Integrated Laboratory Systems

Aluminum Compounds

Review of Toxicological Literature
Abridged Final Report

Prepared for

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EXECUTIVE SUMMARY

Aluminum Compounds was nominated by the Environmental Protection Agency (EPA) Office of Water for toxicity testing based on the limited data found for the potential neurotoxic effects of chronic exposure to the aluminum species existing in water. Aluminum has been extensively reviewed, and this report was prepared primarily from the most recent reviews available—the 1999 Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Aluminum*, the 1997 International Programme on Chemical Safety (IPCS) *Aluminum: Environmental Health Criteria 194*, and the current California EPA draft *Public Health Goal for Aluminum in Drinking Water*.

Aluminum, the most abundant metal in the earth's crust, occurs in only one oxidative state (Al^{3+}) and is found in combination with oxygen, silicon, fluorine, and other elements in soil, rocks, clays, and minerals. Elemental aluminum is clearly metallic, but its compounds are on the borderline between ionic and covalent. The trihalides (e.g., aluminum chloride) are covalent in character, except for the fluorides, which give ions of high charge density and are frequently ionic in character. These compounds can form a variety of complex compounds. For example, aluminum fluoride, having a great affinity for the fluoride ion, can form complexes of the types M_3AlF_6 and $MAlF_4$, which are extremely stable. Upon acidification, the fluoride complexes yield a tetracoordinated fluoroaluminate complex, AlF^-, which acts as a structural analogue of PO_4^{3-}. Small amounts are also found in water in dissolved or ionic form. Soluble salts of weak acids (e.g., carbonates, acetates, sulfides, and cyanides) do not exist in aqueous solution or in water, since they undergo complete hydrolysis, resulting in the precipitation of aluminum hydroxide [$Al(OH)_3$]. Many methods of analysis are available for aluminum, its metabolites, and other biomarkers of exposure and effect.

Aluminum-based products, particularly those for water treatment (e.g., aluminum sulfate [alum], polyaluminum chloride [PAC], and sodium aluminate), are commercially available. Aluminum sulfate was ranked 43rd among the top 50 chemicals during the years 1993 and 1994; annual production has been stable from 1984 to 1997. The production of PAC and aluminum chlorohydrate for use as water treatment chemicals has also been growing. Annual production capacity for aluminum oxide (alumina, calcined, reduction grade) has been fairly constant in the most recent years (1988-1995), while that for anhydrous aluminum chloride slightly increased during the period. The major uses of aluminum and its alloys are in packaging, building and construction, transportation, and electrical applications. Aluminum compounds, likewise, have a wide range of uses in industrial, domestic, consumer, and medicinal products.

Aluminum is ubiquitous. It is released to the environment by both natural processes and anthropogenic sources. The largest source of airborne aluminum-containing particulates is dust from soil, the weathering of rocks, volcanic activity, and human activities, such as mining and agriculture. Aluminum enters natural waters from the weathering of aluminum-containing rocks and minerals, human activity through industrial and municipal discharges, surface run-off, tributary inflow, groundwater seepage, and wet and dry atmospheric deposition. The concentration of aluminum in water, its bioavailability, and its toxicity is governed by chemical speciation. Aluminum is released to soil by the weathering of aluminum-containing rocks and minerals and as a constituent of many mining wastes and solid wastes from coal combustion,

aluminum reduction, and other metal processing operations. Aluminum also occurs naturally in many edible plants.

The ubiquitous nature of aluminum and its many uses make exposure to aluminum unavoidable. For the general population, exposure is mainly through oral intake, and the major sources are drinking water, residues in foods, cooking utensils, food and beverage packaging, and aluminum-containing medications (e.g., antacids and buffered aspirins). Children may additionally ingest aluminum from dirt from unwashed hands or when playing in contaminated soils, vitamin/mineral supplements, treatment for hyperphosphatemia, and from consumer products not normally ingested by adults (e.g., toothpaste). Exposure is also possible from parenteral sources (e.g., dialysis, vaccinations containing aluminum adjuvants, and parenteral solutions). Occupational exposure to aluminum occurs in the refining of the primary metal and in secondary industries that use aluminum products. Greater exposure to aluminum is possible for persons living in the vicinity of industrial emissions sources and hazardous waste sites, undergoing long-term hemodialysis treatment, drinking water from a residential well, and those consuming large quantities aluminum-containing medications. ATSDR has provided the concentrations of aluminum in a variety of products, including drinking water, infant and milk formulas, other beverages, food products, containers for food, as well as the atmosphere.

The aqueous chemistry of aluminum has been extensively reviewed. Concern over the use of aluminum compounds as coagulants in water treatment exists, since their addition usually results in an increase in the amount of aluminum in finished water. (Treatment can also reduce total aluminum content.) Generally, fractionation of aluminum in drinking water occurs by one of three methods. Drinking water production begins with coagulation, followed by flocculation, clarification, filtration, and lastly disinfection. Aluminum removal depends on the transformation of its ions into $Al(OH)_3$ species. Additionally, fluorides are added to many water supplies for the prevention of dental carries, and systemic fluorosis can, therefore, be a problem. In the treated water, fluorides exist as less physiologically active fluoroaluminates.

The Occupational and Safety and Health Administration (OSHA), American Conference of Governmental Industrial Hygienists (ACGIH), and National Institute for Occupational Safety and Health (NIOSH) have established a permissible exposure limit (PEL) or guideline values for aluminum as the dust or metal. EPA regulates aluminum and certain aluminum compounds under the Clean Air Act (CAA), Clean Water Act (CWA), and the Safe Drinking Water Act (SDWA). Aluminum oxide, phosphide, fume, and dust are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986." The reportable quantity limit for aluminum sulfate is 5,000 lb (2,270 kg) and 100 lb (45.5 kg) for aluminum phosphide. A tolerance limit of 0.1 ppm has been set for residues of aluminum phosphide in or on raw agricultural commodities. The Food and Drug Administration (FDA) has received several petitions for the use of aluminum compounds as food additives. Under the Federal Food, Drug, and Cosmetic Act, FDA has amended its regulations for aluminum content in large- and small-volume parenterals used in total parenteral nutrition (TPN), which become effective on January 26, 2001.

Human Toxicity

The effects of aluminum on humans have been extensively reviewed. Overall, there is little indication that aluminum is acutely toxic for the general population; few cases of acute aluminum toxicity during alum therapy (i.e., alum bladder irrigation) have been reported. Prolonged exposure to aluminum, however, can cause systemic toxicity, mainly affecting the gastrointestinal tract and causing neurological and skeletal effects. The production of aluminum-associated bone disease can be accelerated with the simultaneous ingestion of aluminum with citrate compounds. Chronic toxicity occurs almost exclusively in persons undergoing dialysis for renal failure, who are likely to develop osteomalacia or aplastic bone disease, while those undergoing long-term hemodialysis are also subject to dialysis encephalopathy; increased serum fluoride concentration and fluoride intoxication have been observed in the latter group. Respiratory diseases (e.g., pulmonary fibrosis, occupational or potroom asthma, and chronic bronchitis) have been observed primarily in workers in the aluminum industry. Neurological effects, including impairment of cognitive function and motor dysfunction, have also been associated with occupational exposure to aluminum in the workplace air. The accounts of excess lung, kidney, pancreas, and bladder cancer, however, have been linked to other potent carcinogenic chemicals found in the industrial processes. Epidemiological data on workers exposed solely to aluminum or its compounds are not available.

Aluminum is a potent neurotoxic agent in humans. The association between aluminum and characteristics of Alzheimer's disease have prompted numerous studies of all sources of intake of aluminum. Epidemiological and case control studies have examined the potential link between oral exposure to aluminum via drinking water and the disease. The causal role of aluminum, however, remains controversial. Some studies have found a significant relationship between the exposure to aluminum in water and an increased risk of Alzheimer's disease, while other studies have not. The causal role of aluminum is also questionable in amyotrophic lateral sclerosis (ALS), Parkinson's disease, and the dementia complex of Guam. There is, however, convincing evidence that aluminum is the causative agent in dialysis dementia, which is seen in patients undergoing long-term hemodialysis.

Developmental effects such as encephalopathy, bone disease, microcytic anemia, and rickets have occurred in premature infants with reduced or failed renal function receiving aluminum-containing treatment (e.g., dialysate or aluminum-based phosphate binders) and in nonuremic infants receiving parenteral nutrition with aluminum-containing fluids or high doses of aluminum antacids. There are no adequate studies of the long-term effects of aluminum exposure on brain development and skeletal maturation.

No immunotoxicity studies are available. Few cases, however, report of hypersensitivity to aluminum following dermal application or parenteral administration. There have also been no reports of genetic or reproductive effects in humans.

Absorption, Distribution, Metabolism, and Excretion

The human body burden originating from largely insoluble environmental sources of aluminum is very low (about 0.1%). Most aluminum compounds are poorly absorbed through the lungs, skin, and gastrointestinal tract. Uptake from the gastrointestinal tract may be regulated by water solubility of the aluminum species and by mucosally associated luminal metal-binding

ligands. Aluminum is also poorly distributed in most tissues except the lung. Aluminum transport in the blood is about 89% bound to iron transferrin and about 11% as aluminum citrate. Elimination of absorbed aluminum is mainly through the kidney. Chelation with compounds such as desferrioxamine (deferoxamine [DFO]) may increase urinary aluminum excretion.

Of particular concern is the possible enhancement of intestinal absorption in the presence of dietary constituents such as citrate and fluoride. Added or natural fluoride in drinking water may form strong, water-soluble aluminum complexes (one to five fluoride ions per aluminum atom). Slightly acidic pH favors formation of aluminum fluoride and citrate complexes.

The standard American diet contains about 4 g citrate per day. Citrate is known to increase intestinal absorption as well as tissue accumulation of aluminum. Aluminum concentrations in bone and gray matter of rats increased when aluminum was co-administered with citrate and when citrate was administered alone. The bone aluminum concentration in rats treated with aluminum hydroxide plus citrate was 41 times higher than in the bones of control rats treated with aluminum hydroxide alone. However, in one study with human volunteers administered aluminum and citrate in the drinking water, no difference was observed between the plasma concentrations of aluminum in subjects receiving citrate with the drinking water and those that did not. While increasing aluminum absorption, citrate may also enhance urinary excretion, resulting in no significant increase in aluminum plasma concentration in individuals with normal kidney function. The greatest risk of aluminum absorption and distribution after citrate exposure would be for those individuals with renal insufficiency or failure.

Aluminum may form complexes with other dietary acids, for example, malic, oxalic, tartaric, succinic, aspartic, and glutamic acids, which may increase its gastrointestinal absorption. Formation of aluminum maltolate from the dietary constituent maltol (a common food additive) may also occur. The aluminum maltolate complex is also associated with increased aluminum uptake.

Administration of fluoride with aluminum has resulted in decreased fluoride absorption from the intestinal tract, indicating that aluminum-fluoride complexes are not absorbed as readily as fluoride alone. It has been suggested, however, that administration of fluoride alone can cause the co-accumulation of aluminum in bone. Rabbits given only fluoride showed 7- to 11-fold dose-dependent increases in bone aluminum concentrations even when plasma aluminum concentrations showed no significant increase.

Animal Toxicity

Many unpublished studies of aluminum compounds (alone or in mixtures) have been submitted to the EPA.

Acute exposure: Oral and intraperitoneal (i.p.) LD_{50} values for aluminum bromide, chloride, nitrate, and sulfate have been calculated for the mouse, rat, guinea pig, and rabbit. In Dobrá Voda mice, the oral LD_{50} for aluminum chloride was 770 mg/kg bw (5.77 mmol/kg bw) and for aluminum sulfate was 980 mg/kg bw (5.73 mmol/kg bw), while in Swiss Webster mice, the values were 222 mg/kg bw (1.66 mmol/kg bw) and >730 mg/kg bw (4.27 mmol/kg bw), respectively. Additionally, oral LD_{50}s of 164 mg/kg bw (0.615 mmol/kg bw) for aluminum bromide and 286 mg/kg bw (1.34 mmol/kg bw) were found. Intraperitoneal LD_{50} values for the

Swiss Webster mice were 108 mg/kg bw (0.405 mmol/kg bw) for aluminum bromide, 105 mg/kg bw (0.787 mmol/kg bw) for aluminum chloride, 133 mg/kg bw (0.624 mmol/kg bw) for aluminum nitrate, and 40 mg/kg bw (0.23 mmol/kg bw) for aluminum sulfate. In an unspecified strain, the oral LD_{50} was 3850 mg/kg (28.87 mmol/kg) for aluminum chloride and 6200 mg/kg (36.24 mmol/kg) for aluminum sulfate, and the i.p. LD_{50} was 320 mg/kg (1.50 mmol/kg) for aluminum nitrate and 140 mg/kg (0.818 mmol/kg) for aluminum sulfate.

In the Sprague-Dawley rat, the oral LD_{50} values were 162 mg/kg bw (0.607 mmol/kg bw), 370 mg/kg bw (2.77 mmol/kg bw), 261 mg/kg bw (1.23 mmol/kg bw), and >730 mg/kg bw (4.27 mmol/kg bw) for the bromide, chloride, nitrate, and sulfate forms of aluminum. The i.p. LD_{50} values were 82 mg/kg bw (0.31 mmol/kg bw), 81 mg/kg bw (0.61 mmol/kg bw), 65 mg/kg bw (0.31 mmol/kg bw), and 25 mg/kg bw (0.15 mmol/kg bw), respectively. In an unspecified strain, oral LD_{50} values of 380 mg/kg (2.85 mmol/kg) and 760 mg/kg (5.70 mmol/kg) were obtained for aluminum chloride. For aluminum nitrate, oral LD_{50}s of 260 mg/kg (1.22 mmol/kg) and 4280 mg/kg (20.09 mmol/kg) were reported, and an i.p. LD_{50} of 330 mg/kg (1.55 mmol/kg) was calculated.

In both guinea pigs and rabbits, an oral LD_{50} of 400 mg/kg (3.00 mmol/kg) was calculated.

Topical application of aluminum (0.185-0.482 mmol) in the chloride and nitrate forms produced skin damage in mice, rabbits, and pigs. In rats, inhalation of aluminum (50-200 mg/m^3; 45-181 ppm) caused changes in the cytological and enzymatic content of the lavage fluid, while oral intake of a diet (2665 mg Al/kg; 98.78 mmol/kg) containing aluminum resulted in a reduction of food intake and an increased fecal elimination of phosphorus. Intraperitoneal administration (1500 mg/kg; 5.099 mmol Al/kg) produced local toxic myopathy.

