

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of aluminum. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Once mineral-bound aluminum is recovered from ores, it forms metal compounds, complexes, or chelates. Examples of the different forms of aluminum include aluminum oxide, aluminum chlorhydrate, aluminum hydroxide, aluminum chloride, aluminum lactate, aluminum phosphate, and aluminum nitrate. The metal itself is also used. With the exception of aluminum phosphide, the anionic component does not appear to influence toxicity, although it does appear to influence bioavailability. Aluminum phosphide, which is used as a pesticide, is more dangerous than the other forms; however, this is because of the evolution of phosphine gas (a potent respiratory tract and systemic toxin) rather than to the exposure to aluminum.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

3. HEALTH EFFECTS

considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located regarding death following acute- or intermediate-duration inhalation exposure to various forms of aluminum in humans.

Several deaths have been reported after occupational exposure to a finely powdered metallic aluminum used in paints, explosives, and fireworks (Mitchell et al. 1961); it should be noted that changes in production technology have resulted in decreased occupational exposures to finely powdered aluminum. In one case, a 19-year-old male who worked in an atmosphere heavily contaminated with this powder developed dyspnea after 2.5 years. This symptom grew worse, and the man had to stop working 3 months later and died after a further 8 months. Before death, respiratory excursion was poor and chest X-rays showed signs of pulmonary nodular interstitial fibrosis. Of a total of 27 workers examined in this factory,

3. HEALTH EFFECTS

2 died and 4 others had radiological changes on chest X-rays. Total dust in the workplace air was 615–685 mg Al/m³, and respirable dust was 51 mg Al/m³. Chemical analysis showed the dust to be 81% metallic aluminum and 17% various oxides and hydroxides of aluminum. There have also been a number of case reports of deaths of workers exposed to aluminum flake powder (McLaughlin et al. 1962), welding fumes (Hull and Abraham 2002), or smelter fumes (Gilks and Churg 1987); it is likely that the cause of death in these men was respiratory tract damage.

No studies were located that evaluated death from an intermediate-duration inhalation exposure in animals to aluminum or its compounds. Of the experiments performed in animals, none has shown death from inhalation exposure to aluminum or its compounds. For example, no deaths were reported following an acute 4-hour exposure to up to 1,000 mg Al/m³ as aluminum oxide in groups of 12–18 male Fischer 344 rats (Thomson et al. 1986) or following chronic exposure to 2.18–2.45 mg Al/m³ as refractory alumina fiber for 86 weeks in groups of 50 male and female Wistar rats (Pigott et al. 1981).

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, dermal, or body weight effects in humans or metabolic effects in animals after acute-duration inhalation exposure to various forms of aluminum.

The highest NOAEL values and all LOAEL values for inhalation exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. No studies were located regarding respiratory effects following acute-duration inhalation exposure to various forms of aluminum in humans.

A number of studies have examined the potential for airborne aluminum to induce respiratory effects in chronically exposed workers. Exposure to aluminum fumes and dust occurs in potrooms where hot aluminum metal is recovered from ore, in foundries where aluminum alloys are melted and poured into molds, in welding operations, and the production and use of finely powdered aluminum. Because these workers were also exposed to a number of other toxic chemicals including sulfur dioxide, polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, hydrogen fluoride, and chlorine, it is difficult to ascribe the respiratory effects to aluminum. Wheezing, dyspnea, and/or impaired lung function have been

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		
ACUTE EXPOSURE								
Systemic								
1	Rat (Fischer- 344)	5 x 4 hr	Resp	10 M	200 M (multifocal microgranulomas in lungs)		Thomson et al. 1986 Aluminum flakes	
					50 M (increased lactate dehydrogenase, glucose-6-phosphate dehydrogenase, and alkaline phosphatase activity in lavage fluid)			
2	Hamster (Golden Syrian)	3 d 4 or 6 hr/d (NS)	Resp		33 M (alveolar wall thickening and increased number of macrophages; bronchopneumonia)		Drew et al. 1974 Aluminum chlorhydrate	
			Bd Wt		33 M (unspecified decreased body weight)			
3	Hamster (Golden Syrian)	3 d 4 or 6 hr/d (NS)	Resp	3 M	7 M (13% increased lung weight)		Drew et al. 1974 Aluminum chlorhydrate	
4	Hamster (Golden Syrian)	3 d 4 hr/d (NS)	Resp		10 M (approximately 24% increased lung weight)		Drew et al. 1974 Aluminum chlorhydrate	

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		
5	Hamster (Golden Syrian)	3 d 4 hr/d	Resp		31	(alveolar wall thickening and increased number of macrophages and heterophils)	Drew et al. 1974 Aluminum chlorhydrate	
6	Rabbit (New Zealand)	5 d 4 hr/d (NS)	Resp		43	(alveolar wall thickening, increased number of macrophage; 65% increase in lung weight)	Drew et al. 1974 Aluminum chlorhydrate	
INTERMEDIATE EXPOSURE								
Systemic								
7	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d (NS)	Resp	0.061	0.61	(increase in alveolar macrophages; granulomatous lesions in lungs)	Steinhagen et al. 1978 Aluminum chlorhydrate	
			Cardio	6.1				
			Gastro	6.1				
			Hemato	6.1				
			Musc/skel	6.1				
			Hepatic	6.1				
			Renal	6.1				
			Endocr	6.1				
			Dermal	6.1				
			Ocular	6.1				
			Bd Wt	6.1				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		
8	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d	Resp	0.065 M	0.65 M (12% increased relative lung weight)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	5.4				
9	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d (NS)	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 Aluminum chlorhydrate	
			Cardio	6.1				
			Gastro	6.1				
			Hemato	6.1				
			Musc/skel	6.1				
			Hepatic	6.1				
			Renal	6.1				
			Endocr	6.1				
			Dermal	6.1				
			Ocular	6.1				
Bd Wt	6.1							

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		
10	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d	Resp	0.65	5.4 (19-23% increased relative lung weight)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	5.4				
11	Hamster (Golden Syrian)	5 or 6 wk 5 d/wk 6 hr/d	Resp		10 M (alveolar thickening and increased number of foci of macrophages and heterophils)		Drew et al. 1974 Aluminum chlorhydrate	
CHRONIC EXPOSURE								
Systemic								
12	Rat (Wistar)	86 wk 5 d/wk 6 hr/d (NS)	Resp	2.45			Pigott et al. 1981 Aluminum oxide	
13	Rat (Fischer- 344)	12-24 mo 5 d/wk 6 hr/d	Resp	0.65	5.4 (108-274% increased relative lung weight at 2 years)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				
			Bd Wt	0.65				
14	Gn Pig (Hartley)	12-21 mo 5 d/wk 6 hr/d	Resp		0.065 M (21% increased relative lung weight at 2 years)		Stone et al. 1979 Aluminum chlorhydrate	
			Hemato	5.4				

Table 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		

Bd Wt 5.4

^a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; Gn pig = guinea pig; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation
Acute (≤14 days)

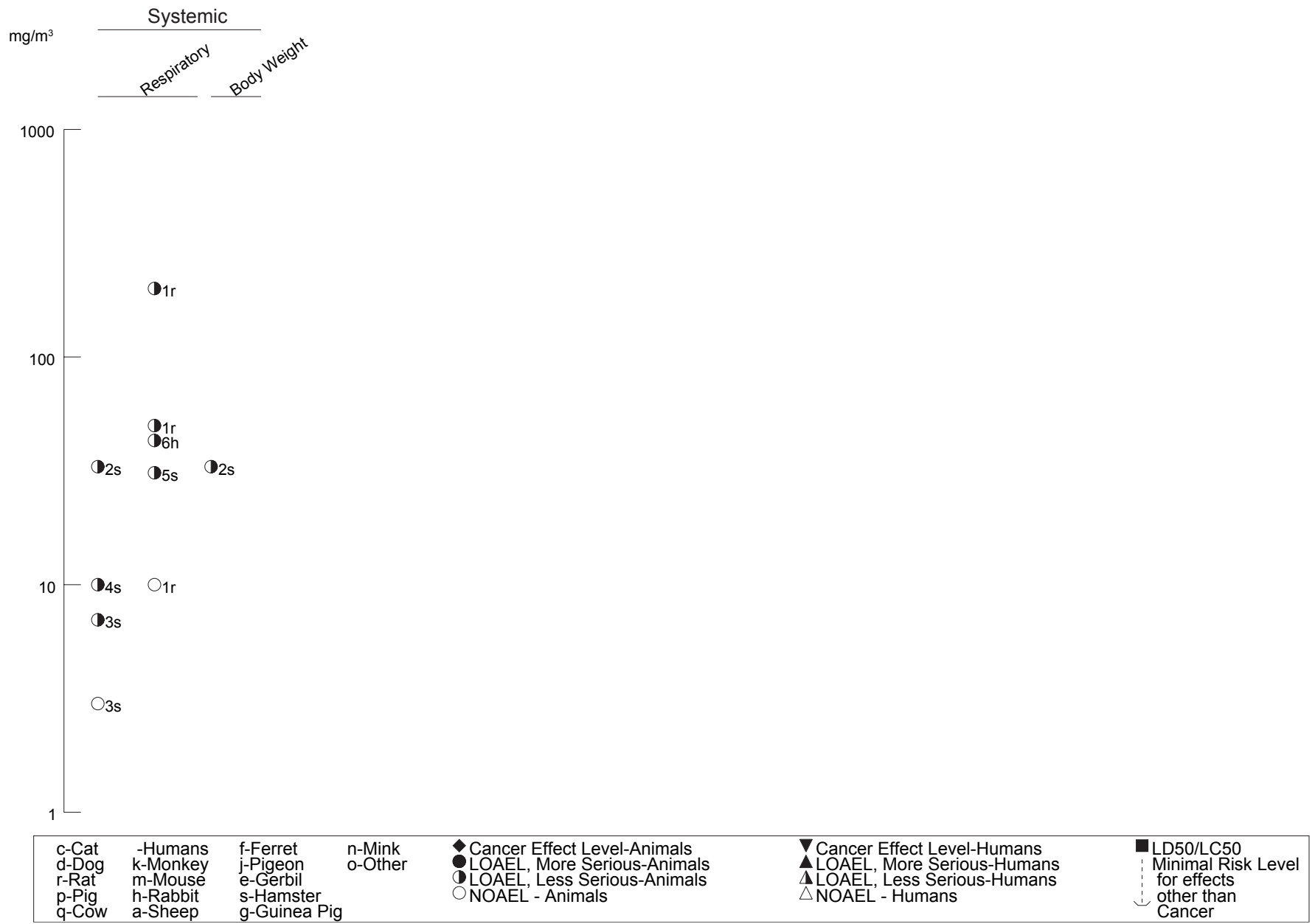


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (Continued)

Intermediate (15-364 days)

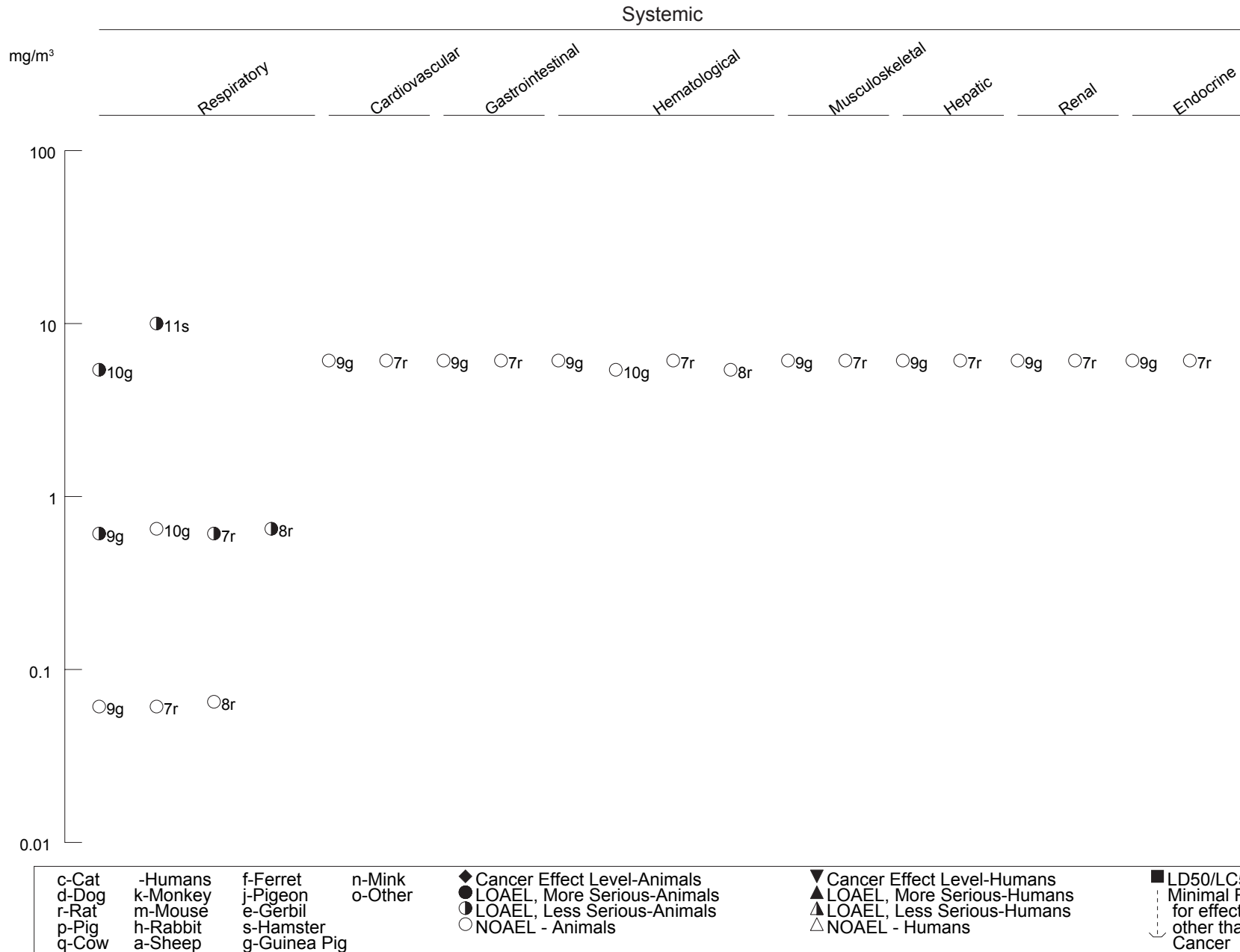


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (Continued)

Intermediate (15-364 days)

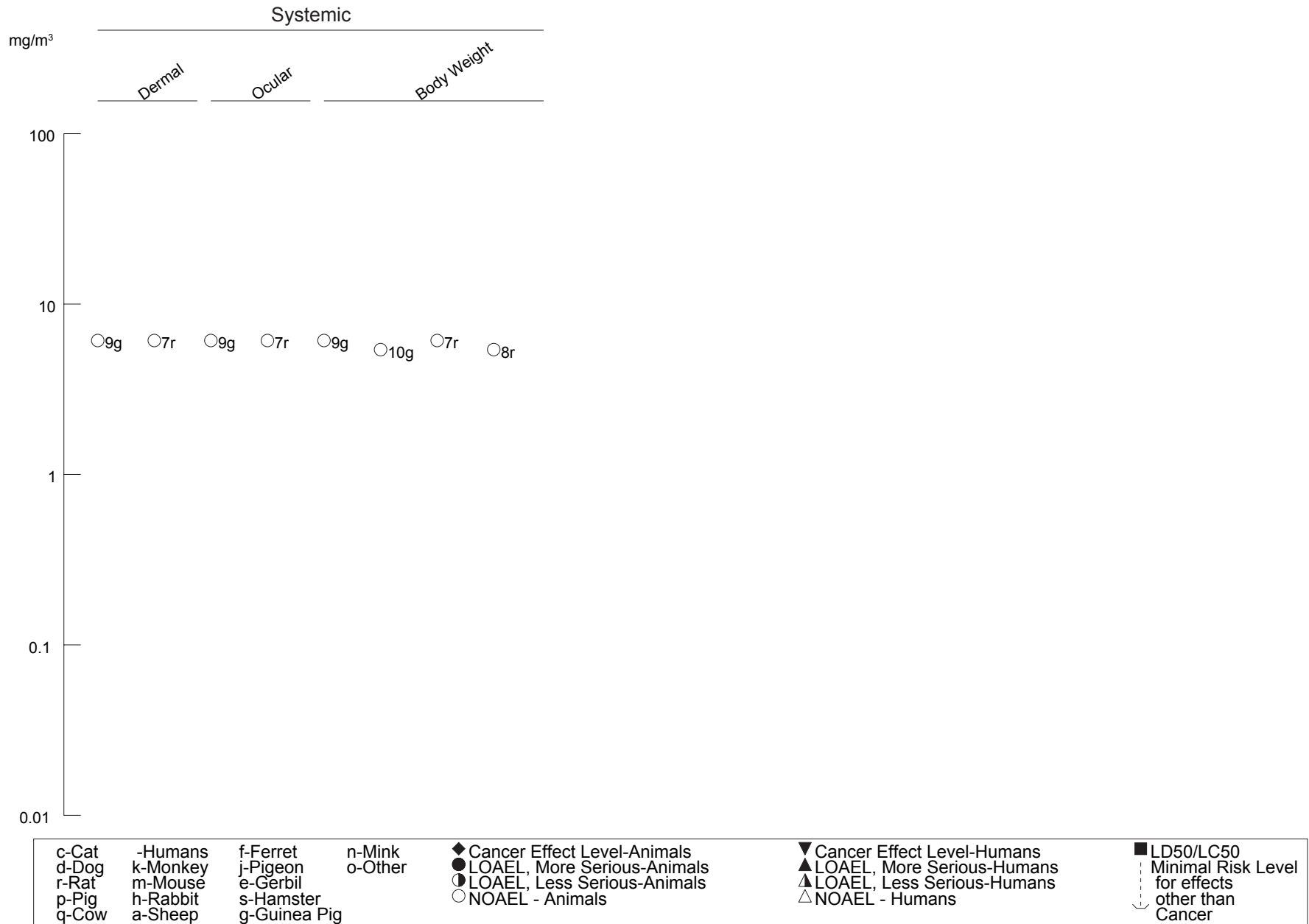
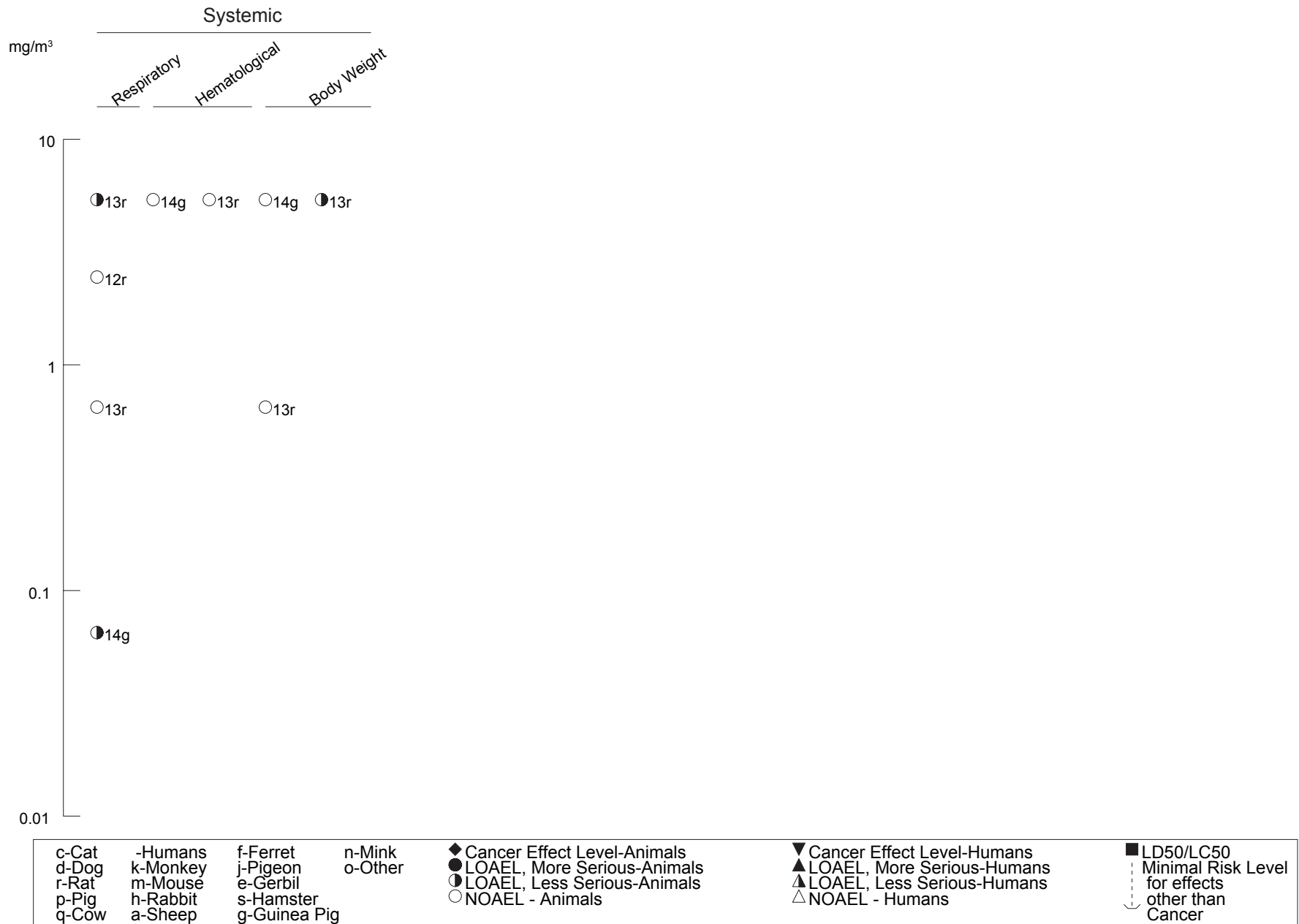


Figure 3-1 Levels of Significant Exposure to Aluminum and Compounds - Inhalation (Continued)

Chronic (≤365 days)



3. HEALTH EFFECTS

observed in potroom workers (Bast-Pettersen et al. 1994; Chan-Yeung et al. 1983; Radon et al. 1999; Simonsson et al. 1985), foundry workers (Al-Masalkhi and Walton 1994; Burge et al. 2000; Halatek et al. 2006), workers exposed to fine aluminum dust (including grinders) (Jederlinic et al. 1990; Korogiannos et al. 1998; Miller et al. 1984b), a worker spray painting with an aluminum paint (Bost and Newman 1993), and welders (Abbate et al. 2003; Herbert et al. 1982; Hull and Abraham 2002; Vandenplas et al. 1998), although other studies have not found a significant effect (Musk et al. 2000). Occupational asthma has been reported in aluminum potroom workers (as reviewed by Abramson et al. 1989 and Kilburn 1998); there is some debate whether the asthma is related to exposure to respiratory irritants, such as hydrogen fluoride and chlorine, or due to aluminum exposure. Case reports provide suggestive evidence that chronic exposure to aluminum may cause occupational asthma. An asthmatic reaction was observed following a bronchial provocation test an aluminum foundry worker (Burge et al. 2000) and an aluminum welder (Vandenplas et al. 1998).

Pulmonary fibrosis is the most commonly reported respiratory effect observed in workers exposed to fine aluminum dust (pyropowder), alumina (aluminum oxide), or bauxite. However, conflicting reports are available on the fibrogenic potential of aluminum. In some of the cases, the fibrosis was attributed to concomitant exposure to other chemicals. For example, pulmonary fibrosis has been observed in a number of bauxite workers or potroom workers (De Vuyst et al. 1986; Gaffuri et al. 1985; Gilks and Churg 1987; Jederlinic et al. 1990; Jephcott 1948; Musk et al. 1980; Riddell 1948; Shaver 1948; Shaver and Riddell 1947); in these workers, it is very likely that there was simultaneous exposure to silica and that the latter was the causative agent rather than the aluminum. Some of the earliest cases of pulmonary fibrosis were reported in German munition workers exposed to pyropowder (Goralewski 1947). Case reports of fibrosis in workers exposed to finely ground aluminum have been also been reported by Edling (1961), McLaughlin et al. (1962), Mitchell et al. (1961), and Ueda et al. (1958). However, other studies have not found any radiological evidence of pulmonary fibrosis in workers exposed to alumina (Meiklejohn and Posner 1957; Posner and Kennedy 1967) or fine aluminum powder (Crombie et al. 1944). It is believed that the conflicting study results are due to differences in the lubricant used to retard surface oxidation during milling (Dinman 1987). Stearic acid is the most commonly used lubricant in the aluminum industry; the stearic acid combines with the aluminum to form aluminum stearate. Exposure to the aluminum stearate does not appear to be fibrogenic to workers (Crombie et al. 1944; Meiklejohn and Posner 1957; Posner and Kennedy 1967). In contrast, the previous and now discontinued use of a nonpolar aliphatic oil lubricant, such as mineral oil, has been associated with fibrosis (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958). Pulmonary fibrosis has also been observed in an aluminum arc welder (Vallyathan et al. 1982), an aluminum production worker exposed to

3. HEALTH EFFECTS

aluminum oxide fumes (Al-Masalkhi and Walton 1994), and in workers in an unspecified aluminum industry (Akira 1995). There is also some evidence suggesting aluminum-induced pneumoconiosis (Hull and Abraham 2002; Korogiannos et al. 1998; Kraus et al. 2000), pulmonary alveolar proteinosis (Miller et al. 1984b), interstitial pneumonia (Herbert et al. 1982), and granulomas (Cai et al. 2007; Chen et al. 1978; De Vuyst et al. 1987); however, these reports are based on a small number of cases, which limits their interpretation.

Respiratory effects typically associated with inhalation of particulates and lung overload have been observed in animals. The pulmonary toxicity of alchlor (a propylene glycol complex of aluminum chlorhydrate), a common component of antiperspirants, was examined in hamsters in a series of studies conducted by Drew et al. (1974). A 3-day exposure to 31 or 33 mg Al/m³ resulted in moderate-to-marked thickening of the alveolar walls due to neutrophil and macrophage infiltration and small granulomatous foci at the bronchioalveolar junction (a likely site of particulate deposition). A decrease in the severity of the pulmonary effects was observed in animals killed 3, 6, 10, or 27 days after exposure termination. Similar pulmonary effects were observed in rabbits exposed to 42 mg Al/m³ for 5 days (Drew et al. 1974). Significant increases in absolute lung weights have been observed in hamsters exposed for 3 days to ≥ 7 mg Al/m³ (no effects were observed at 3 mg Al/m³) and in rabbits exposed to 43 mg Al/m³ for 5 days (no effects were observed in rabbits exposed to 48 or 39 mg Al/m³ for 1 or 4 days, respectively). In rats exposed to aluminum flakes for 5 days, there were alterations in the cytological (increase in the number of polymorphonuclear neutrophils [PMNs]) and enzymatic (increased activity of alkaline phosphatase and lactate dehydrogenase) content of the lavage fluid at ≥ 50 mg Al/m³ and multifocal microgranulomas in the lungs and hilar lymph nodes at ≥ 100 mg Al/m³ (Thomson et al. 1986). The enzymatic changes in the lavage fluid probably resulted from the presence of PMNs, increased phagocytosis of alveolar macrophages, and Type II cell hyperplasia.

