DRAFT OF
PRIORITY DATA NEEDS FOR ALUMINUM

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Public Health Services
Agency for Toxic Substances and Disease Registry

NOTE TO THE READER

The Priority Data Needs documents are intended to characterize substance-specific priority data needs determined via the ATSDR **Decision guide for identifying substance-specific data needs related to toxicological profiles** (54 Federal Register 37618, September 11, 1989). The identified priority data needs reflect the opinion of the Agency, in consultation with other federal programs, of the research necessary for fulfilling its statutory mandate under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA. They are not intended to represent the priority data needs for any other program.

We plan to revise these documents in response to public comments and as additional data becomes available. Therefore, we encourage comments that will make these documents of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
Mail Stop F-32
Atlanta, Georgia 30333

CONTRIBUTORS

DOCUMENT MANAGER(S)/AUTHOR(S):

Sam Keith, M.S.
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Lisa Ingerman, Ph.D., DABT
Daniel Plewak, B.S.
Syracuse Research Corporation, North Syracuse, NY

The document has been reviewed by Dennis Jones, D.V.M., team member for ATSDR's Toxicological Profile for Aluminum. In addition, it was forwarded to the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences for review.

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Aluminum

Prepared by: Agency for Toxic Substances and Disease Registry/

Division of Toxicology and Environmental Medicine (ATSDR/DTEM)

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I. Executive Summary

Aluminum is included in the priority list of hazardous substances identified by ATSDR and the
Environmental Protection Agency (EPA) (ATSDR 2005). This list contains substances that have
been identified at National Priorities List (NPL) sites and determined to pose a human health risk
based on (1) known or suspected human toxicity, (2) frequency of occurrence at NPL sites or
other facilities, and (3) the potential for human exposure to the substance. An updated
Toxicological Profile for Aluminum (Draft for Public Comment) was published by ATSDR in
September 2006. Currently, the updated toxicological profile is being finalized.

Aluminum is the most abundant metal and the third most abundant element in the earth's crust,
comprising about 8.8% by weight (88 g/kg). It does not exist as the free metal in nature; it is
found in most rocks (Lide 2005; Staley and Haupin 1992). Aluminum is a silvery-white,
malleable, and ductile metal. In moist air, a protective oxide coating of aluminum oxide is
formed on its surface. (Lide 2005; O'Neil et al. 2001). For the most part, aluminum compounds
are insoluble in water except under strongly acidic or alkaline conditions (Martell and Motekaitis
1989). Aluminum compounds exist primarily in ionic form in the environment and are therefore
not expected to volatilize.

In 2005, an estimated 2.5 million metric tons of aluminum metal were produced in the United
States while approximately 3.6 million metric tons were recovered from scrap (USGS 2004,
2006). U.S. production of alumina (aluminum oxide) was 4.35 million metric tons in 2003
(USGS 2003, 2006).

Familiar uses of aluminum are for beverage cans, pots and pans, cars, airplanes, siding and roofing, and foil (O'Neil et al. 2001, USGS 2004, 2006). Aluminum compounds are used in many diverse and important industrial applications such as alums (aluminum sulfate) in water-treatment and alumina in abrasives and furnace linings (Lewis 2001; O'Neil et al. 2001). They are found in consumer products such as antacids, astringents, buffered aspirin, food additives, and antiperspirants (Lewis 2001; Lione 1985; O'Neil et al. 2001). Powdered aluminum metal is often used in explosives and fireworks (O'Neil et al. 2001).

The behavior of aluminum in the environment depends upon its coordination chemistry and the characteristics of the local environment, especially pH (Brusewitz 1984; Dahlgren and Ugolini 1989; Filipek et al. 1987; Goenaga and Williams 1988; James and Riha 1989; Litaor 1987; Mulder et al. 1989; Wangen and Jones 1984). Major transport processes in the environment include leaching from geochemical formations and soil particulates to aqueous environments, adsorption onto soil or sediment particulates, and wet and dry deposition from the air to land and surface water (Eisenreich 1980; Golomb et al. 1997; James and Riha 1989; Walker et al. 1988; Wangen and Jones 1984). In the environment, aluminum exists in only one oxidation state (+3), and does not undergo oxidation-reduction reactions (Lide 2005). It can react with other matter in the environment to form various complexes (Brusewitz 1984; Dahlgren and Ugolini 1989; Litaor 1987; Plankey and Patterson 1987).

The general population is exposed to aluminum primarily through the consumption of food items, although minor exposures may occur through ingestion of aluminum in drinking water and inhalation of ambient air (Browning 1969; Miller et al. 1984a; Pennington and Schoen 1995; Saiyed and Yokul 2005; Soni et al. 2001). Individuals who use certain over-the-counter medicinals may be exposed to high levels of aluminum (Lione 1983, 1985; Pennington and Schoen 1995; Soni et al. 2001; Zhou and Yokel 2005). Individuals living in the vicinity of industrial emission sources and hazardous waste sites may be exposed to aluminum via ingestion of contaminated soil or water or by inhalation of airborne particulates containing aluminum. Occupational exposures occur during the mining, processing, production, and recovery of aluminum and aluminum compounds (Nieboer et al. 1995). As with adults, children may be exposed via ingestion of aluminum containing foods and medicinal products. Children may also be exposed via ingestion of aluminum contaminated soil from their unwashed hands or via inhalation of aluminum in resuspended dust during near-ground activities. Premature infants may

be exposed if they are fed soy-based formulas containing high levels of aluminum (Pennington and Schoen 1995).

The available human and animal data indicate that aluminum is poorly absorbed following inhalation, oral, and dermal exposure. Occupational exposure studies in aluminum workers and reports of individuals with renal failure suggest that the nervous system, and possibly the respiratory system, is the principal target of aluminum toxicity. The oral exposure studies in animals provide strong evidence that the nervous system in mature and developing organisms is the most sensitive target of aluminum toxicity. There is also some evidence that aluminum exposure may also result in decreases in pup body weight, delays in physical maturation, and impaired development of the immune system. Increases in tumor occurrence have been observed in aluminum production workers, although the increased cancer risk is probably due to concominant exposure to other carcinogens and not to aluminum. Animal studies are inadequate to assess aluminum carcinogenicity. Adults and children appear to have similar targets of toxicity, although there may be some age-related differences in the toxicokinetic properties of aluminum.

On the basis of the available data, ATSDR has identified the following priority data needs:

Exposure

- Exposure via environmental media for humans living near hazardous waste sites.

- Exposure via environmental media for children living near hazardous waste sites.

Toxicity

- Dose-response data for acute-duration via oral exposure

II. Introduction: ATSDR's Substance-Specific Applied Research Program

A. Legislative

Section 104(i)(5) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of aluminum is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects. Such program shall include, to the extent necessary to supplement existing information, but shall not be limited to--

- laboratory and other studies to determine short, intermediate, and long-term health effects;

- laboratory and other studies to determine organ-specific, site-specific, and system-specific acute and chronic toxicity;

- laboratory and other studies to determine the manner in which such substances are metabolized or to otherwise develop an understanding of the biokinetics of such substances; and

- where there is a possibility of obtaining human data, the collection of such information.

Section 104(i)(5)(C): In the development and implementation of the research program ATSDR is required to coordinate with EPA and NTP to avoid duplication of research being conducted in other programs and under other authorities.

Section 104(i)(5)(D): It is the sense of Congress that the costs for conducting this research program be borne by private industry, either under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or cost recovery under CERCLA.

B. Impact on Public Health

The major purpose of this research program is to supplement the substance-specific informational needs of the public and the scientific community. More specifically for ATSDR, this program will supply necessary information to improve the database to conduct public health assessments.

This is more fully described in the ATSDR Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (54 Federal Register 37618) [henceforth referred to as the ATSDR Decision Guide].

Experience from ATSDR health assessments shows the need for more information for select substances, on both exposure and toxicity, so the Agency can more completely assess human health effects. Exposure data collected from this substance-specific research will complement data being collected on a site-specific basis by ATSDR's Division of Health Studies and the Division of Health Assessment and Consultation. More specifically, the Agency will use the exposure data to help identify populations that need follow-up exposure or health-outcome studies.

Regarding substance toxicity, the collected data will be used to characterize the toxicity of the substance for public and scientific community. For ATSDR, the data are necessary and essential to improve the design and conduct of follow-up health studies.

C. Procedures

Section 104(i)(2) of CERCLA, as amended, requires that ATSDR (1) with EPA develop a list of hazardous substances found at NPL sites (in order of priority), (2) prepare toxicological profiles of those substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The first step in implementing the ATSDR substance-specific research program for aluminum occurred when the data needs for aluminum were determined in the ATSDR Toxicological Profile for Aluminum. Considered a subset of all information gaps on aluminum, these data needs were reviewed by scientists from ATSDR and other federal agencies. They were peer reviewed by an external review panel and made available for public comment. All comments received by ATSDR on the identification of data needs for aluminum were addressed before the toxicological profile was finalized. In preparing the priority data needs document, a literature search was conducted to provide updated information on aluminum.

The purpose of this paper is to take the data needs identified in the Toxicological Profile for Aluminum and subject them to further scientific evaluation. This will lead to priorities and

ultimately to ATSDR's substance-specific research agenda. To effect this step, ATSDR developed and presented a logical scientific approach to priority setting in its Decision Guide.

Briefly, data needs are categorized as exposure or toxicity and are then subcategorized across three levels (Tables 1 and 2). Level I research is a base set of exposure and toxicity information to identify basic characteristics of each substance. Level II research is conducted to confirm the toxicity and exposure indicated by Level I data. Level III research will improve the application of the results of Level II research to people.

The Decision Guide recognized three general principles for setting priorities:

• Not all information gaps identified in toxicological profiles are data needs.

• All data needs are not the same priority.

• Substances should be considered individually, but may be grouped, because of structural similarity or other relevant factors.

Other considerations spelled out in the Decision Guide include:

• All levels of data should be considered in selecting priority data needs.

• Level I gaps are not automatically in the priority grouping. In general, Level I data have priority when there are no higher level data for the same category, and when data are insufficient to make higher level priority testing decisions. For example, priority would generally not be assigned multigenerational animal studies (Level II) if an adequate subchronic study (Level I) had not been conducted that evaluated reproductive organ histopathology.

• Priority for either exposure or toxicity data requires thorough evaluation of research needs in other areas to help achieve a balanced research program for each substance.

The Decision Guide listed the following eight tenets to determine research priorities:

• Development and/or confirmation of appropriate analytical methods.

• Determination of environmental and human exposure levels when analytical methods are available.

• Bioavailability studies for substances of known significant toxicity and exposure.

• Studies available to characterize target organs and dose response.

- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.

- Mechanistic studies on substances with significant toxicity and substantial human exposure.

- Investigation of methods to mitigate toxicity for substances when enough is known about mode of action to guide research.

- Epidemiologic studies designed to link human disease with a substance of known significant toxicity.

These last three "prioritizing" tenets address Level III research. When Level III research is identified as priority, ATSDR will not develop detailed methods to successfully fulfill the data needs. Because there are no standard "testing guidelines" for Level III research, we expect considerable discussion between ATSDR and parties interested in conducting this research. Thus, ATSDR will only announce that its scientists believe that the accumulation of Level III research is appropriate, and it is a priority at this time. ATSDR will state the reasons why this is so.

D. Selection Criteria

ATSDR prepares toxicological profiles on substances that are most commonly found at facilities on the NPL sites and which, in its sole discretion, pose the most significant threat to human health because of their known or suspected toxicity and potential for human exposure.

Briefly, the rationale is as follows:

1. Frequency of Occurrence

Finding: Aluminum is included in the priority list of hazardous substances identified by ATSDR and EPA (ATSDR 2005).

Aluminum has been detected in at least 606 of 1,678 National Priorities List (NPL) hazardous waste sites in the United States (HazDat 2006). Exposure to aluminum at these sites may occur by contacting contaminated air, water, soil, or sediment. ATSDR is presently evaluating the extent of media-specific contamination at these and other sites.

2. Potential for Human Exposure

Finding: ATSDR scientists have determined that there has been significant past human exposure and that the potential exists for current human exposure to aluminum via inhalation, ingestion, and skin contact.

The following is a brief summary of the potential for human exposure to aluminum. For a more detailed discussion of available information, refer to the ATSDR Toxicological Profile for aluminum, Chapter 6, on Potential for Human Exposure (ATSDR 2006).

According to the Toxic Chemical Release Inventory (TRI), total releases of aluminum (fume or dust) to the environment (including air, water, and soil) from 337 large processing facilities were 48.5 million pounds (~2.20×10^4 metric tons) in 2004 (TRI04 2006). In addition, total releases of aluminum oxide (fibrous forms) to the environment (including air, water, and soil) from 60 large processing facilities were 1.32 million pounds (~600 metric tons) in 2004 (TRI04 2006). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005).

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg). It is never found free in nature and is found in most rocks, particularly igneous rocks as aluminosilicate minerals (Lide 2005; Staley and Haupin 1992). Aluminum is also present in air (Cooper et al. 1979; Dzubay 1980; Hoffman et al. 1969; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Pötzl 1970; Sorenson et al. 1974; Stevens et al. 1978), water (DOI 1970; Letterman and Driscoll 1988; Miller et al. 1984a; Schenk et al. 1989), and many foods (Greger 1992; MAFF 1999; Pennington 1987; Schenk et al. 1989). Aluminum enters environmental media naturally through the weathering of rocks and minerals. Anthropogenic releases are in the form of air emissions, waste water effluents, and solid waste primarily associated with industrial processes, such as aluminum production. Because of its prominence as a major constituent of the earth's crust, natural weathering processes far exceed the contribution of releases to air, water, and land associated with human activities (Lantzy and MacKenzie 1979).

The fate and transport of aluminum is largely controlled by environmental factors such as pH, salinity, and the presence of various species with which it may form complexes (Brusewitz 1984;

Dahlgren and Ugolini 1989; Filipek et al. 1987; Goenaga and Williams 1988; James and Riha 1989; Litaor 1987; Mulder et al. 1989; Wangen and Jones 1984). In general, the solubility and mobility of aluminum in soil is greatest when the soil is rich in organic matter capable of forming aluminum-organic complexes and when the pH is low, such as in areas prone to acid rain or in acidic mine tailings (Alvarez et al. 1993; Brusewitz 1984; Dahlgren and Ugolini 1989; Filipek et al. 1987; Goenaga and Williams 1988; James and Riha 1989; Liator 1987; Mulder et al. 1989; Wangen and Jones 1984). The major features of the biogeochemical cycle of aluminum include leaching of aluminum from geochemical formations and soil particulates to aqueous environments, adsorption onto soil or sediment particulates, and wet and dry deposition from the air to land and surface water (Eisenreich 1980; Golomb et al. 1997; James and Riha 1989; Walker et al. 1988; Wangen and Jones 1984).

Generally, aluminum is not bioaccumulated to a significant extent. However, certain plants such as tea leaves and some ferns have been found to accumulate high concentrations of aluminum (Dong et al. 1999; Jansen et al. 2002). Aluminum does not appear to accumulate to any significant degree in cow's milk or beef tissue and is, therefore, not expected to undergo biomagnification in terrestrial food chains (DOE 1984). Similarly, because of its toxicity to many aquatic organisms, including fish, aluminum does not bioconcentrate in aquatic organisms to any significant degree (Rosseland et al. 1990).

As an element, aluminum cannot be degraded in the environment, but may undergo various precipitation or ligand exchange reactions. Aluminum in compounds has only one oxidation state (+3), and would not undergo oxidation-reduction reactions under environmental conditions (Lide 2005). Aluminum can be complexed by various ligands present in the environment (e.g., fulvic and humic acids) (Brusewitz 1984; Dahlgren and Ugolini 1989; Litaor 1987; Plankey and Patterson 1987).

Aluminum has been identified in at least 606 of the 1,678 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for aluminum is not known. Of these sites, 599 are located within the United States, 3 are located in Guam, 3 are located in the Commonwealth of Puerto Rico, and 1 is located in the Virgin Islands.

Since aluminum is ubiquitous in the environment, the general population will be exposed to aluminum by the inhalation of ambient air and the ingestion of food and water. The consumption of foods with aluminum-containing food additives are a major sources of aluminum in the diet (Saiyed and Yokel 2005; Soni et al. 2001). The use of other consumer items such as antiperspirants, cosmetics, internal analgesics (buffered aspirins), anti-ulcerative medications, antidiarrheals, and antacids that also contain aluminum compounds will result in exposure to aluminum (Lione 1983, 1985; Pennington and Schoen 1995; Soni et al. 2001; Zhou and Yokel 2005). While aluminum is naturally present in food and water, the greatest contribution to aluminum in food and water by far is the aluminum-containing additives used in water treatment and in processing certain types of food such as grain-based products and processed cheese (Cech and Montera 2000; DOI 1970; Greger 1992; Letterman and Driscoll 1988; Miller et al. 1984a; Pennington 1987; Saiyed and Yokel 2005; Schenk et al. 1989).

Individuals living in the vicinity of industrial emission sources and hazardous waste sites; individuals with chronic kidney failure requiring long-term dialysis or treatment with phosphate binders; patients requiring intravenous fluids; premature infants fed soy-based formula containing high levels of aluminum; and individuals consuming large quantities of antacids, anti-ulcerative medications, or antidiarrheal medications may also be exposed to high levels of aluminum (Lione 1983, 1985; Pennington and Schoen 1995; Soni et al. 2001; Zhou and Yokel 2005). Individuals living in close proximity to aluminum production facilities or hazardous waste sites may be exposed to aluminum via ingestion of aluminum contained in soil from their unwashed hands when working or playing with contaminated soils and sediments. Children, in particular, are likely to ingest dirt from their unwashed hands or inhale resuspended dust during near-ground activities. If residential wells are the primary source of drinking water, this may also pose a risk to human health via consumption of contaminated drinking water.

Occupational exposures to aluminum occur during the mining and processing of aluminum ore into metal, recovery of scrap metal, production and use of aluminum compounds and products containing these compounds, and in aluminum welding (Nieboer et al. 1995). According to the National Occupational Exposure Study (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983, the industries with the largest numbers of workers potentially exposed to aluminum and aluminum compounds include: plumbing, heating, and air conditioning; masonry and other stonework; electrical work; machinery except electrical; certified air transportation equipment; electrical components;

fabricated wire products; general medical and surgical hospitals; industrial buildings and warehouses; and special dies, tools, jigs, and fixtures (NIOSH 1991).

3. Toxicity

Finding: ATSDR considers that short, intermediate, and/or long-term health effects can result from oral contact of aluminum. Target organs or systems known to be affected include the nervous system and the developing organism.

The following is a brief summary of the toxicology of aluminum. Refer to the ATSDR Toxicological Profile for aluminum chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2006).

Numerous studies have examined aluminum's potential to induce toxic effects in humans exposed via inhalation, oral, or dermal exposure. Most of these findings are supported by a large number of studies in laboratory animals. Occupational exposure studies and animal studies suggest that the lungs and nervous system may be the most sensitive targets of toxicity following inhalation exposure. Respiratory effects, in particular impaired lung function and fibrosis, have been observed in workers exposed to aluminum dust or fumes (Abbate et al. 2003; Akira 1995; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Burge et al. 2000; Chan-Yeung et al. 1983; Chen et al. 1978; De Vuyst et al. 1987; Edling 1961; Hull and Abraham 2002; Jederlinic et al. 1990; Korogiannos et al. 1998; McLaughlin et al. 1962; Miller et al. 1984b; Mitchell et al. 1961; Radon et al. 1999; Simonsson et al. 1985; Ueda et al. 1958; Vallyathan et al. 1982; Vandenplas et al. 1998); however, this has not been consistently observed across studies and it is possible that co-exposure to other compounds contributed to observed effects. Respiratory effects (granulomatous lesions) have also been observed in rats (Steinhagen et al. 1978; Thomson et al. 1986), hamsters (Drew et al. 1974), and guinea pigs (Steinhagen et al. 1978). There is concern that these effects are due to dust overload rather than a direct effect of aluminum in lung tissue. Occupational studies in workers exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding provide suggestive evidence that there may be a relationship between chronic aluminum exposure and subclinical neurological effects such as impairment on neurobehavioral tests for psychomotor and cognitive performance and an increased incidence of subjective neurological symptoms (Akila et al. 1999; Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997;

Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sim et al. 1997; Sjögren et al. 1990, 1996; White et al. 1992). With the exception of some isolated cases (McLaughlin et al. 1962), inhalation exposure has not been associated with overt symptoms of neurotoxicity. A common limitation of these occupational exposure studies is that aluminum exposure has not been well characterized. The available animal inhalation studies (Finelli et al. 1981; Steinhagen et al. 1978; Stone et al. 1979) are inadequate for assessing the potential for aluminum-induced neurotoxicity because the only neurological end points examined were brain weight and histology of the brain; no function tests were performed.

There is limited information on aluminum toxicity following dermal exposure. Application of aluminum compounds to the skin, such as an aluminum-containing antiperspirant, may cause rashes in some people (Brusewitz 1984). Skin damage has been observed in mice, rabbits, and pigs exposed to aluminum chloride or aluminum nitrate, but not following exposure to aluminum sulfate, aluminum hydroxide, aluminum acetate, or aluminum chlorhydrate (Lansdown 1973).