Inhalation studies (3-48 mg Al/m^3; 3-43 ppm) in rabbits and hamsters caused decreases in body weight, significant increases in absolute lung weights, thickening of the alveolar walls, and the occurrence of small granulomatous foci at the bronchioalveolar junction. When rabbits were injected intracisternally with aluminum chloride (1000 µg; 7.500 µmol Al), microglia showed thinner, less complex branching patterns.

Short-term and subchronic exposure: In mice, oral administration of aluminum as aluminum ammonium sulfate decreased dopamine, dihydroxyphenylacetic acid, and homovanillic acid levels in the hypothalamus, and aluminum lactate increased the 2-thiobarbituric acid reactive substances (TBARS) in the brain but decreased brain stem weight.

In rats, oral administration of aluminum as the sulfate, nitrate, chloride, hydroxide, citrate, and lactate resulted in aluminum accumulation in bone, brain, spleen, liver, heart, gastrointestinal tract, and spleen. Significant decreases occurred in body weight, water consumption, urine volume, plasma glutamic-pyruvic transaminase, serum triglycerides, serum iron concentration, and alkaline phosphatase, ATP, ADP, and AMP, as well as in motor activity. Additional health effects include changes in the cytological and enzymatic content of the lavage fluid, inhibition of colony-forming units-erythroid (CFU-E), and neurobehavioral effects. When administered i.p., malondialdehyde was increased in all brain regions as were phospholipase C-δ1 protein levels. Low molecular weight phosphotyrosine phosphatase (LMW-PTP) activity, however, was decreased compared to control rat brains. Subcutaneous (s.c.) injections of aluminum produced a significant decrease in iron levels in plasma and the striatum. Significant aluminum accumulation

was induced in the striatum, hippocampus, and cortex, and in the hippocampus, TBARS production was increased.

In guinea pigs and rabbits, oral administration of aluminum decreased alkaline phosphatase, ATP, ADP, and AMP. In hamsters, inhalation of aluminum as Alchlor produced an increase in the number of alveolar macrophages and heterophils, thickening of alveolar walls, and granulomatous nodules. Rabbits developed glomerular lesions and had tubulointerstitial nephrosis when aluminum was given intravenously (i.v.).

In an *in vitro* assay using cultures of cerebellar neurons from rats. glutamate-induced formation of cGMP and glutamate-induced activation of nitric oxide (NO) synthase were reduced; NO- and *S*-nitroso-*N*-acetylpenicillamine (SNAP)-induced formation of cGMP were also inhibited.

Chronic exposure: Chronic exposure studies in mice, rats, guinea pigs, and rabbits, via the inhalation and oral routes produced similar findings as in subchronic exposure studies. Additionally, in a series of rat experiments where aluminum hydroxide was administered i.p., significant decreases in the hematocrit index, hemoglobin levels, and serum iron concentration in the peripheral blood were observed. Although renal function was the same as in controls, the fractional excretion (FE%) of sodium, the FE% of phosphate, and the urinary excretion of phosphate in treated rats were decreased. In contrast, urinary excretion of calcium was significantly elevated. Furthermore, intracisternal injections produced dose-dependent motor degeneration in the rat.

In rabbits, the inoculums resulted in c-Jun positive staining in the cytoplasm of motor neurons and other smaller neurons. In the ventrolateral regions of the lumbar cord, basophilic inclusions were found in the cytoplasm of motor neurons, some exhibiting features of chromatolysis.

In dogs, oral administration of aluminum as sodium aluminum phosphate produced significant decreases in food consumption in both sexes. Aluminum concentration in the brain was also slightly increased. In males, body and testes weights were markedly reduced.

Synergism/Antagonism: Aluminum competes with cations such as iron and calcium and binds with anions such as fluoride. Certain counter ions increase the bioavailability of aluminum. Citrate enhances the absorption of aluminum in the gastrointestinal tract. Silicic acid, on the other hand, has been observed to decrease the bioavailability of aluminum. In turn, aluminum compounds can decrease the intestinal absorption of iron, fluoride, phosphorus, and calcium. Although fluoride has been seen to exert a protective effect against the biotoxic effect of aluminum, it also has a synergistic effect on the toxicity of aluminum. Aluminum has potentiated fluoride action on osteoblasts and bone. However, it can also exert antagonistic effects; for example, it has inhibited fluoride toxicity in rats, hens, turkey, and sheep. Aluminum fluoride complexes have been found to specifically and persistently activate G protein in several cell systems, as well as exert physiological and biochemical actions in tissues such as the brain, and kidneys. In rats, the toxicity of high dietary aluminum was found to be influenced by magnesium, boron, and manganese. In addition, the dietary level of aluminum has produced age-related effects on levels of copper, iron, zinc, calcium, magnesium, and manganese. Aluminum

may also potentiate the adverse effects of disease states and other biological activities, such as diabetes and iron-induced oxidative stress. In drinking water, the relationship between cognitive impairment and aluminum depends on pH and silica level. At low silica concentrations, high aluminum concentrations had an adverse effect; at high silica and pH levels, however, there was a protective effect.

Reproductive and Teratological Effects: Reproductive toxicity and teratogenicity from aluminum compounds has been reported in a number of papers. Reproductive effects observed in male mice, rats, or dogs given aluminum compounds orally or s.c. included repressed sexual behavior, decreased spermatogenesis, or other effects on the testes, sperm duct, and/or epididymis. Reproductive effects from oral administration to female rats included irregularity of the estrus cycle of female offspring or effects on the ovaries or fallopian tubes in treated adults. Maternal toxicity was observed in several studies in which pregnant mice, rats, or rabbits were administered aluminum compounds orally, i.p., or s.c. during gestation. Developmental toxicity from oral, i.p., or s.c. aluminum compound administration was also noted in some rat and mouse studies. Teratogenic effects induced by oral, i.p., or s.c. administration of aluminum compounds included skeletal or musculoskeletal variations, cleft palate or other craniofacial malformations, cardiovascular system abnormalities, and other unspecified physical effects. Injection of aluminum compounds into the yolk sac of fertilized chicken eggs induced similar developmental malformations. Neurotoxic effects were observed when aluminum compounds were given orally to mice, rats, or rabbits. A number of studies were also found that reported no reproductive, maternal, developmental toxicity or teratogenicity from oral, inhalation, i.p., or s.c. administration of aluminum compounds.

Carcinogenicity: The available carcinogenicity studies do not indicate that aluminum is carcinogenic. No initiation/promotion studies or anticarcinogenicity studies were available.

Genotoxicity: In one acellular assay, aluminum was found to bind to DNA through chelation. It was also found to reduce ^{3}H-thymidine incorporation in a transformed cell line, indicating that aluminum compounds may impede cell cycle progression. Aluminum compounds were not mutagenic in the preponderance of *Salmonella typhimurium* and *Escherichia coli* studies. Only one study reported a positive mutagenic response, in which aluminum acetylacetonate was tested on *S. typhimurium* strain TA104 in the absence of metabolic activation. Effects induced *in vitro* by aluminum compounds included crosslinking of chromosomal proteins in rat ascites hepatoma cells, anaphasic changes in BALB/c mouse 3T3 cells, and formation of DNA-protein crosslinks, micronuclei, sister chromatic exchanges (SCEs), and chromosomal aberrations in cultured human lymphocytes. Effects induced *in vivo* included SCEs in mice and sheep, delayed mitosis in mice and sheep, and formation of micronucleated polychromatic lymphocytes in mice, and chromosomal aberrations in rats and mice.

No cogenotoxicity studies were found. In one antigenotoxicity study, low concentrations of aluminum chloride inhibited the *in vitro* frequency of single- and double-stranded breaks induced by radiation in plasmid DNA.

Immunotoxicity: One *in vitro* immunotoxicity study using mouse macrophage cells found that the release of tumor necrosis factor (TNF)-α increased with increasing particle size and concentration of aluminum oxide, while interleukin (IL)-1α or IL-1β were not affected by treatment. Aluminum lactate, given subchronically in the diet of mice caused immunosuppression, while administration to mice during gestation and lactation induced a decrease in IL-2, interferon (IFN)-γ, and TNF-α in the spleen. Similarly, s.c. treatment of mice with alum at study initiation and two weeks later induced IL-4 production and T-helper cell type 2 (Th2) responses in the absence of IL-4 in mice deficient in either IL-4Rα or Stat6. In rats, aluminum nitrate produced hyperemia in the red pulp of the spleen when given for a month, but an experiment using a higher concentration and a longer duration failed to duplicate this result. Bioceram®, a bioinert ceramic material made from aluminum oxide induced low-grade tissue reactions when implanted s.c.

Neurotoxicity: Dementia in dialysis patients and encephalopathy in infants undergoing parenteral nutrition are well known examples of aluminum intoxication in humans. Numerous *in vitro* studies and epidemiological studies have examined the possible role of aluminum in Alzheimer's disease, other dementias, and cognitive dysfunction.

Numerous animal studies, particularly orally studies in mice and rats, show that aluminum compounds are neurotoxic, but species variation exist. The toxicity is characterized by progressive neurological impairment leading to death associated with repeated seizures. Morphologically, the progressive encephalopathy, associated with neurofibrillary pathology in neurons mostly in the spinal cord, brain stem, and the hippocampus and cingulated gyrus of the cortex, has been induced by aluminum in susceptible animals such as the rabbit, cat, guinea pig, and ferret when given as intrathecal, intracerebral, and subcutaneous injections. For example, in cats and rabbits intracerebral injections of soluble aluminum compounds resulted in impairment in learning and memory, and in rabbits repeated subcutaneous injections affected classical conditioning, while single or repeated intracisternal injection of metallic aluminum altered motor function. Oral administration of aluminum compounds, however, produced no encephalopathy or epilepsy but resulted in behavioral impairment.

Acute Exposure: In axotomized rabbits intracisternally inoculated with aluminum chloride, the number of microglia in the ventrolateral area ipsilateral to the axotomy at day 4 was significantly increased compared to that of the contralateral side and showed thinner, less complex branching patterns compared to controls. In cats, a single injection of aluminum chloride into the hippocampic space resulted in the development of a dementia similar to Alzheimer's disease. In an *in vitro* assay using synaptosomal fractions of rat brain, aluminum chloride caused an increase in mitochondrial acetyl-Coenzyme A (CoA) and a decrease in synaptosoplasmic CoA simultaneously with inhibition of calcium-evoked acetylcholine (ACh) release.

Short-term and Subchronic Exposure: In mice, aluminum ammonium sulfate produced a decrease in dopamine, dihydroxyphenylacetic acid, and homovanillic acid levels in the hypothalamus. Aluminum as the lactate and chloride forms produced reduced motor activity,

decreased hind limb grip strength, decreased startle response, and increased aluminum tissue levels and 2-TBARS in the brain. In another mouse study with aluminum chloride, skilled motor coordination performance (roto-rod treadmill test) was impaired.

Oral studies with aluminum in rats produced accumulated aluminum levels in the brain as well as cognitive deficits and other changes, including decreased maze-learning ability, altered general motor activity, impaired motor coordination, impaired passive avoidance, and visual temporal acuity. Ingestion of aluminum compounds, specifically as the sulfate and the nitrate, was found to not only cause reduced retention of a learned passive avoidance task but also changes in brain chemistry (e.g., increased cyclic adenosine monophosphate levels, decreased concentrations of MAP-2 and other structural proteins, decreased dopamine and 5´-hydroxytryptamine, and increased norepinephrine). Furthermore, a study showed that basal extracellular cGMP was significantly reduced in rats fed aluminum but could be increased with the addition of NMDA or SNAP. NMDA-induced formation of nitric oxide (NO) was reduced, but the NO-induced activation of guanylate cyclase was increased in the brains of treated animals. Administration of aluminum (17 mg/kg/day as aluminum chloride) caused decreased alkaline phosphatase, ATP, ADP, and AMP not only in rats but also in guinea pigs and rabbits.

Intraperitoneal injection of aluminum lactate in rats significantly reduced brain weight and LMW-PTP activity and increased PLC-δ1 protein levels in the cytosolic and particulate fractions, PLC activity in the cytosolic fraction, and lipid peroxidation in the hippocampus, cerebral cortex, and cerebellum. Subcutaneous injections of an aluminum *L*-glutamate suspension induced significant aluminum accumulation in the stratum, hippocampus, and cortex. Iron levels in the striatum were notably decreased and TBARS production increased in the hippocampus compared to controls.

In an *in vitro* assay using cultures of cerebellar neurons from rats, glutamate-induced formation of cGMP and glutamate-induced activation of NOS were reduced. NO- and SNAP-induced formation of cGMP were inhibited; however, no effect on the latter was seen in cultures from prenatally aluminum-exposed rats.

Chronic Exposure: In rats, aluminum chloride caused pathological changes in the brain, such as a scarcity of cells in the ganglionic layer, spongioform changes, and neurofibrillary degeneration, nuclear deformity, and vacuolization of the nuclei. In a separate study, the contents of aluminum and β-APP mRNA in the cortex and immunohistochemical positive index of GFAP in the hippocampus and cortex were significant increased, suggesting that long-term exposure to aluminum results in proliferation of astrocytes and abnormality of β-APP gene expression. In other studies administering aluminum chloride orally in the diet or drinking water (93 µmol-3.4 mmol/kg bw/day), decreased spontaneous locomotor activity, acquisition, retention of learned response, and extinction and relearning of an active avoidance task and impaired maze learning ability were observed. Additionally, lipid peroxidation in the brain was increased but Na^+-, K^+-, and Mg^{2+}-ATPases were decreased. At the highest dose, extended cytoplasmic vacuolization in astrocytes, swelling of astrocytic processes, neuronal vacuolization, and nuclear inclusions were observed. Aluminum nitrate (≤125 mg Al/kg/day) in the diet, however, resulted

in no effects on spontaneous motor activity (open-field) or passive avoidance operant training or performance.

In a series of studies using aluminum fluoride (0.5, 5.0, or 50 ppm) in deionized water for up to a year, increased aluminum levels and histological alterations in the brain, particularly increased numbers of abnormal and damaged neurons and reductions in cell density in areas of the hippocampus and neocortex, occurred. Behavioral tests indicated possible olfactory impairment, but no motor impairment or effects on spatial memory.

A single intracisternal injection of aluminum (1.8, 3.71, or 11.1 µmol) followed by the same dose three months later produced motor degeneration, consisting of slight to extreme chromatolysis, unusual localization of the nucleus, axonal and dendritical degeneration, swollen perikarya, ghost-cell appearance of neurons, and/or neurofibrillary tangle formation in the perikarya of severely damaged motor neurons, were seen.

