2. HEALTH EFFECTS

2.1 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 of 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 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.

2.2 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 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 (LOAEL) 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.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for aluminum An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organs(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposure for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for derrnal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or result from repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis.

As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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.

2.2.1 Inhalation Exposure

2.2.1.1 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, 2 died and 4 others had radiological changes on chest X-rays. Total dust in the workplace air was 615-685 mg Al/m^3, and respirable dust was 51 mg Al/m^3. Chemical analysis showed the dust to be 8 1% metallic aluminum and 17 % various oxides and hydroxides of aluminum The death of a male factory worker chronically exposed to aluminum flake powder has been described (McLaughlin et al. 1962). Prior to death, the man exhibited memory loss, speech difficulties, convulsions, weakness, EEG abnormalities, dysarthria, hemiparesis, and slowed reactions. Neurological symptoms were not found in 53 other male workers at the same factory. It is possible that other factors, such as impaired renal function, in addition to aluminum exposure, contributed to the neurological symptoms and death of the factory worker.

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/m^3 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/m^3 as refractory alumina fiber for 86 weeks in groups of 50 male and female Wistar rats (Pigott et al. 1981). No studies were located that evaluated death from an intermediate-duration inhalation exposure in animals to aluminum or its compounds.

2.2.1.2 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 2-1 and plotted in Figure 2- 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 welding operations, and the production and use of finely powdered aluminum. Wheezing, dyspnea, and impaired lung function have been observed in potroom workers (Bast-Peetersen et al. 1994; Chan-Yeung et al. 1983; Simonsson et al. 1985). Because these workers were also exposed to a number of other toxic chemicals including sulfur dioxide, polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, and hydrogen fluoride, it is difficult to ascribe the respiratory effects to aluminum.

Pulmonary fibrosis is the most commonly reported respiratory effect observed in workers exposed to fine aluminum dust (pyropowder), alumina (aluminum hydroxide), 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 (Devuyst et al. 1986; Gaffuri et al. 1985; Jephcott 1948; Musk et al. 1980; Riddell 1948; Shaver 1948); 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

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	

ACUTE EXPOSURE

Systemic

1	Rat (Fischer- 344)	5 d 4 hr	Resp	10 M	50 M (alterations in cytological and enzymatic content of lavage fluid)		Thomson et al. 1986 Aluminum powder
			Resp	100 M	200 M (multifocal microgranulomas in lungs)		
2	Hamster (Golden Syrian)	3 d 6 hr/d - day 1 4 hr/d - days 2 + 3	Resp		33 M (alveolar wall thickening and increased number of macrophages; bronchopneumonia)		Drew et al. 1974 alchlor
			Bd Wt		33 (unspecified decreased body weight)		
3	Hamster (Golden Syrian)	3 d 4 hr/d	Resp		31 (alveolar wall thickening and increased number of macrophages and heterophils)		Drew et al. 1974 alchlor
4	Hamster (Golden Syrian)	3 d 4 hr/d	Resp	3 M	7 M (15% increased lung weight)		Drew et al. 1974 alchlor
5	Hamster (Golden Syrian)	3 d 4 hr/d	Resp		10 M (approximately 24% increased lung weight)		Drew et al. 1974 alchlor

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL			Reference Chemical Form
					Less serious (mg/m3)		Serious (mg/m3)	
6	Rabbit (New Zealand)	5 d 4 hr/d	Resp		43	(alveolar wall thickening, increased number of macrophages: 65% increase in lung weight)		Drew et al. 1974 alchlor

INTERMEDIATE EXPOSURE

Systemic

7	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d	Resp	0.061	0.61	(increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 Al₂(OH)₅Cl
			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				
8	Rat (Fischer- 344)	6-12 mo 5 d/wk 6 hr/day	Resp	0.61	6.1	(48-112% increased relative lung wt)		Stone et al. 1979 Al₂(OH)₅Cl
			Bd Wt	6.1				
			Bd Wt	5.4				

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
9	Gn Pig (Hartley)	6 mo 5 d/wk 6 hr/d	Resp	0.061	0.61 (increase in alveolar macrophages; granulomatous lesions in lungs)		Steinhagen et al. 1978 $Al_2(OH)_5Cl$
			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			
10	Gn Pig (Hartley)	6-12 mo 5 d/wk 6 hr/day	Resp	0.61	6.1 (22-30% increased relative lung weight)		Stone et al. 1979 $Al_2(OH)_5Cl$
			Bd Wt	6.1			
11	Hamster (Golden Syrian)	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 alchlor

Table 2-1. Levels of Significant Exposure to Aluminum and Compounds - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
CHRONIC EXPOSURE							
Systemic							
12	Rat (Wistar)	86 wk 5 d/wk 6 hr/d	Resp	2.45			Pigott et al. 1981 Al_2O_3
13	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/day	Resp	0.61	6.1 (108-274% increased relative lung weight at 2 yrs)		Stone et al. 1979 $Al_2(OH)_5Cl$
			Hemato	6.1			
			Bd Wt		6.1 (10-20% decrease)		
14	Gn Pig (Hartley)	21 mo 5 d/wk 6 hr/day	Resp	0.061	6.1 (21-41% increased relative lung weight at 2 yrs)		Stone et al. 1979 $Al_2(OH)_5Cl$
			Hemato	6.1			
			Bd Wt	6.1			

[a]The number corresponds to entries in Figure 2-1.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; LT_{50} = time to 50% kill; M = male; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; WBC = white blood cell; wk = week(s).

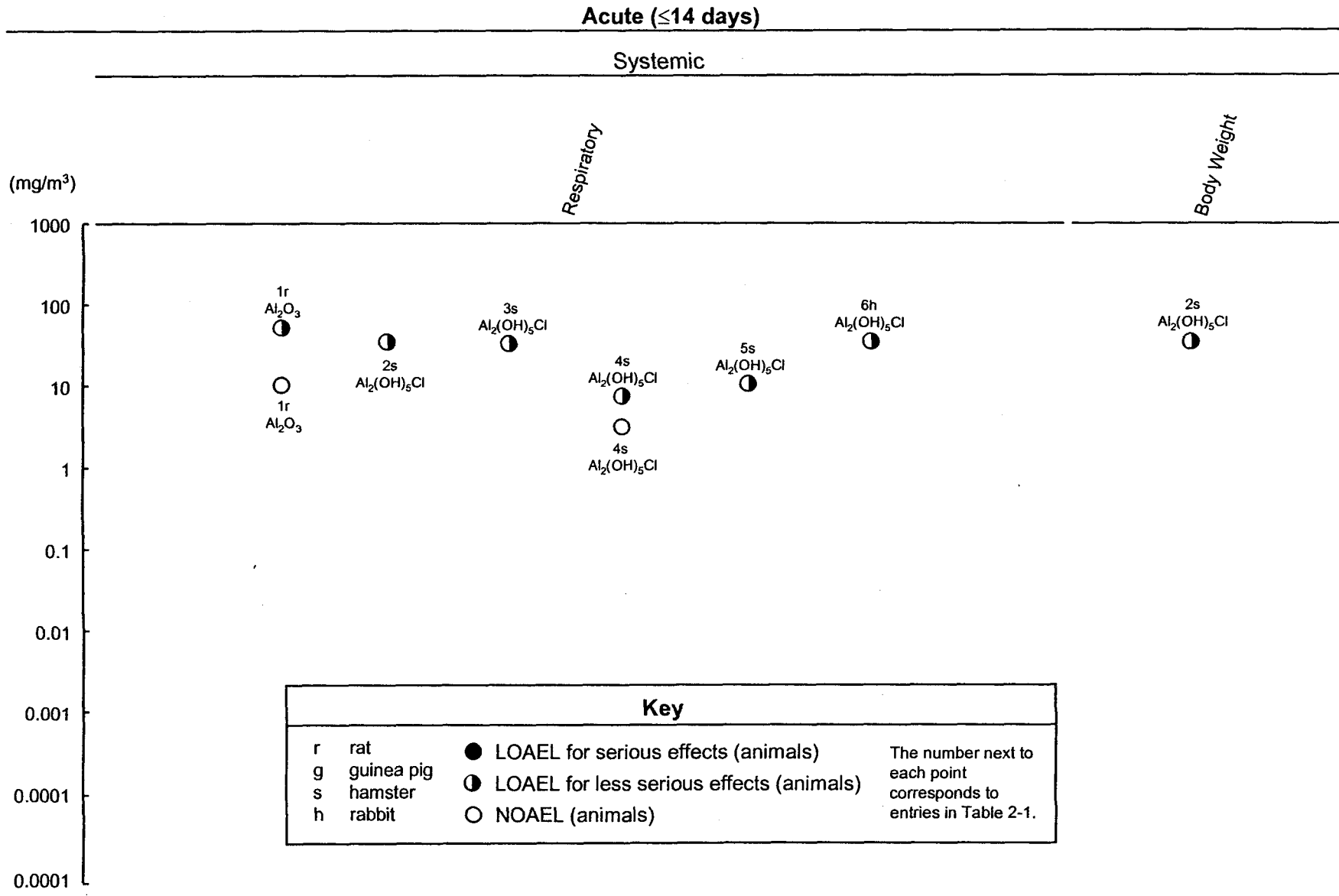# Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation

Acute (≤14 days)

Systemic

Key

r	rat	● LOAEL for serious effects (animals)	The number next to each point
g	guinea pig	◐ LOAEL for less serious effects (animals)	corresponds to
s	hamster		
h	rabbit	○ NOAEL (animals)	entries in Table 2-1.

Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation (cont.)

Intermediate (15-364 days)

Systemic

Respiratory

Cardiovascular

Gastrointestinal

Hematological

(mg/m^3)

1000

100

11s
$Al_2(OH)_5Cl$
◑

10

7g
$Al_2(OH)_5Cl$
◑

◑

9g
$Al_2(OH)_5Cl$
◑

10g
$Al_2(OH)_5Cl$
◑

7g
$Al_2(OH)_5Cl$
○   ○

7g
$Al_2(OH)_5Cl$
○   ○

7g
$Al_2(OH)_5Cl$
○   ○

8r
$Al_2(OH)_5Cl$

9g
$Al_2(OH)_5Cl$

9g
$Al_2(OH)_5Cl$

9g
$Al_2(OH)_5Cl$

1

○
8r
$Al_2(OH)_5Cl$

○
10g
$Al_2(OH)_5Cl$

0.1

○
7g
$Al_2(OH)_5Cl$

○
9g
$Al_2(OH)_5Cl$

0.01

0.001

0.0001

0.00001

Key		
r rat	● LOAEL for serious effects (animals)	The number next to
g guinea pig	◑ LOAEL for less serious effects (animals)	each point
s hamster		corresponds to
h rabbit	○ NOAEL (animals)	entries in Table 2-1.

Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation (cont.)

Intermediate (15-364 days)
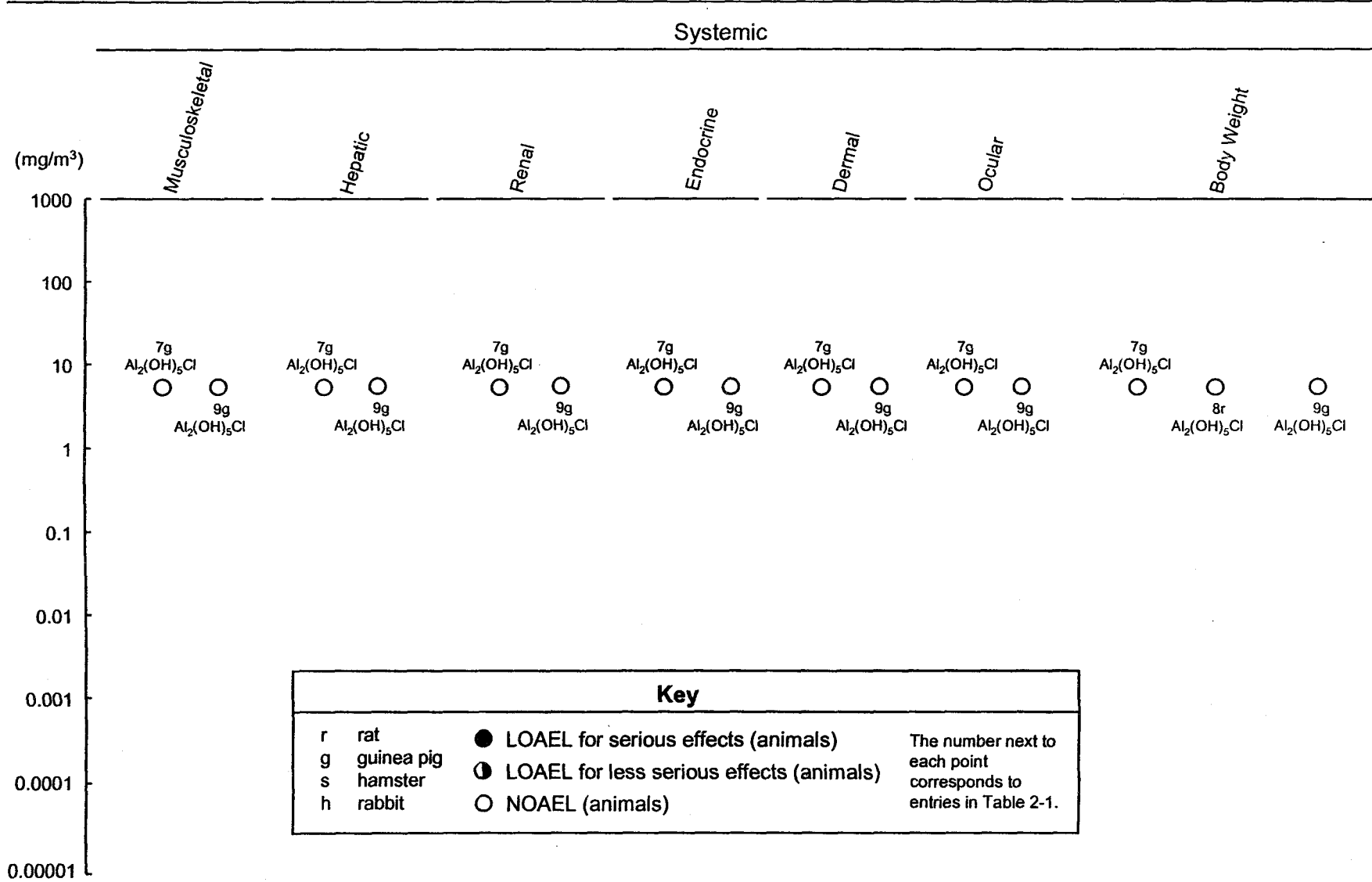
Figure 2-1. Levels of Significant Exposure to Aluminum - Inhalation (cont.)

Chronic (≥365 days)

Systemic
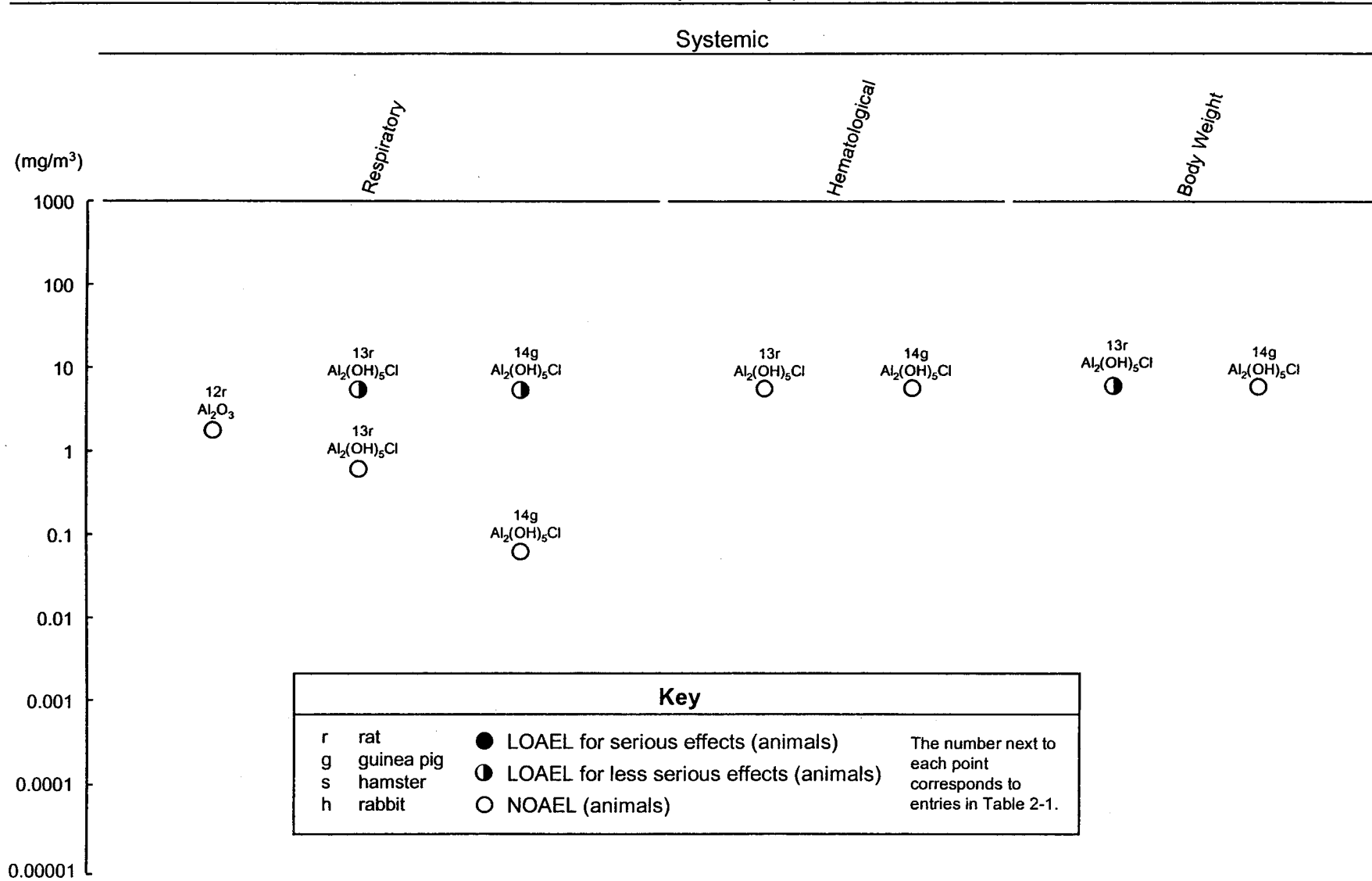
pulmonary fibrosis were reported in German munition workers exposed to pyropowder. Case reports of fibrosis in workers exposed to finely ground aluminum have been also been reported by Edling (1961), McLaughlin et al. (1962) Mitchell et al. (1961) and Ueda et al. (1958). However, other studies have not 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).

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/m^3 resulted in moderate-to-marked thickening of the alveolar walls due to neutrophil and macrophage infiltration and small granulomatous foci at the bronchioloalveolar 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 43 mg Al/m^3 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/m^3 (no effects were observed at 3 mg Al/m^3) and in rabbits exposed to 43 mg Al/m^3 for 5 days (no effects were observed in rabbits exposed to 48 or 39 mg Al/m^3 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/m^3 and multifocal microgranulomas in the lungs and hilar lymph nodes at ≥ 100 mg Al/m^3 (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/m^3 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/m^3 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 absolute and relative lung weight was observed in the rats exposed to 6.1 mg Al/m^3; 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/m^3. Suggestive evidence of alveolar macrophage damage was observed in rats following a 5month exposure (6 hours/day, 5 days/week) to either aluminum chloride (0.37 mg Al/m^3) or aluminum fluoride (0.41 mg Al/m^3); 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).

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/m^3 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/m^3. 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/m^3 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.

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

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. 196 1). 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
pressure measurement) were similar between 22 aluminum workers exposed for 10 years or more and an
unexposed control group of 16 men (Bast-Peetersen et al. 1994).

No histological alterations changes 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/m^3 as aluminum chlorhydrate for
6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 2-l and plotted in
Figure 2- 1.

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/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These
NOAEL values are recorded in Table 2- 1 and plotted in Figure 2-l.

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 7 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/m^3, 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
antithrombogenic effects (Waldron-Edward et al. 197 1).

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/m^3 as aluminum
chlorhydrate for 6-24 months (Steinhagen et al. 1978; Stone et al. 1979). These NOAEL values are
recorded in Table 2-l and plotted in Figure 2-l.

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 by inhalation 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 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). These NOAEL values are recorded in Table 2-l and plotted in Figure 2- 1.

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 7 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).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

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). One study did report an increase in urinary fluoride in male workers chronically exposed by inhalation to aluminum oxide, although control levels also increased slightly (Chan-Yeung et al. 1983). Workers in the aluminum reduction industry are exposed to fluoride as part of the reduction process (see Chapter 4).

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).

The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

Endocrine Effects. No studies were located regarding endocrine effects in humans following acuteor intermediate-duration inhalation exposure to various forms of aluminum. Post-mortem enlargement of 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-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/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 2-l and plotted in Figure 2-l.

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/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 2- 1 and plotted in Figure 2- 1.

Ocular Effects. No studies were located regarding ocular effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminum. Following the cessation of exposure, normal eye examination results were reported 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/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 2-1 and plotted in Figure 2-l.