Although there are fair amounts of human data on the toxicity of aluminum following oral exposure, these data have limited usefulness in predicting toxicity in the general population. The preponderance of human studies are in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-contaminated dialysis fluid and, in many cases, concurrent administration of high oral doses of aluminum to regulate phosphate levels (i.e., reduce uptake of phosphate by binding it in the gut). The very large aluminum exposure levels and impaired renal function result in aluminum accumulation. Dialysis encephalopathy syndrome (also referred to as dialysis dementia) can result from this accumulation of aluminum in the brain. Dialysis encephalopathy is a degenerative neurological syndrome, characterized by the gradual loss of motor, speech, and cognitive functions (Alfrey 1993). Another neurological effect that has been proposed to be associated with aluminum exposure is Alzheimer's disease. Although a possible association was proposed over 40 years ago, this association is still highly controversial and there is little consensus regarding current evidence. A number of studies have found weak associations between living in areas with elevated aluminum levels in drinking water and an increased risk (or prevalence) of Alzheimer's disease (Flaten 1990; Gauthier et al. 2000; Jacqmin et al. 1994; Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Rondeau et al. 2000, 2001); other studies have not found significant associations (Forster et al. 1995; Martyn et al. 1997; Wettstein et al. 1991; Wood et al. 1988). In contrast, no significant associations have

been found between tea consumption or antacid use and the risk of Alzheimer's disease
(Amaducci et al. 1986; Broe et al. 1990; Colin-Jones et al. 1989; Forster et al. 1995; Graves et al.
1990; Heyman et al. 1984; McDowell et al. 1994); although the levels of aluminum in tea and
antacids are very high compared to drinking water, aluminum from these sources is poorly
absorbed. The available data do not suggest that aluminum is a causative agent of Alzheimer's
disease; however, it is possible that it may play a role in the disease development.

Aluminum is found in several ingested over-the-counter products such as antacids and buffered
aspirin; clinical studies on health effects of aluminum medicinals in people with normal renal
function have not been identified. These aluminum-containing products are assumed to be safe in
healthy individuals at recommended doses based on historical use. The assumed safety of
aluminum is also partly due to the generally regarded as safe (GRAS) status of aluminum-
containing food additives. However, there is some indication that adverse effects can result from
long-term use of aluminum-containing medications in some healthy individuals. There are a
number of case reports of skeletal changes (e.g., osteomalacia) in adults and children with normal
kidney function due to long-term antacid use for the treatment of gastrointestinal disorders
(Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998). These
skeletal effects are secondary to hypophosphatemia and phosphate depletion caused by aluminum
impairing phosphorus absorption by binding with dietary phosphorus.

There is a rather extensive database on the oral toxicity of aluminum in animals. These studies
clearly identify the nervous system as the most sensitive target of aluminum toxicity and most of
the animal studies have focused on neurotoxicity and neurodevelopmental toxicity. Other
adverse effects that have been observed in animals orally exposed to aluminum include impaired
erythropoiesis in rats (Garbossa et al. 1998; Vittori et al. 1999), erythrocyte damage (as evidenced
by decreases in hemoglobin, hematocrit, and erythrocyte osmotic fragility, and altered erythrocyte
morphology) in rats (Garbossa et al. 1998; Vittori et al. 1999), increased susceptibility to
infection in mouse dams (Yoshida et al. 1989), delays in pup maturation following exposure of
rats (Colomina et al. 2005), and decreases in pup body weight gain in rats and mice (Colomina et
al. 2005; Golub and Germann 2001; Golub et al. 1992a).

Neurodegenerative changes in the brain, manifested as intraneuronal hyperphosphorylated neuro-
filamentous aggregates, is a characteristic response to aluminum in certain species and nonnatural
exposure situations generally involving direct application to brain tissue, particularly intracerebral

and intracisternal administration and *in vitro* incubation in rabbits, cats, ferrets, and nonhuman primates (Erasmus et al. 1993; Jope and Johnson 1992). Oral studies in rats and mice have not found significant histopathological changes in the brain under typical exposure conditions (Dixon et al. 1979; Domingo et al. 1987b; Florence et al. 1994; Gomez et al. 1986; Lal et al. 1993; Varner et al. 1993, 1994, 1998); however, altered myelination was found in the spinal cord of mouse pups exposed to high levels of aluminum on gestation day 1 through postnatal day 35 (Golub and Tarara 1999). Overt signs of neurotoxicity are rarely reported at the doses tested in the available animal studies; rather, exposure to these doses is associated with subtle neurological effects detected with neurobehavioral performance tests. Significant alterations in motor function, sensory function, and cognitive function have been detected following exposure to adult or weanling rats and mice or following gestation and/or lactation exposure of rats and mice to aluminum lactate, aluminum nitrate, and aluminum chloride. The most consistently affected performance tests were forelimb and/or hindlimb grip strength (Colomina et al. 2005; Donald et al. 1989; Golub et al. 1992a, 1992b, 1995, 2000; Oteiza et al. 1993), spontaneous motor activity (Golub et al. 1989, 1992b), thermal sensitivity (Golub et al. 1992a, 1995, 2000), and startle responsiveness (Golub et al. 1992b; Oteiza et al. 1993). Significant impairments in cognitive function have been observed in some studies (Golub and Germann 2001), although this has not been found in other studies even at higher doses (Colomina et al. 2005; Golub and Germann 1998; Golub et al. 1995).

A number of human studies have examined the occurrence of cancer among aluminum industry workers and found a higher-than-expected cancer mortality rate, but this is probably due to the other potent carcinogens to which they are exposed, such as polycyclic aromatic hydrocarbons (PAHs) and tobacco smoke (Milham 1979; Mur et al. 1987; Rockette and Arena 1983; Theriault et al. 1984). Available cancer studies in animals exposed to aluminum compounds have not found biologically relevant increases in malignant tumors (Hackenberg 1972; Oneda et al. 1994; Pigott et al. 1981; Schroeder and Mitchener 1975a, 1975b). The International Agency for Research on Cancer (IARC) concluded that aluminum production was carcinogenic to humans and that pitch volatiles have fairly consistently been suggested in epidemiological studies as being possible causative agents (IARC 1984). The Department of Health and Human Services (NTP 2005) and EPA (IRIS 2006) have not evaluated the human carcinogenic potential of aluminum.

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for aluminum, ATSDR considered all available published and unpublished information that has been peer-reviewed. From its evaluation of these data, ATSDR is recommending the conduct of specific research or testing.

A. Exposure Data Needs (Table 1)

Three of the eight "prioritizing" tenets presented in the Decision Guide directly address exposure data needs:

• Development and/or confirmation of appropriate analytical method;

• Determination of environmental and human exposure levels when analytical methods are available; and

• Bioavailability studies for substances of known significant toxicity and exposure.

The progressive accumulation of exposure information begins with developing suitable analytical methods to analyze the compound in all relevant biological and environmental media, followed by confirmation of exposure information, before the conduct of any Level III research. However, in order to know what analytes are available to monitor, some basic environmental fate information is generally required and becomes a priority if it is lacking.

Bioavailability and food chain bioaccumulation studies are appropriately placed in Level II, and should be undertaken after analytical methods are developed and the substance has been confirmed at many hazardous waste sites and in environmental media.

1. Levels I & II Data Needs

a. Analytical Methods

Purpose: To determine if available methods are adequate to detect and quantify levels of aluminum in environmental and biological matrices. The methods should be sufficiently specific and sensitive to measure (1) background levels in the environment and the population; and (2) levels at which biological effects might occur.

Finding: A data need has not been identified. Analytical methods are available to detect and quantify levels of aluminum in both biological and environmental matrices.

Graphite furnace atomic absorption spectrometry (GFAAS) is the method of choice for measuring aluminum in whole blood (Gardiner et al. 1981; Gorsky and Dietz 1978; Van der Voet et al. 1985), serum (Alderman and Gitelman 1980; Bettinelli et al. 1985; Gardiner et al. 1981; King et al. 1981; Maitani et al. 1994; Van Landeghem et al. 1994; Wrobel et al. 1995), plasma (Gardiner et al. 1981; Wawschinek et al. 1982), urine (Allain and Mauras 1979; Blotcky et al. 1976; Gorsky and Dietz 1978; Razniewska and Trzcinka-Ochocka 2003; Sanz-Medel et al. 1987), and various biological tissues (Abraham and Burnett 1985, Bouman et al. 1986; LeGendre and Alfrey 1976; Lovell et al. 1993; Maitani et al. 1994; Owen et al. 1994; Wood et al. 1990; Xu et al. 1992). Only one method (HPLC-GFAAS) is available to readily speciate aluminum compounds whose bioavailability and toxicity are a function of the aluminum compound. Other methods used for measuring aluminum in biological materials include accelerator mass spectroscopy (AMS), flame atomic absorption spectrometry (FAAS), eletrothermal atomic absorption spectrometry (ETAAS), neutron activation analysis (NAA), inductively coupled plasma-atomic emission spectrometry (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), and laser microprobe mass spectrometry (LAMMA) (Maitani et al. 1994; Owen et al. 1994; Razniewska and Trzcinka-Ochocka 2003; Van Landeghem et al. 1994). Detection limits are in the low-ppb ($\mu g/m^3$) range for methods measuring aluminum in human blood and urine and in the low-ppm (mg/m^3) range for methods measuring aluminum in human tissues. Makjanic et al. (1998) discusses the problem of tissue contamination from aluminum-containing analytical sampling equipment. More compresensive assessments of this type of contamination would be useful.

Analytical techniques used for measuring aluminum concentrations in environmental samples include GFAAS, FAAS, NAA, ICP-AES, ICP-MS, spectrophotometry using absorbance and fluorescence detection, phosphorimetry, chromatography, and gas chromatography equipped with an electron capture detector (GC/ECD) (Andersen 1987, 1988; AOAC 1990; APHA 1998a, 1998b, 1998c, 1998d; Dean 1989; EPA 1983a, 1983b, 1994a, 1994b, 1994c, 2000; Fernandez de la Campa et al. 1988; Fleming and Lindstrom 1987; Gardiner et al. 1987; NIOSH 1994, 2003a, 2003b, 2003c; OSHA 2001, 2002; USGS 1996). The available analytical methods are sufficiently sensitive to measure levels in soil and water that approach ATSDR's Environmental Media Evaluation Guides (EMEGs) calculated from ATSDR's Minimal Risk Levels (MRLs). It

is not possible to determine if the available methods are adequate to measure levels of aluminum in air that are unlikely to be associated with adverse human health effects since a chronic inhalation MRL has not been derived. The available methods also appear to be sufficiently sensitive to measure background levels of aluminum in the general population as well as levels of aluminum at which health effects might occur after short- or long-term exposure. Detection limits are in the low-ppb ($\mu g/m^3$) range for measuring aluminum in air (NIOSH 1994, 2003a, 2003b, 2003c; OSHA 2001, 2002), water (APHA 1998a, 1998b, 1998c, 1998d; EPA 1983a, 1983b, 1994a, 1994b, 1994c, 2000; USGS 1996), and soil (Flarend and Elmore 1997; Gardiner et al. 1987; Que Hee and Boyle 1988).

Priority Recommendation: A data need has not been identified.

b. Physical/Chemical Properties

Purpose: To determine whether adequate data on the chemical and physical properties of aluminum are available to permit estimation of its environmental fate under various conditions of release, and evaluation of its pharmacokinetics under different exposure durations and routes.

Finding: A data need has been identified. The physical and chemical properties of aluminum, aluminum chloride, aluminum oxide, and aluminum fluoride have been well described (HSDB 2006; Lewis 2001; Lide 2005; O'Neil et al. 2001). Vapor pressure data were not available for aluminum nitrate and aluminum potassium sulfate. Both vapor pressure and boiling point (or decomposition temperature) data were lacking for aluminum hydroxide, aluminum phosphate, aluminum phospide, and aluminum sulfate. Very little physical and chemical property data were available for aluminum chlorhydrate, aluminum lactate, aluminum carbonate, and alchlor. Measured physical and chemical property data would be helpful in giving a more complete description of the aluminum compounds for which these data are lacking; however, enough is known about the physical and chemical properties of aluminum and various aluminum-containing compounds to allow an assessment of the fate of aluminum in the environment (HSDB 2006; Lewis 2001; Lide 2005; O'Neil et al. 2001).

Priority Recommendation: The identified data need is not considered priority since enough is known about the physical and chemical properties of aluminum and various aluminum-containing compounds to allow an assessment of the fate of aluminum in the environment.

c. **Exposure Levels**

(1) Environmental Media

Purpose: To determine whether adequate data are available on the levels of aluminum and aluminum compounds in the ambient and contaminated environments for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A need to obtain reliable and current data on concentrations of aluminum in contaminated environmental media at hazardous waste sites has been identified.

Aluminum is the most abundant metal and the third most abundant element in the earth's crust, comprising about 8.8% by weight (88 g/kg). It is never found free in nature and is found in most rocks, particularly igneous rocks as aluminosilicate minerals (Lide 2005; Staley and Haupin 1992). The concentration of aluminum in soils varies widely, ranging from about 0.07% by weight (0.7 g/kg) to over 10% by weight (100 g/kg) (Sorenson et al. 1974; USGS 1984). Background concentrations of aluminum in rural air typically range from 0.005 to 0.18 $\mu g/m^3$ (Hoffman et al. 1969; Pötzl 1970; Sorenson et al. 1974), whereas concentrations in urban and industrial areas can be considerably higher, ranging from 0.4 to 8.0 $\mu g/m^3$ (Cooper et al. 1979; Dzubay 1980; Kowalczyk et al. 1982; Lewis and Macias 1980; Moyers et al. 1977; Ondov et al. 1982; Pillay and Thomas 1971; Sorenson et al. 1974; Stevens et al. 1978). Concentrations of aluminum are highly variable in drinking water, ranging from <0.001 to 1.029 mg/L (Schenk et al. 1989), but results are rarely given by aluminum species. The use of alum (aluminum sulfate) as a flocculent in water treatment facilities typically leads to increased aluminum concentrations in finished waters (DOI 1970; Letterman and Driscoll 1988; Miller et al. 1984a). In a survey of 186 community water systems, the median aluminum concentration in finished water receiving coagulation treatment using alum was 0.112 mg/L, compared to 0.043 mg/L in finished water that received no coagulation treatment (Miller et al. 1984a). Dissolved aluminum concentrations in surface water and groundwater vary with pH and the humic acid content of the water. High aluminum concentrations in natural water occur only when the pH is <5; therefore, concentrations in most surface waters are very low.

Most unprocessed foods, (with the exception of some herbs and tea leaves) typically contain
<5 mg/kg aluminum (Greger 1992; MAFF 1999; Pennington 1987; Schenk et al. 1989).
Concentrations of aluminum in foods generally ranged from <0.15 mg/kg in eggs, apples, raw
cabbage, corn, and potatoes to 695 mg/kg in American cheese (Greger 1992; MAFF 1999;
Pennington 1987; Schenk et al. 1989).

Priority Recommendation: The identified need is not considered priority. Reliable and current
monitoring data for the levels of aluminum in contaminated media at hazardous waste sites are
needed so that the information obtained on levels of aluminum in the environment and the
resulting body burden of aluminum can be used to assess the potential risk of adverse health
effects in populations living in the vicinity of hazardous waste sites. However, ATSDR has
developed a hazardous substance release/health effects database (HazDat) that includes the extant
data for the 606 NPL sites at which aluminum has been found. This database includes maximum
concentrations of aluminum in on- and off-site media, and an indication of relevant routes of
exposure. Further evaluation of this database is needed first to assess if collection of additional
media-specific data is assigned priority.

(2) Humans

Purpose: To determine whether adequate data are available on the levels of aluminum in human
tissues for the general population and exposed populations for purposes of conducting meaningful
follow-up exposure and health studies.

Finding: A need has been identified. No data are available on the levels of aluminum in body
tissues or fluids for people living near hazardous waste sites.

Measurements of the aluminum content in human biological materials are available. Reported
concentrations of aluminum in blood plasma/serum range from <0.01 to 1.46 mg/L (Berlyne et al.
1970; Drablos et al. 1992; House 1992; Nieboer et al. 1995; Razniewska and Trzcinka-Ochocka
2003; Sorenson et al. 1974; Versieck and Cornelis 1980). Reported mean concentrations of
aluminum in urine were 0.0027–0.0089 mg/L for individuals representative of the general
population and 0.011–0.153 mg/L for individuals with known occupational exposure (Buchta et
al. 2005; Drablos et al. 1992; Liao et al. 2004; Nieboer et al. 1995; Valkonen and Aitio 1997).
Mean concentrations of aluminum measured in breast milk range from 9.2 to 49 μg/L (Baxter et

al. 1991; Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Mandic et al. 1995; Simmer et al. 1990; Weintraub et al. 1986). Studies examing the speciation of aluminum in breast milk would be useful for evaluating bioavailability. Reported mean aluminum concentrations were 270–2,200 and 18.0–460 μg/L measured in the seminal plasma of non-occupationally exposed and occupationally exposed individuals, respectively (Dawson et al. 1998, 2000; Hovatta et al. 1998). A mean aluminum concentration of approximately 14 mg/kg has been measured in hair (Imahori et al. 1979). Reported concentrations of aluminum in bone, brain tissue, sweat, and saliva were 1–3 μg/g dry weight, <0.5 μg/g wet weight, 15.0 μg/L, and 25–102 μg/L, respectively (Nieboer et al. 1995; Omokhodiod and Howard 1994; Sighinolfi et al. 1989). More recent information, particularly for aluminum in blood and urine, would be useful in assessing current exposure levels.

Priority Recommendation: The identified data need to collect additional information is considered priority. For a sound database to serve as a solid foundation for higher level environmental or toxicological research, it should contain exposure information on the levels of aluminum in body tissues or fluids, particularly in populations living near hazardous waste sites. This information is necessary to better define exposure estimates in the general population and the workforce, and to examine the relationship between levels of aluminum in the environment, human tissues levels, and the subsequent development of health effects.

ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 606 NPL sites at which aluminum has been found. This database includes maximum concentrations of aluminum in on and off site media, and an indication of relevant routes of exposure. This database will not, however, supply information on the levels of aluminum (or its metabolites) in the tissues of individuals living near hazardous waste sites or other exposed populations such as workers.

d. Exposures of Children

Purpose: To determine if adequate data on exposures of children to aluminum are available for the purpose of conducting meaningful follow-up exposure and health studies.

*Finding***:** A data need has been identified. As with adults, exposures of children to aluminum from breathing air, drinking water, and eating food is generally low. Additionally, children are

exposed to aluminum used as an adjuvant in vaccine; the aluminum content in the vaccines range from 0.25 to 0.85 mg (Keith et al. 2002). As aluminum is part of the natural environment and found widely in soils, rocks, and foods, exposure to low levels of aluminum is unavoidable. Children are likely to ingest dirt from their unwashed hands or when playing with soils and may therefore be exposed to aluminum in this manner. Children living in proximity to hazardous waste sites or industries that release aluminum to the environment may be exposed to higher levels of aluminum than are found in the natural environment via ingestion of aluminum contained in soil or via inhalation of aluminum from soil that is entrained in air. While aluminum contained in dirt may be in many forms, some of these forms may be embedded in minerals not bioavailable even in the acid environment of the stomach.

Measurements of the aluminum content in tissues, blood, and urine of children who have been exposed to aluminum, as well as unexposed children, are limited. Chiba et al. (2004) reported mean aluminum concentrations of 89.5 and 113.6 mg/kg in hair of children from Kazakhstan and Uzbekistan. Al-Saleh and Shinwari (1996) reported a mean aluminum concentration of 23.21 μg/L in serum samples of girls aged 6–8 years. Hawkins et al. (1994) reported mean blood plasma aluminum concentrations of 8.6 and 9.2–15.2 μg/L in infants fed breast milk and those fed various formulas, respectively Litov et al. (1989) measured mean aluminum plasma concentrations of 9.9, 8.4, and 13.4 μg/L in breastfed infants at birth, 1 month, and 3 months of age, respectively. Infants on soy-based infant formulas, containing 1,600–1,700 μg/L of aluminum, were reported to have mean aluminum plasma concentrations of 8.2–12.4, 7.6–8.5, and 10.8–12.4 μg/L at birth, 1 month, and 3 months of age, respectively. Markesbery et al. (1984) measured a mean aluminum concentration of 0.298 μg/g wet weight in infant brain tissue. Studies measuring aluminum concentrations in tissues, blood, and urine of specialized groups of children (e.g., infants with renal failure or on parenteral nutrition) have also been reported (Advenier et al. 2003; Andreoli 1990; Andreoli et al. 1984; Bougle et al. 1991; Bozynski et al. 1989; Chedid et al. 1991; Goyens and Brasseur 1990; Griswold et al. 1983; Klein et al. 1989; Koo et al. 1986, 1992; Milliner et al. 1987; Moreno et al. 1994; Naylor et al. 1999; Robinson et al. 1987; Roodhooft et al. 1987; Salusky et al. 1986, 1990; von Stockhausen et al. 1990).

Additional monitoring studies that explore the difference between background and elevated aluminum concentrations in children would be useful. While the largest source of aluminum exposure in adults is from aluminum-containing medications and cosmetics, the amount of such products that may be given to children is not known. Additional information on the speciated

intake of available aluminum from soil during childhood activities, or the placental transfer to fetal blood, especially among pregnant women taking antacids as a result of abdominal upsets, would be useful in assessing exposure levels in children.

Data are available on the intake of aluminum in food eaten by children and from their diet (Dabeka and McKenzie 1990; Koo et al. 1988; Pennington 1987; Pennington and Schoen 1995; Simmer et al. 1990; Weintraub et al. 1986). Dietary intakes of aluminum for children ranged from 0.7 mg/day for infants to 11.5 mg/day for 14–16-year-old males. Aluminum intakes per kilogram of body weight for children ranged from 0.10 mg/kg for infants to 0.35 mg/kg for 2-year-old children. It is recognized that the some dietary constituents, particularly citrus juice, can increase the absorption of aluminum (Weberg and Berstad 1986). With the amount of aluminum that is added to food products to enhance food preparation and the amount used in medicines, high exposures can occur. Aluminum concentrations in human breast milk, infant formula, and cow's milk have been reported. The aluminum content of human breast milk generally ranged from 9.2 to 49 μg/L, lower than that reported in infant formulas (Fernandez-Lorenzo et al. 1999; Hawkins et al. 1994; Koo et al. 1988; Simmer et al. 1990; Weintraub et al. 1986). Soy-based infant formulas contain higher concentrations of aluminum, as compared to milk-based infant formulas or breast milk. Recent reports provide average aluminum concentrations ranging from 460 to 930 μg/L for soy-based infant formulas and from 58 to 150 μg/L for milk-based formulas (Fernandez-Lorenzo et al. 1999; Ikem et al. 2002; Navarro-Blasco and Alvarez-Galindo 2003). Infant formulas are much higher in aluminum than human breast milk. Daily intakes of aluminum for infants in the United States were estimated to be 97, 573, and 361 μg/day from milk-based powder formulas, soy-based powder formulas, and hypoallergenic powder formulas, respectively (Ikem et al. 2002).