In a series of rabbit studies where animals were intracisternally inoculated with aluminum chloride (0.750 mmol) at intervals of 28 days for a total of 267 days, basophilic inclusions were observed in the cytoplasm of motor neurons in the ventrolateral regions of the lumbar cord. Some motor neurons exhibited features of chromatolysis. The number of microglia in the region was significantly decreased. Microglia showed thinner, less complex branching patterns and were close to or attached to NFH positive structures in the spinal cord. After day 156, c-Jun positive staining in the cytoplasm of motor neurons and other smaller neurons was observed.

In dogs fed aluminum sodium phosphate, there was slight increase in aluminum concentration in the brain.

Other Data: In erythrocytes from New Zealand white rabbits treated with different aluminum compounds, morphological changes were produced in a metal-speciation dependent manner. Using male Wistar rat liver lysosomes, aluminum strongly inhibited the lysosomal proton activity, with aluminum sulfate showing the greatest inhibitory effect. This, however, did not occur in the absence of ATP and presence of nigericin. In *Nostoc linckia* and *Chlorella vulgaris*, a pH-dependent and non-competitive inhibition of Mg^{2+}- and Ca^{2+}-ATPase activities was observed when exposed to aluminum chloride, aluminum fluoride, sodium fluoride, and a combination of aluminum chloride and sodium fluoride.

In Wistar rat brain homogenate, aluminum has activated the enzymes α-ketoglutarate dehydrogenase and succinate dehydrogenase of the Krebs cycle and decreased the activity of aconitase in a dose-dependent manner. In addition, it inhibited glutamate dehydrogenase, an allostric enzyme that catalyzes a reaction directly connected to the cycle.

A study using *S. typhimurium* TA98 found that aluminum was required for the intracellular transport of fluoride from the incubation medium. In the absence of the metal, the intracellular fluorine concentration was below the detection limit even when fluorine concentration was greater than 589 ppm. With the addition of aluminum, fluorine (>200 ppm) was detected in cells.

Structure-Activity Relationships

In regards to radii, aluminum (Al^{3+}) is similar in size to iron (Fe^{3+}) and magnesium (Mg^{2+}). In biological systems, Al^{3+} has been found to be competitive with Mg^{2+} as well as calcium (Ca^{2+}), although to a lesser extent; for example, it easily displaces both metals from citrate. In processes involving Mg^{2+}, interference by Al^{3+} is possible. It is 10^7 times more effective than Mg^{2+} in promoting polymerization of tubulin to microtubules. The slow ligand-exchange rate for Al^{3+} makes it useless in enzyme active site reactions. The 10^5 times faster rate for Mg^{2+} explains Al^{3+} inhibition of enzymes with Mg^{2+} cofactors. Processes involving rapid Ca^{2+} exchange would be stopped by substitution of Al^{3+}.

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1.0 BASIS FOR NOMINATION

The nomination of Aluminum Compounds by the Environmental Protection Agency (EPA) Office of Water for toxicity testing is based on the limited data found for the potential neurotoxic effects of chronic exposure to the aluminum species existing in drinking water. Studies focusing on the influence that various aluminum complexes, particularly aluminum citrate and aluminum fluoride complexes in the water, have on body burdens, on bone development and metabolic bone disease, and in offspring from exposure to aluminum during pregnancy and lactation were proposed.

2.0 INTRODUCTION AND CHEMICAL PROPERTIES

Aluminum has been extensively reviewed (e.g., IPCS, 1997; Rajwanshi et al., 1997; CAL-EPA, 2000). This report was prepared primarily from the most recent reviews available—the 1999 Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Aluminum*, the 1997 IPCS *Aluminum: Environmental Health Criteria 194*, and the current California EPA draft *Public Health Goal for Aluminum in Drinking Water*. Additional current sources were used to supplement general and/or limited data.

Aluminum, the most abundant metal in the earth's crust, is found in combination with oxygen, silicon, fluorine, and other elements in soil, rocks, clays, and gems such as rubies, sapphires, and turquoise (ATSDR, 1999). Small amounts are also found in water in dissolved or ionic form, typically as complexes with hydroxy ions. Aluminum occurs in only one oxidative state (Al^{3+}). Aluminum compounds are used in a variety of industrial applications (e.g., alum in water treatment) and products (e.g., antacids, food additives, and cosmetics). Because of its ubiquitous state, exposure to aluminum is unavoidable.

2.1 Chemical Identification and Methods of Analysis

2.1.1 Chemical Identification

ATSDR (1999; Table 3-1, pp. 151-161) provides a table regarding the chemical identity of aluminum and several of its compounds, including synonym(s), registered trade name(s), and

several identifications numbers, such as Chemical Abstract Services (CAS) Registry, National Institute for Occupational Safety and Health Registry of Toxic Effects of Chemical Substances (NIOSH RTECS), and Hazardous Substance Data Bank (HSDB). In **Table 1** the Chemical Abstract Services Registry Number (CASRN), chemical formula(s), synonym(s), and trade name(s) are given for those compounds reported by the agency. Additional sources were used for compounds not mentioned in ATSDR (1999) but for which toxicity data were available. (*The Merck Index* provides data for many more aluminum compounds.)

Table 1. Chemical Identification of Aluminum and Its Compounds

Compound [CASRN]	Chemical Formula(s)	Synonyms	Registered Trade Name(s)
Alchlor [52231-93-3]	$Al_2(OH)_5Cl \cdot nH_2O \cdot mC_2H_6O_2$; $Al_2(OH)_5Cl \cdot nH_2O \cdot mC_3H_8O_2$; $Al_2(OH)_4Cl_2 \cdot nH_2O \cdot mC_2H_6O_2$; $Al_2(OH)_4Cl_2 \cdot nH_2O \cdot mC_3H_8O_2$	1,2-Propanediol, aluminum chloride hydroxide complex; 1,2-propanediol, basic aluminum chloride complex; aluminum chloride hydroxide, propylene glycol complex; aluminum chloride hydroxide [$Al_2Cl(OH)_5$], propylene glycol complex	No data available
Aluminum [7429-90-5]	Al	Alumina fibre; metana; aluminum bronze; aluminum dehydrated; aluminum flake; aluminum powder; aluminium	Aluminum-27; Jisc 3108/3110; Metana; Noral Aluminum; Pap-1
Aluminum aceglutamide[a] [12607-92-0]	$C_{35}H_{59}Al_3N_{10}O_{24}$	No data available	No data available
Aluminum acetylacetonate[b,c] [not available]	$Al(C_5H_7O_2)_3$	Aluminum 2,4-pentanedionate	No data available
Aluminum calcium silicate[d] [1327-39-5]	Many different forms are known, the most common of which are $CaAl_2Si_2O_8$ and $Ca_2Al_2SiO_7$.	Calcium aluminosilicate. It occurs in nature as the following minerals: anorthite, bavenite, clinozoisite, didymolite, epistilbite, gehlenite, gismondite, grossularite, heulandite, hibschite, laubanite, laumontite, lawsonite, levynitek margarite, meionite, plazolite, pumpellyite, scolecite, stellerite, vasuvianite, and zoisite	No data available
Aluminum carbonate [not available]	$Al_2O_3 \cdot CO_2$; normal aluminum carbonate $Al_2(CO_3)_3$ is not known as an individual compound	No data available	No data available

Table 1. Chemical Identification of Aluminum and Its Compounds (Continued)

Compound [CASRN]	Chemical Formula(s)	Synonyms	Registered Trade Name(s)
Aluminum chloride [7446-70-0]	$AlCl_3$	Aluminum trichloride; trichloroaluminum; aluminum chloride (1:3)	Pearsall
Aluminum chlorohydrate* [1327-41-9; 11097-68-0; 84861-98-3]	$Al_2ClH_5O_5$ or $Al_2(OH)_5Cl{\cdot}2H_2O$ or $[Al(OH)_2Cl]_x$ or $Al_6(OH)_{15}Cl_3$; $[Al_2(OH)_5Cl]_x$	Aluminum chlorohydroxide; aluminum hydroxychloride; aluminum chloride, basic; aluminum chloride hydroxide, polyaluminum chloride	Astringen; Chlorhydrol; Locron
Aluminum citrate[e] [31142-56-0]	$C_6H_8O_7{\cdot}x$Al	Citric acid, aluminum salt (8CI); 1,2,3-propanetricarboxylic acid, 2-hydroxy-, aluminum salt (9CI)	Tiorco 677
Aluminum flufenamate [16449-54-0][a]	$C_{42}H_{27}AlF_9N_3O_6$	Aluminum salt, flufenamic acid[d]	Alfenamin[d]; Opyrin (Taisho)[d]
Aluminum fluoride [7784-18-1]	AlF_3	Aluminum trifluoride; aluminum fluoride monohydrate; Aluminum fluorure (French)	No data available
Aluminum hydroxide [21645-51-2]	AlH_3O_3 or $Al(OH)_3$	α-Alumina trihydrate; alumina hydrate; alumina hydrated; aluminum oxide trihydrate; aluminum oxide hydrate; aluminum(III) hydroxide; hydrated alumina; hydrated aluminum oxide; aluminum hydrate; aluminum trihydrate; hydrated alumina	Alcoa 331/c 30BF/C 330/C 333; Alugel; Alumigel; BACO AF260; British Aluminum AF260; Calmogastrin; Higilite H 31S/ H 32/ H 42; Hychol 705; Hydrafil; Hydral 705/710; Martinal A/A-S/F-A; Reheis F 1000
Aluminum lactate [18917-91-4]	$C_9H_{15}AlO_9$; $(HOCHCO_2)_3Al$	Aluctyl; aluminum, tris(2-hydroxypropanoato-O^1,O^2); propanoic acid, 2-hydroxy-, aluminum complex; aluminum tris(α-hydroxypropionate)	No data available
Aluminum maltolate[e] [103616-17-7]	$C_{18}H_{15}AlO_9$	Aluminum maltol; Aluminum, tris[3-(hydroxy-κO)-2-methyl-4*H*-pyran-4-onato-κO^4]-, (OC-6-21)-(9CI); Aluminum, tris(3-hydroxy-2-methyl-4*H*-pyran-4-onato-O^3,O^4)-, (OC-6-21)-; maltolate; 4*H*-pyran-4-one, 3-hydroxy-2-methyl-, aluminum complex	No data available
Aluminum nitrate [13473-90-0]	AlN_3O_9	Aluminum trinitrate; aluminum(III) nitrate (1:3); nitric acid, aluminum salt; nitric acid, aluminum (3+) salt	No data available

Table 1. Chemical Identification of Aluminum and Its Compounds (Continued)

Compound [CASRN]	Chemical Formula(s)	Synonyms	Registered Trade Name(s)
Aluminum oxide [1344-28-1]	Al_2O_3	Activated aluminum oxide; α-aluminum, α aluminum oxide; alumina; aluminum sesquioxide; aluminum trioxide; β-aluminum oxide; γ-alumina; γ-aluminum oxide	Almite; Alon; Aloxite; Alumite; Alundum; Campalox; Dispol Alumina; Exolon XW 60; Faserton; Hypalox II; Ludox CL; Martoxin; Microgrit WCA; Poraminar
Aluminum palmitate[d] [555-35-1]	$C_{48}H_{93}AlO_6$; $[CH_3(CH_2)_{14}COO]_3Al$	Hexadecanoic acid aluminum salt; palmitic acid aluminum salt	No data available
Aluminum phosphate [7784-30-7]	$AlPO_4$	Aluminum orthophosphate; phosphoric acid; aluminum salt (1:1); aluminum phosphate tribasic	Alaphos (ingredient); Ukocid (ingredient); Phosphaljel (ingredient); Phosphalugel (ingredient); Phosphalutab (ingredient)
Aluminum phosphide [20859-73-8]	AlP	Aluminum monophosphide; Quick-Phos; Quick-Fume; AlP; Celphos; Detia; Phostoxin	Celphos; Delicia; Delicia Gastoxin; Detia GAS EX-B/EX-T; Phostoxin; Detia phosphine pellets
Aluminum potassium sulfate [10043-67-1]	$AlKO_8S_2$	Sulfuric acid, aluminum potassium salt (2:1:1)	No data available
Aluminum sulfate [10043-01-3]	$Al_2(SO_4)_3$	Alum; peral alum; pickle alum; cake alum; filter alum; papermakers' alum; patent alum; aluminum sulfate (2:3); aluminum trisulfate; dialuminum sulfate; dialuminum trisulfate; sulfuric acid, aluminum salt (3:2)	cake alum; patent alum
Dihydroxyaluminum sodium carbonate[d] [539-68-4]	CH_2AlNaO_5	[Carbonato(1-)-O] dihydroxyaluminum monosodium salt; aluminum sodium carbonate hydroxide	Kompensan (Roerig); Minicid

* Aluminum chlorohydrate is the common name for several different compounds, all containing aluminum, chloride, and hydroxyl ions; therefore, there are several chemical formulas and CAS numbers. Note: No data were found for aluminum calcium silicate, aluminum sodium silicate, and aluminum nitriloacetate complex.
Sources: ATSDR (1999); [a]Lewis (1991); [b]Aldrich (1994-1995); [c]Lide (1991); [d]Budavari (1996); [e]Registry (2000)

2.1.2 Methods of Analysis

ATSDR (1999, pp. 241-250 [also IPCS, 1997]) identifies well-established methods used as the standard methods of analysis for aluminum, its metabolites, and other biomarkers of exposure and effect. For the measurement of levels in biological materials, analytical methods,

which are often combined with front-end separation techniques such as chromatography, include accelerator mass spectroscopy (AMS), graphite furnace atomic absorption spectrometry (GFAAS), flame atomic absorption spectrometry (FAAS), neutron activation analysis (NAA), inductively coupled plasma-atomic emission spectrometry (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), laser ablation microprobe mass analysis (LAMMA), and electrothermal atomic absorption spectrometry (ETAAS). [AAS with electrothermal atomization (ETA-AAS) can be used to detect aluminum in foods; a detection limit of ~0.02 µg/g is obtained in most foods (Delves et al., 1989).] Because of the ubiquitous nature of aluminum, contamination plays a major role in the analysis of aluminum by all techniques except AMS. AMS can accurately assess the concentration of radioactive ^{26}Al and stable ^{27}Al in a few milligrams of material; its detection limit is one atom in 10^{15} (1 part per quadrillion [ppq]).