Similar pulmonary effects were observed in animals following intermediate-duration exposure. An increase in the number of alveolar macrophages and heterophils were observed in hamsters exposed to 10 mg Al/m³ as alchlor for 6 hours/day, 5 days/week for 2, 4, or 6 weeks (Drew et al. 1974). The severity was directly related to exposure duration. Granulomatous nodules and thickening of the alveolar walls due to infiltration of heterophils and macrophages were observed 2 weeks after termination of a 6-week exposure. An increase in the number of alveolar macrophages and granulomatous lesions in the lungs and peribronchial lymph nodes were also observed in rats and guinea pigs exposed to 0.61 or 6.1 mg Al/m³ aluminum chlorhydrate for 6 hours/day, 5 days/week for 6 months (Steinhagen et al. 1978); the severity of the alterations was concentration-related. In addition, statistically significant increases in

3. HEALTH EFFECTS

absolute and relative lung weight were observed in the rats exposed to 6.1 mg Al/m³; the authors noted that pulmonary edema was not observed in these rats. No statistically significant histological alterations or changes in lung weight were observed at 0.061 mg Al/m³. Suggestive evidence of alveolar macrophage damage was observed in rats following a 5-month exposure (6 hours/day, 5 days/week) to either aluminum chloride (0.37 mg Al/m³) or aluminum fluoride (0.41 mg Al/m³); increases in lysozyme levels, protein levels (aluminum chloride only), and alkaline phosphatase (aluminum chloride only) were observed in the lavage fluid (Finelli et al. 1981). Alveolar proteinosis was observed in rats, guinea pigs, and hamsters exposed to ≥ 15 , 20, or 30 mg/m³ of several types of aluminum flake powders; the particle sizes ranged from 2.5 to 4.8 μm (Gross et al. 1973). The investigators noted that aluminum powders did not induce pulmonary fibrosis in the guinea pigs or hamsters; in rats, foci of lipid pneumonitis were observed. A similar exposure to aluminum oxide did not result in alveolar proteinosis, pulmonary fibrosis, or pneumonitis; effects were limited to foci consisting of alveoli filled with macrophages; the particle size of the aluminum oxide dust was much smaller (0.8 μm) than the aluminum flake powders. Interpretation of this study is limited by the lack of incidence data and the high mortality observed in treated and control animals.

There are limited data on the pulmonary toxicity of aluminum in animals following chronic exposure. Increases in relative lung weights (21–274%) have been observed in rats and guinea pigs exposed to 5.1 mg Al/m³ aluminum chlorhydrate for 6 hours/day, 5 days/week for approximately 2 years (Stone et al. 1979). Lung weights were not affected at 0.61 mg Al/m³. It should be noted that this study did not conduct histological examinations of the lungs. Pigott et al. (1981) did not find evidence of lung fibrosis in rats exposed to 2.18 or 2.45 mg/m³ manufactured or aged Saffil alumina fibers; Saffil alumina fiber is a refractory material containing aluminum oxide and about 4% silica. The animals were exposed for 86 weeks followed by a 42-week observation period.

Cardiovascular Effects. No studies were located regarding cardiovascular effects of various forms of aluminum following acute- or intermediate-duration inhalation exposure in humans. Dilation and hypertrophy of the right side of the heart were reported in male factory workers chronically exposed by inhalation to aluminum flake powder and who eventually died (McLaughlin et al. 1962; Mitchell et al. 1961). The cardiac effects may have been secondary to pulmonary fibrosis and poor pulmonary function. Epidemiological studies of aluminum industry workers failed to identify an increase in deaths related to cardiovascular disease (Milham 1979; Mur et al. 1987; Rockette and Arena 1983; Theriault et al. 1984a). Cohort sizes ranged from 340 to 21,829 men. Results of cardiovascular tests (electrocardiogram, blood

3. HEALTH EFFECTS

pressure measurement) were similar between 22 aluminum workers exposed for 10 years or more and an unexposed control group of 16 men (Bast-Pettersen et al. 1994).

No histological alterations were observed in the hearts of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects of various forms of aluminum following acute-, intermediate-, or chronic-duration inhalation exposure in humans or acute- or chronic-duration inhalation exposure in animals. No histological changes were observed in the gastrointestinal tissues of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Hematological Effects. No studies were located regarding hematological effects of various forms of aluminum following acute-duration inhalation exposure in humans. No adverse hematological effects were noted in a group of seven workers following 6 months of exposure to aluminum fumes or dust (Mussi et al. 1984). Exposure levels from personal sampling ranged from 1 to 6.2 mg Al/m³, predominantly as aluminum oxide. Decreased red blood cell hemoglobin and increased erythrocyte sedimentation rates were reported in the case of a male aluminum industry worker chronically exposed by inhalation to aluminum flake powder (McLaughlin et al. 1962). A prolongation of prothrombin time was seen in 30 of 36 aluminum workers chronically exposed by inhalation to alumina dust (Waldron-Edward et al. 1971). The authors suggested that increasing serum aluminum levels may be used to provide beneficial antithrombotic effects (Waldron-Edward et al. 1971).

No studies were located regarding hematological effects in animals after acute-duration inhalation exposure to aluminum or its compounds. No hematological effects were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m³ as aluminum chlorhydrate for 6–24 months (Steinhagen et al. 1978; Stone et al. 1979).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects following acute- or intermediate-duration inhalation exposure to various forms of aluminum in humans. Two case reports have been identified in which finger clubbing was observed in male factory workers chronically exposed to aluminum powder (De Vuyst et al. 1986; McLaughlin et al. 1962). Joint pain was reported by a female worker exposed by inhalation to dried alunite residue (a hydrated sulphate of aluminum and

3. HEALTH EFFECTS

potassium) for 18 months (Musk et al. 1980). Schmid et al. (1995) did not find any significant alterations in bone mineral content (assessed via osteodensitometry) in workers exposed to aluminum powder (average concentration 12.1 mg/m^3) for an average duration of 12.6 years.

No studies were located regarding musculoskeletal effects following acute- or chronic-duration inhalation exposure to aluminum or its compounds in animals. No histological changes were observed in the muscle or bone of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Hepatic Effects. No studies were located regarding hepatic effects in humans following acute- or chronic-duration inhalation exposure to various forms of aluminum. Intermediate occupational inhalation exposure to aluminum fumes, dusts, or powders did not affect liver function or hepatic microanatomy in a group of seven workers as determined from biopsy samples (Mussi et al. 1984).

In animals, no histological or organ weight changes were observed in livers of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). No acute- or chronic-duration inhalation studies examining the liver were identified.

Renal Effects. No studies were located regarding renal effects in humans following acute-duration inhalation exposure to various forms of aluminum.

No adverse effects on renal function or standard urine tests have been noted in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984) or chronic-duration inhalation exposure to metallic aluminum powder (De Vuyst et al. 1987; McLaughlin et al. 1962).

No histological or organ weight changes were observed in kidneys of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Endocrine Effects. No studies were located regarding endocrine effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. Post-mortem enlargement of

3. HEALTH EFFECTS

the thyroid was reported in the case of a male factory worker chronically exposed by inhalation to aluminum flake powder (McLaughlin et al. 1962).

No studies were located regarding endocrine effects in animals following acute- or chronic-duration inhalation exposure to aluminum or its compounds. No adverse histological changes were observed in the adrenal, thyroid, or pituitary glands of Fischer 344 rats or Hartley guinea pigs exposed by inhalation (6 hours/day, 5 days/week) to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Dermal Effects. No studies were located regarding dermal effects in animals following acute- or chronic-duration inhalation exposure to various forms of aluminum. No histologic changes of the skin were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Ocular Effects. No studies were located regarding ocular effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. No adverse effects were observed during an eye examination in a man chronically exposed by inhalation to metallic aluminum and aluminum oxide powders (De Vuyst et al. 1987).

No studies were located regarding ocular effects in animals following acute- or chronic-duration inhalation exposure to aluminum or its compounds. No histological changes were observed in the eyes of Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978).

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to aluminum or its compounds. Unspecified body weight decreases were reported for male Golden Syrian hamsters acutely exposed via whole-body inhalation to 3, 10, or 33 mg Al/m³ as alchlor, a common component of antiperspirants (Drew et al. 1974). In contrast, no body weight effects were observed in Sprague-Dawley rats exposed by inhalation to 0.37 mg Al/m³ as aluminum chloride or 0.41 mg Al/m³ as aluminum fluoride dust for 5 months (Finelli et al. 1981), or in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978) or to 0.61 mg Al/m³ as aluminum chlorhydrate for up to 24 months (Stone et al. 1979). Significant reduction in body weight (>10%) was observed in Fischer 344 rats after 24 months of exposure to 6.1 mg/m³ as aluminum chlorhydrate. No effect on body weight was seen in Hartley guinea

3. HEALTH EFFECTS

pigs similarly exposed (Stone et al. 1979). These NOAEL and LOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

Metabolic Effects. No studies were located regarding metabolic effects in humans following acute- or chronic-duration inhalation exposure to various forms of aluminum. No adverse effect on phosphate metabolism was identified in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after acute- or intermediate-duration inhalation exposure to various forms of aluminum. Helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in the presence of soluble aluminum compounds *in vitro* were found in an individual with sarcoid-like epithelioid granulomas and exposed to metallic aluminum and aluminum dust (De Vuyst et al. 1987). Additional testing 1 year after termination of exposure indicated the man no longer had alveolitis. A significantly higher percentage of CD4⁺CD8⁺ T lymphocytes were observed in aluminum electrolytic workers (He et al. 2003).

Several animal studies have found histological alterations in the lymphoreticular system, in particular granulomas in the hilar lymph nodes; these effects are secondary to the pulmonary effects (Steinhagen et al. 1978; Thomson et al. 1986) and resulted from the removal of aluminum from the lungs by alveolar macrophages.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. A number of studies have investigated the neurotoxic potential in workers chronically exposed to aluminum. With the exception of isolated cases (for example, McLaughlin et al. 1962), none of these studies reported overt signs of neurotoxicity in workers exposed to aluminum dust (potroom and foundry workers) (Bast-Pettersen et al. 1994; Dick et al. 1997; Hosovski et al. 1990; Sim et al. 1997; White et al. 1992), in aluminum welders (Hänninen et al. 1994; Sjögren et al. 1996), or in miners exposed to McIntyre powder (finely ground aluminum and aluminum oxide) (Rifat et al. 1990). Higher incidences of subjective neurological symptoms (e.g., incoordination, difficulty buttoning, problems concentrating, headaches, depression, fatigue) were reported in aluminum potroom or foundry workers at aluminum smelters (Halatek et al. 2005; Iregren et

3. HEALTH EFFECTS

al. 2001; Sim et al. 1997; Sińczuk-Walczak et al. 2003; White et al. 1992), workers exposed to aluminum flake powder (Iregren et al. 2001), and aluminum welders (Bast-Pettersen et al. 2000; Riihimäki et al. 2000; Sjögren et al. 1990). Among the studies examining the potential association between neurological symptoms and aluminum exposure estimates (urinary and/or blood aluminum levels), some found a significant association (Riihimäki et al. 2000; Sińczuk-Walczak et al. 2003) and others did not (Bast-Pettersen et al. 2000; Iregren et al. 2001; Kiesswetter et al. 2007).

Subclinical effects have been reported in various types of aluminum workers. Significant alterations in performance tests assessing reaction time, eye-hand coordination, memory, and/or motor skills were found in aluminum foundry workers (Hosovski et al. 1990; Polizzi et al. 2001), aluminum welders (Akila et al. 1999; Bast-Pettersen et al. 2000; Buchta et al. 2005; Riihimäki et al. 2000; Sjögren et al. 1990), electrolyte workers (He et al. 2003), and miners exposed to McIntyre powder (Rifat et al. 1990). Three studies of aluminum welders did not find significant decrements in neurobehavioral performance as compared to controls; however, significant correlations between aluminum exposure estimates (urinary or plasma aluminum levels or air aluminum levels) and memory and/or reaction-time tests were found (Bast-Pettersen et al. 2000; Buchta et al. 2003; Hänninen et al. 1994). Other studies did not find alterations in neuroperformance tests in aluminum potroom workers (Sim et al. 1997) or aluminum welders (Kiesswetter et al. 2007); two studies in aluminum welders did not find effects on motor performance (Buchta et al. 2003, 2005). A higher incidence of subclinical tremors was found in a study of potroom workers (Bast-Pettersen et al. 1994); another study did not find a significant alteration (Dick et al. 1997). Several studies have examined aluminum's potential to induce quantitative EEG changes; some studies found alterations (Hänninen et al. 1994; Riihimäki et al. 2000; Sińczuk-Walczak et al. 2003) and others did not (Iregren et al. 2001). In general, the available occupational exposure studies poorly characterize aluminum exposure. Some of the studies reported aluminum air concentrations for a single time period (Dick et al. 1997; Sim et al. 1997; Sjögren et al. 1996; White et al. 1992) or a couple of time periods (Buchta et al. 2003; Kiesswetter et al. 2007), but did not have earlier monitoring data when aluminum exposures may have been higher. A meta-analysis using data from most of these studies found a statistically significant decline in performance on the digit symbol neurobehavioral test (Meyer-Baron et al. 2007). Although decreases in performance were observed for other neurobehavioral tests, the differences were not statistically significant. The lack of adequate exposure monitoring data, potential exposure to other neurotoxicants, and the different types of aluminum exposure make it difficult to draw conclusions regarding the neurotoxic potential of inhaled aluminum in workers.

3. HEALTH EFFECTS

Three studies have examined the possible association between occupational exposure to aluminum and the risk of Alzheimer's disease. Two case-control studies did not find a significant association between occupational exposure to aluminum dust or fumes and the risk of Alzheimer's disease (Graves et al. 1998; Salib and Hillier 1996). Another study of former aluminum dust-exposed workers (retired for at least 10 years) found some impairment in some tests of cognitive function; the investigators raised the possibility that cognitive impairment may be a pre-clinical indicator of Alzheimer's disease (Polizzi et al. 2002).

No studies were located regarding neurological effects in animals following acute-duration inhalation exposure to various forms of aluminum. No brain weight or histological changes were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to up to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). No brain weight effects were observed in Sprague-Dawley rats exposed by inhalation to 0.37 mg Al/m³ as aluminum chloride or 0.41 mg Al/m³ as aluminum fluoride for 5 months, although tissues were not examined histologically (Finelli et al. 1981). No brain weights were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m³ as aluminum chlorhydrate for up to 24 months (Stone et al. 1979).

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to various forms of aluminum.

No reliable studies were located regarding reproductive effects in animals following acute- or chronic-duration inhalation exposure to various forms of aluminum. No histological changes were observed in reproductive tissues of Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 6.1 mg Al/m³ as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to various forms of aluminum.

3. HEALTH EFFECTS

3.2.1.7 Cancer

No studies were located regarding cancer effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum.

A reported high incidence of bladder cancer in a region of Quebec, Canada where aluminum production takes place (Wigle 1977) resulted in the initiation of a case-control study (Theriault et al. 1984a). Workers in five aluminum reduction plants were assessed with respect to incidence of bladder cancer. The number of men working in the plants was 300–1,200 except for one plant with 7,800 workers. The number of bladder cancer cases was collected from regional hospitals over a 10-year period, and the number of current or former employees from the aluminum plants identified. For each case, three controls who had never had bladder cancer were selected. Detailed occupational histories of each man (case and controls) were collected from the companies and included each division, department, and job to which the men had been assigned; smoking history; and estimated assessment of tar and PAH exposure (based on benzene soluble material and benz(a)pyrene concentrations in workplace air) for each occupation. An index of lifetime exposure of each worker to tar and PAHs was created. Over the 10-year study period, 488 cases of bladder cancer were found in men from the designated regions. Of these, 96 were identified as being current or former aluminum company employees, and 11 were eliminated from the study because they had worked <12 months at the companies. The distribution of tumors was as follows: transitional epitheliomas grade I (n=3), grade II (n=43), grade III (n=18), and grade IV (n=21). The mean age at diagnosis was 61.7 years, and the mean age at first employment in aluminum work was 28.2 years. The interval between beginning of employment in the aluminum industry and diagnosis was 23.9 years. A higher proportion of cases than controls were smokers. The risk for bladder cancer was highest in workers in Soderberg reactor rooms (where the reduction process takes place), and risk increased steadily with time worked in this department. The risk also increased steadily with estimated exposure to tar and PAHs. The interaction between cigarette smoking and PAH exposure in the generation of bladder cancer was more than additive.

Several studies on cancer mortality patterns have been conducted in aluminum reduction factory workers (Gibbs and Horowitz 1979; Milham 1979; Mur et al. 1987; Rockette and Arena 1983). The workplace inhalation exposure was to aluminum dust or fumes for chronic durations, but the exposure levels were not determined. In addition to aluminum, most workers were concurrently exposed by inhalation to known carcinogens, such as tobacco smoke or PAHs from coal tars. In a historical prospective study of 2,103 aluminum production workers, standardized mortality ratios (SMRs) of 117 for lung cancer

3. HEALTH EFFECTS

(35 cases), 180 for pancreatic cancer (9 cases), and 184 for all lymphatic and hematopoietic cancers (17 cases) were observed (Milham 1979). Smoking histories were not available, and only the SMR for lymphatic and hematopoietic cancers were statistically significant. In a study that focused on mortality from lung cancer in a group of 5,406 aluminum production workers (Gibbs and Horowitz 1979), a dose-response relationship was observed between lung cancer mortality and both years of exposure to tar and “tar-years” in specific occupations. A study of mortality patterns in 21,829 aluminum production workers in the United States (Rockette and Arena 1983) indicated that the risk of lung cancer mortality increased among workers with ≥ 25 years of experience in the carbon bake department, who presumably had higher exposure to potential hydrocarbon carcinogens than other workers. Increased deaths from bladder and hematolymphopoietic cancers were also reported.

Based on current evidence, the International Agency for Research on Cancer (IARC) has stated (IARC 1984) that “the available epidemiological studies provide limited evidence that certain exposures in the aluminum production industry are carcinogenic to humans, giving rise to cancer of the lung and bladder. A possible causative agent is pitch fume.” It is important to emphasize that 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 and is not due to aluminum or its compounds.

No reliable studies were located regarding cancer effects in animals following acute- or intermediate-duration inhalation exposure to aluminum or its compounds. An increase in cancer was not observed in male and female Wistar rats exposed via whole-body inhalation to atmospheres containing 2.18–2.45 mg Al/m³ as alumina fibers ($\approx 96\%$ aluminum oxide) for 86 weeks (Pigott et al. 1981).

3.2.2 Oral Exposure

Major sources of human oral exposure to aluminum include food (due to its use in food additives, food and beverage packaging, and cooking utensils), drinking water (due to its use in municipal water treatment), and aluminum-containing medications (particularly antacid/antiulcer and buffered aspirin formulations) (Lione 1985b). Dietary intake of aluminum, estimated to be in the 0.10–0.12 mg Al/kg/day range in adults (Pennington and Schoen 1995), has not been of historical concern with regard to toxicity due to its presence in food and the generally recognized as safe (GRAS) status of aluminum-containing food additives by the FDA. Users of aluminum-containing medications that are healthy (i.e., have normal kidney function) can ingest much larger amounts of aluminum than in the diet, possibly as high as 12–

3. HEALTH EFFECTS

71 mg Al/kg/day from antacid/antiulcer products and 2–10 mg Al/kg/day from buffered analgesics when taken at recommended dosages (Lione 1985b).

The oral toxicity of aluminum in animals is well-studied, although many of the studies are limited by a lack of reported information on aluminum content in the base diet. Commercial grain-based feeds for laboratory animals contain high levels of aluminum that typically far exceed the aluminum content of the human diet. Commercial laboratory animal chow can significantly contribute to total experimental exposure, as well as provide excess and variable amounts of essential and nonessential trace minerals and metal binding ligands that can alter aluminum uptake in comparison to diets that are semipurified or purified in which trace metal levels are precisely determined (Golub et al. 1992b). Base diets containing 250–350 ppm Al were used in some rat and mouse studies, but this cannot be assumed to be a normal or representative concentration range because analyses for aluminum were not routinely performed, substantial brand-to-brand and lot-to-lot variations are apparent, and formal surveys of aluminum content of laboratory animal feed are not available. For example, concentrations ranging from 60 to 280 ppm Al for Panlab rodent standard diet (Colomina et al. 1998; Domingo et al. 1987a, 1993) and 120–8,300 ppm for Purina Rodent Laboratory Chow (Fleming and Joshi 1987; Provan and Yokel 1990; Varner et al. 1994, 1998) have been reported. Due to the likelihood of significant base dietary exposure to aluminum, studies with insufficient information on aluminum content in the base diet must be assumed to underestimate the actual aluminum intake. The magnitude of the underestimate can be considerable. For example, based on approximate values of 250 ppm (Colomina et al. 1998; Domingo et al. 1993) and 350 ppm (Oteiza et al. 1993) for Al in feed used in some studies in rats and mice, respectively, and using reference values for food consumption and body weight in rats and mice (EPA 1988) for ingestion during the period from weaning to 90 days, estimated doses of 25 mg Al/kg/day (rats) and 68 mg Al/kg/day (mice) may be provided by diet alone. These figures can represent a significant portion of the intake for which Table 3-2 reports health effects in animal studies. Consequently, although studies with inadequate data on base dietary levels of aluminum provide useful information on health effects of aluminum, NOAELs and LOAELs from these studies cannot be assumed to be accurate, they may not be suitable for comparison with effect levels from studies that used diets with known amounts of aluminum, and are not included in Table 3-2 and Figure 3-2. Studies for which data on base dietary aluminum content are available are mainly limited to those conducted by Golub and coworkers (Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1989, 1992a, 1992b, 1994, 1995, 2000; Oteiza et al. 1993) and Domingo and coworkers (Colomina et al. 1992, 1994, 1998, 2005; Domingo et al. 1987a, 1987b, 1989, 1993; Gomez et al. 1986, 1991; Paternain et al. 1988; Roig et al. 2006).