Priority Recommendation: The identified data need to conduct additional studies to assess exposures of children to aluminum is considered priority. Childhood exposure and temporal body burden studies are needed especially for children living near hazardous waste sites. In addition, studies that explore unique exposure pathways for children and childhood-specific means to decrease exposure are also needed.

e. Environmental Fate

Purpose: To determine whether the available data are adequate to estimate exposure to aluminum under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

Finding: A data need has not been identified. Aluminum partitions to air, water, soil, and plant material. As an element, aluminum cannot be degraded in the environment; it can undergo various precipitation or ligand exchange reactions in the environment. Its partitioning to various media is determined by the physical and chemical properties of the aluminum compound and the characteristics of the environmental matrix that affects its solubility (Brusewitz 1984; Dahlgren and Ugolini 1989; Filipek et al. 1987; Goenaga and Williams 1988; James and Riha 1989; Litaor 1987; Mulder et al. 1989; Wangen and Jones 1984). Aluminum is transported through the atmosphere primarily as a constituent of soil and other particulate matter (Eisenreich 1980). Transformations are not expected to occur during transport of aluminum through the atmosphere. Aluminum occurs in natural waters as a result of weathering and erosion processes. Aluminum partitions between solid and liquid phases by reacting and complexing with water molecules, anions, and negatively charged functional groups on humic materials and clay (Bodek et al. 1988). Information on the environmental fate of aluminum is sufficient to permit a general understanding of transport and transformation in all environmental media. No additional information is needed at this time.

Priority Recommendation: A data need has not been identified. Information on the environmental fate of aluminum is sufficient to permit a general understanding of transport and transformation in all environmental media.

f. Bioavailability and Bioaccumulation Potential

Purpose: To determine whether adequate data are available to predict the potential of aluminum to be taken up by people exposed via contaminated air, soil, water, and the food chain, in order to plan and conduct meaningful follow-up exposure and health studies.

Finding: A data need has been identified. Since aluminum is ubiquitous in the environment, the general population will be exposed to aluminum by the inhalation of ambient air and the ingestion

of food and water. The consumption of foods containing aluminum-containing food additives are a major sources of aluminum in the diet (Saiyed and Yokel 2005; Soni et al. 2001). The use of other consumer items such as antiperspirants, cosmetics, internal analgesics (buffered aspirins), anti-ulcerative medications, antidiarrheals, and antacids that also contain aluminum compounds will result in exposure to aluminum. The intake of aluminum from food and drinking water is low, especially compared with that consumed by people taking aluminum-containing medicinal preparations. Based on a reported concentration of 0.112 mg/L and assumining an intake of 2 L of water per day, intake of aluminum from finished water could be approximately 0.2 mg/day (Miller et al. 1984a). Daily intakes of aluminum from food range from 3.4 to 9 mg/day (Biego et al. 1998; MAFF 1999; Pennington and Schoen 1995), whereas aluminum-containing medications contain much higher levels of aluminum; for example, 104–208 mg of aluminum per tablet/capsule/5 mL dose for many antacids (Zhou and Yokel 2005). Aluminum is used as an adjuvant in vaccines; however, the FDA limits the amount of aluminum allowed in these vaccines to no more than 0.85 mg/dose (Baylor et al. 2002). While aluminum is naturally present in food and water, the greatest contribution to aluminum in food and water by far is the aluminum-containing additives used in water treatment and processing certain types of food such as grain-based products and processed cheese. Reliable estimates of aluminum intake by compound in food and water are needed to understand what exposures lead to more significant uptakes.

Aluminum compounds are deposited in the lungs during inhalation (Christie et al. 1963; Steinhagen et al. 1978; Stone et al. 1979; Thomson et al. 1986). Analysis of changes in tissue and serum levels during animal inhalation studies has indicated that lung retention rather than absorption was taking place. Aluminum compounds are also poorly absorbed following ingestion (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). A fractional absorption of 1.5–2% was estimated based on the relationship between urinary aluminum excretion and the airborne soluble aluminum to which workers were exposed (Yokel and McNamara 2001). Very limited information is available regarding absorption following dermal contact; however, this pathway of exposure is not expected to be significant. Additional information on absorption following ingestion of soils contaminated with aluminum compounds and dermal contact would be useful in assessing bioavailability following exposure via these routes, particularly at hazardous waste sites; however, this would require speciation, which is rarely done for environmental samples.

Occupational exposures to aluminum occur during the mining and processing of aluminum ore into metal, recovery of scrap metal, production and use of aluminum compounds and products containing these compounds, milling of aluminum metal and alloys, and in aluminum welding (Nieboer et al. 1995). Individuals living in the vicinity of industrial emission sources and hazardous waste sites; individuals with chronic kidney failure requiring long-term dialysis or treatment with phosphate binders; patients requiring intravenous fluids; infants, especially premature infants fed soy-based formula containing high levels of aluminum; and individuals consuming large quantities of antacids, anti-ulcerative medications, or antidiarrheal medications may also be exposed to high levels of aluminum.

Generally, aluminum is not bioaccumulated to a significant extent. However, certain plants can accumulate high concentrations of aluminum. For example, tea leaves may contain very high concentrations of aluminum, >5,000 mg/kg in old leaves (Dong et al. 1999). Other plants that may contain high levels of aluminum include *Lycopodium* (Lycopodiaceae), a few ferns, *Symplocos* (Symplocaceae), and *Orites* (Proteaceae) (Jansen et al. 2002). Aluminum does not appear to accumulate to any significant degree in cow's milk or beef tissue and is, therefore, not expected to undergo biomagnification in terrestrial food chains (DOE 1984). Similarly, because of its toxicity to many aquatic organisms, including fish, aluminum does not bioconcentrate in aquatic organisms to any significant degree (Rosseland et al. 1990).

Priority Recommendation: The identified data need is not considered a priority. Although additional information on absorption following ingestion of soils contaminated with aluminum compounds and dermal contact would be useful in assessing bioavailability following exposure via these routes, particularly at hazardous waste sites, there are sufficient data to predict the potential for aluminum to be taken up by people exposed via the most relevant routes (i.e., breathing contaminated air or ingesting contaminated food or water). The lack of regulations to require the speciation of aluminum in environmental and occupational samples would likely preclude such information from being available for consideration.

2. Level III Data Needs

a. Registries of Exposed Persons

Purpose: To help assess long-term health consequences of exposure to aluminum in the environment. The ATSDR Division of Health Studies will be asked to consider this substance for selection as a primary contaminant to establish an aluminum subregistry of the National Exposure Registry.

Finding: A data need has been identified. Aluminum has been found in at least 606 NPL hazardous waste sites. At this time, no formal registries exist that identify people known to have been exposed to aluminum. The development of an exposure registry should provide an important reference tool to help assess long-term health consequences of exposure to aluminum. It should also facilitate the conduct of epidemiologic or health studies to assess any increased incidence of chronic disease or late-developing effects such as cancer. An effort is currently under way at ATSDR to identify those sites where humans have been exposed to site contaminants. From those identified sites, ATSDR can determine which sites list aluminum as a contaminant and the size of the potentially exposed population.

Priority Recommendation: The identified data need is not considered priority. The development of an exposure registry would contribute to the current database due to the evidence that aluminum is associated with impaired lung function and fibrosis in workers and subclinical neurological effects. This recommendation will be provided to the ATSDR Division of Health Studies who will judge the extant information on aluminum against their criteria for initiating an exposure registry.

B. Toxicity Data Needs (Table 2)

The five remaining "prioritizing" tenets presented in the Decision Guide address toxicity data needs.

• Studies available for all toxicological profile substances to characterize target organs and dose response.

- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.

- Mechanistic studies on substances with significant toxicity and substantial human exposure.

- Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.

- Epidemiologic studies that will provide a direct answer on human disease for a substance of known significant toxicity.

The following is a brief summary of the toxicity data needs for aluminum. Please refer to the ATSDR Toxicological Profile for Aluminum, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2006). Generally, ATSDR believes that the most relevant route(s) of human exposure to aluminum at waste sites is oral exposure, thus ATSDR scientists believe that the proposed toxicity studies should be conducted via the oral route. Additionally, animal testing should be conducted on the species with metabolism most similar to humans or the most sensitive species.

1. Levels I & II Data Needs

ATSDR determines Minimal Risk Levels (MRLs) which are defined as estimates of daily human exposure to a chemical that are likely to be without appreciable risk of deleterious effects over a specified duration. In order to derive MRLs for acute, intermediate, and chronic exposure durations, ATSDR evaluates the substance-specific database to identify studies of the appropriate route and duration of exposure. Thus, in order to derive acute MRLs, ATSDR evaluates studies of 14 days or less duration that identify the target organs and levels of exposure associated with these effects. Similar studies are identified for intermediate and chronic duration exposures.

Currently, ATSDR is using tools such as physiologically-based pharmacokinetic modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. ATSDR acknowledges that such extrapolations may be done on a substance-by-substance basis after adequate toxicokinetics information has been collected.

As reflected in the Decision Guide, ATSDR assigns priorities to identified data needs for acute/intermediate (Level I) studies by the most relevant route of exposure at Superfund sites. Regarding the need to conduct studies by other routes of exposure, ATSDR usually first requires

toxicokinetic studies for the three routes of exposure to determine the need for the additional route-specific information.

Regarding chronic studies, ATSDR acknowledges that appropriately conducted 90-day studies can generally predict the target organs for chronic exposure. However, they might fall short in accurately predicting the levels of exposure associated with these effects. Although ATSDR acknowledges this fact, it will generally await the results of prechronic and toxicokinetic studies before assigning priority to chronic toxicity studies. Note: Chronic toxicity studies may be separated from cancer bioassays; they require a one-year exposure.

a. Acute-Duration Exposure

Purpose: To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause acute human health effects.

Finding: A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified.

There are no human studies and a small number of animal studies that examined the acute toxicity of inhaled aluminum. The results of these inhalation studies suggest that the lung may be a sensitive target for toxicity (Drew et al. 1974; Thomson et al. 1986); the observed effects are similar to those that occur with dust overload. The data are insufficient to determine if these effects are solely due to dust overload or to an interaction between aluminum and lung tissue; thus, an inhalation MRL was not derived. Additional inhalation studies are needed to evaluate whether the respiratory tract is a target of aluminum toxicity; these studies should also examine potential neurological effects, another sensitive target of aluminum toxicity.

A limited number of studies have examined the acute toxicity of ingested aluminum in humans. Reports associated with acute exposures to aluminum phosphide (Chopra et al. 1986; Khosla et al. 1988) may not be predictive of aluminum toxicity because the observed effects are probably due to the formation of highly toxic phosphine gas rather than aluminum. The remaining database on the acute oral toxicity of aluminum consists of a report of individuals consuming water containing unknown levels of aluminum sulfate for 5 days or more; elevated levels of copper and lead were also detected in the water (Ward 1989). Unspecified gastrointestinal and

bowel problems were reported by an unspecified number of people. The acute systemic toxicity of orally administered aluminum has not been well investigated in animals; most of the available studies examined the developmental toxicity of aluminum (Bernuzzi et al. 1986, 1989a; Cranmer et al. 1986; Domingo et al. 1989; Gomez et al. 1991; McCormack et al. 1979; Misawa and Shigeta 1992; Paternain et al. 1988) or aluminum lethality (Llobet et al. 1987; Ondreicka et al. 1966). Two studies examining potential effects other than developmental toxicity only examined a small number of end points (Garbossa et al. 1996; Ondreicka et al. 1966). The Ondreicka et al. (1966) study examined potential body weight effects and the Garbossa et al. (1996) study examined hematological indices; neither study examined potential neurotoxicity, which has been shown to be the most sensitive end point following intermediate- or chronic-duration exposure. These data were considered inadequate for the derivation of an acute-duration oral MRL for aluminum. Oral exposure studies examining a wide range of potential effects, including neurotoxicity and neurodevelopmental toxicity, are needed to identify the critical target of toxicity and establish dose-response relationships.

There are limited data on the dermal toxicity of aluminum in animals and no studies in humans. A mouse study conducted by Lansdown (1973) found skin damage following application of a number of aluminum compounds. Because aluminum is found in a number of topical products, additional dermal exposure studies would be useful to fully assess the potential toxicity of aluminum following dermal exposure.

Priority Recommendation: The identified data need to conduct additional studies via the oral route of exposure is considered priority. A well-conducted acute oral exposure study examining a variety of end points, including neurobehavioral end points, is needed in order to derive an acute-duration oral MRL for aluminum. This data need is considered priority because oral exposure is the primary route of exposure for individuals living near hazardous waste sites. The need for additional inhalation and dermal exposure studies is not considered priority because they are not the principal routes of exposure for individuals living near hazardous waste sites.

b. Intermediate-Duration Exposure

Purpose: To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause subchronic human health effects.

Finding: A data need to conduct additional studies via inhalation and dermal exposure has been identified. No human studies examining aluminum toxicity in humans following intermediate-duration inhalation exposure were located. Intermediate-duration inhalation studies in animals identified the lung as a sensitive target of toxicity (Drew et al. 1974; Steinhagen et al. 1978). The observed effects include an increase in the number of alveolar macrophages and heterophils, granulomatous nodules, and thickening of the alveolar walls due to infiltration of heterophils and macrophages in hamsters exposed to alchlor (a propylene glycol complex of aluminum chlorhydrate which is a common component of antiperspirants) for 6 weeks (Drew et al. 1974) and an increase in the number of alveolar macrophages and granulomatous lesions in the lungs and peribronchial lymph nodes in rats and guinea pigs exposed to aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). It is not known if these effects, particularly the granulomatous lesions, are a response to dust overload or an interaction of aluminum with lung tissue; thus, an intermediate-duration inhalation MRL was not derived for aluminum. Additional inhalation studies are needed to evaluate the mechanisms of lung toxicity to determine whether the effects are due to dust overload or aluminum; inhalation studies examining a wide-range of potential end points, including the nervous system, would be useful for identifying the most sensitive effect of inhaled aluminum.

There is a limited amount of intermediate-duration human data on the toxicity of ingested aluminum. Neurological and skeletal effects have been observed in uremic patients exposed to aluminum (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989); however, it is not likely that individuals with normal renal function would experience these effects. A fair number of animal studies have examined the toxicity of aluminum following intermediate-duration oral exposure. Although most of the studies focused on the neurotoxicity and neurodevelopmental toxicity of aluminum, the available studies have examined potential systemic (Dixon et al. 1979; Domingo et al. 1987b; Farina et al. 2005; Garbossa et al. 1996, 1998; Gomez et al. 1986; Katz et al. 1984; Ondreicka et al. 1966; Oteiza et al. 1993; Pettersen et al. 1990; Vittori et al. 1999), immunological (Golub et al. 1993; Lauricella et al. 2001; Yoshida et al. 1989), and reproductive (Dixon et al. 1979; Donald et al. 1989; Katz et al. 1984; Krasovskii et al. 1979; Ondreicka et al. 1966; Pettersen et al. 1990) end points. The available intermediate-duration studies clearly identify the nervous system as the most sensitive target of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1989, 1992a, 1992b, 1995; Oteiza et al. 1993). An intermediate-duration oral MRL was derived based on Golub and Germann (2001) and Colomina et al. (2005) developmental toxicity studies; the

critical effects were neurodevelopmental effects and delays in physical maturation. Although the database supports the MRL, additional information is needed to confirm the results of the principal studies due to the use of a suboptimal diet (Golub and Germann 2001) and findings that are not well supported (Colomina et al. 2005); since these were both developmental toxicity studies, this data need will be further discussed in the Developmental Effects section. Additional studies examining the systemic toxicity of aluminum following intermediate-duration oral exposure are not needed at this time.

No studies have examined the dermal toxicity of aluminum in humans or animals. Animal studies would provide useful information on aluminum's potential to induce dermal effects following repeated exposure and whether it can cause systemic or neurological effects.

*Priority Recommendation***:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority because they are not the primary routes of exposure for populations living near hazardous waste sites.

c. Chronic-Duration Exposure

(1) Toxicity Assessment

*Purpose***:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause chronic human health effects.

*Finding***:** A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Respiratory and neurological effects have been observed in workers exposed to finely ground aluminum and aluminum welding fumes. Impaired lung function has been observed in workers employed in various aluminum industries including potrooms, foundries, and welding (Abbate et al. 2003; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Burge et al. 2000; Chan-Yeung et al. 1983; Hull and Abraham 2002; Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b; Radon et al. 1999; Simonsson et al. 1985; Vandenplas et al. 1998). Other studies have provided some suggestive evidence that aluminum exposure can result in occupational asthma (Abramson et al. 1989; Akira 1995; Al-Masalkhi and Walton 1994; Burge et al. 2000; Vandenplas et al. 1998) or pulmonary fibrosis (De Vuyst et al. 1986; Edling 1961; Gaffuri et al. 1985; Jederlinic et al. 1990; Jephcott 1948; McLaughlin et al.

1962; Mitchell et al. 1961; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947; Ueda et al. 1958; Vallyathan et al. 1982). A common limitation of most of these occupational exposure studies is co-exposure to other compounds, such as silica, which can also damage the respiratory tract. Subtle neurological effects have been observed in workers exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Polizzi et al. 2001; Sim et al. 1997; Sjogren et al. 1990, 1996; White et al. 1992). Two studies have examined the chronic inhalation toxicity of aluminum in animals. The first study reported increases in relative lung weights in rats and guinea pigs exposed to aluminum chlorhydrate for approximately 2 years (Stone et al. 1979); however, the study did not include histological examinations of the lungs or other tissues. The second study did not find evidence of lung fibrosis in rats exposed to Saffil alumina fibers (a refractory material containing aluminum oxide and about 4% silica) for 86 weeks followed by a 42-week observation period (Pigott et al. 1981); other potential targets of toxicity were not examined. These data were considered inadequate for derivation of a chronic-duration inhalation MRL. Additional inhalation studies are needed to identify the critical target of aluminum toxicity following inhalation exposure and to establish concentration-response relationships.

Aluminum has been implicated in causing neurological (Banks et al. 1988; Liss and Thornton 1986), musculoskeletal, (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989), and hematopoietic (Jeffery et al. 1996) effects in individuals with impaired renal function. No chronic-duration studies examining potential adverse health effects in individuals with normal renal function were located. Several animal studies have examined the toxicity of aluminum following chronic oral exposure (Farina et al. 2005; Golub et al. 2000; Oneda et al. 1994; Roig et al. 2006; Schroeder and Mitchener 1975a, 1975b). These studies identified two potential targets of toxicity: the nervous system (Golub et al. 2000) and the hematopoietic system (Farina et al. 2005). A chronic-duration oral MRL was derived based on the neurotoxicity observed in the Golub et al. (2000) study. A comparison between the dose-response relationship of neurotoxicity and the alterations in hematological parameters cannot be conducted because the Farina et al. (2005) study did not provide information on the level of aluminum in the base diet and both studies only utilized one aluminum-exposure group. Additional studies on the toxicity of aluminum following chronic-duration exposure utilizing multiple dose levels would be useful in comparing the sensitivity of these two effects.

No studies have examined the chronic toxicity of aluminum following dermal exposure in
humans or animals. Studies are needed to identify the critical targets of toxicity.

Priority Recommendation: The identified data need to conduct additional studies via oral
exposure is not considered priority because the database supports the derivation of a chronic-
duration oral MRL. The need for additional inhalation and dermal exposure studies is not
considered priority because they are not the primary routes of exposure for populations living
near hazardous waste sites.

(2) Cancer Assessment

Purpose: To determine whether populations exposed to aluminum are at an increased risk for
developing cancer for purposes of conducting meaningful follow-up exposure and health studies.
Similar to toxicity end point assessment, when bioassays are indicated because of the potential for
substantial exposure and the lack of information on carcinogenicity, ATSDR will generally only
assign priority to a bioassay conducted via the most relevant route of human exposure at
Superfund sites.

Comparative toxicokinetic information across routes as previously discussed will be assigned
priority and conducted before assigning priority to any additional routes of exposure. In cases
where the assessment of chronic toxicity and carcinogenicity can be combined, they will.

Finding: A data need to conduct additional studies for the carcinogenicity of aluminum via
inhalation, oral, and dermal exposure has been identified. Human data on the carcinogenic
potential of aluminum come from studies of aluminum production workers (Gibbs and Horowitz
1979; Milham 1979; Mur et al. 1987; Rockette and Arena 1983; Theriault et al. 1984; Wigle
1977). These studies found significant increases in the cancer risk (urinary bladder, lymphatic
and hematopoietic, or lung cancer), but the potential risk of cancer in the aluminum production
industry is probably due to the presence of known carcinogens (e.g., PAHs) in the workplace
rather than aluminum or aluminum compounds. No significant increases in cancer risk were
observed in animal studies using inhalation (Pigott et al. 1981) or oral (Hackenberg 1972; Oneda
et al. 1994; Schroeder and Mitchener 1975a, 1975b) exposure; the Oneda et al. (1994) study
found a significant decrease in the risk of spontaneous liver tumors in male mice exposed to very

high oral aluminum doses. However, these studies, with the exception of Oneda et al. (1994), were not adequate to evaluate the carcinogenic potential of aluminum. The Pigott et al. (1981) inhalation study involved exposure to alumina fibers; it is likely that the toxicokinetic (and possibly toxicologic) properties of aluminum dust would differ from aluminum fibers. In the Schroeder and Mitchener studies (1975a, 1975b), the rats and mice were exposed to very low levels of aluminum and it is unlikely that the maximum tolerated dose was achieved. The dose levels used in the Hackenberg (1972) study were not reported; thus, an assessment of whether the maximum tolerated dose was achieved cannot be made. No dermal exposure studies were identified. Additional inhalation, oral, and dermal exposure studies are needed in rats and mice in order to fully evaluate the carcinogenic potential of aluminum.