Body Weight Effects. Unspecified body weight decreases were reported for male Golden Syrian hamsters acutely exposed via whole-body inhalation to 3, 10, or 33 mg Al/m^3 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/m^3 as aluminum chloride or 0.41 mg Al/m^3 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/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978) or to 0.61 mg Al/m^3 as aluminum chlorhydrate for up to 24 months (Stone et al. 1979). Significant reduction in body weight was observed in Fischer 344 rats after 24 months of exposure to 6.1 mg/m^3 as aluminum chlorhydrate. No effect on body weight was seen in Hartley guinea pigs similarly exposed (Stone et al. 1979). These NOAEL and LOAEL values are recorded in Table 2-l and plotted in Figure 2-l.

Metabolic Effects. No studies were located regarding metabolic effects in humans following acuteor 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).

2.2.1.3 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. Sarcoid-like epitheloid granulomas were found in the lungs of a 32-year-old man chronically exposed by inhalation to metallic aluminum and aluminum dust (De Vuyst et al. 1987). These granulomas contained dust identified primarily as aluminum particles. Immunological testing failed to confirm sarcoidosis, but did find helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in the presence of soluble aluminum compounds in vitro. Additional testing one year after termination of exposure indicated the man no longer had alveolitis.

Although 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.

The highest NOAEL values and all reliable LOAEL values for immunological/lymphoreticular effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.4 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 or symptoms of neurotoxicity in workers exposed to aluminum dust (potroom and foundry workers) (Bast-Peetersen et al. 1994; Dick et al. 1997; Hosovski et al. 1990; Simet al. 1997; White et al. 1992), in aluminum welders , (Hlnninen et al. 1994; Sjogren et al. 1996), or miners exposed to McIntyre powder (finely ground aluminum and aluminum oxide) (Rifat et al. 1990). Although no overt neurological effects were observed, subclinical effects have been reported in some of these studies. In the Hanninen et al. (1994) study of aluminum welders, no alterations in neurobehavioral performance tests were found, but significant correlations between urinary aluminum levels and memory test performance and between plasma aluminum levels and visual reaction time tests were found. Additionally, quantitative EEG changes, similar to those found in patients with aluminum encephalopathy, were also found in the welders. Hosovoski et al. (1994) and Sjogren et al. (1990) also found significant alterations in performance tests assessing reaction time, eye-hand coordination, memory, and/or motor skills in aluminum foundry workers and aluminum welders, respectively, and Rifat et al. (1990) found impaired performance on cognitive tests in miners exposed to McIntyre powder. Higher incidences of subjective neurological symptoms (e.g., incoordination, difficulty buttoning, depression, fatigue) were reported in two studies of aluminum potroom workers at an aluminum smelter (Sim et al. 1997; White et al. 1992) and in a study of aluminum welders (Sjiigren et al. 1990). Although Bast-Peetersen et al. (1994) did not find aluminum-related alterations in the incidence of reported neurological symptoms or neurobehavioral performance in potroom workers, they did find a higher incidence of subclinical tremors in the aluminum-exposed workers. In a retrospective study conducted by NIOSH, no alterations in reaction

time (Sim et al. 1997) or incidence of subclinical tremor (Dick et al. 1997) were found in aluminum
potroom workers.

In general, these 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;
Sjogren et al. 1996; White et al. 1992), but did not have earlier monitoring data when aluminum
exposures were higher. The lack of adequate exposure monitoring data and the different types of
aluminum exposure makes it difficult to compare these studies and draw conclusions regarding the
neurotoxic potential of inhaled aluminum in workers.

A case control study by Salib and Hillier (1996) examined the possible relationship between the risk of
Alzheimer's disease and occupational exposure to airborne aluminum. The occupation histories of
patients with a clinical diagnosis of Alzheimer's disease (198 cases) were compared with two control
groups: patients with dementia other than Alzheimer's disease (164 cases) and patients with diagnoses
other than dementia. Occupational histories were obtained from the patients via a questionnaire. No
significant association between occupational exposure to aluminum dust or fumes and the risk of
Alzheimer's disease were found (the odds ratio for the comparison with all controls was 0.98, 95%
confidence interval of 0.53-1.75).

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/m^3 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/m^3 as aluminum chloride or 0.41 mg Al/m^3 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/m^3 as aluminum
chlorhydrate for up to 24 months (Stone et al. 1979). These NOAEL values are recorded in Table 2- 1 and
plotted in Figure 2- 1.

2.2.1.5 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/m^3 as aluminum chlorhydrate for 6 months (Steinhagen et al. 1978). These NOAEL values are recorded in Table 2-l and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

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

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to various forms of aluminum Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 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 5 aluminum reduction plants were assessed with respect to incidence of bladder cancer. The number of men working in the plants was 300-l ,200 except for 1 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, 3 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 less than 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 (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 which focused on mortality from lung cancer in a group of 5,406 aluminum production workers (Gibbs and Horowitz 1979), a doseresponse 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 or more years experiences 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/m^3 as alumina fibers (96% aluminum oxide) for 86 weeks (Pigott et al. 1981).

2.2.2 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, recently 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 12-7 1 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 150-8,300 ppm

for Purina Rodent 5001 Laboratory Chow (Fleming and Joshi 1987; 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 1988d) 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 2-2 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 2-2 and Figure 2-2. 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; Golub et al. 1989, 1992a, 1992b, 1994, 1995; Oteiza et al. 1993) and Domingo and coworkers (Colornina et al. 1992, 1994, 1998; Domingo et al. 1987a, 1987b, 1989, 1993; Gomez et al. 1986, 1991; Paternain et al. 1988). The Golub studies are additionally noteworthy because they tested aluminum lactate, which represents a bioavailable form of aluminum with an anion (lactate) that is a common human dietary constituent.

Although levels of human oral intake of aluminum are well-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 2.3.1.2, 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.

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

| Key to[a] figure | Species (Strain) | Exposure/ duration/ frequency (Specific route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	once (G)				261 (LD$_{50}$)	Llobet et al. 1987 Al(NO$_3$)$_3$
2	Rat (Sprague-Dawley)	once (G)				370 (LD$_{50}$)	Llobet et al. 1987 AlCl$_3$
3	Rat (Sprague-Dawley)	once (G)				162 (LD$_{50}$)	Llobet et al. 1987 AlBr$_3$
4	Mouse (Swiss-Webster)	·once (G)				286 (LD$_{50}$)	Llobet et al. 1987 Al(NO$_3$)$_3$
5	Mouse (Swiss-Webster)	once (G)				222 (LD$_{50}$)	Llobet et al. 1987 AlCl$_3$
6	Mouse (Swiss-Webster)	once (G)				164 (LD$_{50}$)	Llobet et al. 1987 AlBr$_3$
7	Mouse (Dobra Voda)	once (G)				770 M (LD$_{50}$)	Ondreicka et al. 1966 AlCl$_3$
8	Rabbit (New Zealand)	once (GW)				540 F (5/5 died)	Yokel and McNamara 1985 C$_9$H$_{15}$AlO$_9$

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

| Key to[a] figure | Species (Strain) | Exposure/ duration/ frequency (Specific route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Developmental							
9	Mouse (Swiss)	Gd 6-15 (GW)		141			Domingo et al. 1989 AlH₃O₃
INTERMEDIATE EXPOSURE							
Death							
10	Mouse (Swiss-Webster)	Gd 1 - Gd 21 Gd 1 - PND 21 PND 1 - 21 (F)				250 F (death in 1/9 dams at weaning)	Golub et al. 1992a C₉H₁₆AlO₆
Systemic							
11	Rat (Sprague-Dawley)	100 d (W)	Resp	284 F			Domingo et al. 1987b Al(NO₃)₃
			Cardio	284 F			
			Hemato	284 F			
			Hepatic	284 F			
			Bd Wt	284 F			
12	Rat (Sprague-Dawley)	1 mo (W)	Resp	133 F			Gomez et al. 1986 Al(NO₃)₃
			Cardio	133 F			
			Gastro	133 F			
			Hemato	133 F			
			Hepatic	79 F	133 F (hyperemia in the liver; periportal monocytic infiltrate in the liver)		
			Renal	133 F			
			Bd Wt	133 F			
13	Rat (Sprague-Dawley)	16 d (F)	Bd Wt	158 M			Greger and Donnaubauer 1986 AlH₃O₃

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds ⁻ Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
14	Rat (Wistar)	10 weeks (F)	Musc/skel	100 M			Konishi et al. 1996 $C_9H_{15}AlO_9$
15	Mouse (Swiss-Webster)	Gd 1 - PND 21 (F)	Bd Wt	330 F			Donald et al. 1989 $C_9H_{15}AlO_9$
16	Mouse (Swiss-Webster)	6 wk (F)	Renal	130 F			Golub et al. 1989 $C_9H_{15}AlO_9$
17	Mouse (Swiss-Webster)	90d (F)	Bd Wt	195 F			Golub et al. 1992b $C_9H_{15}AlO_9$
18	Mouse (Swiss-Webster)	5 or 7 wk (F)	Hemato	195 F			Oteiza et al. 1993 $AlCl_3$
			Hepatic	195 F			
			Bd Wt	195 F			
19	Dog (Beagle)	26 wk (F)	Cardio	75			Pettersen et al. 1990 $NaAl_3H_{14}(PO_4)_8$
			Hemato	75			
			Renal	75			
			Endocr	75			

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Immunological/Lymphoreticular							
20	Mouse (Swiss-Webster)	Gd 0 - PND 180 (F)		1.2	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. 1993b $C_9H_{15}AlO_9$
21	Mouse (Swiss-Webster)	Gd 1 - PND 31 (F)			155 F (increased susceptibility to infection)		Yoshida et al. 1989 $C_9H_{15}AlO_9$
22	Mouse (Swiss-Webster)	6 wk (F)		195			Yoshida et al. 1989 $C_9H_{15}AlO_9$
Neurological							
23	Rat (Sprague-Dawley)	6.5 months (W)		125			Domingo et al. 1996 $Al(NO_3)_3$
24	Mouse (Swiss-Webster)	Gd 1 - PND 21 (F)		330 F			Donald et al. 1989 $C_9H_{15}AlO_9$
25	Mouse (Swiss-Webster)	6 wk (F)		62[b] F	130 F (decreased total, vertical, and horizontal activity; decreased diurnal period; shortened activity periods)		Golub et al. 1989 $C_9H_{15}AlO_9$

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
26	Mouse (Swiss-Webster)	Gd 1 - Gd 21 Gd 1 - PND 21 PND 1 - 21 (F)				250 F (maternal hindlimb splaying and dragging and seizures at weaning in 1/9 mice)	Golub et al. 1992a $C_9H_{15}AlO_9$
27	Mouse (Swiss-Webster)	90d (F)		4.9 F	195 F (decreased fore- and hindlimb grip strengths and startle response in weanlings)		Golub et al. 1992b $C_9H_{15}AlO_9$
28	Mouse (Swiss-Webster)	Gd 1-PND 170 (F)		7.5	155 (decreased fore- and hindlimb gripstrength and decreased air puff startle response)		Golub et al. 1995 $C_9H_{15}AlO_9$
29	Mouse (Swiss-Webster)	5 or 7 wk (F)		0.6 F	195 F (reduced forelimb and hindlimb grip strength)		Oteiza et al. 1993 $AlCl_3$
30	Dog (Beagle)	26 wk (F)		75			Pettersen et al. 1990 $NaAl_3H_{14}(PO_4)_8$
Reproductive							
31	Rat (Sprague-Dawley)	116 d (GW)		52 F			Domingo et al. 1987c $Al(NO_3)_3$
32	Mouse (Swiss-Webster)	Gd 1 - PND 21 (F)		7.5 F	155 F (altered gestational length)		Donald et al. 1989 $C_9H_{15}AlO_9$
33	Mouse (Swiss-Webster)	Gd 1 - Gd 21 Gd 1 - PND 21 PND 1 - 21 (F)		250 F			Golub et al. 1992a $C_9H_{15}AlO_9$

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds · Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)	Reference Chemical Form
34	Mouse (Dobra Voda)	180 d (W)		49.1				Ondreicka et al. 1966 AlCl₃

Developmental

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)	Reference Chemical Form
35	Rat (Sprague-Dawley)	Gd 6-19 (F)		110				McCormack et al. 1979 AlCl₃
36	Mouse (Swiss-Webster)	Gd 1- PND 21 Gd 1- PND 45 (F)		7.5	155	(decreased forelimb and increased hindlimb grip strength and increased foot splaying in weanlings)		Donald et al. 1989 $C_9H_{15}AlO_9$
37	Mouse (Swiss-Webster)	Gd 1 - PND 35 (F)		330 M				Golub and Germann, 1998 $C_9H_{15}AlO_9$
38	Mouse (Swiss-Webster)	Gd1 - Gd21 Gd1 - PND21 PND1 - 21 (F)			250	(dec. pup weight, crown-rump length, forelimb grip strength in gestation -exposed group, incr. hindlimb grip & tail withdrawal times in gestation & lactation exposed groups, incr. negative geotaxis latency in lactation exposed groups)		Golub et al. 1992a $C_9H_{15}AlO_9$
39	Mouse	Gd 0 - PND 180 (F)		1.2	200	(19% incr. absolute spleen weights; depressed spleen cell concentrations of interleukin-2, interferon-g & tumor necrosis factor-a; deficiency of CD4+ cells in T-cell populations)		Golub et al. 1993b $C_9H_{15}AlO_9$

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds · Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
40	Mouse (Swiss-Webster)	Gd 1-PND 170 (F)		7.5	155 (decreased fore- and hindlimb gripstrength and decreased air puff startle response)		Golub et al. 1995 $C_9H_{15}AlO_9$
41	Mouse (Swiss-Webster)	Gd 1-PND 21 (F)		7.5	155 F (decreased fore- and hindlimb grip strengths and startle response in weanlings)		Golub et al. 1995 $C_9H_{15}AlO_9$
42	Mouse (Swiss-Webster)	Gd 1 - PND 31 (F)			155 F (increased susceptibility to bacterial infection)		Yoshida et al. 1989 $C_9H_{15}AlO_9$

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds ‑ Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Systemic							
43	Rat (Long- Evans)	2.5 yr (W)	Resp	0.6			Schroeder and Mitchener 1975a AlK(SO$_4$)$_2$·12 H$_2$O
			Cardio	0.6			
			Hemato	0.6			
			Hepatic	0.6			
			Renal	0.6			
			Bd Wt	0.6			
44	Mouse (Dobra Voda)	390 d (W)	Musc/skel	49			Ondreicka et al. 1966 AlCl$_3$
			Hepatic	49			
			Renal	49			
			Bd Wt	49			
45	Mouse (B6C3F1)	20 mo (F)	Resp	979			Oneda et al. 1994 AlK(SO$_4$)$_2$·12 H$_2$O
			Cardio	979			
			Gastro	979			
			Hepatic	979			
			Renal	979			
			Bd Wt	979			

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
46	Mouse (CD)	2 yr (W)	Resp	1.2			Schroeder and Mitchener 1975b AlK(SO₄)₂·12 H₂O
			Cardio	1.2			
			Hepatic	1.2			
			Renal	1.2			
			Bd Wt	1.2			
Immunological/Lymphoreticular							
47	Rat (Long- Evans)	2.5 yr (W)		0.6			Schroeder and Mitchener 1975a AlK(SO₄)₂·12 H₂O
48	Mouse (Dobra Voda)	390 d (W)		49			Ondreicka et al. 1966 AlCl₃
49	Mouse (B6C3F1)	20 mo (F)		979			Oneda et al. 1994 AlK(SO₄)₂·12 H₂O
50	Mouse (CD)	2 yr (W)		1.2			Schroeder and Mitchener 1975b AlK(SO₄)₂·12 H₂O
Neurological							
51	Mouse (B6C3F1)	20 mo (F)		979			Oneda et al. 1994 AlK(SO₄)₂·12 H₂O

Table 2-2. Levels of Significant Exposure to Aluminum and Compounds - Oral (continued)

| Key to[a] figure | Species (Strain) | Exposure/ duration/ frequency (Specific route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive							
52	Mouse (Dobra Voda)	390 d (W)		49			Ondreicka et al. 1966 $AlCl_3$

[a]The number corresponds to entries in Figure 2-2.

[b]The intermediate duration oral MRL of 2.0 mg/kg/day was calculated by dividing 62 mg/kd/gay by an uncertainty factor of 30 (3 for extrapolation from animals to humans, and 10 for human variablility).

ad lib = ad libitum; AMP = adenosine monophosphate; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = Gestation day; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MAP 2 = microtubule-associated protein 2; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; PDN = post-natal day; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year

Figure 2-2. Levels of Significant Exposure to Aluminum - Oral

Acute (≤14 days)

(mg/kg/day)

10000	
1000	
100	
10	
1	
0.1	
0.01	
0.001	
0.0001	

Death

Developmental

7m AlCl₃
8h C₉H₁₅AlO₉

2r AlCl₃
4m Al(NO₃)₃
9m AlH₃O₃

1r Al(NO₃)₃
3r AlBr₃
5m AlCl₃
6m AlBr₃

Key

r	rat	■ LD₅₀ (animals)	Minimal risk level for effects other than cancer
m	mouse	● LOAEL for serious effects (animals)	
d	dog	◐ LOAEL for less serious effects (animals)	The number next to each point
h	rabbit	○ NOAEL (animals)	corresponds to entries in Table 2-2.

Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Intermediate (15-364 days)

Systemic

Key

r	rat	■ LD_{50} (animals)
m	mouse	● LOAEL for serious effects (animals)
d	dog	◗ LOAEL for less serious effects (animals)
h	rabbit	○ NOAEL (animals)

Minimal risk level for effects other than cancer

The number next to each point corresponds to entries in Table 2-2.

Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Intermediate (15-364 days)

Key

r	rat	■ LD_{50} (animals)	Minimal risk level for effects other than cancer
m	mouse	● LOAEL for serious effects (animals)	
d	dog	◐ LOAEL for less serious effects (animals)	The number next to each point corresponds to entries in Table 2-2.
h	rabbit	○ NOAEL (animals)	

Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Chronic (≥365 days)

Systemic

(mg/kg/day)

| | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic |

10000

1000   O 45m   O 45m   O 45m   O 45m
AlK(SO₄)₂ • 12H₂0   AlK(SO₄)₂ • 12H₂0   AlK(SO₄)₂ • 12H₂0   AlK(SO₄)₂ₐ · 12H₂0

100   44m   44m
                                                              AlCl₃   AlCl₃
                                                               O   O

10

          46r   46r
   AlK(SO₄)₂ₐ · 12H₂0   43r   43r   AlK(SO₄)₂ₐ · 12H₂0
          O   AlK(SO₄)₂ₐ · 12H₂0   AlK(SO₄)₂ₐ · 12H₂0   O

1   O   O   O   O   O
    43r   43r   46r
AlK(SO₄)₂ₐ · 12H₂0   AlK(SO₄)₂ₐ · 12H₂0   AlK(SO₄)₂ₐ · 12H₂0

0.1

Key

r rat	■ LD₅₀ (animals)
m mouse	● LOAEL for serious effects (animals)
d dog	◑ LOAEL for less serious effects (animals)
h rabbit	O NOAEL (animals)

ᛃ Minimal risk level
  for effects other
ᗰ than cancer

The number next to
each point
corresponds to
entries in Table 2-2.

0.01

0.001

0.0001

48

Figure 2-2. Levels of Significant Exposure to Aluminum - Oral (cont.)

Chronic (≥365 days)

Systemic

Renal *Body Weight* *Immunological/ Lymphoreticular* *Neurological* *Reproductive*

(mg/kg/day)

10000

45m
$AlK(SO_4)_2 \cdot 12H_2O$
1000 ◯

◯ 45m
$AlK(SO_4)_{2A} \cdot 12H_2O$

◯ 49m
$AlK(SO_4)_{2A} \cdot 12H_2O$

◯ 51m
$AlK(SO_4)_{2A} \cdot 12H_2O$

44m
$AlCl_3$
100 ◯

44m
$AlCl_3$
◯

48m
$AlCl_3$
◯

52m
$AlCl_3$
◯

10

46r
$AlK(SO_4)_{2A} \cdot 12H_2O$
◯

46r
$AlK(SO_4)_{2A} \cdot 12H_2O$
◯

50m
$AlK(SO_4)_{2A} \cdot 12H_2O$
◯

1

47r
$AlK(SO_4)_{2A} \cdot 12H_2O$
◯

43r ◯
$AlK(SO_4)_{2A} \cdot 12H_2O$

◯
43r
$AlK(SO_4)_{2A} \cdot 12H_2O$

0.1

0.01

0.001

0.0001

Key

r	rat	■ LD_{50} (animals)	Minimal risk level for effects other than cancer
m	mouse	● LOAEL for serious effects (animals)	
d	dog	◐ LOAEL for less serious effects (animals)	The number next to each point corresponds to entries in Table 2-2.
h	rabbit	◯ NOAEL (animals)	

2.2.2.1 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, but actual doses are
unclear due to insufficient information on aluminum intake from the base diet. For the nitrate form, LD_{50}
(lethal dose, 50% kill) 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, LD_{50} 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). For aluminum bromide, LD_{50} values
of 162 and 164 mg Al/kg have been reported in Sprague-Dawley rats and Swiss Webster mice,
respectively (Llobet et al. 1987). The LD_{50} 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 5 of 5 lactating
female New Zealand rabbits (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 appears to be 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
9 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 (a common human food additive) and base levels of aluminum in the feed for 26 weeks
(Pettersen et al. 1990). In chronic-duration studies, no consistent differences in mortality rate were
observed between male and female Wistar rats (30/sex/group) exposed for 24 months to unspecified
levels of aluminum phosphide/ammonium carbamate in the feed and rats fed control diets (Hackenberg
1972). All reliable LOAEL values for death in each species and duration category are recorded in
Table 2-2 and plotted in Figure 2-2.