GFAAS is the most commonly used method for determining low parts-per-billion (µg/L) levels of aluminum in serum, plasma, whole blood, urine, and biological tissues, primarily because it offers the best combination of sensitivity, simplicity, and cost (ATSDR, 1999). When employed as a detector for high-performance liquid chromatography (HPLC), it can analyze for species of complexed or bound aluminum. The limits of detection for GFAAS are 2.3 µg/L (2.3 ppb) for whole blood, and are in the low parts-per-billion levels for urine and biological tissues. NAA is another technique used to determine low levels of aluminum in biological tissues and urine. This technique has been shown to exhibit good sensitivity and to be relatively independent from matrix effects and interferences, although it is higher in cost and more difficult to perform. ICP-AES, a multi-elemental technique also relatively free of chemical interferences, is an excellent alternative to GFAAS; limits of detection are about 1 and 4 ppb of urine and blood, respectively. Although it is more costly, ICP-MS can measure the presence of more than 75 elements in a single scan, with detection limits down to parts per trillion (ppt) levels (two or three orders of magnitude lower than those obtained by ICP-AES). It can detect aluminum levels in urine and saliva as low as 0.02 µg/mL (20 ppb) and in blood serum as low as 0.001 µg/mL (1 ppb). Used as a detector for aluminum in tissue fractions separated by size-exclusion chromatography (SEC), detection limits of 0.05 µg/g (50 ppb) have been reported in femur, kidney, and brain. LAMMA

is used for the analysis of aluminum in brain tissue affected with Alzheimer's disease, with detection limits in the low parts-per-million range. It simultaneously images and analyzes features in unstained and untreated tissue sections, therefore avoiding contamination problems associated with tissue preparation.

Many analytical techniques are also available for the measurement of aluminum concentrations in environmental samples (ATSDR, 1999). These include GFAAS, FAAS, NAA, ICP-AES, ICP-MS, spectrophotometry using absorbance and fluorescence detection, phosphorimetry, and gas chromatography equipped with an electron capture detector (GC/ECD).

Many of the methods are those approved by federal agencies and organizations (ATSDR, 1999). NIOSH has recommended FAAS (Method 7013) and ICP-AES (Method 7300) for detecting aluminum and other elements in filter samples of workplace air particulates, with working ranges of 0.5-10 mg/m^3 for a 100-L air sample and 0.005-2.0 mg/m^3 for a 500-L air sample, respectively. EPA has recommended GFAAS (Method 202.1) and FAAS (Method 202.2) for measuring low levels of aluminum in water and wastewater. Detection limits of 3 µg of aluminum/L of sample and 100 µg of aluminum/L of sample were obtained, respectively.

Additionally, spectrophotometry and GC/ECD have been used to measure low parts-per-billion levels of aluminum in water; for the former technique, a sample detection limit of 4 ppb was reported (ATSDR, 1999). In the field and in the laboratory, flow-injection systems using absorbance and fluorescence detection have been used, with detection limits as low as 0.3 µg/L, while ion chromatography using spectrophotometric detection and on-line preconcentration had a detection limit less than 1 µg/L in aqueous samples. Ion-interaction reversed-phase liquid chromatography with fluorescence detection can detect aluminum as the 8-hydroxyquinoline-5-sulfonic acid complex in environmental water samples (Paull et al., 2000). For the measurement of low parts-per-billion aluminum levels in dialysis fluids, GFAAS is commonly used (ATSDR, 1999). It has also been used to measure levels in soil, and NAA has been used in fly ash. ICP-AES has been used to measure aluminum in rocks, soils, volcano magma, and print, and with pressurized digestion, ICP-AES detection has determined aluminum in air particulates and filters.

2.2 Physical-Chemical Properties

ATSDR (1999; Table 3-2, pp. 162-171) provides a table listing physical and chemical properties of aluminum and several of its compounds, including molecular weight, physical state, melting and boiling points, solubilities in water and organic solvents, and vapor pressure. **Table 2** reports some of these properties. Additional sources were used for compounds not mentioned in ATSDR (1999) but for which toxicity data were available. (*The Merck Index* provides data on many more aluminum compounds.) The **Appendix** presents the speciation of aluminum in biological systems.

Elemental aluminum is clearly metallic, but its compounds are on the borderline between ionic and covalent character (Cotton and Wilkinson, 1962). The trihalides of aluminum (e.g., aluminum chloride), except for the fluorides, are covalent in character; the fluorides of metals give ions of high charge density and are frequently ionic in character (Kleinberg et al., 1960). In aqueous solution, the trihalides are easily hydrated and their solutions exhibit a high electrical conductivity. The aluminum halides can also form complexes with alcohols, ethers, ketones, and aldehydes. The trihalides can form a variety of additional complex compounds. For example, aluminum fluoride, having a great affinity for fluoride ion, can form complexes of the types $M_3(AlF_6)$ (e.g., cryolite $Na_3[AlF_6]$) and $MAlF_4$. These fluoride complexes are extremely stable, and upon acidification yield a tetracoordinated fluoroaluminate complex, AlF_4^-, which acts as a structural analogue of PO_4^{3-} with a bond length equal to the P-O bond (Martin, 1986; Bigay et al., 1987; both cited by Husaini et al., 1996). With β-diketones, aluminum forms compounds that are also covalent in character, such as aluminum acetylacetonate (Kleinberg et al., 1960).

The aluminum(III) cation is sufficiently large to prefer a coordination number of six toward the small fluorine atom, so it adopts structures which are infinitely extended arrays of aluminum and fluorine atoms, leading to a high melting point (Cotton and Wilkinson, 1962). With the other halides, aluminum prefers a coordination number of four, and thus dimeric structures are formed, which have low melting points and may be split by reaction with donor molecules.

Table 2. Physical-Chemical Properties of Aluminum and Its Compounds

Compound	Molecular Weight	Physical State	Odor	Melting Point (°C)	Boiling Point (°C)	Density at 25 °C	Solubility	
							Water at 25 °C	Organic Solvents
Aluminum	26.98	tin-white with bluish tint malleable, ductile metal; crystalline solid	metallic odor when dust is inhaled	660	2327, 2450, 2467	2.70	insoluble; rapidly oxidized at 180 °C	soluble in alkalies and acids
Aluminum aceglutamide[a]	1084.98	no data available	no data available	no data available	no data available	no data available	no data available	no data available
Aluminum acetylaceto-nate[b,c]	324.31	colorless, monoclinic crystals	no data available	190-193	315	3.3	practically insoluble	very soluble in alcohol; soluble in ether and benzene
Aluminum carbonate	145.97	white lumps or powder	no data available	no data available	no data available	no data available	insoluble	dissolves in hot hydro-chloric or sulfuric acid
Aluminum chloride	133.34	white (when pure), ordinarily gray, or yellow to greenish crystals	strong odor of hydro-chloric acid	volatilizes without melting; 190 at 2.5 atm and 194 at 5.2 atm	182.7 at 752 mm Hg; sublimes readily at 178 or 181	2.44	reacts explosively, evolving hydrogen chloride gas	freely soluble in benzophenone, benzene, nitrobenzene, carbon tetrachloride, chloroform; soluble in alcohol and ether
Aluminum chlorohydrate	174.46	glassy solid	no data available	no data available	no data available	no data available	dissolves, forming slightly turbid colloidal solutions (up to 55% w/w)	no data available
Aluminum fluoride	83.98	white, colorless, or triclinic hexagonal crystals	no data available	1291; sublimes at 1272 (760 mm Hg)	1276 (sublimatio n point)	2.88	0.559 g/100 mL	sparingly soluble in acids and alkalies; insoluble in alcohol and acetone
Aluminum hydroxide	77.99	white bulky, amorphous powder	no data available	300	no data available	2.42	practically insoluble; forms gels on prolonged contact	soluble in alkaline aqueous solutions or in hydro-chloric and sulfuric acid
Aluminum lactate	294.18	colorless or white-yellowish powder	no data available	no data available	no data available	no data available	freely soluble	no data available
Aluminum maltolate[d]	402.18	no data available	no data available	no data available	no data available	no data available	no data available	no data available

Table 2. Physical-Chemical Properties of Aluminum and Its Compounds (Continued)

Compound	Molecular Weight	Physical State	Odor	Melting Point (°C)	Boiling Point (°C)	Density at 25 °C	Solubility	
							Water at 25 °C	Organic Solvents
Aluminum nitrate	213.00; 375.15 (hydrate)	white nonahydrate, deliquescent crystals	odorless	73	decomposes at 135	1.72 (hydrate)	very soluble (63.7 g/100 cc)	very slightly soluble in acetone; almost insoluble in ethyl acetate and pyridine
Aluminum oxide	101.94	white crystalline powder	no data available	~2000, 2030, or 2054	~3000	3.97	practically insoluble; soluble in cold water (0.000098 g/100 cc; 980 ppb)	slowly soluble in aqueous alkaline solutions; practically insoluble in nonpolar organic solvents
Aluminum palmitate[e]	793.24	white to yellowish mass or powder	no data available	no data available	no data available	no data available	practically insoluble	practically insoluble in alcohol; when fresh, dissolves in petroleum ether or oil turpentine
Aluminum phosphate	121.95	white infusible powder or crystals	no data available	>1460	no data available	2.56 at 23 °C	insoluble	very slightly soluble in concentrated hydrochloric or nitric acid
Aluminum phosphide	57.96	dark gray or dark yellow crystals	garlic odor	does not melt or decompose thermally at temperatures up to 1000	no data available	2.85 at 15 °C	decomposes	no data available
Aluminum potassium sulfate	258.21	white powder	no data available	no data available	no data available	no data available	50 g/L	insoluble in alcohol
Aluminum sulfate	342.14	white, lustrous crystals, pieces, granules, or powder	odorless	decomposes at 770 or 1040	no data available	2.71	soluble in 1 part water	soluble in dilute acids; practically insoluble in alcohol
Dihydroxyaluminum sodium carbonate[e]	144.00	amorphous powder or poorly formed crystals	no data available	no data available	no data available	2.144	no data available	no data available

Note: Alchlor is not included because no data were available. No data were also found for aluminum calcium silicate, aluminum sodium silicate, and aluminum nitriloacetate complex. Sources: ATSDR (1999); [a]Lewis (1991); [b]Aldrich (1994-1995); [c]Lide (1991); [d]Registry (2000); [e]Budavari (1996)

Soluble aluminum salts of weak acids, such as carbonates, acetates, sulfides, and cyanides, do not exist in aqueous solution or in water, since they undergo complete hydrolysis, resulting in the precipitation of aluminum hydroxide (Kleinberg et al., 1960; Cotton and Wilkinson, 1962). As an acid, salts containing the hydrated ions $[Al(OH)_4]^-$ and $[Al(OH)_6]^{3-}$ occur. Alkali metal aluminates, salts of a weak acid, are extensively hydrolyzed, and addition of carbon dioxide precipitates aluminum hydroxide from their solutions.

2.3 Commercial Availability

General Chemicals, with 34 alum plants and 45% of the market, is the largest U.S. producer of alum (aluminum sulfate) (Boswell, 1998). Additionally, its plant in East St. Louis, IL, manufactures polyaluminum chloride (PAC). Geo Specialty Chemicals is the second largest U.S. producer of alum. It has 11 plants in the Southeast, which is its primary market for the compound. PAC and aluminum chlorohydrate are also made in facilities located in Baltimore, MD, and Balsrrop, LA. Other suppliers of PAC include Nalco and Imperial West, while Cytec manufactures alum (Chapman, 1995; Chem. Mark. Rep., 1996). Delta Chemical Corporation (2000), based in Baltimore, MD, manufactures a variety of PACs, which fall under the trade name DelPAC (e.g., DelPAC 2020 and DelPAC 2500) and are high performance coagulants, as well as sodium aluminate and alum.

United States Aluminate Company, an aluminum chemical manufacturer serving customers in the titanium dioxide, catalyst, zeolite, pulp and paper, construction, bioenzyme, and municipal and industrial water treatment industries, produces high-quality aluminum-based products, including alum and sodium aluminate (US Aluminate, 2000). It is headquartered in Baltimore, MD, and has plants in Ashtabula and Cincinnati, OH.

Aluminum chloride is marketed as the anhydrous and hydrous form (Heydorn et al., 1985). Available data indicate that in 1985, three U.S. companies were producing the anhydrous form, and six U.S. firms were producing the hydrous form. Also in that year, two companies were producing aluminum fluoride and 24 were producing aluminum sulfate. Sodium aluminate is

produced for captive consumption and for merchant use. As of 1985, 11 U.S. companies were producing the compound for the latter.

Many other aluminum compounds are available from Aldrich (1989-1999).

3.0 PRODUCTION PROCESSES

ATSDR (1999, pp. 173-175) provides the production processes for aluminum and several of its compounds. Aluminum is produced from raw materials including bauxite (which contains 40 to 60% aluminum oxide [Al_2O_3]), cryolite (Na_3AlF_6), aluminum fluoride, fluorspar (CaF_2), corundum ($Al_2O_3 \cdot xH_2O$), and kaolin materials. The basic method used in producing aluminum metal involves three major steps: refinement of bauxite by the Bayer process to produce alumina, electrolytic reaction of alumina by the Hall-Heroult process to produce aluminum, and then casting of aluminum into ingots.

Aluminum chloride is produced by the reaction of bauxite with coke and chlorine at a temperature of around 875 °C (ATSDR, 1999). The anhydrous form occurs from the chlorination of aluminum metal and is sold in technical (99.0% pure with an iron content less than 100 ppm) and reagent grade (iron content of less than 10 ppm) (Heydorn et al., 1985). Although it is the procedure used by most companies, some have employed a carbo-chlorination process, using clay as the starting material. Hydrous aluminum chloride can be produced from the anhydrous form by dissolving it in dilute hydrochloric acid. It is usually produced by dissolving hydrated alumina in concentrated hydrochloric acid, followed by the addition of gaseous HCl.

Aluminum fluoride can be produced by several processes (ATSDR, 1999). It is made by heating ammonium hexafluoroaluminate to red heat under nitrogen; by the action of fluorine or hydrogen fluoride gas on aluminum trihydrate at high temperatures, and then calcining the hydrate formed; by fusing cryolite or sodium fluoride with aluminum sulfate; or by the reaction of fluosilicic acid on aluminum hydrate.

Aluminum hydroxide is produced from bauxite (ATSDR, 1999). The ore is dissolved in a solution of sodium hydroxide, yielding aluminum hydroxide, which is precipitated from the solution by neutralization or by autoprecipitation (Bayer process).