IARC concluded that aluminum production was carcinogenic to humans and that pitch volatiles have fairly consistently been suggested in epidemiological studies as being possible causative agents (IARC 1984). The Department of Health and Human Services (NTP 2005) and EPA (IRIS 2006) have not evaluated the human carcinogenic potential of aluminum.

Priority Recommendation: The identified data need to conduct additional studies via inhalation, oral, and dermal exposure is not considered priority. Although oral exposure is the primary route of exposure for people living at hazardous waste sites, the need for oral cancer studies is not considered a priority because the available data do not provide suggestive evidence that aluminum is carcinogenic. The need for inhalation and dermal exposure studies are not considered priority because these are not the primary routes of exposure for individuals living near hazardous waste sites.

d. Genotoxicity

Purpose: To evaluate the mechanism of aluminum-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned genotoxicity studies if information is lacking to assess the genotoxic potential of this substance both *in vivo* (mouse micronucleus) and *in vitro* (Ames *Salmonella*). This is particularly true if there are human data to suggest that the substance may act by a genotoxic mechanism to cause cancer, reproductive toxicity, etc., or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

***Finding*:** A data need to conduct additional genotoxicity studies has been identified. There are no human data on the genotoxicity of aluminum. One study examined the *in vivo* genotoxicity of aluminum and found clastogenic changes in mice receiving an intraperitoneal injection of aluminum chloride (Manna and Das 1972). *In vitro* studies in mammalian and bacterial systems have not found mutagenic alterations (DiPaolo and Casto 1979; Kanematsu et al. 1980; Marzin and Phi 1985); one study found evidence of cross-linking between chromosomal proteins and DNA in mammalian cells (Wedrychowski et al. 1986). Further genotoxicity studies, particularly *in vivo* exposures, would be useful for confirming whether aluminum exposure induces clastogenic effects.

***Priority Recommendation*:** The identified data need to conduct additional genotoxicity studies is not considered priority because there is no suggestive evidence that aluminum is carcinogenic.

e. Endocrine Disruption

***Purpose*:** To determine whether populations potentially exposed to aluminum are at an increased risk to develop toxicity of the endocrine system for purposes of conducting meaningful follow-up exposure and health studies. Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to screening studies that examine effects on a) male and female reproductive organs, and b) other endocrine organs including hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, paraganglia, and pineal body. Such screening level studies include, but are not limited to, *in vitro* studies [e.g., (1) Estrogen Receptor Binding/Transcriptional Activation Assay, (2) Androgen Receptor Binding/Transcriptional Activation Assay, and 3) Steroidogenesis Assay with Minced Testis], and *in vivo* studies [e.g., (1) Rodent

3-day Uterotropic Assay, (2) Rodent 20-day Pubertal Female Assay with Thyroid, (3) Rodent 5–
7-day Herschberger Assay].

If any of the following is true, then ATSDR will consider assigning Level II priority to
2-generation reproductive studies: if (1) there are suggestions that aluminum may have endocrine
disrupting potential from Level I studies; or (2) if there have been human anecdotal reports of
endocrine disrupting effects following aluminum exposure; or (3) if there are structurally similar
compounds that affect the endocrine system.

As before, priority will be assigned to studies conducted by the most relevant route of human
exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated
before assigning priority to studies conducted via additional routes of exposure.

Findings: A data need to conduct additional studies on the endocrine system via inhalation, oral,
and dermal exposure has been identified. There are no human or animal data on the potential of
aluminum to disrupt the endocrine system and no *in vitro* studies were located regarding
endocrine disruption of aluminum. The available systemic (Dixon et al. 1979; Domingo et al.
1987b; Farina et al. 2005; Garbossa et al. 1996, 1998; Gomez et al. 1986; Katz et al. 1984;
Ondreicka et al. 1966; Oteiza et al. 1993; Pettersen et al. 1990; Vittori et al. 1999), developmental
(Colomina et al. 1992, 2005; Gomez et al. 1991; Paternain et al. 1988), and reproductive (Dixon
et al. 1979; Donald et al. 1989; Katz et al. 1984; Krasovskii et al. 1979; Ondreicka et al. 1966;
Pettersen et al. 1990) toxicity studies did not indicate any effects that are suggestive of endocrine
disruption. However, additional *in vitro* and *in vivo* studies designed to assess endocrine
disruption would be provide more conclusive evidence on whether aluminum exposure can result
in endocrine disruption.

Priority Recommendation: The identified data need to conduct additional studies on the
endocrine system via inhalation, oral, and dermal exposure is not considered priority. There are
no data to suggest that the endocrine system would be a target of toxicity for aluminum.

f. Reproductive Toxicity

Purpose: To determine whether populations potentially exposed to aluminum are at an increased
risk to develop reproductive effects for purposes of conducting meaningful follow-up exposure

and health studies. ATSDR scientists believe it is important to acquire reproductive toxicity data in order to consider the needs of susceptible populations. It is desirable to have information on reproductive toxicity before developing MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If any of the following is true, then ATSDR will consider assigning priority to multigeneration animal studies: (1) If any indication is found in the 90-day studies that the reproductive system of either male or female animals is a target organ of substance exposure; or (2) if there have been human anecdotal reports of reproductive effects following substance exposure; or (3) if there are structurally similar compounds that affect reproduction.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

Finding: A data need to conduct additional reproductive toxicity studies via inhalation, oral, or dermal exposure has not been identified. No studies were located regarding reproductive effects of various forms of aluminum following inhalation, oral, or dermal exposure in humans. No histological alterations were observed in the reproductive tissues of rats or guinea pigs exposed to airborne aluminum chlorhydrate (Steinhagen et al. 1978); this study did not examine reproductive function. In general, the results of oral reproductive toxicity studies in animals suggest that aluminum is not associated with alterations in fertility (Dixon et al. 1979; Domingo et al. 1987c), mating success (Dixon et al. 1979; Ondreicka et al. 1966), or number of implantations, implantation losses, or litter size (Bernuzzi et al. 1989b; Domingo et al. 1987c, 1989; Golub et al. 1992a; Gomez et al. 1991; Misawa and Shigeta 1992). No studies have examined reproductive end points in animals following dermal exposure. Further studies in this area do not appear to be necessary at this time; the oral studies provide good evidence that aluminum is not a reproductive toxicant and there is no evidence to suggest that the toxicity of aluminum is route-dependent.

Priority Recommendation: No data needs were identified.

g. Developmental Toxicity

Purpose: To determine whether populations potentially exposed to aluminum are at an increased risk for developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, Agency scientists believe it is important to assess the developmental toxicity data.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. ATSDR acknowledges that, in some circumstances, developmental studies may be assigned priority if the following statements are true: (1) if a two-generation reproductive study provides preliminary information on possible developmental toxicity of aluminum, (2) if there are human anecdotal reports of developmental effects following aluminum exposure, *or* (3) if structurally similar compounds have caused developmental effects.

As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

Finding: A data need to conduct additional developmental studies via inhalation, oral, or dermal exposure has been identified.

No studies examining the potential of aluminum to induce developmental effects in humans exposed to aluminum via inhalation, ingestion, or dermal contact were located. There are some reports of osteomalacia and encephalopathy in infants or children with renal failure and premature infants (Andreoli et al. 1984; Finberg et al. 1986; Griswold et al. 1983; Pivnick et al. 1995); however, there responses are probably not indicative of responses expected in normal infants. No animal inhalation or dermal exposure studies examining developmental end points were located; studies by these routes of exposure are needed to evaluate whether the developing organism is also a target of toxicity following inhalation or dermal exposure to aluminum and to establish dose-response relationships.

The results of oral developmental toxicity studies in animals suggest that aluminum does not increase the occurrence of malformations or anomalies. Delays in skeletal ossification have been

observed in some studies (Colomina et al. 1992; Gomez et al. 1991; Paternain et al. 1988); these delays typically occur at doses associated with decreases in pup body weight. Decreases in pup body weight gain have also been reported in a number of studies (Bernuzzi et al. 1986, 1989a, 1989b; Colomina et al. 2005; Domingo et al. 1987a, 1987c, 1989; Golub and Germann 2001; Golub et al. 1992a; Gomez et al. 1991; Misawa and Shigeta 1992; Paternain et al. 1988; Sharma and Mishra 2006); however, these decreases were most often observed at doses associated with effects on maternal body weight (Colomina et al. 2005; Domingo et al. 1989; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1992a, 1995; Gomez et al. 1991; McCormack et al. 1979).

There is strong evidence that aluminum impairs neurodevelopment; neurobehavioral deficits have been observed in oral studies of weanling and young developing mice and rats exposed to aluminum during gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone (Bernuzzi et al. 1986, 1989a, 1989b; Colomina et al. 2005; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Misawa and Shigeta 1992; Muller et al. 1990). The most frequently affected neurobehavioral effects in the exposed weanlings and young mice included alterations in grip strength (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1992a, 1995) and thermal sensitivity (Golub et al. 1992a, 1995).

Although the neurodevelopmental toxicity of aluminum is well-documented in animals, there are a number of data needs that preclude fully assessing the significance of the findings to human health (Golub and Domingo 1996). An important issue not adequately addressed in the existing studies is the potential for effects on more complex central nervous system functions, including learning and memory and sensory abilities. Several studies have examined potential effects on cognitive function. Many of these studies found no adverse effects (Colomina et al. 2005; Golub and Germann 1998; Golub et al. 1995). However, some studies noted that the aluminum-exposed animals performed better than controls. This may be due to an increase in food motivation, suggesting that studies involving food rewards may not accurately assess aluminum-induced cognitive effects. One study utilizing the Morris water maze test, which does not involve food motivation, found deficits in learning (Golub and Germann 2001); however, another study (Colomina et al. 2005) did not find similar deficits. Differences in the study designs preclude direct comparisons between the Golub and Germann (2001) and Colomina et al. (2005) studies.

Additional cognitive function tests are needed to determine whether this is also a target of aluminum neurotoxicity.

There is also some evidence that gestational exposure may result in some delays in physical maturation, such as delay in vagina opening, testes descent, and incisor eruption (Colomina et al. 2005), and may affect the immune system in young mice (Golub et al. 1993; Yoshida et al. 1989) Additional studies are needed to confirm these results and to assess whether the effects are secondary to maternal toxicity, particularly decreases in body weight gain.

The intermediate-duration oral MRL was based on the neurodevelopmental effects observed in the Golub and Germann (2001) study; the Colomina et al. (2005) developmental study was selected as a co-principal study. Although the database supports this MRL, additional information is needed to confirm the results of the principal studies. A suboptimal diet was used in the Golub and Germann (2001) study to mimic typical intake of young adults; the impact of this diet on the developmental toxicity of aluminum is not known. At the lowest dose tested in the Colomina et al. (2005) study, statistically significant delays in maturation were observed in the offspring; there are only limited data to confirm or refute the identification of delays in maturation as a critical effect of aluminum.

Priority Recommendation: The identified data need to conduct additional developmental toxicity studies via inhalation, oral, and dermal exposure is not considered priority. The available oral exposure studies clearly identify the developing nervous system as a target of aluminum toxicity; additional studies would allow for a further characterization of this target and assessment of other potentially developmental targets. The need for additional inhalation and dermal exposure studies is not considered priority because these are not the primary routes of exposure for populations living near hazardous waste sites.

h. Immunotoxicity

Purpose: To evaluate the mechanism of aluminum-induced toxicity for purposes of defining target organs and future mitigation activities. There is evidence to suggest that the immune system might be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned to the

evaluation of the immune system (lymphoid tissue, blood components) as an end point in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as defined by the NTP.

For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) have similar structural activity to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

Finding: A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified.

A few reports indicate hypersensitivity in children and adults who received aluminum-containing vaccines (Böhler-Sommeregger and Lindemayr 1986; Castelain et al. 1988; Veien et al. 1986). Several children and one adult who had previous injections of vaccines or allergens in an aluminum-based vehicle showed hypersensitivity to aluminum chloride in a patch test (Böhler-Sommeregger and Lindemayr 1986; Veien et al. 1986). Dermal hypersensitivity to aluminum appears to be rare in humans. A human oral exposure study (Gräske et al. 2000) did not find alterations in the concentrations of immunoglobulin, interleukin, natural killer cells, or B- or T-lymphocyte populations in humans ingesting an antacid suspension for 6 weeks. No other human exposure studies examining immunological end points were located.

Histological alterations have been observed in the lymphoreticular system, particularly granulomas in the hilar lymph nodes, of animals exposed to airborne aluminum (Steinhagen et al. 1978; Thomson et al. 1986); these effects were probably secondary to the pulmonary effects rather than the result of direct damage to lymphoreticular tissue. Inhalation studies conducting immune function tests are needed to fully assess the potential immunotoxicity of aluminum.

There is limited information on the immunotoxic potential of aluminum following oral exposure. No histopathological alterations were observed in rats following oral administration of aluminum (Dixon et al. 1979; Domingo et al. 1987b; Gomez et al. 1986; Katz et al. 1984; Ondreicka et al. 1966; Oneda et al. 1994). Proliferation of lymph node cells were observed in mice exposed to aluminum citrate via gavage for 22 weeks; however, no response was observed in spleen cells (Lauricella et al. 2001). These results suggest that the immune response may be cell-specific or dose-specific. No alterations in susceptibility to infection were observed in mice exposed to

dietary aluminum lactate for 6 weeks beginning at 6 weeks of age (Yoshida et al. 1989). However, there is some indication that gestational exposure to aluminum may impair immune development. An increase in susceptibility to bacterial infection was observed in mice exposed to aluminum lactate in the diet from conception through 10 days of age (Yoshida et al. 1989) and a deficiency of CD4+ cells in T-cell populations was observed in the mice exposed to dietary aluminum lactate from conception through 6 months of age (Golub et al. 1993). A battery of immune function tests following developmental and intermediate- or chronic-duration oral exposure may provide important information on characterizing the immunotoxic potential of aluminum, especially the age-sensitivity of effects.

No studies have examined the immunotoxicity of aluminum following dermal exposure. Although aluminum-related dermal sensitivity appears to be very rare in humans, further studies are necessary to fully assess this end point.

Priority Recommendation: The identified data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure is not considered priority. Although the primary route of exposure for populations living near hazardous waste sites is ingestion, the need for immune function tests is not considered priority at this time because the available data do not provide suggestive evidence that immunotoxicity would be a more sensitive end point than neurotoxicity or neurodevelopmental toxicity. The need for inhalation and dermal exposure studies is not considered priority because these are not the primary routes of exposure to aluminum.

i. Neurotoxicity

Purpose: To evaluate the mechanism of aluminum-induced toxicity to define target organs and future mitigation activities. There is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the absence of any information on the nervous system as a target organ, priority will be assigned evaluation of the nervous system as an end point in 90-day studies (Level I) before assigning priority to a neurotoxicology battery.

It may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in

90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) have similar structural activity to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

Finding: A data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal routes of exposure has been identified.

There are suggestive data that the nervous system may be a sensitive target in humans. Subtle neurological effects, such as impaired performance on neurobehavioral tests and increases in objective symptoms, have been observed in workers exposed to aluminum dust and fumes, McIntyre powder, or welding fumes (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Polizzi et al. 2001; Sim et al. 1997; Sjogren et al. 1990, 1996; White et al. 1992). Although a number of studies have examined the possible association between aluminum exposure and Alzheimer's disease (Flaten 1990; Forbes et al. 1992, 1994; Forster et al. 1995; Gauthier et al. 2000; Graves et al. 1998; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Polizzi et al. 2002; Rondeau et al. 2000, 2001; Salib and Hillier 1996; Sohn et al. 1996; Wettstein et al. 1991; Wood et al. 1988), a causal link between aluminum exposure and Alzheimer's disease has not been shown, and a number of factors may influence the risk of developing Alzheimer's disease. Nevertheless, continued monitoring of aluminum intake and incidence of neurological disease in humans is important to clarify aluminum's potential role in the Alzheimer's disease process.

The neurotoxicity of aluminum is well-documented in animals and has been manifested following oral exposure; however, there are very limited data on neurotoxicity following inhalation or dermal exposure. Inhalation studies have included histological examinations of the brain (Steinhagen et al. 1978; Stone et al. 1979), but not neurobehavioral function tests; no dermal exposure neurotoxicity studies were located. Studies are needed by these routes of exposure to establish whether it is a sensitive target following inhalation or dermal exposure.

In rats and mice orally exposed to aluminum for intermediate or chronic durations, neurotoxicity is manifested in neuromotor, behavioral, and cognitive changes (Bilkei-Gorzo 1993; Commissaris et al. 1982; Connor et al. 1989; Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1989, 1992a, 1992b, 1995, 2000; Jing et al. 2004; Oteiza et al. 1993; Zhang et al. 2003).

Additional low-dose studies in which levels of aluminum in the base diet are adequately characterized would be useful in establishing the NOAEL/LOAEL boundary. Oral exposure studies are also needed to evaluate the potential neurotoxicity of aluminum following acute-duration exposure and to confirm or refute the potential for aluminum to induce cognitive effects. Research issues related to neurodevelopmental effects of aluminum are discussed in the Data Needs section on Developmental Toxicity.

Priority Recommendation: The identified data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure is not considered priority. The need for additional oral studies is not considered a priority because the available data strongly support the identification of neurotoxicity as the most sensitive target of aluminum toxicity. The need for inhalation and dermal studies is not considered a priority because these are not the primary routes of exposure for populations living near hazardous waste sites.

j. Toxicokinetics

Purpose: To evaluate the disposition of aluminum across species and routes of exposure to elucidate target organs and mechanisms of toxicity, and to assess the need to conduct studies by routes other than the primary route of exposure.

Finding: A data need to assess the toxicokinetics of aluminum following inhalation, oral, and dermal exposure has been identified.

Increases in plasma and/or urinary levels of aluminum in workers exposed to airborne aluminum provide evidence of the absorption of aluminum (Gitelman et al. 1995; Mussi et al. 1984; Sjögren et al. 1985), but these studies do not provide quantitative data. Based on the relationship between urinary aluminum excretion and the airborne soluble aluminum to which workers were exposed, Yokel and McNamara (2001) estimated that the fractional absorption was 1.5–2%. Animal data do not provide quantitative data on the absorption of inhaled aluminum; studies measuring absorption of a variety of aluminum compounds would provide valuable information for assessing the risk of exposure to airborne aluminum compounds.

Available data indicate that the gastrointestinal absorption of aluminum is often in the range of 0.1–0.6% in humans, although absorption of poorly available aluminum compounds such as

aluminum hydroxide can be <0.01% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983; Hohl et al. 1994; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). Bioavailability of aluminum varies mainly due to differences in the form of the ingested compound and dietary constituents (i.e., the kinds and amounts of ligands in the stomach with which absorbable aluminum species can be formed). The apparent 10-fold or greater range in aluminum absorption has not been systematically documented using a variety of aluminum compounds and the most suitable analytical techniques. Radiochemical studies are desired because they facilitate accurate quantitation of the small percentages of ingested aluminum that are absorbed without requiring the use of large bolus doses and provide a means to trace endogenous aluminum from administered aluminum and distinguish from endogenous aluminum or from aluminum contamination of samples (Priest 1993). Additional toxicokinetic studies using [26]Al would help to better characterize the likely range of aluminum bioavailability. Information on the bioavailability of aluminum in rodent laboratory feed would also be useful for extrapolating from animal to human exposure. Studies investigating the extent of absorption of aluminum into the placenta and fetal blood circulation would be useful in assessing the relevance of developmental effects in animals to human exposures.

Very little information on the dermal absorption of aluminum was located. A study in humans estimated that approximately 0.012% of aluminum in aluminum chlorhydrate applied to the underarm was absorbed. Studies examining the dermal absorption of a variety of aluminum compounds are needed.

There are limited data on the distribution of aluminum following inhalation or dermal exposure, although it is likely that the distribution would be similar to distribution following oral exposure. Ingested aluminum is not equally distributed throughout the body; higher levels are found in the bone, spleen, liver, and kidney (Greger and Donnaubauer 1986; Greger and Sutherland 1997; Zafar et al. 1997). In the blood, aluminum is primarily found in the plasma bound to transferrin (Ganrot 1986; Harris and Messori 2002; Martin 1986). Metabolism of the element does not occur (Ganrot 1986). Absorbed aluminum is primarily excreted in the urine with a small amount of absorbed aluminum excreted in the feces (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Recker et al. 1977; Sjögren et al. 1985, 1988). A main deficiency is whether aluminum can cross into the brains of healthy humans in sufficient amounts to cause neurological diseases.

Further animal experiments, possibly using ^{26}Al as a tracer, would be useful in determining which, if any, levels and routes of exposure may lead to increased aluminum uptake in the brain.

The animal data indicate that the nervous system is the most sensitive target of toxicity for aluminum following oral exposure, as summarized in the Data Needs sections on Neurotoxicity and Developmental Toxicity. Human data also suggest that the nervous system is a sensitive target; a number of neurological effects have been observed in aluminum workers (Bast-Pettersen et al. 1994; Buchta et al. 2003, 2005; Dick et al. 1997; Hänninen et al. 1994; Hosovski et al. 1990; Iregren et al. 2001; Polizzi et al. 2001; Rifat et al. 1990; Riihimäki et al. 2000; Sim et al. 1997; Sjogren et al. 1990, 1996; White et al. 1992). The toxicokinetic properties of aluminum have been studied in humans and animals. The results of these studies suggest that the absorption, distribution, and excretion properties of aluminum are similar across species. There are very few comparative studies examining the toxicokinetic properties of different aluminum compounds; these studies would be useful.

