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Provisional Peer Reviewed Toxicity Values for

Aluminum
(CASRN 7429-90-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
i.v.	intravenous
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ALUMINUM (CASRN 7429-90-5)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

INTRODUCTION

Verified toxicity values for aluminum (Al) and its compounds are unavailable on IRIS or HEAST (U.S. EPA, 2006, 1997), except for a chronic oral RfD of 4E-4 mg/kg-day for aluminum phosphide. However, occupational guidelines and standards have been established for a number of chemical and physical forms of Al, including, from ACGIH, 8-hour TWA-TLVs of 10 mg/m^3 for the compound as a metal dust or oxide, 5 mg/m^3 as "pyro" powders or welding fumes, and 2 mg/m^3 for soluble salts or organic forms of the metal (ACGIH, 1998). From NIOSH, 10-hour TWA-RELs of 10 mg/m^3 are specified for "total" Al dust versus 5 mg/m^3 for the respirable portion (NIOSH, 1994). NIOSH covers all other forms of the metal by identical values to those specified by ACGIH (ACGIH, 1998). OSHA PELs for Al include an 8-hour TWA value of 15 mg/m^3 for "total" metal dust, versus 5 mg/m^3 for the respirable portion (NIOSH, 1994). The U.S. EPA's CARA list (U.S. EPA, 1994) cites a HEA for Al (U.S. EPA, 1987), and ATSDR has updated its toxicological profile of the element (ATSDR, 1998).

The U.S. FDA (2000) has specified a maximum aluminum concentration of 25 mcg/L in large-volume parenterals (LVP) used in total parenteral nutrition (TPN). The FDA regulation applies to all LVPs used in TPN, including but not limited to parenteral amino acid solutions, highly concentrated dextrose solutions, parenteral lipid emulsions, sodium chloride and electrolyte solutions, and sterile water for injection.

Research papers pertinent to the potential toxicological and carcinogenic effects of Al were sought through computer searches of the HSDB, RTECS, MEDLINE and TOXLINE (and its subfiles) databases, covering the time period 1995-1999. The literature searches were conducted in June, 1999.

REVIEW OF PERTINENT DATA

The review by Stokinger (1981) gives an account of Al as an all-pervasive component of products that are central to the daily lives of most Americans. For example, the metal is a crucial part of manufactured products for the building, automobile and container industries, while Al as powder or flake is a component in a number of consumer products, such as paints, fireworks, etc. Al complexes and minerals are used in the brewing and paper industries, and as coagulants for water purification. Aluminum oxide finds application in abrasives, as a catalyst or absorbent, and as a component in fillers. Aluminum chloride is included in cosmetic formulations such as deodorants.

Human exposure to Al arises principally from food and water, through its widespread use in food additives, packaging and cooking utensils and Al-containing medications, particularly antacid, buffered aspirin, anti-ulcer and anti-diarrheal formulations (Marquis, 1989; Lione, 1985). Pennington and Schoen (1995) estimated daily Al intakes of 0.1-0.3 mg/kg-day for infants and children 6 months-6 years of age and 0.1-0.18 mg/kg-day for older children and adults, based on the FDA Total Diet Study (1993) and the U.S. Department of Agriculture Nationwide Food Consumption Survey (1987-1988). These data are in broad agreement with those of Wilhelm et al. (1995) who reported the dietary intake of Al in German children (living in the Duisberg area) as ranging from 0.008 to 0.11 mg Al/kg-day. In addition, these values are consistent with a range of 1-20 mg/day (0.014-0.3 mg/kg -day) for normal oral daily Al intake from food and water reported by other investigators (Ganrot, 1986; Iyengar et al., 1987; Wilhelm et al., 1990). However, users of Al-containing medications can ingest much larger amounts of the element, possibly as high as 840-5000 mg/day (12-71 mg/kg-day) from antacids, 126-728 mg/day (1.8-10.4 mg/kg-day) from buffered aspirins and 828 mg/day (11.8 mg/kg-day) from anti-ulcer compounds when taken at recommended dosages (Lione, 1985).

Toxicokinetics of Aluminum

There is a large amount of information available on the absorption, transfer from tissue to tissue and elimination of Al from the body, including data that have been amassed from studies on either human volunteers or laboratory animals. In general, the chemical appears to be poorly absorbed from the gastrointestinal tract, though the portion of the load that is retained will vary depending on the concentration, the chemical species administered, the fasting or fed state of the

host, gastrointestinal pH, animal model, etc. For example, Yokel and McNamara (1988) administered single oral doses of a number of Al compounds (both water soluble and insoluble) to New Zealand white rabbits and obtained absorbed proportions of the load ranging from 0.27% to 27%. Fractional uptake of Al in humans under normal conditions (i.e., with no intake of large quantities of Al from medicine) was estimated to be 0.1-0.3% assuming an intake of 20 mg Al/day (0.3 mg Al/kg-day) and urinary excretion of 20-50 µg Al/day (0.3-0.7 µg Al/kg-day) (Ganrot, 1986). However, little information is available on the actual mechanism by which the element and its compounds are transported across the brush border. (Wilhelm et al., 1990; Lione, 1985).

Although the overall extent of Al absorption is poor following oral exposure, there may be significant intake of the compound by those taking large amounts of Al compounds in patented remedies. As stated, absorption of Al is influenced by gastrointestinal conditions and content because Al can form various complexes with different solubilities and oxidation states depending on pH and interactions with dietary constituents. At low pH (3-5) in aqueous solutions, the soluble (ionic) forms of the Al prevail (Al^{3+}); at high pH (>8), Al in the form of soluble aluminum oxide is present; and at pH 5-8, the element is predominantly in the form of aluminum hydroxide, which is insoluble (van der Voet and de Wolff, 1986; Wilhelm et al., 1990). Ingested constituents that can influence absorption by forming complexes with Al include phosphate, fluoride, calcium, citrate and lactate. For example, Al is used to bind dietary phosphorus and decrease its absorption as a control for hyperphosphatemia, and citrate and lactate are complexing agents that can significantly increase Al absorption (Slanina et al., 1984, 1985, 1986; Partridge et al., 1989; Domingo et al., 1991; Ittel et al., 1991; Lione, 1985; Wihelm et al., 1990).

A number of recent reports of studies on the gastrointestinal absorption of Al have examined the influence of organic anions such as citrate. In general, the presence of such components appears to enhance the absorption of Al, within narrow limits. For example, Deng et al. (1998) administered a single oral dose of either distilled water, 2 mmoles/L aluminum chloride or 2 mmoles/L aluminum chloride plus 2 mmoles/L sodium citrate to six male Wistar rats/group. Animals were bled at 1, 2 and 4 hours after dosing, then terminated after 6 hours. Inductively coupled plasma (ICP) was used to measure Al concentrations in blood, bone (tibia), kidney, liver and the intestinal wall. Irrespective of treatment, the appearance of Al in the blood of dosed groups peaked after 1 hour, with the concentration of the element at higher levels in those animals receiving citrate in addition to aluminum chloride. In those animals receiving aluminum chloride alone, significant tissue concentrations of the element were restricted to the gastrointestinal wall. Those receiving citrate displayed measurable quantities of the element in several of the other monitored tissues, including bone.

Sutherland and Greger (1998a) used a similar dosing regimen to examine the kinetics of absorption and elimination of Al in male Sprague-Dawley rats that had received a single oral dose of 0, 0.25, 0.5 or 1 mmoles/L/kg body weight aluminum lactate in 1 mL of 16% citrate. Concentrations of Al in serum, liver, kidney or bone (tibia) were measured at various post-dosing time intervals up to 6 hours. Depending on the dose, absorption factors for Al of up to 4.2% of the administered dose were observed, with the greater proportion retained in bone. The authors reported a slower rate of absorption in those animals receiving Al at the higher doses, an

observation potentially indicating reduced gut motility and/or saturation of the transcellular absorption processes at the higher concentrations. Aluminum deposited in kidney and bone appeared to turn-over at a slower rate than in the liver.

The influence of citrate on the gastrointestinal absorption of Al in man was examined directly by Taylor et al. (1998) who administered a drink containing Al and citrate to three volunteers. Aluminum and citrate concentrations were monitored in serial blood and urine samples for up to 24 hours. The kinetics of citrate and Al differed markedly, the former peaking in plasma after 32 minutes, versus 87 minutes for Al. This suggests that Al probably does not cross the gastrointestinal barrier as the citrate. Furthermore, the authors reported that the overall extent of Al absorption had probably not exceeded 1% in their experiment, a finding that contrasts with the higher values reported by Sutherland and Greger (1998a) in Sprague-Dawley rats and by Deng et al. (1998) in Wistar rats.

As discussed in a report by Glynn et al. (1999), gastrointestinal absorption of Al from aqueous media will be almost impossible to predict, because of the likelihood that the element will become absorbed to food particles in the intestinal lumen. Accordingly, depending on the dose, mode of delivery and caloric state of the experimental animal (fed/fasted), significant amounts of aqueous forms of Al will be absorbed only when available binding sites on food have become saturated. This presents an inherently complex overall picture of the element's absorption since, additionally, the normal dietary content of Al will be substantial. Thus, it may be assumed that some sequestered Al will be absorbed along with non-sequestered water soluble forms of the element, while the rest will be retained within the gastrointestinal tract.

Sutherland and Greger (1998b) used their aluminum lactate in 16% citrate dosing regimen to examine the comparative importance of biliary versus urinary excretion of Al. Five to seven male Sprague-Dawley rats/group who had previously received an implanted bile cannula were treated by gavage. Another similarly-treated cohort of five animals/group were housed in metabolic cages immediately after dosing to provide 0- to 3-hour and 3- to 6-hour urine specimens. At termination, all animals were sacrificed and exsanguinated, and tissue, bile and urine samples were measured by graphite furnace atomic absorption spectroscopy. Among the key findings to emerge from this study was the incremental appearance of Al in bile as early as 15 minutes after dosing. However, overall amounts of Al were greater in the 3-hour urine samples than those that had accumulated in bile samples collected within a similar time frame. The fact that control rats excreted 3 times more Al in bile than in urine during the first 3 hours after dosing led the authors to conclude that, at low exposure to Al (in controls receiving Al solely from food), the liver is capable of excreting the element to the bile, a mechanism that becomes saturated as the level of Al administration becomes increased. Thereafter, urinary excretion becomes the primary route of elimination in circumstances of Al overload.

Aluminum can also be absorbed by inhalation as indicated by age-related deposition in the lungs of the general population and exposure-related increased blood and urine concentrations in workers exposed to Al (Bast-Pettersen et al., 1994; Sjogren et al., 1996; Hosovski et al., 1990; Wilhelm et al., 1990; U.S. EPA, 1987). Aluminum occurs primarily in particulate form in the ambient atmosphere and as various dusts and fumes during its production and use. Common forms of inhaled Al include aluminum oxide (alumina; Al_2O_3), pyro powders

(powder and flake Al-treated to reduce surface oxidation), Al welding fume and soluble salts (e.g., aluminum chloride and sulfate) (ACGIH, 1998).

Neurotoxicity as a Primary Toxicological Effect of Aluminum

One of the greatest health concerns regarding Al is its neurological effects. The first evidence for Al-induced neurotoxicity in humans was seen in patients who, as a result of receiving long-term hemodialysis for chronic renal failure, developed a degenerative neurological syndrome (dialysis dementia) characterized by the gradual loss of motor, speech and cognitive functions (Alfrey, 1993). This dementia, attributable to Al in the dialysate, is usually fatal within 6-9 months after the first clinical signs appear. In addition, many patients received high oral doses of Al to act as phosphate binders. Autopsies of these patients revealed increased concentrations of Al in the gray matter and cerebral spinal fluid (CSF) but no evidence of neurofibrillary degeneration (NFD) despite the elevated Al levels. Once the connection between Al and dialysis dementia was established, Al was removed from dialysis fluid and the incidence of dementia rapidly declined, thereby strengthening the argument that Al was a causal agent in dialysis dementia (Ganrot, 1986).