Aluminum nitrate is formed by dissolving aluminum or aluminum hydroxide in dilute nitric acid; the solution is then allowed to crystallize (ATSDR, 1999).

Aluminum oxide is produced during the recovery of bauxite, which is crushed, ground, and kiln dried (ATSDR, 1999). It is then leached with sodium hydroxide, yielding sodium aluminate, from which alumina trihydrate is precipitated and calcined (Bayer process).

Aluminum phosphide is made from red phosphorus and aluminum powder (ATSDR, 1999).

Aluminum sulfate is produced from the reaction of freshly precipitated pure aluminum hydroxide, bauxite, or kaolin, with sulfuric acid; the resulting solution is then evaporated and allowed to crystallize (ATSDR, 1999). This yields the commercial grade (iron content less than 0.75% Fe_2O_3 for dry and 0.35% Fe_2O_3 for liquid) (Heydorn et al., 1985). The iron-free grade (iron content less than 0.01% Fe_2O_3) is produced using the same process with the exception that alumina trihydrate is used instead of bauxite or kaolin.

Sodium aluminate, which exists in several forms depending on the manufacturing process used, is usually produced from the direct reaction of alumina trihydrate with sodium hydroxide (Heydorn et al., 1985).

4.0 PRODUCTION, IMPORT, AND EXPORT VOLUMES

ATSDR (1999, pp. 175-179) provides the production, import, and export volumes for aluminum, which are summarized in **Table 3**.

Although aluminum chloride is marketed as both the anhydrous and hydrous form, production of the latter has not been reported since 1980, when 5.2 thousand metric tons (12 million lb) were produced (Heydorn et al., 1985). Recent data for anhydrous aluminum chloride in thousand metric tons (million lb) were 34 (75), 37 (82), 46 (101), 51 (112), and 54 (119) in 1988, 1990, 1992, 1994, and 1995, respectively (ATSDR, 1999). During these same years, annual production capacity for aluminum oxide (alumina, calcined, reduction grade) remained fairly constant, averaging 4980 thousand metric tons (11.1 billion lb).

Table 3. Production, Import, and Export Volumes* for Aluminum

Year	Primary Production	Secondary Recovery	Import	Export
1991	4121 (9.1)	2290 (5.0)	1490 (3.3)	1760 (3.9)
1992	4042 (8.9)	2760 (6.1)	1730 (3.8)	1450 (3.2)
1993	3695 (8.1)	2940 (6.5)	2540 (5.6)	1210 (2.7)
1994	3299 (7.3)	3090 (6.8)	3380 (7.4)	1370 (3.0)
1995	3375 (7.4)	3190 (7.0)	2970 (6.5)	1610 (3.5)
1996	3577 (7.9)	3310 (7.3)	2810 (6.2)	1500 (3.3)
1997	3603 (7.9)	3690 (8.1)	3100 (6.8)	1600 (3.5)
1998	3700 (8.1)	-	-	-

* Data are given in thousand metric tons (billion lb).
Source: ATSDR (1999)

Annual U.S. production of aluminum sulfate (commercial, 17% Al_2O_3) has also been stable from 1984 to 1997, ranging from 1047 thousand metric tons (2.3 billion lb) in 1992 to a high 1268 thousand metric tons (2.8 billion lb) in 1985 (Chem. Eng. News, 1998; ATSDR, 1999). In 1993 and 1994, it was one of the top 50 chemicals produced in the United States, holding the rank at 43. Earlier production values as well as import and export volumes (for the years 1955 to 1984) are available from the *CEH (Chemical Economics Handbook) Product Review* for aluminum chemicals (Heydorn et al., 1985). [Other data provided: Production for aluminum fluoride has not been reported since 1982 when 76 thousand metric tons (170 million lb) were produced. Merchant production for sodium aluminate (62.2% Al_2O_3 basis) was last reported in 1984; the value was 45 thousand metric tons (99 million lb). Import volumes are also given for the period 1964-1985.]

With the global market for water treatment chemicals growing at a slow to moderate rate, organic coagulants and flocculants and PAC top the product list (Boswell, 1998; Ouellette, 1999). In 1997, North American consumption of all coagulants and flocculants (organic and inorganic) was $1.3 billion, with alum and PAC along with other inorganics making up 30% of the market (an estimated 14% and 5% of consumption, respectively) (Boswell, 1998; PR Newswire, 1998). The growth of the U.S. alum market, estimated between 2 and 5%, is largely due to the Safe Drinking Water Act (SDWA), the Disinfectants/Disinfection By-Products (D/DBP) Rule

amendment to the SDWA, which limits the amount of total organic carbon allowed in water at the point of primary disinfection, as well as increases in the paper industry. Approximately 45% of the market for alum and related aluminum products is for the paper industry and another 45% for municipal water treatment. The annual growth of PAC is estimated between 15 and 20%. Although it is not as widely produced or used, the market for aluminum chlorohydrate is also growing.

5.0 USES

Among the numerous applications of aluminum and its alloys, the major uses are in packaging (25% consumption; e.g., drink cans and foil for pie plates and frozen foods), building and construction (15%; siding and roofing, doors, and windows), transportation (34%; bodies, trim, and mechanical parts of cars, boats, and planes), and electrical applications (8%; overhead transmission lines, cable sheathing, and wiring) (ATSDR, 1999).

Aluminum compounds, likewise, have a wide range of uses in industrial, domestic, consumer, and medicinal products. **Table 4** summarizes the uses of several of these compounds.

Because aluminum is more efficient at binding phosphorus than iron, resulting in the greater reduction of sludge, alum, aluminum chlorohydrate, and several high basicity PAC products were being considered over the iron salts as the preferred coagulants for wastewater (Boswell, 1998). PAC, which contains a larger amount of aluminum than alum, was taking over some market share from alum and the iron salts. However, with the passing of the D/DBP Rule amendment to the SDWA in 1998, the use of PAC and alum became limited (Jarvis, 2000). Furthermore, restriction has been placed on the levels of sulfate in potable water. Ferric chloride, therefore, is currently the preferred coagulant. Other commercially available polynuclear aluminum coagulants are polyaluminum silicate-sulfate (PASS) and acidified bauxite (PAX) (Milette and Basisio, 1989; Masschelein, 1992; both cited by LaZerte et al., 1997).

Besides water treatment, alum's other principal market is the pulp and paper industry; together they account for about 95% of consumption (Heydorn et al., 1985). The major use of alum in the pulp and paper industry is to precipitate rosin size on paper fibers. PAC, however,

Table 4. Uses of Aluminum Compounds

Compounds	Uses
alums*	as a hardening agent and setting accelerator for gypsum plaster; in tanning and dyeing; in styptic pencils (former use)
aluminas*	in water treatment; as an accelerator for concrete solidification (high alumina cements)
alkoxides*	in varnishes; for textile impregnation; in cosmetics; as an intermediate in pharmaceutical production
borate*	in the production of glass and ceramics
carbonate*	in antacids
chlorides	anhydrous form: as an acid catalyst (especially in Friedel-Crafts-type reactions); as a chemical intermediate for other aluminum compounds; in the cracking of petroleum; in the manufacture of rubbers and lubricants; as an antiperspirant hexahydrate form: in the preservation of wood; in the disinfection of stables and slaughterhouses; in deodorants and antiperspirants; in cosmetics as an astringent; in the refinement of crude oil; in dyeing fabrics; in manufacture of parchment paper
chlorohydrate	as the active ingredient in many antiperspirants and deodorants
hydroxide	in stomach antacids (including Maalox®, Mylanta®, and Delcid®); as a desiccant powder; in antiperspirants and dentifrices[a]; in packaging materials; as a chemical intermediate; as a filler in plastics, rubber, cosmetics, and paper; as a soft abrasive for brass and plastics; as a glass additive to increase mechanical strength and resistance to thermal shock, weathering, and chemicals; in ceramics; to lower the plasma phosphorus levels of patients with renal failure
isopropoxide*	in the soap and paint industries; in waterproofing textiles
nitrate	in antiperspirants; for tanning leather; as a corrosion inhibitor; in the preparation of insulating papers; on transformer core laminates; in incandescent filaments; in cathode ray tube heating elements
oxide	in the production of aluminum; in the manufacture of abrasives, refractories, ceramics, electrical insulators, catalysts and catalyst supporters, paper, spark plugs, crucibles and laboratory works, adsorbent for gases and water vapors, chromatographic analysis, fluxes, light bulbs, artificial gems, heat resistant fibers, food additives (dispersing agent), and in hollow-fiber membrane units used in water desalination, industrial ultrafiltration, and hemodialysis; as a dosimeter for measuring personnel radiation exposure
phosphate	in over-the-counter stomach antacids
phosphide	as an insecticidal grain fumigant
silicate*	as a component of dental cement; in antacids and food additives
sulfate	as a flocculent for water purification systems and sewage treatment; in the paper and pulp industry; in fireproofing and waterproofing cloth; in clarifying oils and fats; in waterproofing concrete; in antiperspirants; in tanning leather; as a mordant in dyeing; in agricultural pesticides; as an intermediate in the manufacture of other chemicals; as a soil conditioner to increase acidity of plants; in cosmetics and soap; in the preparation of aluminum acetate ear drops Solutions containing 5-10% aluminum sulfate: as local applications to ulcers; to arrest foul discharges from mucous surfaces
trioxide*	as an absorbent, abrasive, and refractory material

Sources: ATSDR (1999); *IPCS (1997)
[a] used as an abrasive in toothpaste; however, due to its costliness for the developing world, there is a drive towards using calcium carbonate ($CaCO_3$) (Williams, 2000)

is taking over alum's share since rosin-sized and unsized paper grades are being produced at high pH levels (PR Newswire, 1998). Given via intravesical irrigation, alum, furthermore, has also been used for decades to control severe hemorrhagic cystitis (Kravoussi et al., 1986; cited by Nakamura et al., 2000). It is also added as an adjuvant to allergenic extracts for hyposensitization or in the preparation of vaccines (May et al., 1986; cited by Klein, 1997).

Like alum, sodium aluminate markets include water treatment and papermaking industry (Heydorn et al., 1985). In the latter, it is a substitute for aluminum sulfate. In the former, it is used to treat potable water and industrial wastewater, serving as a water softener, as a flocculant to trap suspended solids, and to precipitate inorganic phosphates. Captive production of sodium aluminate is chiefly for the manufacture of sodium aluminosilicates and to coat titanium dioxide pigments to improve the pigment's resistance to ultraviolet light.

Additionally, water-soluble aluminum phthalocyanine-polymer conjugates are used as photosensitizers for photodynamic therapy of cancer (Brasseur et al., 1999). In a further application, a knee joint patellofemorotibial metal/polymer porous-coated uncemented prosthesis and its uni-compartmental model, intended for implantation to replace a knee joint or part of it, respectively, have a femoral component made of a surface-hardened titanium-aluminum-vanadium alloy, and tibial and patellar resurfacing components made of an ultra-high molecular weight polyethylene compound fixed to a metal base made of the alloy (FDA, 2000b).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

ATSDR (1999, pp. 188-217) provides data on the releases and the fate of aluminum to the environment. Aluminum is released to the environment by both natural processes and anthropogenic sources, with the former the greater contributor. According to the Toxic Chemical Release Inventory (TRI) (note: only certain types of facilities are required to report; therefore, an exhaustive list is not available), in 1996, a reported 5,605,000 lb of aluminum was released to the environment (air, water, and soil) from 264 large processing facilities. Of this total, 1,683,000 lb were released to the air (accounting for about 30% of total environmental releases), 48, 989 lb to water (0.9%), and 3,873,000 lb to soil (69%). An additional 12,754 lb of aluminum were released

indirectly to publicly owned treatment works (POTWs), some of which may have been ultimately released to surface waters.

Furthermore, 466,000 lb of aluminum oxide were released to the environment (air, water, and soil) from 41 large processing facilities in 1996 (ATSDR, 1999). Of this total, 107,000 lb were released to the air (accounting for 23% of total environmental releases), 505 lb to water (0.1%), and 358,000 lb to soil (77%). An additional 1,328 lb was released indirectly to POTWs.

Degradation does not occur since aluminum is an element (ATSDR, 1999).

6.1 Air

The largest source of airborne aluminum-containing particulates is dust from soil, the weathering of rocks, volcanic activity, and human activities, such as mining and agriculture (ATSDR, 1999). Aluminum is found as silicates, oxides, and hydroxides in the particles, which are deposited onto land and water by wet and dry deposition. Aluminosilicates from aluminum dust comprise up to 14% of the earth's surface (Casdorph and Walker, 1995).

Levels of aluminum vary in the atmosphere, depending on the location of the sampling site, meteorological conditions (e.g., summer versus winter), and the level of industrial activity or traffic in the area (ATSDR, 1999). They are expected to be low in areas near the ocean and high in areas with wind-blown soil. Background levels of aluminum in the atmosphere generally range from 0.005 to 0.18 ng/m^3, but are significantly higher in U.S. cities and industrial areas, which range from about 0.4 to 10 ng/m^3. In the late 1960s to mid-1970s, concentrations up to 8678 ng/m^3 were measured (IPCS, 1997).

Anthropogenic releases are primarily to the atmosphere and account for about 13% of atmospheric aluminum (ATSDR, 1999). The major anthropogenic sources of aluminum-containing particulate matter include coal combustion, aluminum production, and other industrial activities processing crustal minerals. Aluminum levels ranging from 100 to 1000 ppm have been found in air particulate emissions from iron and steel foundries and brass and bronze refineries. High concentrations have also been observed in coal stack emissions from power plants in both the eastern and western United States. Additionally, motor vehicle emissions add 0.9 to 9% of

the observed elemental concentration of aluminum in the air. Aluminosilicates, which can be manmade, are found in products such as talcum powder, asbestos, cat-box litter, table salt, and cigarette smoke (Casdorph and Walker, 1995).

Because aluminum in compounds cannot be oxidized, atmospheric transformations are not expected to occur during transport (ATSDR, 1999). However, if aluminum metal particles are released during anthropogenic activities such as metal processing, they would be rapidly oxidized.

6.2 Water

Aluminum enters natural waters from the weathering of aluminum-containing rocks and minerals (ATSDR, 1999). Levels in surface waters are also affected directly or indirectly by human activity through industrial and municipal discharges (e.g., in the effluent from aluminum manufacturing facilities), surface run-off (e.g., from the weathering of sulfide ores in inactive mines and tailings dumps), tributary inflow, groundwater seepage, and wet and dry atmospheric deposition (e.g., acid precipitation).