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (G)				261 (LD50)	Llobet et al. 1987 Aluminum nitrate	
2	Rat (Sprague-Dawley)	once (G)				370 (LD50)	Llobet et al. 1987 Aluminum chloride	
3	Rat (Sprague-Dawley)	once (G)				162 (LD50)	Llobet et al. 1987 Aluminum bromide	
4	Mouse (Swiss-Webster)	once (G)				286 (LD50)	Llobet et al. 1987 Aluminum nitrate	
5	Mouse (Swiss-Webster)	once (G)				222 (LD50)	Llobet et al. 1987 Aluminum chloride	
6	Mouse (Swiss-Webster)	once (G)				164 (LD50)	Llobet et al. 1987 Aluminum bromide	
7	Mouse (Dobra Voda)	once (G)				770 M (LD50)	Ondreicka et al. 1966 Aluminum chloride	
8	Mouse (Dobra Voda)	once (G)				980 M (LD50)	Ondreicka et al. 1966 Aluminum sulfate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
9	Rabbit (New Zealand)	once (GW)				540 F (5/5 died)	Yokel and McNamara 1985 Aluminum lactate	
Developmental								
10	Rat (Sprague-Dawley)	Gd 6-19 (F)		110			McCormack et al. 1979 Aluminum chloride	
11	Mouse (Swiss)	Gd 6-15 (GW)		141 F			Domingo et al. 1989 Aluminum hydroxide	
INTERMEDIATE EXPOSURE								
Systemic								
12	Rat (NS)	100 d (W)	Bd Wt		97 M (decreased body weight gain in aged rats)		Colomina et al. 2002 Aluminum nitrate	Citric acid was added to water to increase absorption.
13	Rat (Sprague-Dawley)	100 d (W)	Cardio	284 F			Domingo et al. 1987b Aluminum nitrate	
			Hemato	284 F				
			Hepatic	284 F				
			Renal	284 F				
			Bd Wt	284 F				

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
14	Rat (Sprague-Dawley)	1 mo (W)	Resp	133 F			Gomez et al. 1986 Aluminum nitrate	
			Cardio	133 F				
			Gastro	133 F				
			Hemato	52 F	79 F (hyperemia in the red pulp of the spleen)			
			Hepatic	79 F	133 F (hyperemia in the liver, periportal monocytic infiltrate in liver)			
			Renal	133 F				
			Bd Wt	133 F				
15	Rat (Wistar)	10 wk (F)	Musc/skel	90 M			Konishi et al. 1996 Aluminum lactate	
			Bd Wt	90 M				
16	Rat (Sprague-Dawley)	8 mo (W)	Hemato		230 F (decreased hemoglobin, hematocrit and haptoglobin levels, increased reticulocyte levels; inhibition of CFU-E proliferation)		Vittori et al. 1999 Aluminum citrate	
17	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)	Bd Wt	330 F			Donald et al. 1989 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
18	Mouse (Swiss-Webster)	6 wk (F)	Bd Wt	130 F			Golub et al. 1989 Aluminum lactate	
19	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)	Bd Wt		250 F (decreased body weight gain in lactating mice)		Golub et al. 1992a Aluminum lactate	
20	Mouse (Swiss-Webster)	90 d (F)	Bd Wt	195 F			Golub et al. 1992b Aluminum lactate	
21	Mouse (Swiss-Webster)	7-10 wk (F)	Bd Wt	170 F			Oteiza et al. 1989 Aluminum lactate	
22	Mouse (Swiss-Webster)	5 or 7 wk (F)	Hemato	195 F			Oteiza et al. 1993 Aluminum chloride	
			Hepatic	195 F				
			Bd Wt	195 F				
23	Dog (Beagle)	6 mo (F)	Cardio	88			Katz et al. 1984 Aluminum phosphate	
			Hemato	88				
			Hepatic	88				
			Renal	88				
			Endocr	88				
			Ocular	88				

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
24	Dog (Beagle)	26 wk (F)	Cardio	75			Pettersen et al. 1990 Aluminum phosphate	
			Hemato	75				
			Renal	75				
			Endocr	75				
Immuno/ Lymphoret								
25	Human	3 x/d 6 wk (F)		25			Gräske et al. 2000 Aluminum hydroxide	
26	Rat (Sprague-Dawley)	100 d (W)		259 F			Domingo et al. 1987b Aluminum nitrate	
27	Rat (Sprague-Dawley)	1 mo (W)		52 F	79 F (hyperemia in the red pulp of the spleen)		Gomez et al. 1986 Aluminum nitrate	
28	Mouse (Swiss-Webster)	Gd 0- pnd 180 (F)			200 (in offspring: 19% increased absolute spleen weights; depressed spleen cell concentrations of interleukin-2, interferon-g and tumor necrosis factor-a; deficiency of CD4+ cells in T-cell populations)		Golub et al. 1993 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
29	Mouse (Swiss-Webster)	6 wk (F)		107 F			Yoshida et al. 1989 Aluminum lactate	
30	Mouse (Swiss-Webster)	Gd 1- pnd 31 (F)			155 F (increased susceptibility to bacterial infection in dams)		Yoshida et al. 1989 Aluminum lactate	
Neurological								
31	Rat (NS)	100 d (W)		97 M			Colomina et al. 2002 Aluminum nitrate	Citric acid was added to water to increase absorption.
32	Rat (Sprague-Dawley)	6.5 mo (W)		125 M			Domingo et al. 1996 Aluminum nitrate	Citric acid was added to water to improve aluminum absorption.
33	Rat (Wistar)	daily 3 mo (W)		21.5 M	43.1 M (impairment of post-rotatory nystagmus)		Mameli et al. 2006 Aluminum chloride	
34	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)		330 F			Donald et al. 1989 Aluminum lactate	
35	Mouse (Swiss-Webster)	NR (F)		100 M			Golub and Germann 1998 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
36	Mouse (Swiss-Webster)	6 wk (F)		62 F	130 F (decreased total activity and vertical activity)		Golub et al. 1989 Aluminum lactate	
37	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)		250 F			Golub et al. 1992a Aluminum lactate	
38	Mouse (Swiss-Webster)	90 d (F)			195 F (decreased forelimb and hindlimb grip strengths and startle response, decreased total activity, horizontal activity, and percent interval with high activity counts)		Golub et al. 1992b Aluminum lactate	
39	Mouse (Swiss-Webster)	Gd 1- pnd 170 (F)		100 M	200 M (increased cage mate aggression)		Golub et al. 1995 Aluminum lactate	
40	Mouse (Swiss-Webster)	5 or 7 wk (F)			195 F (reduced forelimb and hindlimb grip strength)		Oteiza et al. 1993 Aluminum chloride	
41	Dog (Beagle)	26 wk (F)		75			Pettersen et al. 1990 Aluminum phosphate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Reproductive								
42	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)			155 F	(altered gestational length)	Donald et al. 1989 Aluminum lactate	
43	Mouse (Swiss-Webster)	Gd 1-21 Ld 1-21 Gd 1- Ld 21 (F)		250 F			Golub et al. 1992a Aluminum lactate	
Developmental								
44	Rat (Sprague-Dawley)	15 d pre mating Gd 1- Ld 21 (W)			103	(decreased forelimb grip strength, decreased pup body weight)	Colomina et al. 2005 Aluminum nitrate	Citric acid was added to water to increase absorption.
					53	(delay in vaginal opening)		
45	Mouse (Swiss-Webster)	Gd 1- Ld 21 (F)			155	(decreased forelimb and increased hindlimb grip strength and increased foot splay in weanlings)	Donald et al. 1989 Aluminum lactate	
46	Mouse (Swiss-Webster)	Gd 1- pnd 35 (F)		330 M			Golub and Germann 1998 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
47	Mouse (Swiss-Webster)	Gd 0- Ld 21, pnd 21-35 (F)		26 ^b	130	(impaired performance on the water maze test in females, shorter latency to fall in wire suspension test in males)	Golub and Germann 2001 Aluminum lactate	Diet levels of phosphorus, calcium, magnesium, iron, and zinc were marginally adequate.
48	Mouse (Swiss-Webster)	Gd 1- pnd 35 (F)			330	(altered myelination in spinal cord)	Golub and Tarara 1999 Aluminum lactate	
49	Mouse (Swiss-Webster)	Gd 1-19 Gd 1- Ld 21 Ld 1-21 (F)			250	(decrease in pup weight, crown-rump length, forelimb grip strength in gestation exposed group, increase in hindlimb grip and tail withdrawal times in gestation and lactation exposed groups, increase in negative geotaxis latency in lactation exposed groups)	Golub et al. 1992a Aluminum lactate	
50	Mouse (Swiss-Webster)	Gd 1- pnd 21 (F)			155	(decreased fore- and hindlimb grip strengths and startle response)	Golub et al. 1995 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
51	Mouse (Swiss-Webster)	Gd 1- pnd 31 (F)		330			Yoshida et al. 1989 Aluminum lactate	Assessed immunotoxicity.
CHRONIC EXPOSURE								
Systemic								
52	Rat (Sprague-Dawley)	Gd 1- Ld 21 weaning-1 yr of age or 2 yr of age (W)	Bd Wt	103 M			Roig et al. 2006 Aluminum nitrate	Citric acid was added to water to increase absorption.
53	Rat (Long- Evans) (W)	2.5 yr	Resp	0.6			Schroeder and Mitchener 1975a Aluminum sulfate	
			Cardio	0.6				
			Hepatic	0.6				
			Renal	0.6				
			Bd Wt	0.6				
54	Mouse (Swiss-Webster)	2 yr conception to 24 mo (F)	Bd Wt		100 F (20% decrease in body weight gain)		Golub et al. 2000 Aluminum lactate	

Table 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
55	Mouse (Swiss)	lifetime (W)	Resp	1.2			Schroeder and Mitchener 1975b Aluminum sulfate	
			Cardio	1.2				
			Hepatic	1.2				
			Renal	1.2				
			Bd Wt	1.2				
Neurological								
56	Rat (Sprague-Dawley)	Gd 1- Ld 21 weaning-1 yr of age or 2 yr of age (W)		103 M			Roig et al. 2006 Aluminum nitrate	Citric acid was added to water to increase absorption.
57	Mouse (Swiss-Webster)	2 yr conception to 24 mo (F)			100 ^c	(decreased forelimb and hindlimb grip strength, decreased thermal sensitivity)	Golub et al. 2000 Aluminum lactate	

a The number corresponds to entries in Figure 3-2.

b Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.9 mg Al/kg/day; dose divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.3 mg Al/kg/day; dose divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CFU-E = colony-forming unit-erythroid; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Immuno/Lymphoret = immunological/lymphoreticular; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NR = not reported; pnd = post-natal day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral
Acute (≤14 days)

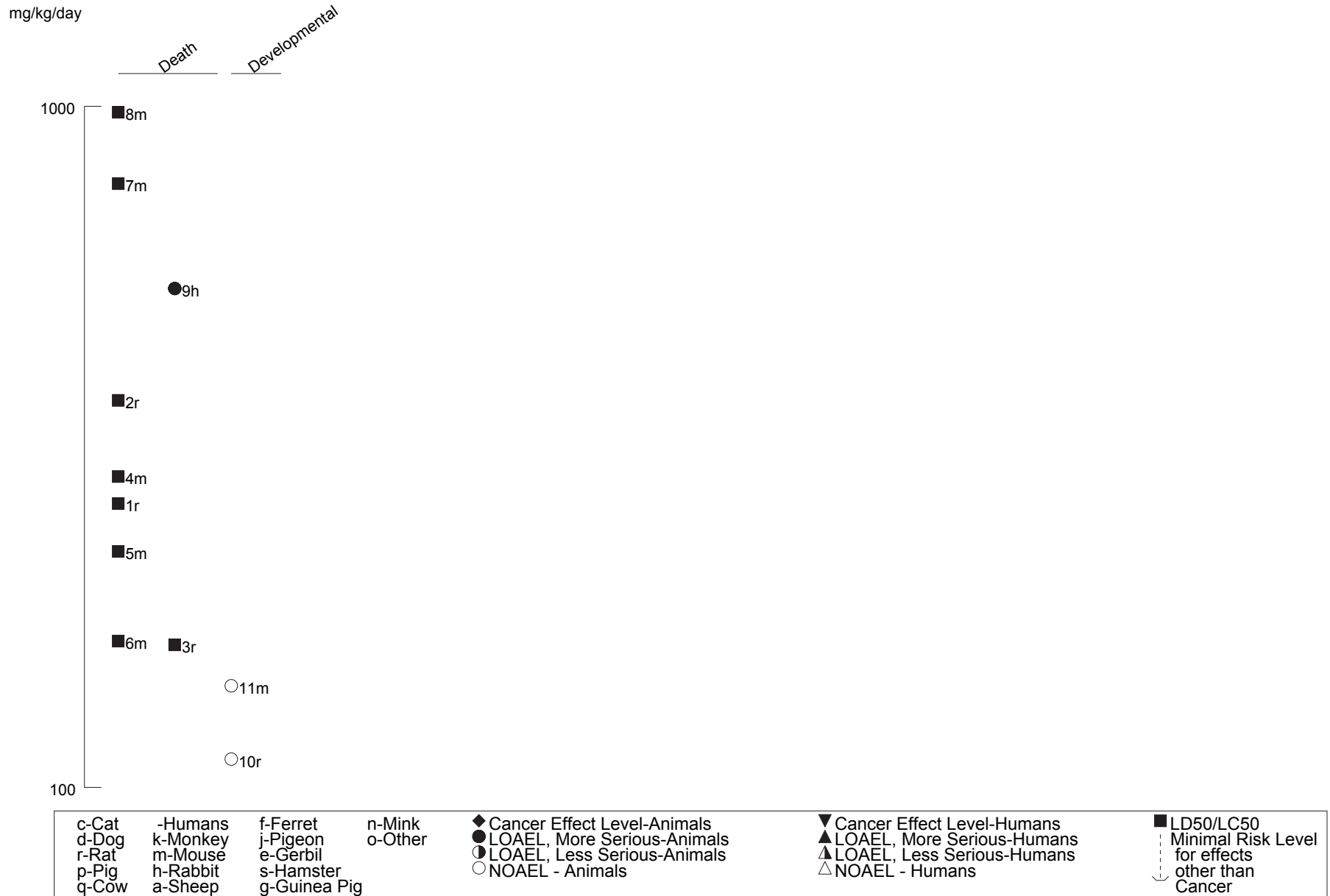


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (Continued)

Intermediate (15-364 days)

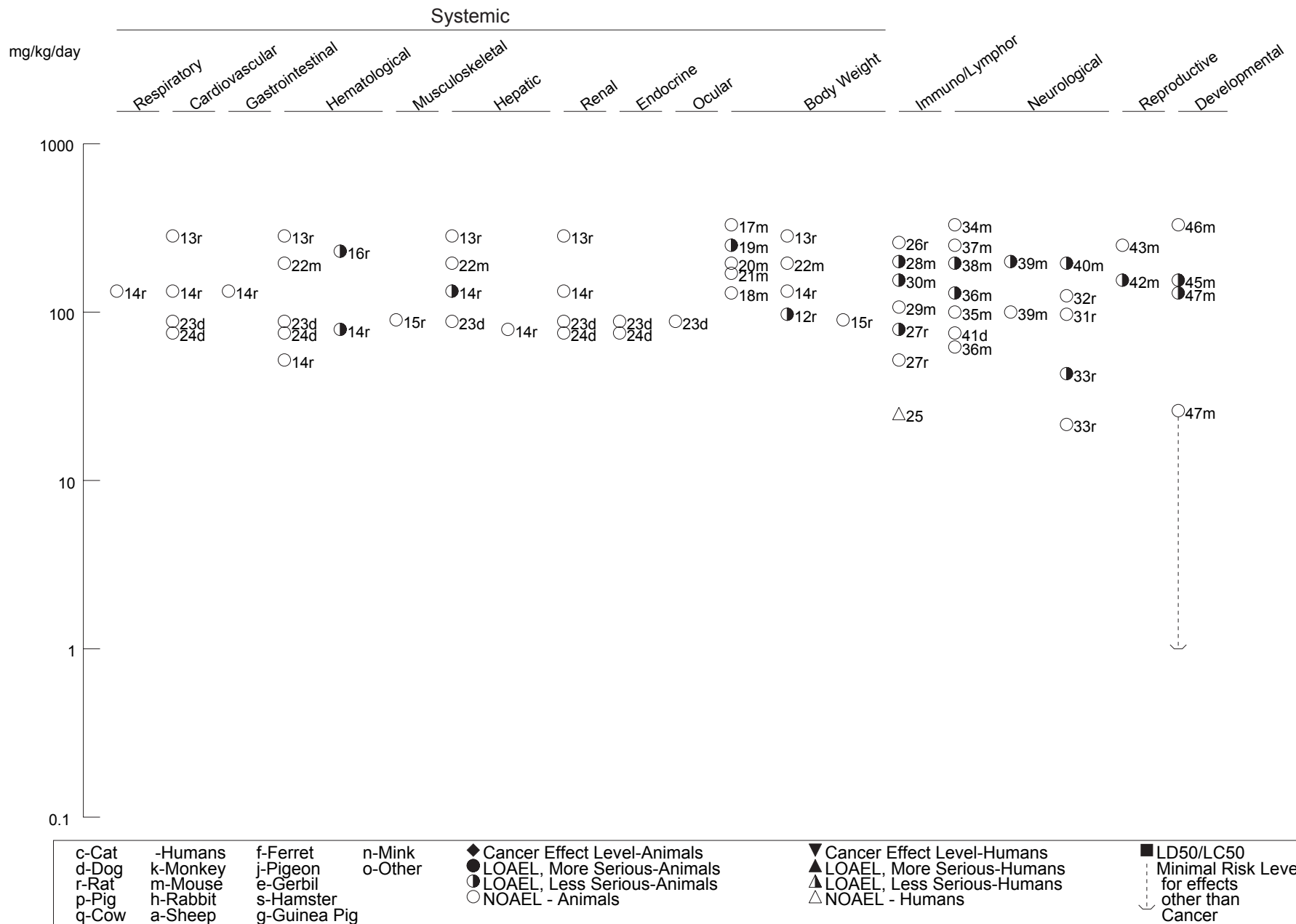
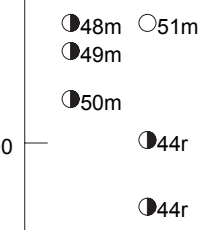
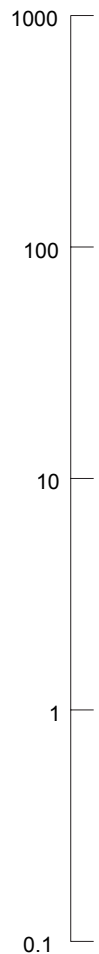


Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (Continued)

Intermediate (15-364 days)

mg/kg/day

Developmental

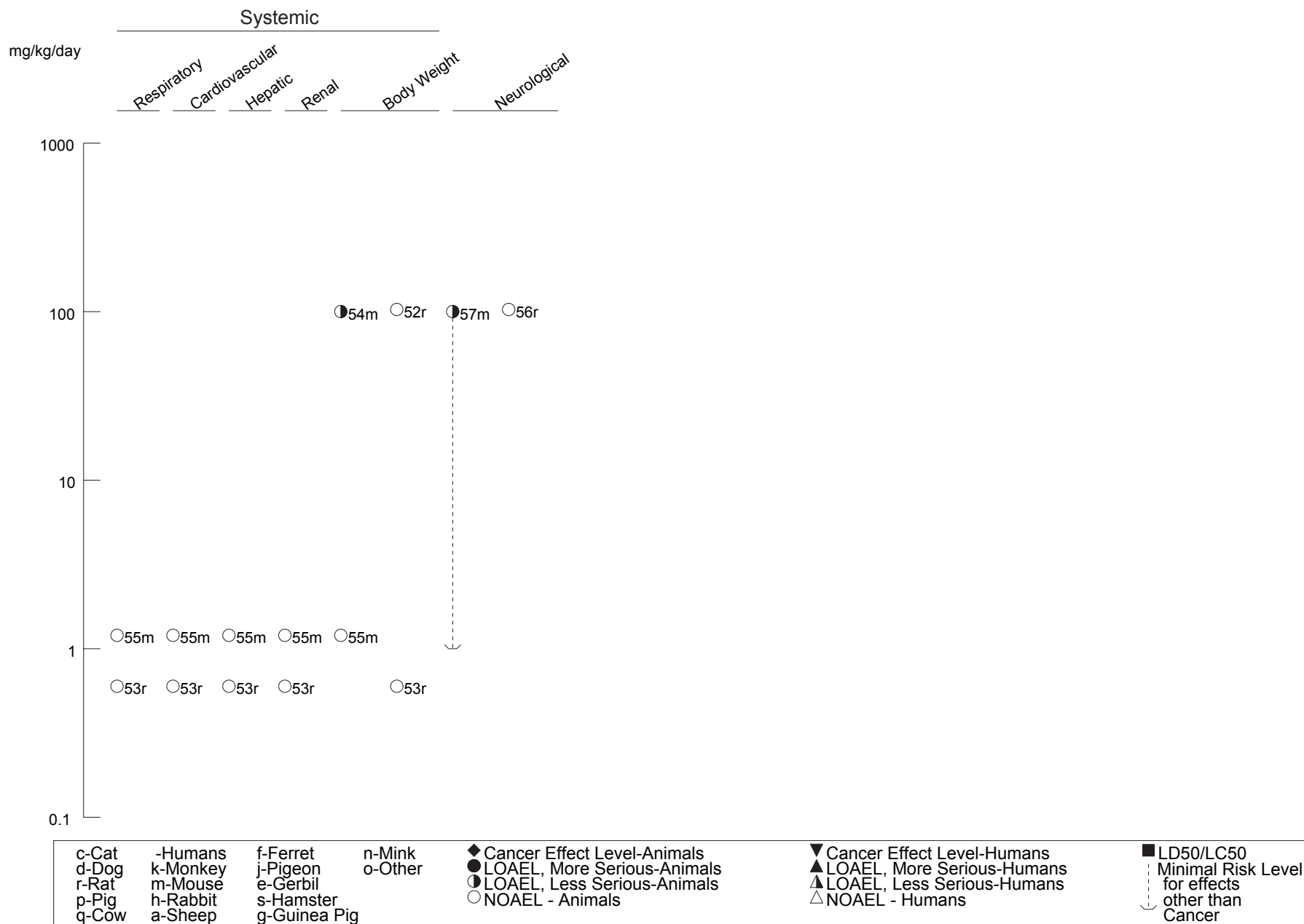


c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		◐ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	for effects
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	other than
q-Cow	a-Sheep	g-Guinea Pig				Cancer

ALUMINUM
3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to Aluminum and Compounds - Oral (Continued)

Chronic (≥365 days)



3. HEALTH EFFECTS

Although levels of human oral intake of aluminum may be characterized, it is important to recognize that the amount of aluminum ingested does not provide an actual estimate of exposure without information on bioavailability of the form of aluminum ingested. Similarly, effective doses in the animal studies, including the exact underestimate of aluminum intake in animal studies with insufficient information on aluminum in the base diet, cannot be known without information on bioavailability of the aluminum. As discussed in Section 3.3.1.2, the bioavailability of aluminum is influenced by the form in which it is ingested and the presence of other substances in the gastrointestinal tract, particularly complexing moieties in foods, which may significantly enhance or hinder absorption.

3.2.2.1 Death

No aluminum-related deaths in healthy humans have been reported after oral exposure. One aluminum compound that can be life threatening to humans is aluminum phosphide, a grain fumigant. Accidental or volitional ingestion (to commit suicide) of large amounts has caused death (Chopra et al. 1986; Khosla et al. 1988). The toxicity from this compound is due to the exposure to phosphine gas, which is produced in the gastrointestinal tract after the aluminum phosphide is ingested.

Aluminum caused death in laboratory animals only at doses that are high compared to normal human exposure. Data on acute lethality of ingested aluminum are summarized below. For aluminum bromide, LD₅₀ (lethal dose, 50% kill) values of 162 and 164 mg Al/kg have been reported in Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). For the nitrate form, LD₅₀ values of 261 and 286 mg Al/kg have been reported for Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). For the chloride form, LD₅₀ values of 370, 222, and 770 mg Al/kg have been reported for Sprague-Dawley rats, Swiss Webster mice, and male Dobra Voda mice, respectively (Llobet et al. 1987; Ondreicka et al. 1966). The LD₅₀ for aluminum sulfate in male Dobra Voda mice was reported as 980 mg Al/kg (Ondreicka et al. 1966). Time to death and clinical signs were not reported in these studies. A single gavage exposure to 540 mg Al/kg as aluminum lactate was fatal to all 5 lactating female New Zealand rabbits tested (Yokel and McNamara 1985). Time to death was reported as 8–48 hours.

Intermediate-duration oral exposure to aluminum has also been shown to cause death. Mortality occurred in female Swiss Webster mice exposed to aluminum lactate in the diet for 42 days throughout gestation and lactation at doses of 184 or 280 mg Al/kg/day (Golub et al. 1987), but not at 330 mg Al/kg/day in a different study (Donald et al. 1989) by the same group of investigators. Severe signs of neurotoxicity (ataxia, paralysis) were noted prior to the deaths. The effects in the Golub et al. (1987) study appear to be

3. HEALTH EFFECTS

related to semipurified diet composition. In particular, the formulation of the diet was revised by Donald et al. (1989) (and in subsequent studies by Golub and coworkers) by adding a “more generous provision” of several essential nutrients, particularly trace minerals (including calcium, magnesium, phosphate), to avoid the toxicity associated with the aluminum in the original diet. One of nine pregnant Swiss Webster mice that consumed 250 mg Al/kg/day as aluminum lactate in the revised purified diet died (Golub et al. 1992a). No mortality was observed in male Sprague-Dawley rats (7–10 per group) orally exposed to 70 mg Al/kg/day as aluminum chloride in water for 30, 60, or 90 days (Dixon et al. 1979), or up to 158 mg Al/kg/day as aluminum hydroxide in the feed for 16 days (Greger and Donnaubauer 1986); these doses do not include aluminum in the base diet. No male or female Beagle dogs (4/sex/group) died following dietary exposure to 75–80 mg Al/kg/day as sodium aluminum phosphate and base levels of aluminum in the feed for 26 weeks (Pettersen et al. 1990). In chronic-duration studies, exposure to aluminum at 100 mg Al/kg/day as aluminum lactate in the diet or 103 mg Al/kg/day as aluminum nitrate with added citric acid in drinking water did not result in significant alterations in mortality (Golub et al. 2000; Roig et al. 2006).

All reliable LOAEL values for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values for oral exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-2 and plotted in Figure 3-2; only studies providing information on the levels of aluminum in the base diet are included in Table 3-2 and Figure 3-2.

Respiratory Effects. No studies were located regarding respiratory effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause pulmonary edema in persons following accidental or volitional ingestion (Chopra et al. 1986; Khosla et al. 1988). The toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding respiratory effects of various forms of aluminum following acute-duration oral exposure in animals. Intermediate- and chronic-duration studies found no organ weight or histological changes in the lungs in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking

3. HEALTH EFFECTS

water (base dietary aluminum not reported) for 30, 60, or 90 days (Dixon et al. 1979), rats exposed to 133 mg Al/kg/day as aluminum nitrate in drinking water and base diet for 1 month (Gomez et al. 1986), rats or mice exposed to 0.6 and 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water (base dietary aluminum not reported), respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b), or mice exposed to 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994).

Cardiovascular Effects. No studies were located regarding cardiovascular effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause tachycardia, hypotension, cardiovascular electrocardiographic abnormalities, subendocardial infarction, and transient atrial fibrillation in persons who either ingested it accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding cardiovascular effects of aluminum or its compounds following acute-duration oral exposure in animals. No histological changes were observed in the hearts of male Sprague-Dawley rats given up to 70 mg Al/kg/day as aluminum chloride in drinking water (base dietary aluminum not reported) for 30, 60, or 90 days (Dixon et al. 1979). Similarly, no organ weight or histological changes were found in the hearts of female Sprague-Dawley rats that ingested 133 or 284 mg Al/kg/day as aluminum nitrate in drinking water and base diet for up to 1 month (Gomez et al. 1986) or 100 days, respectively (Domingo et al. 1987b). No organ weight or histological changes were observed in the hearts of dogs that consumed up to 75 mg Al/kg/day (Katz et al. 1984) or 88 mg Al/kg/day (aluminum levels of base diet not provide) (Pettersen et al. 1990) as sodium aluminum phosphate in the diet for 6 months.

Cardiovascular effects were not observed in animals following chronic-duration exposure to aluminum compounds. No histological changes were observed in the hearts of male and female Long Evans rats or Swiss mice given 0.6 or 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water, respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b) or B6C3F1 mice that ingested 979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). Aluminum levels in the base diet were not reported in these rat and mouse studies, although the animals were fed a low-metal diet in metal-free environmental conditions in the Schroeder and Mitchener (1975a, 1975b) studies.

3. HEALTH EFFECTS

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Unspecified gastrointestinal and bowel problems were reported by people who, for 5 days or more, may have consumed water that contained unknown levels of aluminum sulfate accidentally placed in a water treatment facility in England (Ward 1989). Forty-eight of the exposed persons were examined, but the number of people with gastrointestinal complaints was not reported. It should be noted that the water supply also contained elevated levels of copper and lead which leached from the plumbing systems due to the greater acidity of the water ($\text{pH} < 4$). Aluminum and copper levels in body tissues were reported as elevated in scalp hair and fingernails. Acute-duration oral exposure to aluminum phosphide has been shown to cause vomiting and abdominal pain in persons who ingested it either accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, as noted above, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

No studies were located regarding gastrointestinal effects of aluminum or its compounds following acute-duration oral exposure in animals. No organ weight or histological changes were observed in the gastrointestinal tissues of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water and base diet for up to 1 month (Gomez et al. 1986), or in male or female B6C3F1 mice that ingested 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994).

Hematological Effects. No studies were located regarding hematological effects of various forms of aluminum following acute-, intermediate-, or chronic-duration exposure in humans after oral exposure to aluminum or its compounds.