Amyotrophic Lateral Sclerosis (ALS) and Parkinson's Disease (PD) are other neurological diseases which have been associated with Al exposure. ALS is a progressive disease of the Central Nervous System (CNS) that is characterized by an accumulation of neurofibrillary tangles. In Guam, southern West New Guinea and parts of Japan, there is an unusually high prevalence of ALS and PD. This may be related to the natural abundance of Al coupled with the virtual lack of magnesium and calcium in the drinking water supplies and soil of these areas. In a study designed to evaluate effects of high Al and low calcium levels in the diet, much like the conditions associated with Guam and other similar areas, cynomolgus monkeys were placed on a low calcium diet either with or without supplemental Al and manganese (Garruto et al., 1989). Chronic calcium deficiency alone produced neurodegenerative effects, although neurofibrillary changes were most frequently seen in the monkeys on a low calcium diet supplemented with Al and manganese.

Though a cause and effect relationship between Al and three forms of chronic encephalopathy in humans: senile dementia of the Alzheimer type (SDAT, Alzheimer's Disease), endemic Amyotrophic Lateral Sclerosis (ALS) and endemic Parkinsonism-dementia (PD, a mixture of Parkinsonism and senile dementia) has been suggested, there is no firm evidence that it plays a causal role in the development of these diseases (Ganrot, 1986; Lione, 1985). The condition is degenerative and characterized by the progressive loss of speech, motor and cognitive functions, with death typically occurring within 1-6 months. Autopsies of patients revealed increased concentrations of Al in the gray matter and cerebral spinal fluid (CSF), though with no conclusive evidence of NFD or other neuropathological changes despite the elevated Al levels.

The neurotoxicity of Al is well documented in certain animal species. Aluminum induces a spectrum of behavioral abnormalities and brain neurofibrillary degenerative changes in rabbits and cats when injected intracranially or parenterally in high doses, though hamsters and monkeys are less sensitive (Ganrot, 1986; Lione, 1985). Such studies have been designed as models for

the possible neurotoxicological effects of Al in humans. However, it should be noted that the neurofibrillary changes in affected animals differ in morphological detail from those associated with SDAT. As discussed further in the Oral Toxicity section, oral doses of Al can also induce neurobehavioral effects in adult mice and rats and in their developing offspring. In general, such neurotoxic effects of Al appear to be more subtle than those induced through routes of administration that by-pass the gastrointestinal tract, perhaps reflecting the lower doses of Al reaching the brain.

Recent reports of studies on the effects of Al on neurotoxicity in animals have sought to define the biochemical mechanisms that are impaired when Al crosses the blood-brain barrier. However, a unifying concept has yet to emerge, though the passage of the element into various regions of the brain has been clearly demonstrated (Deloncle et al., 1995). Among the many biochemical functions and processes that appear to be perturbed by the presence of Al in the brain are the peroxidation status of biological membranes (Katyal et al., 1997; Deloncle et al., 1999), inhibition of the neuronal glutamate-nitric oxide-cyclic GMP pathway (Cucarella et al., 1998), and the marked reduction of protein- and non-protein-bound thiols and the specific activity of Na^{+}/K^{+} and Mg^{++} ATPases (Katyal et al., 1997). The relative importance of each of these mechanisms and how (or whether) they interact to bring about the observed physiological changes remains unclear.

Other Effects of Aluminum

Osteomalacia was frequently observed among long-term dialysis patients with neurological signs and is commonly attributed to Al overload (Ganrot, 1986; Lione, 1985). This bone condition is characterized by widened osteoid (unmineralized bone matrix) with no fibrosis, reduced mineralization rate, skeletal pain and a strong tendency for fractures, lack of response to vitamin D therapy and increased Al concentration in bone. Effects on bone histology and elevated bone Al levels have also been observed in patients with normal renal function who received total parenteral nutrition with Al-contaminated casein as a protein source, and in parenteral Al loading induced osteomalacia in rats and dogs (Lione, 1985).

There are a number of published reports of studies in which the carcinogenicity of aluminum compounds has been evaluated. These include oral exposure studies in which the compounds were made available to experimental animals in the drinking water or diet (Schroeder and Mitchener, 1975a,b: Oneda et al., 1994), and inhalation epidemiological studies, in which the incidence of tumor formation in persons exposed to aluminum-containing dusts and fumes in an occupational setting was compared to unexposed individuals (Spinelli et al., 1991; Thériault et al., 1984, 1990; Armstrong et al., 1986; Tremblay et al., 1995; Selden et al., 1997; Cullen et al., 1996; Dufresne et al., 1996; Ronneberg and Langmark, 1992). However, it has been generally concluded that the inferential association between exposure to Al and marginally increased incidences of tumors of the bladder and/or lung are confounded because of the co-exposure of subjects in such settings to other harmful and potentially carcinogenic substances, such as polycyclic aromatic hydrocarbons (PAHs and coal tar pitch volatiles (CTPV) (Ronneberg and Langmark, 1992). Therefore, the issue of the potential carcinogenicity of Al compounds remains uncertain.

Human Studies

Oral Exposure

Few reports have been identified that address the toxicological effects of Al in humans exposed orally. Furthermore, in a review, Reiber et al. (1995) pointed to the conflicting findings that have been reported when the incidence of neurological symptoms has been assessed in relation to Al exposure in either cross-sectional, ecological or case-control epidemiological studies. Among the more recent studies that have used this approach, Martyn et al. (1997) discussed the findings of a case-control study involving 441 men in England and Wales who were afflicted with either Alzheimer's disease, brain cancer, dementia or other neurological conditions. Assessing the historical exposure of these subjects failed to establish a link between Al in drinking water at the prevailing concentrations (below 0.2 mg/L) and the incidence of one or more of the conditions under investigation. No data were located regarding the oral carcinogenicity of aluminum compounds in humans.

Inhalation Exposure

Neurobehavioral effects were evaluated in a group of 87 Al foundry workers who were occupationally exposed to 4.6-11.5 mg/m^3 Al fumes and dust for a mean of 12.0 years [standard deviation (SD) 4.5 years, shortest exposure 6 years] compared to an unexposed control group (n=60) who were matched for age, job seniority and social status to exposed subjects (Hosovski et al., 1990). It is reported that environmental Al concentrations were measured for each worker separately during the winter and summer, implying that personal sampling may have been used and that the contributing concentrations are time-weighted averages. In certain places, the number of particles ranged as high as 329-1020/cm^2 air, and dust particle sizes were ≤1, 1-5 and ≤5 microns in 65.6, 26.6 and 7.6% of the samples, respectively. Tests of psychomotor ability (simple and complex reaction time, oculomotor coordination), intellectual ability (Wechsler intelligence, performance intelligence and verbal intelligence quotients and Wechsler subtests on information processing, memory, understanding, calculation, coding, picture completion, picture grouping, object assembling, assembling of cubes and common concepts) and cerebral damage (Bender visual motor test) were conducted. Performance of the exposed workers was found to be significantly ($p<0.02$) impaired on the complex reaction time, oculomotor coordination, memory, coding, picture completion and object assembling tests. However, the investigators noted that the performance deficits had no clinical manifestations, and that additional studies were probably needed to confirm the possibility of cerebral damage. The study yielded a lowest available non-duration adjusted LOAEL of 4.6 mg Al/m^3 for psychomotor and cognitive impairment during repeated 8-hour occupational exposures (Hosovski et al., 1990), that could be corrected for discontinuous exposure (10 m^3/20 m^3 and 5 days/7 days) to yield a $LOAEL_{HEC}$ of 1.64 mg/m^3 Al.

Aluminum oxide powders were administered to Canadian miners (mainly underground gold and uranium miners) in known exposures as a means of prophylaxis against silicosis (Stokinger, 1981; Rifat et al., 1990). Data in which more than 42 million Al treatments (≈150,000 man-years) had been given over a period of 27 years ending in 1971 were reviewed

by Stokinger (1981). The effectiveness of this treatment is uncertain but no lung damage or other ill effects (not specified) were observed. The powders (McIntyre powder) were prepared by grinding Al pellets so that 96% of the particles were ≤1.2 μm in diameter. During this process most of the particles became oxidized to aluminum oxide; the powder contained 85% aluminum oxide and 15% elemental Al. According to Stokinger (1981), recommended exposure concentrations were 30,000 particles of respirable size per cubic centimeter (ppcc) for 10 minutes/day or 10,000-20,000 ppcc for 20 minutes/day (total treatment days not indicated). Rifat et al. (1990) stated that the recommended exposure was to an Al dust concentration of 20,000-34,000 parts per ml air in the miners' changing rooms before each shift for 10 minutes. Stokinger (1981) reported that the 30,000 ppcc concentration corresponds to ≈350 mg/m^3, which is equivalent to an 8-hour average concentration of 2 mg/m^3. Based on the Stokinger (1981) data and the fact that one unspecified study used levels 30 times higher than advised, the TLV of 10 mg/m^3 is recommended for Al dust (ACGIH, 1998).

The increasing awareness of the potential neurotoxicity of Al has resulted in a number of investigations of the incidence of neurotoxicological symptoms in Al workers. Although treatment with McIntyre powder had not produced apparent adverse effects, a neurobehavioral evaluation of male miners (261 exposed to McIntyre powder, 346 unexposed) who started working between 1940 and 1979 (additional duration data not reported) was performed in 1988-1989 (Rifat et al., 1990). There were no significant differences between exposed and unexposed miners in reported diagnoses of neurological disorder. Results of cognitive testing (Mini-Mental State Examination for general cognitive function, Ravens colored progressive matrices test for reasoning and Symbol Digit Modalities Test for spatial perceptual accuracy and information processing), however, showed that the exposed group had significantly ($p \leq 0.001$) impaired performance on at least one test, and when all test scores were summed. Also, the likelihood of scores in the impaired range increased with duration of exposure.

A neurologic syndrome was described in Al smelting plant potroom workers (White et al., 1992). Twenty-five men were evaluated for suspected work-related neurologic illness based on findings in three patients studied previously. The average duration of employment was 18.7 years (SD, 3.6; range, 12-23 years), 15 of the patients were working at the time of evaluation, and 10 had taken early retirement or medical leave due to workplace-related symptoms (mean length of time since exposure was 1.3 years ranging from 0.2-5 years). Quantitative exposure level data were not reported, but 21 of the workers had been employed in the potroom prior to installation of fume hoods for a mean duration of 5.3 years (range 3-7 years). Symptoms most often reported by the patients were frequent loss of balance (88%), memory loss (84%) and joint pain (84%); other symptoms included dizziness (80%), numbness (80%), parasthesias (72%) and tremor (68%). Neurologic examinations showed mild to moderate signs of lack of coordination (tremor, dyssynergy of upper extremity limb movement or ataxia) in 84% of the patients. Neuropsychologic effects were evaluated in 21 of the patients using the Wechsler Adult Intelligence Scale-Revised (intellectual functioning), Wide Range Achievement Test-Revised (academic functioning), Halstead-Reitan Neuropsychological Test Battery (neuropsychological assessment) and Minnesota Multiphasic Personality Inventory (personality functioning). Memory function was assessed with the Wechsler Memory Scale (14 patients) and Wechsler Memory Scale-Revised (8 patients). The memory function evaluation showed mild to moderate impairment on subtests of immediate recall for verbal or visual information (70-75% of the

tested patients) and delayed verbal or visual recall (50-70%). Other effects included mild or moderate impairment on Halstead-Reitan tests of abstract reasoning and flexible thinking (42% of the tested patients), memory for tactile information (53%) and sustained attention and discrimination of tonal and speech patterns (44 and 64%, respectively). On the Wechsler memory and Halstead-Reitan tests, mild and moderate impairment was defined as scores 1.5-2 and ≥2 standard deviations below the mean of the normal population, respectively. Most (89%) of the patients tested with the Minnesota Multiphasic Personality Inventory had abnormally elevated scores (≥2 SDs above the population mean) indicative of clinical depression. Significant positive correlations were found between severity of incoordination (signs and symptoms) and degree of exposure (qualitative) before the introduction of the ventilation hoods.