The concentration of aluminum in water, as well as its bioavailability and toxicity, is controlled by the chemical speciation of aluminum (IPCS, 1997). (See Section 6.2.1 for further details.) Levels of dissolved aluminum in water vary with pH and the humic-derived acid content of the water (ATSDR, 1999). At pH<5, the concentration is high. Levels up to 269 mg/L were found in surface water samples contaminated with acidic mine drainage (pH 2.1-3.4) and collected at seven different locations in the vicinity of abandoned coal mines in west-central Indiana. Between pH 6 and 8, aluminum is only sparingly soluble. Since the pH of 95% of naturally occurring water is between 6 and 9, the aluminum concentration in most natural waters is extremely low (<0.1 mg/L [ppm]). Humic acid content also plays a role. At neutral pH levels, high dissolved aluminum levels were found in lakes with a high humic acid content.

In raw surface water samples dissolved aluminum concentrations have ranged from 0.001 to 2.76 mg/L in the United States and in finished drinking waters, from 0.003 to 2.67 mg/L (ATSDR, 1999). Aluminum salt coagulants, used in the treatment of potable drinking water, result in approximately 11% of unretained aluminum being transported through a water

distribution system. (See Section 6.2.3 for further details on water treatment.) Finished drinking water samples receiving no coagulation treatment had aluminum levels ranging from 0.016 to 1.167 mg/L (median of 0.043 mg/L), while water receiving alum coagulation treatment had levels ranging from 0.014 to 2.670 mg/L (median of 0.112 mg/L). In treated water at facilities using alum coagulation treatment of raw waters, levels ranged from about 0.01 to 1.3 mg/L (mean of about 0.157 mg/L). In a 1989 study, aluminum levels in drinking water collected from outlets in the western and central parts of the United States were found to be <0.1 ppm. Aluminum levels in household tap water ranged from 0 to 1.029 ppm. Areas with high aluminum concentrations in tap water included Peoria, IL (0.467 ppm), Coos Bay, OR (0.483 ppm), Watertown, SD (0.502 ppm), Waco, TX (0.520 ppm), Yellowstone National Park, WY (0.608 ppm), Philadelphia, PA (0.688 ppm), and Charleston, SC (1.029 ppm).

Compared to aluminum levels in freshwater lakes and streams, marine waters contain much lower aluminum concentrations (<0.001 mg/L; <1 ppb) (ATSDR, 1999). At neutral pH, groundwater wells generally contain aluminum levels less than 0.1 mg/L (<100 ppb); acid precipitation, however, can cause a greater than tenfold increase. In a 1984 study, levels (in finished water obtained from groundwater) ranged from 0.014 to 0.290 mg/L (median of 0.031 mg/L) and in surface water ranged from 0.016 to 1.167 mg/L (median 0.043 mg/L). Additionally, aluminum concentrations were greater than 0.05 mg/L in 55% of the raw surface water samples and in only 4% of the raw groundwater samples.

In atmospheric precipitation (i.e., rain and snow), aluminum concentrations up to 1.2 mg/L have been measured (ATSDR, 1999). The acid-leached concentrations of aluminum in rainwater samples collected in the North Atlantic for seven rainfall events ranged from 1.14 to 35.2 µg/L (ppb); total (dissolved plus particulate) aluminum concentrations ranged from 6.1 to 824 µg/L. During storms, higher concentrations of adsorbed aluminum occurred in the presence of high levels of suspended solids in stream surface water than in their absence.

6.2.1 Speciation of Aluminum in Water

The aqueous chemistry of aluminum has been extensively reviewed (e.g., Driscoll and Schecher, 1989). Three major categories define the various aluminum fractions in water (Srinivasan et al., 1999). These are the following: (1) total aluminum, which is the sum of suspended, colloidal, and monomeric forms of aluminum; (2) particulate aluminum, which is the sum of suspended and colloidal aluminum; and (3) monomeric aluminum, which is further divided into the two forms non-labile (aluminum associated with dissolved organic carbon) and labile (aquo, and hydroxide, fluoride, and sulfate complexes of aluminum). See **Figure 1**.

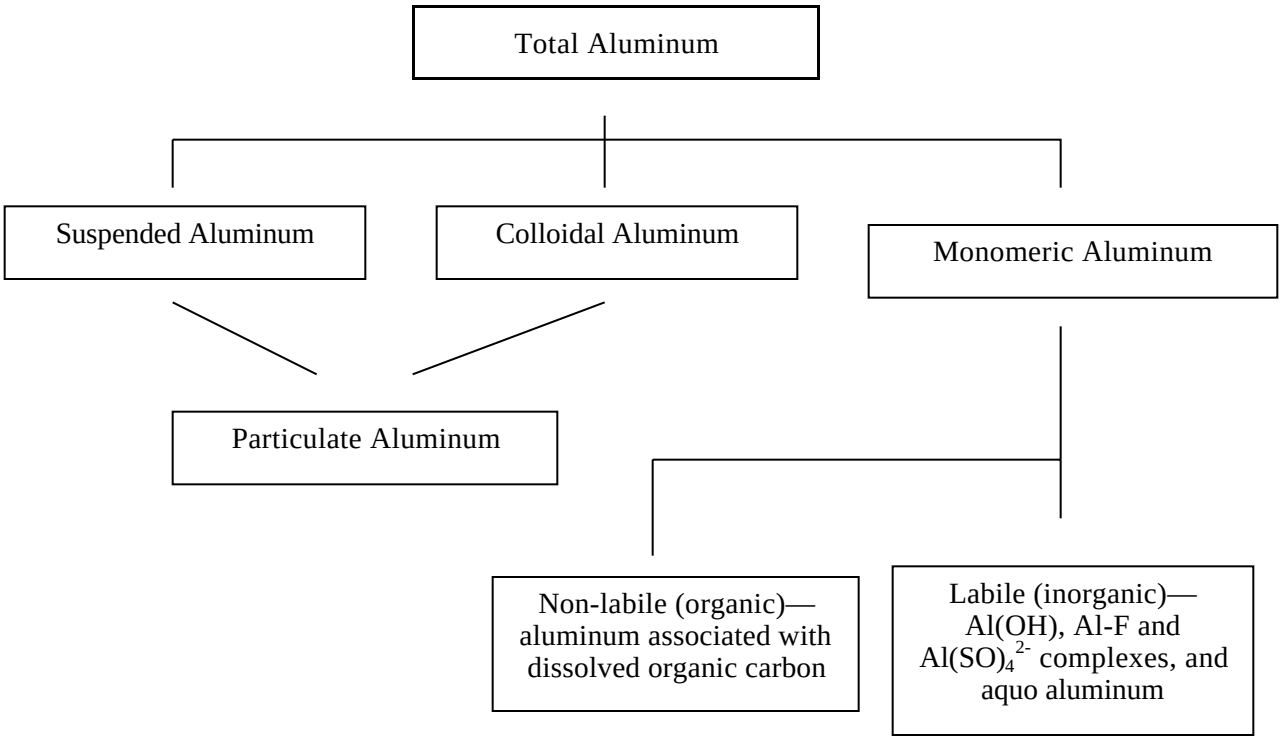

Figure 1. The Various Fractions of Aluminum in Water
Source: Srinivasan et al. (1999)

Raw Water: The solubility of aluminum in equilibrium with solid phase $Al(OH)_3$ depends on the surrounding pH (IPCS, 1997). The aquo complex $Al(H_2O)_6^{3+}$ predominates at pH<4. As the pH (and/or temperature increases), the hydrated trivalent aluminum ion undergoes hydrolysis,

initially forming the $Al(OH)(H_2O)_5^{2+}$ ion and then hydroxyaluminum species such as $Al(OH)_2^+$, $Al(OH)_3$ (insoluble), $Al(OH)_4^-$, $Al_2(OH)_2^{4+}$, and $Al(OH)_5^{2-}$, and eventually hydroxy polymers such as $Al_{13}(OH)_{32}^{7+}$ (IPCS, 1997; ATSDR, 1999). [Fluoride ions can substitute in these complexes; however, in neutral and alkaline solutions, aluminum has greater affinity for the hydroxide ion (LaZerte et al., 1997).] Between pH 5 and 6, the predominant hydrolysis products are $Al(OH)^{2+}$ and $Al(OH)_2^+$; between pH 5.2 and 8.8, the solid $Al(OH)_3$ is most prevalent; and above pH 9, the soluble species $Al(OH)_4^-$ is the predominant species and the only species present above pH 10. Throughout the pH gradient (pH 4.7 and 10.5), polymeric aluminum hydroxides can be found. As polymers come together, aluminum hydroxide becomes large enough to precipitate from solution. Additionally, at pH>7.0 the aluminum hydroxide complexes dominate when the content of dissolved organic matter and silicate is low. At lower pH, aluminum sulfate complexes exist, as well as aluminum-humic acid and aluminum-fulvic acid complexes.

Coagulation of natural organic matter (NOM) in surface water (specifically, the Seine river near Paris, France) with aluminum produced flocs consisting mostly of polysaccharides (other biopolymers analyzed: aminosugars, polyhydroxy aromatics, and proteins), which decreased with increasing aluminum concentration, demonstrating the preferential binding between the metal and polysaccharides (Mason et al., 2000). Using a combination of solid state ^{27}Al NMR and Small Angle X-ray Scattering (SAXS), the presence of organically complexed aluminum and/or dimeric aluminum species, with aluminum in the flocs greater than 99% monomeric, was determined. The coagulation mechanism, therefore, is complexation for flocs formed with aluminum and NOM, where the structure of the aggregates is controlled by the NOM (i.e., structure is sensitive to pH variation, whereas speciation is not significantly affected).

Treated Water: The use of aluminum-based coagulants for the removal of particulate, colloidal, and dissolved substances in water usually results in an increase in the amount of aluminum in the finished water, with a portion of the coagulant remaining as residual aluminum, which consists of

dissolved and particulate species (Srinivasan et al., 1999). However, treatment can also decrease the total aluminum content. For example, use of PAC as the coagulant lowered the mean concentration of aluminum in raw waters from 960 µg/L to a mean value of 120 µg/L in finished water (Schintu et al., 2000). Generally, a concentration between 1 and 5 mg/L is desired with addition of an aluminum salt during water treatment (LaZerte et al., 1997).

The speciation of aluminum in the treated water depends on pH, temperature of the water during treatment, the type of organic and inorganic ligands in the raw water, and treatment conditions (e.g., the amount of coagulant employed) and therefore varies from one plant to another (Srinivasan et al., 1999). While much of the aluminum in raw water is bound with inorganic colloids or large organic molecules, treatment yields a greater amount of mononuclear species, specifically low-molecular-mass chemically reactive labile species.

In addition to aluminum-based coagulants, fluorides are added to many water supplies for the prevention of dental caries (Pitter, 1985). In natural water, the most likely soluble forms of fluorine are the free anion F^-, the undissociated hydrofluoric acid HF, and complexes with aluminum, iron, and boron; in treated water, fluorides exist as less physiologically active fluoroaluminates. In a theoretical study of the forms of fluorine in drinking water after coagulation with alum with artificial fluoridation (optimum free F^- concentration of 1.0 mg/L), fluoroaluminates were nearly all converted to hydroxoaluminates in neutral and alkaline solutions (pH≥7), and the concentration of the free F^- equaled that of the total fluoride concentration; the predominant part of fluorides is present probably in non-complexed form. At a pH of 6, only three complexes, AlF^{2+}, AlF_2^+, and AlF_3 were thought to be significant. Given an alum dosage of 40 mg/L (0.12 mM Al), an operational pH from 5.5 to 7.5, and the presence of organics and fluoride at low concentrations (<1 mg/L), the amount of dissolved aluminum was observed to be a simple function of pH and primarily composed of $Al(OH)_2^+$ and $Al(OH)_4^-$ (Sung and Rezania, 1985). At a pH range of 6.4 to 6.5, the minimum amount of soluble aluminum was about 30 µg/L, and the addition of fluoride at a level of 1 mg/L was found to increase the amount of soluble aluminum by a factor of 10.

Systemic fluorosis, therefore, can be a problem and is particularly so in developing countries, and a safe, efficient, and simple defluoridation process resulting in treated water free from residual aluminum is still underdevelopment (Agarwal et al., 1999). Fluoride removal has been conducted using activated alumina (e.g., Rubel and Woosley, 1979; Belle and Jersale, 1984; Rubel, 1984; Schoeman and Botha, 1985; Hao and Huang, 1986) and combinations with the compound (e.g., activated alumina with a carbon dioxide acidizing method [Xu, 1994] and fluidized activated alumina adsorption [Bishop and Sancoucy, 1978]) as well as activated aluminum oxide (Zhou, 1984). Polyaluminum species CF-1 and PC85-3 removed excess fluorides from water to an acceptable level for drinking use, but activated alumina and bone carbon were more effective filter (Qu and Et, 1994). Other materials employed for defluoridation include an electrocoagulation process using bipolar aluminum electrodes and aluminum sulfate and aluminum basic polychloride (Mameri et al., 1988; N'Dao et al., 1992). Recently, the possibility of removing fluoride and heavy metals from water using alum-treated flyash or PAC has been investigated (Malhotra et al., 1997; Mehrotra et al., 1999).

6.2.2 Fractionation of Aluminum in Drinking Water

Fractionation of aluminum in drinking water at ambient temperature generally occurs by one of three methods (Srinivasan et al., 1999). In the method of Driscoll and Letterman (1988; cited by Srinivasan et al., 1999), total reactive aluminum is separated out using acid digestion (HNO_3) at pH 1 for one hour; total monomeric aluminum is fractionated by extraction with 8-hydroxyquinoline; and the cation exchange-treated monomeric aluminum is passed through a strongly acidic cation-exchange resin. In the method by Van Benschoten and Edzwald (1990; cited by Srinivasan et al., 1999), total reactive aluminum is fractionated with acid digestion at pH 2 for one hour to obtain soluble aluminum; total dissolved aluminum is separated out by filtration of the acid-soluble aluminum through a 0.22 µm-pore size filter; dissolved monomeric aluminum is fractionated by rapid extraction with 8-hydroxyquinoline; dissolved organically bound aluminum is separated out by filtering the sample through a column with a strongly acidic cation exchange resin followed by acidification; and dissolved organic monomeric aluminum was

fractionated by passing the filtered sample again through resin and analyzed without acidification. In the method by Gardner and Gunn (1991; cited by Srinivasan et al., 1999), total aluminum is separated out by acid digestion; dissolved aluminum is separated out by passing the sample through a 0.45 µm-pore size filter; low-molecular weight aluminum is fractionated by dialysis; and the chemically labile aluminum is measured by its speed of reaction with an aluminum binding agent.