2.2.2.2 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 2-2 and plotted
in Figure 2-2.

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 pathologic
changes in the lungs of rats and mice. No organ weight or histological changes were observed in the
lungs of groups of 7-10 male Sprague-Dawley rats given 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). No
adverse organ weight or histological changes were found in the lungs of groups of 10 female Sprague-
Dawley rats that ingested 133 or 284 mg Al/kg/day as aluminum nitrate in drinking water and base diet
for 1 month or 100 days, respectively (Domingo et al. 1987b; Gomez et al. 1986). Similarly, in chronic-
duration exposures, lung histology was normal in male and female Long Evans rats and Swiss mice given
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), male and female Wistar

rats fed a diet containing unspecified quantities of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972), male and female Dobra Voda mice given 19.3 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966) and in male and female B6C3Fl mice given 1979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994). Although data on aluminum in the base diet used by Schroeder and Mitchener (1975a, 1975b) were not reported, the animals were exposed to a low-metal diet and metal-free environmental conditions.

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

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 atria1 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 male and female Beagle dogs (4-6/sex/dose) that consumed up to 75 (Pettersen et al. 1990) or 93 (Katz et al. 1984) mg Al/kg/day as sodium aluminum phosphate (a common human food additive) in the diet for 6 months; the doses in the Katz et al. (1984) study do not include aluminum in the base diet.

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 Wistar rats fed a diet containing an unspecified amount of aluminum phosphide/ammonium carbamate for 24 months

(Hackenberg 1972). Similarly, no histological changes were observed in the hearts of male and female Long Evans rats or Swiss mice (52 of each sex) 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 B6C3Fl mice (60 per sex) 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..

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

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 (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 acuteduration 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 and female Beagle dogs that consumed 93 mg Al/kg/day as sodium aluminum phosphate (a human food additive) in the diet for 6 months (Katz et al. 1984); the dog dose does not include base dietary aluminum. Similarly, no histological changes were observed in the gastrointestinal tissues of male Wistar rats fed a diet containing an unspecified amount of aluminum phosphide/ammonium carbamate for 24 months

(Hackenberg 1972) or in male or female B6C3Fl mice that ingested 2979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1979).

The highest NOAEL values for gastrointestinal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

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. No adverse hematological changes were observed in rats following a single oral dose of 50 mg Al/kg as aluminum chloride (Krasovskii et al. 1979). The method of oral exposure and level of aluminum in the base diet were not reported.

With intermediate-duration oral exposure to aluminum nitrate or aluminum chloride, no hematological changes have been observed. Female Sprague-Dawley rats given up to 133 or 284 mg Al/kg/day as aluminum nitrate in drinking water for up to 1 month (Gomez et al. 1986) or 100 days (Domingo et al. 1987b), respectively, had no changes in total protein, glucose, cholesterol, uric acid, urea, creatinine, GOT, GPT, hematocrit, or hemoglobin. Female Swiss Webster mice that consumed 195 mg Al/kg/day as aluminum chloride in the diet for 5 or 7 weeks had no change in hematocrit levels (Oteiza et al. 1993). Similarly, no changes in hematocrit, hemoglobin concentration, erythrocyte count, or leukocyte count were reported for male and female Beagle dogs that consumed up to 75 (Pettersen et al. 1990) or 93 (Katz et al. 1984) mg Al/kg/day as sodium aluminum phosphate (a common human food additive) in the diet for 6 months. Similarly, no hematological effects were observed in male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water for 180 days (Ondreicka et al. 1966). The doses for all but one of the above studies (Katz et al. 1984) include aluminum in the base diet.

No changes in hematological parameters were observed in rats and mice following chronic-duration oral exposure. Erythrocyte count, total and differential leukocyte counts, packed cell volume, and hemoglobin concentration were unaffected in male Wistar rats fed a diet containing an unspecified amount of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972). No hematological effects were observed in male and female Long Evans rats given 0.6 mg Al/kg/day as aluminum sulfate in drinking water for 2.5 years (Schroeder and Mitchener 1975a) or male and female Dobra Voda mice given 49 mg Al/kg/day in drinking water and base diet for 390 days (Ondreicka et al.

1966). Data on base dietary aluminum were not reported by Schroeder and Mitchener (1975a), although the rats were fed a low-metal diet in metal-free environmental conditions.

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

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). Therefore, it is difficult to ascribe these effects to aluminum alone. 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 1993b) 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 Sections 2.5 and 2.9.

No studies were located regarding musculoskeletal effects of various forms of aluminum following acute-duration exposure in animals. 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 and base diet for 10 weeks (Konishi et al. 1996), femurs of male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months

(Hackenberg 1972), or in the femurs of male and female Dobra Voda mice exposed to 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966).

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

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

No studies were located regarding hepatic effects of various forms of aluminum following acute-duration exposure in animals. No organ weight or histological changes were observed in the livers of male Sprague-Dawley rats given 70 mg Al/kg/day as aluminum chloride in drinking water (aluminum in the base diet not reported) for 30,60, or 90 days (Dixon et al. 1979). Similarly, no hepatic histological changes were observed in male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 180 days (Ondreicka et al. 1966).

Exposure to aluminum nitrate has been shown to cause minor hepatic effects. Hyperemia and periportal lymphomonocytic 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); however, these effects were not found at higher doses with longer exposures (Domingo et al. 1987b). No liver weight or histological changes occurred in female Sprague-Dawley rats given up to 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days (Domingo et al. 1987b). No histological changes were observed in 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). No liver weight changes were observed in female Swiss Webster mice that consumed 195 mg Al/kg/day as aluminum chloride in feed (Oteiza et al. 1993). Similarly, no organ weight or histological effects were observed in the livers of male and female Beagle dogs that consumed up to 93 mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984). Mild hepatocyte vacuolation was found in high-dose males in groups of 4 male and 4 female Beagle dogs orally exposed to up to 80 mg Al/kg/day in the feed for 26 weeks (Pettersen et al. 1990), but the authors concluded the hepatic effects in the males resulted from a drastic reduction in food consumption. The

doses in all but two of the above studies (Dixon et al. 1979; Katz et al. 1984) include aluminum in the base diet.

In chronic-duration exposures, liver histology was normal in male and female Long Evans rats and Swiss mice given 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), male and female Wistar rats fed a diet containing unspecified quantities of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972), male and female Dobra Voda mice given 19.3 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966), and in male and female B6C3Fl mice given $\leq$ 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994). Although data on aluminum in the base diet used by Schroeder and Mitchener (1975a, 1975b) were not reported, the animals were exposed to a low-metal diet and metal-free environmental conditions.

Reliable NOAEL and LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

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.

No studies were located regarding renal effects of various forms of aluminum following acute-duration exposure in animals. No adverse histological changes were found in the kidneys of male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 180 days (Ondreicka et al. 1966). Normal histology was observed in the kidneys of female Sprague-Dawley rats given 133 mg Al/kg/day as aluminum nitrate in drinking water for 1 month (Gomez et al. 1986), and in male and female Beagle dogs that consumed up to 93 mg Al/kg/day as sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984). However, mild tubular "glomerulanephritis" was observed in high-dose male Beagle dogs that consumed 75 mg Al/kg/day as sodium aluminum phosphate in the diet for 26 weeks (Pettersen et al. 1990). This effect is not considered to be adverse because it was

mild in severity, not accompanied by clinical evidence of kidney dysfunction, and was not observed in female dogs fed diets containing a comparable concentration of aluminum. The doses in all but one of the above studies (Katz et al. 1984) include aluminum in the base diet.

In chronic-duration exposures, kidney histology was normal in male and female Long Evans rats and Swiss mice given 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), male and female Wistar rats fed a diet containing unspecified quantities of aluminum phosphide/ ammonium carbamate for 24 months (Hackenberg 1972), male and female Dobra Voda mice given 19.3 mg Al/kg/day as aluminum chloride in drinking water and base diet for 390 days (Ondreicka et al. 1966), and in male and female B6C3Fl mice given $\leq$ 979 mg Al/kg/day as aluminum potassium sulfate in the feed (base dietary aluminum not reported) for 20 months (Oneda et al. 1994). Although data on aluminum in the base diet used by Schroeder and Mitchener (1975a, 1975b) were not reported, the animals were exposed to a low-metal diet and metal-free environmental conditions.

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

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 93 (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. These organs were also normal in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ ammonium carbamate for 24 months (Hackenberg 1972).

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

Dermal Effects. No studies were located regarding dermal effects of various forms of aluminum following intermediate- or chronic-duration 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. For more information on this study, see Gastrointestinal Effects, above.

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). No histological changes were observed in the skin of male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972).

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

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 93 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. Normal ocular histology was observed in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ ammonium carbamate for 24 months (Hackenberg 1972).

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

Reductions in body weight gain and food consumption were observed in male Wistar rats that ingested feed containing 273 mg Al/kg/day as aluminum sulfate and base dietary aluminum for 8 days (Ondreicka et al. 1966). These effects were not evident after 24 days of exposure, suggesting that they were transient. There were no body weight changes in female Wistar rats that consumed as much as 192 mg Al/kg as aluminum chloride in the feed (aluminum in the base diet not reported) on gestation days (Gd) 8-20 (Bernuzzi et al. 1986b), although a 19-20% decrease in maternal body weight gain

occurred in Sprague-Dawley rats exposed to 38-77 mg Al/kg/day as aluminum nitrate by gavage and base diet on Gd 6-14 (Paternain et al. 1988). Factors contributing to the occurrence of an effect in the Paternain et al. (1988) gestational exposure study could include increased absorption of aluminum due to the bolus method of treatment and increased bioavailability of aluminum nitrate compared to aluminum chloride (Yokel and McNamara 1988).

Effects on body weight have been infrequently and inconsistently observed in intermediate-duration oral exposure studies of aluminum in animals. For example, no changes in body weight were found in male Sprague-Dawley rats that ingested up to 158 mg Al/kg/day as aluminum hydroxide in the diet for 16 days (Greger and Donnaubauer 1986), male and female Long Evans rats administered to up to 104 mg Al/kg/day as aluminum chloride once daily by gavage for 90 days (Bilkei-Gorzo 1993), or female Sprague-Dawley rats that ingested 259 mg Al/kg/day as aluminum nitrate in drinking water for as long as 100 days (Domingo et al. 1987b; Gomez et al. 1986), although transient decreases in body weight occurred in male Sprague-Dawley rats given 346 mg Al/kg/day as aluminum sulfate in drinking water for 4 weeks (Connor et al. 1989). No changes in body weight were observed in female Swiss Webster mice that ingested 130 or 170 mg Al/kg/day as aluminum lactate in the diet for 6 weeks (Golub et al. 1989) or 90 days, respectively (Golub et al. 1992b), or female Swiss Webster mice that ingested 260 mg Al/kg/day as aluminum chloride in the diet for 5 or 7 weeks (Oteiza et al. 1993). Body weight gain was decreased approximately 20% 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 similarly designed different study (Donald et ai. 1989) by the same group of investigators; the effect on body weight appears to be related to a nutritional insufficiency in the semipurified diet used by Golub et al. (1987). The doses in all but one of the above studies (Bilkei-Gorzo 1993) include aluminum in the base diet.

No conclusive changes in body weight were observed in male and female Beagle dogs that consumed 88 mg Al/kg/day as sodium aluminum phosphate in the feed for 6 months (base dietary aluminum not included in the dose) (Katz et al. 1984). Another 6-month study of sodium aluminum phosphate in Beagles found a marked (not quantified), but transient, decrease in body weight gain associated with dietary exposure to 75 mg Al/kg/day (included base dietary aluminum) (Pettersen et al. 1990). The health significance of the effect is unclear because it only persisted for one and a half weeks, was attributed to concurrent palatability-related decreased food consumption, and did not occur in both sexes (only occurred in males).

No body weight effects were observed in rats or mice following chronic-duration exposure to aluminum compounds. The body weights of male and female Dobra Voda mice were similar to controls following exposure to 49 mg Al/kg/day as aluminum chloride in drinking water and base diet for 180 or 390 days (Ondreicka et al. 1966). No effect on body weight was seen in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972). The administration of 0.6 mg Al/kg/day as aluminum sulfate in drinking water to male and female Long Evans rats for 2.5 years also did not affect body weight (Schroeder and Mitchener 1975a). Data on base dietary aluminum were not reported by Schroeder and Mitchener (1975a), although the rats were fed a low-metal diet in metal-free environmental conditions.

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

Metabolic Effects. No studies were located regarding metabolic effects of various forms of aluminum in humans or animals.

2.2.2.3 Immunological and Lymphoreticular Effects

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

No studies were located regarding immunological effects of various forms of aluminum following acuteduration exposure in animals. An intermediate-duration study with female Sprague-Dawley rats found that 79 mg Al/kg/day as aluminum nitrate in drinking water caused hyperemia in the red pulp of the spleen when ingested for 1 month (Gomez et al. 1986). However, the significance of this finding is unclear because immune function was not evaluated, and 284 mg Al/kg/day as aluminum nitrate in drinking water for 100 days did not affect organ weight or cause histological changes in the spleens of female Sprague-Dawley rats (Domingo et al. 1987b). Additionally, no organ weight or histological changes in the spleen and/or thymus were observed in 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), male and female Dobra Voda mice given 49 mg Al/kg/day as aluminum chloride in drinking water for 180 or 390 days (Ondreicka et al. 1966), 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 Dixon et al. (1979) and Oneda et al. (1994) include aluminum in the base diet.

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-y and tumor necrosis factor-a, and a deficiency of CD4+ cells in T-cell populations were observed in Swiss Webster mice that were exposed to aluminum from conception through 6 months of age (Golub et al. 1993b). 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 that were 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 195 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.

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

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects of various forms of aluminum following intermediate-duration oral exposure in humans. Memory loss, fatigue, depression, behavioral changes, and learning impairment were reported in 5 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.

A large number of epidemiology and case-control studies have examined the potential association between oral aluminum exposure and Alzheimer's disease. A number of these studies have been criticized for flawed patient selection, poor comparability of exposed and control groups, poor exposure assessment, poor assessment of health outcomes, and weak statistical correlations (Nieboer et al. 1995; Schupf et al. 1989). Studies conducted by Martyn et al. (1989), McLachlan et al. (1996), and Michel et al. (1990) have found an association between oral exposure to aluminum and an increased risk of Alzheimer's disease. In a survey study conducted by Martyn et al. (1989), the incidence of Alzheimer's disease in individuals under the age of 70 was estimated from computerized tomographic (CT) records. The 1,203 subjects lived in 88 county districts within England and Wales. Data on aluminum concentrations in the municipal water over a lo-year period were obtained from water authorities and water companies. The subjects were classified as having probable Alzheimer's disease, possible Alzheimer's disease, other causes of dementia, or epilepsy. The relative risks of Alzheimer's disease were elevated in the subjects living in districts with aluminum water concentrations of ≈0.01 mg/L. However, the relative risk exceeded unity only in the subjects with aluminum water concentrations of >0.11 mg/L (relative risk of 1.5, 95% confidence interval of 1.1-2.2).

McLachlan et al. (1996) also found a significant association between Alzheimer's disease and aluminum drinking water concentrations of ≥0.10 mg/L. In this case-control study of residents in Ontario, Canada, the diagnosis of Alzheimer's was based on a clinical history of dementia and the histopathologic findings of widespread neuritic plaques with amyloid cores and neurofibrillary tangles in neocortical and subcortical structures. Aluminum concentrations in the municipal water supplies were compared between the 296 cases and the 295 control cases (125 cases had no histopathological alterations in the brain and 170 had other neurodegenerative diseases such as Huntington's disease, schizophrenia, and multiple sclerosis). The odds ratio for Alzheimer's disease at drinking water concentrations of ≥0.10 mg/L was 1.7 (95% confidence intervals of 1.2-2.6).

Unlike the Martyn et al. (1989) and McLachlan et al. (1996) studies, Michel et al. (1990) found increased risks of Alzheimer's disease in subjects living in areas with low aluminum concentrations in drinking water. This study examined 2,792 subjects at least 65 years of age living in South-Western France. Alzheimer's disease was clinically diagnosed. Aluminum concentrations in drinking water ranged from 0.01 to 0.16 mg/L for the 40 cases of probable Alzheimer's disease. The relative risks for probable Alzheimer's disease was 1.16 (significantly different from 1) for 0.01 mg/L and 4.52 for 0.1 mg/L.

In contrast, several studies did not find a significant association between aluminum exposure and the risk of Alzheimer's disease (Forster et al. 1995; Martyn et al. 1997; Wettstein et al. 1991). A case-control study by Forster et al. (1995) examined several risk factors, including aluminum exposure, in 109 patients under 65 years of age with presenile dementia of the Alzheimer's type and in 109 age and sex matched controls. Aluminum exposure was assessed using mean aluminum concentrations in drinking water in the place of residence 10 years before the onset of dementia and the mean aluminum concentrations in drinking water at birthplace (only analyzed in 80 pairs). The aluminum concentration in drinking water was not significantly related to risk of presenile dementia; it should be noted that at the higher aluminum concentrations, there were a small number of cases and controls (43 pairs with aluminum drinking water concentrations of >0.09 mg/L and 2 pairs with aluminum drinking water levels of >0.149 mg/L).

Similar to the Martyn et al. (1989) study, Martyn et al. (1997) used CT records to identify individuals with Alzheimer's disease; 106 cases were identified. Three sets of controls were used: patients with other types of dementia (99 cases), patients with brain cancer (226 cases), and patients with other neurologic disorders (441 cases). The subjects (or next of kin) were mailed questionnaires that asked for all addresses (with dates of residence), and the investigators used this information to gather quantitative data for aluminum concentrations in the municipal water for each address and period of residence. No significant associations were found between the risk of Alzheimer's disease (as compared to each control group) and aluminum levels in drinking water.

In the Wettstein et al. (1991) study, senile dementia was used as a surrogate for Alzheimer's disease because in the area examined, 73% of individuals with dementia show significant Alzheimer changes on autopsy. The subjects consisted of 400 and 405 residents living in two Swiss cities with low (0.004 mg/L) or high (0.098 mg/L) aluminum concentrations in drinking water. The subjects were between 81 and 85 years of age and lived in the area for at least 15 years. Senile dementia was assessed using the mnestic and naming subtest of the Mini Mental Status test (Zurich variant). Performance on mnestic and naming tests did not significantly differ between the high and low exposure groups. Thus, the study authors concluded that there was no relationship between aluminum concentrations in drinking water and the risk of Alzheimer's disease.

Although some of these studies suggest that there may be a relationship between high aluminum intake and Alzheimer's disease, the epidemiologic data do not establish a cause and effect relationship; the relationship between Alzheimer's disease and aluminum is discussed in more detail in Section 2.5.

Uremic persons represent a population at risk for aluminum-related dementia (Alfrey 1993b). 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 (1993b) 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 ma1 seizures, coma, and death. Plasma levels of aluminum are typically greater than 500 μg/L (normal levels are approximately 10 μg/L). The classical type results from chronic 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 1993b; 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. For more information, see Sections 2.5 and 2.9.

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 2.2.2.6, 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 2.2.2, 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 2-2. Bioavailability is another issue complicating comparison of NOAELs and LOAELs because there can be a marked difference in absorption (i.e., actual doses) of aluminum depending on the form in which it is ingested. As discussed in Section 2.3.1.2, absorption of aluminum can be 10-fold higher for relatively bioavailable forms such as aluminum citrate compared to less available forms such as aluminum hydroxide.

A number of the studies of aluminum with adequately reported dietary information are intermediate-duration neurotoxicity and neurodevelopmental studies in Swiss-Webster mice that were performed by one group of investigators (Golub and coworkers) using 500 and/or 1,000 ppm concentrations of Al as aluminum lactate in a common semipurified diet formulation. Aluminum lactate was tested because it represents a bioavailable form of aluminum and lactate is a common human dietary constituent. Most of the studies by Golub and coworkers also used similar standardized observational end points and test batteries for assessing neurobehavioral function. The use of similar testing protocols, and the same semipurified diet with known aluminum content within the range of human diet content and minimal batch-to-batch variations, indicates that studies by Golub and coworkers (Donald et al. 1989; Golub et al. 1989, 1992a, 1992b; Oteiza et al. 1993) are the most reliable data set for comparing neurotoxicity effect levels. Although these studies all used the same dietary levels of aluminum, variations in daily aluminum intakes (mg Al/kg/day) from the 500 and 1,000 ppm Al diets occurred due to differences in food intake consequent to factors such as age of animal (e.g., higher in weanlings than adults) and time of exposure (e.g., higher during lactation than during pregnancy or in adults that are not pregnant or lactating). Information on concentrations of aluminum in the base diet is also available for a few other neurotoxicity studies (Domingo et al. 1987b, 1996; Gomez et al. 1986; Vamer et al. 1993, 1994, 1998); these studies used commercial rather than semi-purified diets, indicating that excess and variable amounts of essential and nonessential trace minerals and metal binding ligands were present that can alter aluminum uptake in comparison to semipurified or purified diets in which trace metal levels are precisely determined (Golub et al. 1992b).