Repeated exposure to aluminum appears to adversely affect the hematological system of rats and mice. Significant decreases in hemoglobin, hematocrit, and/or erythrocyte osmotic fragility were observed in rats exposed to 420 mg Al/kg/day as aluminum citrate in drinking water for 15 weeks (Garbossa et al. 1998), mice exposed to 13 mg Al/kg as aluminum citrate administered via gavage 5 days/week for 22 weeks (Garbossa et al. 1996), rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999), and rats exposed via drinking water to 54.7 mg Al/kg/day as aluminum sulfate in a sodium citrate solution for 18 months (Farina et al. 2005). Exposure to lower concentrations or for shorter durations resulted in no significant damage to the erythrocytes. No alterations in hemoglobin, hematocrit, and/or erythrocyte osmotic fragility were observed in mice exposed to 13 mg Al/kg as aluminum citrate or aluminum chloride administered via gavage 5 days/week for 2 weeks

3. HEALTH EFFECTS

(Garbossa et al. 1996), rats exposed to 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986), mice exposed to 195 mg Al/kg/day as aluminum citrate in the diet for 5 or 7 weeks (Oteiza et al. 1993), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), rats exposed to 27 mg Al/kg as aluminum citrate administered via gavage 5 days/week for 15 weeks (Garbossa et al. 1996), or dogs exposed to 75 or 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984; Pettersen et al. 1990). The studies conducted by Domingo et al. (1987b), Gomez et al. (1986), Oteiza et al. (1993), Pettersen et al. (1990), and Vittori et al. (1999) provided information on the levels of aluminum in the base diet; the remaining studies did not provide this information. As highlighted by the Garbossa et al. (1996) study, which used multiple durations, the erythrocytic effects appear to be duration sensitive. No alterations in hemoglobin or hematocrit levels were observed in mice exposed to 13 mg Al/kg as aluminum citrate administered via gavage for 2 weeks; however, significant decreases in these parameters were observed when the exposure was continued for 22 weeks. Additionally, aluminum can alter mature erythrocyte morphology; anisocytosis (abnormal variations in cell size), anisochromia (unequal degree of cell staining), and poikilocytosis (abnormal variation in cell shape) have been observed in rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999). Hyperemia in the red pulp of the spleen was reported in rats exposed to 79 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986); this may be indicative of erythrocyte damage.

There is some evidence that aluminum may affect iron levels in blood; however, this has not been well studied and the results are not consistent across studies. Vittori et al. (1999) did not find significant alterations in plasma iron levels or total iron binding capacity in rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months; however, impaired iron uptake and decreased iron incorporation into heme were measured in bone marrow cells. Farina et al. (2005) found significant decreases in blood iron concentrations and no change in total iron binding capacity in rats exposed to 54.7 mg Al/kg/day as aluminum sulfate in a sodium citrate solution in drinking water for 18 months. Florence et al. (1994) reported decreases in serum iron levels, total iron binding capacity, and transferring saturation in rats exposed to 75 mg Al/kg/day as aluminum citrate in the diet for 6 months; however, the statistical significance of these findings was not reported.

Several studies have shown that aluminum can adversely affect erythropoiesis. Intermediate-duration exposure has been associated with significant inhibition of colony forming units-erythroid (CFU-E) development in bone marrow of mice exposed to 13 mg Al/kg as aluminum citrate or aluminum chloride administered via gavage 5 days/week for 2 or 22 weeks (Garbossa et al. 1996), rats exposed to 27 mg

3. HEALTH EFFECTS

Al/kg as aluminum citrate administered via gavage 5 days/week for 15 weeks (Garbossa et al. 1998), rats exposed to 420 mg Al/kg/day as aluminum citrate in drinking water for 15 weeks (Garbossa et al. 1998), and rats exposed to 230 mg Al/kg/day as aluminum citrate in drinking water for 8 months (Vittori et al. 1999); the aluminum content of the base diet was not reported in the Garbossa et al. (1996, 1998) studies. Chronic-duration studies did not examine this end point.

Musculoskeletal Effects. Joint pains were common symptoms reported in people in England who, for 5 days or more, consumed unknown levels of aluminum sulfate in drinking water which also contained elevated levels of copper and lead (Ward 1989). Osteomalacia has been observed in healthy individuals following long-term use of aluminum-containing antacids and in individuals with kidney disease. There are numerous case reports of osteomalacia and rickets in otherwise healthy infants and adults using aluminum-containing antacids for the treatment of gastrointestinal illnesses (i.e., ulcers, gastritis, colic) (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998). The aluminum in the antacids binds with dietary phosphorus and prevents its absorption resulting in hypophosphatemia and phosphate depletion. Osteomalacia, characterized by a softening of the bone and resulting in increased spontaneous fractures and pain, has been well documented in dialyzed uremic adults and children exposed to aluminum-contaminated dialysate or orally administered aluminum-containing phosphate-binding agents (Andreoli et al. 1984; Griswold et al. 1983; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989). Decreased aluminum urinary excretion caused by impaired renal function and possibly an increase in gastrointestinal absorption of aluminum (Alfrey 1993) results in increased aluminum body burden leading to markedly increased bone aluminum levels and the presence of aluminum between the junction of calcified and noncalcified bone. For more information on renal patients and aluminum, see Section 3.10.

Although long-term oral exposure to aluminum results in an increase in aluminum levels in the bone (Ahn et al. 1995; Konishi et al. 1996), there is no histological evidence that under normal physiological conditions that the accumulation of aluminum alters the bone structure. No histological alterations were observed in the tibias of male Wistar rats fed 100 mg Al/kg/day as aluminum lactate (aluminum levels in the base diet not reported) for 10 weeks (Konishi et al. 1996).

Hepatic Effects. No studies were located regarding hepatic effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Hepatic dysfunction was reported in 1 of 15 people acutely exposed to unspecified amounts of aluminum phosphide (Khosla et al. 1988).

3. HEALTH EFFECTS

However, the toxicity, as noted above was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

Most animal studies did not find significant alterations in liver weights or liver histology following intermediate- or chronic-duration oral exposure. Hyperemia and periportal monocytic infiltrate were observed in the livers of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986). Mild hepatocyte vacuolation was found in male dogs exposed to 75 mg Al/kg/day in the diet for 26 weeks (Pettersen et al. 1990), but the study authors concluded that the hepatic effects probably resulted from a drastic reduction in food consumption and a decrease in body weight.

The remaining studies conducting liver histopathological examinations did not find significant alterations in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking water for 30, 60, or 90 days (Dixon et al. 1979), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966), dogs exposed to 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984), mice exposed to 979 mg Al/kg/day as aluminum sulfate in the diet for 20 months (Oneda et al. 1994), or rats or mice exposed to 0.6 or 1.2 mg Al/kg/day as aluminum sulfate, respectively, in drinking water for a lifetime (Schroeder and Mitchener 1975a, 1975b). Only the Domingo et al. (1987b) and Ondreicka et al. (1966) studies included the levels of aluminum in the base diet.

Renal Effects. No studies were located regarding renal effects of various forms of aluminum following intermediate- or chronic-duration exposure in humans. Acute-duration oral exposure to aluminum phosphide has been shown to cause renal failure, significant proteinuria, and anuria in persons who ingested it either accidentally or in suicide attempts (Chopra et al. 1986; Khosla et al. 1988). However, toxicity was probably due to the formation of highly toxic phosphine gas rather than to aluminum exposure.

Several intermediate- or chronic-duration studies examined for possible effects on the kidneys; most studies did not find any adverse effects. Mild tubular “glomerularnephritis” was observed in dogs exposed to 75 mg Al/kg/day as sodium aluminum phosphate in the diet for 26 weeks (Pettersen et al. 1990); however, the study investigators did not consider this effect to be adverse because it was not accompanied by clinical evidence of kidney dysfunction. The effect may have been secondary to the

3. HEALTH EFFECTS

drastic reduction in feed intake and decreased body weight also observed in these dogs. No alterations in kidney histopathology were observed in rats exposed to 70 mg Al/kg/day as aluminum chloride in drinking water for 30–90 days (Dixon et al. 1979), rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966), dogs exposed to 88 mg Al/kg/day as aluminum phosphate in the diet for 6 months (Katz et al. 1984), mice exposed to 979 mg Al/kg/day as aluminum sulfate in the diet for 20 months (Oneda et al. 1994), or rats or mice exposed to 0.6 or 1.2 mg Al/kg/day as aluminum sulfate, respectively, in drinking water for a lifetime (Schroeder and Mitchener 1975a, 1975b). With the exception of the Domingo et al. (1987b), Pettersen et al. (1990), and Ondreicka et al. (1966) studies, information on the levels of aluminum in the base diet was not reported.

Endocrine Effects. No studies were located regarding endocrine effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

No studies were located regarding endocrine effects of aluminum or its compounds following acute-duration exposure in animals. No organ weight or histological changes were observed in the thyroid, adrenal, or pituitary glands of male and female Beagle dogs that consumed up to 75 (Pettersen et al. 1990) or 88 (Katz et al. 1984) mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months; the doses in the Katz et al. (1984) study do not include aluminum in the base diet.

Dermal Effects. No studies were located regarding dermal effects of various forms of aluminum following intermediate- or chronic-duration oral exposure in humans. Skin rashes were common symptoms reported by 48 people in England who consumed drinking water containing unknown levels of aluminum sulfate for approximately 5 days (Ward 1989). The water also contained elevated levels of copper and lead.

No studies were located regarding dermal effects of aluminum or its compounds following acute-duration exposure in animals. A localized loss of fur on the tip of the snout was observed in mice that ingested 130 mg Al/kg/day as aluminum lactate and base dietary aluminum for 6 weeks, but the effect was considered to be a sign of poor condition in the colony and not clearly attributable to aluminum exposure (Golub et al. 1989).

Ocular Effects. No studies were located regarding ocular effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

3. HEALTH EFFECTS

No studies were located regarding ocular effects of various forms of aluminum following acute-duration exposure in animals. No adverse ocular changes were found in male and female Beagle dogs that consumed up to 88 mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984); these doses do not include aluminum in the base diet.

Body Weight Effects. No studies were located regarding body weight effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

Most studies have not found significant alterations in body weight gain in rats or mice following acute exposure to 73–192 mg Al/kg/day as aluminum lactate or aluminum hydroxide with citric acid (Bernuzzi et al. 1986; Domingo et al. 1989; Gomez et al. 1991; Misawa and Shigeta 1992), intermediate-duration exposure to 20–399 mg Al/kg/day as aluminum lactate, aluminum chloride, aluminum hydroxide, or aluminum nitrate (Bernuzzi et al. 1989b; Bilkei-Gorzo 1993; Domingo et al. 1987b; Donald et al. 1989; Golub et al. 1989, 1992b, 1995; Gomez et al. 1986; Greger and Donnaubauer 1986; Konishi et al. 1996; Ondreicka et al. 1966; Oteiza et al. 1989), or chronic-duration exposure to 0.6–979 mg Al/kg/day as aluminum nitrate with citric acid, aluminum lactate, or aluminum sulfate (Golub et al. 2000; Oneda et al. 1994; Roig et al. 2006; Schroeder and Mitchener 1975a, 1975b). Of the studies reporting reductions of body weight gain, many involved gestational and/or lactational exposure; significant decreases in body weight gain were observed in rats administered via gavage 409 mg Al/kg/day as aluminum hydroxide with citric acid on gestation days 6–15 (Gomez et al. 1991), rats administered via gavage 38 mg Al/kg/day as aluminum nitrate on gestation days 6–14 (Paternain et al. 1988), rats administered via gavage 70 mg Al/kg/day as aluminum chloride on gestation days 0–16 (Sharma and Mishra 2006), and mice exposed to 200 or 250 mg Al/kg/day aluminum lactate in the diet on gestation day 0 through lactation day 21 (Golub et al. 1987, 1992a). A decrease in body weight was also observed in aged rats exposed to 97 mg Al/kg/day as aluminum nitrate with citric acid for 100 days (Colomina et al. 2002) and rats administered via gavage 53 mg Al/kg/day as aluminum chloride for 30 days (Rajasekaran 2000). In a lifetime exposure study, Golub et al. (2000) reported a 20% decrease in body weight gain in female mice exposed to 100 mg Al/kg/day as aluminum lactate in the diet; however, in a separate group of mice similarly exposed to 100 mg Al/kg/day as aluminum lactate, no significant alterations in body weight gain were observed (Golub et al. 2000).

3. HEALTH EFFECTS

3.2.2.3 Immunological and Lymphoreticular Effects

There are limited data on the potential for aluminum to induce immunological effects in humans. Intermediate-duration exposure to 25 mg Al/kg/day as aluminum hydroxide in the form of an antacid suspension for 6 weeks did not affect immunoglobulin and interleukin concentrations or production, natural killer (NK) cells, or B- and T-lymphocyte populations or proliferation; a significant reduction in, primed cytotoxic T- cells (CD8+CD45R0+ population) was observed (Gräske et al. 2000). The toxicological significance of this finding in the absence of other alterations is not known.

Very few animal studies examined the potential immunotoxicity of aluminum. Intermediate-duration exposure of mice to 13 mg Al/kg/day as aluminum citrate administered via gavage 5 days/week for 22 weeks resulted in a significantly higher proliferation of lymph node cells and had no effect on spleen cell proliferation (Lauricella et al. 2001). This suggests that while aluminum might induce alterations in cell immune response, the stimulating or suppressing effects could depend on the dose, route of administration, exposure duration, or cell population. There is some evidence that developmental exposure to aluminum may adversely affect the immune system in young animals. A 19% increase in spleen weights, depressed spleen cell concentrations of interleukin-2, interferon- γ and tumor necrosis factor- α , and a deficiency of CD4+ cells in T-cell populations were observed in Swiss Webster mice exposed to aluminum from conception through 6 months of age (Golub et al. 1993). The maternal animals consumed 200 mg Al/kg/day as aluminum lactate in the diet from conception through lactation and the offspring were subsequently fed the same diet as the dams. Susceptibility to bacterial infection was increased in offspring of Swiss-Webster mice exposed to dietary aluminum lactate in a dose of 155 mg Al/kg from conception through 10 days of age, but not in 6-week-old mice exposed to 107 mg Al/kg/day for 6 weeks (Yoshida et al. 1989). Susceptibility to infection was evaluated by assessing survival following intravenous inoculation with *Listeria monocytogenes* at the end of the exposure periods.

No organ weight or histological changes in spleen and/or thymus were observed in female Sprague-Dawley rats exposed to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b), male Sprague-Dawley rats given 70 mg Al/kg/day as aluminum chloride in drinking water for 30, 60, or 90 days (Dixon et al. 1979), or male and female mice exposed to 979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). The doses in all of the above studies except Lauricella et al. (2001), Dixon et al. (1979), and Oneda et al. (1994) include aluminum in the base diet.

3. HEALTH EFFECTS

The highest reliable NOAEL value and all reliable LOAEL values in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

The neurotoxicity of aluminum following oral exposure has been well established in humans with renal insufficiency and animals; however, it has not been adequately investigated in healthy humans. The human database consists of case reports of acute accidental or intentional exposure to aluminum, an acute exposure study in healthy individuals, studies of patients undergoing dialysis treatment, and studies examining the possible association between aluminum ingestion and Alzheimer's disease.

Memory loss, fatigue, depression, behavioral changes, and learning impairment were reported in five children who, over a 5-day period, consumed drinking water containing unknown levels of aluminum sulfate, which was accidentally placed in a water-treatment facility in England (Ward 1989). The water also contained elevated levels of copper and lead, a highly neurotoxic element, which leached from the plumbing systems due to the greater acidity of the water. Thus, the role of aluminum in the onset of the neurological symptoms is unclear. Acute-duration oral exposure to aluminum phosphide (19–157 mg Al/kg) caused altered sensorium in 4 of 16 persons who ingested it either accidentally or in suicide attempts (Khosla et al. 1988). Restlessness and loss of consciousness were observed in 10 of 15 people who ingested unknown amounts of aluminum phosphide (Chopra et al. 1986). The toxicity associated with aluminum phosphide ingestion was probably due to the formation of highly toxic phosphine gas rather than the aluminum exposure.

Uremic persons represent a population at risk for aluminum-related dementia (Alfrey 1993). Prolonged dialysis with aluminum-containing dialysates, possibly combined with oral treatment with aluminum hydroxide to control hyperphosphatemia, has produced a characteristic neurotoxicity syndrome which has been referred to as “dialysis dementia” (Alfrey 1987; King et al. 1981; Mayor et al. 1985; Wills and Savory 1989). Alfrey (1993) describes two types of aluminum neurotoxicity in uremic patients: acute and classical. The acute form is caused by high levels of aluminum in the dialysate, the co-ingestion of aluminum-containing phosphate binders and citrate, or the rapid rise in serum aluminum following desferoxamine treatment. The onset of neurotoxicity is rapid and marked by confusion, muscle twitching, grand mal seizures, coma, and death. Plasma levels of aluminum are typically >500 µg/L; normal levels are approximately 1–3 µg/L (House 1992; Liao et al. 2004). The classical type results from chronic

3. HEALTH EFFECTS

parenteral or oral aluminum exposures and is characterized by a gradual onset of neurobehavioral disorders and, eventually, death. These neurological effects have been observed in adults and children (Alfrey 1993; Griswold et al. 1983). Plasma levels are estimated to be 100–200 µg/L. Limiting aluminum exposure in uremic persons (for example, the use of aluminum-free dialysates and aluminum-free phosphate binding agents) essentially eliminates these neurotoxic effects.

Alzheimer's disease is a neurodegenerative disorder, which is manifested clinically as a progressive deterioration of memory and cognition. The primary neuropathological characteristics of Alzheimer's disease are neuronal loss and the formation of neurofibrillary tangles, senile plaques with amyloid deposits and neuropil threads, and cerebrovascular amyloid deposition. The etiology of Alzheimer's disease is complex, with genetics playing a critical role; there is also evidence that the environment may modify the risk. The possible association between aluminum and Alzheimer's disease was proposed over 40 years ago; however, the evidence that aluminum may or may not be a risk factor is inconsistent and inconclusive. A number of lines of evidence have been used to support the relationship between aluminum and Alzheimer's disease (Flaten 2001; Munoz 1998); these include elevated levels of aluminum in the brains of individuals with Alzheimer's disease, the well-established neurotoxicity of aluminum, and epidemiology studies finding a geographical association between aluminum levels in drinking water and Alzheimer's disease. In the last 25 years, a number of epidemiology and animal studies have investigated this possible association; an animal model that fully mimics human Alzheimer's disease has not been identified. Many of the epidemiology studies have been criticized for flawed patient selection, poor comparability of exposed and control groups, poor exposure assessment, inaccurate diagnosis of Alzheimer's disease, and weak statistical correlations (Nieboer et al. 1995; Schupf et al. 1989). A number of these studies have found significant associations between individuals living in areas with elevated aluminum levels in drinking water and the prevalence of Alzheimer's disease (or a surrogate such as dementia or cognitive impairment) (Flaten 1990; Forbes et al. 1992, 1994; Gauthier et al. 2000; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990; Neri and Hewitt 1991; Rondeau et al. 2000, 2001); the aluminum content of the water typically exceeded 0.10 mg Al/L. The odds ratios (or relative risks) were typically <2.0 (Flaten 1990; Jacqmin et al. 1994; Martyn et al. 1989; McLachlan et al. 1996; Neri and Hewitt 1991), although some studies, particularly studies that controlled for other risk factors such as age, education level, and family history of dementia, estimated higher odds ratios (Gauthier et al. 2000; Rondeau et al. 2000). In contrast, several studies did not find significant associations between aluminum exposure and the risk of Alzheimer's disease (or cognitive impairment) (Forster et al. 1995; Martyn et al. 1997; Sohn et al. 1996;

3. HEALTH EFFECTS

Wettstein et al. 1991; Wood et al. 1988); the levels of aluminum in the drinking water were similar to the levels in studies finding positive associations.

Additionally, there are studies that examined the possible association between Alzheimer's disease and ingestion of aluminum from sources other than drinking water, particularly tea and antacids. The aluminum levels in tea are typically 10–50 times higher than levels found in drinking water; similarly, the levels of aluminum in antacids (typically containing aluminum hydroxide) are very high compared to drinking water levels. No significant associations between tea consumption (Forster et al. 1995; McDowell et al. 1994) or antacid use (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) and Alzheimer's disease have been found. A small scale study did find a significant relationship between consumption of food containing aluminum additives and the risk of Alzheimer's disease (Rogers and Simon 1999); however, this was based on a very small number of cases. The contrast between the results of the drinking water studies, many of which found a weak association between living in areas with high aluminum levels in drinking water and Alzheimer's disease, and the tea and antacid studies may be due to the difference in aluminum bioavailability. The presence of tannins and other organic constituents found in tea may significantly reduce aluminum absorption; the aluminum hydroxide found in antacids is poorly absorbed. Although the aluminum speciation was not provided in most drinking water studies, in a study by Gauthier et al. (2000), organic monomeric aluminum was the only aluminum species significantly associated with Alzheimer's disease. The bioavailability of organic aluminum compounds such as aluminum citrate, aluminum lactate, and aluminum maltolate is much greater than for inorganic aluminum compounds (Froment et al. 1989a; Yokel and McNamara 1988).

In conclusion, the available data suggest that aluminum is not likely the causative agent in the development of Alzheimer's disease. However, aluminum may play a role in the disease development by acting as a cofactor in the chain of pathological events resulting in Alzheimer's disease (Flaten 2001).

Amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia (PD) are neurodegenerative diseases that have also been associated with aluminum exposure. ALS is a progressive disease of the central nervous system that is characterized by an accumulation of neurofibrillary tangles. In Guam, Southwest New Guinea, and the Kii Peninsula of Honshu Island in Japan, there is an unusually high prevalence of ALS and PD. This may be related to the natural abundance of highly bioavailable aluminum compounds coupled with the virtual lack of magnesium and calcium in the areas' drinking water supplies and soil. The consumption of the neurotoxic seed of the false sago palm tree may also play a key role in the

3. HEALTH EFFECTS

prevalence of ALS and PD in these areas. It has been proposed that long-term dietary deficiencies of calcium, rendering a secondary hyperparathyroid state, in the presence of highly bioavailable aluminum compounds and enhanced gastrointestinal absorption of aluminum can result in neuronal degeneration. In a study designed to evaluate effects of high aluminum and low calcium levels in the diet, much like the conditions associated with Guam and other similar areas, *Cynomolgus* monkeys were placed on a low calcium diet either with or without supplemental aluminum and manganese (Garruto et al. 1989). Chronic calcium deficiency alone produced neurodegenerative effects, although neurofibrillary changes were most frequently seen in the monkey on a low calcium diet supplemented with aluminum and manganese.

There are limited data on the neurotoxicity of ingested aluminum in healthy individuals. An acute exposure study conducted by Molloy et al. (2007) did not find any significant alterations in performance in neurobehavioral tests with a mean aluminum blood level of 280–300 µg/L at the time of testing. Although neurotoxicity of aluminum has not been established or adequately studied in people who are healthy (i.e., have normal renal function), there is conclusive evidence that aluminum compounds are neurotoxic in orally-exposed animals. As discussed below and in Section 3.2.2.6, numerous intermediate-duration studies in mice and rats found various neurotoxic effects in exposed adults and developing offspring.

Many of the animal neurotoxicity studies are complicated by a lack of reported information on aluminum content in the base diet. This is an important issue because, as discussed in the introduction to Section 3.2.2, commercial rodent laboratory feed has a high aluminum content which can significantly contribute to total exposure. Dosages in studies with insufficient information on aluminum content in the base diet therefore must be assumed to underestimate the actual experimental dosages. The magnitude of the underestimate may be considerable, particularly for maternal dietary intake during lactation (an exposure period used in many neurobehavioral studies of aluminum in mice), which can be markedly (often 2-fold) higher than in nonlactating adults. Consequently, although aluminum studies with inadequate data on base dietary levels of aluminum provide useful information on neurotoxicity, NOAELs and LOAELs from these studies cannot be assumed to be accurate and are not suitable for comparing with effect levels from studies that used diets with known amounts of aluminum. There is particular concern for the adequacy of neurotoxicity NOAEL and LOAEL values for aluminum because sensitive neurotoxic effects may occur in rodents at aluminum intake levels close to those provided by commercial diet alone. Based on these concerns, only neurotoxicity studies providing information on base dietary aluminum content are included in Table 3-2.

3. HEALTH EFFECTS

In general, oral exposure to aluminum is not associated with marked signs of neurotoxicity in animals. In a study by Golub et al. (1987), ataxia, splaying and dragging of hindlimbs, and paralysis were observed in mouse dams exposed to 200 mg Al/kg/day as aluminum lactate during gestation and lactation. Other studies involving exposure to higher aluminum doses have not noted significant increases in the incidence of overt signs of neurotoxicity (Donald et al. 1989; Golub et al. 1992a). It is possible that the levels of essential trace minerals in the diet used by Golub et al. (1987) were too low and may have contributed to the severity of the observed effects. The diet formulation used by this group was revised by adding a “more generous provision” of several essential nutrients, particularly trace minerals (including calcium, magnesium, phosphate), to avoid the marked maternal neurotoxicity associated with their absence in the original diet (Donald et al. 1989). Due to the apparent nutritional insufficiency of the diet used by Golub et al. (1987), the results of this study are not included in Table 3-2. Another overt sign of toxicity is an increase in cage mate aggression in male mice exposed to 200 mg Al/kg/day from gestation day 1 through postnatal day 170 (Golub et al. 1995).

The overall weight of evidence strongly indicates that oral exposure to aluminum results in functional and cognitive alterations. Motor function and sensory function are affected by aluminum exposure.

Decreases in forelimb and/or hindlimb grip strength have been observed in mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993) or 13 weeks (Golub et al. 1992b; Oteiza et al. 1993) and in mice exposed to 100 mg Al/kg/day for over 2 years (Golub et al. 2000). In contrast, no alterations in grip strength were observed in mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day (Donald et al. 1989) as aluminum lactate in the diet on gestation day 1 through lactation day 21 or in mice exposed to 200 mg Al/kg/day on gestation day 1 through postnatal day 170 (Golub et al. 1995). No significant alterations have been observed for footsplay or negative geotaxis following intermediate duration exposure to 195 mg Al/kg/day or 200 mg Al/kg/day as aluminum lactate in the diet (Golub et al. 1992b, 1995; Oteiza et al. 1993) or mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in diet on gestation day 1 through lactation day 21 (Donald et al. 1989). A chronic-duration study found impaired performance on the negative geotaxis test after 18 months of exposure to 100 mg Al/kg/day as aluminum lactate in the diet, but not after 24 months of exposure (Golub et al. 2000).