6.2.3 Water Treatment Processes

Drinking water production begins with coagulation, followed by flocculation, clarification, filtration, and finally disinfection (LaZerte et al., 1997). Aluminum removal depends on the transformation of the aluminum ions into $Al(OH)_3$ species (Srinivasan et al., 1999). Treatment therefore involves chemical precipitation by pH adjustment (pH range 6.5-8.0). The addition of sulfate expands this range of coagulation (lowers the limit of pH to 6.0) while serving as a catalyst in the formation of solid $Al(OH)_3$ particles.

Treatment by cation-exchange resin, reverse osmosis, and electrodialysis is the most effective process for the removal of aluminum in water (90-100% efficiency), whereas processes involving aeration and stripping, anion-exchange resin, and chemical oxidation/disinfection are poor (0-20% efficiency) (Srinivasan et al., 1999). Lime softening and coagulation coupled with sedimentation and filtration are moderately effective methods (0-70% efficiency).

The treatment of the water supply is not without problems (Srinivasan et al., 1998, 1999). The increased aluminum concentration in treated water can enhance turbidity through the post-precipitation of a hydrous aluminum precipitate in the distribution system, limit the disinfection process by enmeshing and protecting microorganisms, and reduce the carrying capacity of pipes with the accumulation of aluminum hydrolysis products on their walls. Reduction of residual aluminum, which consists primarily of particulate and dissolved forms of aluminum, as much as possible is, therefore, essential. Since particulate aluminum is mostly derived from turbidity-causing substances, the elimination of turbidity from raw water will reduce its presence in treated waters. Particulate aluminum can be readily removed by solid-

liquid separation facilities such as clarifiers (93-96% efficiency observed) and filters (75-87% efficiency observed using sand filtration). Preliminary data indicate that the soluble aluminum fraction can be removed by granular activated carbon (65% efficiency).

6.3 Soil and Sediment

Aluminum, found in soil complexed with electron-rich species such as fluoride, sulfate, and phosphate, is released to soil by the weathering of aluminum-containing rocks and minerals and as a constituent of many mining wastes and solid wastes from coal combustion, aluminum reduction, and other metal processing operations (ATSDR, 1999). Its concentration in soils varies widely, ranging from about 700 mg/kg to over 100,000 mg/kg. Varying concentrations can be found in different soil samples taken from the same area. For example, in different soils of Missouri, aluminum concentrations ranged from 4,800 to 58,000 mg/kg, while in Hawaii, aluminum contents were much higher with concentrations ranging from 79,000 to 317,000 mg/kg. In cultivated and uncultivated soil samples collected during a number of field studies, levels ranged from 7,000 mg/kg to over 100,000 mg/kg (mean of 33,000 mg/kg) for subsurface soils in the eastern United States, from 5,000 mg/kg to over 100,000 mg/kg (mean of 54,000 mg/kg) for subsurface soils in the western United States, and from 13,000 to 76,000 mg/kg (mean of 57,000 mg/kg) for surface horizon soils in Colorado. Aluminum levels in soil also vary with different vegetation types. For example, concentrations in the soils of coniferous forests are often higher than in soils of beech forests.

6.4 Other Environmental Media

Aluminum also occurs naturally in many edible plants (ATSDR, 1999). Acid rain ensures that more aluminum is available for plant uptake, which often occurs and is concentrated in root tissue. Concentrations vary. For example, aluminum content in tea (1% extract) has been measured from 0.378-2.445 mg/L (ppm), whereas in herbal tea, the levels were from 0.140-1.065 mg/L. In ash samples from cultivated plants such as lima beans, cabbage, and tomatoes, values

ranged from 50-30,000 mg/kg (ppm). (See Section 7.0 for more details of aluminum in plants and foods.)

7.0 HUMAN EXPOSURE

ATSDR (1999; pp. 183-130) provides a chapter dedicated to human exposure to aluminum. The large quantity of aluminum in nature and its many uses make exposure to aluminum unavoidable. Exposure for the generally population is mainly through oral intake, and the major sources are drinking water (from the use of aluminum in municipal water treatment), residues in foods, cooking utensils, food and beverage packaging, and aluminum-containing medications (e.g., antacids and buffered aspirins). Additionally, children may ingest aluminum from dirt from unwashed hands or when playing in contaminated soils, vitamin/mineral supplements, treatment for hyperphosphatemia, and from consumer products not normally ingested by adults (e.g., toothpaste) (ATSDR, 1999; Golub and Domingo, 1997). The daily ingestion of aluminum is 30 to 50 mg for almost every individual (Casdorph and Walker, 1995). Other sources for potential exposure to aluminum for children are vaccinations containing aluminum adjuvants, parenteral feeding of premature infants, and dialysis fluids. Other routes of potential exposure to aluminum are via inhalation of atmospheric dust and through the skin (e.g., via use of antiperspirants) (ATSDR, 1999; IPCS, 1997).

Occupational exposure to aluminum occurs in the refining of the primary metal and in secondary industries that use aluminum products, such as aircrafts, automotives, and metal products (ATSDR, 1999). Exposure estimates have been <1 mg per 8-hour shift, assuming that 10 m^3 was inhaled per shift, for aluminum process and production workers (IPCS, 1997). Reported as total dust or particulate matter, other values were 1.67 mg/m^3 for potroom workers, 10 mg/m^3 for metal inert gas (MIG) welders, 1 mg/m^3 for TIG welders, and 1.1 mg/m^3 for those in aluminum soldering of aluminum cables. In workers at an aluminum fluoride plant, mean aluminum levels in urine were 0.011±0.007 mg/L for 15 plant workers, 0.032±0.023 mg/L for 7 foundry workers, and 0.054±0.063 mg/L for 12 potroom workers; the mean level was 0.005±0.003 mg/L for 230 unexposed controls (ATSDR, 1999). The most recent National

Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983 estimated that over 3.3 million workers were potentially exposed to aluminum and its compounds. ATSDR (1999; Table 5-8, p. 223) summarizes the results of this survey. The industries with the largest numbers included plumbing, heating and air conditioning; masonry and other stonework; electrical work; machinery except electrical; certified air transportation equipment; electrical components; fabricated wire products; general medical and surgical hospitals; industrial buildings and warehouses; and special dyes, tools, jigs, and fixtures.

Greater exposure to aluminum is possible for persons living in the vicinity of industrial emission sources and hazardous waste sites, undergoing long-term hemodialysis treatment, drinking water from a residential well, and those consuming large quantities of antacid formulations, anti-ulcerative medications, buffered analgesics, or kaolin-based antidiarrheal medications (ATSDR, 1999).

Below, the sources of potential aluminum exposure have been broken down into topics and discussed separately. (For easier reading, all units of mg/kg, µg/g, µg/L, and mg/L are presented in "ppm".)

Drinking water: Since large aluminum concentrations only occur at a pH <5 and about 95% of natural waters have a pH >6, human exposure to aluminum from water is not great (ATSDR, 1999). Because speciation of aluminum in drinking water is complicated with interactions of pH and various counter ions, measures other than total aluminum are currently not possible (CAL-EPA, 2000). Concentrations in finished waters have been measured from undetectable to 1.029 ppm throughout the United States. As discussed in Section 6.2, the median concentrations of aluminum in drinking water not receiving coagulation treatment and that receiving coagulation treatment were 0.043 ppm and 0.112 ppm, respectively. If an estimated 2 L is being consumed daily by adults, a corresponding 0.08 and 0.224 mg of aluminum is taken in per day (about 1% of the daily 7-9 mg from dietary sources). It is estimated that the daily consumption is 1 to 10 mg of aluminum by most adults from natural sources.

Tea: Tea is a major source of aluminum in the daily diet (Casdorph and Walker, 1995). Those made from Assam, Darjeeling, Ceylon, and some supermarket blends contain a greater amount of aluminum, and those brewed had levels in the range of 2 to 6 ppm, depending on the quality of the water. Using soft tap water, higher levels of aluminum were found (average of 1.6 ppm) compared to tea brewed in hard water. In addition, the substitution of milk for lemon in tea may be better since the absorption of aluminum from the gut is enhanced by citrate.

Beverages, food, and food products: Exposure to aluminum through food is low (ATSDR, 1999). In the Food and Drug Administration (FDA)'s 1991 Total Diet Study, reported daily dietary intakes were from 8 to 9 mg for adult males, ~7 mg for adult females, 11.5 mg for 14- to 16-year-old males, 6.8 mg for ten-year-olds, 6.5 mg for six-year-olds, 4.6 mg for two-year-olds, and 0.7 mg for infants. With low aluminum dietary intake (median of 24 mg/day for adults), there is no major concern regarding its toxicity.

The major contributors of aluminum are grain products (24-49%), dairy products (17-36%), desserts (9-26%), and beverages (5-10%) (ATSDR, 1999). ATSDR (1999; Table 5-4, pp. 207-210) provides a table giving the aluminum concentrations in a number of beverages, foods, and food products. The concentrations vary widely, depending upon the food product, the type of processing used, and the location from which they originate. For beverages (fruit juices, soft drinks, instant and whole coffee, etc.), the levels ranged 0.02-4.3 ppm; for animal products (cooked beef, cheese, milk, etc.), 0.06-14.10 ppm; for fruits (apples, peaches, dried raisins, etc.), 0.05-3.1 ppm; for grains (bread, cereal, rice, spaghetti, etc.), 0.040-400 ppm; vegetables and legumes (corn, peanut butter, potatoes, etc.), 0.1-25.2 ppm; and for dried herbs and spices (basil, cinnamon, thyme, etc.), 82-3,082 ppm. Other food products for which aluminum concentrations were reported were baking powder (2,300 ppm), Oreo cookies (12.7 ppm), and nondairy creamer (25.7-94.3 ppm). Unprocessed foods typically contain <5 ppm aluminum. Measured levels range from ~0.1 ppm in eggs, apples, raw cabbage, corn, and cucumbers to 7.16 ppm in lettuce.

Aluminum compounds are used as additives in many processed foods (e.g., processed cheeses, baked goods, grain products, and nondairy cream substitutes) (ATSDR, 1999).

Common food additives containing aluminum are acidic sodium aluminum phosphate (leavening agent in cake mixes, frozen dough, and self-rising flour [6.5% aluminum]), basic sodium aluminum phosphate (emulsifying agent in processed cheese [3.5%]), aluminum sulfates (acidifying agents [e.g., sodium aluminum sulfate is in baking powders {5.9%}; aluminum sulfate is part of food-starch modifiers {1.3%}; and aluminum ammonium sulfate and aluminum potassium sulfate are used as pickling salts {6.0 and 5.7%, respectively}]), bentonite (materials-handling aid), aluminum color additives (lakes) from various food dyes, and aluminum silicates (anti-caking agents [16.0%]) (ATSDR, 1999; Casdorph and Walker, 1995). Additionally, maltol is used as a food additive worldwide (Maitani et al., 1996).

The potential for accumulation of aluminum has been studied in several aquatic species including fish, amphibians, crustaceans, snails, aquatic insects, and aquatic plants (ATSDR, 1999). Because aluminum is not significantly bioaccumulated in most fish and shellfish (bioconcentration factor values are less than 300), consumption of contaminated fish does not appear to be a significant source of aluminum exposure in humans. Average concentrations (wet weight basis) of aluminum found in the four shellfish categories surveyed by the Food and Drug Administration (FDA) in the mid-1980s were 23±23 ppm in hardshell clams, 115±110 ppm in softshell clams, 33±26 ppm in Eastern oyster, and 30±28 ppm in Pacific oyster. An average of 1 and 0.4 ppm of aluminum were found in the muscle tissue of cod and bluefish tuna, respectively, from the Northwest Atlantic Ocean.

Exposure to aluminum is also possible from natural dietary supplements (ATSDR, 1999).

Milk or infant formulas: Potential exposure to aluminum also arises from the intake of infant milk formulas (ATSDR, 1999). Levels were reported to be lowest in human breast milk and cow's milk, bottled sterile water and glucose water, and most oral multivitamin preparations and highest in modified infant formulas, such as soy formulas, premature infant formulas, and products for specific metabolic disorders. The mean concentrations of aluminum in the latter group range from 0.14 to 3.74 ppm for liquid formulas and from 6.25 to 11.8 ppm for powdered formulas. Compared with a liter of breast milk (0.012-0.147 ppm), the aluminum content per

liter of reconstituted formula was up to 63 times greater. ATSDR (1999; Table 5-5, p. 213) gives aluminum levels in breast milk, humanized infant reconstituted formulas, and in special purpose infant reconstituted formulas. For breast milk, a mean concentration of 0.049 ppm was reported. For humanized infant formulas, the mean concentrations ranged from 0.072 ppm (Similac powder) to 1.463 ppm, while for special purpose infant formulas, the levels ranged from 0.062 ppm (special formulas, specifically Delact powder) to 1.711 ppm (soy formulas, specifically Posobee powder). Soy formulas had the largest concentrations of aluminum, means ranging from 1.192 ppm (Isomil powder) to 1.711 ppm (Prosobee powder). Based on human breast milk or cow's milk containing <0.05 ppm aluminum and ready-to-use milk-based and soy-based formulas containing 0.01-0.36 and 0.40-6.4 ppm aluminum, respectively, infants ingest 3 µg of aluminum a day when fed the former versus up to 2.1 mg aluminum a day when fed certain soy-based formulas, which is 700 times greater. Goat's milk, which usually contains no aluminum, has been recommended as an alternative (Casdorph and Walker, 1995).

Containers for food: Cooking foods in aluminum pots and pans or storing foods in aluminum foil or cans may result in increased aluminum concentrations in food (ATSDR, 1999). In precooked foods such as applesauce, green beans, beef, eggs, ham, pudding, rice, and tomato sauce, levels ranged from <0.1 to 21.6 ppm, while concentrations in the foods after cooking in conditioned aluminum pans ranged from 0.24 to 125 ppm compared to <0.1 to 3.4 ppm when cooked in stainless steel pans. The more acidic the food, the greater the migration of aluminum. The extent of exposure to aluminum from leaching from cookware, however, is uncertain (Rajwanshi et al., 1997). For example, studies have shown that the presence of fluoride results in aluminum leaching from cookware (Casdorph and Walker, 1995). When 1 ppm of fluoride in water, adjusted to a pH 3, was boiled in an aluminum container, almost 200 ppm of aluminum was released in 10 minutes and 600 ppm with prolonged boiling; without fluoride <0.2 ppm was measured. Rajwanshi et al. (1997) found levels ranging from 4.9 to 8.1 ppm under the same conditions during the first 10 minutes. Discrepancies were the result of several factors, including the composition and type of food cooked as well as the aluminum utensil used; previous use of

the utensil; duration of cooking; the presence of salt, sugar, and other ions; and the method of analysis.

