limits for Al inhalation based on an eight hour time weighted average exposure of 15 mg/m³ for total Al dust and 5 mg/m³ for respirable fraction (29 CFR 1910.1000, 1974).

The State of Arizona has established a drinking water guideline of 0.073 mg/L for aluminum (ATSDR, 1997).

The State of Maine has established a drinking water guideline of 1.43 mg/L for aluminum (ATSDR, 1997).

ATSDR has determined no minimum risk levels (MRLs) for any exposure duration for aluminum.

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

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

The International Agency for Research on Cancer has classified aluminum 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 aluminum and Al compounds under the Clean Air Act, but these agents are not designated as hazardous air pollutants.

U.S. EPA regulates aluminum 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.

U.S. EPA has established a tolerance of 0.1 ppm for residues of the rodenticide aluminum phosphide in or on the raw agricultural commodities of almonds, barley, corn, dates, rice, sesame seeds, and wheat when used as a post-harvest treatment (40CFR180.225, 1977).

DRAFT

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