Priority Recommendation: The identified data need to assess the toxicokinetics of aluminum following inhalation, oral, and dermal exposure is not considered priority. The additional studies are needed to more fully characterize the toxicokinetic properties of aluminum, particularly potential differences between aluminum compounds. However, the need for these studies is not considered priority because the available data provide sufficient information to evaluate the absorption, distribution, and excretion of aluminum for the purposes of elucidating target organs and mechanisms of toxicity.

2. Level III Data Needs

a. Epidemiologic Studies

Purpose: To evaluate the extant epidemiologic database and to propose the conduct of additional studies that may lead to cause- and effect- findings. The ATSDR Division of Health Studies will be informed of all candidate substances.

Finding: A data need has been identified.

There are numerous reports of adverse health effects, primarily respiratory and neurological effects, in workers exposed to airborne aluminum (Abbate et al. 2003; Abramson et al. 1989; Akira 1995; Al-Masalkhi and Walton 1994; Bast-Pettersen et al. 1994; Bost and Newman 1993; Buchta et al. 2003, 2005; Burge et al. 2000; Chan-Yeung et al. 1983; De Vuyst et al. 1986; Dick et al. 1997; Edling 1961; Gaffuri et al. 1985; Hänninen et al. 1994; Hosovski et al. 1990; Hull and Abraham 2002; Iregren et al. 2001; Jederlinic et al. 1990; Jephcott 1948; Korogiannos et al. 1998; McLaughlin et al. 1962; Miller et al. 1984b; Mitchell et al. 1961; Musk et al. 1980; Polizzi et al. 2001; Radon et al. 1999; Riddell 1948; Rifat et al. 1990; Riihimäki et al. 2000; Shaver 1948; Shaver and Riddell 1947; Sim et al. 1997; Simonsson et al. 1985; Sjogren et al. 1990, 1996; Ueda et al. 1958; Vallyathan et al. 1982; Vandenplas et al. 1998; White et al. 1992). However, a common limitation of the occupational exposure data is that the exposure levels have not been well quantified and workers were often exposed to a number of other chemicals; additional studies examining potential adverse health effects in aluminum workers and monitoring exposure levels are needed. A number of studies have examined the possible association between Alzheimer's disease and aluminum exposure in air (Polizzi et al. 2002; Salib and Hillier 1996) and drinking water (Flaten 1990; Forbes et al. 1992, 1994; Forster et al. 1995; Gauthier et al. 2000; Graves et al. 1998; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Rondeau et al. 2000, 2001; Sohn et al. 1996; Wettstein et al. 1991; Wood et al. 1988). These studies have reported conflicting results and have been criticized for poor subject selection, exposure assessment, and diagnosis of Alzheimer's disease. Further studies are important in helping to determine whether there is a cause-and-effect relationship between chronic aluminum exposure and the development of Alzheimer's disease. There are also a number of studies reporting bone damage and neurological effects in individuals with chronic renal failure (Alfrey 1993); however, kidney failure increases the risk for developing effects related to aluminum and other substances; thus, these data have limited usefulness in predicting health effects in the general population. Aluminum is found in a number of over-the-counter products, such as antacids; however, controlled studies examining potential adverse effects in healthy individuals ingesting these products long-term have not been located and are needed.

Priority Recommendation: The identified data need to conduct epidemiologic studies on aluminum is not considered priority. Aluminum is ubiquitous in the diet and has been identified

at over 600 hazardous waste sites, and thus, all people are potentially exposed to this chemical. Although there are a number of limitations with the large number of epidemiology studies examining the potential toxicity of aluminum, these studies have identified target organs that have been confirmed in animal studies. If either worker or general populations with appropriate exposures can be identified, epidemiologic studies should be undertaken with special emphasis on neurotoxicity and respiratory tract toxicity.

b. Mechanism of Toxic Action

Purpose: To evaluate the mechanism of aluminum-induced toxicity to define target organs and future mitigation activities.

Finding: A data need has been identified.

Human and animal studies clearly identify the nervous system as the target of aluminum toxicity. However, the mechanism of toxicity has not been elucidated. Numerous mechanisms have been proposed (Erasmus et al. 1993; Jope and Johnson 1992; Strong et al. 1996) and it is likely that more than one mechanism is involved. The main sites of action of aluminum are difficult to discern because the studies have been performed using a variety of exposure methods (including a number of different *in vivo* injections and *in vitro* systems) and animal species, and a number of typical effects are not common to all species and exposure circumstances (i.e., are only expressed using certain models of neurotoxicity). Although insufficient data are available to fully understand the mechanism(s) of aluminum toxicity, some general processes that are involved have been identified. Changes in cytoskeletal proteins, manifested as hyperphosphorylated neurofilamentous aggregates within the brain neurons, is a characteristic response to aluminum in certain species (e.g., rabbits, cats, ferrets, and nonhuman primates) and exposure situations (e.g., intracerebral and intracisternal administration). The neurofilamentous aggregates appear to mainly result from altered phosphorylation, apparently by posttranslational modifications in protein synthesis, but may also involve proteolysis, transport, and synthesis (Jope and Johnson 1992; Strong et al. 1996). Interactions between these processes probably contribute to the induction of the phosphorylated neurofilaments. Each of the processes can be influenced by kinases, some of which are activated by second messenger systems. For example, aluminum appears to influence calcium homeostasis and calcium-dependent processes in the brain via impairment of the phosphoinositide second messenger-producing system (which modulates

intracellular calcium concentrations); calcium-activated proteinases may be affected, which could alter the distribution and concentration of cytoskeletal proteins and other substates (Gandolfi et al. 1998; Jope and Johnson 1992; Julka and Gill 1995; Mundy et al. 1995; Nostrandt et al. 1996; Sarin et al. 1997; Shafer and Mundy 1995). Another process that may contribute to neurodegeneration is apoptosis (Fu et al. 2003; Ghribi et al. 2001; Johnson et al. 2005; Suarez-Fernandez et al. 1999). The species (rodents) in which aluminum-induced neurobehavioral effects (e.g., changes in locomotor activity, learning, and memory) have been observed fail to develop significant cytoskeletal pathology, but exhibit a number of neurochemical alterations following *in vivo* or *in vitro* exposure (Erasmus et al. 1993; Strong et al. 1996). Studies in these animals indicate that exposure to aluminum can affect permeability of the blood-brain barrier (Yokel et al. 2002; Zheng 2001), cholinergic activity (Kaizer et al. 2005; Kohila et al. 2004; Zatta et al. 2002), signal transduction pathways (Montoliu and Felipo 2001), and lipid peroxidation (Deloncle et al. 1999; El-Demerdash 2004; Fraga et al. 1990; Nehru and Anand 2005), as well as impair the neuronal glutamate nitric oxide-cyclic GMP pathway (Cucarella et al. 1998; Hermenegildo et al. 1999; Llansola et al. 1999; Rodella et al. 2004), and interfere with metabolism of essential trace elements (e.g., iron) because of similar coordination chemistries and consequent competitive interactions. Additional studies are needed to further elucidate the mechanism of aluminum neurotoxicity and to further examine species differences.

Priority Recommendation: The identified data need is not considered priority. Although research is needed for further elucidation of mechanisms of aluminum toxicity, this research is not given high priority at this time because of the need to further define targets of low-level exposure in humans and to identify threshold levels that cause adverse health effects.

c. Biomarkers

Purpose: To evaluate the need to develop additional biomarkers of exposure and effect for purposes of future medical surveillance that can lead to early detection and treatment.

Finding: A data need has been identified.

Although aluminum can be measured in blood (Alfrey et al. 1980; Arieff et al. 1979; Ganrot 1986), urine (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Mussi et al. 1984; Recker et al. 1977; Sjögren et al. 1985, 1988), and feces (Greger and Baier 1983), the aluminum

body burden rapidly declines upon termination of exposure (except in the lungs, where retention takes place). Also, tissue levels do not correlate with exposure except that higher-than-average tissues levels of aluminum are indicative of aluminum exposure; the available data suggest that duration of exposure (Sjögren et al. 1988), aluminum compound (Greger and Baier 1983; Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004), age (Gomez et al. 1997), and kidney function (Alfrey et al. 1980; Arieff et al. 1979) may influence the levels of aluminum in tissues and urine. There is some suggestive evidence that erythrocyte aluminum levels may be reflective of long-term aluminum exposure (Priest 2004), but a possible relationship between ingestion and erythrocyte aluminum levels has not been established. Additional studies examining the possible relationship between urine, blood, or other tissue levels and aluminum exposure would be useful in establishing biomarkers of exposure.

No biomarkers of effect have been identified for aluminum. The mechanism of action for aluminum toxicity has not been fully elucidated and there is considerable research in identifying the mechanism(s) of neurotoxicity (Cucarella et al. 1998; Deloncle et al. 1999; El-Demerdash 2004; Fraga et al. 1990; Hermenegildo et al. 1999; Kaizer et al. 2005; Kohila et al. 2004; Llansola et al. 1999; Montoliu and Felipo 2001; Nehru and Anand 2005; Rodella et al. 2004; Yokel et al. 2002; Zatta et al. 2002; Zheng 2001). Studies on the mechanism of action of aluminum may lead to biochemical tests that can be used in the early identification of aluminum toxicity.

Priority Recommendation: The identified data need is not considered priority. The lack of a specific biomarker of effect for aluminum is not considered essential to conduct human studies because there is no unique disease state associated with aluminum.

d. Clinical Methods for Mitigating Toxicity

Purpose: To determine whether any efforts are currently under way to mitigate the effects of exposure to aluminum.

Finding: A data need has been identified.

The mechanisms of absorption of aluminum have not been established. Studies designed to elucidated these mechanisms would be useful for establishing methods or treatments for reducing absorption and distribution of aluminum to sensitive targets. The chelating agent desferrioxamine

(DFO) has been used to reduce the aluminum body burden (Haddad et al. 1998; Yokel et al. 2001b); however, the clinical usefulness of DFO is limited by a variety of toxic effects. Other chelators, such as 1,2-dimethyl-3-hydroxypyrid-4-one and (4-methyl-6-trifluoromethyl-6-pyrimidin-2-il)-hydrazine, have also been shown to reduce the aluminum body burden (Gomez et al. 1999; Missel et al. 2005; Yokel et al. 1997). Studies that identify other methods for reducing aluminum body burden would be useful. The mechanism of toxicity has not been established for most of the toxic end points. Additional information on the mechanisms of toxicity would be useful for developing methods for reducing the toxicity of aluminum.

Priority Recommendation: The identified data need is not considered priority. The mechanism of action has not been fully elucidated, no unique disease has been associated with aluminum exposure, and populations with specific substance-induced adverse health effects have not been identified.

e. Children's Susceptibility

Purpose: To determine whether adequate data exist to identify potential health effects from exposures to aluminum during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

Finding: A data need to conduct additional studies relevant to children's susceptibility via inhalation, oral, and dermal exposure has been identified.

Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

The available data suggest that the targets of aluminum toxicity in children would be similar to those in adults. However, there is conflicting evidence on whether the threshold of toxicity, particularly neurotoxicity, would be lower in children. Multiple species studies using a relevant route of exposure, such as ingestion, and examining a wide range of effects in immature, mature, and older animals would be useful in assessing children's susceptibility to the toxicity of

aluminum. Additionally, there are no studies on the influence of immature renal function on aluminum retention in the body and no studies on the long-term effects of aluminum exposure on skeletal maturation or neurotoxicity. There are some data suggesting age-related differences in the toxicokinetic properties of aluminum. A study in rats found higher levels of aluminum in the brain and bone of aged rats (aged 18 months) compared to young rats (aged 21 days) (Gomez et al. 1997a); similar findings were observed in the controls and aluminum-treated rats.

Priority Recommendation: The identified data need to conduct additional studies on children's susceptibility via inhalation, oral, and dermal exposure is not considered priority. Additional studies on mechanisms of action and toxicokinetics of aluminum in immature and adult animals need to be conducted and evaluated before assigning priority to the identified data need.

IV. Summary: Prioritization of Data Needs for Aluminum

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for aluminum and proceeds through assessing the need for epidemiologic studies. As stated previously, much information is available on aluminum, though some of the studies are very old. This does not mean that data derived from older studies are not adequate. ATSDR agrees with the National Research Council in that it is not appropriate to judge the quality of past and future studies solely by the standards of today.

Building a sound basic data foundation for higher level environmental research via the Decision Guide requires the determination of human exposure levels and media-specific data on aluminum. Although a lot of information is available, a need to evaluate existing data on concentrations of aluminum in contaminated environmental media at hazardous waste sites has been identified.

Furthermore, a need to collect data on levels of aluminum in body tissues and fluids for populations living near hazardous waste sites has been identified. This information is necessary to establish a database that can be used to assess the need to conduct follow-up human health studies of adult and children populations exposed to aluminum.

One effort is now under way at ATSDR that will examine the extant data at the 606 NPL sites at which aluminum has been found. When complete, this database will include maximum concentrations of aluminum in on-site and off-site media, and an indication of relevant routes of exposure. This database will be developed and evaluated before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on the levels of aluminum (or its metabolites) in the tissues of adults and children living near hazardous waste sites or other exposed populations such as workers.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following exposure priority data needs (Table 3):

- Exposure via environmental media for humans living near hazardous waste sites.

- Exposure via environmental media for children living near hazardous waste sites.

B. Toxicity

The toxicity of aluminum has been examined in a number of inhalation, oral, and dermal exposure studies. The results of these studies, particularly the oral exposure studies, have identified the nervous system as the most sensitive target of toxicity in mature and immature animals. Delays in growth and maturation may also be sensitive targets of aluminum in developing organisms. Additional acute oral exposure studies are needed for identifying sensitive targets, establishing dose-response relationships, and deriving an acute-duration oral MRL.

These nonhuman research needs are justified because of the widespread domestic and environmental contamination of aluminum, and the possibility that significant past exposures have affected many people.

Thus, on the basis of the findings given in Section II and above, ATSDR recommends the initiation of research or studies to fill the following toxicity priority data needs (Table 3):

- Dose-response data for acute-duration via oral exposure

V. References

Abbate C, Giorgianni C, Brecciaroli R, et al. 2003. Spirometric function in non-smoking workers exposed to aluminum. Am J Ind Med 44(4):400-404.

Abraham JL, Burnett BR. 1983. Quantitative analysis of inorganic particulate burden *in situ* in tissue sections. Scan Electron Microsc 2:681-696.

Abramson MJ, Wlodarczyk JH, Saunders NA, et al. 1989. Does aluminum smelting cause lung disease? Am Rev Respir Dis 139:1042-1057.

Advenier E, Landry C, Colomb V, et al. 2003. Aluminum contamination of parenteral nutrition and aluminum loading in children on long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 36(4):448-453.

Akila R, Stollery BT, Riihimaki V. 1999. Decrements in cognitive performance in metal inert gas welders exposed to aluminum. Occup Environ Med 56(9):632-639.

Akira M. 1995. Uncommon pneumoconioses: CT and pathologic findings. Radiology 197(2):403-409.

Alderman FR, Gitelman HJ. 1980. Improved electrothermal determination of aluminum in serum by atomic absorption spectroscopy. Clin Chem 26:258-260.

Alfrey AC. 1987. Aluminum metabolism and toxicity in uremia. J UOEH 9 Suppl:123-132.

Alfrey AC. 1993. Aluminum toxicity in patients with chronic renal failure. Ther Drug Monit 15(6):593-597.

Alfrey AC, Hegg A, Craswell P. 1980. Metabolism and toxicity of aluminum in renal failure. Am J Clin Nutr 33(7):1509-1516.

Allain P, Mauras Y. 1979. Determination of aluminum in blood, urine, and water by inductively coupled plasma emission spectrometry. Anal Chem 51(13):2089-2091.

Al-Masalkhi A, Walton SP. 1994. Pulmonary fibrosis and occupational exposure to aluminum. J Ky Med Assoc 92:59-61.

Al-Saleh I, Shinwari N. 1996. Aluminum in Saudi children. Biometals 9:385-392.

Alvarez E, Perez A, Calvo R. 1993. Aluminum speciation in surface waters and soil solutions in areas of sulphide mineralization in Galicia (N.W. Spain). Sci Total Environ 133:17-37.

Amaducci LA, Fratiglioni L, Rocca WA, et al. 1986. Risk factors for clinically diagnosed Alzheimer's disease: A case-control study of an Italian population. Neurology 36(7):922-931.

Andersen JR. 1987. Graphite furnace atomic absorption spectrometric screening methods for determination of aluminum in hemodialysis concentrates. J Anal Atom Spectrom 2:257-259.

Andersen JR. 1988. Aluminum in peritoneal dialysis fluids as determined by stabilized temperature platform furnace atomic absorption spectrometry. J Pharm Biomed Anal 6(1):29-33.

Andreoli SP. 1990. Aluminum levels in children with chronic renal failure who consume low-phosphorus infant formula. J Pediatr 116(2):282-285.

Andreoli SP, Bergstein JM, Sherrard DJ. 1984. Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. N Engl J Med 310:1079-1084.

AOAC. 1990. Method 990.08: Metals in solid wastes. Inductively coupled plasma atomic emission method. First action 1990. In: Helrich K, ed. Changes in official methods of analysis of the Association of Official Analytical Chemists. First Supplement. Arlington, VA: Association of Official Analytical Chemists, Inc., 14-17, 43.

APHA. 1998a. Method 3113 B: Metals by atomic absorption spectroscopy. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association/American Water Works Association/Water Environment Federation, 3-24 to 3-31.

APHA. 1998b. Method 3120 B: Metals by plasma emission spectroscopy. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association/American Water Works Association/Water Environment Federation, 3-37 to 3-43.

APHA. 1998c. Method 3125: Metals by inductively coupled plasma/mass spectroscopy. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association/American Water Works Association/Water Environment Federation, 3-44 to 3-52.

APHA. 1998d. Method 3500-Al: Aluminum. In: Clesceri LS, Greenberg AE, Eaton AD, et al., eds. Standard methods for the examination of water and wastewater. Washington, DC: American Public Health Association, American Water Works Association, Water Environment Federation, 3-56 to 3-59.

Arieff AI, Cooper JD, Armstrong D, et al. 1979. Dementia, renal failure, and brain aluminum. Ann Intern Med 90(5):741-747.

ATSDR. 2005. Notice of the revised priority list of hazardous substances that will be the subject of toxicological profiles. Agency for Toxic Substances and Disease Registry. Fed Regist 70:72840-72842.

ATSDR. 2006. ATSDR toxicological profile for aluminum. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp22.html. October 30, 2006.

Banks WA, Kastin AJ, Fasold MB. 1988. Differential effect of aluminum on the blood-brain barrier transport of peptides, technetium and albumin. J Pharmacol Exp Ther 244:579-585.

Bast-Pettersen R, Drablos PA, Goffeng LO, et al. 1994. Neuropsychological deficit among elderly workers in aluminum production. Am J Ind Med 25(5):649-662.

Bast-Pettersen R, Skaug V, Ellingsen D, et al. 2000. Neurobehavioral performance in aluminum welders. Am J Ind Med 37(2):184-192.

Baylor NW, Egan W, Richman P. 2002. Aluminum salts in vaccines–US perspective. Vaccine 20(Suppl 3):S18-S23.

Baxter MJ, Burrell JA, Crews H, et al. 1991. Aluminum levels in milk and infant formulae. Food Addit Contam 8(5):653-660.

Berlyne GM, Ben-Ari J, Pest D, et al. 1970. Hyperaluminaemia from aluminum resins in renal failure. Lancet 2(7671):494-496.

Bernuzzi V, Desor D, Lehr PR. 1986. Effects of prenatal aluminum exposure on neuromotor maturation in the rat. Neurobehav Toxicol Teratol 8:115-119.

Bernuzzi V, Desor D, Lehr PR. 1989a. Effects of postnatal aluminum lactate exposure on neuromotor maturation in the rat. Bull Environ Contam Toxicol 42(3):451-455.

Bernuzzi V, Desor D, Lehr PR. 1989b. Developmental alterations in offspring of female rats intoxicated by aluminum chloride or lactate during gestation. Teratology 40(1):21-27.

Bettinelli M, Baroni U, Fontana F, et al. 1985. Evaluation of the L'vov platform and matrix modification for the determination of aluminum in serum. Analyst 110:19-22.

Bilkei-Gorzo A. 1993. Neurotoxic effect of enteral aluminum. Food Chem Toxicol 31(5):357-361.

Blotcky AJ, Hobson D, Leffler JA, et al. 1976. Determination of trace aluminum in urine by neutron activation analysis. Anal Chem 48:1084-1088.

Bodek I, Lyman WJ, Reehl WF, et al., eds. 1988. Aluminum (Al). Environmental inorganic chemistry: Properties, processes, and estimation methods. New York, NY: Pergamon Press, 6.7-1 to 6.7-9.

Böhler-Sommeregger K, Lindemayr H. 1986. Contact sensitivity to aluminum. Contact Dermatitis 15(5):278-281.

Bost TW, Newman LS. 1993. Metal-induced interstitial lung diseases: A clinicopathologic approach. Semin Resp Med 14(3):197-211.

Bougle D, Bureau F, Voirin J, et al. 1991. Aluminum levels in term and premature infants on enteral nutrition. Trace Elem Med 8:172-174.

Bouman AA, Platenkamp AJ, Posma FD. 1986. Determination of aluminum in human tissues by flameless atomic absorption spectroscopy and comparison of references values. Ann Clin Biochem 23(Part 1):97-101.