Significant decreases in spontaneous motor activity have also been reported in rats and mice exposed to aluminum chloride or aluminum lactate in the diet for at least 6 weeks. Effects are typically observed at doses of 130 mg Al/kg/day and higher. A decrease in total spontaneous activity, vertical activity

3. HEALTH EFFECTS

(rearing), and horizontal activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989). In mice exposed to 195 mg Al/kg/day, decreases in total activity, horizontal activity, and percentage of intervals with high activity counts were found after 90 days of exposure, but not after 45 days of exposure (Golub et al. 1992b). Decreases in spontaneous motor activity have also been observed in rats exposed to aluminum chloride in the diet for 7 weeks or 11 months (Commissaris et al. 1982); the amounts of aluminum added to the diet were 184 and 66 mg Al/kg/day, respectively; however, the aluminum content of the basal diet was not reported. Gavage exposure to a relatively low dose (53 mg Al/kg/day as aluminum chloride; aluminum content of the diet not reported) was also associated with a decrease in spontaneous motor activity. Exposure to lower doses of aluminum lactate or aluminum nitrate (with added citric acid) has not been associated with decreases in motor activity. No alterations in motor activity (as assessed in open field tests) were found in rats exposed to 97 mg Al/kg/day for 100 days (Colomina et al. 2002), 125 mg Al/kg/day for 6.5 months (Domingo et al. 1996), or 103 mg Al/kg/day for 1 or 2 years (Roig et al. 2006). Similarly, no alterations in total activity or horizontal activity were observed in mice exposed to 100 mg Al/kg/day as aluminum lactate in the diet during gestation, lactation, and postnatally until 2 years of age (Golub et al. 2000). However, the investigators noted that the automated activity monitor used in this study did not detect vertical movement of the older rats and that their previous study (Golub et al. 1989) found that vertical movement was more sensitive than horizontal movement. Another chronic-duration study (Roig et al. 2006) found no significant alterations in the total distance traveled or the total number of rearings in rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) from gestation day 1 through 2 years of age. Exposure to doses as high as 1,252 mg Al/kg/day as aluminum hydroxide (aluminum content of the basal diet was not reported) for 30 or 60 days (Thorne et al. 1986, 1987); the poor absorption of aluminum hydroxide probably contributed to this very high NOAEL.

Several tests of sensory function have resulted in significant alterations. Decreases in thermal sensitivity were observed following chronic exposure of mice to 100 mg Al/kg/day as aluminum lactate in the diet (Golub et al. 2000). Changes in thermal sensitivity was not observed in mice exposed to 195 mg Al/kg/day as aluminum lactate for 5–7 weeks (Oteiza et al. 1993) or 13 weeks (Golub et al. 1992b) or mouse dams exposed to 250 mg Al/kg/day (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989). As with thermal sensitivity, conflicting results have been observed for startle responsiveness. Decreased responses to auditory and/or air puff stimuli were observed in mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993) or 90 days (Golub et al. 1992b). However, no changes in startle responsiveness were observed in mice exposed to 250 or 330 mg Al/kg/day as

3. HEALTH EFFECTS

aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989; Golub et al. 1992a). Impairment of post-rotatory nystagmus was observed in rats exposed to 43.1 mg Al/kg/day as aluminum chloride in drinking water (dietary aluminum levels not reported) for 3 months; no alterations were observed at 21.5 mg Al/kg/day (Mameli et al. 2006).

The potential effect of aluminum on cognitive function has been assessed in a number of studies using passive avoidance, operant training, or water maze tests. Aluminum does not appear to adversely affect performance on passive avoidance or operant training tests at lower oral doses. No significant alterations have been observed in rats exposed to 97 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 100 days (Colomina et al. 2002), rats exposed to 125 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 6.5 months (Domingo et al. 1996), or rats exposed to 830 mg Al/kg/day or as high as 1,252 mg Al/kg/day as aluminum hydroxide in the diet (aluminum levels of basal diet were not reported) for 60 or 30 days, respectively (Thorne et al. 1987). Another study found improved performance on operant training tasks in mice exposed to 100 mg Al/kg/day in the diet for an intermediate duration (Golub and Germann 1998); the authors attributed this to an increase in food motivation in the aluminum-exposed mice. It is not known if an increased food motivation also influenced the results of the other studies. At higher aluminum doses, performance on operant training tasks is adversely affected. Impaired retention of learned responses were observed in rats exposed to 346 mg Al/kg/day as aluminum sulfate in the drinking water (aluminum content of the diet was not reported) (Connor et al. 1989) or 70 mg Al/kg/day as aluminum chloride in drinking water (aluminum content of the basal diet was not reported) for 90 days (Zhang et al. 2003). Another study found impaired learning (more trials were needed to reach the acquisition criterion), but no effect on retention or recall in rats exposed to 66 mg Al/kg/day as aluminum chloride in the diet (aluminum content of the basal diet was not reported) (Commissaris et al. 1982).

Because maze tests did not typically involve a food reward, these studies controlled for the potential confounder of food motivation. Impaired learning in a labyrinth maze test was observed in rats receiving gavage doses of 6 mg Al/kg/day as aluminum chloride or 35 mg Al/kg/day as aluminum hydroxide with citric acid (aluminum content of the diet was not reported) for 90 days (Bilkei-Gorzo 1993). In Morris water maze tests, impaired learning and memory was observed following gavage doses of 500 mg Al/kg/day of an unreported aluminum compound for 90 days (Jing et al. 2004). In contrast, no significant alterations in performance on the water maze test were found in rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water for a chronic duration (Roig et al. 2006).

3. HEALTH EFFECTS

A number of studies have conducted histopathological examinations of the brain of rats, mice, and dogs following oral exposure to aluminum and have not found significant alterations (Dixon et al. 1979; Domingo et al. 1987b; Gomez et al. 1986; Katz et al. 1984; Oneda et al. 1994; Pettersen et al. 1990); the aluminum doses ranged from 70 to 979 mg Al/kg/day. In contrast to these results, Abd El-Rahman (2003) reported spongioform changes in the neurons of the hippocampus, nuclear deformity, neurofibrillary degeneration, and foci of demyelination in rats receiving gavage doses of 85.9 mg Al/kg/day as aluminum sulfate (aluminum content of the diet was not reported).

Neurotoxicity has been extensively studied in developing mice and rats that were exposed to aluminum during gestation, lactation, and/or directly via diet following weaning. As summarized in Section 3.2.2.6, effects on reflexes and simple motor behaviors were commonly found in aluminum-exposed developing animals, whereas effects on learning and memory have not been consistently shown.

All reliable NOAEL and LOAEL values for neurological effects in adults in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects of various forms of aluminum following acute-, intermediate-, or chronic-duration oral exposure in humans.

Several studies evaluated reproductive effects of acute-duration oral exposure to aluminum in animals. An increased incidence of resorptions occurred in female BALB/c mice treated with 41 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) on gestation days 7–16 (Cranmer et al. 1986). No reproductive effects were observed in female Sprague-Dawley rats exposed to 158 mg Al/kg/day as aluminum hydroxide or aluminum citrate by gavage and base diet from gestation day 6 to 15 (Gomez et al. 1991), or in THA rats treated with 73.1 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) from gestation day 7 to 16 (Misawa and Shigeta 1992). In a study of female reproductive system development (Agarwal et al. 1996), offspring of rats that were gavaged with aluminum lactate on gestation days 5–15 showed a transient irregularity of the estrus cycle (increased number of abnormal cycle lengths) at 250 mg Al/kg/day; doses as high as 1,000 mg Al/kg/day did not affect other end points (gonad weights, anogenital distance, time to puberty, duration of induced pseudopregnancy, or numbers of superovulated oocytes). The inconsistent findings summarized above may reflect differences in susceptibility among different strains/species of animals or compound

3. HEALTH EFFECTS

differences in toxicity or bioavailability. Additionally, because levels of aluminum in the base diet were not reported by Agarwal et al. (1996), Misawa and Shigeta (1992), or Cranmer et al. (1986), the doses in these studies are likely to underestimate actual aluminum intake.

In a combination acute- and intermediate-duration study, no adverse effects on fertility or other general reproductive indices were found in female rats that were exposed to 38–77 mg Al/kg/day as aluminum nitrate by gavage and base diet for 14 days prior to mating with males that were similarly treated for 60 days pre-mating (Domingo et al. 1987c). These exposures were continued throughout mating, gestation, parturition, and weaning and caused a reduction in the growth of the offspring in all treated groups, but the effects were negligible and transient (slight decreases in body weight, body length, and tail length observed on postpartum days 1 and 4 were no longer evident at time of weaning). An intermediate-duration oral study in male rats found that sperm count was decreased following exposure to 2.5 mg Al/kg/day as aluminum chloride for 6–12 months (Krasovskii et al. 1979). The method of oral exposure was not specified but is presumed to be gavage, no information on aluminum in the base diet was reported, and reproductive function was not evaluated. No adverse reproductive effects were seen in male Sprague-Dawley rats, as assessed by plasma gonadotropin levels, histopathological evaluation, and serial matings, following exposure to 70 mg Al/kg/day as aluminum chloride in drinking water for up to 90 days (Dixon et al. 1979); this dose does not include base dietary aluminum.

Mating success (numbers of litters and offspring) was not affected in a three-generation study with Dobra Voda mice that were exposed to 49 mg Al/kg/day as aluminum chloride in drinking water and base diet over a period of 180–390 days (Ondreicka et al. 1966). No reproductive effects were observed in pregnant Swiss Webster mice that consumed 250 mg Al/kg/day as aluminum lactate throughout gestation and lactation (Golub et al. 1992a). However, an alteration in gestation length was observed in pregnant Swiss Webster mice that consumed 155 mg Al/kg/day as aluminum lactate in the diet during gestation and lactation (Donald et al. 1989). The effect on gestation length was small but statistically significant; all litters in the control group (7.5 mg Al/kg/day) were born on gestation day 18, whereas 4 of 17 litters exposed to ≥ 155 mg Al/kg/day were born earlier or later (gestation days 17, 19, or 20).

No organ weight or histological changes were observed in the gonads of male and female Beagle dogs that consumed 93 mg Al/kg/day as acidic sodium aluminum phosphate (a common human food additive) in the diet for 6 months (Katz et al. 1984); this dose does not include base dietary aluminum. In another study with dogs, two of four male Beagles that were fed 75 mg Al/kg/day as basic sodium aluminum phosphate and base dietary aluminum for 26 weeks had decreased testicular weight and moderate

3. HEALTH EFFECTS

seminiferous tubule germinal epithelial cell degeneration and atrophy (Pettersen et al. 1990). No changes in reproductive tissue weight or histology occurred in the males at lower doses (≤ 27 mg Al/kg/day) or in female Beagles similarly exposed to ≤ 80 mg Al/kg/day. The investigators concluded that the testicular changes appeared to be secondary to palatability-related reductions in food consumption and body weight, and therefore, are not clearly direct effects of aluminum.

Chronic studies showed no histological changes in the testes or ovaries of male and female Wistar rats fed a diet containing unspecified levels of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972), or in B6C3F1 mice that ingested 979 mg Al/kg/day as dietary aluminum potassium sulfate for 20 months (Oneda et al. 1994). The doses in the latter study do not include aluminum in the base diet. Neither mouse study assessed reproductive function.

The highest reliable NOAEL and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects of various forms of aluminum following acute- or chronic-duration oral exposure in healthy humans. The only human data on developmental effects come from infants with renal failure and premature infants. Their responses are probably not indicative of responses expected in normal infants. Osteomalacia and increased bone and serum levels of aluminum were reported in three infants with kidney failure who had been treated orally with >100 mg of Al/kg/day as aluminum hydroxide from the first or sixth month of life (Andreoli et al. 1984; Griswold et al. 1983), and in healthy infants ingesting aluminum-containing antacids (Pivnick et al. 1995). Progressive encephalopathy was also observed among children with severe renal disease ingesting aluminum-containing phosphate binders (Finberg et al. 1986; Griswold et al. 1983).

A large number of studies have examined the developmental toxicity of aluminum in rats and mice. A variety of effects have been found including decreased pup survival/increased pup mortality, decreased growth, delayed maturation, and impaired neurodevelopment. Increases in pup mortality, typically occurring within the first 4 postnatal days, have been observed in rats exposed to 155 mg Al/kg/day as aluminum chloride in the diet on gestational days 8–20 (Bernuzzi et al. 1986), 200 mg Al/kg/day as aluminum lactate administered via gavage on postnatal days (PND) 5–14 (Bernuzzi et al. 1989a), and 272 mg Al/kg/day as aluminum chloride or 378 mg Al/kg/day as aluminum lactate in the diet on gestation

3. HEALTH EFFECTS

days 1–20. Interpretation of the results of these studies is limited by the lack of information on the aluminum content of the basal diet. Another study found a decrease in the number of live pups per litter and an increase in the number of dead young per litter on PND 21 in the offspring of rats administered via gavage 51 mg Al/kg/day as aluminum nitrate for 14 days prior to mating, on gestation days 1–20, and lactation days 1–21 (Domingo et al. 1987c). The gavage administration route may have influenced the results of this study; other studies involving exposure to aluminum nitrate, aluminum citrate, or aluminum lactate via drinking water or diet have not reported increases in mortality at doses as high as 330 mg Al/kg/day as aluminum lactate in the diet on gestation days 1 through PND 35 (Colomina et al. 1992, 2005; Golub and Germann 1998, 2001; Golub et al. 1992a, 1995; McCormack et al. 1979).

Numerous studies have reported decreases in pup body weight gain (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). Since some of these studies did not report the aluminum content of the basal diet, their usefulness in establishing dose-response relationships is limited. With few exceptions, most studies have shown that aluminum does not adversely affect birth weight in the absence of 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). The possible exception to this finding was decreases in birth weight observed in the offspring of rats administered aluminum nitrate via gavage at doses of ≥ 38 mg Al/kg/day on gestation day 1 through lactation day 21 (Domingo et al. 1987c) or 77 mg Al/kg/day on gestation day 14 through lactation day 21 (Domingo et al. 1987a); neither study reported whether there were significant effects on maternal body weight gain. Paternain et al. (1988) also reported a decrease in pup body weight in rats receiving gavage doses of 38 mg Al/kg/day as aluminum nitrate on gestation days 6–14; a decrease in maternal weight gain was also reported at this dose level. Although most studies did not find effects on birth weights, several studies did find decreases in post-birth pup body weights; however, this finding was not consistent across studies. Lower pup body weights starting on PND 10 were observed in mouse pups exposed to aluminum during gestation only, during lactation only, or during gestation and lactation (Golub et al. 1992a); a decrease in maternal body weight gain was observed in the dams exposed during lactation. This study suggests that aluminum may influence growth directly and may not be only related to changes in maternal body weight during lactation. Similarly, decreases in body weights were observed on PND 12, 16, and 21 in the pups exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid) on gestation day 1 through lactation day 21; a decrease in maternal food and water intake was also observed at this dose level (Colomina et al. 2005). A third study found decreases in pup body weight at PND 21 in

3. HEALTH EFFECTS

mice exposed to 130 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001). The lower body weights were still present at 5 months of age even though aluminum exposure was stopped on PND 35; an increase in food intake was also observed in these animals. In contrast to these studies, no adverse effects on body weight were observed in mouse pups exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 21 or 35 (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995).

Gestational exposure to aluminum does not appear to result in an increase in the occurrence of malformation and anomalies, although reductions in ossification have been observed (Gomez et al. 1991; Sharma and Mishra 2006). Delays in ossification were observed at doses that also resulted in decreases in pup body weight. Some alterations in physical maturation have been observed in rats exposed to aluminum nitrate in drinking water (with added citric acid) on gestation day 1 through lactation day 21 (Colomina et al. 2005). The observed effects included significant delay in vagina opening at 53 or 103 mg Al/kg/day, testes descent at 103 mg Al/kg/day, and incisor eruption in males at 53 mg Al/kg/day. No effects on days to pinna detachment or eye opening were observed. No delays on pinna detachment, eye opening, or incisor eruption were observed in rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet not reported) on gestation days 8–20 (Misawa and Shigeta 1992).

Animal studies provide strong evidence that gestational and/or lactational exposure to aluminum impairs the development of the nervous system. Potential neurodevelopmental effects have been evaluated using a variety of functional tests and cognitive tests. Because comparisons between studies are difficult due to differences in the exposure period, subroute of exposure, lack of information on the aluminum levels in the basal diet, and age of assessment, the results for each test will be presented separately. Significant impairment in the righting reflex and grasping reflex were observed in rat pups exposed to 272 mg Al/kg/day as aluminum chloride or 194 mg Al/kg/day as aluminum lactate in the diet (aluminum content of the basal diet was not reported) on gestation days 1–20 (Bernuzzi et al. 1989b); no reflex alterations were observed at 96 mg Al/kg/day for aluminum chloride or aluminum lactate. Impairment of the righting reflex was also observed in the offspring of rats exposed to 155 mg Al/kg/day as aluminum chloride on gestation days 8–20 (Bernuzzi et al. 1986); grasping reflex was not significantly affected at this dose level or at 192 mg Al/kg/day. Exposure of pups to gavage doses of 300 mg Al/kg/day as aluminum lactate on PND 5–14 did not adversely affect the grasping reflex (Bernuzzi et al. 1989a). Righting reflex was also not affected in pups exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

3. HEALTH EFFECTS

Four studies examined temperature sensitivity; increases in sensitivity were observed in the offspring of mice exposed to 250 mg Al/kg/day as aluminum lactate in the diet on lactation days 1–21 (Golub et al. 1992a) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 42 (Golub et al. 1995). No effects were observed in mice exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 or to 250 mg Al/kg/day as aluminum lactate in the diet on gestation days 1–21 (Golub et al. 1992a).

A variety of motor function tests have been used to assess neurodevelopmental toxicity. Dosing pups with 300 mg Al/kg/day as aluminum lactate on PND 5–14 resulted in impairment of the suspension test and locomotor coordination (Bernuzzi et al. 1989a). Locomotor coordination was also altered in rat offspring exposed to 399 mg Al/kg/day as aluminum chloride in the diet on gestation days 1–20 (Bernuzzi et al. 1989b). No effects on the suspension test or locomotor coordination were observed in the offspring of rats exposed to 192 mg Al/kg/day as aluminum chloride in the diet on gestation days 8–20 (Bernuzzi et al. 1986). No information on the aluminum content of the basal diet was reported in the Bernuzzi studies. Alterations in the performance on the negative geotaxis test were found in mouse pups exposed to 250 mg Al/kg/day as aluminum lactate in the diet on lactation days 1–21 (Golub et al. 1992a) and in rat pups exposed to 399 mg Al/kg/day as aluminum chloride in the diet on gestation days 1–20 (Bernuzzi et al. 1989b), 200 mg Al/kg/day as aluminum lactate administered to pups on PND 5–14 (Bernuzzi et al. 1989a), or 155 mg Al/kg/day as aluminum chloride in the diet on gestation days 8–20 (Bernuzzi et al. 1986). No alterations in negative geotaxis results were found in mice exposed to 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 21 (Donald et al. 1989; Golub et al. 1995) or in rat pups exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Exposure to aluminum during gestation and/or lactation has consistently resulted in decreases in forelimb and/or hindlimb grip strength. Decreases in grip strength have been observed in mice exposed to 155 mg Al/kg/day as aluminum lactate in diet on gestation day 1 through lactation day 21 (Donald et al. 1989; Golub et al. 1995), 250 mg Al/kg/day as aluminum lactate on gestation days 1–21 or lactation days 1–21 (Golub et al. 1992a), or 130 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001) and in rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005). In other motor tests, increases in the number of rotations on a rotarod and a shorter latency to fall in a wire suspension test were observed in mice exposed to 260 or 130 mg Al/kg/day, respectively, as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 2001). Foot splay

3. HEALTH EFFECTS

has been observed in the mice exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Donald et al. 1989), but not in mice exposed to 250 mg Al/kg/day as aluminum lactate in the diet on gestation days 1–21 or lactation days 1–21 (Golub et al. 1992a). In open field tests of motor activity, significant delays in pivoting, longer latencies, and more rearings were observed in the offspring of rats administered via gavage 73 mg Al/kg/day as aluminum chloride (aluminum content of the diet was not reported) (Misawa and Shigeta 1992). No effect on open field tests were observed in rat pups exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (citric acid added) on gestation day 1 through lactation day 21 (Colomina et al. 2005).

Cognitive function effects were evaluated in passive avoidance tests, operant conditioning tests and water maze tests. No adverse effects were observed in operant conditioning tests in mice exposed to 155 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through lactation day 21 (Golub et al. 1995) or 330 mg Al/kg/day as aluminum lactate in the diet on gestation day 1 through PND 35 (Golub and Germann 1998) and in passive avoidance tests in rats exposed to 103 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid) on gestation day 1 through lactation day 21 (Colomina et al. 2005). The studies in mice noted that the aluminum-exposed pups often performed better than the controls; this may be due to an increase in food motivation in the aluminum-exposed rats rather than a direct effect on cognitive function. Impaired learning, as measured using the Morris water maze, was observed in mice exposed to 260 mg Al/kg/day as aluminum lactate in the diet from gestation day 0 to PND 21 and on PND 21–35 (tested at 90 days of age) (Golub and Germann 2001). When the salient and nonsalient cues were rotated, an increase in the escape latency was found at 130 and 260 mg Al/kg/day. The investigators found exposure to >130 mg Al/kg/day resulted in differences in how the mice used the salient and nonsalient cues; no effects were observed at 26 mg Al/kg/day. A study in rats exposed to 103 mg Al/kg/day (Colomina et al. 2005) did not find any significant effects in the water maze test. However, this study did not use probe trials; the alteration observed in the Golub and Germann studies were detected in the probe trials.

The highest reliable NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to various forms of aluminum.

3. HEALTH EFFECTS

Animal bioassays have found no conclusive evidence for carcinogenicity of aluminum. Significantly increased incidences of gross tumors were reported for Long Evans rats (only in males) and Swiss mice (only in females) given 0.6 or 1.2 mg Al/kg/day as aluminum potassium sulfate in drinking water, respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b). Aluminum levels in the base diet were not reported in these studies, although the animals were fed a low-metal diet in metal-free environmental conditions. At gross necropsy, 13/25 (52%) aluminum-treated male rats were found to have tumors compared to 4/26 (15.4%) controls. Six of the tumors in the aluminum-treated males were malignant compared to two malignancies in the control rats. The incidences of gross tumors in the female mice were 19/41 (46.3%) and 14/47 (29.8%) in exposed and control groups, respectively. The incidence of “lymphoma leukemia” was significantly increased (10/41 versus 3/47 in controls) in the female mice. A dose-response relationship could not be determined for either species because only one aluminum dose was used and the types of tumors and organs in which they were found were not specified. Very few study details were reported in this paper and it is unclear if the investigators grouped several types of tumors into the “lymphoma leukemia” category. Another study in rats (Wistar) found no increase in the incidence of neoplasms in male and female rats fed diets containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972).

There were no exposure-related increased incidences of tumors, other proliferative lesions or nonneoplastic lesions in 60 male or 60 female B6C3F1 mice that ingested ≤ 979 mg Al/kg/day as aluminum potassium sulfate in the diet for 20 months (Oneda et al. 1994). The level of aluminum in the base diet was not reported. The incidence of spontaneous hepatocellular carcinoma was significantly decreased in the high-dose males (5.5% compared to 20.5% in controls).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to various forms of aluminum.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, ocular, body weight, or metabolic effects in humans or animals after dermal exposure to various forms of aluminum.

3. HEALTH EFFECTS

The highest NOAEL values and all LOAEL values for dermal exposure from each reliable study for systemic effects in each species and duration category for aluminum are shown in Table 3-3.

Musculoskeletal Effects. Information on potential musculoskeletal effects associated with dermal exposure of aluminum is limited to a case report of a woman reporting bone pain after a 4-year exposure to aluminum chlorhydrate in antiperspirant (Guillard et al. 2004). No osseous abnormalities were detected via radiography, and C-reactive protein levels and bone-specific serum parameters (alkaline phosphatase, γ -glutamyl transferase, calcium, phosphate) were within reference ranges; however, plasma aluminum levels were approximately 10 times higher than reference levels. Termination of aluminum exposure resulted in decreases in plasma aluminum levels and a disappearance of bone pain.

No studies were located regarding musculoskeletal effects in animals following dermal exposure to aluminum.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to various forms of aluminum. Aluminum compounds are widely used in antiperspirants without harmful effects to the skin or other organs (Sorenson et al. 1974). Some people, however, are unusually sensitive to topically applied aluminum compounds. Skin irritation was reported in subjects following the application of aluminum chloride hexahydrate in ethanol used for the treatment of axillary or palmar hyperhidrosis (excessive sweating) (Ellis and Scurr 1979; Goh 1990) or the use of a crystal deodorant containing alum (Gallego et al. 1999).

No studies were located regarding dermal effects in animals following intermediate- or chronic- duration dermal exposure to various forms of aluminum.

Skin damage has been observed in female TF_1 Carworth mice, New Zealand rabbits, and Large White pigs following the application of 10% aluminum chloride (0.005–0.1 g Al) or aluminum nitrate (0.006–0.013 g Al) for 5 days; but not from aluminum sulfate, hydroxide, acetate, or chlorhydrate (Lansdown 1973). The damage consisted of hyperplasia, microabscess formation, dermal inflammatory cell infiltration, and occasional ulceration. These results suggest that the development of adverse dermal effects from exposure to aluminum depends upon its chemical form.

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal

Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL	Less Serious	Serious		
ACUTE EXPOSURE							
Systemic							
Mouse (TFI)	5 d 1 x/d	Dermal	2.5 F Percent (%)	5 F (slight to moderate hyperplasia) Percent (%)	25 F (severe hyperplasia with focal ulceration) Percent (%)	Lansdown 1973 Aluminum chloride	
Mouse (TFI)	5 d 1 x/d	Dermal	25 F Percent (%)			Lansdown 1973 Aluminum chlorhydrate	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)			Lansdown 1973 Aluminum sulfate	
Mouse (TFI)	5 d 1 x/d	Dermal		10 F (epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin) Percent (%)		Lansdown 1973 Aluminum chloride	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)			Lansdown 1973 Aluminum hydroxide	
Mouse (TFI)	5 d 1 x/d	Dermal	10 F Percent (%)			Lansdown 1973 Aluminum acetate	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal

(continued)

Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Mouse (TFI)	5 d 1 x/d	Dermal		10 F Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)	Lansdown 1973 Aluminum nitrate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)	Lansdown 1973 Aluminum chloride	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	25 Percent (%)			Lansdown 1973 Aluminum acetate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)			Lansdown 1973 Aluminum sulfate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)			Lansdown 1973 Aluminum hydroxide	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal

(continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Rabbit (New Zealand)	5 d 1 x/d	Dermal	10 Percent (%)			Lansdown 1973 Aluminum acetate	
Rabbit (New Zealand)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)	Lansdown 1973 Aluminum nitrate	
Pig (Large White)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)	Lansdown 1973 Aluminum chloride	
Pig (Large White)	5 d 1 x/d	Dermal	25 Percent (%)			Lansdown 1973 Aluminum chlorhydrate	
Pig (Large White)	5 d 1 x/d	Dermal	10 Percent (%)			Lansdown 1973 Aluminum sulfate	
Pig (Large White)	5 d 1 x/d	Dermal	10 Percent (%)			Lansdown 1973 Aluminum hydroxide	

Table 3-3 Levels of Significant Exposure to Aluminum and Compounds - Dermal

(continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL	Less Serious	Serious		
Pig (Large White)	5 d 1 x/d	Dermal	10 F Percent (%)			Lansdown 1973 Aluminum acetate	
Pig (Large White)	5 d 1 x/d	Dermal		10 Percent (%)	(epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)	Lansdown 1973 Aluminum nitrate	

d = day(s); F = female; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; x = time(s)

3. HEALTH EFFECTS

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after intermediate- or chronic-duration dermal exposure to various forms of aluminum.