White et al. (1992) noted two other studies that described neurologic problems among Al smelter workers. Thus, an evaluation of 444 electrolysis workers found neuropsychiatric changes in 123 (28%), "neurotic syndromes" in 89 (20%) and "slight pyramidal and cerebellar changes" in 39 (9%) (Langauer-Lewowicka and Braszczynska, 1983). In the second study, symptoms including mental confusion, concentration and memory problems were described in six potroom workers (Cawthon, 1988).

In another study of Al production workers, neuropsychological effects were assessed in 38 elderly men who had been exposed for at least 10 years exclusively in the potroom (n=14), foundry (n=8) or other manual labor departments of the same plant (n=16, control group) (Bast-Pettersen et al., 1994). The mean ages and employment durations of the groups were in the ranges of 62.5-63.5 and 19.2-19.6 years, respectively. The men were examined soon after or just before retirement in 1991. Limited environmental monitoring data indicates that the degree of Al exposure varied between the subgroups and over the years. Average annual total dust concentrations in the potroom were reduced significantly from 9.5 mg/m^3 in 1977 to 3.0 mg/m^3 in 1990. Aluminum levels were not specifically reported, but the average Al content in the total potroom dust was approximately 20% by weight; other constituents of the dust included fluoride and coal tar pitch components. Data from an Al uptake/excretion study of workers from the same plant indicated that the level of Al exposure was approximately 8 times higher in the potroom than in the foundry (0.48 and 0.06 mg/m^3, respectively) (Drablos et al., 1992). Medical examinations (including lung function, standard laboratory tests and serum and urine Al concentrations) and a neuropsychological test battery were performed. The battery assessed six mental functions (neuropsychiatric symptoms, motoric/sensoric, reaction time, psychomotor speed/efficiency, memory/learning and intelligence) using a questionnaire and 15 different objective tests. Some subtle deficits were found in potroom workers that were not considered to be indicative of a significant neurological syndrome. The findings in potroom workers included a subclinical tremor as indicated by results of a static steadiness test [time scores on one of two test indices were significantly worse in comparison with the control group (84% slower, p=0.03)], and possible tendencies (i.e., test results that were about 1 SD below normal mean values but not statistically significant) for increased risk of impaired visuospatial organization (Block Design subtest of the Wechsler Adult Intelligence Scale) and psychomotor tempo (one Halstead ReitanTrail Making test). Although these findings were not considered to be indicative of a neurologic syndrome, it was suggested that they may be early signs of CNS impairment. Additionally, the finding of a subclinical tremor seems to be consistent with the tremor and other

signs of incoordination observed in 84% of the patients in the White et al. (1992) study summarized above.

Studies of Al welders are consistent with those of Al smelter workers in indicating that occupational exposure to Al can be neurotoxic. CNS function was evaluated in 17 welders who had an average of 15 years (range 5-27 years) experience, with the last 4 years exclusively with Al (Hanninen et al., 1994). Most of the welders had equipment that ventilated the welding masks but the respiratory protection was not always used. The assessment included measurements of serum and urinary Al, neuropsychological tests (simple reaction time, three tests for psychomotor speed, two tests for visual and spatial ability, four memory tests and two verbal ability tests), a symptom questionnaire and neurological interview, quantitative electroencephalography (QEEG) and P-300 event-related auditory-evoked responses. Serum and urine Al levels were 3.5 and 8.5 times higher, respectively, than an unexposed reference population. The welders performed normally on the neuropsychological tests, although correlation analysis of test scores and exposure parameters showed weak negative associations between the four memory tests and urinary Al level and a positive association between the variability (standard deviation) of visual reaction times and serum Al levels. Analysis of the QEEG data showed that serum Al levels were positively correlated with the amount of delta and theta activity in the brain frontal region and negatively correlated with the amount of alpha activity in the frontal region. Results of this study (disturbances of memory and attention, QEEG changes similar to those in patients with Al encephalopathy) were interpreted as consistent with known CNS effects of Al, but insufficient for establishing a definite relationship between Al exposure and effects.

In another study of Al welders, CNS evaluations were performed on 38 men who had at least 5 years exposure (mean 17.1 years) and a control group of 44 railway track welders exposed to metal fumes other than Al (mean 13.8 years) (Sjogren et al., 1996). Limited monitoring data indicated that the median exposure to welding fumes was 10 mg/m^3 and that the Al content was 40% of the total fumes. Symptom questionnaires, psychological tests (simple reaction time, finger tapping speed and endurance, digit span, vocabulary, tracking, symbol digit coding, cylinders, olfactory threshold and Luria-Nebraska motor scale), neurophysiological indices [electroencephalography, P-300 auditory-evoked responses, brain-stem auditory evoked responses and diadochokinesis (ability to perform rapidly alternating movements with one limb)] and blood and urine Al levels were assessed. The blood and urine Al concentrations were approximately 3 and 7 times higher in the Al welders than in the controls, but there were no clear correlations between duration of exposure to Al and concentration of Al in blood or urine. The Al welders reported more acute CNS symptoms (e.g., concentration difficulties) and had decreased motor function in five tests (finger tapping in non-dominant hand, two tasks from the Luria-Nebraska motor scale, pegboard peg movement with dominant hand, amplitude of diadochokinesis in dominant hand) when compared to the control group. Urinary Al concentration was significantly correlated with acute CNS symptoms, but not with any of the performance measures. To further study possible dose-effect relationships of Al exposure, the Al welders were combined with the control group and divided into three exposure categories according to urinary Al levels, using the 50^{th} and 75^{th} percentiles as category dividers. The group with the highest mean urinary Al level had significantly more acute CNS symptoms and significantly reduced performance on one of the motor function tests (a Luria-Nebraska motor

scale task) when compared to the group with the lowest Al level. In an earlier study of 65 welders with ≥10 years of exposure to Al fumes, the highest exposure category (based on exposure duration) was 2.8 times more likely than unexposed workers to have three or more neuropsychiatric symptoms (Sjogren et al., 1990).

A body of epidemiological evidence has pointed to an increased incidence of cancers of various kinds in workers employed in the aluminum production industry. However, as discussed in a review by Ronneberg and Langmark (1992), the concern about potential cancer hazards in the aluminum industry has primarily arisen because of exposures to polycyclic aromatic hydrocarbons (PAHs) and coal tar pitch volatiles (CTPVs) rather than to Al *per se*. Thus, while a number of studies have provided inferential data linking occupationally exposed aluminum workers with an increased risk of developing tumors of the bladder or lung (Gibbs, 1985; Thériault et al., 1984, 1990; Armstrong et al., 1986; Spinelli et al., 1991; Pearson et al., 1993; Tremblay et al., 1995), it would be unwise to ascribe any excess tumor formation to the effects of Al in view of the concurrent exposure to well-documented carcinogenic PAHs such as benzo(a)pyrene. The issue is further complicated by the likely exposure of production workers to other substances such as fluorides, sulfur dioxide, aromatic amines and asbestos (Ronneberg and Langmark, 1992; Tremblay et al., 1995; Dufresne et al., 1996), and to the possible effects of cigarette smoking in affected individuals. Consequently, these studies have failed to provide direct evidence for the carcinogenicity of Al fumes and dusts.

Animal Studies

Oral Exposure

Numerous subchronic animal studies were located in the biomedical/toxicological literature but only those that define the threshold region of the oral dose-response relationship are summarized in this paper. A major limitation of many of the studies of Al toxicity is the lack of complete information on total dietary (e.g., food and drinking water) intake of Al and of other elements that are known to effect Al biokinetics and toxicity (e.g., calcium and magnesium). Estimated or reported dosages used in studies in which Al content of the basal diets are not reported must be assumed to underestimate the actual experimental dosages. The magnitude of the underestimate may be considerable. For example, a range of Al contents of 200-1200 mg Al/kg for commercial grain-based diets (Golub et al., 1992b) would provide 30-200 mg Al/kg bw-day in a subchronic or chronic mouse bioassay [based on U.S. EPA (1988) default values for body weight and food intake]. On this basis, studies in which complete dietary Al intakes were not reported or could not be estimated may provide some information about the hazards of oral exposure to Al but are inappropriate for establishing NOAELs or LOAELs for the critical effect of Al. NOAELs and LOAELs from studies that provide estimates of total Al dosages, or otherwise provide information relevant to determining the NOAEL/LOAEL boundary for the critical effect of Al are presented in Table 1 and are summarized below.

Systemic toxicity

Groups of 10 female Sprague-Dawley rats were administered aluminum nitrate nonahydrate in sugar-containing drinking water at doses of 360, 720 and 3600 mg/kg-day (26, 52

and 259 mg Al/kg bw-day, respectively) for 100 days (Domingo et al., 1987). A control group received sugar-containing distilled water only. Sugar had been added to the drinking water of all groups to reduce the taste-aversive effects of Al. The level of Al in the diet was not reported. Animals were housed in metabolic cages to facilitate the collection of fecal and urine samples. Food and water consumption were measured daily, body weights were noted weekly and blood samples were taken at monthly intervals and at termination to monitor clinical chemistry and hematological parameters. At termination, all animals were necropsied, and the weights of major organs (brain, heart, lungs, kidneys, liver and spleen) were monitored. Aluminum concentrations were measured in various tissues, pieces of which were processed for histopathological examination. A significant decrease ($p<0.05$) in body weight gain was observed in the 259 mg Al/kg-day group, attributed by the authors to decreased food intake. Overall, no consistent variations in hematological (hemoglobin, hematocrit) or clinical chemistry (SGOT, SGPT, alkaline phosphatase, urea, creatinine, total protein, cholesterol, glucose) parameters were observed. No histopathological alterations in the heart, liver, kidney, spleen, brain and cerebellum were observed. Interpretation of these data was complicated by the concurrent exposure of the rats to high doses of nitrate of up to 475 times the RfD for nitrate (1.6 mg nitrate-nitrogen/kg-day) which is based on methemoglobinemia in humans (U.S. EPA, 1999). Therefore, because of nitrate co-exposure, the absence from the study design of a food-restricted control group and uncertainty surrounding the contribution of Al in food, the apparent effect of Al on body weight gain cannot be conclusively attributed to Al alone.