Bozynski ME, Sedman AB, Naglie RA, et al. 1989. Serial plasma and urinary aluminum levels and tissue loading in preterm twins. JPEN J Parenter Enteral Nutr 13(4):428-431.

Broe GA, Henderson AS, Creasey H, et al. 1990. A case-control study of Alzheimer's disease in Australia. Neurology 40(11):1698-1707.

Browning E. 1969. Aluminum. In: Browning E, ed. Toxicity of industrial metals. New York, NY: Appleton-Century-Crofts, 3-22.

Brusewitz S. 1984. Aluminum. Vol. 203. Stockholm, Sweden: University of Stockholm, Institute of Theoretical Physics.

Buchta M, Kiesswetter E, Otto A, et al. 2003. Longitudinal study examining the neurotoxicity of occupational exposure to aluminum-containing welding fumes. Int Arch Occup Environ Health 76(7):539-548.

Buchta M, Kiesswetter E, Schaper M, et al. 2005. Neurotoxicity of exposures to aluminium welding fumes in the truck trailer construction industry. Environ Toxicol Pharmacol 19(3):677-685.

Burge PS, Scott JA, McCoach J. 2000. Occupational asthma caused by aluminum. Allergy 55(8):779-780.

Carmichael KA, Fallon MD, Dalinka M, et al. 1984. Osteomalacia and osteitis fibrosa in a man ingesting aluminum hydroxide antacid. Am J Med 76(6):1137-1143.

Castelain PY, Castelain M, Vervloet D, et al. 1988. Sensitization to aluminium by aluminium-precipitated dust and pollen extracts. Contact Dermatitis 19(1):58-60.

Cech I, Montera J. 2000. Spatial variations in total aluminum concentrations in drinking water supplies studied by geographic information system (GIS) methods. Water Res 34(10):2703-2712.

Chan-Yeung M, Wong R, MacLean L, et al. 1983. Epidemiologic health study of workers in an aluminum smelter in British Columbia, Canada: Effects on respiratory system. Am Rev Respir Dis 127:465-469.

Chedid F, Fudge A, Teubner J, et al. 1991. Aluminium absorption in infancy. J Paediatr Child Health 27(3):164-166.

Chen W-J, Monnat RJJ, Chen M, et al. 1978. Aluminum induced pulmonary granulomatosis. Hum Pathol 9(6):705-711.

Chiba M, Sera K, Hashizume M, et al. 2004. Element concentrations in hair of children living in environmentally degraded districts of the East Aral Sea region. J Radioanal Nucl Chem 259(1):149-152.

Chines A, Pacifici R. 1990. Antacid and sucralfate-induced hypophosphatemic osteomalacia: A case report and review of the literature. Calcif Tissue Int 47(5):291-295.

Chopra JS, Kalra OP, Malik VS, et al. 1986. Aluminum phosphide poisoning: A prospective study of 16 cases in one year. Postgrad Med J 62:1113-1116.

Christie H, MacKay RJ, Fisher AM. 1963. Pulmonary effects of inhalation of aluminum by rats and hamsters. Am Ind Hyg Assoc J 24:47-56.

Colin-Jones D, Langman MJ, Lawson DH, et al. 1989. Alzheimer's disease in antacid users. Lancet 1(8652):1453.

Colomina MT, Gomez M, Domingo JL, et al. 1992. Concurrent ingestion of lactate and aluminum can result in developmental toxicity in mice. Res Commun Chem Pathol Pharmacol 77(1):95-106.

Colomina MT, Roig JL, Torrente M, et al. 2005. Concurrent exposure to aluminum and stress during pregnancy in rats: Effects on postnatal development and behavior of the offspring. Neurotoxicol Teratol 27(4):565-574.

Commissaris RL, Cordon JJ, Sprague S, et al. 1982. Behavioral changes in rats after chronic aluminum and parathyroid hormone administration. Neurobehav Toxicol Teratol 4(3):403-410.

Connor DJ, Harrell LE, Jope RS. 1989. Reversal of an aluminum-induced behavioral deficit by administration of deferoxamine. Behav Neurosci 103(4):779-783.

Cooper JA, Watson JG, Huntzicker JJ. 1979. Summary of the Portland Aerosol Characterization Study (PACS). Presented at the 72nd Annual Meeting of the Air Pollution Control Association, Cincinnati, Ohio, June 24-29, 1979. Cincinnati, OH: Air Pollution Control Association, 1-16.

Cranmer JM, Wilkins JD, Cannon DJ, et al. 1986. Fetal-placental-maternal uptake of aluminum in mice following gestational exposure: Effect of dose and route of administration. Neurotoxicology 7(2):601-608.

Cucarella C, Montoliu C, Hermenegildo C, et al. 1998. Chronic exposure to aluminum impairs neuronal glutamate-nitric oxide-cyclic GMP pathway. J Neurochem 70:1609-1614.

Dabeka RW, McKenzie AD. 1990. Aluminum levels in Canadian infant formulae and estimation of aluminum intakes from formulae by infants 0-3 months old. Food Addit Contam 7(2):275-282.

Dahlgren RA, Ugolini FC. 1989. Aluminum fractionation of soil solutions from unperturbed and tephra-treated spodosols, Cascade Range, Washington, USA. Soil Sci Soc Am J 53:559-566.

Dawson EB, Evans DR, Harris WA, et al. 2000. Seminal plasma trace metal levels in industrial workers. Biol Trace Elem Res 74(2):97-105.

Dawson EB, Ritter S, Harris WA, et al. 1998. Comparison of sperm viability with seminal plasma metal levels. Biol Trace Elem Res 64:215-219.

Day JP, Barker J, Evans LJA, et al. 1991. Aluminum absorption studied by [26]Al tracer. Lancet 337(8753):1345.

Dean JR. 1989. Ion chromatographic determination of aluminum with ultraviolet spectrophotometric detection. Analyst 114:165-168.

Deloncle R, Huguet F, Babin P, et al. 1999. Chronic administration of aluminium L-glutamate in young mature rats: Effects on iron levels and lipid peroxidation in selected brain areas. Toxicol Lett 104(1-2):65-73.

DeVoto E, Yokel RA. 1994. The biological speciation and toxicokinetics of aluminum. Environ Health Perspect 102(11):940-951.

De Vuyst P, Dumortier P, Rickaert F, et al. 1986. Occupational lung fibrosis in an aluminum polisher. Eur J Respir Dis 68(2):131-140.

De Vuyst P, Dumortier P, Schandenè L, et al. 1987. Sarcoidlike lung granulomatosis induced by aluminum dusts. Am Rev Respir Dis 135(2):493-497.

Dick RB, Krieg EFJ, Sim MA, et al. 1997. Evaluation of tremor in aluminum production workers. Neurotoxicol Teratol 19(6):447-453.

DiPaolo JA, Casto BC. 1979. Quantitative studies of *in vitro* morphological transformation of Syrian hamster cells by inorganic metal salts. Cancer Res 39(3):1008-1013.

Dixon RL, Sherins RJ, Lee IP. 1979. Assessment of environmental factors affecting male fertility. Environ Health Perspect 30:53-68.

DOE. 1984. A review and analysis of parameters for assessing transport of environmentally released radionuclides through agriculture. U.S. Department of Energy. ORNL-5786.

DOI. 1970. Trace metals in waters of the United States. A five year summary of trace metals in rivers and lakes of the United States (Oct. 1, 1962-Sept. 30, 1967). Cincinnati, OH: U.S. Department of the Interior, Federal Water Pollution Control Administration, Division of Pollution Surveillance.

Domingo JL, Gomez M, Bosque MA, et al. 1989. Lack of teratogenicity of aluminum hydroxide in mice. Life Sci 45(3):243-247.

Domingo JL, Llobet JM, Gomez M, et al. 1987a. Nutritional and toxicological effects of short-term ingestion of aluminum by the rat. Res Commun Chem Pathol Pharmacol 56(3):409-419.

Domingo JL, Paternain JL, Llobet JM, et al. 1987b. The effects of aluminum ingestion of reproduction and postnatal survival in rats. Life Sci 41(9):1127-1131.

Donald JM, Golub MS, Gershwin ME, et al. 1989. Neurobehavioral effects in offspring of mice given excess aluminum in diet during gestation and lactation. Neurotoxicol Teratol 11(4):345-351.

Dong D, Xie Z, Du Y, et al. 1999. Influence of soil pH on aluminum availability in the soil and aluminum in tea leaves. Commun Soil Sci Plant Anal 30(5/6):873-883.

Drablos PA, Hetland S, Schmidt F et al. 1992. Uptake and excretion of aluminum in workers exposed to aluminum fluoride and aluminum oxide. Proceedings of the second international conference on aluminum and health, Tampa, FL, February 2-6, 1992. New York, NY: Aluminum Association, 157-160.

Drew RT, Gupta BN, Bend JR, et al. 1974. Inhalation studies with a glycol complex of aluminum-chloride-hydroxide. Arch Environ Health 28(6):321-326.

Dzubay TG. 1980. Chemical element balance method applied to dichotomous sampler data. Ann NY Acad Sci 338:126-144.

Edling NPG. 1961. Aluminum pneumoconiosis: A roentgendiagnostic study of five cases. Acta Radiol 56:170-178.

Eisenreich SJ. 1980. Atmospheric input of trace metals to Lake Michigan (USA). Water Air Soil Pollut 13(3):287-301.

El-Demerdash FM. 2004. Antioxidant effect of vitamin E and selenium on lipid peroxidation, enzyme activities and biochemical parameters in rats exposed to aluminum. J Trace Elem Med Biol 18(1):113-121.

EPA. 1983a. Method 202.1: Aluminum (atomic absorption, direct aspiration). Methods for the chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600479020. http://web1.er.usgs.gov/nemi/method_pdf/5267.pdf. March 21, 2006.

EPA. 1983b. Method 202.2: Aluminum (AA, furnace technique). Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600479020. http://web1.er.usgs.gov/nemi/method_pdf/5268.pdf. March 21, 2006.

EPA. 1994a. Method 200.7: Inductively coupled plasma-atomic emission spectrometric method for trace element analysis of water and wastes. In: Methods for the determination of metals in environmental samples. Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600R94111. http://web1.er.usgs.gov/nemi/method_pdf/4690.pdf. March 21, 2006.

EPA. 1994b. Method 200.8: Determination of trace elements in waters and wastes by inductively coupled plasma - mass spectrometry. In: Methods for the determination of metals in environmental samples. Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600R94111. http://web1.er.usgs.gov/nemi/method_pdf/4665.pdf. March 21, 2006.

EPA. 1994c. Method 200.9: Trace elements in water, solids, and biosolids by stabilized temperature graphite furnace atomic absorption spectrometry. In: Methods for the determination of metals in environmental samples. Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600R94111. http://web1.er.usgs.gov/nemi/method_pdf/4797.pdf. March 21, 2006.

EPA. 2000. Method 6010C: Inductively coupled plasma-atomic emission spectrometry. In: Test methods for evaluating solid waste, physical/chemical methods. Washington, DC: U.S. Environmental Protection Agency. SW846. http://www.epa.gov/sw-846/pdfs/6010c.pdf. March 21, 2006.

EPA. 2005. Guidelines for carcinogen risk assessment. Washington, DC: U.S. Environmental Protection Agency. EPA630P03001F.

Erasmus RT, Savory J, Wills MR, et al. 1993. Aluminum neurotoxicity in experimental animals. Ther Drug Monit 15:588-592.

Farina M, Rotta LN, Soares FA, et al. 2005. Hematological changes in rats chronically exposed to oral aluminum. Toxicology 209(1):29-37.

Fernandez de la Campa MR, Garcia MED, Sanz-Medel A. 1988. Room-temperature liquid phosphorimetry of the aluminum-ferron chelate in micellar media. Determination of aluminum. Anal Chim Acta 212:235-243.

Fernandez-Lorenzo JR, Cocho JA, Rey-Goldar ML, et al. 1999. Aluminum contents of human milk, cow's milk, and infant formulas. J Pediatr Gastroenterol Nutr 28(3):270-275.

Filipek LH, Nordstrom DK, Ficklin WH. 1987. Interaction of acid mine drainage with waters and sediments of West Squaw Creek in the West Shasta mining district, California. Environ Sci Technol 21:388-396.

Finberg L, Dweck HS, Holmes F, et al. 1986. Aluminum toxicity in infants and children. Pediatrics 78:1150-1154.

Finelli VN, Que Hee SS, Niemeier RW. 1981. Influence of exposure to aluminum chloride and fluoride dusts on some biochemical and physiological parameters in rats. In: Brown SS, Davies DS, eds. Organ-directed toxicity: Chemical indices and mechanisms. New York, NY: Pergamon Press, 291-295.

Flarend RE, Elmore D. 1997. Aluminium-26 as a biological tracer using accelerator mass spectrometry. In: Zatta PF, Alfrey AC, eds. Aluminum toxicity in infants' health and disease. Singapore: World Scientific, 16-39.

Flaten TP. 1990. Geographical associations between aluminum in drinking water and death rates with dementia (including Alzheimer's disease), Parkinson's disease and amyotrophic lateral sclerosis in Norway. Environ Geochem Health 12(1-2):152-167.

Fleming RF, Lindstrom RM. 1987. Precise determination of aluminum by instrumental neutron activation. J Radioanal Nucl Chem 113:35-42.

Florence AL, Gauthier A, Ponsar C, et al. 1994. An experimental animal model of aluminum overload. Neurodegeneration 3(4):315-323.

Forbes WF, Hayward LM, Agwani N. 1992. Geochemical risk factors for mental functioning, based on the Ontario Longitudinal Study of Aging (LSA). I. Results from a preliminary investigation. Can J Aging 13(2):269-281.

Forbes WF, McAiney CA, Hayward LM, et al. 1994. Geochemical risk factors for mental functioning, based on the Ontario Longitudinal Study of Aging (LSA). II. The role of pH. Can J Aging 13(2):249-266.

Forster DP, Newens AJ, Kay DWK, et al. 1995. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: A case-control study in northern England. J Epidemiol Commun Health 49(3):253-258.

Fraga CG, Oteiza PI, Golub MS, et al. 1990. Effects of aluminum on brain lipid peroxidation. Toxicol Lett 51(2):213-219.

Fu HJ, Hu QS, Lin ZN, et al. 2003. Aluminum-induced apoptosis in cultured cortical neurons and its effect on SAPK/JNK signal transduction pathway. Brain Res 980(1):11-23.

Gaffuri E, Donna A, Pietra R, et al. 1985. Pulmonary changes and aluminum levels following inhalation of alumina dust: A study on four exposed workers. Med Lav 76(3):222-227.

Gandolfi L, Stella MP, Zambenedetti P, et al. 1998. Aluminum alters intracellular calcium homeostasis in vitro. Biochim Biophys Acta 1406(3):315-320.

Ganrot PO. 1986. Metabolism and possible health effects of aluminum. Environ Health Perspect 65:363-441.

Garbossa G, Galvez G, Castro ME, et al. 1998. Oral aluminum administration to rats with normal renal function. 1. Impairment of erythropoiesis. Hum Exp Toxicol 17(6):312-317.

Garbossa G, Gutnisky A, Nesse A. 1996. Depressed erythroid progenitor cell activity in aluminum-overloaded mice. Miner Electrolyte Metab 22(4):214-218.

Gardiner PE, Stoeppler M. 1987. Optimisation of the analytical conditions for the determination of aluminum in human blood plasma and serum by graphite furnace atomic absorption spectrometry. Part 2. Assessment of the analytical method. J Anal Atom Spectrom 2:401-404.

Gardiner PE, Ottaway JM, Fell GS, et al. 1981. Determination of aluminum in blood plasma or serum by electrothermal atomic absorption spectrometry. Anal Chim Acta 128:57-66.

Gauthier E, Fortier I, Courchesne F, et al. 2000. Aluminum forms in drinking water and risk of Alzheimer's disease. Environ Res 84(3):234-246.

Ghribi O, Dewitt DA, Forbes MS, et al. 2001. Co-involvement of mitochondria and endoplasmic reticulum in regulation of apoptosis: Changes in cytochrome *c*, Bcl-2 and Bax in the hippocampus of aluminum-treated rabbits. Brain Res 903(1-2):66-73.

Gibbs GW, Horowitz I. 1979. Lung cancer mortality in aluminum reduction plant workers. J Occup Med 21:347-353.

Gitelman HJ, Alderman FR, Kurs-Lasky M, et al. 1995. Serum and urinary aluminum levels of workers in the aluminum industry. Ann Occup Hyg 39(2):181-191.

Goenaga X, Williams DJA. 1988. Aluminum speciation in surface waters from a Welsh upland area. Environ Pollut 52:131-149.

Golomb D, Ryan D, Eby N, et al. 1997. Atmospheric deposition of toxics onto Massachusetts Bay-I. Metals. Atmos Environ 31:1349-1359.

Golub MS, Domingo JL. 1996. What we know and what we need to know about developmental aluminum toxicity. J Toxicol Environ Health 48(6):585-597.

Golub MS, Germann SL. 1998. Aluminum effects on operant performance and food motivation of mice. Neurotoxicol Teratol 20(4):421-427.

Golub MS, Germann SL. 2001. Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior of Swiss Webster mice. Neurotoxicol Teratol 23(4):365-372.

Golub MS, Tarara RP. 1999. Morphometric studies of myelination in the spinal cord of mice exposed developmentally to aluminum. Neurotoxicology 20(3):953-959.

Golub MS, Donald JM, Gershwin ME, et al. 1989. Effects of aluminum ingestion on spontaneous motor activity of mice. Neurotoxicol Teratol 11(3):231-235.

Golub MS, Germann SL, Han B, et al. 2000. Lifelong feeding of a high aluminum diet to mice. Toxicology 150(1-3):107-117.

Golub MS, Gershwin ME, Donald JM, et al. 1987. Maternal and developmental toxicity of chronic aluminum exposure in mice. Fundam Appl Toxicol 8(3):346-357.

Golub MS, Han B, Keen CL, et al. 1994. Auditory startle in Swiss Webster mice fed excess aluminum in diet. Neurotoxicol Teratol 16(4):423-425.

Golub MS, Han B, Keen CL, et al. 1995. Behavioral performance of Swiss Webster mice exposed to excess dietary aluminum during development or during development and as adults. Toxicol Appl Pharmacol 133(1):64-72.

Golub MS, Han B, Keen CL, et al. 1992b. Effects of dietary aluminum excess and manganese deficiency on neurobehavioral endpoints in adult mice. Toxicol Appl Pharmacol 112(1):154-160.

Golub MS, Keen CL, Gershwin ME. 1992a. Neurodevelopmental effect of aluminum in mice: Fostering studies. Neurotoxicol Teratol 14(3):177-182.

Golub MS, Takeuchi PT, Gershwin ME, et al. 1993. Influence of dietary aluminum cytokine production by mitogen-stimulated spleen cells from Swiss Webster mice. Immunopharmacol Immunotoxicol 15(5):605-619.

Gomez M, Domingo JL, Llobet JM, et al. 1986. Short-term oral toxicity study of aluminum in rats. Arch Farmacol Toxicol 12(2-3):145-151.

Gomez M, Domingo JL, Llobet JM. 1991. Developmental toxicity evaluation of oral aluminum in rats: Influence of citrate. Neurotoxicol Teratol 13(3):323-328.

Gomez M, Esparza JL, Domingo JL, et al. 1999. Chelation therapy in aluminum-loaded rats: Influence of age. Toxicology 137(3):161-168.

Gomez M, Sanchez DJ, Llobet JM, et al. 1997. The effect of age on aluminum retention in rats. Toxicology 116(1-3):1-8.

Gorsky JE, Dietz AA. 1978. Determination of aluminum in biological samples by atomic absorption spectrophotometry with a graphite furnace. Clin Chem 24:1485-1490.

Gorsky JE, Dietz AA, Spencer H, et al. 1979. Metabolic balance of aluminum studied in six men. Clin Chem 25(10):1739-1743.

Goyens P, Brasseur D. 1990. Aluminum and infants. (Comment on: Pediatrics 84(6):1105-1107). Pediatrics 86(4):650-652.

Gräske A, Thuvander A, Johannisson A, et al. 2000. Influence of aluminum on the immune system – an experimental study on volunteers. Biometals 13(2):123-133.

Graves AB, Rosner D, Echeverria D, et al. 1998. Occupational exposures to solvents and aluminum and estimated risk of Alzheimer's disease. Occup Environ Med 55:627-633.

Graves AB, White E, Koepsell TD, et al. 1990. The association between aluminum-containing products and Alzheimer's disease. J Clin Epidemiol 43:35-44.

Greger JL. 1992. Dietary and other sources of aluminum intake. Aluminum in biology and medicine. Ciba Found Symp 169:26-49.

Greger JL, Baier MJ. 1983. Excretion and retention of low or moderate levels of aluminum by human subjects. Food Chem Toxicol 21(4):473-477.

Greger JL, Donnaubauer SE. 1986. Retention of aluminum in the tissues of rats after the discontinuation of oral exposure to aluminum. Food Chem Toxicol 24(12):1331-1334.

Greger JL, Sutherland JE. 1997. Aluminum exposure and metabolism. Crit Rev Clin Lab Sci 34(5):439-474.

Griswold WR, Reznik V, Mendoza SA et al. 1983. Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. Pediatr 71(1):56-58.

Hackenberg U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphide. Toxicol Appl Pharmacol 23:147-158.

Haddad CM, Shannon MW, Winchester JF. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders, 186.

Hänninen H, Matikainen E, Kovala T, et al. 1994. Internal load of aluminum and the central nervous system function of aluminum welders. Scand J Work Environ Health 20(4):279-285.

Harris WR, Messori L. 2002. A comparative study of aluminum(III), gallium(III), indium(III), and thallium(III) binding to human serum transferrin. Coord Chem Rev 228:237-262.

Hawkins NM, Coffey S, Lawson MS, et al. 1994. Potential aluminum toxicity in infants fed special infant formula. J Pediatr Gastroenterol Nutr 19(4)377-381.