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.

No studies were located regarding immunological/lymphoreticular effects in animals after dermal exposure to various forms of aluminum.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after acute- or intermediate-duration dermal exposure to various forms of aluminum. Graves et al. (1990) examined the association between Alzheimer's disease and the use of aluminum-containing antiperspirants in a case-control study using 130 matched pairs. The Alzheimer's disease was clinically diagnosed at two geriatric psychiatric centers; the controls were friends or nonblood relatives of the Alzheimer patients. Information on lifetime use of antiperspirants/deodorant was collected via a telephone interview with the subject's spouse. No association was found between Alzheimer's disease and antiperspirant/deodorant use, regardless of aluminum content (odds ratio of 1.2; 95% confidence interval of 0.6–2.4). When only users of aluminum-containing antiperspirants/deodorants were examined, the adjusted odds ratio was 1.6 (95% confidence interval of 1.04–2.4). A trend ($p=0.03$) toward a higher risk of Alzheimer's with increasing use of aluminum-containing antiperspirants/ deodorants was also found.

3. HEALTH EFFECTS

No studies were located regarding the following health effects in humans or animals after dermal exposure to various forms of aluminum:

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

Although aluminum complexes with deoxyribonucleic acid (DNA), particularly at lower pHs (Dyrssen et al. 1987; Karlik et al. 1980), negative results have been observed in *in vitro* assays (summarized in Table 3-4) for reverse mutations in *Salmonella typhimurium* (Marzin and Phi 1985), DNA damage in *Escherichia coli* (Olivier and Marzin 1987), rec assay using *Bacillus subtilis* (Kada et al. 1980; Kanematsu et al. 1980; Nishioka 1975), forward mutations in the thymidine kinase locus of L5178Y mouse lymphoma cells (Oberly et al. 1982), and morphological transformation in Syrian hamster cells (DiPaola and Casto 1979). However, other studies have shown that aluminum can induce DNA cross-linking in rat ascites hepatoma cells (Wedrychowski et al. 1986), micronuclei formation in human peripheral blood lymphocytes (Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990), and chromosome aberrations in human peripheral blood lymphocytes (Roy et al. 1990). Using FISH analysis, Migliore et al. (1999) was unable to conclude whether the micronuclei resulted from clastogenic and aneuploidogenic mechanism, although a higher (not statistically significant) percentage of micronuclei contained whole chromosomes. An *in vivo* study also found significant increases in chromosome aberrations in the bone marrow cells of mice receiving an intraperitoneal dose of aluminum chloride (Manna and Das 1972). There was a significant increase in chromatid-type aberrations over the controls, and these occurred in a nonrandom distribution over the chromosome complement; no dose-response relationship could be demonstrated, although the highest dose of aluminum chloride did produce the greatest number of aberrations.

3.4 TOXICOKINETICS

Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Approximately 0.1–0.6% of ingested aluminum is usually absorbed, although absorption of less bioavailable forms, such as aluminum hydroxide, can be on the order of 0.1%. The unabsorbed aluminum is excreted in the feces. The bioavailability of aluminum is strongly influenced by the aluminum compound and the presence of dietary constituents which can complex with aluminum and

3. HEALTH EFFECTS

Table 3-4. Genotoxicity of Aluminum *In Vitro*

Species (test system)	End point	Results	Reference
<i>Salmonella typhimurium</i>	Gene mutation	–	Marzin and Phi 1985
<i>Escherichia coli</i>	DNA damage	–	Olivier and Marzin 1987
<i>Bacillus subtilis</i>	Rec assay	–	Kada et al. 1980; Kanematsu et al. 1980; Nishioka 1975
L5178Y mouse lymphoma cells	Forward mutation	–	Oberly et al. 1982
Syrian hamster embryo cells	Transformation assay	–	DiPaola and Casto 1979
Rat ascites hepatoma cells	DNA cross-linking	+	Wedrychowski et al. 1986
Human peripheral blood lymphocytes	Micronuclei formation	+	Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990
Human peripheral blood lymphocytes	Chromosome aberrations	+	Roy et al. 1990

– = negative result; + = positive result

3. HEALTH EFFECTS

thereby enhance or inhibit its absorption. The main mechanism of absorption is probably passive diffusion through paracellular pathways. Aluminum binds to various ligands in the blood and distributes to every organ, with highest concentrations found in bone and lung tissues. Absorbed aluminum is excreted principally in the urine and, to a lesser extent, in the bile. Studies on aluminum uptake and elimination rates indicate that a near steady-state is maintained in most healthy adults, with aluminum body burdens varying slightly up and down over time with an overall small rate of increase over the lifespan. Nevertheless, blood and tissue aluminum levels are increased in persons exposed to high levels of aluminum, such as those associated with long-term use of antacids. The levels return to normal upon cessation of exposure. Under certain atypical conditions (e.g., poor renal function with increased aluminum load), levels of aluminum in the body may raise high enough to cause toxicity in humans. The main target organs under these conditions appear to be the central nervous system and bone. The molecular mechanism of aluminum bone and neurotoxicity has not been established.

Aluminum can form complexes with many molecules in the body (organic acids, amino acids, nucleotides, phosphates, carbohydrates, macromolecules). Many aluminum compounds have low solubility products, so their “free” aluminum ions (e.g., hydrated $\text{Al}(\text{H}_2\text{O})_6^{3+}$) occur in very low concentrations. The toxicokinetics of aluminum can vary, depending on the nature of these complexes. For example, aluminum bound in a low-molecular-weight complex could be filtered at the renal glomeruli and excreted, while aluminum in a high-molecular-weight complex (aluminum transferrin) would not.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Evidence for absorption of aluminum after inhalation exposure in humans is available from several occupational studies. Occupational exposure to aluminum fumes, dusts, and flakes has resulted in increases in serum, tissue, and urinary levels of aluminum. Significantly higher serum aluminum levels were observed in 279 workers exposed to aluminum powder as compared to unexposed workers; the pre-shift plasma levels were 4.92 and 3.60 $\mu\text{g}/\text{L}$, respectively (Gitelman et al. 1995); no significant differences in post-shift plasma levels were found between the aluminum workers (5.12 $\mu\text{g}/\text{L}$) and unexposed controls (4.16 $\mu\text{g}/\text{L}$). Results of an autopsy on a stone mason presumably exposed to aluminum showed that tissue levels of aluminum were substantially higher than those of a group of 24 individuals presumably not exposed to aluminum in the workplace (Teraoka 1981). Following an 8-hour exposure to a time-weighted average (TWA) concentration of 2.4 mg/m^3 aluminum, urinary levels in 3 previously unexposed volunteers rose from 3 to 4–14 $\mu\text{g}/\text{L}$ (Sjögren et al. 1985). Increased urinary

3. HEALTH EFFECTS

aluminum levels have also been observed in workers exposed to 0.025 (median respirable concentration) or 5 mg/m³ (TWA concentrations) aluminum dust (Gitelman et al. 1995; Mussi et al. 1984) or 2.4 or 5 mg/m³ (TWA concentrations) aluminum fumes (Mussi et al. 1984; Sjögren et al. 1985). Indirect evidence for inhalation absorption of aluminum was reflected in a fall in urinary aluminum levels from 82 to 29 µg/L in workers following a 16–37-day exposure-free interval (Sjögren et al. 1988).

The percentage of aluminum absorbed following inhalation exposure was not reported in occupational toxicokinetic studies (Gitelman et al. 1995; Mussi et al. 1984; Pierre et al. 1995; Sjögren et al. 1985, 1988). However, 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). Data from Mussi et al. (1984) suggest that the fractional absorption of aluminum from lung to blood is higher in individuals exposed to aluminum fumes as compared to aluminum dust. This is consistent with knowledge that particle size influences the deposition pattern in the lungs and absorption.

It is considered that systemic absorption of airborne aluminum occurs via the lungs, gastrointestinal tract after mucociliary clearance from the respiratory tract (ICRP 1994), or intranasal absorption via olfactory neurons. Gitelman et al. (1995) found a better correlation between respirable aluminum air concentrations and urinary aluminum output than between total aluminum air concentrations and urinary aluminum output, suggesting that some of the aluminum was absorbed through the lungs. Studies by Perl and Good (1987) and Zatta et al. (1993) have demonstrated that aluminum may directly enter the brain via the olfactory tract; the aluminum crosses the nasal epithelium and reaches the brain via axonal transport.

Several animal studies indicate that aluminum is retained in the lung after inhalation exposure to aluminum oxide (Christie et al. 1963; Thomson et al. 1986) and aluminum chlorhydrate (Steinhagen et al. 1978; Stone et al. 1979). However, no significant increases in aluminum in tissues other than the lungs or serum were seen, indicating that lung retention rather than absorption was taking place (Steinhagen et al. 1978; Stone et al. 1979).

3.4.1.2 Oral Exposure

Aluminum present in food and drinking water is poorly absorbed through the gastrointestinal tract. Several small scale human studies estimated aluminum absorption efficiencies of 0.07–0.39% following administration of a single dose of the radionuclide aluminum-26 (²⁶Al) in drinking water (Hohl et al.

3. HEALTH EFFECTS

1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). Fractional absorption was estimated by measuring aluminum levels in urine; it is likely that most of these studies (with the exception of Stauber et al. 1999) underestimated gastrointestinal absorption because the amount of aluminum retained in tissues or excreted by non-renal routes was not factored into the absorption calculations. Several animal studies also utilized ^{26}Al to estimate aluminum bioavailability from drinking water. When aluminum levels in urine and bone were considered, absorption rates of 0.04–0.06% were estimated in rats (Drueke et al. 1997; Jouhannau et al. 1993); when liver and brain aluminum levels were also considered, an absorption rate of 0.1% was estimated (Jouhannau et al. 1997). Another study that utilized a comparison of the area under the plasma aluminum concentration-time curve after oral and intravenous administration of ^{26}Al estimated an oral aluminum bioavailability of 0.28% (Yokel et al. 2001a).

Two human studies examined the bioavailability of aluminum in the diet. An absorption efficiency of 0.28–0.76% was estimated in subjects ingesting 3 mg Al/day (0.04 mg Al/kg/day) or 4.6 mg Al/day (0.07 mg Al/kg/day) (Greger and Baier 1983; Stauber et al. 1999). When 125 mg Al/day (1.8 mg Al/kg/day) as aluminum lactate in fruit juice was added to the diet, aluminum absorption decreased to 0.094% (Greger and Baier 1983). Yokel and McNamara (2001) suggested that the bioavailability of aluminum from the diet is 0.1% based on daily urinary excretion levels of 4–12 μg and average aluminum intakes by adults in the United States of 5,000–10,000 $\mu\text{g}/\text{day}$.

The bioavailability of aluminum is dependent on the form in which it is ingested and the presence of dietary constituents with which the metal cation can complex (see Section 3.5.1). Ligands in food can have a marked effect on absorption of aluminum, as they can either enhance uptake by forming absorbable (usually water soluble) complexes (e.g., with carboxylic acids such as citric and lactic), or reduce it by forming insoluble compounds (e.g., with phosphate or dissolved silicate). Evidence strongly suggests that the complexing agent of most importance to aluminum uptake in humans is citric acid (or its conjugate base citrate), which is a constituent of many foods and beverages and can be present in the gut in high concentrations (Reiber et al. 1995). It is well-documented in both human and animal studies that blood and tissue levels of aluminum can be increased by simply increasing the consumption of citric acid (i.e., with no concurrent increase in aluminum ingestion), or other dietary chelators such as ascorbic acid and lactic acid (DeVoto and Yokel 1994; Domingo et al. 1991; Florence et al. 1994; Molitoris et al. 1989; Partridge et al. 1989; Slanina et al. 1984, 1985, 1986; Testolin et al. 1996; Weberg and Berstad 1986). The amount of a 976 mg (approximately 14 mg/kg) dose of aluminum as aluminum hydroxide in antacid tablets absorbed by 7–10 volunteers were estimated as 0.004, 0.03, or 0.2% when the antacids were

3. HEALTH EFFECTS

suspended in tap water (pH 9.2), orange juice (pH 4.2), or citric acid (pH 2.4), respectively (Weberg and Berstad 1986). Absorption was estimated as the amount excreted in urine in 72 hours divided by the amount ingested. A more recent study using ^{26}Al estimated aluminum absorption rates of 0.523, 0.0104, and 0.136% in two subjects receiving a single dose of aluminum citrate, aluminum hydroxide, or aluminum hydroxide dissolved in a citrate solution, respectively (Priest et al. 1996). This is consistent with another study reporting absorption levels of 0.37–0.57% in humans ingesting 280 mg Al as aluminum hydroxide in sodium citrate and citric acid (Taylor et al. 1998). A fourth study reported a higher absorption level (1%) in one subject administered ^{26}Al in a sodium citrate solution (Day et al. 1991).

A comparison of the bioavailability of different aluminum compounds was conducted by Yokel and McNamara (1988). Bioavailability in rabbits following a single maximum safe dose was estimated by comparing areas under the plasma concentration-time curves after oral and intravenous dosing. The estimated bioavailability of the water-soluble compounds aluminum chloride (333 mg Al/kg), aluminum nitrate (934 mg Al/kg), aluminum citrate (1,081 mg Al/kg), and aluminum lactate (2,942 mg Al/kg) in rabbits was 0.57, 1.16, 2.18, and 0.63%, respectively. Aluminum absorption in rabbits similarly treated with the water-insoluble compounds aluminum hydroxide (780 mg Al/kg), aluminum borate (2,736 mg Al/kg), aluminum glycinate (1,351 mg Al/kg), and aluminum sucrose sulfate (20,867 mg Al/kg) was 0.45, 0.27, 0.39, and 0.60%, respectively (Yokel and McNamara 1988). Similarly, Schönholzer et al. (1997) examined aluminum absorption following oral exposure to ^{26}Al in rats. The bioavailability of aluminum hydroxide, aluminum citrate, aluminum citrate with added sodium citrate, or aluminum maltolate following a single gavage dose was 0.1, 0.7, 5.1, and 0.1%, respectively.

The presence of food in the stomach appeared to delay the absorption of ^{26}Al , but did not significantly alter the amount of aluminum absorbed in rats (Yokel et al. 2001a). Aluminum bioavailability was 0.23% with no food in the stomach and 0.21% when food was present. Similarly, there were no differences in absorption when the ^{26}Al was added to hard water (300 mg calcium carbonate/L added) or soft water.

Considering the available human and animal data as discussed above, it is likely that the oral absorption of aluminum can vary 10-fold based on chemical form alone. Although bioavailability appears to generally parallel water solubility, insufficient data are available to directly extrapolate from solubility in water to bioavailability. Additionally, due to available dietary ligands such as citrate, lactate, and other organic carboxylic acid complexing agents, the bioavailability of any particular aluminum compound can be markedly different in the presence of food than under empty stomach conditions.

3. HEALTH EFFECTS

3.4.1.3 Dermal Exposure

There are limited human data on the dermal absorption of aluminum. Aluminum compounds are common additives in underarm antiperspirants. The active ingredient is usually an aluminum chlorhydrate salt, which is thought to form an obstructive plug of aluminum hydroxide within the sweat duct (Hostynek et al. 1993; Reiber et al. 1995). Using ^{26}Al labeled aluminum chlorhydrate applied to the underarm of two subjects, Flarend et al. (2001) estimated that 0.012% of the applied aluminum was absorbed through the skin. The study investigators cautioned against using these results to extrapolate dermal absorption following repeated exposure to aluminum.

Dermal absorption studies were not located for animals; however a study by Anane et al. (1995) found increased levels of aluminum in the urine of mice exposed to 0.1 or 0.4 $\mu\text{g/day}$ aluminum chloride (0.01–0.04 $\mu\text{g Al/day}$) applied daily to a 4 cm^2 shaved area for 130 days. Interpretation of this study is limited due to the lack of control measures to prevent the animals from licking their fur and thus ingesting aluminum.

3.4.1.4 Other Routes of Exposure

Flarend et al. (1997) estimated aluminum absorption in rabbits following intramuscular injection of ^{26}Al labelled aluminum hydroxide or aluminum phosphate adjuvants used for vaccines. Aluminum from both solutions was absorbed, appearing in the blood as early as 1 hour after injection. Three times as much aluminum from the aluminum phosphate adjuvant was absorbed during the first 28 days after exposure; since the terminal phase of the blood concentration curve was not reached by that time, this difference may be due to differences in the rate of absorption.

3.4.2 Distribution

Aluminum occurs normally in all body tissues of humans (Ganrot 1986). The total body burden of aluminum in healthy human subjects is approximately 30–50 mg (Alfrey 1981, 1984; Alfrey et al. 1980; Cournot-Witmer et al. 1981; Ganrot 1986; Hamilton et al. 1973; Tipton and Cook 1963). Normal levels of aluminum in serum are approximately 1–3 $\mu\text{g/L}$ (House 1992; Liao et al. 2004). Of the total body burden of aluminum, about one-half is in the skeleton, and about one-fourth is in the lungs (Ganrot 1986). The normal level of aluminum in adult human lungs is about 20 mg/kg wet weight (w/w) and increases with age due to an accumulation of insoluble aluminum compounds that have entered the body via the

3. HEALTH EFFECTS

airways (Ganrot 1986). Most of the aluminum in other parts of the body probably originates from food intake. Reported normal levels in human bone tissue range from 5 to 10 mg/kg (Alfrey 1980; Alfrey et al. 1980; Cournot-Witmer et al. 1981; Flendrig et al. 1976; Hamilton et al. 1973; Tipton and Cook 1963). Aluminum is also found in human skin (Alfrey 1980; Tipton and Cook 1963), lower gastrointestinal tract (Tipton and Cook 1963), lymph nodes (Hamilton et al. 1973), adrenals (Stitch 1957; Tipton and Cook 1963), and parathyroid glands (Cann et al. 1979). Low aluminum levels (0.3–0.8 mg/kg w/w) are found in most soft tissue organs, other than the lungs (Hamilton et al. 1973; Tipton and Cook 1963).

The normal level of aluminum in the human brain ranges from 0.25 to 0.75 mg/kg w/w, with gray matter containing about twice the concentration found in the white matter (Alfrey et al. 1976; Arieff et al. 1979; McDermott et al. 1978; Roider and Drasch 1999). There is evidence that with increasing age of humans, aluminum concentrations may increase in the brain tissue (Alfrey 1980; Crapper and DeBoni 1978; Markesbery et al. 1981; McDermott et al. 1979; Stitch 1957; Tipton and Shafer 1964); aluminum levels in serum may also increase with aging (Zapatero et al. 1995).

3.4.2.1 Inhalation Exposure

Limited information is available regarding the distribution of aluminum following inhalation exposure in humans or animals. Results of an autopsy of a stone mason presumed to have been exposed to aluminum by inhalation indicated elevated concentrations of aluminum in the lungs (2,000 ppm), hilar lymph nodes (3,200 ppm), liver (130 ppm), and spleen (520 ppm) (Teraoka 1981). The aluminum levels in the tissues of control subjects were 230, 2,000, 19, and 22 ppm, respectively. Rats and guinea pigs given intermediate or chronic inhalation exposures to aluminum chlorhydrate accumulated aluminum primarily in the lungs (Steinhagen et al. 1978; Stone et al. 1979). The only other organs with significant accumulation of aluminum were the adrenal glands (Stone et al. 1979) and the peribronchial lymph nodes (Steinhagen et al. 1978; Stone et al. 1979). No appreciable aluminum accumulation was observed in the brain, heart, spleen, kidneys, or liver of either species.

During inhalation exposure to aluminum and its compounds, the lungs distribute and deposit the material based on particle size (ICRP 1994). A portion of the particles are exhaled, some are trapped in the nasopharyngeal and upper respiratory areas and deposited in the gastrointestinal tract by mucosal movement and mucocilliary action, and a portion of the small particles reach the alveoli where they can be transferred to blood (especially for soluble compounds), or taken up by alveolar macrophages through

3. HEALTH EFFECTS

phagocytosis and transported to pulmonary lymph nodes for insoluble compounds. Pulmonary concentration of aluminum increases with age.

3.4.2.2 Oral Exposure

There are limited data on the distribution of aluminum in humans. Clearance of ^{26}Al from the blood was assessed in two male volunteers orally exposed to 100 mg aluminum as aluminum chloride (Hohl et al. 1994). Plots of the serum and urine concentrations showed several slope changes, indicating that the clearance from blood involves one central and three peripheral compartments with turnover rates ranging from 0.003 to 9 h^{-1} .

The distribution of aluminum in animals after oral exposure has been evaluated in a number of studies (Cranmer et al. 1986; Deng et al. 2000; Dlugaszek et al. 2000; Domingo et al. 1993; Gomez et al. 1997a, 1997b; Greger and Donnaubauer 1986; Julka et al. 1996; Ogasawara et al. 2002; Santos et al. 1987; Sutherland and Greger 1998; Walton et al. 1995; Yokel and McNamara 1985; Yokel et al. 1999; Zafar et al. 1997). These studies are particularly informative because they demonstrate that, although bioavailability of aluminum is low, aluminum tissue concentrations can increase substantially following oral exposure, and provide information on distribution of aluminum in various tissues. Aluminum is not equally distributed throughout the body following oral exposure. Aluminum accumulation was typically higher in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lung (Greger and Sutherland 1997). Eight days after a single gavage dose of 2.6 mg of ^{26}Al as aluminum chloride, the descending order of aluminum levels was bone>spleen>liver>kidney (Zafar et al. 1997). To evaluate the retention of aluminum in tissues following oral exposure, rats were fed a diet supplemented with aluminum hydroxide for an intermediate-duration exposure period (Greger and Donnaubauer 1986). Relative to controls, treated rats had increased aluminum concentrations in bone, muscle, and kidneys. Aluminum concentrations in these tissues decreased significantly 3 days after withdrawal of aluminum hydroxide from the diet. Tissue concentrations of aluminum were similar for treated and control rats 7 days after withdrawal.

Once into the blood, aluminum is believed to be present almost exclusively in the plasma where it is bound mainly to transferrin (Ganrot 1986; Harris and Messori 2002; Martin 1986); recent data suggest that over 90% of the aluminum in serum is bound to transferrin (Harris and Messori 2002). There is *in vitro* evidence indicating that aluminum can bind to the iron-binding sites of transferrin (Moshtaghi and Skillen 1986), and that Al^{+3} may compete with similar ions in binding to transferrin (Ganrot 1986). As

3. HEALTH EFFECTS

reviewed by Priest (2004), approximately 10% of the aluminum in blood is found in the erythrocytes; peak levels occur 1 day after peak serum aluminum levels were reached. The half-life of aluminum in the erythrocytes appears to longer than the half-life in plasma. In addition to binding with transferrin, Al^{+3} is also known to bind to a considerable extent to bone tissue, primarily in the metabolically active areas of the bone (Ganrot 1986).

Cellular uptake of aluminum by organs and tissues is believed to be relatively slow and most likely occurs from the aluminum bound to transferrin (Ganrot 1986). It is likely that the density of transferrin receptors in different organs influences the distribution of aluminum to organs (Morris et al. 1989). Within cells, Al^{+3} accumulates in the lysosomes, cell nucleus, and chromatin. In organs composed of postmitotic cells, this accumulation would be expected to lead to an increase of the Al^{+3} concentration; however, in other organs, a steady state is expected to be reached between the Al^{+3} accumulation and the elimination of dead cells that are replaced by cells with a lower Al^{+3} content. The cells that accumulate the most aluminum are large, long-lived postmitotic cells, such as in neurons (Ganrot 1986).

In addition to distribution of aluminum to the brain (hippocampus), bone, muscle, and kidneys of orally exposed animals, there is evidence in animals that aluminum crosses the placenta and accumulates in the fetus and distributes to some extent to the milk of lactating mothers (Cranmer et al. 1986; Golub et al. 1996; Yokel 1985; Yokel and McNamara 1985). Aluminum levels were increased in both fetuses and placentas of mice treated throughout gestation with aluminum chloride (Cranmer et al. 1986). The concentration of aluminum in milk of rats that ingested 420 mg Al/kg/day as aluminum lactate in the diet during gestation and lactation increased at least 4-fold beginning on postnatal day 12 (Golub et al. 1996). Peak concentrations of aluminum were detected in the milk of lactating rabbits 12–24 hours after a single large gavage dose of aluminum lactate; however, the amount of aluminum in milk as a percentage of the total oral dose was not reported (Yokel and McNamara 1985). Aluminum levels of rabbit pups exposed during lactation were not significantly different from levels in control pups, suggesting that only a small amount of the aluminum in breast milk is absorbed by the offspring (Yokel 1985).

Age-related differences in the distribution of aluminum has been observed in rats exposed to 0, 50, or 100 mg Al/kg/day as aluminum nitrate in the drinking water with added citrate (Gomez et al. 1997a). The levels of aluminum in the brain and bone were significantly higher in the older rats (16 months of age at study beginning) compared to young (21 days of age) or adult (8 months of age) rats; this was observed in the control and aluminum-treated rats. Liver aluminum levels were significantly higher in adult and older rats as compared to the young rats.

3. HEALTH EFFECTS

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to aluminum or its compounds. Elevated levels of aluminum have been observed in the liver, brain, lung, and kidneys of Swiss mice dermally exposed to 0.4 µg/day aluminum chloride (0.04 µg Al/day) for 20 days during gestation (Anane et al. 1997). Elevated levels of aluminum were also observed in the fetus, providing evidence of transplacental transfer of aluminum. As noted previously, this study did not prevent the mice from licking their fur.