Some recent studies have identified a number of potential toxicological responses in laboratory animals exposed orally to Al compounds in a subchronic or chronic dosing regimen. In most cases, however, only one dose level was employed in the study compared to controls, and since the amount of Al in the diet was not given, the resulting dose level represents an incremental dose of Al compared to that of controls as baseline. However, while these studies may offer inadequate quantitative dosimetric information for NOAEL/LOAEL identification and consequent RfD development, they provide an qualitative indication of a range of potential toxicological responses that might be induced in humans exposed to the element. For example, Garbossa et al. (1998) studied the potential for water-soluble Al to affect the erythropoietic integrity of late erythroid progenitor cells in the bone marrow. Three groups of five male Wistar rats/group were either (1) gavaged with citrate at a dose of 1.0 μm Al/g-day (27 mg/kg-day), 5 days/week, for 15 weeks, (2) had drinking water containing 100 mmol Al/L made available to them as the citrate for the same length of time or (3) maintained as controls. As calculated by the authors, the dose associated with the applied concentration of Al in drinking water approximated to 14-17 μmol/g-day (420 mg/kg-day). Rats had access to a standard chow diet, though with no indication of the baseline concentration of Al provided therein. At the end of the in-life phase of the study, all rats were sacrificed, and samples of blood were obtained for hematological investigation. Femoral bone marrow cells were flushed with physiological medium, stimulated with recombinant human erythropoietin, then monitored for the comparative incidence of colony-forming units-erythroid (CFU-E). Further tests were carried out to monitor the osmotic fragility and average life-span of erythrocytes from each test group. The animals in the group receiving Al at the higher dose showed decreased hematocrit, hemoglobin concentration, median osmotic fragility and erythrocyte life-span values compared to controls. The content of Al increased in the serum and bone of both exposed groups, the distribution of concentrations in bone correlating inversely with the extent of an animal's CFU-E development.

That Al in drinking water may have the ability to cause histopathological changes and altered hepatic enzyme activities was suggested by Basu et al. (1997) who made available aluminum chloride in drinking water to groups of eight male Sprague-Dawley rats at a dose of 50 mg/kg-day (10.1 mg Al/kg-day) for 40 days. Additionally, other groups of similarly-treated rats received drinking water containing either 0, 50, 100, 200 or 400 ppm (mg/L) added calcium (Ca), as the chloride. The authors reported increased specific activities of acid and alkaline phosphatases in liver 10,000 x g supernatants from Al-receiving animals versus controls, and in alkaline phosphatase activity in equivalent kidney preparations. The presence of Ca in the drinking water appeared to reverse these changes, plus the accompanying histopathological features associated with them.

Konishi et al. (1996) examined the ability of Al and Ca to cause opposite and potentially harmful effects in laboratory animals, in relation to the well-documented association between Al and the onset of osteomalacia. Male STD Wistar rats were divided into four groups (n=4), receiving either (1) a normal diet (Group I), (2) a normal diet supplemented with Al (Group II), (3) a Ca-deficient diet (Group III) or (4) a Ca-deficient diet with supplemental Al (Group IV), for 10 weeks. Blood samples were taken at termination, and then animals were perfused with paraformaldehyde/glutaraldehyde fixative. Levels of Ca, iron (Fe) and Al in serum and bone were measured by atomic absorption spectrophotometry, and sections of the resected right tibia were prepared for histopathological examination after decalcification in 5% formic acid in 10% formalin.

There were statistically-significant changes in body weight gain when those of groups 3 and 4 were compared to animals from groups 1 and 2, the values for the latter groups remaining constant from about 4 weeks of dosing. In discussing their histopathological findings, the authors described no decrease in the thickness of cortical bone in Group II compared to control, while bone specimen from Groups III and IV showed “an increase in osteoid as well as osteoblasts and osteoclasts”, in addition to other disturbances of ossification. Such effects were considered to suggest bone fragility, with changes being more marked in Group IV compared to III. The amount of Al in the tibia of exposed rats was significantly greater in Group II than in Group I, whereas the average levels in Groups III and IV showed a further increase in Al deposition, most notably in group IV. There were also differences among the groups in the concentration of Fe in bone (tibia), and in the concentrations of Al, Ca, Fe and the levels of parathyroid hormone in blood. The authors concluded that Ca deficiency appeared to potentiate the deposition of orally administered Al in bone, and the attendant inhibition of ossification. Iron deposition was also thought to play a role in the osteogenic disturbance, where Ca is deficient.

A histopathological investigation indicated profound changes in the cerebrovascular and neuronal integrity when male Long-Evans rats (n=9) were exposed for 52 weeks to 0.5 ppm aluminum fluoride in drinking water (Varner et al., 1998). This corresponded to an Al dose of 0.019 mg/kg-day, based on a default drinking water consumption of 0.057 L/day, and a default body weight of 0.472 kg for male Long-Evans rats (U.S. EPA, 1988). Duel control groups received either NaF (fluoride controls) or double distilled deionized water. Tissue levels of Al were measured in brain, liver and kidney by the use of a direct current plasma technique.

Animals receiving aluminum fluoride showed poor survival compared to the other groups, with 6/9 having died by week 48. The tissue concentrations of Al were increased in the brain and kidney compared to both the control groups, with Al-fluorescence being used to demonstrate that Al deposition was mostly in the vasculature. Morphological and histopathological changes due to treatment were apparent in the liver, kidney and spleen. Some changes in neuronal integrity were also evident in the hippocampus and neocortex. Other cytological changes in the brain were associated with chromatid clumping, pyknosis and vacuolation.

A report by Somova et al. (1997) describes a study in which 10 male Wistar rats/group received either 0, 5 or 20 mg/kg-day aluminum chloride by gavage in water for 6 months. At termination, all animals were exsanguinated, then subjected to a necropsy in which excised pieces of liver, kidney and cardiac and skeletal muscle were taken for histopathological examination. Pieces of brain were examined by electron as well as light microscopy, and all tissues were monitored for Al concentration by atomic absorption spectrophotometry. As tabulated by the authors, Al in plasma and all of the listed tissues was dose-dependently increased to levels that were statistically significantly greater than controls. However, though described in qualitative terms and illustrated photographically, the Al-induced lesions did not receive a quantitative treatment in the report. Thus, while at least some of the low dose rats displayed NFD (neuro fibrillar degeneration) of the hippocampal region of the brain, insufficient data are provided in the report to apply this observation to the identification of a NOAEL or LOAEL.

Dietary experiments

Six Beagle dogs/sex/group were fed a diet providing either, in males, 0, 118, 317 or 1034 mg/kg-day sodium aluminum phosphate (0, 3.4, 9.0 or 29.4 mg Al/kg-day, respectively) or, in females, 0, 112, 361 or 1087 mg/kg-day sodium aluminum phosphate (0, 3.2, 10.3 or 30.9 mg Al/kg bw-day, respectively), for 6 months (Katz et al., 1984). No information was available on the level of Al in the diet, and no compound-related effects on body weight gain, hematological and clinical chemistry parameters (parameters not specified) or histopathological endpoints (major organs and tissues examined) were observed. A highest NOEL of 30.9 mg Al/kg-day could be tentatively identified in this study, but this would not include the contribution of Al from the basal diet, nor reflect the identification of any toxicological effects, since the NOEL occurred at the upper limit of the dose-response curve.

Neurotoxicity

A number of studies have been reported in which neurotoxicological/neurobehavioral effects have been explicitly evaluated. In others, the effects of Al on neurological developmental have been addressed. For example, Golub et al. (1989) fed diets containing Al as the lactate at 25 (controls), 500 or 1000 mg Al/kg diet (3.3, 65 or 130 mg Al/kg-day) to groups of 15 female Swiss-Webster mice for 6 weeks (Golub et al., 1989). No mice were exposed to lactate alone. While no statistically significant differences in food intake or body weight gain were observed, mice fed the highest Al concentration gained less weight than the controls or low-dose group. As reported by the authors, a significant decrease (20%) in spontaneous motor activity (i.e., total, vertical and horizontal movement) was observed in the 130 mg Al/kg-day group. Activity in the

65 mg Al/kg-day group was not significantly different than the controls. Thus, the highest NOAEL is 65 mg Al/kg-day and the LOAEL is 130 mg Al/kg-day.

Neurobehavioral effects of aluminum lactate were evaluated in groups of 12 female N:NIH Swiss-Webster mice (4.5-5.5 weeks old) that were fed 25 (controls) or 1000 mg Al/g diet for 90 days (Golub et al., 1992a). Based on a food factor of 0.19 kg diet/kg body weight/day calculated using an algorithm relating food consumption to body weight (U.S. EPA, 1988) and reported body weight data (the time-weighted average weight is 25.4 g), the dosage in the treated mice is estimated to be 190 mg Al/kg bw-day. No mice were exposed to lactate alone. A neurobehavioral test battery used by Donald et al. (1989) was administered at the beginning of the experiment (day 0) and after 45 and 90 (±3) days, with motor activity evaluated at the latter two time points. Aluminum levels were measured in brain, femur and liver at the end of the exposure period.

Body weight was significantly increased in the treated mice but no exposure-related changes in food intake or overt signs of neurotoxicity were observed. Results of the neurobehavioral tests showed significantly decreased hindlimb grip strength at 90 days, decreased air puff startle response at 90 days and decreased auditory startle response at 45 days in the treated mice. Spontaneous motor activity was reduced at 90 days as indicated by decreased total activity counts, horizontal activity counts and percentage of intervals with high activity counts. Aluminum concentrations in the brain and liver were increased approximately 3-fold in the treated mice, but brain and liver lipid peroxidation indices were not altered.

Male Wistar rats (6-8 per group) were exposed continuously for 6 months to food containing 1.52 mg Al/kg (normal diet) or 1000 mg Al/kg as aluminum chloride with citrate (Florence et al., 1994). The average daily Al intake was estimated to be 0.13 or 84 mg Al/kg bw-day, assuming a body weight of 0.305 kg (arithmetic mean of default mature weight of male Wistar rats and the starting weight in this study of 0.11 kg) and a food intake of 0.026 kg food/kg bw-day, calculated using an algorithm relating food intake to body weight (U.S. EPA, 1988). The citrate content of the diet was in a 1:1 stoichiometric proportion to Al, therefore, the estimated daily intake was 598 mg/kg-day. Rats exposed to Al developed histopathological abnormalities in brain tissue, not specific to any brain region, characterized by extensive cytoplasmic vacuolization in astrocytes, swelling of astrocytic processes, particularly of astrocyte end-feet abutting blood vessels. Neurons also exhibited vacuolization and nuclear inclusions. Although no specific behavioral assays were reported, the investigators noted that "no significant behavioral changes were observed". Accordingly, the functional significance of the histopathological lesions is uncertain. The lesions appear to differ from the NFD observed with parenteral Al exposures (Kowall et al., 1989; Wakayama et al., 1993); or from exposures to Al in combination with calcium deprivation (Garruto et al., 1989; Kihira et al., 1995; Mitani, 1992). The LOAEL for histopathological changes in the brain was 84 mg Al/kg-day.

Male Sprague-Dawley rats (40 per group) were exposed in drinking water to 0, 50 or 100 mg Al/kg bw-day as aluminum nitrate with citric acid for 6.5 months beginning at 21 days of age, 8 months of age or 16 months of age (Domingo et al., 1996). The citric acid dosage was 355 or 710 mg/kg-day in the 50 or 100 mg Al/kg bw-day groups, respectively. Controls did not receive citric acid. Dietary Al intake was not reported; the rats were maintained on Panlab rat

chow. Animals from control and exposed groups were subjected to a number of neurobehavioral tests, and at termination, Al levels were measured in various excised regions of the brain. The authors observed the highest Al levels in the olfactory bulb and rhachidical bulb, while the cortex and thalamus were the regions showing the lowest Al content. However, compared to controls, there were no significant effects ($p>0.05$) of Al (with citric acid) on spontaneous motor activity (open-field) or passive avoidance operant training or performance (grid floor shock, light/dark shuttle box). Thus, the NOAEL was 100 mg Al/kg-day with citric acid; although this does not include the Al contribution from food. This study is listed on Table 1 because the NOAEL, although probably underestimated because of unreported Al intake from food, is still lower than the LOAELs from other studies.