Brewing coffee in a new aluminum pot can add 0.88 mg (immediately after brewing) to 1.18 mg aluminum (after a further 12-hour storage in the pot and reheating) to each cup (ATSDR, 1999). Percolators, however, only increase the aluminum content by 0.4 mg and 0.58 mg, respectively. Ground coffee beans contain 51.8 ppm of aluminum.

In canned drinks stored at 15-20 °C, aluminum levels ranged from <0.1 to 74 ppm (ATSDR, 1999). The study concluded that there appeared to be little basis for concern about the ingestion of aluminum when the internal protective coating of cans remains intact, the cans are stored properly, and the contents are consumed in a reasonable period of time. Aluminum, however, was observed to migrate from unlacquered aluminum cans, with beverage concentrations increasing with storage time. Aluminum levels ranged from 0.046-0.170 ppm in Coca-Cola® (pH 2.5, storage for 40-101 days) and from 0.014-0.250 ppm in diet Coca-Cola® (pH 3.0, storage for 44-173 days).

Medications: The intake of aluminum-containing medications such as antacids, buffered aspirins, kaolin-based antidiarrheal agents, and anti-ulcerative drugs at their recommended doses results in greater amounts of aluminum in the body versus that from the intake of food (ATSDR, 1999). It is estimated that from 126 to 5000 mg of aluminum are consumed, which is 6 to 250 times greater than that from food. Aluminum content per dose (single tablet or 5 mL liquid) ranges from 35-208 mg for antacids, 9-52 mg for buffered aspirins, 36-1,450 mg for antidiarrheal drugs, and is 207 mg for an anti-ulcerative drug. Casdorph and Walker (1995) provide the aluminum content of various antacids, buffered aspirin, and antidiarrheal drugs, as well as douches, sold over-the-counter.

Atmospheric dust: As discussed in Section 6.1, background levels of aluminum in the atmosphere generally range from 0.005 to a maximum of 0.18 ng/m^3 in the United States (ATSDR, 1999). If the daily inhalation rate is taken to be 20 m^3, then the maximum total amount of aluminum would

be 3.6 ng/day, which is negligible compared with the estimated dietary intake for adults. When taking into consideration the air in urban and industrial area, which ranges from 0.4-10 ng/m^3, the total amount of aluminum inhaled would range from 8 to 200 ng/day, which is also negligible. Higher exposures are also possible from dusts arising from soil, particularly in industrial or agricultural areas, and from the metal surfaces of air conditioners.

Other products: Exposure may also occur through the use of aluminum-containing products, such as cosmetics and medical treatments (ATSDR, 1999). For example, higher than normal levels are found in patients undergoing long-term hemodialysis treatment. Another source of aluminum exposure is from the use of parenteral solutions (e.g., calcium gluconate, phosphate salts, multivitamin solutions, and human albumin solutions), since aluminum compounds are used in their manufacture or as a result of poor purification or contamination, such as from filters, filter aides, buffer solutions, anticoagulants, and the container itself (Klein, 1997; ATSDR, 1999). Significant contamination occurs in the small-volume parenterals versus the large-volume solutions (Klein, 1997). The main source of aluminum contamination was casein hydrolysate. Aluminum concentrations (µmol/L) ranged from 2-75 in sodium phosphate (3 mmol/L solution), 97-102 in potassium phosphate, 10-187 in calcium gluconate, 43-68 (25% solution; 18 for a 5% solution) in albumin, 3-51 for factor VIII, 8-21 for factor IX, 33-67 in multivitamin infusates, and was 9 in plasminate (50 g/L solution), 25 for heparin (1 mU/L solution), 5 in trace metal solutions, 135 in calcium glucoheptonate solutions, and 35 in magnesium sulfate solutions.

Measurement of aluminum levels in body tissues has been found to be method-dependent (ATSDR, 1999). Normal values range from 0.14-6.24 ppm in whole blood and from 0.13-0.16 ppm in plasma, while in serum levels are generally <0.01 ppm. Aluminum concentrations in urine typically range from 0.0027-0.0081 ppm. In bone, background levels are about 1-3 ppm (dry weight). In brain tissues (mostly gray matter), the background aluminum levels range from 1-3 ppm (dry weight) or <0.5 ppm (wet weight). Urinary and serum concentrations present good estimates of recent exposure, with the latter also providing an estimate of cumulative exposure (Kilburn, 1999).

8.0 REGULATORY STATUS

ATSDR (1999; Table 7-1, pp. 253-269) provides a table listing international, national, and state regulations and guidelines for aluminum and its compounds in air, water, and other media.

The Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit (PEL) of 15 mg/m^3 for total aluminum dust and 5 mg/m^3 for respirable fractions as an 8-hour time-weighted average (TWA) (ATSDR, 1999). The American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute for Occupational Safety and Health (NIOSH) have set guideline values that range from 2 mg/m^3 for soluble salts to 10 mg/m^3 for aluminum metal.

The Environmental Protection Agency (EPA) regulates aluminum and certain aluminum compounds under the Clean Air Act (CAA) and has promulgated performance standards for primary and secondary aluminum plants (ATSDR, 1999). It also regulates aluminum under the Clean Water Act (CWA) and the Safe Drinking Water Act (SDWA). It has established a secondary maximum contaminant level for aluminum in drinking water at a concentration range of 0.05-0.2 mg/L. Furthermore, it regulates aluminum levels in effluents from several point-source categories, including electroplating, inorganic chemical manufacturing, iron and steel manufacturing, ore mining and dressing, coil coating, porcelain enameling, metal finishing, aluminum forming, nonferrous metals manufacturing, and metal molding and casting. EPA recommends that the highest concentrations of aluminum in fresh water that aquatic organisms can be exposed indefinitely and for a brief period, resulting in no unacceptable effect, are 87 and 750 µg/L, respectively. Regarding compounds, aluminum oxide and aluminum phosphide are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" along with aluminum as fume or dust. EPA has established a reportable quantity (RQ) limit of 5,000 lb (2,270 kg) for aluminum sulfate and 100 lb (45.4 kg) for aluminum phosphide. A tolerance limit of 0.1 ppm has been set for residues of aluminum phosphide in or on raw agricultural commodities such as almonds, barley,

corn, dates, rice, sesame seeds, and wheat when it is used as a fumigant for post-harvest treatment.

The Association for the Advancement of Medical Instrumentation (AAMI) recommends that water used in the preparation of dialysate solution consist of <10 µg aluminum per liter (ATSDR, 1999). [The pH of the water of dialysate should be 7.4; a pH other than this increases the amount of dialyzable aluminum (Cornelius and Schutyser, 1984; Savory and Wills, 1984; both cited by Santos et al., 1986).]

In 1998, the Food and Drug Administration (FDA) amended Section 178.3130 of the food additive order to provide for the safe use of aluminum borate as an antistatic and/or antifogging agent for olefin polymers intended for use as food-packaging materials (Food Chem. News, 1999). As of December 31, 1998, three petitions regarding aluminum were still pending. As a direct additive, a petition was made by the International Association of Color Manufacturers to amend section 25.32(k) to provide for the safe use of D&C Red No. 28 and its aluminum lake to color food and dietary supplements. As an indirect additive, a petition was announced by Alcoa Separations Technology to amend Section 177.2910 to clear use of an ultra-filtration membrane consisting of a zirconium oxide membrane containing up to 5% yttrium oxide on a porous aluminum oxide support. Finally, a veterinary petition was made by Milwhite for the use of sodium calcium aluminosilicate, hydrated, as a binder for aflatoxin contamination in feeds. Recently, FDA amended the food additive regulations to provide for the safe use of hydroxybis[2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy-12*H*-dibenzo[*d,g*][1,3,2]dioxa-phosphocin 6-oxidato]aluminum as a clarifying agent for polypropylene and polypropylene copolymers intended for use in contact with food (FDA, 2000c).

Under the Federal Food, Drug, and Cosmetic Act, FDA (2000a) has amended its regulations adding certain labeling requirements for aluminum content in large- and small-volume parenterals as well as pharmacy bulk packages used in total parenteral nutrition (TPN). Furthermore, FDA has specified an upper limit of 25 µg Al/L for all large-volume parenterals used in TPN therapy and has required that applicants submit validated assay methods for the determination of aluminum content in parenteral drug products. The rule becomes effective on

January 26, 2001. FDA has also suggested 4-5 µg Al/kg/day as a possible safe upper limit for aluminum intake from TPN solutions in uremic patients (Klein et al., 1998; cited by CAL-EPA, 2000).

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APPENDIX: SPECIATION IN BIOLOGICAL SYSTEMS

The following discussion is largely based on the review by Martin (1997). Dissociation constants for aluminum complexes are provided in **Table 5**.

Only the Al^{3+} oxidation state needs to be considered in biological systems. Aluminum is comparable in size to atoms of iron and magnesium. This is important since ionic radii frequently have a greater effect on molecular activity than charge. Aluminum often appears to compete with magnesium for oxygen donor ligands and biological processes. Aluminum is most strongly bound by oxygen atoms in carboxylate, deprotonated hydroxy (as in catecholates and serine and threonine), phosphate groups, and other compounds that contain negatively charged oxygen atoms. Unlike heavy metals, which are bound by sulfhydryl and amine groups, aluminum is not bound to sulfhydryl groups and is only bound to amines as part of multidentate ligand systems (e.g., NTA or EDTA).

In water, the rate of ligand exchange of the aquo complex $Al(H_2O)_6^{3+}$ ($1.3\ sec^{-1}$) with water molecules outside the inner coordination sphere is much slower than that of several other aquo metal complexes, and other aluminum complexes have an even slower ligand exchange rate. This low exchange rate means that aluminum binding can inhibit the activity of enzymes that have metals of similar effective ionic radius as cofactors (e.g. Fe^{3+}, Mg^{2+}).

In aqueous solution, two species of aluminum predominate, the octahedral aluminum hexahydrate [$Al(H_2O)_6^{3+}$] at pH < 5.5 and the tetrahedral aluminate [$Al(OH)_4^-$] at pH > 6.2. In the narrow pH range 5.6-6.2, successive deprotonations give the species $Al(OH)^{2+}$, $Al(OH)_2^+$, and a soluble $Al(OH)_3$. $Al(OH)_3$ precipitates at neutral pH. At pH 7.5, the maximum concentration of total aluminum is about 8 µM (0.22 ppm), mostly as $Al(OH)_4^-$, and the free aluminum concentration is only 3 pM. Polynuclear complexes in aqueous solution are unlikely to occur at less than 10 µM (0.27 ppm) total aluminum.

Ligands present, their stability constants with Al^{3+}, and the mole ratio of total Al(III) to total ligand also influence the amount of free Al^{3+} in aqueous solution. When Al^{3+} displaces a proton from an acidic ligand to form complexes, the amount of the free cation in neutral aqueous solution is pH-dependent.

Absorbed Al^{3+} readily forms low-molecular-weight complexes, physically bound macromolecular complexes, or covalently bound macromolecular complexes (Ganrot, 1986; cited by ATSDR, 1999). Aluminum may form low-molecular-weight complexes with carbohydrates, amino acids, phosphates, nucleotides, and other organic acids. These low-molecular-weight complexes may be very stable chelates and metabolically active. Much of the aluminum may form macromolecular complexes with biological compounds for which it has a high affinity, such as proteins, polynucleotides, and glycosaminoglycans. The macromolecular complexes are expected to be less metabolically active than the low-molecular-weight complexes and may be so stable that binding is considered to be irreversible.

The insoluble compounds formed with phosphate have variable compositions, with aluminum speciation ranging from an amorphous $AlPO_4$ at low pH to the formation of $Al(OH)_3$ at high pH. Within the cell, ATP is the predominant small molecule aluminum binder, effectively competing for solid $AlPO_4$. Because aluminum binds so strongly to phosphates, processes involving ATP or ADP may also transfer aluminum.

Probably the most important aluminum complex for intestinal absorption is that with citrate, and at concentrations of 0.1 mM in the blood plasma, citrate is the most important small molecule that binds Al^{3+}. Aluminum easily displaces alkaline earth metals from their citrate complexes. Citrate will solubilize Al^{3+} from the insoluble $Al(OH)_3$ and $AlPO_4$, resulting in greater bioavailability of Al^{3+}. At low pH values, such as might occur in the stomach, Al-citrate complexes are favored with some formation of Al^{3+}-oxalate around pH 2-3; however, most aluminum is absorbed in the small intestine where the pH may not be as low as in the stomach (Martin, 1986). Treatment of humans with citrate or citric acid along with aluminum compounds results in significant increases in tissue and urine aluminum concentrations, especially when high doses of aluminum are administered. At lower aluminum doses, it appears that the co-administration of citrate does not significantly raise the concentration of aluminum in tissue or plasma when compared to subjects dosed with low doses of aluminum alone (Greger, 1992).

Aluminum may also form relatively strong complexes with one to five fluoride ions (Martin, 1986). The fluoride-Al^{3+} complex is stronger than the fluoride-Fe^{3+} complex, which is different than with other ligands.

When there is an absence of phosphates, citrate, transferrin, and nucleotides, then catecholine may be the major aluminum binding species. Neurotransmitters, such as DOPA and epinephrine are known to bind aluminum at picomolar concentrations at neutral pH. Aluminum may bind to the catechol moiety of norepinephrine and may disrupt neurochemical processes. It is interesting that in a recent study with rats it was found that aluminum had both a positive and negative effect, depending on the length of aluminum exposure, on the transport of methionine, which is a precursor for catecholamines and choline (Sedrowicz et al., 1998).

Table 5. Dissociation Constants for Complexes with Aluminum (Al^{3+})

Ligand	Complex	-log K_D
Fluoride	AlF^{2+}	6.2
Hydroxide	$Al(OH)^{2+}$	8.5
Malonate (Mal)	Al(Mal)	7.6
Phosphate	$Al(HPO4)^{+}$	9.7
Salicylate (Sal)	$Al(Sal)^{+}$	14.1
Citrate (Cit)	$Al(Cit)^{0}$	8.1
EDTA	$Al(EDTA)^{-}$	24.1
Transferrin	$AlTf^{-}$	13.0

Source: Rowatt et al. (1997)