Neuromotor, behavioral, and cognitive changes have been observed in oral studies of exposed female adult mice. Overall motor activity was 20% lower and activity periods were 35% shortened compared to controls in mice that ingested 130 mg Al/kg/day as aluminum lactate for 6 weeks (Golub et al. 1989). There were no effects on activity or any clinical signs at 62 mg Al/kg/day, indicating that this is a NOAEL for neurotoxicity. Comprehensive neurobehavioral testing of mice that were exposed to 195 mg Al/kg/day as dietary aluminum lactate for 90 days also found reduced motor activity, as well as decreased hindlimb grip strength, decreased startle responsiveness, and increased tissue levels of aluminum (brain and liver, but not bone), but no clinical signs of neurotoxicity (Golub et al. 1992b). Adult mice that consumed 195 mg Al/kg/day as aluminum chloride for 5-7 weeks in a diet that also contained 3.5% sodium citrate (Oteiza et al. 1993) showed neurotoxic effects similar to those observed by Golub et al. (1992b). The citrate is likely to have enhanced the responses in comparison to those found in the Golub et al. (1992b) study without citrate, because grip strength was reduced in forelimbs as well as hindlimbs, and aluminum levels were increased in bone as well as in central nervous system and liver tissue. Only single exposure levels were tested by Golub et al. (1992b) and Oteiza et al. (1993), precluding identification of NOAELs in these studies. Performance in a skilled motor coordination test (roto-rod treadmill) was impaired in mice that were reportedly exposed to a lower level of aluminum (1.1 mg Al/kg/day as aluminum chloride in drinking water) for 100 days (Sahin et al. 1995b), but the actual effect level (total dose) is unknown due to lack of data on levels of aluminum in the base diet. The NOAEL for neurotoxicity in mice of 62 mg Al/kg/day (Golub et al. 1989) is used to calculate an intermediate oral MRL of 2.0 mg Al/kg/day as described in the footnote to Table 2-2 and in Appendix A.

Marked signs of neurotoxicity, including ataxia, splaying and dragging of hindlimbs, and paralysis, occurred in maternal mice that were exposed to estimated doses of 184 mg Al/kg/day (Golub et al. 1987) or 250 mg Al/kg/day (Golub et al. 1992a) as aluminum lactate during gestation and lactation. The dissimilarity in the LOAELs for these effects is attributable to the composition of semipurified diet used by Golub et al. (1987) which differed from that used subsequently. In particular, the diet formulation was revised in the Donald et al. (1989) and later Golub studies 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 (Golub et al. 1987). 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 2-2.

Some information is available on oral neurotoxicity of aluminum in species other than mice. No effects on spontaneous motor activity (open-field) or passive avoidance operant training or performance (grid floor shock, light/dark shuttle box) were found in rats that were co-exposed to $\leq$ 125 mg Al/kg/day as aluminum nitrate and citric acid($<$ 355 mg/kg/day) in drinking water and the base diet for 6.5 months beginning at 21 days, 8 months, or 16 months of age (Domingo et al. 1996). Cognitive deficits and other changes, were found in other studies in rats as summarized below, but the effect levels in these studies cannot be assumed to be accurate due to insufficient information on base dietary aluminum. Because dietary aluminum is likely to have significantly contributed to total intake, the reported dosages may considerably underestimate actual doses. Maze-learning ability was decreased and brain aluminum levels were increased in rats that were treated for 90 days by gavage with 6 or 20 mg Al/kg/day as aluminum chloride, 104 mg Al/kg/day as aluminum hydroxide, or 35 mg Al/kg/day as aluminum hydroxide plus 30 mg/kg citric acid (Bilkei-Gorzo 1993). Altered general motor activity, as well as impaired motor coordination (roto-rod treadmill performance) and visual temporal acuity (increased critical flicker frequency), were observed in rats that were treated with 45 mg Al/kg/day of aluminum chloride for 28 days (Bowdler et al. 1979). Motor activity and acquisition of shuttle-box avoidance behavior were reduced in rats exposed to 86 mg Al/kg/day as aluminum chloride for 11 months (Commissaris et al. 1982), although there was no effect on retention or extinction of the learned behavior. Rats that were exposed to aluminum hydroxide in the diet at doses of 1,252 mg Al/kg/day as weanlings for 60 days or 83 1 mg Al/kg/day as adults for 30 days had no clear effects on open-field activity or performance on passive avoidance and visual discrimination-reversal learning tasks in rats (Thorne et al. 1986, 1987). Although there were no definite differences between exposed and control groups in any of the tests, some responses appeared to be correlated with increased brain aluminum content in the younger rats (e.g., reduced activity level and performance on the learning tasks), suggesting that the young animals were less affected than the adults.

Other intermediate-duration oral studies in rats evaluated effects of aluminum on brain chemistry as well as neurobehavioral performance. Rats that consumed 5 1 mg Al/kg/day as aluminum chloride in drinking water for 180 days had alterations in behavior (reduced spontaneous locomotor activity, impaired learning, extinction and relearning of an active avoidance task, impaired maze relearning ability) and brain chemistry (increased lipid peroxidation, decreased activity of Na^+-, K^+-, and Mg^{2+}-ATPases) (La1 et al. 1993). Ingestion of 490 mg Al/kg/day as aluminum sulfate in drinking water for 4-12 weeks caused reduced retention of a learned passive avoidance task and changes in brain chemistry (e.g., increased cyclic adenosine monophosphate levels, decreased concentrations of MAP-2 and other structural

proteins), although no effects on an active avoidance task, maze performance, or locomotor activity were observed (Connor et al. 1988, 1989; Jope and Johnson 1992). Injection of the aluminum chelator deferoxamine returned the passive avoidance performance of the aluminum-exposed rats to control levels in a dose-dependent manner, indicating that the behavioral impairment was a specific and reversible toxic effect that was not due to nonspecific mechanisms affecting general motor activity (Connor et al. 1989). Changes in brain biogenic amines (decreased dopamine and 5-hydroxytryptamine, increased norepinephrine) occurred in rats that were treated with 21.4 mg Al/kg/day as aluminum nitrate by gavage for 6 weeks, but behavioral performance was not evaluated (Flora et al. 1991). None of these studies included information on levels of base dietary aluminum.

No histopathological changes in the brain were found in rats that ingested drinking water providing 51 mg Al/kg/day as aluminum chloride for 180 days (La1 et al. 1993), $\leq$70 mg Al/kg/day as aluminum chloride for 90 days (Dixon et al. 1979), 133 mg Al/kg/day as aluminum nitrate for 1 month (Gomez et al. 1986) or 284 mg Al/kg/day as aluminum nitrate for 100 days (Domingo et al. 1987b), or in dogs that consumed $\leq$ 80 mg Al/kg/day as dietary sodium aluminum phosphate for 26 weeks (Pettersen et al. 1990). In the only one of these rat studies to also evaluate behavioral changes, La1 et al. (1993) found that 5 1 mg Al/kg/day for 180 days did cause reduced spontaneous locomotor activity and impaired learning responses in an active avoidance task. Histopathologic changes were observed in the brain of rats that were fed 92 mg Al/kg/day as aluminum chloride and a high level of citrate (598 mg/kg/day) for 6 months (Florence et al. 1994). These alterations were not specific to any brain region and included extensive cytoplasmic vacuolization in astrocytes, swelling of astrocytic processes, and neuronal vacuolization and nuclear inclusions. No "significant behavioral changes" were observed; however, neurobehavioral tests were not performed by Florence et al. (1994). Increased aluminum levels and histological alterations in the brain (particularly increased numbers of abnormal and damaged neurons and reductions in cell density in areas of the hippocampus and neocortex) also occurred in rats that received an estimated 12 mg Al/kg/day as aluminum fluoride in drinking water and base diet for 45-52 weeks (Varner et al. 1993, 1994, 1998); behavioral tests indicated possible olfactory impairment, but no motor functional changes or effects on spatial memory. Unusual exposure conditions preclude identifying relevant LOAELs for brain histopathology. In particular, the induction of brain lesions by Florence et al. (1994) is apparently due to greatly enhanced uptake of aluminum by the massive co-exposure to citrate compared to normal human citrate intake (62 mg/kg/day), because the purpose of the study was to develop an animal model of aluminum overload. Similarly, the brain alterations observed by Varner et al. (1993, 1994, 1998) likely resulted from enhanced availability of aluminum because the aluminum

fluoride in drinking water was prepared to form an optimum fluoroaluminum species capable of crossing the gut and vascular barriers. The doses for all but two of the above studies (Dixon et al. 1979; La1 et al. 1993) include aluminum in the base diet.

Information on chronic oral neurotoxicity of aluminum in animals is limited to a 20 month diet study in mice which found no histopathologic changes in the brain following ingestion of estimated doses as high as 979 mg Al/kg/day as dietary aluminum potassium sulfate (Oneda et al. 1994). These doses do not include aluminum in the base diet.

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 2.2.2.6, 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 2-2 and plotted in Figure 2-2.

2.2.2.5 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 BALBk mice treated with 41 mg Al/kg/day as aluminum chloride by gavage (aluminum in base diet not reported) on Gd 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 Gd 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 Gd 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 Gd 5-15 showed a transient irregularity of the oestrus 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 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 Gd 18, whereas 4 of 17 litters exposed to $\geq$ 155 mg Al/kg/day were born earlier or later (Gd 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 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 sodium aluminum phosphate and
base dietary aluminum for 26 weeks had decreased testicular weight and moderate 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 ($\leq$ 27 mg Al/kg/day) or in female Beagles
similarly exposed to $\leq$ 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 B6C3Fl mice that ingested $\leq$ 979 mg Al/kg/day as dietary aluminum potassium
sulfate for 20 months (Oneida 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 2-2 and plotted in Figure 2-2.

2.2.2.6 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 3 infants with kidney failure who had been treated orally with more than 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).

Maternal and embryo/fetal effects of oral gestational exposure to aluminum have been studied in rats and
mice. Information on total aluminum doses (experimental plus baseline dietary aluminum) is available
for most of these studies (Colomina et al. 1992, 1994; Domingo et al. 1987a; Domingo et al. 1987a,

1989; Gomez et al. 1991; McCormack et al. 1979; Paternain et al. 1988). The total doses for all but

McCormack et al. (1979) are not highly reliable because the base dietary intake is an assumed value

based on a wide range of concentrations (60-280 ppm) reported for the same commercial diet (Panlab) in

only three studies (Colornina et al. 1998; Domingo et al. 1987a, 1993), indicating the potential for large

batch-to-batch variations. Rats that ingested up to 110 mg Al/kg/day in feed that contained added

aluminum chloride on Gd 6, 9, 12, 15, and 18 did not experience maternal toxicity, embryo/fetal toxicity,

teratogenicity, fetal growth retardation, or significantly increased fetal whole carcass concentrations of

aluminum (McCormack et al. 1979). The 110 mg Al/kg/day dose is not a definite NOAEL because the

intermittent daily exposure schedule could have missed a critical developmental time for inducing

effects. Concurrent administration of parathyroid hormone by subcutaneous injection, which increased

tissue levels of aluminum by presumably enhancing its absorption, increased the percentage of resorbed

or dead fetuses. As summarized below, other studies in rats also indicate that aluminum was fetotoxic

under conditions that enhanced its uptake (e.g., intake with citrate or nitrate, and/or as a bolus by

gavage) .

No maternal toxicity or effects on embryo/fetal viability or fetal development occurred in rats that were

exposed to 158 mg Al/kg body weight/day as aluminum hydroxide or aluminum citrate by gavage and

commercial base diet on Gd 6-15 (Gomez et al. 1991). In contrast, effects in dams (reduced weight gain)

and fetuses (reduced body weight and skeletal variations [increased delayed occipital and sternebrae

ossification and increased absence of xiphoids]) were found in rats exposed to 158 mg Al/kg/day as

aluminum hydroxide concurrently with citric acid at 62 mg/kg/day (Gomez et al. 1991). Similar effects

(decreased maternal body weight and skeletal changes [delayed ossification, hypoplastic deformed ribs])

were induced in rats exposed to 38-77 mg Al/kg/day as aluminum nitrate by gavage and base diet on

Gd 6-14 (Patemain et al. 1988). Additionally, similar exposure to 38-77 mg Al/kg/day as aluminum

nitrate in a single generation reproduction study caused transient reduction in growth of rat offspring

(Domingo et al. 1987c). Although a LOAEL of 38 mg Al/kg/day could be identified for developmental

toxicity based on skeletal effects, the value is inappropriate for several reasons. This effect level may be

unnaturally low and not relevant to human environmental exposure because the skeletal changes could be

related to phosphate depletion caused by excess binding with aluminum in the maternal gut due to the

bolus administration. Enhanced bioavailability is another possible reason for this low LOAEL because

aluminum nitrate was shown to be twice as bioavailable as aluminum chloride in rats (Yokel and

McNamara 1988) (see Section 2.3.1.2). Also, commercial diets contain excess and variable amounts of

essential and nonessential trace minerals, and metal binding ligands were present that can alter aluminum

uptake in comparison to semipurified or purified diets in which trace metal levels are precisely determined (Golub et al. 1992b). Additionally, evidence for developmental growth effects (e.g., decreased fetal weight, delayed skeletal maturation) in animals exposed to high levels of nitrate (NRC 1995) suggests that the skeletal changes caused by aluminum nitrate may not be entirely attributable to aluminum; these effects are likely secondary to maternal or fetal methemoglobinemia rather than a direct effect of aluminum.

Gestational exposure studies in mice also indicate that compound bioavailability and the presence of dietary components that promote uptake are factors affecting the developmental toxicity of aluminum In a study designed to evaluate the influence of lactate on the developmental toxicity of aluminum mice were exposed to an estimated dose of 83 mg Al/kg/day as aluminum lactate, aluminum hydroxide, or aluminum hydroxide concurrent with lactic acid (570 mg/kg/day) by gavage and base diet on Gd 6-15 (Colomina et al. 1992). Effects observed in the aluminum lactate-treated mice included reduced maternal food consumption and body weight gain, reduced fetal body weight, and 13-15% increased incidences of cleft palate, dorsal hyperkyphosis (i.e., excessive flexion of spine), and delayed parietal ossification. No exposure-related developmental effects occurred in the fetuses that were exposed to aluminum hydroxide alone or combined with lactic acid. Other studies by the same group of investigators also found no developmental changes in mice that were exposed to $\leq$ 141 mg Al/kg/day as aluminum hydroxide (Domingo et al. 1989), or 129 mg Al/kg/day as aluminum hydroxide alone or combined with ascorbic acid (85 n&kg) (Colomina et al. 1994), by gavage and base diet on Gd 6-15. No developmental effects occurred in mice that were gavaged with $\leq$ 61 mg Al/kg/day as aluminum chloride on Gd 7-16 (Cranmer et al. 1986), but the actual dose of aluminum is not known due to lack of information on aluminum content in the base diet in this study.

Other studies in mice suggest that developmental exposure to aluminum may adversely affect the immune systems. As summarized in Section 2.2.2.3, increased susceptibility to bacterial infection and other immunologic alterations were found in gestationally- and neonatally-exposed young animals (Golub et al. 1993b; Yoshida et al. 1989).

Neurodevelopmental effects of aluminum have been investigated in a large number of oral studies in mice and rats, but determination of accurate effect levels in many of these studies is precluded by a lack of information'on aluminum content in the base diet. As discussed in Section 2.2.2.4, most of the neurodevelopmental studies of aluminum with adequately reported dietary information were performed

in mice by the same group of investigators (Golub and associates) who evaluated aluminum lactate in a common semipurified diet with known aluminum content using similar testing methods (Donald et al. 1989; Golub et al. 1992a, 1992b, 1994, 1995; Golub and Germann 1998). Aluminum lactate was tested because it represents a bioavailable form of aluminum and lactate is a common human dietary constituent. As discussed below, neurodevelopmental deficits have been observed in weanling and young mice and rats exposed during gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone. The most frequently observed behavioral patterns are indicative of altered and delayed reflex and neuromotor development. Performance of learning and memory tasks by mice and rats have not been consistently shown to be disrupted by developmental oral aluminum exposure, although extensive cognitive testing has not been performed (Domingo 1995; Golub and Domingo 1996).

Effects indicative of altered neuromotor maturation occurred at estimated doses as low as 155 mg Al/kg/day in mice exposed to aluminum lactate in studies with adequate base dietary aluminum information (Donald et al. 1989; Golub et al. 1995). Lower doses of aluminum were not tested in these or other adequately reported studies in mice or rats. Effects observed at the 155 mg Al/kg/day LOAEL included increased fore- and hindlimb grip strengths, increased foot splay, and increased latency to remove tail from hot water in offspring that were exposed during gestation and lactation and tested as weanlings (Donald et al. 1989), and decreased grip strength and decreased air-puff startle response in offspring exposed during gestation and lactation, or from gestation through adulthood, and tested as adults (Golub et al. 1995). The pattern of effects (types and magnitude of responses) in mice exposed during development and tested as adults was similar to that in mice exposed subchronically for up to 90 days only as adults (Golub et al. 1992b; Oteiza et al. 1993) (see Section 2.2.2.4). This indicates that it is likely that the effects were induced during the preweaning period and not further intensified by continuing exposure, and that the differences in effects seen in the younger (weanling) mice after developmental exposure are due to age at evaluation rather than age at exposure (Golub et al. 1995). Findings in other mouse studies by Golub and coworkers using similar or higher estimated doses of aluminum lactate corroborate the neuromotor alterations summarized above, including increased grip strength, increased tail withdrawal time from hot water, and negative geotaxis latency (as well as decreased weight and crown-rump length) in weanlings following gestation and/or lactation exposure (Golub et al. 1992a), and reduced auditory startle responsiveness in pups exposed during gestation and lactation, or from gestation continuing into postweaning, and tested at 52 days of age (Golub et al. 1994). In contrast to impaired neuromotor responses, mice exposed to $\geq$155 mg Al/kg/day during

development and/or as adults showed enhanced performance during training and performance of foodmotivated operant learning tasks (Golub et al. 1995; Golub and Germann 1998).

Neurodevelopmental effects in oral studies of aluminum in rats are summarized below, but doses in these studies cannot be assumed to be accurate because they may considerably underestimate actual aluminum intake due to insufficient information on aluminum in base diets. Offspring of rats that were gestationally exposed to 73.1 mg Al/kg/day as aluminum chloride by gavage showed delays in pivoting and longer latencies and more rearings in an open field test (Misawa and Shigeta 1992). Effects observed in rat pups that were pre- or postnatally exposed to 100-400 mg Al/kg/day as aluminum chloride or lactate included delays in neuromotor maturation (e.g., impaired grasping and righting reflexes and locomotor coordination), reduced body weight, and/or increased mortality, although there was no effect on learning ability in offspring that were gestationally exposed to 400 mg Al/kg/day and tested on postnatal day 65 using operant conditioning (Bemuzzi et al. 1986b, 1989a, 1989b; Muller et al. 1990). Rats that were treated with 100 or 200 mg Al/kg/day as aluminum lactate on postnatal days 5-14 and tested at postnatal days 50 and 100 showed no alterations in learning ability based on tests of motivation (avoidance of an aversion light or alimentary motivation) and achievement (pressing on a lever or radial maze performance), although a small reduction in general activity was observed at 200 mg Al/kg/day (Cherroret et al. 1992). Weanling rats that were exposed to 83 1 mg Al/kg/day as aluminum hydroxide in the diet for 60 days had no effects on open field activity or performance in passive avoidance and radial maze learning tasks (Thome et al. 1987).

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

2.2.2.7 Genotoxic Effects

No studies were located regarding genetic effects of various forms of aluminum following oral exposure in humans or animals. Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

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

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. Multiple tumors and lymphoma leukemia were significantly increased in the female mice. A doseresponse 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. Nevertheless, the authors did not consider aluminum potassium sulfate to be carcinogenic. 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 male or female B6C3Fl 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).

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2.2.3.2 Systemic Effects

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

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 2-3.

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 some types of aluminum-containing antiperspirants and develop skin rashes which may be aluminum-related. (Brusewitz 1984).

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, 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.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after intermediateor 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 (Bijhler-Sommeregger and Lindemayr 1986; Veien et al. 1986). Dermal hypersensitivity to aluminum appears to be rare in humans.