Groups of six male albino rats were administered 0 or 25 mg Al/kg bw-day as aluminum nitrate in normal saline by gavage, 10% ethanol in drinking water, or 25 mg Al/kg bw-day by gavage combined with 10% ethanol in drinking water, 6 days/week for 6 weeks (Flora et al., 1991). The level of Al in the diet was not reported. Urinary Δ-aminolevulinic acid (ALA), blood ALA-dehydratase (ALAD), blood zinc protoporphyrin (ZPP), glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) in serum and liver and brain biogenic amines and their metabolites [dopamine (DA), norepinephrine (NE), 5-hydroxytryptamine (5-HT), homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5-HIAA)] were evaluated at the end of the treatment period. Treatment with Al alone caused significantly increased blood ALAD ($p<0.01$), decreased liver GPT ($p<0.05$), decreased brain DA ($p<0.01$), increased brain NE ($p<0.05$) and decreased brain 5-HT ($p<0.05$). Compared to treatment with Al alone, concurrent exposure to ethanol and Al produced significantly decreased ALAD, increased ALA, increased ZPP, increased liver GPT, increased serum GOT and increased brain HVA. Significant changes found only in the combined Al and ethanol group included increased serum GPT, increased brain NE and decreased brain 5-HT. Treatment with ethanol alone only inhibited blood ALAD. The rats were co-exposed to relatively high levels of nitrate [comparable to those in the Domingo et al. (1987) subchronic study], but it seems likely that some of the changes (i.e., effects on brain chemicals) are related to aluminum which is known to be neurotoxic. Because the toxicological significance of the changes is unclear due to lack of evaluation of neurobehavioral performance and other endpoints, there is uncertainty whether the 25 mg Al/kg-day dose is a NOAEL or a LOAEL, an uncertainty compounded by the absence of information about the level of Al in the basal diet.

Reproductive/developmental toxicity

A number of studies have been carried out to examine the effects of Al compounds on developmental toxicity, particularly their effects on postnatal neurobehavioral development. For example, Bernuzzi et al. (1989) exposed groups of 6-12 pregnant Wistar rats to aluminum chloride or aluminum lactate in the diet on gestational days 1 through 21. The rats received nominal daily doses of 0, 100, 300, 400 mg Al/kg as aluminum chloride or 0, 100, 200 or 400 mg Al/kg as aluminum lactate. No rats were exposed to lactate alone, and information regarding level of Al in the basal diet was not reported. On the average, there was a less than 10% decrease in maternal body weight gain and no effect on food or water intake. No significant difference in litter size was observed. However, postnatal mortality increased 55% and 26% in offspring of the rats exposed to 300 or 400 mg Al/kg-day, respectively. The offspring of dams

fed ≥300 mg Al/kg-day weighed significantly less than controls on postnatal day 1. Decreased body weight was also observed on postnatal days (PD) 4 and 14 in the offspring of rats fed 400 mg Al/kg-day as aluminum lactate. The following tests were used to assess neuromotor development (maturation): righting reflex, grasping reflex, negative geotaxis, suspension test and locomotor coordination. The tests were performed on PDs 4, 6, 9, 12 and 20, respectively. Impairment of neuromotor development (righting and grasping reflexes) was observed in the pups exposed to ≥200 mg Al/kg-day. Impaired grasping reflex was also observed in the 100 mg/kg-day aluminum lactate group. Offspring of rats fed 400 mg/kg-day also exhibited altered performance on the locomotor coordination test.

A follow-up study by the same research group found that ingestion of 400 mg Al/kg bw-day as aluminum lactate had no effect on postnatal mortality, body weight and righting and grasping reflex tests (Muller et al., 1990), although significant differences between control and exposure groups were noted in locomotor coordination and operant conditioning tests. Significant differences between controls and exposed groups in the negative geotaxis test were limited to those pups of dams treated during the second and third weeks of gestation, a finding interpreted by the authors to indicate the possibility of long-term effects on the central nervous system of trans-placenta exposure to Al during a later organogenic phase. According to Muller et al. (1990), the contradictions between this and their earlier study (Bernuzzi et al., 1989) could be related to environmental modifications. In particular, the mothers and pups were much more protected in the Muller et al. (1990) study than in the previous one because they were housed in plastic cages instead of wire mesh cages and received cotton to build nests. Body temperature of the pups, therefore, may have been more adequately maintained in the Muller et al. (1990) study. As discussed in this study, toxicity in pups can be confounded by insufficient body temperature, and delayed pup weight gain could explain the differences in neuromotor performance.

Muller et al. (1990) administered diets supplemented with 0 or 400 mg Al/kg bw-day as aluminum lactate to groups of 6-9 pregnant Wistar rats on days 1-7, 1-14 or 1-21 of gestation. No rats were exposed to lactate alone, and information regarding level of Al in the basal diet was not reported. Neuromotor development was assessed on postnatal days 4, 6, 9, 12 and 20 using tests of righting reflex, grasping reflex, negative geotaxis, suspension and locomotor coordination, respectively. Learning ability was also tested on PD 65 using operant conditioning. No effects on maternal body weight or food intake were observed in dams exposed on gestational days 1-7 or 1-14. In the dams exposed on gestational days (GD) 1-21, a significant decrease in maternal body weight (26 and 35%, respectively) was observed on days 16 and 19 of gestation. Decreased food intake was also observed on day 19 of gestation. No effects on litter size, postnatal mortality or postnatal body weight were observed. Impairment of neuromotor development ($p<0.05$) was observed in two of the five tests (negative geotaxis and locomotor coordination); no differences between the three treated groups were observed. For the operant conditioning test, there were significant differences ($p<0.05$) between the treated and control young rats. No differences between the three treated groups were observed. The LOAEL for developmental toxicity is 400 mg Al/kg-day, but this does not include the contribution of Al from the basal diet.

Groups of 10 pregnant Sprague Dawley rats were administered 180, 360 or 720 mg/kg-day aluminum nitrate nonahydrate by gavage (13, 26, 52 mg Al/kg bw-day) on GDs 6-14

(Paternain et al., 1988). A vehicle (water) only control group was used. The level of Al in the diet was not reported. Aluminum exposed dams gained significantly less weight than the controls. No significant effects on the numbers of litters, corpora lutea, total implants, live fetuses, resorptions or runt fetuses were observed. Significant decreases in fetal body weight and tail length were observed at all three Al doses; decreased fetal body length was also observed at the 52 mg Al/kg-day dose level. No dose-related external or visceral malformations were observed in the offspring. However, a significant increase in the incidence of skeletal malformations (delayed ossification, hypoplastic deformed ribs) was observed at all three treatment levels. In addition, the incidence of hematomas was significantly increased at the high dose. Because the rats were co-exposed to relatively high levels of nitrate [comparable to those in the Domingo et al. (1987) subchronic study], the effects of treatment cannot be conclusively attributed to Al alone, in the absence of a nitrate-exposed control group.

By contrast to the striking findings of potentially teratogenic effects of aluminum nitrate in Sprague-Dawley rats, as described above (Paternain et al., 1988), equivalent experiments by Domingo et al. (1989) in Swiss mice did not reveal any reproductive, developmental or teratogenic effects of Al, when administered to dams as the hydroxide. Domingo et al. (1989) administered by gavage 0, 66.5, 133 or 266 mg/kg-day aluminum hydroxide (0, 23.9, 47.8 or 95.5 mg Al/kg bw-day) to groups of 20 pregnant Swiss mice on GD 6-15. The level of Al in the diet was not reported. The dams were killed on GD 18. No compound-related effects were observed on maternal mortality, clinical signs, body weight, food intake or absolute or relative heart, lung, spleen, liver, kidney and brain weights. In addition, no compound-related effects were observed on numbers of implantations, resorptions, live and dead fetuses, sex ratio and the incidences of external malformations, internal soft-tissue defects or skeletal abnormalities. Therefore, this study identifies a NOEL of 95.5 mg Al/kg-day by default for reproductive, developmental and teratogenic toxicity in mice. However, neuromotor development was not assessed and the contribution of Al from the basal diet was not stated in the report.

A number of studies have been designed to evaluate the influence of citrate or lactate on the potential developmental toxicity of Al. For example, Gomez et al. (1991) exposed groups of 15-19 pregnant Sprague-Dawley rats to either distilled water (controls) or 133 mg Al/kg bw-day in the form of either aluminum hydroxide (384 mg/kg-day), aluminum citrate (1064 mg/kg-day) or aluminum hydroxide (384 mg/kg-day) concurrent with citric acid (62 mg/kg-day) by gavage on GD 6-15. The level of Al in the diet was not reported and no rats were exposed to citric acid alone. Terminations were performed on GD 20. Maternal and fetal evaluations showed exposure-related effects only in the group exposed to aluminum hydroxide and citric acid concurrently. Significant changes included reduced maternal body weight gain on GDs 6-20 (but not at sacrifice on day 20), reduced fetal body weight and some skeletal variations (increased delayed occipital and sternebrae ossification and increased absence of xiphoides). No effects were seen on maternal food consumption or clinical signs, maternal absolute or relative liver, kidney or brain weights, gravid uterine weight, corpora lutea/dam, implantations/litter, pre- or postimplantation loss/litter, viable or nonviable implants/litter, fetal sex ratio or fetal malformations (external, visceral or skeletal). This study identified a stand alone minimum LOAEL of 133 mg Al/kg-day for non-neurobehavioral developmental toxicity of aluminum hydroxide and aluminum citrate in rats. Although confidence in this LOAEL is low (because aluminum hydroxide administered concurrently with citric acid induced did developmental

effects and because the dose does not include a contribution of Al from the basal diet) the value is consistent with the developmental NOAEL of 95.5 mg Al/kg-day for aluminum hydroxide in mice (Domingo et al., 1989).

In a similar experimental protocol, groups of 11-13 pregnant female Swiss albino (CD-1) mice were administered 57.5 mg Al/kg bw-day as either aluminum hydroxide (166 mg/kg-day), aluminum lactate (627 mg/kg-day) or aluminum hydroxide (166 mg/kg-day) concurrent with lactic acid (570 mg/kg-day) by gavage on gestation days 6-15 (Colomina et al., 1992). Other groups were treated with lactic acid alone (570 mg/kg-day, equivalent to the amount in 627 mg/kg of aluminum lactate) or distilled water (controls). The level of Al in the diet was not reported. Fetal evaluations were performed on GD 18, including examinations for skeletal and visceral abnormalities in approximately two-thirds and one-third of the pups, respectively. The investigators noted that the dose of Al (57.5 mg/kg-day) is equivalent to ingestion of 3.5 g Al/day by a 60 kg person, which is higher than the usual quantities of Al ingested therapeutically for peptic disorders. Maternal body weight gain was significantly lower than control values in the aluminum lactate-treated mice when evaluated over GDs 6-9 (92%), 6-12 (55.6%) and 0-18 (38.5%) and in the mice treated with combined aluminum hydroxide and lactic acid evaluated over GDs 6-12 (37.8%), 6-15 (42.7%) and 0-18 (15.7%). The decreased maternal weight gain in the aluminum lactate group was accompanied by significantly reduced food consumption during gestation days 6-18. Significant developmental and/or teratological effects in the aluminum lactate group included 16% reduced fetal body weight ($p<0.01$) and increased incidences of cleft palate (13.2%, $p<0.05$), dorsal hyperkyphosis (i.e., excessive flexion of spine) (13.5%, $p<0.05$) and delayed parietal ossification (15.4%, $p<0.01$). These developmental effects were not observed in any of the control or aluminum hydroxide exposed pups, and the only other significant changes in the other groups were decreased maternal relative liver weight and delayed fetal parietal ossification in the lactic acid only exposure group. Other types of internal or skeletal malformations or variations were not found in any of the fetuses. Additionally, no effects were seen on maternal absolute or relative kidney weight, gravid uterine weight, numbers of implantation sites/litter, live or dead fetuses, resorptions, postimplantation loss/litter, litters with dead fetuses or fetal sex ratio in any of the groups. By analogy to the findings of the Domingo et al. (1989) and Gomez et al. (1991) studies, the lack of developmental effects of aluminum hydroxide at the tested dose could be related to low solubility and absorption.