3.4.2.4 Other Routes of Exposure

When there is inadequate elimination of aluminum from the body, as in nondialyzed uremic patients, increased aluminum concentrations are detected in serum, bone tissue, liver, spleen, brain, and skeletal muscle (Alfrey et al. 1980; Arieff et al. 1979). In hemodialysis patients exposed by infusion to large amounts of aluminum over long periods of time (with inadequate removal of aluminum by the kidneys and dialysis machines), increased aluminum concentrations are observed mostly in the spleen, followed by the liver and skeletal system (Alfrey 1980; Alfrey et al. 1980). A study in rabbits found a significantly lower serum half-life in renally-impaired animals, as compared to renally-intact animals (27 hours versus 14 hours); this is likely due to the diminished volume of distribution in the renally-impaired rabbits (Yokel and McNamara 1988).

The distribution of aluminum following intravenous, subcutaneous, intraperitoneal, and intramuscular exposure has been evaluated in studies with experimental animals (Cranmer et al. 1986; Du Val et al. 1986; Flarend et al. 1997; Leblondel and Allain 1980; Yokel and McNamara 1985, 1989; Yokel et al. 2001b). Results of these animal studies indicate that aluminum distributes to a number of tissues, organs, and biological fluids (Du Val et al. 1986; Leblondel and Allain 1980; Yokel and McNamara 1989).

In rabbits given a single intravenous dose of aluminum lactate, aluminum concentrations did not increase above controls in the cerebellum, white brain tissue, hippocampus, spinal cord, adrenal glands, bone, heart, testes, or thyroid (Yokel and McNamara 1989). Treated animals did have significant increases of aluminum in the liver, serum, bile, kidneys, lungs, and spleen. Throughout the 128 day study, the liver of exposed rabbits had over 80% of the total body burden of aluminum. Persistence of aluminum in the various tissues, organs, and fluids varied. Estimated half-times of aluminum were 113, 74, 44, and 42 days in the spleen, liver, lungs, and serum, respectively. The kidneys of treated rabbits demonstrated

3. HEALTH EFFECTS

two half-times with an initial time of 4.2 and 2.3 days for the renal cortex and renal medulla, respectively, and a second half-time of >100 days for kidney in general; the relative amounts subject to each half-time were not addressed. The half-life of aluminum in the brain of rats receiving an intravenous dose of aluminum citrate was approximately 150 days (Yokel et al. 2001b).

Subcutaneous injection of rabbits with aluminum chloride daily for 28 days was associated with significant accumulation of aluminum (measured at the end of the exposure period) in bone, followed in order by significantly increased aluminum concentrations in renal cortex, renal medulla, liver, testes, skeletal muscle, heart, brain white matter, hippocampus, and plasma (Du Val et al. 1986). Because the brain tissue of treated rabbits had the lowest aluminum concentrations of the tissues evaluated, the authors suggested that there was a partial blood-brain barrier to entry of aluminum.

Distribution of aluminum to tissues following intraperitoneal exposure depends in part on the type of aluminum compound administered and on the aluminum concentration in blood (Leblondel and Allain 1980). Mice were administered 54 mg Al/kg as aluminum chloride, nitrate, lactate, or gluconate by a single intraperitoneal injection. The blood concentrations of aluminum, which reached a peak within 20 minutes, increased significantly with gluconate (99.5 mg/L), increased to high levels with lactate (4.5 mg/L), and increased marginally with nitrate and chloride (0.3 mg/L). Aluminum concentrations in the brain tissue of treated mice significantly increased only with aluminum gluconate and only at extremely high blood aluminum concentrations of 20–100 mg/L; the half-life of aluminum in the brain was approximately 90 minutes. At blood aluminum concentrations of 2–4 mg/L, there was no increase in brain aluminum with any of the compounds evaluated. Interpretation of this study is limited by the short monitoring period (apparently 80 minutes); thus, the study does not take into consideration possible differences in absorption rate between aluminum compounds. Differences in brain aluminum levels following administration of different aluminum compounds may also be due to the presence of carrier systems that can transport aluminum into or out of the brain; this has been demonstrated for aluminum citrate (Allen et al. 1995).

Following intramuscular administration of aluminum hydroxide or aluminum phosphate vaccine adjuvants in rabbits, increased levels of ²⁶Al were found in the kidney, spleen, liver, heart, lymph nodes, and brain (in decreasing order of aluminum concentration) (Flarend et al. 1997).

There is also evidence from animal studies indicating that aluminum administered parenterally accumulates to a small extent in the milk of lactating mothers, and that aluminum crosses the placenta and

3. HEALTH EFFECTS

accumulates in fetal tissue (Cranmer et al. 1986; Yokel and McNamara 1985; Yumoto et al. 2000). Intraperitoneal exposure of pregnant mice to aluminum chloride on gestation days 7–16 has been associated with significantly increased concentrations of aluminum in both placental and fetal tissues (Cranmer et al. 1986). Following a single subcutaneous injection of ^{26}Al on gestation day 15, 0.2 and 0.21% of the dose was detected in the placenta and fetus, respectively, 5 days after the injection (Yumoto et al. 2000). Within the fetus, the level of ^{26}Al in the brain was as high as 30% of that in the fetal liver; in contrast, the level of ^{26}Al in the brain of the dam was only 1% of the level in the liver. Intravenous, intraperitoneal, or subcutaneous exposure of lactating rats, rabbits, or mice to aluminum lactate or aluminum chloride has been associated with increased concentrations of aluminum in milk (Muller et al. 1992; Yokel and McNamara 1985). The amount of aluminum detected in milk 24 hours after exposure was estimated to be 2.4% of the intravenous dose and 3.3% of the subcutaneous dose (Yokel and McNamara 1985). Subcutaneous injection of ^{26}Al in rats on lactation day 1 through 20, resulted in significant elevation in aluminum levels in the suckling rats (Yumoto et al. 2000, 2003). On lactation day 2, elevated levels of ^{26}Al were detected in the liver, but not in the kidney, brain, or blood; ^{26}Al was detected in these tissues on lactation day 9 (Yumoto et al. 2000).

3.4.3 Metabolism

As an element, aluminum is always found attached to other chemicals, and these affinities can change within the body. In living organisms, aluminum is believed to exist in four different forms: as free ions, as low-molecular-weight complexes, as physically bound macromolecular complexes, and as covalently bound macromolecular complexes (Ganrot 1986). The free ion, Al^{+3} , is easily bound to many substances and structures; therefore, its fate is determined by its affinity to each of the ligands and their relative amounts and metabolism. Aluminum may also form low-molecular-weight complexes with organic acids, amino acids, nucleotides, phosphates, and carbohydrates. These low-molecular-weight complexes are often chelates and may be very stable. The complexes are metabolically active, particularly the nonpolar ones. Because aluminum has a very high affinity for proteins, polynucleotides, and glycosaminoglycans, much of the aluminum in the body may exist as physically bound macromolecular complexes with these substances. Metabolically, these macromolecular complexes would be expected to be much less active than the smaller, low-molecular-weight complexes. Aluminum may also form complexes with macromolecules that are so stable that they are essentially irreversible. For example, evidence suggests that the nucleus and chromatin are often sites of aluminum binding in cells (Crapper McLachlan 1989; Dyrssen et al. 1987; Ganrot 1986; Karlik et al. 1980).

3. HEALTH EFFECTS

3.4.4 Elimination and Excretion**3.4.4.1 Inhalation Exposure**

Urinary excretion is the primary route of elimination of absorbed aluminum after inhalation exposure in humans. Elevated levels of aluminum in urine have been detected in aluminum welders and aluminum flake workers (Letzel et al. 1996; Ljunggren et al. 1991; Mussi et al. 1984; Pierre et al. 1995; Rossbach et al. 2006; Schaller et al. 2007; Sjögren et al. 1985, 1988). Six volunteers had urinary levels of 14–414 µg/L aluminum compared to concentrations of <3 µg/L prior to a 1-day exposure to 0.3–10.2 mg Al/m³ in welding fumes (Sjögren et al. 1985). The urinary aluminum levels of 7 welders exposed occupationally to aluminum fumes or dust for 6 months were increased 3-fold after an 8-hour workshift compared to concentrations at the beginning of the day (Mussi et al. 1984). Several investigators (Letzel et al. 1996; Rossbach et al. 2006; Sjögren et al. 1988) have found a linear relationship between post-shift urinary aluminum levels and levels of aluminum in air among welders.

Occupational exposure studies suggest that the urinary excretion of aluminum is biphasic. The excretion half-time for the first phase ranged from 7.5 to 9 days among workers exposed to welding fumes or aluminum dust (Pierre et al. 1995; Sjögren et al. 1985, 1988). The half-times for the second phase ranged from 6.8 to 24 weeks (Schaller et al. 2007; Sjögren et al. 1988, 1991); the wide range of half-times may reflect the character of the inhaled aluminum (welding fume particles or aluminum flake particles) and the duration of exposure.

No studies were located regarding excretion in animals after inhalation exposure to aluminum or its compounds.

3.4.4.2 Oral Exposure

Following ingestion in humans, absorbed aluminum from the blood is eliminated in the kidney and excreted in the urine (Gorsky et al. 1979; Greger and Baier 1983; Kaehny et al. 1977; Recker et al. 1977; Sutherland and Greger 1998). The unabsorbed aluminum is excreted primarily in the feces. An acute exposure of 4 days to 54.3 mg Al/kg as aluminum carbonate produced peak concentrations ranging from 4- to 10-fold elevation in base-line urinary levels; the average urinary excretion rate being 495 µg/day during exposure (Recker et al. 1977). In humans, 0.09 and 96% of the aluminum intake per day was cleared through the urine and feces, respectively, during exposure to 1.71 mg Al/kg/day as aluminum lactate in addition to 0.07 mg Al/kg/day in basal diet for 20 days (Greger and Baier 1983). Urinary

3. HEALTH EFFECTS

aluminum concentrations were significantly elevated in volunteers who received aluminum hydroxide and aluminum carbonate (Kaehny et al. 1977). Patients taking aluminum antacids in the diet had only a 3-fold increase in urinary aluminum levels (Gorsky et al. 1979), suggesting that most of the aluminum hydroxide was not absorbed and was excreted directly into the feces.

Excretion of aluminum may be lower in premature compared to full-term infants (Bougle et al. 1991). Plasma levels of aluminum in premature infants were 14.6 µg/L compared to 7.8 µg/L in full-term infants, and absolute urinary excretion was reduced. The aluminum-creatinine ratio in the urine was similar in both groups, indicating that the lower excretion in the premature infants may be due to lower metabolic and glomerular filtration rates, thus increasing the risk of aluminum accumulation in this group.

Excretion data collected in animal studies are consistent with the results from human studies. A single oral dose of 11 mg aluminum resulted in a 14-fold increase in urine aluminum levels, as compared to baseline levels, in healthy Sprague-Dawley rats (Ittel et al. 1987). The aluminum was primarily excreted during the first 24-hour period, and was comparable to baseline levels 5 days postexposure. Similarly exposed uremic rats excreted more aluminum than the healthy rats; the study authors postulated that this increase in excretion was probably due to increased gastrointestinal absorption. Rats administered a single dose of one of eight aluminum compounds (all contained 35 mg aluminum) excreted in the urine 0.015–2.27% of the initial dose (Froment et al. 1989b). The range most likely reflects differences in gastrointestinal absorption. Following administration of a single dose of 6.7–27 mg Al/kg, 1.3–2.8% of the dose was excreted within the first 3 hours; the percent of the dose excreted in the urine did not differ among the three dose groups (Sutherland and Greger 1998).

Fecal aluminum represents unabsorbed aluminum as well as aluminum excreted via bile. Within 15 minutes of rats receiving a gavage dose of 6.7–27 mg Al/kg, the levels of aluminum in bile were significantly higher than in controls (Sutherland and Greger 1998). The percentage of the total dose excreted in bile during the first 3 hours after dosing ranged from 0.06 to 0.14%. In the control group, 25.0 mmol aluminum were excreted in the bile compared to 7.9 mmol in the urine.

3.4.4.3 Dermal Exposure

No studies were located regarding the excretion in humans and animals after dermal exposure to aluminum or its compounds.

3. HEALTH EFFECTS

3.4.4.4 Other Routes of Exposure

Human and animal studies have investigated the aluminum retention in the body. Within the first day of receiving a single injection of ^{26}Al citrate, approximately 59% of the dose was excreted in the urine of six subjects; 72 and 1.2% was excreted in the urine and feces, respectively, during the first 5 days (Talbot et al. 1995). At the end of 5 days, it was estimated that 27% of the dose was retained in the body (Priest et al. 1995; Talbot et al. 1995). When ^{26}Al levels were monitored more than 3 years after a single subject received the injection, a half-life of approximately 7 years was calculated (Priest et al. 1995). However, when the subject was re-examined approximately 10 years after the injection, a half-life of about 50 years was estimated (Priest 2004).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen

3. HEALTH EFFECTS

1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

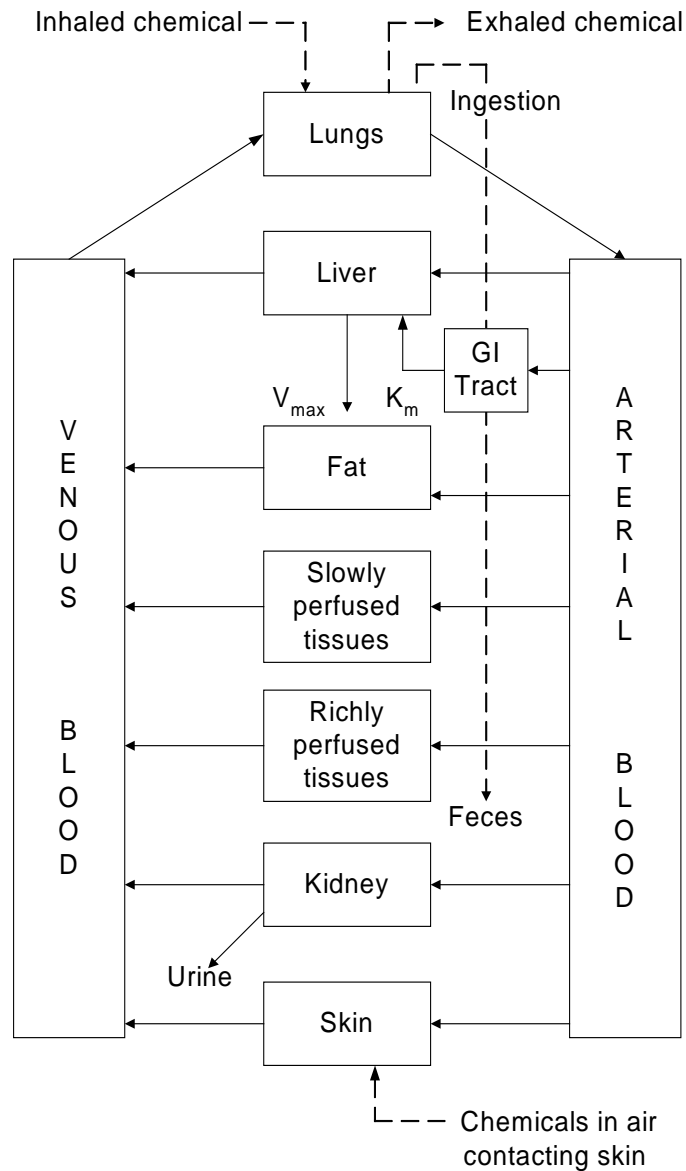
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for aluminum exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

A PBPK/PD model that can be used in risk assessment to predict the concentrations of aluminum delivered to target tissues (particularly the brain) or to examine the relationship between target tissue dose and the observed responses was not located. However, a biokinetic model has been developed to describe the absorption, distribution, and excretion of aluminum (Kislinger et al. 1997; Nolte et al. 2001; Steinhausen et al. 2004). This model allows for the prediction of aluminum levels under different physiological conditions such as renal failure or iron deficiency/overload. The model is an open compartment model comprised of a central compartment, three peripheral compartments, additional compartments for the gastrointestinal tract (stomach, duodenum, and residual intestinal tract), and excretion primarily via kidney output into urine. The central compartment comprises the blood plasma and interstitial fluid; in both compartments, the aluminum is bound to large proteins such as transferrin

3. HEALTH EFFECTS

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan et al. 1994

3. HEALTH EFFECTS

and to small soluble molecules such as citrate. The peripheral compartments are: (1) the liver and spleen, which are supplied by aluminum from plasma transferrin (this compartment is characterized by a rapid exchange with the central compartment and no significant long-term storage of aluminum); (2) the muscles, heart, and kidney tissues, which are supplied aluminum from interstitial transferrin; and (3) the bones, which are supplied by aluminum from interstitial tissue citrate (this compartment is characterized by rapid accumulation of aluminum and long-term storage). Aluminum is primarily excreted via ultrafilterable citrate-bound aluminum of plasma via the kidneys into the urine; a minor excretion path is transport of transferrin-bound aluminum of plasma via the liver into the residual intestinal tract.

3.5 MECHANISMS OF ACTION

The mechanism of action for aluminum toxicity is not known, but the element is known to compete in biological systems with cations, especially magnesium (Macdonald and Martin 1988) despite an oxidation state difference, and to bind to transferrin and citrate in the blood stream (Ganrot 1986). It may also affect second messenger systems and calcium availability (Birchall and Chappell 1988), and irreversibly bind to cell nucleus components (Crapper McLachlan 1989; Dyrssen et al. 1987). Aluminum has also been shown to inhibit neuronal microtubule formation. However, much more work is needed before a mechanism can be proposed.

3.5.1 Pharmacokinetic Mechanisms

Gastrointestinal absorption of aluminum is low, generally in the range of 0.01–0.6% in humans as discussed in Section 3.3.1.2. Absorption of aluminum compounds is largely determined by its ionic availability in the aqueous conditions of the gut, which is mainly related to pH, the presence of complexing ligands with which the metal can form absorbable aluminum species, and the chemical form (type of anion) of the ingested compound (DeVoto and Yokel 1994; Reiber et al. 1995). In acidic aqueous conditions such as in the stomach (pH \approx 2) aluminum primarily occurs as a monomolecular hexahydrate, $\text{Al}(\text{H}_2\text{O})_6^{+3}$, which is generally abbreviated Al^{+3} and referred to as “free” aluminum (Reiber et al. 1995). The acidic conditions and mixing/residence time in the stomach appear to ensure that the majority of consumed aluminum will be solubilized to monomolecular species (most likely free Al^{+3}), regardless of the compound and form (e.g., food, drinking water or antacid tablets) in which it was ingested. The solubilized aluminum that is in the stomach can recomplex with the anion from the original aluminum compound that was ingested or form new complexes with dietary ligands. The dietary constituents that appear to play a particularly important role in the complexation process include simple mono-, di-, and tricarboxylic acids (particularly citric acid). The vast majority of the solubilized

3. HEALTH EFFECTS

aluminum is not complexed. As pH increases in the duodenum, a series of aluminum hydroxy complexes are formed by successive deprotonation so that in near-neutral conditions such as in the intestines, the predominant form is aluminum hydroxide ($[\text{Al}(\text{OH})_3]$), which is rapidly precipitated as insoluble by the near-neutral pH conditions, and is ultimately excreted in the feces.

The mechanism by which aluminum is absorbed and the chemical forms of aluminum able to pass through the intestinal wall are not completely understood (DeVoto and Yokel 1994; Exley et al. 1996; Lione 1985a; Priest 1993; Reiber et al. 1995; van der Voet 1992; Wilhelm et al. 1990). Available data, mainly results of *in vitro* (everted gut) and *in situ* (intestinal perfusion) studies in rats (e.g., Feinroth et al. 1982; Froment et al. 1989b; Provan and Yokel 1990), suggest that aluminum is mainly absorbed as neutral complexes by passive diffusion through intercellular tight junction (paracellular channel) pathways (i.e., via spaces between cells rather than through the cells themselves). However, adequate information is not available to rule out transcellular transport (cellular internalization), and both paracellular and transcellular pathways may be involved. Transcellular transport is also likely to be a passive process; possible mechanisms include cell-mediated endocytosis, simple diffusion of neutral and possibly lipophilic aluminum complexes, and facilitative diffusion via cation-specific channels (Exley et al. 1996). Active transport of Al^{+3} via iron absorption pathways may also contribute to the absorption of aluminum, but the role of iron pathways in aluminum absorption is incompletely elucidated (DeVoto and Yokel 1994) and complicated by the primary differences in oxidation states (2+ and 3+), which would argue against the two following an identical pathway. The predominant uptake mechanism remains unresolved due to insufficient data in the existing studies, particularly failure to characterize or control for intraluminal conditions affecting aluminum absorption, especially pH differences which can influence aluminum speciation, presence of dietary and other gut substances that can influence solubility of aluminum via formation of complexes, and quantity of available aluminum. These data insufficiencies complicate reconciling different results and postulated mechanisms between studies, and extrapolating to human *in vivo* physiochemical conditions (i.e., identifying the chemical form and mechanism of aluminum absorption in humans).

As previously discussed, absorption of aluminum is markedly increased by the presence of citrate. The mechanism is not fully characterized, but it is thought that citrate enhances gut bioavailability by increasing the permeability of the paracellular channels, possibly via disruption in calcium homeostasis (DeVoto and Yokel 1994; Exley et al. 1996; Froment et al. 1989b; Molitoris et al. 1989; Provan and Yokel 1988). It currently appears that aluminum is not absorbed across the gastrointestinal epithelium as a citrate complex, but that citrate expedites the absorption of aluminum by maintaining the aluminum in a

3. HEALTH EFFECTS

form that can be readily incorporated into one or more mechanisms of absorption (Exley et al. 1996). This mechanism may be unique to the aluminum-citrate complex, which would be consistent with the apparent greater bioavailability of aluminum citrate compared to other carboxylic acid chelates. Other factors such as parathyroid hormone (through stimulation of $1,25(\text{OH})_2\text{D}_3$ production) and vitamin D have also been suggested to enhance the absorption of aluminum, but the data are largely inconclusive.

Mechanisms of inhalation absorption of aluminum are not well characterized, although it seems likely that relatively large aluminum-containing particles retained in the respiratory tract are cleared to the gastrointestinal tract by ciliary action. As has been observed with typical particulates (ICRP 1994), it is hypothesized that aluminum particles that are small enough ($<5 \mu\text{m}$ diameter) to penetrate the lung's protective removal mechanisms may contribute to overall body levels by dissolution and direct uptake from alveoli into the blood stream, or by macrophage phagocytosis (Priest 1993; Reiber et al. 1995).

3.5.2 Mechanisms of Toxicity

In the cases in which human aluminum toxicity has occurred, the target organs appear to be the lung, bone, and the central nervous system. No specific molecular mechanisms have been elucidated for human toxicity to aluminum. In animal models, aluminum can also produce lung, bone, and neurotoxicity, as well as developmental effects in offspring.

Bone Toxicity. Two types of osteomalacia have been associated with aluminum exposure. The first type has been observed in healthy individuals using aluminum-containing antacids to relieve the symptoms of gastrointestinal disorders such as ulcers, colic, or gastritis. The aluminum in the antacids binds with dietary phosphorus and impairs gastrointestinal absorption of phosphorus. The observed osteomalacia and rickets is directly related to the decreased phosphate body burden. Osteomalacia is well documented in dialyzed uremic patients exposed to aluminum via dialysis fluid or orally administered aluminum used to control hyperphosphatemia. In the case of the uremic patient, bone aluminum levels are markedly increased and the aluminum is present between the junction of calcified and noncalcified bone (Alfrey 1993). The osteomalacia is characterized by increased mineralization lag time, osteoid surface, and osteoid area, relatively low parathyroid hormone levels, and mildly elevated serum calcium levels.

Neurotoxicity. Various neurotoxic effects of aluminum have been induced in animals, ranging from neurobehavioral and neurodevelopmental alterations following repeated oral exposures in mice and rats to neurodegenerative pathological changes in the brain caused by acute parenteral administration in

3. HEALTH EFFECTS

nonrodent species. Numerous mechanistic studies of aluminum neurotoxicity have been performed, but no single unifying mechanism has been identified (Erasmus et al. 1993; Jope and Johnson 1992; Strong et al. 1996); 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). Similar neurofibrillary pathological changes have been associated with several neurodegenerative disorders, suggesting that the cause of aluminum-related abnormal neuronal function may involve changes in cytoskeletal protein functions in affected cells. 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 substrates (Gandolfi et al. 1998; Jope and Johnson 1992; Julka and Gill 1995; Kaur and Gill 2005; Kaur et al. 2006; 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 Felipe 2001), lipid peroxidation (Deloncle et al. 1999; El-Demerdash 2004; Fraga et al. 1990; Khanna and Nehru 2007;

3. HEALTH EFFECTS

Nehru and Anand 2005), and impair neuronal glutamate nitric oxide-cyclic GMP pathway (Cucarella et al. 1998; Hermenegildo et al. 1999; Llansola et al. 1999; Rodella et al. 2004), as well as interfere with metabolism of essential trace elements (e.g., iron) because of similar coordination chemistries and consequent competitive interactions.

3.5.3 Animal-to-Human Extrapolations

The appropriateness of extrapolating health effects of aluminum in animals to humans cannot be conclusively determined due to limitations of the human database. Information on toxicity of aluminum in humans is not extensive because the preponderance of studies are in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-containing dialysis fluid and, in many cases, concurrent administration of high oral doses of aluminum to regulate phosphate levels. No clinical studies on health effects of aluminum medicinals in people with normal renal function have been performed, largely due to the fact that exposures typically consist of over-the-counter products such as antacids and buffered aspirins that have been 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 FDA-approved GRAS status of aluminum-containing food additives. Other human data largely consist of studies of aluminum-exposed workers that are limited by the lack of quantitative exposure data and/or co-exposure to other chemicals. Subtle neurological effects have been observed in workers chronically exposed to aluminum dust or aluminum fumes, but these studies only provide suggestive evidence that there may be a relationship between chronic aluminum exposure and neurotoxic effects in humans. Aluminum is generally considered to be neurotoxic in animals, and there is an adequate basis to conclude that neurotoxicity/neurodevelopmental toxicity is the critical effect of oral exposure in animals. Whether the subtle neurotoxic effects seen in adult and developing animals exposed to relatively low doses of aluminum would definitely manifest in humans under similar exposure conditions remains to be determined.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a

3. HEALTH EFFECTS

naturally occurring estrogen, or other such endocrine effect[s]...”. To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to aluminum. No *in vitro* studies were located regarding endocrine disruption of aluminum.