HazDat. 2006. Aluminum. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/hazdat.html. July 05, 2006.

Hermenegildo C, Saez R, Minoia C, et al. 1999. Chronic exposure to aluminum impairs the glutamate-nitric oxide-cyclic GMP pathway in the rat *in vivo*. Neurochem Int 34(3):245-253.

Heyman A, Wilkinson WE, Stafford JA, et al. 1984. Alzheimer's disease: A study of epidemiological aspects. Ann Neurol 15(4):335-341.

Hoffman GL, Duce RA, Zoller WH. 1969. Vanadium, copper, and aluminum in the lower atmosphere between California and Hawaii. Environ Sci Technol 3:1207-1210.

Hohl C, Gerisch P, Korschinek G, et al. 1994. Medical application of ^{26}Al. Nucl Instr Meth Phys Res B 92:478-482.

Hosovski E, Mastelica Z, Sunderic D, et al. 1990. Mental abilities of workers exposed to aluminum. Med Lav 81(2):119-123.

House RA. 1992. Factors affecting plasma aluminum concentrations in nonexposed workers. J Occup Med 34:1013-1017.

Hovatta O, Venalainen E-R, Kuusimaki L, et al. 1998. Aluminum, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men. Hum Reprod 13(1):115-119.

HSDB. 2006. Aluminum. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. April 06, 2006.

Hull MJ, Abraham JL. 2002. Aluminum welding fume-induced pneumoconiosis. Hum Pathol 33(8):819-825.

IARC. 1984. Polynuclear aromatic compounds. Part 3: Industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding. Vol. 34. Lyon, France: World Health Organization, International Agency for Research on Cancer, 37-64.

Ikem A, Nwankwoala A, Odueyungbo S, et al. 2002. Levels of 26 elements in infant formula from USA, UK, and Nigeria by microwave digestion and ICP-OES. Food Chem 77(4):439-447.

Imahori A, Fukushima I, Shiobara S, et al. 1979. Multielement neutron activation analysis of human scalp hair. A local population survey in the Tokyo metropolitan area. J Radioanal Chem 52(1):167-180.

Iregren A, Sjogren B, Gustafsson K, et al. 2001. Effect on the nervous system in different groups of workers exposed to aluminium. Occup Environ Med 58(7):453-460.

IRIS. 2006. Aluminum phosphide. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/index.html. March 08, 2006.

Jacqmin H, Commenges D, Letenneur L, et al. 1994. Components of drinking water and risk of cognitive impairment in the elderly. Am J Epidemiol 139(1):48-57.

Jacqmin-Gadda H, Commenges D, Letenneur L, et al. 1996. Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 7:281-285.

James BR, Riha SJ. 1989. Aluminum leaching by mineral acids in forest soils: I. Nitric-sulfuric acid differences. Soil Sci Soc Am J 53:259-264.

Jansen S, Broadley MR, Robbrecht E, et al. 2002. Aluminum hyperaccumulation in angiosperms: A review of its phylogenetic significance. Bot Rev 68(2):235-269.

Jederlinic PJ, Abraham JL, Churg A, et al. 1990. Pulmonary fibrosis in aluminum oxide workers. Investigation of nine workers with pathologic examination and microanalysis in three of them. Am Rev Respir Dis 142:1179-1184.

Jeffery EH, Abreo K, Burgess E, et al. 1996. Systemic aluminum toxicity: Effects on bone, hematopoietic tissue, and kidney. J Toxicol Environ Health 48(6):649-665.

Jephcott CM. 1948. Fume exposure in the manufacture of alumina abrasives. Occup Med 5:701-709.

Jing Y, Wang Z, Song Y. 2004. Quantitative study of aluminum-induced changes in synaptic ultrastructure in rats. Synapse 52(4):292-298.

Johnson VJ, Kim SH, Sharma RP. 2005. Aluminum-maltolate induces apoptosis and necrosis in Neuro-2a cells: Potential role for p53 signaling. Toxicol Sci 83(2):329-339.

Jones KC, Bennett BG. 1986. Exposure of man to environmental aluminum-An exposure commitment assessment. Sci Total Environ 52(1-2):65-82.

Jope RS, Johnson GVW. 1992. Neurotoxic effects of dietary aluminum. Aluminum in biology and medicine. Ciba Found Symp 169:254-267.

Julka D, Gill KD. 1995. Development of a possible peripheral marker for aluminum neurotoxicity. Med Sci Res 23:311-314.

Kaehny WD, Hegg AP, Alfrey AC. 1977. Gastrointestinal absorption of aluminum from aluminum-containing antacids. N Engl J Med 296(24):1389-1390.

Kaizer RR, Correa MC, Spanevello RM, et al. 2005. Acetylcholinesterase activation and enhanced lipid peroxidation after long-term exposure to low levels of aluminum on different mouse brain regions. J Inorg Biochem 99(9):1865-1870.

Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat Res 77:109-116.

Katz AC, Frank DW, Sauerhoff MW, et al. 1984. A 6-month dietary toxicity study of acidic sodium aluminum phosphate in beagle dogs. Food Chem Toxicol 22(1):7-9.

Keith LS, Jones DE, Chou C-HSJ. 2002. Aluminum toxicokinetics regarding infant diet and vaccinations. Vaccine S13-S17.

Khosla SN, Nand N, Khosla P. 1988. Aluminum phosphide poisoning. J Trop Med Hyg 91:196-198.

King SW, Savory J, Wills MR. 1981. The clinical biochemistry of aluminum. CRC Crit Rev Clin Lab Sci 14:1-20.

Klein GL, Snodgrass WR, Griffin MP, et al. 1989. Hypocalcemia complicating deferoxamine therapy in an infant with parenteral nutrition-associated aluminum overload: Evidence for a role of aluminum in the bone disease of infants. J Pediatr Gastroenterol Nutr 9:400-403.

Kohila T, Parkkonen E, Tahti H. 2004. Evaluation of the effects of aluminum, ethanol and their combination on rat brain synaptosomal integral proteins *in vitro* and after 90-day oral exposure. Arch Toxicol 78(5):276-282.

Koo WWK, Kaplan LA, Bendon R, et al. 1986. Response to aluminum in parenteral nutrition during infancy. J Pediatr 109(5):877-883.

Koo WWK, Kaplan LA, Krug-Wispe SK. 1988. Aluminum contamination of infant formulas. J Parenter Enteral Nutr 12(2):170-173.

Koo WWK, Krug-Wispe SK, Succop P, et al. 1992. Sequential serum aluminum and urine aluminum: Creatinine ratio and tissue aluminum loading in infants with fractures/rickets. Pediatrics 89(5 Part 1):877-881.

Korogiannos C, Babatsikou F, Tzimas S, et al. 1998. Aluminum compounds and occupational lung disease. Eur Respir J 12(Suppl 28):139S.

Kowalczyk GS, Gordon GE, Rheingrover SW. 1982. Identification of atmospheric particulate sources in Washington, DC, using chemical element balances. Environ Sci Technol 16:79-90.

Krasovskii GN, Vasukovich LY, Chariev OG. 1979. Experimental study of biological effects of lead and aluminum following oral administration. Environ Health Perspect 30:47-51.

Lal B, Gupta A, Gupta A, et al. 1993. Aluminum ingestion alters behaviour and some neurochemicals in rats. Indian J Exp Biol 31(1):30-35.

Lansdown AB. 1973. Production of epidermal damage in mammalian skins by some simple aluminum compounds. Br J Dermatol 89:67-76.

Lantzy RJ, MacKenzie FT. 1979. Atmospheric trace metals: Global cycles and assessment of man's impact. Geochim Cosmochim Acta 43(4):511-525.

Lauricella AM, Garbossa G, Nesse A. 2001. Dissimilar behavior of lymph cells in response to the action of aluminum. *In vitro* and *in vivo* studies. Int Immunopharmacol 1(9-10):1725-1732.

LeGendre GR, Alfrey AC. 1976. Measuring picogram amounts of aluminum in biological tissue by flameless atomic absorption analysis of a chelate. Clin Chem 22:53-56.

Letterman RD, Driscoll CT. 1988. Survey of residual aluminum in filtered water. J Am Water Works Assoc 80(4):154-158.

Lewis RJ, ed. 2001. Hawley's condensed chemical dictionary. New York, NY: John Wiley & Sons, Inc., 39-46, 118, 555.

Lewis C, Macias ES. 1980. Composition of size-fractionated aerosol in Charleston, West Virginia. Atmos Environ 14:185-194.

Liao YH, Yu HS, Ho CK, et al. 2004. Biological monitoring of exposures to aluminium, gallium, indium, arsenic, and antimony in optoelectronic industry workers. J Occup Environ Med 46(9):931-936.

Lide DR, ed. 2005. CRC handbook of chemistry and physics. New York, NY: CRC Press, 4-3 to 4-4, 4-44 to 4-46, 4-79.

Lione A. 1983. The prophylactic reduction of aluminum intake. Food Chem Toxicol 21(1)103-109.

Lione A. 1985. Aluminum intake from non-prescription drugs and sucralfate. Gen Pharmacol 16(3):223-228.

Liss L, Thornton DJ. 1986. The rationale for aluminum absorption control in early stages of Alzheimer's disease. Neurobiol Aging 7(6):552-554.

Litaor MI. 1987. Aluminum chemistry: Fractionation, speciation, and mineral equilibria of soil interstitial waters of an alpine watershed, Front Range, Colorado. Geochim Cosmochim Acta 51:1285-1295.

Litov RE, Sickles VS, Chan GM, et al. 1989. Plasma aluminum measurements in term infants fed human milk or a soy-based infant formula. (Comment in: Pediatrics 86(4):650-652). Pediatrics 84(6):1105-1107.

Llansola M, Minana MD, Montoliu C, et al. 1999. Prenatal exposure to aluminum reduces expression of neuronal nitric oxide synthase and of soluble guanylate cyclase and impairs glutamatergic neurotransmission in rat cerebellum. J Neurochem 73(2):712-718.

Llobet JM, Domingo JL, Gomez M, et al. 1987. Acute toxicity studies of aluminum compounds: Antidotal efficacy of several chelating agents. Pharmacol Toxicol 60:280-283.

Lovell MA, Ehmann WD, Markesbery WR. 1993. Laser microprobe analysis of brain aluminum in Alzheimer's disease. Ann Neurol 33(1):36-42.

MAFF. 1999. MAFF UK - 1997 Total diet study: Aluminium, arsenic, cadmium, chromium, copper, lead, mercury, nickel, selenium, tin and zinc. Ministry of Agriculture, Fisheries and Food. Joint Food Safety and Standards Group. Food Surveillance Information Sheet Number 191. http://archive.food.gov.uk/maff/archive/food/infsheet/1999/no191/191tds.htm. June 06, 2006.

Maitani T, Kubota H, Hori N, et al. 1994. Distribution and urinary excretion of aluminum injected with several organic acids into mice: Relationship with chemical state in serum studied by the HPLC-ICP method. J Appl Toxicol 14(4):257-261.

Makjanic J, McDonald B, Chen CPLH, et al. 1998. Absence of aluminum in neurofibrillary tangles in Alzheimer's disease. Neurosci Lett 240(3):123-126.

Mandić ML, Grgic J, Grgic Z, et al. 1995. Aluminum levels in human milk. Sci Total Environ 170:165-170.

Manna GK, Das RK. 1972. Chromosome aberrations in mice induced by aluminum chloride. Nucleus 15:180-186.

Markesbery WR, Ehmann WD, Alauddin M, et al. 1984. Brain trace element concentrations in aging. Neurobiol Aging 5:19-28.

Martell AE, Motekaitis RJ. 1989. Coordination chemistry and speciation of Al (III) in aqueous solution. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum. Chelsea, MI: Lewis Publishers, Inc., 3-17.

Martin RB. 1986. The chemistry of aluminum as related to biology and medicine. Clin Chem 32(10):1797-1806.

Martyn CN, Coggon DN, Inskip H, et al. 1997. Aluminum concentrations in drinking water and risk of Alzheimer's disease. Epidemiol 8:281-286.

Martyn CN, Osmond C, Edwardson JA, et al. 1989. Geographical relation between Alzheimer's disease and aluminum in drinking water. Lancet 1(8629):59-62.

Marzin DR, Phi HV. 1985. Study of the mutagenicity of metal derivatives with *Salmonella-typhimurium* TA102m. Mutat Res 155(1-2):49-51.

Mayor GH, Lohr TO, Sanchez TV, et al. 1985. Aluminum metabolism and toxicity in renal failure: A review. J Environ Pathol Toxicol Oncol 6(1):43-50.

McCormack KM, Ottosen LD, Sanger VL, et al. 1979. Effect of prenatal administration of aluminum and parathyroid hormone on fetal development in the rat (40493). Proc Soc Exp Biol Med 161:74-77.

McDowell I, Hill G, Lindsay J, et al. 1994. The Canadian study of health and aging: Risk factors for Alzheimer's disease in Canada. Neurology 44:2073-2080.

McLachlan DRC, Bergeron C, Smith JE, et al. 1996. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. Neurology 46(2):401-405.

McLaughlin AIG, Kazantzis G, King E, et al. 1962. Pulmonary fibrosis and encephalopathy associated with the inhalation of aluminum dust. Br J Ind Med 19:253-263.

Michel P, Commenges D, Dartigues JF, et al. 1990. Study of the relationship between Alzheimer's disease and aluminum in drinking water. Neurobiol Aging 11:264.

Milham S Jr. 1979. Mortality in aluminum reduction plant workers. J Occup Med 21(7):475-480.

Miller RG, Kopfler FC, Kelty KC, et al. 1984a. The occurrence of aluminum in drinking water. J Am Water Works Assoc 76:84-91.

Miller RR, Churg AM, Hutcheon M, et al. 1984b. Pulmonary alveolar proteinosis and aluminum dust exposure. Am Rev Respir Dis 130(2):312-315.

Milliner DS, Malekzadeh M, Lieberman E, et al. 1987. Plasma aluminum levels in pediatric dialysis patients: Comparison of hemodialysis and continuous ambulatory peritoneal dialysis. Mayo Clin Proc 62(4):269-274.

Misawa T, Shigeta S. 1992. Behavioral effects of repeated aluminum administration in the rat. Tokai J Exp Clin Med 17:155-159.

Missel JR, Schetinger MR, Gioda CR, et al. 2005. Chelating effect of novel pyrimidines in a model of aluminum intoxication. J Inorg Biochem 99(9):1853-1857.

Mitchell J, Manning GB, Molyneux M, et al. 1961. Pulmonary fibrosis in workers exposed to finely powdered aluminum. Br J Ind Med 18:10-20.

Montoliu C, Felipo V. 2001. Aluminum interferes with NMDA receptor-associated signal transduction and with the process of glutamate neurotoxicity in cerebellar neurons in culture. Neurotoxicology 22(4):535.

Moreno A, Dominguez C, Ballabriga A. 1994. Aluminum in the neonate related to parenteral nutrition. Acta Paediatr 83(1):25-29.

Moyers JL, Ranweiler LE, Hopf SB, et al. 1977. Evaluation of particulate trace species in Southwest desert atmosphere. Environ Sci Technol 11(8):789-795.

Mulder J, Vanbreemen N, Eijck HC. 1989. Depletion of soil aluminum by acid deposition and implications for acid neutralization. Nature 337:247-249.

Muller G, Bernuzzi V, Desor D, et al. 1990. Developmental alterations in offspring of female rats orally intoxicated by aluminum lactate at different gestation periods. Teratology 42(3):253-261.

Mundy WR, Freudenrich T, Shafer TJ, et al. 1995. *In vitro* aluminum inhibition of brain phosphoinositide metabolism: Comparison of neonatal and adult rats. Neurotoxicology 16:35-44.

Mur JM, Moulin JJ, Meyer-Bisch C, et al. 1987. Mortality of aluminum reduction plant workers in France. Int J Epidemiol 16:257-264.

Musk AW, Greeville HW, Tribe AE. 1980. Pulmonary disease from occupational exposure to an artificial aluminum silicate used for cat litter. Br J Ind Med 37(4):367-372.

Mussi I, Calzaferri G, Buratti M, et al. 1984. Behaviour of plasma and urinary aluminum levels in occupationally exposed subjects. Int Arch Occup Environ Health 54(2):155-161.

Navarro-Blasco I, Alvarez-Galindo JI. 2003. Aluminum content of Spanish infant formula. Food Addit Contam 20(5):470-481.

Nayak P. 2002. Aluminum: Impacts and disease. Environ Res 89(2):101-115.

Naylor KE, Eastell R, Shattuck KE, et al. 1999. Bone turnover in preterm infants. Pediatr Res 45(3):363-363.

Nehru B, Anand P. 2005. Oxidative damage following chronic aluminium exposure in adult and pup rat brains. J Trace Elem Med Biol 19(2-3):203-208.

Neri LC, Hewitt D. 1991. Aluminum, Alzheimer's disease, and drinking water. Lancet 338(8763):390.

Nieboer E, Gibson BL, Oxman AD, et al. 1995. Health effects of aluminum: A critical review with emphasis on aluminum in drinking water. Environ Rev 3(1):29-81.

NIOSH. 1991. National occupational exposure survey matrix. Cincinnati, OH: Department of Health and Human Services, National Institute for Occupational Safety and Health. December 11, 1996.

NIOSH. 1994. Method 7013: Aluminum and compounds, as Al. NIOSH manual of analytical methods (NMAM). Washington, DC: National Institute for Occupational Safety and Hazards. http://www.cdc.gov/niosh/nmam/pdfs/7013.pdf. March 21, 2006.

NIOSH. 2003a. Method 7300: Elements by ICP (nitric/perchloric acid ashing). NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication 94-113. http://www.cdc.gov/niosh/nmam/pdfs/7300.pdf. March 21, 2006.

NIOSH. 2003b. Method 7303: Elements by ICP (hot block/HCl/HNO3 digestion). NIOSH manual of analytical methods (NMAM). Washington, DC: National Institute for Occupational Safety and Hazards. http://www.cdc.gov/niosh/nmam/pdfs/7303.pdf. March 21, 2006.

NIOSH. 2003c. Method 7301: Elements by ICP (aqua regia ashing). NIOSH manual of analytical methods (NMAM). Washington, DC: National Institute for Occupational Safety and Hazards. http://www.cdc.gov/niosh/nmam/pdfs/7301.pdf. March 21, 2006.

Nostrandt AC, Shafer TJ, Mundy WR, et al. 1996. Inhibition of rat brain phosphatidylinositol-specific phospholipase C by aluminum: Regional differences, interactions with aluminum salts, and mechanisms. Toxicol Appl Pharmacol 136(1):118-125.

NTP. 2005. Report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. March 08, 2006.

Omokhodion FO, Howard JM. 1994. Trace elements in the sweat of acclimatized persons. Clin Chim Acta 231(1):23-28.

Ondov JM, Zoller WH, Gordon GE. 1982. Trace element emissions of aerosols from motor vehicles. Environ Sci Technol 16(6):318-328.

Ondreicka R, Ginter E, Kortus J. 1966. Chronic toxicity of aluminum in rats and mice and its effects on phosphorus metabolism. Br J Ind Med 23(4):305-312.

Oneda S, Takasaki T, Kuriwaki K, et al. 1994. Chronic toxicity and tumorigenicity study of aluminum potassium sulfate in B6C3F1 mice. In Vivo 8(3):271-278.

O'Neil MJ, Smith A, Heckelman PE, et al. 2001. Aluminum and aluminum compounds. The Merck index. An encyclopedia of chemicals, drugs, and biologicals. Whitehouse Station, NJ: Merck & Co., Inc., 59-65.

OSHA. 2001. Method ID-109-SG: Aluminum oxide in workplace atmospheres. Sampling and analytical methods. Occupational Safety and Health Administration. U.S. Department of Labor. http://www.osha.gov/dts/sltc/methods/inorganic/t-id109sg-pv-02-0110-m/t-id109sg-pv-02-0110-m.html. March 07, 2006.

OSHA. 2002. Method ID-121: Metal and metalloid particulates in workplace atmospheres (atomic absorption). Sampling and analytical methods. Occupational Safety and Health Administration. U.S. Department of Labor. http://www.osha.gov/dts/sltc/methods/inorganic/id121/id121.html. March 21, 2006.

Oteiza PI, Keen CL, Han B, et al. 1993. Aluminum accumulation and neurotoxicity in Swiss-Webster mice after long-term dietary exposure to aluminum and citrate. Metabolism 42(10):1296-1300.

Owen LMW, Crews HM, Bishop NJ, et al. 1994. Aluminum uptake from some foods by guinea pigs and the characterization of aluminum in *in vivo* intestinal digesta by SEC-ICP-MS. Food Chem Toxicol 32(8):697-705.

Paternain JL, Domingo JL, Llobet JM, et al. 1988. Embryotoxic and teratogenic effects of aluminum nitrate in rats upon oral administration. Teratology 38:253-257.

Pennington JAT. 1987. Aluminum content of foods and diets. Food Addit Contam 5(2):161-232.

Pennington JAT, Schoen SA. 1995. Estimates of dietary exposure to aluminum. Food Addit Contam 12(1):119-128.

Pettersen JC, Hackett DS, Zwicker GM, et al. 1990. Twenty-six week toxicity study with KASAL (basic sodium aluminum phosphate) in beagle dogs. Environ Geochem Health 12(1-2):121-123.

Pigott GH, Gaskell BA, Ishmael J. 1981. Effects of long term inhalation of alumina fibres in rats. Br J Exp Pathol 62(3):323-331.

Pillay KKS, Thomas CC Jr. 1971. Determination of the trace element levels in atmospheric pollutants by neutron activation analysis. J Radioanal Chem 7:107-118.

Pivnick EK, Kerr NC, Kaufman RA, et al. 1995. Rickets secondary to phosphate depletion: A sequela of antacid use in infancy. Clin Pediatr 34(2):73-78.