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

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference Chemical Form
				Less serious	Serious	
ACUTE EXPOSURE						
Systemic						
Mouse (TFI)	5 d 1x/d	Dermal	10% F			Lansdown 1973 AlH_3O_3
Mouse (TFI)	5 d 1x/d	Dermal	25% F			Lansdown 1973 $Al_2(OH)_5Cl$
Mouse (TFI)	5 d 1x/d	Dermal	10% F			Lansdown 1973 $Al(C_2H_2O_2)_3$
Mouse (TFI)	5 d 1x/d	Dermal	2.5% F	5% F (slight to moderate hyperplasia)	25% F (severe hyperplasia with focal ulceration)	Lansdown 1973 $AlCl_3$
Mouse (TFI)	5 d 1x/d	Dermal		10% F (epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $AlCl_3$
Mouse (TFI)	5 d 1x/d	Dermal	10% F			Lansdown 1973 $Al_2(SO_4)_3$
Mouse (TFI)	5 d 1x/d	Dermal		10% F (epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $Al(NO_3)_3$

Table 2-3. Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

| Species (Strain) | Exposure/ duration/ frequency | System | NOAEL | LOAEL | | Reference Chemical Form |
				Less serious	Serious	
Rabbit (New Zealand)	5 d 1x/d	Dermal	10%			Lansdown 1973 $Al(C_2H_2O_2)_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal		10% (epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $Al(NO_3)_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal	10%			Lansdown 1973 $Al_2(SO_4)_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal		10% (epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 $AlCl_3$
Rabbit (New Zealand)	5 d 1x/d	Dermal	10%			Lansdown 1973 AlH_3O_3
Rabbit (New Zealand)	5 d 1x/d	Dermal	25%			Lansdown 1973 $Al_2(OH)_5Cl$
Pig (Large White)	5 d 1x/d	Dermal	10% F			Lansdown 1973 $Al(C_2H_2O_2)_3$

Table 2-3. Levels of Significant Exposure to Aluminum and Compounds - Dermal (continued)

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL	LOAEL		Reference Chemical Form
				Less serious	Serious	
Pig (Large White)	5 d 1x/d	Dermal		10% (epidermal change: hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 Al(NO₃)₃
Pig (Large White)	5 d 1x/d	Dermal	10%			Lansdown 1973 Al₂(SO₄)₃
Pig (Large White)	5 d 1x/d	Dermal		10% (epidermal damage; hyperkeratosis, acanthosis, microabscesses; aluminum deposition in keratin)		Lansdown 1973 AlCl₃
Pig (Large White)	5 d 1x/d	Dermal	10%			Lansdown 1973 AlH₃O₃
Pig (Large White)	5 d 1x/d	Dermal	25%			Lansdown 1973 Al₂(OH)₅Cl

d = day(s); F = female; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level

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

2.2.3.4 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 were 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.

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

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

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

2.3 TOXICOKINETICS

Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Occupational exposure to fine powders of aluminum metal has resulted in pulmonary effects as a result of particulate deposition in the lung and subsequent pulmonary fibrosis. Approximately 0.1% of ingested aluminum is usually absorbed, although absorption of more bioavailable forms can be on the order of 1%. The unabsorbed aluminum is excreted in the feces. The 10-fold range in absorption of aluminum is largely due to differences in bioavailability related to the form of ingested aluminum and the presence of dietary constituents which can complex with aluminum and 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 steady-state is maintained in most healthy adults, with aluminum body burdens neither increasing nor decreasing over time. 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 rise 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). "Free" aluminum ions (e.g., $Al(H_20)_6^{3+}$) 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 would not.

Toxicokinetic data for aluminum have been somewhat limited by a paucity of radioisotope tracer experiments, which have only recently been conducted with aluminum due to the lack of a suitable and convenient radioisotope. ^{28}Al can be produced, but it has a half-life of only 2.3 minutes (Ganrot 1986). Recently, ^{26}Al (half-life 7.2×10^5 years) has been produced by accelerator mass spectrometry. Although ^{26}Al is not widely available to researchers, it has been used in a number of human and animal studies to

assess the toxicokinetic properties of aluminum (Day et al. 1991; Flarend et al. 1997; Hohl et al. 1994; Priest et al. 1995, 1996; Schiinholzer et al. 1997; Walton et al. 1995).

2.3.1 Absorption

2.3.1.1 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 preshift plasma levels were 4.92 and 3.60 µg/L, respectively (Gitehnan et al. 1995). Results of an autopsy on a stonemason 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 µg/L to 4-414 µg/L (Sjiigren et al. 1985). Increased urinary aluminum levels have also been observed in workers exposed to 0.025 (median respirable concentration) or 5 mg/m^3 (TWA concentrations) aluminum dust (Gitelman et al. 1995; Mussi et al. 1984) or 2.4 or 5 mg/m^3 (TWA concentrations) aluminum fumes (Mussi et al. 1984; Sjiigren 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 (Sjogren et al. 1988).

The percentage of aluminum absorbed following inhalation exposure was not reported in the occupational toxicokinetic studies (Gitelman et al. 1995; Mussi et al. 1984; Pierre et al. 1995; Sjogren et al. 1985, 1988). 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. However, it is not known if a possible difference in particle size between the aluminum fumes and aluminum dust influenced absorption.

It is possible that systemic absorption of airborne aluminum occurs via the lungs, gastrointestinal tract after mucociliary clearance from the respiratory tract (ICRP 1994), or via the olfactory tract. 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 Per1 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 or serum were seen, indicating that lung retention rather than absorption was taking place (Steinhagen et al. 1978; Stone et al. 1979).

2.3.1.2 Oral Exposure

Human studies indicate that only a small percentage of aluminum that is normally ingested in the diet and drinking water is absorbed. Most estimates of average gastrointestinal absorption of aluminum under normal dietary conditions are in the range of 0.1-0.3%, although some human studies indicate that absorption of the more bioavailable forms, particularly complexes of aluminum with particular carboxylic acids, (e.g., aluminum citrate), may be on the order of 1% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983b; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993; Priest et al. 1996). In a representative study by Greger and Baier (1983b), eight healthy people ingested a control diet (5 mg Al/day) or the same diet supplemented with aluminum lactate (120 mg Al/day) in alternating 20-day periods, with the subjects receiving sodium lactate instead of aluminum lactate during the control phases. Based on the fraction of aluminum intake excreted in the urine per day, gastrointestinal absorption was estimated to be 0.78% during the control periods and 0.09% during the test periods. Blood levels of aluminum increased slightly only during the test period and quickly returned to normal during the control period. The 5 and 125 mg Al/day doses (0.07 and 1.8 Al/kg/day assuming a body weight of 70 kg) are within the normal range of aluminum intake in the United States, although aluminum lactate may have a different bioavailability than the forms of aluminum typically found in the diet (e.g., additives such as sodium aluminum phosphate, aluminum sulfates, and aluminum silicates [see Section 5.4.41).

People on antacid therapy consume much higher amounts of aluminum than in the diet, commonly up to several grams of aluminum per day ingested as large bolus doses or as much as a half gram of aluminum

throughout the day as aluminum hydroxide (a relatively insoluble form of aluminum) (Reiber et al. 1995). Although aluminum intake during antacid treatment can be substantial (i.e., two to three orders of magnitude higher than normal intake), usually greater than 99% of the ingested aluminum is still recovered in the feces and blood aluminum levels still rarely rise more than 50% higher than the preantacid level (Gorsky et al. 1979; Kaehny et al. 1977; Reiber et al. 1995), indicating that aluminum uptake is mainly controlled by factors other than the amount of ingested aluminum. As discussed in Section 2.4.1, most ingested aluminum is unlikely to be absorbed as it is precipitated in the small intestine and excreted in the feces. However, even though only a small percentage of ingested aluminum is absorbed, significant body burdens could arise, especially in individuals with impaired renal function, because antacids are commonly used in large quantities over long periods of time.

The absorption of aluminum depends on its bioavailability in the aqueous and varying pH conditions of the gut. Aluminum bioavailability is mainly related to the form in which it is ingested and the presence of dietary constituents with which the metal cation can complex (see Section 2.4.1). 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; Partridge et al. 1989; Molitoris et al. 1989; Slanina et al. 1984, 1985, 1986; Testolin et al. 1996; Weberg and Berstad 1986). For example, the percentages 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 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.

Most of the estimates of aluminum uptake summarized above are based on the assumption that urinary excretion represents absorption, although a few values were determined using the anthropogenic radioactive isotope [26]Al in combination with a sophisticated analytical technique (accelerator mass

spectrometry) (Day et al. 1991; Priest et al. 1996; Sch nholzer et al. 1997). Isotopic tracer techniques have been infrequently used in absorption studies of aluminum because [26]Al (the only isotope with a biologically usable half-life) is not readily available and inexpensive in the quantities necessary for radiochemical detection. Radiotracer studies are favorable because they facilitate accurate quantification of the very small percentages of ingested aluminum that are absorbed and provide a means to distinguish administered radioactive aluminum from stable endogenous aluminum and from aluminum contamination of samples (Priest 1993). A radiochemical determination of the likely range of aluminum bioavailabilities has only recently been performed. Priest et al. (1996) determined the fraction of aluminum taken up by two male volunteers following administration of a single dose of [26]Al-labeled aluminum citrate (aqueous solution) or aluminum hydroxide (colloidal suspension in water) directly to the stomach using a pediatric feeding tube; there was a 3-week interval between dosing. These forms of aluminum were used because it was suspected that they would be either relatively bioavailable (citrate) or relatively nonbioavailable (hydroxide). Based on analyses of [26]Al in the blood (collected at 1, 4, and 24 hours after dosing) and excreta (urine and feces were collected for 6 days), the absorbed fractions were determined to be 0.5% for aluminum citrate and 0.01% for aluminum hydroxide. Similar exposure to aluminum ([26]Al) hydroxide simultaneously with trisodium citrate resulted in 0.14% absorption of aluminum; this exposure likely represents a more normal exposure scenario (e.g., following the ingestion of aluminum in orange juice) than ingestion of pure aluminum citrate. The uptake of aluminum citrate was about a factor of two lower than a value of 1% previously determined in a study of [26]Al-labeled aluminum citrate using one subject (Day et al. 1991). Due to the use of a considerably higher quantity of citrate by Day et al. (1991), the small number of subjects in both studies, and other factors that could contribute to inter-subject variability in absorption (e.g., presence of food in the gut), Priest et al. (1996) concluded that aluminum absorption must at least equal 1% under some circumstances and 0.5% is probably close to the maximum bioavailability in adults and older children under normal ingestion exposure conditions. Schoriholzer et al. (1997) also examined aluminum absorption following oral exposure to [26]Al. Wistar rats received a single gavage dose of aluminum hydroxide, aluminum citrate, aluminum citrate with added sodium citrate, or aluminum maltolate. Fractional intestinal absorptions of 0.1, 0.7, 5.1, and 0. 1%, respectively, were estimated.

The influence of some of the aforementioned factors on aluminum absorption is further illustrated by the findings of two animal studies which estimated bioavailability differences by comparing areas under plasma concentration-time curves (AUC) after oral and intravenous dosing (Yokel and McNamara 1988). Using a single oral dose of aluminum chloride, aluminum absorption was estimated to be 0.57% in

rabbits treated with 333 mg Al/kg (Yokel and McNamara 1988). Following a single maximum safe oral dose 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, aluminumabsorption was 0.57, 1.16, 2.18, and 0.63%, respectively (Yokel and McNamara 1988). 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). Nitrate, therefore, was the most bioavailable form of aluminum after citrate. However, although aluminum citrate was more bioavailable than aluminum nitrate as determined from AUC, aluminum from aluminum nitrate reached a higher peak concentration in blood.

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, ranging from approximately 0.1% for relatively nonbioavailable water insoluble forms such as aluminum hydroxide to relatively bioavailable soluble forms such aluminum citrate. 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. Aluminum lactate is often used in animal oral toxicity studies (Section 2.2.2) because it is intermediate in bioavailability between inorganic complexes (e.g., aluminum hydroxide and aluminum silicates) and aluminum complexed with organic acids (e.g., citrate), and does not introduce nonbiological anions at the same time. Due to the range of possible bioavailabilities, the amount of aluminum ingested does not provide a estimate of exposure without information on bioavailability of the form in which it is ingested.

2.3.1.3 Dermal Exposure

No studies were located regarding aluminum absorption in humans after dermal exposure to aluminum or its compounds. 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 (Reiber et al. 1995). The possibility that aluminum in antiperspirants may be absorbed directly through the skin has been suggested (Graves et al. 1990), but this hypothesis has not been clinically confirmed.

A study by Anane et al. (1995) provides evidence that aluminum is absorbed through the skin. Increased levels of aluminum were observed in the urine of mice exposed to 0.1 or 0.4 μg/day aluminum chloride (0.01-0.04 μg Al/day) applied daily to a 4 cm^2 shaved area for 130 days.

2.3.1.4 Other Routes of Exposure

Aluminum uptake occurred in patients with chronic renal failure during hemodialysis treatment (Alfrey 1993b; Berlyne et al. 1970). Aluminum in dialysate water passed through the dialysis membrane and entered directly into the blood, resulting in increased serum aluminum levels in patients after dialysis. This toxicity has been largely prevented by eliminating aluminum from the water used to prepare the dialysate (AAMI 1998), substituting calcium-containing phosphate-binding agents for those containing aluminum and avoidance of the concomitant ingestion of citrate- and aluminum-containing compounds (Alfrey 1993b).

2.3.2 Distribution

Aluminum occurs normally in the 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. 1972/73; Tipton and Cook 1963). Of the total body burden of aluminum about one-half is in the skeleton, and about one-fourth is in the lungs (Ganrot 1986). Most of the aluminum detected in lungs is probably due to accumulation of insoluble aluminum compounds that have entered the body via the airways (Ganrot 1986). Most of the aluminum in other parts of the body probably originates from food intake.

The normal level of aluminum in adult human lungs is about 20 mg/kg wet weight (w/w) and increases with age due to buildup; 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. 1972/73; Tipton and Cook 1963). 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. 1972/73; Tipton and Cook 1963).

There is relatively good agreement in the published literature that 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).

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. 1972/73), adrenals (Stitch 1957; Tipton and Cook 1963), and parathyroid glands (Cann et al. 1979). There is evidence that with increasing age of humans, aluminum concentrations may increase in the lungs and brain tissue (Alfrey 1980; Crapper and DeBoni 1978; Markesbery et al. 1981; McDermott et al. 1979; Stitch 1957; Tipton and Shafer 1964).

2.3.2.1 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.

Following inhalation exposure, the lungs receive aluminum mostly as particles of poorly soluble compounds (Ganrot 1986). ICRP (1994) reports that 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 assumed to be taken up by alveolar macrophages through phagocytosis, then transported up the bronchial tract, and ultimately swallowed. The remainder of aluminum is probably taken up by macrophages in the lung tissue where it remains indefinitely. It has been observed that the lungs have the highest aluminum concentration compared to other organs, and that the pulmonary concentration of aluminum increases with age.

2.3.2.2 Oral Exposure

There are limited data on the distribution of aluminum in humans. Clearance of [26]Al from the blood was assessed in 2 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; Domingo et al. 1993; Gomez et al. 1997a, 1997b; Greger and Donnaubauer 1986; Julka et al. 1996; Santos et al. 1987; Walton et al. 1995; Yokel and McNamara 1985). 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. Animal evidence suggests that aluminum accumulates in the brain and is preferentially distributed to the hippocampus. Acute oral exposure of weanling rats to both 1,25-dihydroxyvitamin-D$_3$ and 160 mg Al/kg/day as either aluminum hydroxide or aluminum citrate has been associated with significantly elevated aluminum concentrations in the cerebral cortex and hippocampus (Santos et al. 1987). In treated animals, the hippocampus aluminum concentration was about 53 times higher than that observed in the control group and approximately 32 times higher than that found in other areas of the brain (cortex, cerebellum). The potential role of 1,25-dihydroxyvitamin-D$_3$ in this preferential accumulation was not determined; however, it was suggested that the preferential deposition of aluminum in the hippocampus may play an important pathogenic role in aluminumneurotoxicity (Santos et al. 1987). Using [26]Al, Walton et al. (1995) showed that a single low dose oral exposure to aluminum sulfate can result in a substantial increase in brain aluminum levels in rats. In 6 of the 8 exposed rats, brain aluminum levels were 10 to 300 times higher than control values (brain aluminum levels in the remaining 2 rats were similar to control levels).

Results of several studies with experimental animals indicate that administration of vitamin D and 1,25-dihydroxyvitamin-D$_3$ enhances the accumulation and retention of aluminum in tissues (e.g., bone, kidneys, muscle, and heart) following oral exposure to aluminum compounds (Anthony et al. 1986; Burnatowska-Hledin et al. 1986; Chan et al. 1998).

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.

In addition to distribution of aluminum to the brain (hippocampus), bone, muscle, and kidneys of orally exposed animals, there is limited animal evidence indicating that aluminum has the potential to cross the placenta and accumulate in the fetus and to be distributed to some extent to the milk of lactating mothers (Cranmer et al. 1986; Golub et al. 1996a; Yokel 1985; Yokel and McNamara 1985). Increased concentrations of aluminum were detected 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. 1996a). 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). However, 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).

Once into the blood, aluminum is believed to be present almost exclusively in the plasma where it is bound mainly to transferrin (Ganrot 1986; Martin 1986; öman and Martin 1994); Ohman and Martin (1994) showed that 89% of the aluminum in serum is bound to transferrin. There is *in vitro* evidence indicating that aluminum can bind to the iron-binding sites of transferrin (Moshtaghie and Skillen 1986), and that AL^{+3} may compete with similar ions in binding to transferrin (Ganrot 1986). 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. 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).

2.3.2.3 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.

2.3.2.4 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).

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). 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. 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, 42, 4.2, and 2.3 days in the spleen, liver, lungs, serum renal cortex, and renal medulla, respectively. The kidneys of treated rabbits also demonstrated a second half-time which exceeded 100 days.

Subcutaneous injection of rabbits with aluminum chloride daily for 28 days was associated with significant accumulation of aluminum 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 either 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. At blood aluminum concentrations of 2-4 mg/L, there was no increase in brain aluminum with any of the compounds evaluated.

Following intramuscular administration of aluminum hydroxide or aluminum phosphate vaccine adjuvants in rabbits, increased levels of ^{26}Al 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 accumulates in fetal tissue (Cranmer et al. 1986; Yokel and McNamara 1985). Jntraperitoneal exposure of pregnant mice to aluminum chloride on Gd 7-l 6 has been associated with significantly increased concentrations of aluminum in both placental and fetal tissues (Cranmer et al. 1986). Both intravenous and subcutaneous exposure of lactating rabbits and mice to aluminum lactate has been associated with increased concentrations of aluminum in milk (Yokel and McNamara 1985; Golub et al. 1996). 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. Because of the limited gastrointestinal absorption of aluminum and the limited distribution of aluminum to milk, it was suggested that there would be little risk of aluminum toxicity in suckling offspring of nursing females exposed to aluminum

2.3.3 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 affnrity 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; Dryssen et al. 1987; Ganrot 1986; Karlik et al. 1980).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

The kidney is the major route of excretion of absorbed aluminum after inhalation exposure in humans. Six volunteers had urinary levels of 14-414 µg/L aluminum compared to concentrations of < 3 µg/L prior to a l-day exposure to 0.3-10.2 mg Al/m^3 in welding fumes (Sj gren 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 g-hour workshift compared to concentrations at the beginning of the day (Mussi et al. 1984). In another occupational study, workers exposed to 1.5 mg/m^3 for 0.3-21 years eliminated the highest levels of urinary aluminum concentrations (82 µg/L) immediately after exposure (Sjögren et al. 1988). After an exposure-free period of 16-37-days, levels decreased to a mean concentration of 29 µg/L. These studies indicate that urinary levels were related to exposure concentration; however, quantitative correlations, as well as elimination of aluminum in the feces, were not reported.

A relationship between the duration of aluminum exposure and urinary concentrations has been found in humans (Sjogren et al. 1985, 1988). Welders exposed to 0.2-5.3 mg/m³ (8-hour workshift) for more than 10 years had a urinary aluminum half-time of at least 6 months compared to 9 days for individuals exposed for less than 1 year (Sjogren et al. 1988). The excretion half-time was 8 hours following a single exposure to aluminum welding fumes (Sjogren et al. 1985); a half-time of 7.5 hours was estimated in workers exposed to aluminum dust (Pierre et al. 1995). However, if urinary concentrations were measured after an exposure-free period, the level was related to total number of exposed years. Apparently, the longer the exposure, the greater the retention of aluminum in humans.

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

2.3.4.2 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 1983b; Kaehny et al. 1977; Reeker et al. 1977). 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 concentration being 495 µg/day during exposure (Reeker 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 rug Al/kg/day as aluminum lactate in addition to 0.07 mg Al/kg/day in basal diet for 20 days (Greger and Baier 1983b). Urinary 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 a 3-fold increase in urinary aluminum levels (Gorsky et al. 1979). However, elimination may have been affected by other complications (i.e., osteoporosis, alcoholism calcium intake) in these patients.

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 a lower glomerular filtration rate, 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. Sprague-Dawley 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 difference in the excretion rates most likely reflects differences in gastrointestinal absorption.

2.3.4.3 Dermal Exposure

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

2.3.4.4 Other Routes of Exposure

Human and animal parenteral exposure studies indicate that the major excretion route of aluminum is through the kidneys. In a subject administered a single intravenous dose of ^{26}Al citrate, 40 times more aluminum was excreted in the urine than in the feces (Priest et al. 1995). In dogs that were studied to evaluate the renal handling of aluminum the controls excreted 37% of the aluminum load, while dogs dialyzed with tap water containing aluminum eliminated only a small fraction of aluminum (Kovalchik et al. 1978). In both groups of dogs, urinary excretion was the major route of elimination of aluminum Bile excretion was >0. 1% of the aluminum load. When aluminum was administered via the external jugular vein, aluminum excretion was found to occur in the distal tubule of the kidney in pigs (Monteagudo et al. 1988). Yokel and McNamara (1985) did not find any age-related differences in the systemic clearance or half-time of aluminum in rabbits following parenteral administration of aluminum lactate.

2.3.5 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 et al. 1987; Andersen and Krishnan 1994). 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 parametrization, (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 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substancespecific 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) is 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 2-3 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.