3.7 CHILDREN’S SUSCEPTIBILITY

This section discusses potential health effects from exposures 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.

Relevant animal and *in vitro* models are also discussed.

3. HEALTH EFFECTS

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

3. HEALTH EFFECTS

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There is a limited amount of information available on the toxicity of aluminum in children. As with adults, neurological and skeletal (osteomalacia) effects have been observed in children with impaired renal function (Andreoli et al. 1984; Griswold et al. 1983). These effects are related to an abnormal accumulation of aluminum due to exposure to aluminum-contaminated dialysate, use of aluminum containing phosphate binding gels, and impaired renal excretion of aluminum. These effects are not likely to occur in children with normal renal function. Skeletal effects have also been observed in children on long-term total parenteral nutrition containing elevated levels of aluminum. Another subpopulation of children that may be particularly sensitive to the toxicity of aluminum is preterm infants. The observed elevated plasma aluminum levels may be due to the higher aluminum content of premature infant formula and/or limited renal capacity of preterm infants to excrete aluminum (Tsou et al. 1991). Bougle et al. (1991) reported plasma aluminum levels of 14.6 µg/L in preterm infants compared to 7.8 µg/L in full-term infants; decreased urinary aluminum levels at comparable creatinine normalized rates were also found. Bishop et al. (1997) found significant decreases in the Bayley Mental Development Index in pre term infants receiving a standard intravenous feeding solution compared to pre term infants receiving an aluminum-depleted feeding solution. Growth reduction, hypotonia, muscle weakness, and craniosynostosis (premature ossification of the skull and obliteration of the sutures) have been observed in healthy infants following prolonged used of oral antacids for the treatment of colic (Pivnick et al. 1995). These effects were related to secondary hypophosphatemia caused by aluminum binding to phosphate in the gut and markedly reduced phosphate absorption.

Most of the available data come from animal studies that examined the distribution, neurotoxicity, and skeletal toxicity of aluminum at several ages (e.g., gestationally exposed, neonatal, young, adult, and older animals). Yokel and McNamara (1985) did not find any age-related differences in the systemic clearance or half-time of aluminum lactate in rabbits following intravenous, oral, or subcutaneous exposure. Oral exposure to aluminum nitrate resulted in higher brain aluminum levels in young rats as compared to older rats, but there was no difference in toxicity between young and adult rats (Gomez et al. 1997a). In other tissues examined, the aluminum levels in the young rats tended to be lower than in the adult or older animals (Gomez et al. 1997b). Fetal exposure may result in a higher distribution of aluminum to the brain, as compared to adults. In the fetuses of rats receiving a single subcutaneous injection of aluminum on gestation day 5, the amount of the radiolabelled aluminum in the brain was 30%

3. HEALTH EFFECTS

higher than in the liver; in the dams, brain aluminum levels were only 1% of the levels found in the liver (Yumoto et al. 2000).

Aluminum is distributed transplacentally, and elevated levels of aluminum have been measured in the fetus and placenta following oral, dermal, or parenteral exposure to aluminum (Anane et al. 1997; Cranmer et al. 1986; Yumoto et al. 2000). There is also evidence that oral or parenteral exposure to aluminum can result in elevated levels in breast milk (Golub et al. 1996; Muller et al. 1992; Yokel 1985; Yokel and McNamara 1985; Yumoto et al. 2000, 2003); the form of aluminum in breast milk was not reported. Although levels of aluminum in breast milk were elevated in aluminum-exposed rabbit does, the concentrations in the pups were not significantly different from control levels, suggesting that the aluminum was poorly absorbed (Yokel 1985). In contrast, subcutaneous injection of ^{26}Al in rats on lactation day 1 through 20 resulted in significant elevation in aluminum levels in the suckling rats (Yumoto et al. 2000).

The most sensitive known effect following oral exposure to aluminum is neurotoxicity. Neurotoxic effects have been observed in adult animals, weanling animals, and in animals exposed during gestation, gestation and lactation, and lactation-only (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 1998, 2001; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Oteiza et al. 1993). When neurological tests were performed in adult mice exposed to aluminum during development (gestation and lactation exposure) (Golub et al. 1995), the pattern of neurological effects (alterations in grip strength and startle response) was similar to those observed in mice exposed to aluminum as adults (Golub et al. 1992b; Oteiza et al. 1993) and in mice exposed to aluminum during development and adulthood (Golub et al. 1995). Additionally, the LOAELs for these effects were similar in the three groups, thus suggesting that the developing fetus and children may have a similar sensitivity as adults to the neurotoxic effects of aluminum.

A series of studies in which rabbits received subcutaneous doses of aluminum lactate suggest that the neurotoxicity of aluminum may be age-dependent. Subcutaneous administration of aluminum lactate resulted in alterations in learning and memory in gestationally-exposed rabbits and adult rabbits. A biphasic effect (enhancement after low doses and attenuation after high doses) on learning and memory was observed in the *in utero*-exposed rabbits (treatment on gestational days 2 through 27) (Yokel 1985) and an attenuated effect was observed in the adults (Yokel 1987), but no effects were observed in neonatal or immature rabbits (Yokel 1987). The apparent age-dependence of the toxicity of aluminum in

3. HEALTH EFFECTS

this study may be a reflection of the different ages at evaluation rather than age of exposure (Golub et al. 1995).

Another aluminum effect which appears to be age-related is skeletal toxicity. Increased carpal joint width, suggestive of poor bone calcification, was observed in immature rabbits receiving 20 subcutaneous doses of aluminum lactate, but was not seen in neonatal or adult rabbits (Yokel 1987).

A study by Sanchez et al. (1997) found significant age-related effects on aluminum interactions with essential elements (e.g., calcium, magnesium, zinc). Decreases in concentration of some essential elements in a number of tissues were observed in young rats orally exposed to aluminum lactate (as compared to adults); the decreases included liver and spleen calcium levels, bone magnesium levels, and brain manganese levels.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to aluminum are discussed in Section 3.8.1.

3. HEALTH EFFECTS

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by aluminum are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Aluminum

Aluminum can be measured in the blood, bone, urine, and feces (see Chapter 7 for description of available methods). Since aluminum is found naturally in a great number of foods, it is found in everyone. Unfortunately, exposure levels cannot be related to serum or urine levels very accurately, primarily because aluminum is very poorly absorbed by any route and its oral absorption in particular can be quite affected by other concurrent intakes. There is an indication that high exposure levels are reflected in urine levels, but this cannot be well quantified as much of the aluminum may be rapidly excreted. Aluminum can also be measured in the feces, but this cannot be used to estimate absorption.

3.8.2 Biomarkers Used to Characterize Effects Caused by Aluminum

There are no known simple, noninvasive tests which can be used as biomarkers of effects caused by aluminum. D'Haese et al. (1995) proposed the use of the DFO (deferoxamine) test to identify individuals with aluminum-related bone disease/aluminum overload. This test involves administering a challenge dose of the chelator deferoxamine to individuals with suspected aluminum-induced bone disease. However, iron supplementation may interfere with the test results (Huang et al. 2001).

3. HEALTH EFFECTS

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (Agency for Toxic Substances and Disease Registry 1990) and for information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

It is well documented that citrate, a common component of food, markedly enhances the gastrointestinal absorption of concurrently ingested aluminum (Alfrey 1993; Day et al. 1991; DeVoto and Yokel 1994; Froment et al. 1989b; Molitoris et al. 1989; Priest et al. 1996; Provan and Yokel 1988; Slanina et al. 1986; Weberg and Berstad 1986; Yokel and McNamara 1988). The effect has been shown with a variety of aluminum compounds and several forms of citrate in both experimental and clinical studies. The combination of citrate and aluminum has been responsible for a number of deaths in uremic patients, and the clinical implications of the interaction has led some investigators to advise against concomitant exposure to aluminum and citrate in any form (e.g., antacids and orange juice), especially to patients with impaired renal function. As discussed in Sections 3.3.1.2 and 3.5.1, citrate complexes with aluminum to form a species that is particularly bioavailable in the near-neutral pH conditions of the intestines.

Unlike citrate, it is likely that the presence of silicic acid in food and drink will decrease the bioavailability of aluminum by providing a strong competitive binding site for it within the gut contents, thus making the metal less available for absorption (Priest 1993). This is supported by two studies that show a decrease in retention of aluminum in response to higher doses of silicon when human volunteers ingested both chemicals together (Bellia et al. 1996; Edwardson et al. 1993; Jugdaohsingh et al. 2000); Jugdaohsingh et al. (2000) only found this effect when oligometric silica was administered (monomeric silica did not affect aluminum absorption). As discussed in Section 3.5.1, there are some data that suggest that aluminum absorption can be enhanced by parathyroid hormone and vitamin D, but the data are inconclusive.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to aluminum than will most persons exposed to the same level of aluminum in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of aluminum, or compromised function of organs affected by aluminum. Populations who are at greater risk due to their unusually high exposure to aluminum are discussed in Section 6.7, Populations with Potentially High Exposures.

3. HEALTH EFFECTS

The major population at risk for aluminum loading and toxicity consists of individuals with renal failure. In a study by Alfrey (1980), 82% of nondialyzed uremic patients and 100% of dialyzed uremic patients had an increased body burden of aluminum. The decreased renal function and loss of the ability to excrete aluminum, ingestion of aluminum compounds to lessen gastrointestinal absorption of phosphate, the aluminum present in the water used for dialysate, and the possible increase in gastrointestinal absorption of aluminum in uremic patients can result in elevated aluminum body burdens. The increased body burdens in uremic patients has been associated with dialysis encephalopathy (also referred to as dialysis dementia), skeletal toxicity (osteomalacia, bone pain, pathological fractures, and proximal myopathy), and hematopoietic toxicity (microcytic, hypochromic anemia). Preterm infants may also be particularly sensitive to the toxicity of aluminum due to reduced renal capacity (Tsou et al. 1991).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to aluminum. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to aluminum. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to aluminum:

Schonwald S. 2004. Aluminum. In: Dart RC, ed. *Medical toxicology*. 3rd ed. New York, NY: Lippincott, Williams, and Wilkins, 1387-1390.

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

Leikin JB, Paloucek FP. 2002. *Leikin and Paloucek's poisoning and toxicology handbook*. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 214-217.

3.11.1 Reducing Peak Absorption Following Exposure

There are limited data on reducing aluminum absorption following exposure. There is good evidence that aluminum is absorbed by a pericellular energy-independent and sodium-dependent process (Provan and Yokel 1988). If this is correct, then treatments that block pericellular processes can be used to minimize or prevent intestinal uptake of aluminum. Ranitidine may also decrease aluminum absorption (Leikin and Paloucek 2002).

3. HEALTH EFFECTS

3.11.2 Reducing Body Burden

In persons with normal renal function, the body burden can be reduced simply by limiting exposure (Schonwald 2004). Avoidance of aluminum-containing products, such as aluminum-containing phosphate binding gels, dialysate, and parenteral solutions, is recommended for patients with renal failure. Avoidance of co-administration of aluminum compounds and citrate compounds is also advised. Administration of a chelator such as desferrioxamine (DFO) may also help reduce aluminum body burden. DFO is a chelating agent that competes with complexing ligands such as transferrin and citrate that might deliver aluminum to tissues or otherwise redistribute it within the body. For example, DFO treatment has been used to facilitate the removal of aluminum from bone and its entry into the blood where it can be removed by hemodialysis (Haddad et al. 1998). DFO is also used in dialyzed uremic patients for the treatment of neurological, hematopoietic, and skeletal toxicity. In rats, administration of DFO resulted in a large reduction in the half life of aluminum in the brain; 55 days in the DFO-treated rats versus 150 days in controls (Yokel et al. 2001b). It should be noted that the clinical usefulness of DFO is limited by a variety of toxic effects including hypotension, skin rashes, stimulation of fungal growth, and possibly cataract formation. There is some evidence that other chelators may also be effective in reducing aluminum body burden. 1,2-Dimethyl-3-hydroxypyrid-4-one was shown to enhance urinary aluminum excretion in aluminum-loaded rats (Gomez et al. 1999; Yokel et al. 1997). Another study showed that (4-methyl-6-trifluoromethyl-6-pyrimidin-2-yl)-hydrazine was effective in decreasing the levels of aluminum in the brains of mice (Missel et al. 2005), although DFO was more effective in lowering the brain aluminum levels. Tiron (4,5-dihydroxy-1,3-benzene disulfonic acid di-sodium salt) administered during aluminum exposure to pregnant rats resulted in significant decreases in aluminum levels in the blood, brain, placenta, and fetus (Sharma and Mishra 2006). Another chelator tested in this study, 4-trichloromethyl-1-H-pyrimidin-2-one, was not effective. Administration of folic acid, melatonin, silicic acid, and beer (due to its silicon content) has been shown to decrease accumulated aluminum in tissues including bone, kidney, and brain in rats or mice (Abd-Elghaffar et al. 2005; Baydar et al. 2005; Gonzalez-Muñoz et al. 2007).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action for aluminum toxicity is not fully understood; thus, there are no known ways of interfering with its mechanism of action. Some pathways of aluminum chloride toxicity include induced lipid peroxidation, altered enzyme activity, overexpression of hippocampal A β immunoreactivity, and biochemical parameters. These toxic effects were shown to be improved in rats or mice when

3. HEALTH EFFECTS

administered vitamin E, vitamin C, selenium, beer (due to its silicon content), centrophenoxine (an anti-aging drug), and the herbal medicines *Dipsacus asper Wall* extract and *Bacopa moniera* (Chinoy et al. 2004; El-Demerdash 2004; Gonzalez-Muñoz et al. 2007; Jyoti and Sharma 2006; Nedzvetsky et al. 2006; Nehru and Bhalla 2006; Nehru et al. 2007; Saba-El Rigal 2004; Zhang et al. 2003).

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, 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 conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of aluminum.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Aluminum

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to aluminum are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of aluminum. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Information on human health effects from inhaled aluminum is available from epidemiological studies and case studies of aluminum workers. This includes data on death, chronic effects, and cancer.

3. HEALTH EFFECTS

Figure 3-4. Existing Information on Health Effects of Aluminum

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●			●		●				●
Oral	●	●	●	●		●				
Dermal		●	●		●					

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●	●	●						●
Oral	●	●	●	●	●	●	●	●		●
Dermal		●								

Animal

● Existing Studies

3. HEALTH EFFECTS

Information on oral exposure is available only from specialized cases, such as people who consumed a grain fumigant to try to commit suicide, individuals consuming large doses of aluminum-containing antacids, and dialyzed and nondialyzed uremic patients consuming aluminum compounds prescribed as phosphate binding agents. Information on dermal effects in humans is available from patch tests.

In animals, information on effects from inhalation exposure is available for pure aluminum flakes, aluminum chlorhydrate antiperspirants, and a propylene glycol complex of aluminum chlorhydrate. Effects following oral exposure to several aluminum salts are available for adults and newborn animals. One acute dermal study is available.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are no studies that examined the acute toxicity of aluminum following inhalation, oral, or dermal exposure. A small number of animal studies have 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 would 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. The acute systemic toxicity of orally administered aluminum has not been well investigated; most of the available data 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 Garbossa et al. (1996) examined hematological indices; neither study examined for potential neurological effects, which has been shown to be the most sensitive end point following intermediate- or chronic-duration exposure. Oral exposure studies that examined a wide range of potential effects, including neurotoxicity, are needed to identify the critical target of toxicity and establish dose-response relationships. There are limited data on the dermal toxicity of aluminum. 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

3. HEALTH EFFECTS

products, additional dermal exposure studies would be useful to fully assess the potential toxicity of aluminum following dermal exposure.

Intermediate-Duration Exposure. There is a limited amount of intermediate-duration human data on the toxicity of aluminum. Neurological and skeletal effects have been observed in uremic patients (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. Intermediate-duration inhalation studies in animals identified the lung as a sensitive target of toxicity (Drew et al. 1974; Steinhagen et al. 1978; Stone et al. 1979). 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. A fair number of 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. A series of studies conducted by Mahieu and associates (Mahieu et al. 1998, 2003, 2005, 2006) found small changes in sodium and phosphate excretion and urine concentrating ability (under conditions of water deprivation), but no changes in overall renal function (glomerular filtration rate or clearance), in rats administered aluminum hydroxide or aluminum lactate via intraperitoneal injection. Although several oral exposure studies did not find histological alterations in the kidneys, none of these studies examined renal function; the results of the Mahieu studies suggest the need for a study examining renal function following oral exposure to aluminum. 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) co-principal studies; the critical effect was neurodevelopmental effects and delays in physical maturation. No studies have examined the dermal toxicity of aluminum; animal studies would provide useful information on

3. HEALTH EFFECTS

aluminum's potential to induce dermal effects following repeated exposure and whether it can cause systemic or neurological effects.

Chronic-Duration Exposure and Cancer. 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. 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, foundry, and welders (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; Sjögren et al. 1990, 1996; White et al. 1992). Inhalation animal studies have focused on the pulmonary toxicity of aluminum (Pigott et al. 1981; Stone et al. 1979). 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. Several studies have examined the systemic 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

3. HEALTH EFFECTS

following chronic-duration exposure utilizing multiple dose levels would be useful in comparing the sensitivity of these two effects.

The available data do not indicate that aluminum is a potential carcinogen. It has not been shown to be carcinogenic in epidemiological studies in humans, nor in animal studies using inhalation, oral, and other exposure routes (Oneda et al. 1994; Ondreicka et al. 1966; Pigott et al. 1981; Schroeder and Mitchener 1975a, 1975b). Although these studies have limitations ranging from use of only one species to a single exposure level and limited histological examinations, the evidence strongly suggests that aluminum is not carcinogenic, indicating that additional carcinogenicity testing is not warranted at this time.

Genotoxicity. Several *in vitro* studies have found significant increases in the occurrence of micronuclei formation (Banasik et al. 2005; Migliore et al. 1999; Roy et al. 1990) and chromosome aberrations (Roy et al. 1990) in human lymphocytes; no human *in vivo* studies were identified. 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 (DiPaola and Casto 1979; Kada et al. 1980; Kanematsu et al. 1980; Marzin and Phi 1985; Nishioka 1975; Oberly et al. 1982; Olivier and Marzin 1987). Further genotoxicity studies, particularly *in vivo* exposures, would be useful for verifying the results of the Manna and Das (1972) study and for evaluating other potential end points of genotoxicity.

Reproductive Toxicity. 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. A number of oral-exposure studies examining reproductive end points in several animal species were identified. In general, the results of these studies 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). Further studies in this area do not appear to be necessary at this time.

Developmental Toxicity. No studies human studies examining the potential of aluminum to induce developmental effects in humans exposed to aluminum via inhalation, ingestion, or dermal contact were located. Developmental toxicity studies in animals have shown that oral gestational exposure to

3. HEALTH EFFECTS

aluminum induced skeletal variations such as delayed ossification in rats and mice under conditions that enhanced its uptake, particularly maternal intake of compounds that are highly bioavailable (e.g., aluminum citrate and nitrate), concurrent exposure to dietary constituents that contribute to increased absorption of aluminum (e.g., citrate), and/or bolus administration by gavage (Colomina et al. 1992; Gomez et al. 1991; Paternain et al. 1988). There is some evidence that oral developmental exposure to aluminum affected the immune system in young mice (Golub et al. 1993; Yoshida et al. 1989) and may delay physical maturation (Colomina et al. 2005). Neurobehavioral deficits have been observed in oral studies of weanling and young developing mice and rats exposed to aluminum by 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 increases in grip strength and landing foot splay and decreased thermal sensitivity. The effects most commonly found in mice exposed during development and tested as adults, or tested only as adults, included decreases in spontaneous motor activity, grip strength, and startle responsiveness, indicating that the pattern of neurobehavioral impairment in developing animals was different from adults.

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. This type of animal testing would help determine the generality or specificity of aluminum neurodevelopmental toxicity and provide a better basis for its assessment in children. Additional information that is needed to more fully characterize the neurodevelopmental toxicity of aluminum includes data on whether effects are transient and reversible or whether they persist and cause permanent changes after exposures are terminated. Additionally, it would be informative to verify that the central nervous system is the critical developmental end point for aluminum by obtaining data on effects in noncentral nervous system organs known to be targets of aluminum toxicity in adults. Additional investigations of the skeletal component of the aluminum developmental toxicity syndrome are particularly needed because permanent effects on bone growth and strength could occur during periods of rapid mineralization not investigated in existing studies, such as early infancy and adolescence. New developmental toxicity studies should include a range of low oral doses that encompasses the

3. HEALTH EFFECTS

neurotoxicity NOAEL on which the intermediate-duration MRL is based, as well adequately characterized levels of aluminum in the base diet.

Additional information on compound bioavailability is also needed to better evaluate the developmental toxicity of aluminum. Because the developmental effects of orally administered aluminum appear to be dependent on the bioavailability of the form in which it is administered and the presence of dietary components that promote aluminum uptake, additional information on compound-related differences in aluminum uptake and effectiveness during pregnancy and postnatal development would help in assessing the relevance of the animal data to oral exposures in humans. For example, gavage administration of low doses of aluminum (38–77 mg Al/kg/day) as aluminum nitrate during gestation induced skeletal variations in rats (Paternain et al. 1988), indicating that the LOAEL for this effect is below the neurotoxicity NOAEL of 62 mg Al/kg/day for aluminum lactate in adult mice used to derive the MRL. The Paternain et al. (1988) LOAEL was not considered to be appropriate for MRL consideration due to concern that gavage does not realistically represent environmental aluminum intake (i.e., the LOAEL could be unnaturally low compared to dietary exposure because the skeletal effects could be related to phosphate binding caused by the bolus administration), and that nitrate represents an unusually bioavailable form of aluminum. Additional information on the bioavailability of different forms and amounts of aluminum exposure would help establish how well oral aluminum exposure regimens in animals (e.g., gavage as tested by Paternain et al. [1988]) approximate the oral bioavailability of aluminum from water or food in humans. This kind of information is needed to verify that the MRL is based on the most appropriate end point (i.e., neurotoxicity in adults rather than skeletal developmental toxicity), especially considering that no NOAEL has been identified for either skeletal developmental effects (Paternain et al. 1988) or neurodevelopmental effects (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1992a, 1992b, 1994, 1995). Information on fetal uptake of aluminum administered in forms that have been already evaluated for prenatal developmental toxicity could indicate if the aluminum nitrate in the Paternain et al. (1988) study was effective because it is the most available to the fetus.

Immunotoxicity. A few reports indicate hypersensitivity in children and adults who have received aluminum-containing vaccines (Bergfors et al. 2005; Böhler-Sommeregger and Lindemayr 1986; Castelain et al. 1988; Veien et al. 1986). 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

3. HEALTH EFFECTS

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. The available inhalation studies did not conduct function tests. Histopathological examination of lymphoreticular tissues has shown no effect after oral administration of aluminum in rats (Dixon et al. 1979; Domingo et al. 1987b; Gomez et al. 1986; Katz et al. 1984; Ondreicka et al. 1966). Alteration in lymph node proliferation was observed in rats (Lauricella et al. 2001), and there is some evidence that developmental exposure to aluminum can affect the immune system in young mice (Golub et al. 1993; Yoshida et al. 1989). 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. Aluminum-related dermal sensitivity appears to be very rare in humans; further studies do not appear to be necessary.

Neurotoxicity. 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; Sjögren 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 role in the Alzheimer's disease process.

The neurotoxicity of aluminum is well-documented in animals and has been manifested following oral or parenteral routes of exposure; however, there are very limited data on neurotoxicity following inhalation or dermal exposure. Inhalation studies have conducted histological examinations of the brain (Steinhagen et al. 1978; Stone et al. 1979), but have not conducted 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, the neurotoxicity is manifested in neuromotor,

3. HEALTH EFFECTS

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. Additionally, neurotoxicology studies measuring blood aluminum levels would be useful in determining the relevance of the animal data to humans. Research issues related to neurodevelopmental effects of aluminum are discussed in the Data Needs section on Developmental Toxicity.

Epidemiological and Human Dosimetry Studies. 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; Sjögren 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. 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 aluminum-related effects; 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

3. HEALTH EFFECTS

examining potential adverse effects in healthy individuals ingesting these products long-term have not been located and are needed.

Biomarkers of Exposure and Effect. Reliable methods for determining tissue and plasma levels of aluminum exist. The mechanism of action for aluminum toxicity is not known, hence it is not known whether biomarkers of effect exist or not.

Exposure. 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 correlate with increased exposure. 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.

Effect. No biomarkers of effect have been identified for aluminum. The mechanisms of action for aluminum toxicity is not known 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.

Absorption, Distribution, Metabolism, and Excretion. 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 range in aluminum absorption has not been

3. HEALTH EFFECTS

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 and provide a means to distinguish endogenous aluminum from administered aluminum and from aluminum contamination of samples (Priest 1993). Additional toxicokinetic studies using ^{26}Al would help to better characterize the likely range of aluminum bioavailability. This kind of information is needed because an amount of aluminum ingested does not provide an estimate of exposure without information on bioavailability of the form in which it is ingested. In particular, if bioavailability in a particular human scenario differs from bioavailability in the MRL study, or is not known, extrapolation may not be appropriate because exposure depends on bioavailability as well as intake. 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.

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.

Comparative Toxicokinetics. The animal data indicate that the nervous system is a 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; Sjögren et al. 1990, 1996; White et al. 1992). The toxicokinetic properties of aluminum have been

3. HEALTH EFFECTS

studied in human 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 in extrapolating toxicity data across species.

Methods for Reducing Toxic Effects. The mechanisms of absorption of aluminum have not been established. Studies that elucidated these mechanisms would be useful for establishing methods or treatments for reducing absorption and distribution of aluminum to sensitive targets. The chelating agent 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-yl)-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.

Children's Susceptibility. 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 the 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.

3. HEALTH EFFECTS

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

There are a large number of ongoing studies covering many aspects of aluminum toxicity. Studies supported by the federal government are listed in Table 3-5.

3. HEALTH EFFECTS

Table 3-5. Ongoing Studies on Aluminum

Investigator	Study Topic	Institution	Sponsor
Longnecker M	Use of aluminum in toenails as a biomarker of exposure		National Institute of Environmental Health Sciences
Yokel R	Aluminum bioavailability from foods	University of Kentucky	National Institute of Environmental Health Sciences
Bondy S	Aluminum/iron interactions in neurodegenerative disease	University of California Irvine	National Institute of Environmental Health Sciences
DeWitt DA	Mechanism of aluminum-induced neurodegeneration in Alzheimer's disease	Liberty University	National Institutes of Health
Swyt-Thomas CR	Role of aluminum in Alzheimer's disease		National Institutes of Health

Source: FEDRIP 2006