In a more recent study, pregnant Swiss mice were administered gavage doses of 0 or 104 mg Al/kg bw-day as aluminum hydroxide on days 6-15 of gestation (Colomina et al., 1994). Dietary Al intake was not reported; the mice were maintained on Panlab rodent chow. Compared to controls, there were no effects ($p>0.05$) of Al on maternal body or organ weight, number of implantations per litter, number of resorptions per litter, number of dead fetuses per litter, percentage of positive post-implantation loss, sex ratio or fetal body weight per litter. Gross external, visceral or skeletal examination of fetuses revealed no abnormalities or developmental variations. Thus, the NOAEL for development effects from this study is 104 mg Al/kg-day, however, this does not include the Al contribution from food. Thus, based on this study and the previous study (Colomina et al., 1992), aluminum lactate appears to be more potent as a developmental toxicant in mice than the less water soluble aluminum hydroxide.

Groups of 16 pregnant Swiss-Webster mice were fed 25 (control group), 500 or 1000 mg Al/kg diet as aluminum lactate throughout gestation and lactation (Donald et al., 1989). The control diet was fed to pups that were selected for post-weaning neurobehavioral assessment. Reported maternal doses were 5, 100 and 200 mg Al/kg bw-day at the beginning of pregnancy and 10.5, 210 and 420 mg Al/kg bw-day near the end of lactation. No mice were exposed to lactate alone. There were no treatment-related changes in maternal survival, body weight (measured on GD 0 and 16 and PDs 0, 5, 10, 15 and 20), food intake, toxic signs or neurobehavior (evaluated after pups were weaned at PD 21 using the same test battery used for the pups and described below), or on litter size or postnatal growth and development in pups as assessed by body weight, toxic signs on PDs 0-55, and by crown-rump length on PDs 0 and 20. Neurobehavioral maturation was tested in two pups per litter on PDs 8-18 with a 12-item test battery (fore- and hindlimb grasp, fore- and hindpaw placement on sticks of 2 widths, vibrissa placing, visual placing, auditory and air puff startle, eye opening and screen grasp, cling and climb). A neurobehavioral test battery was administered to six pups per litter at age 25 days (4 days postweaning) or 39 days (fore- and hindlimb grip strengths, temperature sensitivity of tail, negative geotaxis, startle reflex to air puff and auditory stimuli) or age 21 and 35 days (foot splay). The pre-weaning neurobehavioral testing showed that a significant ($p=0.007$) number of pups in the high dose group had impaired vertical screen climb performance. The postweaning neurobehavioral assessment showed significantly ($p<0.05$) altered performance on several tests. These included decreased forelimb grip strength at age 39 days in the low dose group, increased hindlimb grip strength at age 25 days in both low and high dose groups, increased foot splay distance at age 21 days in both low and high dose groups and at age 35 days in the low dose group, and increased forelimb grip strength at age 25 days and decreased thermal sensitivity at age 25 and 39 days in the high dose group. There were no treatment-related changes in concentrations of Al in pup liver or bone (brain tissue was not analyzed).

In a more recent study of similar design by the same group of investigators, groups of 14 and 9 female Swiss Webster mice (6-8 weeks old) were fed 25 (control) or 1000 mg Al/g diet as aluminum lactate, respectively, during gestation and lactation (Golub et al., 1992b). The 1000 mg/g concentration was selected based on the demonstration of neurobehavioral effects in weanlings at this level (Donald et al., 1989). No mice were exposed to lactate alone. Using food intake and body weight values estimated from reported data, maternal doses are estimated to be approximately 4.3 and 174 mg Al/kg bw-day at the beginning of gestation and 4.8 and 607 at the end of the lactation period. At birth, litters were fostered either within or between groups to provide four groups of offspring that were exposed to excess Al via maternal diet during gestation, lactation, both or neither (i.e., 25 ppm during gestation and lactation, 1000 ppm during gestation and 25 ppm during lactation, 25 ppm during gestation and 1000 ppm during lactation, and 1000 ppm during gestation and lactation). Maternal effects included significantly ($p\leq0.015$) reduced (10-12%) body weight gain and food intake in the treated group during late pregnancy and lactation, and signs of neurotoxicity (hindlimb splaying and dragging) in one treated dam at postnatal day 21 (weaning); this dam had seizures and died 4 days later. No treatment-related effects on litter size, birth weight, crown-rump length, righting ability at birth, sex ratio or postnatal survival were observed. Both gestation-only and lactation-only exposure caused significantly ($p<0.05$) decreased body weight gain in the treated pups beginning on postnatal day 10; combined gestation and lactation exposure produced the greatest decrease (approximately 24% at weaning). Neurobehavioral testing using the same battery as Donald et al. (1989) was

performed at weaning on the dams and on a total of 12, 16, 12 and 6 pups (1 male and 1 female pup per litter) from the control, gestation-only, lactation-only and combined gestation and lactation groups, respectively. Results of this testing showed effects only in pups, including significantly decreased forelimb grip strength after gestation-only exposure, increased hindlimb grip strength after both gestation and lactation exposure, decreased temperature sensitivity after lactation-only exposure, and longer negative geotaxis latency after lactation-only exposure. In general, the findings of this study are consistent with those of Donald et al. (1989) in showing neurodevelopmental effects at the 1000 mg/kg dietary concentration, although intake dosages are dissimilar at the end of lactation. Using the dosage at the beginning of gestation, this study defines a LOAEL of 174 mg/kg-day for developmental effects.

The Donald et al. (1989) study differs from that of Golub et al. (1992b) in that offspring were not fostered, were tested at a later age (25 vs. 21 days), were allowed 4 days of recovery from the treated diet prior to testing, participated in other behavioral tests currently, and experienced no growth retardation. The effects found only in the cross-fostered groups in the Golub et al. (1992b) study (lower forelimb strength after gestation exposure and altered negative geotaxis latencies after lactation only exposure) were not observed by Donald et al. (1989). Increased footsplay was observed by Donald et al. (1989) but not by Golub et al. (1992b), perhaps due to an opposing effect of smaller pup body size in this study. Neither gestation or lactation exposure affected pup brain or liver Al concentrations, but lactation exposure caused significantly lower manganese and iron concentrations in liver and manganese concentrations in brain.

In a further extension of the two previous studies (Donald et al., 1989; Golub et al., 1992b), pregnant female Swiss-Webster mice were exposed continuously to a semi-purified diet containing 7 (control), 500 or 1000 mg Al/kg from the time of conception, through pregnancy and lactation (Golub et al., 1995). At weaning, pups were exposed to the same Al diet as their mothers (500 or 1000 mg Al/kg) until they were 150-170 days of age or were switched to the control diet (7 mg Al/kg) for the same time period. Based on reported dosages in previous studies by the same investigators, estimated daily dosages for mice exposed to 1000 mg Al/kg diet were as follows: 200 mg/kg bw-day in pregnant mice, 420 mg/kg-day in lactating mice and 130 mg/kg-day in offspring (Golub et al., 1994); doses for the mice exposed to 500 mg Al/kg diet were assumed to be approximately half of that of mice fed 1000 mg Al/kg, or 100 mg/kg-day in pregnant mice, 210 mg/kg-day in lactating mice and 65 mg/kg-day in offspring. Compared to the control diet, the Al diet had no effect on dam weight, gestation length, litter size, pup weight, offspring growth or organ weights. Operant conditioning (nose poke) of offspring for delayed spatial alternation or discrimination reversal tasks was initiated at 50 days of age and continued 5 days/week for a total of 35 sessions. A neurobehavioral test battery was conducted when the offspring were 150-170 days of age (forelimb and hindlimb grip strength, temperature sensitivity, negative geotaxis, air puff and auditory startle response). Maternal and pre-weaning exposure to 500 mg Al/kg significantly affected ($p<0.05$) operant training in the offspring, but not performance after training in delayed spatial alternation or discrimination reversal tasks (i.e., decreased number of training sessions to achieve the training criteria). This exposure also significantly decreased forelimb and hindlimb grip strength and puff startle response ($p<0.05$). Pre-weaning and combined pre- and post-weaning exposure to 1000 mg Al/kg significantly increased ($p<0.05$) incidence of cagemate aggression at the time behavioral

testing. No effects were observed on auditory startle response, temperature sensitivity or negative geotaxis in offspring. Histopathological examination of the brain and spinal cord revealed no treatment-related changes. Thus, the LOAEL for combined maternal and pre-weaning exposure on neurobehavioral effects in mice would approximate to 100 mg Al/kg-day (estimated daily maternal dosage).

Pregnant Charles River CD rats were administered gavage doses of 0, 250, 500 or 1000 mg Al/kg bw-day ("experiment A") or 0, 5, 25, 50, 250 or 500 mg Al/kg bw-day ("experiment B") as aluminum lactate in distilled water on GDs 5-15 (Agarwal et al., 1996). Dietary Al intake was not reported. Offspring were examined for body weight, anogenital distance, oestrus cycle regularity (after puberty), duration of pseudopregnancy induced by mechanical stimulation of the cervix, oocyte production induced by an injection of human chorionic gonadotropin, and male and female gonad weights. Aluminum had no effect on litter size and no consistent effects on birth weight were observed. For example, birth weights were decreased in male offspring from dams that received 250 mg Al/kg-day, but not at higher dosages, and the effect was observed only in experiment A. Female offspring birth weights decreased at certain dosage levels in experiment A and increased at these same dosage levels in experiment B. Similar inconsistencies between experiment A and B were observed for gonadal weights, anogenital distance, time to puberty (vaginal opening), duration of pseudopregnancy or numbers of superovulated oocytes. A significantly increased ($p<0.05$) number of abnormal oestrus cycle lengths (defined as less than 4 days or greater than 5 days) occurred in offspring from dams that received 250 mg Al/kg-day (in experiment A, the endpoint was not measured in experiment B). However, the effect was most pronounced in the first three oestrus cycles (of five observed) and not detected by the 5th cycle. Thus, the NOAEL for temporary disturbance of the oestrus cycle in offspring of dams administered Al is 250 mg Al/kg-day. NOAELs for all other reproductive endpoints in this study were 1000 mg Al/kg-day. These NOAELs do not include the contribution of Al in food.

In a three-generation study, Ondreicka et al. (1966) exposed initial groups of seven female and three male Dobra Voda mice to either 0 or 19.3 mg Al/kg bw-day as aluminum chloride in drinking water. The diet also contained 160 to 180 ppm Al, giving an estimated intake of 27-31 mg/kg-day based on default values for food consumption and body weight for chronic exposure of mice (U.S. EPA, 1988). Using this estimate, the total Al intakes (drinking water and food) were 27 mg/kg-day (controls) and 46.3 mg/kg-day (exposed group). The P_0 group produced three litters (designated F_{1a}, F_{1b} and F_{1c}) and the F_{1a} group produced two litters (designated F_{2a} and F_{2b}) from which the weanlings were exposed to Al in the drinking water starting at 4 weeks of age. There was no difference in body weight gain among the groups in the P_0 generation, a result that contrasted with the striking decrease in this parameter in the treated F_{1b}, F_{1c}, F_{2a} and F_{2b} groups. Though no effects on erythrocyte count, hemoglobin levels or histopathology of the liver, spleen and kidneys were observed in the P_0, F_1 or F_2 generations at the end of the study and no significant differences were seen in the number of litters or offspring between the exposed and control groups, the study identified a LOAEL of 46.3 mg Al/kg-day, based on the observed changes in body weight gain.