There were no PBPK models for aluminum located in the literature. However, physiologically and mechanistically based models have been developed using basic information for estimating the deposition and elimination of a range of compounds; one recent model is described in ICRP (1994). Although this model is not specific to aluminum it provides information that may be useful for risk assessment, tissue dosirnetry, and species extrapolations.

2.4 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 (Gannot 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; Dryssen 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.

2.4.1 Pharmacokinetic Mechanisms

Gastrointestinal absorption of aluminum is low, generally in the range of 0.1-1 % in humans as discussed in Section 2.3.1.2. Absorption of aluminum compounds is largely determined by its bioavailability in the aqueous conditions of the gut, which is mainly related to pH, the presence of complexing ligands with

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance
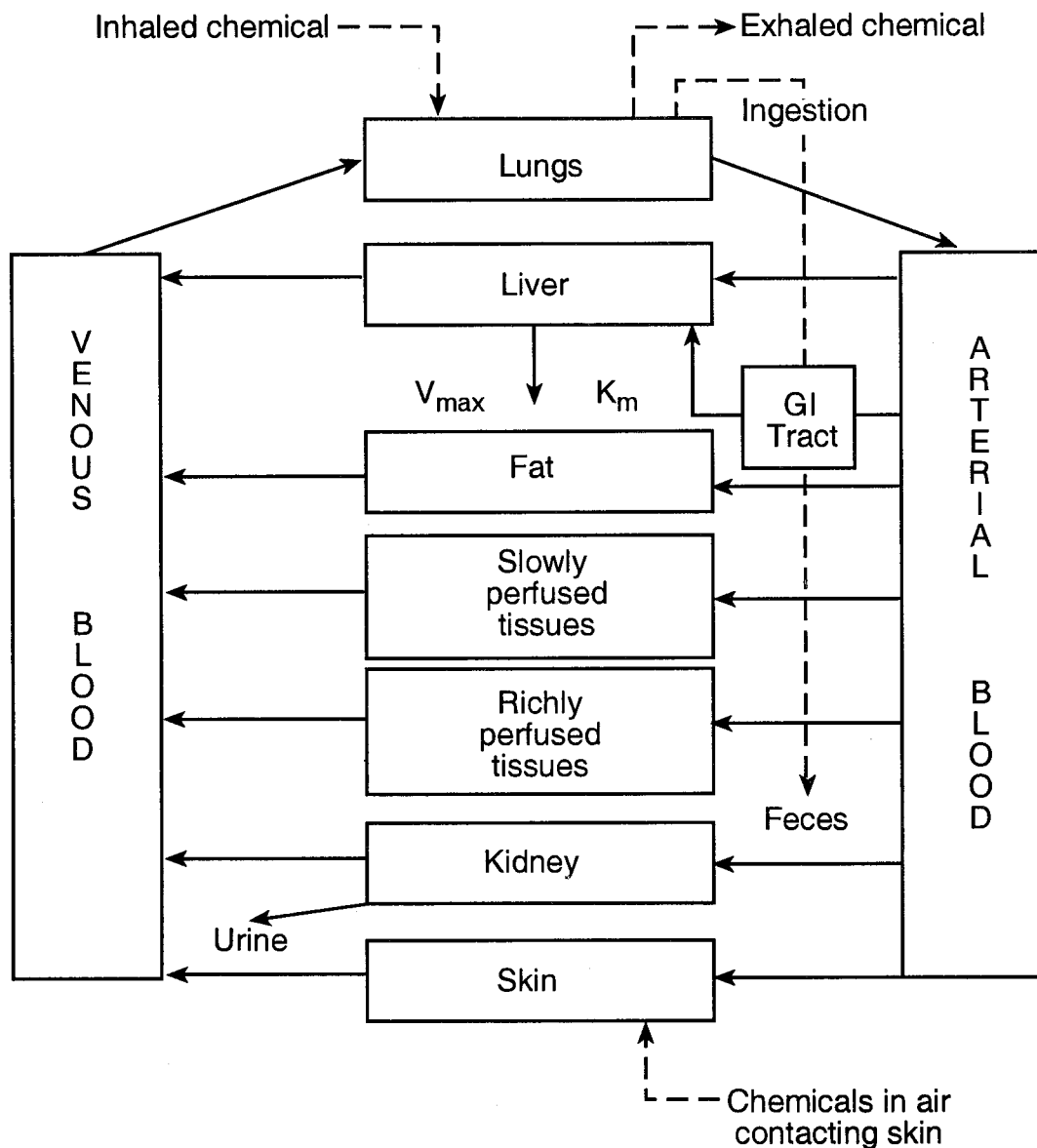
Source: adapted from Krishnan et al. 1994

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 and feces or by exhalation.

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≈ 2) aluminum primarily occurs as a monomolecular hexahydrate, $Al(H_2O)_6^{+3}$, which is generally abbreviated Al^{+3} and referred to as "free" aluminum (Reiber et al. 1995). As pH increases, 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 ($[Al(OH)_3]$) an insoluble precipitate. 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 de solubilized aluminum is not complexed, is rapidly precipitated as insoluble (unabsorbable) aluminum hydroxide in the duodenum 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 et al. 1985a; Priest 1993; Rieber 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 1989), suggest that aluminum is mainly absorbed as neutral complexes by passive diffusion through paracellular 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 cellmediated 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 intercellular tight junctions (paracellular channels), possibly via disruption in calciumhomeostasis (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 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 $1,25(OH)_2D_3$ 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 μm diameter) to penetrate the lung's protective removal mechanisms may contribute to overall body levels by dissolution and direct uptake into the blood stream or by macrophage phagocytosis (Priest 1993; Reiber et al. 1995).

2.4.2 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.

Lung Toxicity. There have been several cases of lung fibrosis in humans as the result of occupational exposure to aluminum dusts (Jordan 1961; Mitchell et al. 1961), and signs of lung damage have also been produced in rats, hamsters, and guinea pigs after exposure to several aluminum compounds (Drew et al. 1974; Finelli et al. 1981; Steinhagen et al. 1978; Thomson et al. 1986). The lung effects observed in humans and animals are suggestive of dust overload. Dust overload occurs when the volume of dust in the lungs markedly impairs pulmonary clearance mechanisms. Lung overload is not dependent on the inherent toxicity of the compound, and dust overloading has been shown to modify both the dosimetry and toxicological effects of the compound (Morrow 1988). When excessive amounts of widely considered benign dusts are persistently retained in the lungs, the resultant lung effects are similar to those observed following exposure to highly toxic dusts. The excessive levels of dust in the lung lead to excessive engulfment of particles by alveolar macrophages resulting in a progressive loss of alveolar macrophage mobility and an aggregation of alveolar macrophages (Morrow 1992). The relative or complete loss of alveolar macrophage mobility increases the likelihood of direct particle-epithelial cell interactions, often resulting in a prolonged inflammatory response, and interstitial localization of dust particles.

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 1993b). 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. Chelation therapy with deferoxamine and reducing oral aluminum exposure to the minimum practicable have been used'to successfully treat this condition. The pathogenesis and treatment of aluminum-related bone disease have been reviewed (Sherrard and Andress 1989).

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

nonrodent species (see Sections 2.2.2.4, 2.2.2.6, and 2.5). 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). 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 of general processes that are involved have been identified. Changes in

cytoskeletal proteins, manifested as hyperphosphorylated neurofilamentous aggregates within the brain

cells, 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 proteins 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 iufluence calcium homeostasis and

calcium-dependent processes in the brain via impairment of the phosphoinositide second messenger-

producing system (which modulates intracellular calcium concentrations); calcium-activated proteinases

may be affected which could alter the distribution and concentration of cytoskeletal proteins and other

substates (Jope and Johnson 1992).

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, cholinergic activity, signal transduction pathways, lipid

peroxidation, and glucose metabolism as well as interfere with metabolism of essential trace elements

(e.g., iron) because of similar coordination chemistries and consequent competitive interactions. Signal

pathways are important in all cells and control differentiation and proliferation, neurotransmitter release,

and synaptic plasticity. Glucose metabolism may also be affected by aluminum due to specific inhibition of hexokinase and glucose-6-phosphate dehydrogenase (Erasmus et al. 1993; Strong et al. 1996).

Developmental Toxicity. Developmental toxicity of aluminum includes neurodevelopmental changes and skeletal effects in orally-exposed rodents (see Section 2.2.2.6). Neurobehavioral deficits have been observed in mice exposed via diet as adults, as well as in weanling and young developing animals exposed by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995). The most frequently affected behaviors in mice exposed as adults, or exposed during development and tested as adults, included decreases in motor activity, grip strength, and startle responsiveness. The effects most commonly found in exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity, indicating that the pattern of neurobehavioral impairment in developing animals was different from adults (i.e., the developmental syndrome did not included changes in spontaneous motor activity and startle responsiveness). It is not known whether the potential mechanisms of aluminum neurotoxicity identified in adults (see preceding section) parallel those active in the developing fetus and/or young animal. For example, aluminum competition for essential element uptake could be important during the development of the nervous system but less important for nervous system function in an adult animal (Strong et al. 1996).

Gestational exposure to 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 relatively highly bioavailable (e.g., aluminum citrate or nitrate) and/or as bolus doses by gavage (Colomina et al. 1992; Gomez et al. 1991; Paternain et al. 1988). Given the relatively high bioavailability of the developmentally toxic forms of aluminum and bolus administration, it is possible that the skeletal changes are consequent to phosphate depletion caused by excess binding with aluminum in the maternal gut.

2.4.3 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 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.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview. Aluminum is the third most common component of the earth's crust. Aluminum is a common trace element that has no known biological function. Exposure occurs primarily by ingestion. 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 compounds), and aluminum-containing medications (particularly antacid/antiulcer and buffered aspirin formulations) (Lione 1985b). Based on the FDA's 1993 Total Diet Study dietary exposure model and the 1987-1988 United States Department of Agriculture (USDA) Nationwide Food Consumption Survey, Pennington and Schoen (1995) estimated daily aluminum intakes of 0.10 mg Al/kg/day for 6- to 11-month-old infants, 0.30-0.35 mg Al/kg/day for 2- to 6-year-old children, 0.11 mg Al/kg/day for 10-year-old children, 0.15-0.18 mg Al/kg/day for 14- to 16-year-old males and females, and 0.10-0.12 mg Al/kg/day for adult (25- to 30- to 70+-year-old) males and females. These values are generally lower than the range of average intakes estimated in earlier reports (e.g., 0.2-0.6 mg Al/kg/day in adults) (Ganrot 1986; Greger 1985; Iyengar et al. 1987; Pennington 1987; Wilhelm et al. 1990), although Greger (1992) estimated that most adults consume from 0.01 to 0.1 mg Al/kg/day. Users of

aluminum-containing medications that are healthy (i.e., have normal renal function) can ingest much larger amounts of aluminum than in the diet, possibly as high as 12-7 1 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). Long-term use of many aluminum-containing medications (e.g., antacids for minor gastric distress, buffered aspirin for rheumatoid arthritis) appears to increase with age and is most common in elderly populations who simultaneously experience reduced renal function associated with advancing age (Lione 1985b). Aluminum antacids are also widely used to treat gastroesophageal reflux, esophagitis, and other peptic disorders in infants with normal renal function; pediatric doses appear to be similar to those recommended in adults (Tsou et al. 1991). Dosing and safety guidelines for aluminum antacids in infants have not been conclusively established (Tsou et al. 1991).

Gastrointestinal absorption of aluminum is low, generally in the range of 0.1-0.3% in humans, although absorption of particularly bioavailable forms such as aluminum citrate may be on the order of 1% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983b; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993). Although large bolus doses of as much as half a gramof ahuninum throughout the day can be ingested during antacid therapy, absorption is still usually less than 1% of the intake amount (Gorsky et al. 1979; Kaehny et al. 1977; Reiber et al. 1995). Bioavailability of aluminum varies depending mainly on the chemical form of the ingested compound (i.e., type of anion) and, particularly, the kinds and amounts of ligands present in the stomach (i.e., dietary content) with which the metal can form absorbable aluminum species (DeVoto and Yokel 1994; Reiber et al. 1995). The acidic conditions of the stomach appear to ensure that the majority of consumed aluminum will be solubilized to Al^{+3} regardless of the chemical form or medium in which it is ingested. The solubilized aluminum competes for available ligands in the stomach but only a small portion of the Al^{+3} is complexed, causing it to remain soluble in the higher pH of the small intestine and therefore be available for uptake. Some of the solubilized Al^{+3} is likely to recomplex with the anion that was part of the aluminum compound originally ingested. The dietary ligands that seem to play the most important role in this process include resident carboxylic acids and common dietary constituents, particularly citric acid/citrate. Because the vast majority of the solubilized aluminum is not complexed, it is rapidly precipitated as insoluble unabsorbed aluminum hydroxide by the near-neutral intestinal pH conditions, and is ultimately excreted in the feces. Given the apparent 10-fold range in the gastrointestinal absorption of aluminum the amount of aluminum ingested does not necessarily provide an actual estimate of uptake without information on the bioavailability of the form in which it is ingested.

Little information is available on oral toxicity of aluminum in healthy people. The preponderance of human studies are in patients with reduced renal function who accumulated aluminum as a result of long-term intravenous hemodialysis therapy with aluminum-containing dialysis fluid and, in many cases, concurrent administration of high oral doses of aluminum to regulate phosphate levels (i.e., reduce uptake of phosphate by binding it in the gut). 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 GRAS status of aluminum-containing food additives. Recent data, however, indicate that adverse effects can result from long-term use of aluminum-containing medications in some healthy individuals. There are a number of case reports of skeletal changes (e.g., osteomalacia) in adults and children with normal kidney function due to repeated antacid use, although studies or case reports investigating possible non-overt effects of aluminum-containing medications in healthy people, such as subtle neurotoxic changes, have not been performed. Several epidemiology and case-control studies have found associations between oral exposure to aluminum and an increased incidence of Alzheimer's disease, but none of the data conclusively establish a cause and effect relationship. The fact that Alzheimer's disease may largely be a genetic disorder further complicates the issue. Studies in rats and mice clearly show that oral exposure to relatively low doses of aluminum causes neurobehavioral effects in adult and developing animals, indicating that neurotoxicity is the critical end point of concern for aluminum. Issues relevant to children are explicitly discussed in Sections 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Inhalation and dermal aluminum exposures are not associated with significant adverse health risks. Respiratory and neurological effects are the only consistent health effects from inhaled aluminum Respiratory effects, in particular fibrosis, have been observed in some workers exposed to aluminum dust containing nonpolar aliphatic lubricants; these lubricants are no longer used in the production process. Aluminum industry workers appear to be the only population at risk for the development of aluminum-related pulmonary toxicity. Poor industrial hygiene may increase the risk of lung toxicity in occupational exposures. Subtle neurological effects (e.g., altered performance on neurobehavioral tests, increased reporting of subjective symptoms) have also been observed in workers exposed to aluminum dust and aluminum fumes. Dermal aluminum application, such as an aluminum-containing antiperspirant, may cause rashes in some people.

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for aluminum Results from human and animal studies suggest that the respiratory tract, particularly the lung, is a sensitive target of airborne aluminum toxicity. Interpretation of the human data is complicated by the lack of exposure assessment and the potential for concomitant exposure to other toxic compounds. The most convincing evidence that aluminum exposure results in lung effects in humans comes from studies of workers exposed to fine aluminum dust (pyropowder) or alumina (aluminum hydroxide). Fibrosis has been observed in workers at facilities which used a nonpolar aliphatic oil lubricant to retard surface oxidation (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958); this type of lubricant is no longer used. Fibrosis was not observed when stearic acid was used as a lubricant (Crombie et al.' 1944; Meiklejohn and Posner 1957; Posner and Kennedy 1967). Acute-, intermediate-, and chronic-duration animal studies have also reported respiratory effects. These respiratory effects include increases in alveolar macrophages, granulomatous lesions in the lungs and peribronchial lymph nodes, and increases in lung weight (Drew et al. 1974; Klosterkotter 1960; Pigott et al. 1981; Steinhagen et al. 1978; Stone et al. 1979). The lung effects observed in humans and animals are suggestive of dust overload. Dust overload occurs when the volume of dust in the lungs markedly impairs pulmonary clearance mechanisms. Lung overload is not dependent on the inherent toxicity of the compound and dust overloading has been shown to modify both the dosimetry and toxicological effects of the compound (Morrow 1988). When excessive amounts of widely considered benign dusts are persistently retained in the lungs, the resultant lung effects are similar to those observed following exposure to highly toxic dusts. Because it is unclear whether the observed respiratory effects are related to aluminum toxicity or to dust overload, inhalation MRLs based on respiratory effects were not derived.

Subtle neurological effects have also been observed in workers chronically exposed to aluminum dust or fumes. These effects include impaired performance on neurobehavidral tests, increased reporting of subjective neurological symptoms, and altered EEGs (Bast-Peetersen et al. 1994; Hanninen et al. 1994; Hosovski et al. 1990; Rifat et al. 1990; Sjogren et al. 1996; White et al. 1992). Poor characterization of aluminum exposure precludes using these studies to develop an inhalation MRL for aluminum.

Oral MRLs

Data on health effects of ingested aluminum in humans are unsuitable for MRL consideration because studies have centered on specific patient populations (i.e., dialysis, neurodegenerative disease) and are not the types typically used in risk evaluation. 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-contaminated dialysate, use of aluminum-containing phosphate binding agents, and possible increased gastrointestinal absorption. Although providing evidence that aluminum is an important etiologic factor in dialysis-related health disorders, particularly the neurological syndrome dialysis encephalopathy, the effects are manifested under unnatural exposure conditions in which the gastrointestinal barrier is bypassed and aluminum excretion is impaired by the poor renal function. No clinical studies on health effects of aluminum medicinals in people with normal renal function have been performed. There are case reports of skeletal changes (e.g., osteomalacia) consequent to long-term ingestion of antacids in healthy adults and children with normal kidney function (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998), but these effects are attributable to a loca action (phosphate depletion caused by binding of phosphate with aluminum in the stomach), and only suggest that typical antacid doses may not be safe for all people and indicate that non-overt effects of aluminum have not been adequately characterized in humans.

Derivation of an MRL(s) for aluminum based on animal studies is complicated by limitations in the database. Early animal studies often used injection routes to produce the pathology seen in humans, and there is no set of standard toxicology studies (e.g., subchronic, chronic, developmental, multigeneration) of aluminum; this is partly due to the GRAS status of aluminum food additives. Oral exposure studies in animals began to appear in the literature during the past 10-15 years, but these aluminum studies were designed to address basic science questions and not serve as a basis for risk evaluation. Additionally, information on aluminum content in the base diet is not reported in many of the studies. As discussed in the introduction to Section 2.2.2, commercial laboratory animal feeds contain high levels of aluminum that can significantly contribute to total experimental exposure. 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 feed concentrations of 250 and 350 ppm aluminum reported in some rat and mouse studies, respectively (Colomina et al. 1998; Domingo et al. 1993; Oteiza et al. 1993), estimated doses of 25 mg Al/kg/day (rats) and 68 mg Al/kg/day (mice), which represents

significant portions of lethal doses for these species, could be provided by diet alone. 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, are not suitable for comparing with effect levels from studies that used diets with known amounts of aluminum, and are inappropriate for MRL consideration. Concern for the adequacy of NOAEL and LOAEL values for aluminum is greatest for sensitive neurotoxic effects, which could occur in rodents at aluminum intake levels close to those provided by commercial diet alone.

No acute- or chronic-duration oral MRLs were derived for aluminum due to insufficient data on NOAELs and LOAELs for these exposure categories. This data insufficiency is due to an inadequate number of studies having sufficient dose information (most did not report the level of aluminum in the base diets) and/or information on sensitive toxicity end points. Acute oral studies of aluminum are essentially limited to lethality (LD_{50}) determinations and studies of growth and malformation end points in rats and mice. Developmental effects associated with acute (i.e., gestation-only) exposure to aluminum mainly include reduced fetal body weight and increased fetal skeletal variations (Bernuzzi et al. 1986b, 1989b; Colomina et al. 1992; Gomez et al. 1991; Misawa and Shigeta 1992). Information on chronic oral toxicity of aluminum is essentially limited to lifetime studies in rats and mice (Oneda et al. 1994; Schroeder and Mitchener 1975a, 1975b) that found no histopathological changes, but did not evaluate known or possible sensitive end points (e.g., neurotoxicity and skeletal effects).

*An MRL of 2.0 mg Al/kg/day has been derived for intermediate-duration oral exposure to aluminum and its compounds.

Comparison of effect levels in mice and rats from intermediate-duration studies with adequate dose information (i.e., doses that include aluminum in the base diet), and with no exposure to moieties which may greatly enhance bioavailability and/or contribute to toxicity (e.g., citrate and nitrate), indicate that neurotoxicity is the critical end point of concern for aluminum Although neurotoxicity of aluminum has not been established in people with normal renal function, the data for dialysis encephalopathy (as well as some occupational studies) establish that the human nervous system is susceptible to aluminum, and neurotoxicity is a well-documented effect of aluminum in orally-exposed in mice and rats. Neurobehavioral impairments have been observed in animals orally-exposed for intermediate durations, as well as in weanlings and young animals exposed by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone. The lowest tested reliable neurotoxic doses (i.e., among those that include base dietary aluminum) are in

mice. The most frequently affected behaviors in mice exposed as adults, or exposed during development and tested as adults, included decreases in motor activity, grip strength, and startle responsiveness, and neurobehavioral effects most commonly found in exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity, indicating that the spectrum of effects is different in adult and developing animals (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995). Neurobehavioral effects that have been associated with oral exposure to aluminum in rats include impairments in motor coordination and operant learning (Bernuzzi et al. 1989a; Bilkei-Gorzo 1993; Cherroret et al. 1992; Commissaris et al. 1982; Muller et al. 1990, 1993a; Thorne et al. 1986, 1987).