Plankey BJ, Patterson HH. 1987. Kinetics of aluminum-fulvic acid complexation in acidic waters. Environ Sci Technol 21:595-601.

Polizzi S, Pira E, Ferrara M, et al. 2001. Neurotoxic effects of aluminum among foundry workers. Neurotoxicology 22(4):540.

Polizzi S, Pira E, Ferrara M, et al. 2002. Neurotoxic effects of aluminum among foundry workers and Alzheimer's disease. Neurotoxicology 23(6):761-774.

Pötzl K. 1970. Inorganic chemical analyses of nonpolluted aerosols sample at 1800 meters altitude. J Geophys Res 75:2347-2352.

Priest ND. 1993. Satellite symposium on 'Alzheimer's disease and dietary aluminum': The bioavailability and metabolism of aluminum compounds in man. Proc Nutr Soc 52:231-240.

Priest ND. 2004. The biological behaviour and bioavailability of aluminum in man, with special reference to studies employing aluminum-26 as a tracer: Review and study update. J Environ Monit 6(5):375-403.

Priest ND, Talbot RJ, Newton D, et al. 1998. Uptake by man of aluminum in a public water supply. Hum Exp Toxicol 17(6):296-301.

Que Hee SS, Igwe OJ, Boyle JR. 1988. Elemental alterations during the exposure of 1,2-dichloroethane (EDC), disulfiram (DSF), and EDC-DSF to male Sprague-Dawley rats. Biol Trace Elem Res 18:61-80.

Radon K, Nowak D, Szadkowski D. 1999. Lack of combined effects of exposure and smoking on respiratory health in aluminium potroom workers. Occup Environ Med 56(7):468-472.

Razniewska G, Trzcinka-Ochocka M. 2003. ET-AAS as a method for determination of aluminum in blood serum and urine. Chem Analityczna 48:107-113.

Recker RR, Blotcky AJ, Leffler JA, et al. 1977. Evidence for aluminum absorption from the gastrointestinal tract and bone deposition by aluminum carbonate ingestion with normal renal function. J Lab Clin Med 90:810-815.

Riddell AR. 1948. Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:710-717.

Rifat SL, Eastwood MR, Crapper-McLachlan DR, et al. 1990. Effect of exposure of miners to aluminum powder. Lancet 336(8724):1162-1165.

Riihimäki V, Hanninen H, Akila R. 2000. Body burden of aluminum in relation to central nervous system function among metal inert-gas welders. Scand J Work Environ Health 26(2):118-130.

Robinson MJ, Ryan SW, Newton CJ, et al. 1987. Blood aluminium levels in preterm infants fed parenterally or with cows' milk formulae. Lancet 2(8569):1206.

Rockette HE, Arena VC. 1983. Mortality studies of aluminum reduction plant workers: Potroom and carbon department. J Occup Med 25:549-557.

Rodella L, Ricci F, Borsani E, et al. 2004. Exposure to aluminium decreases nitric oxide synthetase expression in the rat cerebral cortex in time dependent manner. J Histochem Cytochem 52(Suppl 1):S25.

Roig JL, Fuentes S, Teresa CM, et al. 2006. Aluminum, restraint stress and aging: Behavioral effects in rats after 1 and 2 years of aluminum exposure. Toxicology 218(2-3):112-124.

Rondeau V, Commenges D, Jacqmin-Gadda H, et al. 2000. Relation between aluminum concentrations in drinking water and Alzheimer's disease: An 8-year follow-up study. Am J Epidemiol 152(1):59-66.

Rondeau V, Jacamin-Gadda H, Commenges D, et al. 2001. Aluminum in drinking water and cognitive decline in elderly subjects: The Paquid cohort. (Comment on: Am J Epidemiol 153(7):695-703). Am J Epidemiol 154(3):288-290.

Roodhooft AM, van de Vyver FL, D'Haese PC, et al. 1987. Aluminum accumulation in children on chronic dialysis: Predictive value of serum aluminum levels and desferrioxamine infusion test. Clin Nephrol 28(3):125-129.

Rosseland BO, Eidhuset TD, Staurnes M. 1990. Environmental effects of aluminum. Environ Geochem Health 12:17-27.

Saiyed SM, Yokel RA. 2005. Aluminum content of some foods and food products in the USA, with aluminum food additives. Food Addit Contam 22(3):234-244.

Salib E, Hillier V. 1996. A case-control study of Alzheimer's disease and aluminum occupation. Br J Psychiatry 168(2):244-249.

Salusky IB, Coburn JW, Foley J, et al. 1986. Effects of oral calcium carbonate on control of serum phosphorus and changes in plasma aluminum levels after discontinuation of aluminum-containing gels in children receiving dialysis. J Pediatr 108(5 Part 1):767-770.

Salusky IB, Coburn JW, Nelson P, et al. 1990. Prospective evaluation of aluminum loading from formula in infants with uremia. J Pediatr 116:726-729.

Sanz-Medel A, Roza RR, Alonso RG, et al. 1987. Atomic spectrometric methods (atomic absorption and inductively coupled plasma atomic emission) for the determination of aluminum at the parts per billion level in biological fluids. J Anal Atom Spectrom 2(2):177-184.

Sarin S, Julka D, Gill KD. 1997. Regional alterations in calcium homeostasis in the primate brain following chronic aluminum exposure. Mol Cell Biochem 168:95-100.

Schenk RU, Bjorksten J, Yeager L. 1989. Composition and consequences of aluminum in water, beverages and other ingestibles. In: Lewis TE, ed. Environmental chemistry and toxicology of aluminum. Chelsea, MI: Lewis Publishers, Inc., 247-269.

Schroeder HA, Mitchener M. 1975a. Life-term studies in rats: Effects of aluminum, barium beryllium and tungsten. J Nutr 105(4):421-427.

Schroeder HA, Mitchener M. 1975b. Life-term effects of mercury, methyl, mercury, and nine other trace metals on mice. J Nutr 105:452-458.

Shafer TJ, Mundy WR. 1995. Effects of aluminum on neuronal signal transduction: Mechanisms underlying disruption of phosphoinositide hydrolysis. Gen Pharmacol 26(5):889-895.

Sharma P, Mishra KP. 2006. Aluminum-induced maternal and developmental toxicity and oxidative stress in rat brain: Response to combined administration of Tiron and glutathione. Reprod Toxicol 21(3):313-321.

Shaver CG. 1948. Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:718-728.

Shaver CG, Riddell AR. 1947. Lung changes associated with the manufacture of alumina abrasives. J Ind Hyg Toxicol 29:145-157.

Sighinolfi GP, Gorgoni C, Bonori O, et al. 1989. Comprehensive determination of trace elements in human saliva by ETA-AAS. Mikrochim Acta 97(3-4):171-179.

Sim M, Dick R, Russo J, et al. 1997. Are aluminum potroom workers at increased risk of neurological disorders? Occup Environ Med 54(4):229-235.

Simmer K, Fudge A, Teubner J, et al. 1990. Aluminum concentrations in infant formulae. J Paediatr Child Health 26(1):9-11.

Simonsson BG, Sjoberg A, Rolf C, et al. 1985. Acute and long-term airway hyperreactivity in aluminum-salt exposed workers with nocturnal asthma. Eur J Respir Dis 66:105-118.

Sjögren B, Elinder C-G, Lidums V, et al. 1988. Uptake and urinary excretion of aluminum among welders. Int Arch Occup Environ Health 60(2):77-79.

Sjögren B, Gustavsson P, Hogstedt C. 1990. Neuropsychiatric symptoms among welders exposed to neurotoxic metals. Br J Ind Med 47(10):704-707.

Sjögren B, Lidums V, Hakansson M, et al. 1985. Exposure and urinary excretion of aluminum during welding. Scand J Work Environ Health 11(1):39-43.

Sjögren B, Ljunggren KG, Almkvist O, et al. 1996. A follow-up study of five cases of aluminosis. Int Arch Occup Environ Health 68(3):161-164.

Sohn S-J, Shin J-H, Park Y-S, et al. 1996. Components of drinking water and risk of cognitive impairment in the rural elderly. Chonnam J Med Sci 9(2):189-193.

Soni MG, White SM, Flamm WG, et al. 2001. Safety evaluation of dietary aluminum. Regul Toxicol Pharmacol 33(1):66-79.

Sorenson JRJ, Campbell IR, Tepper LB, et al. 1974. Aluminum in the environment and human health. Environ Health Perspect 8:3-95.

Staley JT, Haupin W. 1992. Aluminum and aluminum alloys. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 2: Alkanolamines to antibiotics (glycopeptides). New York: John Wiley & Sons, Inc., 248-249.

Stauber JL, Florence TM, Davies CM, et al. 1999. Bioavailability of Al in alum-treated drinking water. J Am Water Works Assoc 91(11):84-93.

Steinhagen WH, Cavender FL, Cockrell BY. 1978. Six month inhalation exposures of rats and guinea pigs to aluminum chlorhydrate. J Environ Pathol Toxicol 1:267-277.

Steinhausen C, Kislinger G, Winklhofer C, et al. 2004. Investigation of the aluminum biokinetics in humans: A 26Al tracer study. Food Chem Toxicol 42(3):363-371.

Stevens RK, Dzubay TG, Russwurm G, et al. 1978. Sampling and analysis of atmospheric sulfates and related species. Atmos Environ 12:55-68.

Stone CJ, McLaurin DA, Steinhagen WH, et al. 1979. Tissue deposition patterns after chronic inhalation exposures of rats and guinea pigs to aluminum chlorhydrate. Toxicol Appl Pharmacol 49:71-76.

Strong MJ, Garruto RM, Joshi JG, et al. 1996. Can the mechanisms of aluminum neurotoxicity be integrated into a unified scheme? J Toxicol Environ Health 48:599-613.

Suarez-Fernandez MB, Soldado AB, Sanz-Medel A, et al. 1999. Aluminum-induced degeneration of astrocytes occurs via apoptosis and results in neuronal death. Brain Res 835(2):125-136.

Theriault G, Cordier S, Tremblay C, et al. 1984a. Bladder cancer in the aluminum industry. Lancet 1(8383):947-950.

Thomson SM, Burnett DC, Bergmann JD, et al. 1986. Comparative inhalation hazards of aluminum and brass powders using bronchopulmonary lavage as an indicator of lung damage. J Appl Toxicol 6(3):197-209.

TRI04. 2006. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. March 16, 2006.

Ueda M, Mizoi Y, Maki Z, et al. 1958. A case of aluminum dust lung: A necropsy report. Kobe J Med Sci 4:91-99.

USGS. 1984. Element concentrations in soils and other surficial materials of the conterminous United States. Alexandria, VA: U.S. Geological Survey. Geological Survey Professional Paper 1270.

USGS. 1996. Method I-1472-95: Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory. Determination of dissolved aluminum and boron in water by inductively coupled plasma-atomic emission spectrometry. Denver, CO: U.S. Geological Survey. Open-File Report 96-149. http://web1.er.usgs.gov/nemi/method_pdf/8915.pdf. March 21, 2006.

USGS. 2003. Bauxite and alumina. Minerals yearbook: Vol. I. Metals and minerals. U.S. Geological Survey.

USGS. 2004. Aluminum. Minerals yearbook: Vol. I. Metals and minerals. U.S. Geological Survey.

USGS. 2006. Aluminum. Mineral Commodity Summaries, January 2006. U.S. Geological Survey.

Valkonen S, Aitio A. 1997. Analysis of aluminum in serum and urine for the biomonitoring of occupational exposure. Sci Total Environ 199:103-110.

Vallyathan V, Berferon WN, Robichaux PA, et al. 1982. Pulmonary fibrosis in an aluminum arc welder. Chest 81(3):372-374.

Vandenplas O, Delwiche JP, Vanbilsen ML, et al. 1998. Occupational asthma caused by aluminum welding. Eur Resp J 11(5):1182-1184.

van der Voet GB, de Haas EJM, de Wolff FA. 1985. Monitoring of aluminum in whole blood, plasma, serum, and water by a single procedure using flameless atomic absorption spectrophotometry. J Anal Toxicol 9:97-100.

Van Landeghem GF, D'Haese PC, Lamberts LV, et al. 1994. Quantitative HPLC/ETAAS hybrid method with an on-line metal scavenger for studying the protein binding and speciation of aluminum and iron. Anal Chem 66(2):216-222.

Varner JA, Horvath WJ, Huie CW, et al. 1994. Chronic aluminum fluoride administration. 1. Behavioral observations. Behav Neural Biol 61(3):233-241.

Varner JA, Huie C, Horvath W, et al. 1993. Chronic AlF3 administration: II. Selected histological observations. Neurosci Res Commun 13(2):99-104.

Varner JA, Jensen KF, Horvath W, et al. 1998. Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water: Alterations in neuronal and cerebrovascular integrity. Brain Res 784(1-2):284-298.

Veien NK, Hattel T, Justesen O, et al. 1986. Aluminum allergy. Contact Dermatitis 15:295-297.

Versieck J, Cornelis R. 1980. Measuring aluminum levels. N Engl J Med 302(8):468-469.

Vittori D, Nesse A, Perez G, et al. 1999. Morphologic and functional alterations of erythroid cells induced by long-term ingestion of aluminum. J Inorg Biochem 76(2):113-120.

von Stockhausen HB, Schrod L, Bratter P, et al. 1990. Aluminum loading in premature infants during intensive care as related to clinical aspects. J Trace Elem Electrolytes Health Dis 4:209-213.

Walker WJ, Cronan CS, Patterson HH. 1988. A kinetic-study of aluminum adsorption by aluminosilicate clay-minerals. Geochim Cosmochim Acta 52:55-62.

Wangen LE, Jones MM. 1984. The attenuation of chemical elements in acidic leachates from coal mineral wastes by soils. Environ Geol Water Sci 6:161-170.

Ward NI. 1989. Environmental contamination of aluminum and other elements in North Cornwall as a result of the Lowermoor water treatment works incident. In: Vernet J-P, ed. Heavy metals in the environment. Edinburgh: CEP Consultants, 118-121.

Wawschinek O, Petek W, Lang J, et al. 1982. The determination of aluminum in human plasma. Mikrochim Acta 1:335-339.

Weberg R, Berstad A. 1986. Gastrointestinal absorption of aluminum from single doses of aluminum containing antacids in man. Eur J Clin Invest 16(5):428-432.

Wedrychowski A, Schmidt WN, Hnilica LS. 1986. The in-vivo cross-linking of proteins and DNA by heavy metals. J Biol Chem 261(7):3370-3376.

Weintraub R, Hams G, Meerkin M, et al. 1986. High aluminum content of infant milk formulas. Arch Dis Child 61(9):914-916.

Wettstein A, Aeppli J, Gautschi K, et al. 1991. Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. Int Arch Occup Environ Health 63(2):97-103.

White DM, Longstreth WTJ, Rosenstock L, et al. 1992. Neurologic syndrome in 25 workers from an aluminum smelting plant. Arch Intern Med 152:1443-1448.

Wigle DT. 1977. Bladder cancer: possible new high risk occupation. Lancet 2(8028):83-84.

Wills MR, Savory J. 1989. Aluminum and chronic renal failure: Sources, absorption, transport, and toxicity. CRC Crit Rev Clin Lab Sci 27(1):59-107.

Wood CM, McDonald DG, Ingersoll CG, et al. 1990. Effects of water acidity, calcium, and aluminum on whole body ions of brook trout (*Salvelinus fontinalis*) continuously exposed from fertilization to swim-up: A study by instrumental neutron activation analysis. Can J Fish Aquat Sci 47(8):1593-1603.

Wood DJ, Cooper C, Stevens J, et al. 1988. Bone mass and dementia in hip fracture patients from areas with different aluminum concentrations in water supplies. Age Ageing 17(6):415-419.

Woodson GC. 1998. An interesting case of osteomalacia due to antacid use associated with stainable bone aluminum in a patient with normal renal function. Bone 22(6):695-698.

Wrobel K, Gonzalez EB, Wrobel K, et al. 1995. Aluminum and silicon speciation in human serum by ion-exchange high-performance liquid chromatography-electrothermal atomic absorption spectrometry and gel electrophoresis. Analyst 120(3):809-815.

Xu N, Majidi V, Markesbery WR, et al. 1992. Brain aluminum in Alzheimer's disease using an improved GFAAS method. Neurotoxicology 13(4):735-743.

Yokel RA, McNamara PJ. 2001. Aluminium toxicokinetics: An updated minireview. Pharmacol Toxicol 88(4):159-167.

Yokel RA, Meurer KA, Hong CB, et al. 1997. Short-term oral 3-hydroxypyridin-4-one dosing increases aluminum excretion and partially reverses aluminum-induced toxicity in the rabbit independent of chelator lipophilicity. Drug Metab Dispos 25(2):182-190.

Yokel RA, Rhineheimer SS, Sharma P, et al. 2001. Entry, half-life, and desferrioxamine-accelerated clearance of brain aluminum after a single ^{26}Al exposure. Toxicol Sci 64(1):77-82.

Yoshida S, Gershwin ME, Keen CL, et al. 1989. The influence of aluminum on resistance to *Listeria monocytogenes* in Swiss-Webster mice. Int Arch Allergy Appl Immunol 89:404-409.

Zafar TA, Weaver CM, Martin BR, et al. 1997. Aluminum (Al^{26}) metabolism in rats. Proc Soc Exp Biol Med 216(1):81-85.

Zatta P, Ibn-Lkhayat-Idrissi M, Zambenedetti P, et al. 2002. *In vivo* and *in vitro* effects of aluminum on the activity of mouse brain acetylcholinesterase. Brain Res Bull 59(1):41-45.

Zhang ZJ, Qian YH, Hu HT, et al. 2003. The herbal medicine *Dipsacus asper wall* extract reduces the cognitive deficits and overexpression of β-amyloid protein induced by aluminum exposure. Life Sci 73(19):2443-2454.

Zheng W. 2001. Neurotoxicology of the brain barrier system: New implications. J Toxicol Clin Toxicol 39(7):711-719.

Zhou Y, Yokel RA. 2005. The chemical species of aluminum influence its paracellular flux across and uptake into Caco-2 cells, a model of gastrointestinal absorption. Toxicol Sci 87(1):15-26.

Table 1. Exposure Data Needs

Exposure	Level I	Level II	Level III
Analytical	Methods for parent compound in REM*	Methods for degradation products in REM*	
	Methods for parent compound in blood or urine	Methods for parent compound/metabolites/biomarkers	
	Structure-activity relationships (SAR)		
Physical chemical properties	Water solubility		
	Volatility/vapor pressure		
	K_{ow}		
	Henry's law		Registries of exposed persons
Exposure levels	Production volume ⎤ may be	Monitoring in REM*	Human dosimetry studies
	⎟ used in lieu		
	Use ⎟ of monitor-	Monitoring for human exposure (personal	Epidemiology
	⎟ ing data	sampling, biomarkers of	Disease registries
	Release/ ⎦	exposure, tissue levels)	
	disposal		
		Exposures of children	
Environmental fate	Aerobic/anaerobic Biodegradation in H_2O Oxidation Hydrolysis Aerosolization Photoreactivity Volatilization Soil adsorption/desorption	Small field plot studies Monitoring for products in REM*	
Bioavailability		Food chain bioaccumulation	
		Availability from REM* (analytical or toxicity) emphasize *in vivo*	

*REM = Relevant Environmental Media

Table 2. Toxicity Data Needs

Toxicity	Level I	Level II	Level III
Single dose exposure	Single dose disposition Skin/eye irritation Acute toxicity		
Repeated dose exposure	14-day by relevant route 90-day subchronic	Comparative toxicokinetics*	
Chronic exposure	Structure-activity relationships (SAR)	1-Year chronic 2-Year bioassay	Epidemiology*
Genotoxicity*	Ames Micronucleus	Additional genotoxicity studies*	Mechanism of toxic action*
Endocrine disruption	*In vivo* & *in vitro* screen	2-Generation reproductive study	
Reproductive toxicity	Extended repro workup in subchronic	2-Generation or continuous breeding	Biomarkers*
			Clinical methods for mitigating toxicity*
Developmental toxicity*	Short term *in vivo* screen*	2-Species developmental*	Children's susceptibility**
Immunotoxicity	Use subchronic results	Immunotox battery	
Neurotoxicity	Neuropath in subchronic	Neurotox battery	
Sensitization	Dermal sensitization		
Carcinogenicity	Use muta & subchronic results	2-Year bioassay	

*Useful data for examining children's susceptibility issues

**Data needed for addressing children's susceptibility issues include genotoxicity (Level II), developmental toxicity (Levels I and II), epidemiology, mechanism of toxic action, biomarkers, and clinical methods for mitigating toxicity (Level III)

Table 3. ATSDR Substance-Specific Applied Research Program for Aluminum

	EXPOSURE		
	Level I	Level II	Level III
Analytical			
Physical chemical properties	prop of aluminum compounds		
Exposure levels		exp levels in env media	potential candidate for exposure registry
		EXP LEVELS IN HUMANS	
		EXP LEVELS IN CHILDREN	
		bioavailability potential	
Environmental fate			
Bioavailability			
	TOXICITY		
	Level I	Level II	Level III
Acute	inhal, *ORAL*, dermal		
Repeated	inhal, dermal	toxicokinetics	
Chronic		inhal, oral, dermal	epidem
Genotoxicity		*In vivo* genotoxicity studies	mechanisms
Endocrine disruption	*in vitro* and *in vivo* screen		
Reproductive toxicity			biomarkers
			mitigation
Developmental toxicity		inhal, oral, dermal	
Children's susceptibility			inhal, oral, dermal
Immunotoxicity	inhal, oral, dermal immune function test		
Neurotoxicity	inhal, oral, dermal		
Carcinogenicity		inhal, oral, dermal	

UPPER CASE: Priority Data Needs identified for aluminum