Other toxicological effects of aluminum

In a study designed to determine the effects of oral Al exposure on susceptibility to bacterial infection, female Swiss-Webster mice (13-14 per group) were exposed to a diet containing 25 (control), 500 or 1000 mg Al/kg as aluminum lactate during pregnancy, through lactation and for 10 days following weaning of the pups (Yoshida et al., 1989). Based on reported dosages in previous studies by the same investigators, estimated daily dosages for mice exposed to 1000 mg Al/kg diet are as follows: 200 mg/kg-day during pregnancy and 420 mg/kg-day during lactation; doses for the mice exposed to 500 mg Al/kg diet are assumed to be approximately half of that of mice fed 1000 mg Al/kg, or 100 mg/kg-day in pregnant mice and 210 mg/kg-day in lactating mice (Golub et al., 1994). At weaning, dams and pups were inoculated with a tail vein injection of *Listeria monocytogenes* and monitored for mortality for 10 days. In a separate experiment, female mice, 6 weeks of age, were exposed to the same dietary Al levels for 6 weeks and then inoculated with *L. monocytogenes*. Estimated Al dosages were 5, 98 or 195 mg Al/kg bw-day for the 25, 500 or 1000 mg Al/kg dietary levels, respectively, based on a default food factor of 0.195 kg diet/kg bw-day assuming a reference "subchronic" food intake and body weight for female B6C3F1 mice over the period from weaning to 90 days (U.S. EPA, 1988). Inoculation resulted in significantly greater ($p<0.025$) mortality in dams exposed to 500 or 1000 mg Al/kg diet compared to controls. There were no differences in mortality between the groups of inoculated pups or between groups of inoculated adult mice exposed to Al for 6 weeks. The LOAEL for pregnant mice was 100 mg Al/kg bw-day and the NOAEL for adult, non-pregnant mice was 195 mg Al/kg bw-day. Although the exposure duration in this study was only 7 weeks, it is included in Table 1 because it provides the only dose-response data on the effects of Al on resistance to pathogens.

Carcinogenicity studies

Schroeder and Mitchener (1975a) exposed 52 Long-Evans rats/sex/group to 0 or 5 ppm Al as potassium aluminum sulfate in drinking water for life. Based on default values for drinking water consumption and body weight for this strain of rat in a chronic study (U.S. EPA, 1988), these values are equivalent to Al doses of 0.472 and 0.67 mg/kg-day, for males and females, respectively. Study endpoints included body and heart weight; serum glucose, cholesterol and uric acid; and urinary protein, glucose and pH. All animals were necropsied at the time of natural death, and histological examinations were carried out on heart, lung, kidney, liver, spleen and gross tumors, for approximately 50% of the animals in the group. The only remarkable finding was a significant increase ($p<0.005$) in gross tumor incidence in exposed male rats [13/25 (52%) compared to 4/26 (15%) in controls], although the tumor sites were not reported. Six of the tumors in the exposed males (46% of total) were considered malignant compared to two malignant tumors (50% of total) in the male controls. There were no significant differences in tumor incidences between exposed and control females.

In another study by the same investigators, 54 Swiss mice/sex/group were exposed to drinking water containing 0 or 5 ppm Al as aluminum potassium sulfate for life (Schroeder and Mitchener, 1975b). Based on default values for drinking water consumption and body weight for B6C3F1 mice in a chronic study (U.S. EPA, 1988), these values approximate to Al doses of 1.2 mg/kg-day in both males and females. Study endpoints included body weight, gross pathology,

and some limited histology of the heart, lung, liver, kidney and spleen. The incidences of gross tumors were 15/41 (36.6%) and 11/38 (28.9%) in exposed and control males, respectively, and 19/41 (46.3%) and 14/47 (29.8%) in exposed and control females, respectively, differences that did not achieve statistical significance by Fisher's exact test, although incidences of multiple tumors and lymphoma leukemia were considered by the authors to be significantly increased in females ($p<0.025$ and $p<0.05$, respectively). However, a definitive assessment of aluminum carcinogenicity in both this and the rat study (Schroeder and Mitchener, 1975a) is precluded by the limitations of the pathology examinations and reporting.

In a more recent study, the tumorigenic potential of aluminum potassium sulfate was assessed in B6C3F1 mice chronically exposed in the diet (Oneda et al., 1994). Sixty animals/sex/group were fed a diet containing 0, 1.0, 2.5, 5.0 or 10.0% (w/w) for 20 months. These concentrations of aluminum potassium sulfate (as the dodecahydrate) are equivalent to 0, 569, 1422, 2844 and 5687 ppm Al. Using food factors calculated with an algorithm relating food consumption to body weight (U.S. EPA, 1988) and body weight data estimated from growth curves reported by the investigators, the dosages of aluminum are estimated to be 0, 95, 237, 483 or 1024 mg Al/kg-day in males and 0, 97, 242, 512 or 1110 mg Al/kg-day in females. Clinical signs, food consumption, and body weight were evaluated weekly. Hematology, clinical chemistry or urine endpoints were not assessed. Necropsies that included organ weight measurements and comprehensive histological examinations (including brain) were performed on all animals, including those that died during the course of the study. Survival rates were higher than control values in all treated male and female groups, ranging from 86.7-95.0% compared to 73.3% in males and 86.7-91.7% compared to 78.3% in females. No changes in food consumption were observed, but body weight gain was increased in both sexes at 95-97 and 237-242 mg Al/kg-day (weights were 10-23% higher than controls at end of study), was similar to controls in both sexes at 483-512 mg Al/kg-day, and decreased in both sexes at 1024-1110 mg Al/kg-day (11-16% lower than controls at end of study). There were no exposure-related increased incidences of tumors, other proliferative lesions or non-neoplastic lesions. In fact, the incidence of spontaneous hepatocellular carcinomas was significantly decreased in males at 1024 mg Al/kg-day (5.5% compared to 20.5% in controls, $p<0.01$).

Inhalation Exposure

Groups of 20 weanling Fischer 344 rats/sex and 20 weanling Hartley guinea pigs/sex were exposed to 0, 0.25, 2.5 or 25 mg/m^3 aluminum chlorhydrate [$Al_2(OH)_5Cl{\geq}x(H_2O)$] for 6 hours/day, 5 days/week for 6 months (Steinhagen et al., 1978). Analysis of the aluminum chlorhydrate by the investigators showed it to contain 24.5% Al, indicating that the animals were exposed to 0, 0.061, 0.61 and 6.1 mg Al/m^3. Body weights were measured weekly for the first 8 weeks and biweekly thereafter. At the end of the exposure period, 10 animals (5/sex) of each species were sacrificed for organ weight measurements (heart, lung, liver, kidney, spleen and brain) and histological examination of the lungs, liver and kidney. In addition, comprehensive histological examinations were performed on animals in the control and 6.1 mg AL/m^3 groups. The remainder of the animals was used for hematology evaluation (RBC, WBC, hematocrit and hemoglobin) and Al measurements in blood and tissues. Apparent effects of Al included multifocal granulomatous pneumonia in both species at ≥0.61 mg Al/m^3, significantly increased absolute and relative lung weights in both species, and decreased body weight gain in rats and

minimal lung edema in guinea pigs at 6.1 mg Al/m^3. The granulomatous reaction was characterized by foci of giant vacuoled particle-containing macrophages in the lungs and macrophages that did not appear to contain vacuoles or other evidence of phagocytized material in the peribronchial lymph nodes. There was a significant dose-related accumulation of Al in the lungs of both species at ≥0.061 mg Al/m^3. However, a NOAEL of 0.061 mg/m^3 could be identified for the onset of compound-induced histopathological effects.

In other studies, groups of 14-30 guinea pigs, rats and hamsters were exposed to fine metallic Al powders (pyro, atomized and flaked) at concentrations of 15, 30, 50 or 100 mg powder/m^3 air for 6 hours/day, 5 days/week for 6 months (Gross et al., 1973). Alveolar proteinosis occurred in exposed animals of all three species after 2 months of exposure, but fibrosis or other pulmonary changes did not develop. Similarly, groups of 23 or 46 rats and 48 hamsters were exposed to undetermined concentrations of Al fumes or Al powder (20% Al, 80% $Al(OH)_3$) for morning hours only or morning and afternoon for up to 20 months (Christie et al., 1963). Effects were similar for both forms of Al in both species, including initial increased alveolar macrophage proliferation followed by nodular hyalinized areas, with development of pneumonia but no fibrosis.

Exposure to 2.18 mg Al fibers/m^3 for 6 hours/day, 5 days/week for up to 86 weeks produced slightly increased alveolar macrophages and some irritation of the nasal passages in a group of 50 Alderly Park rats (Pigott et al., 1981). Finally, a study by Drew et al. (1974) observed the development of granulomatous nodules also developed in male hamsters that were exposed to 8 mg Al/m^3 of *Alchlor* (a propylene glycol complex of aluminum-chloride-hydroxide) for 6 hours/day, 5 days/week for 20 or 30 exposures. The alterations persisted at the longest post treatment observation (6 weeks) and consistently developed at the bifurcation of the bronchioloalveolar ducts, which is a likely site of particulate deposition.

DERIVATION OF A PROVISIONAL CHRONIC RfD FOR ALUMINUM

This survey of the toxicological effects of Al in rodents suggests that neurotoxicological and developmental (including neurodevelopmental) endpoints are among the most sensitive indicators of Al toxicity. However, as vehicles for the development of toxicity values such as a provisional chronic RfD, the latter group of studies are considered to be more appropriate, since the level of exposure to Al appears to be better characterized. In fact, neurobehavioral deficits have been observed in mice and rats exposed during various stages of development and in subchronic studies (Bernuzzi et al., 1989; Donald et al., 1989; Golub et al., 1989, 1992a, b, 1995; Muller et al., 1990), as described above. These deficits include impaired operant learning, changes in grip strength, altered startle response and impaired motor coordination. In addition, several studies have shown that oral Al can produce histopathological changes in the CNS, although the histopathological lesions have yet to be causally related to the neurobehavioral deficits. Thus, Florence et al. (1994) reported histopathological changes in the brain of rats exposed to dietary Al for 6 months, the changes including the appearance of vacuolation of the cell body and cell processes of astrocytes in the brain and swelling of astrocytic processes. In addition, more localized vacuolization of neurons in the brain also was observed. These changes

were observed in rats exposed to elevated Al in the diet and are distinct from the NFD that has been observed in rats, rabbits and monkeys maintained on elevated dietary Al in combination with reduced dietary calcium (Garruto et al., 1989; Kihira et al., 1994; Mitani, 1992; Yano et al., 1989; Yoshida et al., 1990) or in rabbits administered intracisternal or intraventricular injections of Al (Kowall et al., 1989; Wakayama et al., 1993). Interpretation of the low-calcium studies is complicated by the observation that NFD was observed in animals maintained on low-calcium diets without excess Al and was enhanced by the addition of excess Al to these diets (Garruto et al., 1989; Kihira et al., 1994). Furthermore, Al has been shown to inhibit the gastrointestinal absorption of calcium (Orihuela et al., 1996), an effect that may exacerbate the calcium deprivation induced by low calcium diets. Thus, it is not clear whether calcium deprivation enhances the neurotoxicity of Al or Al exacerbates the adverse effects of calcium deprivation.