A LOAEL of 130 mg Al/kg/day is identified for decreased spontaneous motor activity in adult mice that were exposed to dietary aluminum lactate for 6 weeks (Golub et al. 1989). Overall activity was reduced about 20% compared to controls due to less frequent occurrence of the highest activity states, which usually occurred during the diurnal period of peak activity. The duration of peak activity periods was also reduced (about 35% compared to controls) and vertical movement (primarily rearing and feeding) was more affected than horizontal movement (primarily locomotion), but there was no shift in the diurnal activity cycle or any prolonged periods of inactivity. No effects on motor activity occurred at 62 mg Al/kg/day, indicating that this is the NOAEL. Mice that ingested doses higher than 130 mg Al/kg/day as aluminum chloride for 49 days or aluminum lactate for 90 days, and were tested using a standardized neurotoxicity screening battery, also showed decreased motor activity, as well as decreased grip strength and startle responsiveness (Golub et al. 1992b; Oteiza et al. 1993). Depressed motor activity has also been observed in exposed adult rats, suggesting that this effect is a consistent neurobehavioral outcome associated with ingested aluminum (Golub et al. 1992b).

Neurodevelopmental effects occurred at dose levels similar to the 130 mg Al/kg/day LOAEL for neurotoxicity in adult mice. A LOAEL of 155 mg Al/kg/day is identified for neurotoxicity in the offspring of mice exposed to dietary aluminum lactate during gestation and lactation, and tested as weanlings or adults (Donald et al. 1989; Golub et al. 1995). Lower dose levels were not tested in these studies, precluding determination of a NOAEL for neurodevelopmental toxicity. Effects observed at the 155 mg Al/kg/day neurodevelopmental LOAEL included increased fore- and hindlimb grip strengths, landing foot splay, and latency to remove tail from hot water in offspring tested as weanlings (Donald et al. 1989), and decreased grip strength, decreased air-puff startle response, and improved performance during operant training in offspring tested as adults (Golub et al. 1995).

Effects were reported at doses lower than the 130 mg Al/kg/day neurotoxicity LOAEL in several studies (Colomina et al. 1992; Domingo et al. 1987c; Florence et al. 1994; Paternain et al. 1988; Varner et al. 1993, 1994, 1998), but the LOAELs from these studies are inappropriate for MRL consideration. Colomina et al. (1992) found reduced fetal body weight and increased incidences of cleft palate and skeletal variations in fetuses of mice exposed to an estimated total dose of 83 mg Al/kg as aluminum lactate by gavage plus base dietary aluminum on Gd 6-15. Paternain et al. (1988) observed decreased maternal body weight and an increased incidence of skeletal variations, but no consistent effects on external or visceral malformations, in rats exposed to estimated total doses of 38-77 mg Al/kg/day as aluminum nitrate by gavage plus base dietary aluminum on Gd 6-14. Similar exposure to 38-77 mg Al/kg/day as aluminum nitrate in a single generation reproduction study caused transient reduction in growth of rat offspring (Domingo et al. 1987c). These studies are inappropriate for MRL consideration due to concern for the method of oral exposure since Savage does not realistically represent environmental aluminum intake. In particular, effect levels in the gavage studies may be unnaturally low compared to dietary exposure because the skeletal changes could be related to phosphate depletion caused by excess binding with aluminum in the maternal gut due to the bolus treatments. Additionally, the relatively low LOAELs in the Paternain et al. (1988) and Domingo et al. (1987c) studies may be related to the use of aluminum nitrate because data in rats indicate that aluminum from aluminum nitrate is twice as bioavailable as from aluminum chloride (Yokel and McNamara 1988) (see Section 2.3.1.2). Other studies found histopathologic changes in the brain of rats exposed by diet to 92 mg Al/kg/day as aluminum chloride in combination with an unnaturally high level of citrate for 6 months (Florence et al. 1994), or to 12 mg Al/kg/day as aluminum fluoride in drinking water and the base diet for 45-52 weeks (Varner et al. 1993, 1994, 1998). Unusual exposure conditions preclude identifying relevant LOAELs for brain histopathology from these studies. In particular, the effects appear to be due to greatly enhanced bioavailability because both studies were designed to maximize the uptake of aluminum (i.e., by the massive co-exposure to citrate, and the use of aluminum fluoride to form an optimum fluoroaluminum species capable of crossing the gut and blood-brain vascular barriers).

Considering the studies with adequate dose information and appropriate exposure conditions, including compound bioavailability, the 62 mg Al/kg/day NOAEL for neurotoxicity in adult mice (Golub et al. 1989) is the most suitable basis for calculating an intermediate MRL. This NOAEL was identified using aluminum lactate, a representative form of aluminum that is intermediate in bioavailability between inorganic complexes such as aluminum hydroxide and carboxylic acid complexes such as aluminum citrate. Using the 62 mg Al/kg/day NOAEL and an uncertainty factor of 30 (3 for extrapolation from

animals to humans and 10 for human variability), the MRL is calculated to be 2.0 mg Al/kg/day. An uncertainty factor of three was used for interspecies extrapolation because daily aluminum intake by humans in antacids is approximately 3-5 times lower than LD_{50} values for aluminum compounds in rats and mice, suggesting that humans are not more sensitive than rodents. The intermediate-duration MRL of 2.0 mg Al/kg/day is approximately 6-35 times lower than typical daily intake of aluminum from long-term use of antacids (12-7 1 mg Al/kg/day [Lione 1985b]), and approximately 20 times higher than recent estimates of adult dietary intake of aluminum (0.10-0.12 mg Al/kg/day [Pennington and Schoen 19951). Given the apparent lo-fold range in the gastrointestinal absorption of aluminum depending on compound, and considering that the bioavailability of aluminum in antacid preparations may be different than that of the aluminum lactate used in the Golub et al. (1989) study, information on the bioavailability of the form ingested should be considered in the use of the MRL. The MRL represents an estimate of daily human exposure that is likely to be without an appreciable risk of adverse health effects. It is not intended to support clean-up or other regulatory action, but to serve as a guideline for health assessors to consider when making recommendations to protect populations living in the vicinity of a hazardous waste site or substance emission.

Death. Aluminum is not thought to be life-threatening to healthy humans. Studies of people receiving extremely high doses of oral aluminum in antacids have not shown any human deaths from aluminum However, in the past, aluminum-related deaths have been reported for persons with renal disease dialyzed with aluminum-containing solutions, uremic patients exposed to dietary aluminum hydroxide to treat hyperphosphatemia and sodium citrate to correct metabolic acidosis (Kirschbaum and Schoolwerth 1989), and workers exposed by inhalation to fine powders of aluminum metal. Only very large doses (hundreds of mg/kg) of aluminum cause death in laboratory animals.

Systemic Effects

Respiratory Effects. There are numerous reports of respiratory effects in workers chronically exposed to airborne aluminum In many cases, the workers were also exposed to a number of other toxicants which may have been the causative agent. Pulmonary fibrosis has been observed in some groups workers exposed to fine aluminum dust (pyropowder) (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958). The pulmonary fibrosis has only been associated with pyropowders utilizing nonpolar aliphatic oil lubricants, such as mineral oil; exposure to pyropowder which used stearic acid as a

lubricant does not result in fibrosis (Crombie et al. 1944; Meiklejohn and Posner 1957; Posner and Kennedy 1967).

A number of respiratory effects have been observed in animals, including increases in the number of alveolar macrophages, and granulomatous foci in the lungs and peribronchial lymph nodes (Drew et al. 1974; Steinhagen et al. 1978). These respiratory effects are typically associated with inhalation of particulates and lung overload and may not be directly related to aluminum-induced toxicity to lung tissue.

Cardiovascular Effects. Altered heart rate has been observed in humans following oral exposure to aluminum phosphide (Chopra et al. 1986; Khosla et al. 1988); however, the cardiotoxicity probably resulted from exposure to phosphine gas, rapidly released from aluminum phosphide in the mouth and stomach, rather than the aluminum Oral exposure in rodents and dogs to other forms of aluminum has not been shown to affect heart weight or histology.

Gastrointestinal Effects. In humans, acute-duration oral exposure to unknown amounts of aluminum sulfate was reported to cause gastric distress (Ward 1989). Acute oral exposure to unknown amounts of aluminum phosphide produced vomiting and abdominal cramping (Chopra et al. 1986; Khosla et al. 1988).

Hematological Effects. Hematological effects have not been observed in humans or animals with normal renal function. However, microcytic, hypochromatic anemia has been observed in individuals with impaired renal function. The anemia is unresponsive to iron therapy. The severity of the anemia correlates with plasma and erythrocyte aluminum levels and can be reversed by terminating aluminum exposure and chelation therapy with DFO.

Musculoskeletal Effects. The occurrence of osteomalacia has been well-documented in uremic adults and children (Griswold et al. 1983; King et al. 1981; Mayor et al. 1985; Sherrard and Andress 1989; Wills and Savory 1989). The osteomalacia is directly related to the markedly increased aluminum levels in the bone. This type of aluminum-induced osteomalacia is not likely to occur in healthy individuals; in uremic patients, the impaired renal function and inefficient removal of aluminum during dialysis results in significantly increased aluminum body burdens. However, an osteomalacia associated with hypophosphatemia has been observed in otherwise healthy individuals following long-term use of

aluminum-containing antacids for the treatment of gastrointestinal disorders (Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998). In these cases, the osteomalacia is not related to aluminum deposition in bone, rather the aluminum binds with dietary phosphorus in the gastrointestinal tract and prevents its absorption. 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). High levels of copper and lead were also present in drinking water; thus, it is difficult to ascribe this nonspecific symptom to aluminum exposure. No histological alterations in the have been observed in the tibia or femur of rats and mice orally exposed to aluminum for 10 to 24 months (Hackenberg 1972; Konishi et al. 1996; Ondreicka et al. 1966).

Hepatic Effects. Acute oral aluminum exposure is not hepatotoxic. Intermediate-duration oral exposure has generally been reported to be nonhepatotoxic, but relatively minor hepatotoxicity has been occasionally observed. Hyperemia and periportal lymphomonocytic 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). These effects were not observed at higher doses with longer exposures (Gomez et al. 1986).

Endocrine Effects. Little is known about the effects of aluminum on endocrine systems. The oral administration of sodium aluminum phosphate to male and female Beagle dogs for 6 months did not alter thyroid, adrenal, or pituitary gland weight or microanatomy (Katz et al. 1984; Pettersen et al. 1990). These organs were also normal in male and female Wistar rats fed a diet containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972).

Renal Effects. 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; Koshla et al. 1988). The majority of animal studies indicate aluminum exposure does not affect renal weight or histology.

Dermal Effects. Skin rashes were commonly reported by 48 people who drank water containing unknown amounts of aluminum sulfate (Ward 1989). 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 some types of antiperspirants and develop skin rashes, which may be

caused by the aluminum (Brusewitz 1984). 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-O. 1 g) or aluminum nitrate (0.006-0.013 g) applied 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.

Ocular Effects. Limited information suggests aluminum does not cause ocular toxicity (Hackenberg

1972; Katz et al. 1984; Steinhagen et al. 1978).

Body Weight Effects. Aluminum-related effects on body weight are equivocal and, for *ad libitum* oral

water exposure, may be related to the palatability of the test solution. Decreases in body weight gain

have been observed in hamsters exposed to 3, 10, or 33 mg Al/m^3 as alchlor (Drew et al. 1974) and in rats

exposed to 6.1 mg Al/m^3 as aluminum chlorhydrate for 24 months (Stone et al. 1979). However, other

acute-, intermediate-, and chronic-duration studies did not find any significant alterations in rats or

guinea pigs exposed to similar concentrations of aluminum chlorhydrate (Steinhagen et al. 1978; Stone et

al. 1979) or 0.37-0.41 mg Al/m^3 as aluminum chloride or aluminum fluoride dust (Finelli et al. 198 1).

A 19% decrease in maternal body weight gain was observed in pregnant Sprague-Dawley rats given

38 mg Al/kg/day as aluminum nitrate via gavage on Gd 6-14 (Paternain et al. 1988). Decreased body

weight was observed in male Wistar rats that consumed 273 mg Al/kg/day as aluminum sulfate in the diet

for 8 days, but food consumption was also decreased in this study (Ondreicka et al. 1966). No body

weight effects were observed in male or pregnant female Wistar rats acutely exposed to up to

192 mg Al/kg as aluminum chloride either in feed (Bernuzzi et al. 1986b) or drinking water (Ondreicka et

al. 1966).

In general, no adverse body weight effects have been observed in rats, mice, or dogs following

intermediate-duration oral administration of aluminum compounds (Domingo et al. 1987b; Donald et al.

1989; Golub et al. 1989; Gomez et al. 1986; Ondreicka et al. 1966). A 19% decrease in maternal body

weight on postnatal day 20 was observed in Swiss Webster mice that consumed approximately

500-1,000 mg Al/kg/day as aluminum lactate in the diet throughout gestation and lactation (Golub et al.

1987), but this appears to be related to a nutritional insufficiency in the test diet. Transient body weight

decreases were observed in male Sprague-Dawley rats given 346 mg Al/kg/day as aluminum sulfate in

drinking water for 4 weeks (Connor et al. 1989).

No body weight effects were observed in rats or mice following chronic-duration exposure to aluminum compounds (Hackenberg 1972; Ondreicka et al. 1966; Oneda et al. 1994; Schroeder and Mitchener 1975a).

Male Long Evans rat pups administered aluminum hydroxide (14 mg Al/kg/day) in water for 60 days beginning on postnatal day 22 exhibited decreased body weights (Thorne et al. 1987). This was not related to a direct effect of aluminum, but to the palatability of the water. The effects on body weight during the initial rejection of the aluminum-treated water were so severe that body weights in the treated group never recovered to control levels. A palatability-related marked reduction in body weight was also observed in dogs exposed to aluminum potassium sulfate in the diet (Pettersen et al. 1990).

Metabolic Effects. No adverse effect on phosphate metabolism was identified in humans following intermediate-duration inhalation exposure to aluminum fumes or dust (Mussi et al. 1984).

Other Systemic Effects. Swiss Webster mice that consumed 130 mg Al/kg/day as aluminum lactate in the diet for 6 weeks had an increased incidence of fur loss (Golub et al. 1989); this effect was not repeated in later studies.

Immunological and Lymphoreticular Effects. 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 (Bohler-Sommeregger and Lindemayr 1986; Veien et al. 1986). Sarcoid-like epithelioid granulomas were found in the lungs of a 32-year-old man chronically exposed to metallic aluminum and aluminum dust (De Vuyst et al. 1987). Immunological testing failed to confirm sarcoidosis, but did find helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in presence of the soluble aluminum compound. Additional testing one year after termination of exposure indicated the man no longer had alveolitis.

Granulomatous lesions have been observed in the hilar and peribronchial lymph nodes of animals exposed to aluminum powder (Thomson et al. 1986) or aluminum chlorhydrate (Steinhagen et al. 1978). Oral studies in mice found that developmental exposure to aluminum impaired the immune system in young animals (Golub et al. 1993b; Yoshida et al. 1989). These data suggest that immunotoxicity of aluminum may be a concern in some exposure scenarios.

Neurological Effects. Aluminum is generally considered to be a neurotoxic agent, and effects have been observed in humans and animals following inhalation-, oral-, and parenteral-exposure. A number of occupational studies have investigated the neurotoxic potential of airborne aluminum in chronically exposed workers; the workers were exposed to aluminum dust in the form of McIntyre powder, aluminum dust and fumes in potrooms, and aluminum fumes during welding. Collectively, these studies provide suggestive evidence that there may be a relationship between chronic aluminum exposure and subclinical neurological effects such as impairment on neurobehavioral tests for psychomotor and cognitive performance and an increased incidence of subjective neurological symptoms (Hanninen et al. 1974; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjögren et al. 1996; White et al. 1992). With the exception of some isolated cases (for example, McLaughlin et al. 1962), inhalation exposure has not been associated with overt symptoms of neurotoxicity. A common limitation of the occupational exposure studies is that aluminum exposure has been well characterized. The available animal inhalation studies (Finelli et al. 1981; Steirihagen et al. 1978; Stone et al. 1979) are inadequate for assessing aluminum-induced neurotoxicity because the only neurological end points examined were brain weight and histology of the brain. The studies were not designed to assess subtle neurological alterations.

A possible relationship between aluminum and Alzheimer's disease was proposed over 30 years ago; this association is still highly controversial and there is little consensus regarding current evidence. As reviewed by Armstrong et al. (1996), the basis of this relationship was the finding of increased aluminum levels in the brains of individuals with Alzheimer's disease, neurofibrillary lesions in experimental animals, and the findings that aluminum interacts with various components of the pathological lesions in the brains of individuals with Alzheimer's disease. 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. There is some evidence to suggest that aluminum has an effect on production of the protein tau which is an important constituent of helical and straight filaments which comprise the neurofibrillary tangles, and that aluminum can influence amyloid precursor protein or promote the polymerization of the β-amyloid fragment. However, even if it could be established that aluminum was important in the production of the protein tau and/or β-amyloid, it would not necessarily indicate a primary role for aluminum in Alzheimer's disease pathology.

Individuals with Alzheimer's disease were reported to have more aluminum than usual in the neurofibrillary tangles in the hippocampus or cortical parts of their brains, but normal (as compared to control) levels of aluminum in hair, serum or spinal fluid (Shore and Wyatt 1983). This evidence suggests that Alzheimer's patients may have a reduced blood-brain barrier for aluminum; several investigators (Banks et al. 1988; Liss and Thorton 1986; Shore and Wyatt 1983) suggest that the altered blood-brain barrier in Alzheimer's disease may be a consequence and not the cause of the disease. More recent studies (Landsberg et al. 1992; Makjanic et al. 1998) utilizing nuclear microscopy without chemical staining techniques did not find increased aluminum levels in the pyramidal neurons in brain tissue or in plaque cores of patients with Alzheimer's disease. When conventional techniques for tissue preparation (fixation and osmication) and nuclear microscopy were used, elevated aluminum levels were detected, suggesting that the staining technique introduced contamination or produced elemental redistribution, and that aluminum is not associated with Alzheimer's disease (Makjanic et al. 1998).

Epidemiology and case-control studies that examined the possible relationship between Alzheimer's disease and aluminum report conflicting results. No increases in Alzheimer's disease-related deaths were observed in workers exposed to airborne aluminum (Salib and Hillier 1996). Some studies designed to show the possible relationship between oral exposure to aluminum and the incidence of Alzheimer's disease have found significant associations (Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990), but other studies did not find a significant relationship (Forster et al. 1995; Martyn et al. 1997; Wettstein et al. 199 1). Forbes and McLachlan (1996) suggest that the relationship between aluminum and Alzheimer's disease is not linear, but rather forms a J- or U-shaped curve, and that the association may only exist at higher exposure levels (aluminum levels in water of $\geq$ 1 mg/L). However, individuals on renal dialysis who have received large amounts of aluminum orally or intravenously also can develop encephalopathy, but they do not develop the type of histopathology (tangles and plaques) associated with Alzheimer's disease (Hamdy 1990). There is no consensus on whether, collectively, the human studies provide sufficient evidence for suggesting an association between aluminum and Alzbeimer's disease; the human data do not establish cause and effect.

A sufficient animal model for human Alzheimer's disease has not been developed. Although animals, particularly rabbits, exposed to aluminum develop neurofibrillary tangles (Crapper-McLachlan and Farnell 1985b), the neurofibrillary tangles are both structurally and biochemically different from those associated with Alzheimer's disease (Per1 and Brody 1980). Some recently developed animal models appear to mimic several aspects of the disease, such as co-injection of aluminum and paired helical

filaments into a rodent brain inducing the aggregation of other plaque and neurofibrillary tangles and injection of aluminum salts inducing the accumulation of neurofilaments in swollen parikarya and proximal axonal enlargements of certain neuronal populations in the brain and spinal cord (as discussed in Singer et al. 1997). Alzheimer's disease appears to be a heterogenous disease with numerous risk factors or etiologies including genetic and environmental factors (Gautrin and Gauthier 1989; King et al. 198 1; St. George-Hyslop 1995; Schellenberg 1995a, 1995b). Evidence is equivocal on the possible relationship between aluminum and Alzheimer's disease, and the animal data are inadequate to support a conclusion.

Amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia (PD) are neurodegenerative diseases which 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 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.

Whereas a causal role for aluminum in the etiology of Alzheimer's and other human neurodegenerative diseases has not been established, data on dialyzed patients provide convincing evidence that aluminum is the causative agent in "dialysis dementia". Dialysis dementia is a degenerative neurological syndrome, characterized by the gradual loss of motor, speech, and cognitive functions, that has developed in patients who received long term hemodialysis for chronic renal failure (Alfrey 1993b). It is caused by exposure to aluminum in dialysate and/or to high oral doses of aluminum used as phosphate binders to control hyperphosphatemia in uremic patients, has occurred in people with renal failure who were not dialyzed,

and has been observed in infants and young children as well as adults (Alfrey 1993b; Griswold et al. 1983).