Donald et al. (1989) and Golub et al. (1995) are co-principal studies that identify a LOAEL of 100 mg Al/kg-day for minimal neurotoxicity in the offspring of mice exposed to dietary aluminum lactate (soluble aluminum) during gestation and lactation. The neurotoxicity associated with this LOAEL is consistent with LOAELs from other developmental and subchronic neurobehavioral studies in mice and rats which used higher dietary dosages of aluminum lactate or aluminum chloride (Golub et al., 1989, 1992a,b; Bernuzzi et al., 1989; Muller et al., 1990). Of the above, Golub et al., (1995) is the only study in which a histopathological examination of the brain and spinal cord was conducted and no abnormalities were reported. The Florence et al. (1994) study indicates that histopathological abnormalities of the CNS can occur in rats exposed subchronically to 84 mg/kg-day; although this is lower than the LOAEL for neurobehavioral effects, it was not chosen as the principal study because the functional significance of the histopathological lesions are uncertain.

A number of studies were identified that, at face value, appeared to indicate LOAELs at lower doses than the 100 mg Al/kg-day value selected herein, for example, Paternain et al. (1988) and Colomina et al. (1992). However, in these as in many of the studies under consideration, insufficient information on dietary Al (Al content and/or feed type) was reported to permit a reliable estimation of the overall dose level to which the animals were subjected.

Other developmental studies with aluminum hydroxide and/or citrate in mice and rats identified a NOAEL which are equivalent (95.5 mg Al/kg-day), or a minimum LOAEL that was greater (133 mg Al/kg-day) than the 100 mg Al/kg-day critical LOAEL (Domingo et al., 1989; Gomez et al., 1991), an overlap potentially related to differences in effective doses due to variations in unreported Al dietary content and factors affecting absorption such as chemical form (e.g., the use of less absorbable aluminum hydroxide). In addition, the LOAEL of 43.3 mg Al/kg-day for decreased body weight gain in mice exposed to aluminum chloride for 180-390 days (Ondreicka et al., 1966) was thought be inappropriate for risk assessment due to the small sample size and to the poor reporting of study details. Aluminum nitrate caused alterations in levels of brain biogenic amines and hepatic and hematological indices in rats exposed to 21.4 mg Al/kg-day for 6 weeks (Flora et al., 1991). This dose is not a LOAEL because insufficient information is available to determine if the effects are adverse.

Therefore, the LOAEL of 100 mg Al/kg-day for minimal neurotoxicity in the offspring of mice (Donald et al., 1989, Golub et al., 1995) is selected as the basis for the provisional chronic

RfD. The LOAEL is considered minimal because the results of the postweaning neurobehavioral test battery indicate that performance deficits may be marginal. In particular, of the three observed effects (decreased forelimb and increased hindlimb grip strengths, increased hindlimb foot splay distance), one effect (increased grip strength) has unclear toxicological significance and two effects (increased grip strength and foot splay distance) did not persist after 2 weeks of no further exposure.

Application of an uncertainty factor (UF) of 100 (3 for use of a minimal LOAEL, 10 for interspecies extrapolation and 3 for intrahuman variability where the critical effects have been observed in a sensitive sub-group) results in a provisional RfD of

p-RfD = 1E-0 mg Al/kg-day.

The provisional RfD of **1E-0** mg Al/kg-day is approximately 3-fold higher than estimated normal daily Al intake of approximately 0.2-0.3 mg/kg-day (Iyengar et al., 1987; Ganrot, 1986; Wilhelm et al., 1990). Chronic users of medications such as antacids, buffered aspirins and antiulceratives would be expected to ingest much larger amounts of Al, possibly as high as 10-70 mg/kg-day. However, these subjects would not represent the most sensitive population (developing infants), as indicated by the animal data.

Low confidence is placed in the co-critical studies, because they only identify a LOAEL for a sensitive effect and evaluated comparatively small numbers of animals. Confidence in the data base is low because the most reliable supporting data for neurotoxicity of Al in humans are of limited general relevance (e.g., dialysis encephalopathy is manifested in patients with impaired renal function and excessive Al uptake from intravenous exposure). In fact, neurotoxicity remains to be assessed in animals chronically exposed to Al, and developmental morphology has not been adequately investigated in two animal species. These limitations in the Al data base do not increase uncertainty in the RfD; therefore, a data base uncertainty factor was not used. However, reflecting the low confidence in the co-critical studies, there is low overall confidence in the RfD.

DERIVATION OF A PROVISIONAL CHRONIC RfC FOR ALUMINUM

Al seems to be the most likely cause for the generally and consistently reported psychomotor and cognitive effects (particularly signs of impaired coordination) in Al production workers and welders (Bast-Pettersen et al., 1994; Rifat et al., 1990; Hosovski et al., 1990; White et al., 1992; Hanninen et al., 1994; Sjogren et al., 1990, 1996). In addition, there is strong evidence that Al is neurotoxic by other routes of exposure. Thus, a degenerative neurological syndrome (dialysis dementia) has been documented in humans with chronic renal failure, apparently due to an increased exposure to Al from dialysis treatment and/or ingestion of phosphate binding agents which contain Al (Alfrey, 1993). This syndrome is characterized by gradual loss of motor, speech and cognitive functions. Neurotoxicity, particularly neuromuscular effects such as decreased motor activity, startle responsiveness and grip strength, has also been observed in mice following subchronic oral exposure and in the offspring of mice and rats exposed orally during gestation and/or lactation. Based on this information, as well as evidence

that Al is absorbed by Al production workers and welders, the hypothesis that the occupational studies are indicative of a neurotoxic effect of Al appears to be justified. However, the only occupational study that has yielded suitable monitoring data is that of Hosovski et al. (1990), in which workers were exposed to presumed time-weighted average (TWA) concentrations of 4.6-11.5 mg Al/m^3 magnitude for an average of 12 years. Using 4.6 mg Al/m^3 as the LOAEL for psychomotor and cognitive impairment for an 8-hour occupational exposure (Hosovski et al., 1990) and corrections for discontinuous exposure (10 m^3/20 m^3 and 5 days/7 days), the $LOAEL_{HEC}$ is 1.64 mg/m^3. Applying an uncertainty factor of 300 for intrahuman variability (10), use of a LOAEL (10) and an incomplete database (3) yields a provisional RfC of

p-RfC = 1.64 mg/m^3/300 = 5E-3 mg/m^3.

The lack of inhalation developmental studies may increase uncertainty in the database because oral data in animals indicate that neurotoxic and morphological developmental effects may occur at lower doses than neurotoxicity in adults. Additionally, there is uncertainty related to the lack of corroborating data on air concentrations associated with neurotoxicity. Confidence in the critical study is low to medium because only a LOAEL was identified. Confidence in the database is medium because (1) there are no corroborating data on effect levels (NOAELs and additional LOAELs), (2) no data are available for developmental neurotoxicity by the inhalation route and (3) a well-designed two-generation reproduction study is lacking. Reflecting the low to medium confidence in the critical study and database, there is low to medium confidence in the provisional RfC.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ALUMINUM

Weight-Of-Evidence Classification

A considerable number of epidemiological studies have examined the incidence of excess tumor formation in persons occupationally exposed to Al in the form of dusts or fumes. In general, a body of inferential evidence exists for an increase in cancer of the bladder and lung through such occupational exposure to Al, although conclusions linking these responses to the effects of Al are confounded by attendant co-exposure to other harmful emissions such as PAHs and by cigarette smoking. A 20-month exposure of B6C3F1 mice to Al potassium sulfate dodecahydrate in the diet at concentrations up to 10% w/w displayed no indication of compound-related carcinogenicity and, in general, no indication of adverse toxicological effects of any kind (Oneda et al., 1994). Similarly, the life-time exposure of Swiss mice and Long-Evans rats to 5 ppm Al as aluminum potassium sulfate in drinking water provided no convincing evidence for the carcinogenicity of Al compounds (Schroeder and Mitchener, 1975a,b). Gene reversion experiments on Al compounds resulted in negative results in *S. typhimurium* (Ahn and Jeffrey, 1994). Taking all of the evidence of Al carcinogenicity together, and in accordance with the U.S. EPA (2005) cancer guidelines, aluminum is classified as *inadequate information to assess carcinogenic potential*. The basis for this classification is insufficient evidence in epidemiological/occupational studies, lack of demonstrated carcinogenicity or mutagenicity in

available animal studies, lack of positive evidence of non-carcinogenicity and lack of mode of action data for aluminum.

Quantitative Estimates of Carcinogenic Risk

Due to insufficient data, a provisional oral slope factor and inhalation unit risk could not be developed.

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Table 1. Summary of oral toxicity data for aluminum[a]

Study	Type	Species	Al	Exposure Concentration (ppm)	Exposure Dosage (mg Al/kg-day)	Exposure Frequency and Duration	Critical Effect	NOAEL (mg Al/kg-day)	LOAEL (mg Al/kg-day)	FEL (mg Al/kg-day)
Ondreicka et al., 1966	Subchronic 3-gen dietary	Dobra Voda mice	chloride	--	27 (control), 46	Continuous, 180-390 days	Decreased body weight gain in F1 and F2.	--	46	--
Golub et al., 1989	Subchronic dietary	S-W mice	lactate	25 (control), 500,1000	3.3 (control), 65,130	Continuous, 6 weeks	Decreased spontaneous motor activity; decreased weight gain.	65	130	--
Golub et al., 1992a	Subchronic dietary	S-W mice	lactate	25 (control), 1000	190	Continuous, 90 days	Decreased hindlimb grip, decreased spontaneous motor activity, decreased startle response.	--	190	--
Florence et al., 1994	Subchronic dietary	Wistar rat	chloride (with citric acid)	1.52 (control), 1000	0.13 (control), 84	Continuous, 6 months	Histopathological changes in brain astrocytes and neurons.	--	84	--
Domingo et al., 1996	Subchronic drinking water	Sprague Dawley rats	nitrate (with citric acid)	--	0, 50, 100 (plus unreported dietary Al)	Continuous, 6.5 months	Operant conditioning and performance	100	--	--
Yoshida et al., 1989	Subchronic dietary	S-W mice	lactate	25 (control), 500, 1000	5 (control), 98, 195	Continuous, 7 weeks	Increased mortality from *L. monocytogenes* inoculation	195	--	--
Donald et al., 1989	Developmental dietary	S-W mice	lactate	25 (control), 500, 1000	5 (control), 100, 200	Continuous, gestation and lactation	Neurobehavioral effects.	--	100	--
Golub et al., 1992b	Developmental dietary	S-W mice	lactate	25 (control), 1000	4 (control), 174	Continuous, gestation and lactation	Neurobehavioral effects.	--	174	--
Golub et al., 1995	Developmental dietary	S-W mice	lactate	7, 500, 1000	1 (control), 100, 200	Continuous, gestation, lactation to maturity	Neurobehavioral effects.	--	100	--

Table 1. Summary of oral toxicity data for aluminum[a]

Study	Type	Species	Al	Exposure Concentration (ppm)	Exposure Dosage (mg Al/kg-day)	Exposure Frequency and Duration	Critical Effect	NOAEL (mg Al/kg-day)	LOAEL (mg Al/kg-day)	FEL (mg Al/kg-day)
Yoshida et al., 1989	Developmental dietary	S-W mice	lactate	25 (control), 500, 1000	4 (control), 100, 200	Continuous, gestation and lactation	Increased mortality of dams from *L. monocytogenes* inoculation	--	100	--

[a]Studies for which total dosages were reported or could be estimated (unless otherwise noted).