The neurotoxic potential of aluminum is well-established in experimental animals. Neurodegenerative changes in the brain, manifested as intraneuronal hyperphosphorylated neurotilamentous aggregates, is a characteristic response to aluminum in certain species and nonnatural exposure situations generally involving direct application to brain tissue, particularly intracerebral and intracisternal administration and *in vitro* incubation in rabbits, cats, ferrets, and nonhuman primates (Erasmus et al. 1993; Jope and Johnson 1992). Oral studies in rats and mice found no significant histopathological changes in the brain under typical exposure conditions (i.e., when bioavailability of aluminum was not intentionally maximized, such as by concurrent exposure to citrate) (Dixon et al. 1979; Domingo et al. 1987b; Florence et al. 1994; Gomez et al. 1986; La1 et al. 1993; Varner et al. 1993, 1994, 1998), although neuromotor, behavioral, and cognitive changes have been observed consistently in these species. Neurobehavioral deficits occurred in mice exposed via diet as adults, as well as in weanling and young developing annuals exposed by gestation, combined gestation and lactation, combined gestation and lactation followed by postweaning ingestion, or postweaning ingestion alone (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 19928, 1994, 1995; Oteiza et al. 1993). The most frequently affected behaviors in mice exposed as adults, or exposed during development and tested as adults, included decreases in motor activity, grip strength, and startle responsiveness, The effects most commonIy found in exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity. The reason for the different effects on grip strength (decreased and increased) is unclear, but could be related to age of the animal at exposure and/or testing. Assessment of grip strength is a routine method for assessing neuromuscular function in rodents (Meyer et al. 1979). Orally-exposed rats have shown impairments in motor coordination and operant learning (Bernuzzi et al. 1989a; Bilkei-Gorzo 1993; Bowdler et al. 1979; Cherroret et al. 1992; Commissaris et al. 1982; Connor et al. 1988, 1989; Jope and Johnson 1992; La1 et al. 1993; Muller et al. 1990, 1993a; Thorne et al. 1986, 1987), while others have shown more rapid learning (Golub et al. 1998).

Considering the evidence for neurobehavioral effects of aluminum in humans exposed occupationally, and during dialysis therapy, and in animals exposed orally and by various unnatural routes of exposure, it is evident that neurotoxicity is an important effect of concern for aluminum Comparison of effect levels in mice and rats from intermediate-duration oral studies with adequate dose information (i.e., doses that include aluminum in the base diet), and exposure conditions that did not unnaturally enhance

bioavailability (e.g., without co-ingestion of high levels of citrate or exposure to highly bioavailable aluminum compounds), indicate that neurotoxicity is the most sensitive end point for aluminum. A LOAEL of 130 mg Al/kg/day was identified for decreased spontaneous motor activity in adult mice that were exposed to dietary aluminum lactate for 6 weeks (Golub et al. 1989). Observations of depressed motor activity in other studies of mice, as well as in rats, suggest that this effect is a consistent neurobehavioral outcome associated with ingested aluminum and an appropriate basis for human risk evaluation. The NOAEL for decreased spontaneous motor activity, 62 mg Al/kg/day, was used to derive the intermediate duration MRL for oral exposure to aluminum. The MRL is 6-35 times lower and $\approx$20 times higher than daily intake of aluminum from long-term antacid and dietary exposure, respectively (Lione 1985b; Pennington and Schoen 1995). Given the preponderance of evidence that aluminum is neurotoxic, considering that the gastrointestinal absorption of aluminum compounds may vary 10-fold and the bioavailability of aluminum in antacid preparations and human diet may be different than that of the aluminum lactate used in the MRL study, and recognizing that the neurotoxicity of aluminum-containing antacids and other medications has not been studied in people with normal renal function, there appears to be a potential for neurotoxic effects of aluminum in healthy individuals.

Reproductive Effects. There are no human studies that indicate that aluminum affects reproduction. Oral studies in male and female animals show some inconsistencies, as summarized below, but generally indicate that reproductive toxicity is not an effect of concern for aluminum-exposed people. An increased incidence of resorptions occurred in mice that were gestationally exposed to aluminum chloride by gavage (Crammer et al. 1986), but no reproductive effects were found in rats similarly exposed to aluminum chloride, hydroxide, or citrate (Gomez et al. 1991; Misawa and Shigeta 1992). The inconsistent findings in these acute-duration studies may reflect differences in susceptibility among different strains/species of animals or compound differences in toxicity or bioavailability. Offspring of rats that were gavaged with aluminum lactate during gestation had a transient irregularity of the oestrus cycle, but no other effects on end points of female reproductive system development (gonad weights, anogenital distance, time to puberty, duration of induced pseudopregnancy, or numbers of superovulated oocytes) were induced (Agarwal et al. 1996). An intermediate-duration study found no effects on fertility or other general reproductive indices in female rats that were exposed to aluminum nitrate by gavage from 14 days prior to mating (with treated males) through weaning of the offspring (Domingo et al. 1987c). Sperm count was reported to be decreased in male rats exposed to aluminum chloride for 6-12 months (Krasovskii et al. 1979), but reproductive function was not evaluated, and no adverse reproductive effects were seen in male rats, as assessed by plasma gonadotropin levels, histopathological

evaluation and serial matings, following exposure to aluminum chloride in the drinking water for up to 90 days (Dixon et al. 1979). No organ weight or histological changes were observed in the gonads of male and female Beagle dogs that were exposed to sodium aluminum phosphate in the diet for 6 months (Katz et al. 1984; Pettersen et al. 1990).

Developmental Effects. Studies in human infants indicate that only certain children are affected by aluminum. Excessive aluminum accumulation and encephalopathy may occur in premature infants with reduced renal function given dialysis with aluminum-containing intravenous fluid (Polinsky and Gruskin 1984; Sedman et al. 1985). Bone disease has also been reported in infants with renal failure who were treated orally with aluminum hydroxide (Andreoli et al. 1984).

Developmental toxicity studies in animals have shown that oral gestational exposure to 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). Given the relatively high bioavailability of the developmentally toxic forms of aluminum and bolus administration, it is possible that the skeletal changes are consequent to phosphate depletion caused by excess binding with aluminum in the maternal gut. Neurobehavioral deficits have been observed in oral studies with 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 (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995; Muller et al. 1990). The most frequently affected behaviors in exposed weanlings and young animals included increases in grip strength and landing foot splay, decreased thermal sensitivity, and negative geotaxis. The effects most commonly found in mice exposed during development and tested as adults, or tested only as adults, included decreases in motor activity, grip strength, and startle responsiveness, indicating that the pattern of neurobehavioral impairment in developing animals was different from adults. Studies using intraperitoneal injections in rats (Benett et al. 1973, intravenous injections in mice (Wide 1984), and subcutaneous injections in rabbits (Yokel 1985, 1987) similarly found that aluminum can cause delays in neurobehavioral and skeletal development in pups. Teratogenic changes have not been associated with gestational exposure to aluminum

There is sufficient evidence from oral studies in animals to conclude that aluminum is potentially developmentally toxic in humans, especially under conditions in which aluminum is particularly bioavailable or in which renal dysfunction facilitates aluminum accumulation. There is concern for neurodevelopmental effects because aluminum-exposed animals appear to be more sensitive to these effects than skeletal changes, especially under natural (i.e., nonbolus) oral exposure conditions. Since it is well-documented that gastrointestinal absorption of aluminum may be significantly enhanced by certain normal dietary constituents such as citrate, the available developmental toxicity data suggest that it would be prudent to avoid excess intake of aluminum-containing compounds during gestation and lactation.

Genotoxic Effects. Some of the neurotoxic effects of aluminum can be partially explained by its genotoxic and subcellular effects on DNA in neurons and other cells demonstrated *in vitro.* These effects have been summarized (Crapper-McLachlan 1989; Crapper-McLachlan and Farnell 1985b). They include nuclear effects such as binding to DNA phosphates and bases, increasing histone-DNA binding, altering sister chromatid exchange, and decreasing cell division. Cytoplasmic effects include conformational changes in calmodulin and increasing intracellular calcium; although these effects may not specifically be caused by interactions with DNA, they will signiftcantly affect neuronal functions. Since aluminum accumulates in DNA structures in the cell nucleus, it may alter protein-DNA interactions. This is particularly important for the calcium-binding protein, calmodulin. This can affect the calcium-modulated second messenger system which is activated by neurotransmitters. Interference with DNA and protein synthesis may also be part of the mechanism that is involved in the creation of the neural filaments that compose the neurofibrillary tangles seen in Alzheimer's patients (Bertholf 1987).

Data from *in vivo* (intraperitoneal) exposures of mice to aluminum chloride also indicate that this compound is clastogenic. Mice were injected intraperitoneally with 0.01, 0.05, or 0.1 molar aluminum chloride, and bone marrow cells were examined for chromosomal aberrations. There was a significant increase in chromatid-type aberrations over the controls, and these occurred in a nonrandom distribution over the chromosome complement (Manna and Das 1972). No dose-response relationship could be demonstrated, although the highest dose of aluminum chloride did produce the greatest number of aberrations. These data are supported by *in vitro* studies that show that aluminum chloride causes cross-linking of chromosomal proteins and DNA in ascites hepatoma cells from Sprague-Dawley rats (Wedrychowski et al. 1986). Cross-linking agents frequently produce clastogenic effects due, presumably, to conformational distortions that prohibit proper DNA replication. Micromolar aluminum

levels have also been shown to reduce ^{3}H-thymidine incorporation in a transformed cell line (UMR 106-01), which indicates that aluminum may impede cell cycle progression (Blair et al. 1989). Generalizations to normal, untransformed cells, however, cannot be made.

There are also data that indicate that aluminum does not directly interact with DNA in mutagenicity tests. These data come from negative transformation assays in Syrian hamster cells (DiPaolo and Casto 1979), negative ret (recombination repair) assays in *Bacillus subtilis* (Kanematsu et al. 1980), and negative *Ames* assays in *Salmonella typhimurium* (Marzin and Phi 1985). These data are summarized in Table 2-4.

Cancer. Aluminum is not known to cause cancer in humans. Some workers in the aluminum industry have had a higher-than-expected cancer mortality rate, but this is probably due to the other potent carcinogens to which they are exposed, such as PAHs and tobacco smoke (Milham 1979; Mur et al. 1987; Rockette and Arena 1983; Theriault et al. 1984a).

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 due to the presence of known carcinogens (e.g., PAHs) in the workplace and is not due to aluminum or its compounds.

Available cancer studies of aluminum in animals do not indicate that aluminum is carcinogenic (Hackenberg 1972; Oneda et al. 1994; Pigott et al. 1981; Schroeder and Mitchener 1975a, 1975b).

2.6 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 due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Table 2-4. Genotoxicity of Aluminum *In Vitro*

Species (test system)	End point	Results[a]	Reference
Salmonella typhimurium	Gene mutation	–	Marzin and Phi 1985
Bacillus subtilis	Rec assay	–	Kanematsu et al. 1980
Rat osteoblasts	Thymidine incorporation	+	Blair et al. 1989
Syrian hamster embryo cells	Transformation assay	–	DiPaolo and Casto 1979
Rat ascites hepatoma cells	DNA cross-linking	+	Wedrychowski et al. 1986

[a]– = negative result; + = positive result

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 5.6 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 and 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 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 the newborn who has a low glomerular filtration rate and has 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 while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per

kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for 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 (Griswold et al. 1983; Andreoli et al. 1984). 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. Another subpopulation of children that may be particularly sensitive to the toxicity of aluminum is preterm infants. The observed elevated plasma aluminum levels are probably due to the limited renal capacity of preterm infants to excrete aluminum (Tsou et al. 1991). Bougle et al. (199 1) 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 were also found. Growth failure, hypotonia, muscle weakness, and craniosynotosis have been observed 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).

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 (Donald et al. 1989; Golub and Germann 1998; 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. Although Thorne et al. (1986, 1987) did not find a significant relationship between aluminum exposure and open field activity or performance on learning tasks, they did find a correlation between activity and performance and brain aluminum content, which suggested that younger animals (weanling rats exposed for 60 days to dietary aluminum) were less affected than the adults (exposed to dietary aluminum for 30 days). Skeletal variations such as delayed ossification have also been observed in oral developmental toxicity studies (Colornina et al. 1992; Gomez et al. 1991; Paternain et al. 1988).

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 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 aluminumlactate, but was not seen in neonatal or adult rabbits (Yokel 1987).

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). There is also evidence that oral or parenteral exposure to aluminum can result in elevated levels in breast milk (Yokel and McNamara 1985). 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).

A recent 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.

2.7 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 (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or 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 2.7.1.

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 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organisms 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 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Aluminum

Aluminum can be measured in the blood, urine, and feces (see Chapter 6 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.

2.7.2 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.

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

2.8 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 1993b; 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 2.3.1.2 and 2.4.1, 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). Similarly, aluminum oxide powders were administered via inhalation to miners as a means of prophylaxis against silicosis (Rifat et al. 1990; S tokinger 198 1); the effectiveness of this treatment is uncertain, but no lung damage or other ill effects have been observed. Aluminum hydroxide, commonly found in antacids, can decrease the intestinal absorption of fluoride and phosphorus in humans (Carmichael et al. 1984; Chines and Pacitici 1990; Pivnick et al. 1995; Spencer et al. 1980; Woodson 1998).

As discussed in Section 2.4.1, there are some data that suggest that aluminum absorption can be enhanced by parathyroid hormone and vitamin D, but the data are inconclusive.

There are some data showing age-related effects of the dietary concentration of aluminum on the retention and localization of the essential elements copper, iron, zinc, calcium magnesium and manganese (Sanchez et al. 1997). 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. In older animals, there was an increase of calcium magnesium manganese, and zinc in the testes and spleen. However, the significance, if any, of these changes is not clear.

2.9 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 may result in reduced detoxification or excretion of aluminum or compromised function of target organs affected by aluminum. Populations who are at greater risk due to their unusually high exposure to aluminum are discussed in Section 5.7, Populations With Potentially High Exposure.

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). Pre-term infants may also be particularly sensitive to the toxicity of aluminum due to reduced renal capacity (Tsou et al. 1991)

2.10 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.

Ellenhorn, MS, Barceloux, DG. 1988. Medical toxicology diagnosis and treatment of human poisoning. New York, NY (Elsevier). 1009-1011.

Haddad, CM, Winchester, JF. 1990. Clinical Management of poisoning and drug overdose. 2nd ed. Philadelphia, PA (WB Saunders) 1029.

2.10.1 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.

2.10.2 Reducing Body Burden

In persons with normal renal function, the body burden can be reduced simply by limiting exposure. Avoidance of aluminum-containing products is also recommended for patients with renal failure; in particular, use of nonaluminum containing phosphate binding gels, avoidance of co-administration of aluminum compounds and citrate compounds, and use of aluminum free dialysate and parenteral solutions. Administration of a chelator such as desferrioxamine (DFO) may also help reduce aluminum body burden. DFO is a chelating agent that reduces the ability of metals to bind to biological tissues. 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 and Winchester 1990). DFO is also used in dialyzed uremic patients for the treatment of neurological, hematopoietic, and skeletal toxicity. 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.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action for aluminum toxicity is not known; thus there are no known ways of interfering with its mechanism of action.

2.11 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.

2.11.1 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 2-4. 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* (ATSDR 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. 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.

2. HEALTH EFFECTS

Figure 2-4. Existing Information on Health Effects of Aluminum and Compounds

Human

Animal

● Existing Studies

Effects following oral exposure to several aluminum salts are available for adults and newborn animals. One acute dermal study is available.

2.11.2 Identification of Data Needs: Children's Susceptibility

Several animal studies have examined potential age-related differences in the distribution, neurotoxicity, skeletal toxicity, and interactions of aluminum. However, conflicting results have been found and the database is not adequate to assess whether these differences are due to the animal species tested, the aluminum compound used, or the route of exposure. 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. Multiple species studies 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.

2.11.3 Identification of Data Needs

Acute-Duration Exposure. Excluding developmental and neurological toxicity, there are few data regarding the acute effects of aluminum exposure. A series of animal inhalation studies suggest that the lung may be a sensitive target for toxicity (Drew et al. 1974). The observed effects are similar to those which 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. The acute systemic toxicity of orally administered aluminum has not been well investigated, and systemic targets of toxicity have not been established. Data were insufficient to derive an acute-duration oral MRL. This is due to lack of data on sensitive toxicity end points and a lack of studies with sufficient dose information (aluminum levels in the base diet were not reported). However, further studies using this time-frame would not be particularly helpful in defining the human risk potential at hazardous waste sites since, if toxicity were to develop in the brain or bone, it would be after a very large cumulative exposure, which would take a long time, considering the poor absorption of aluminum.

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). 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 itialation MRL was not derived for aluminum. The central nervous system is the most sensitive target for intermediate-duration oral exposure to aluminum, and the MRL is based on a neurotoxic effect (reduced spontaneous motor activity) in mice (Golub et al. 1989). As discussed in the Data Needs section on Neurotoxicity, additional studies could confirm that motor activity is the most sensitive and appropriate neurotoxic end point for risk evaluation of aluminum, because no other neurotoxicity end points were tested in the MRL study. Nonneurotoxicity studies using this time-frame would not be particularly helpful in defining the human risk potential of aluminum at hazardous waste sites.

Chronic-Duration Exposure and Cancer. Aluminum has been implicated in causing neurological (Banks et al. 1988; Liss and Thorton 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. Pulmonary fibrosis has been associated with exposure to finely ground aluminum pyropowders which used nonpolar aliphatic oil lubricants (Edling 1961; McLaughlin et al. 1962; Mitchell et al. 1961; Ueda et al. 1958). 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 (Hanninen et al. 1974; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjijgren et al. 1996; White et al. 1992). Inhalation animal studies have focused on the pulmonary toxicity of aluminum (Stone et al. 1979). Data were considered inadequate for derivation of a chronic-duration inhalation MRL. Occupational exposure studies did not adequately characterize exposure and the animal studies did not examine sensitive end points of pulmonary toxicity. Several studies have examined the systemic toxicity of aluminum following chronic oral exposure (Oneda et al. 1994; Ondreicka et al. 1966; Schroeder and Mitchener 1975a). A chronic-duration oral MRL was not derived because the chronic-duration oral studies did not evaluate known or possible sensitive end points (e.g., neurotoxicity and skeletal effects). Chronic-duration animal studies are needed to identify target organs and to assess the human risk to chronic, increased, and greater-than-average aluminum exposures.

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). 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.

Genotoxicity. Animal data are available that indicate that aluminum may interact with neuronal DNA to alter gene expression and protein formation (Bertholf 1987; Crapper-McLachlan 1989; Crapper-McLachlan and Farnell 1985b). It is possible that this is a mechanism by which aluminum might exert its effects in the brains of patients with Alzheimer's disease. Further information on the mechanisms of aluminums effects on neurons would be helpful in determining whether aluminum has effects on gene expression that can adversely affect the human brain.

There are no human data to indicate that aluminum acts to cause cancer by genotoxic mechanisms. There are data from intraperitoneal exposures of mice to aluminum chloride that indicate that this compound is clastogenic (Manna and Das 1972). Although many carcinogens are also clastogens, there is no one-to-one relationship between these effects. Further genotoxicity studies, particularly *in vivo* exposures, would be useful for determining if clastogenic effects occur in additional species and at lower doses. In view of the negative carcinogenicity data for aluminum the significance of the clastogenic effects in one experiment is unclear.

Reproductive Toxicity. There are no human studies that indicate that aluminum affects reproduction. Animal studies in rats, mice, and dogs have shown that aluminum apparently does not affect reproduction. Finally, pharmacokinetic data do not indicate that the reproductive organs are target organs (Dixon et al. 1979; Ondreicka et al. 1966). Further studies in this area do no: appear to be necessary.

Developmental Toxicity. Developmental toxicity studies in animals have shown that oral gestational exposure to 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. 1993b

Yoshida et al. 1989). 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 (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1987, 1992a, 1992b, 1994, 1995; 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 systems 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 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) LOAEZL 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 et al. 1992a, 1992b, 1994, 1995; Golub and Germann 1998). 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 who have received aluminum-containing vaccines (Bohler-Sommeregger and Lindemayr 1986; Veien et al. 1986). 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), although there is some evidence that developmental exposure to aluminum can affect the immune system in young mice (Golub et al. 1993b 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. Any new developmental toxicity studies should include a range of low oral doses that encompasses the neurotoxicity NOAEL on which the intermediate-duration MRL is based, as well adequately characterized levels of aluminum in the base diet. 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 (Hanninen et al. 1994; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjogren et al. 1996; White et al. 1992). There are several studies that have found an association between aluminum concentrations in drinking water and the risk for Alzheimer's disease (Martyn et al. 1989; McLachlan et al. 1996; Michel et al. 1990). However, 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 aluminums role in the Alzheimer's disease process. Apart from whether or not aluminum is involved in the development of Alzheimer's disease, there is the question of whetheror not it exacerbates the symptoms of the disease. Additional analytical studies are needed to identify the extent to which aluminum may incorporate into portions of the brain and, in particular, the neurofibrillary tangles associated with Alzheimer's disease, but those procedures, solutions, and equipment should strictly prevent unintended aluminum contamination of the tissues to be valid (Makjanic et al. 1998).

The neurotoxicity of aluminum is well-documented in animals and has been manifested following various routes of exposure, including neuromotor, behavioral, and cognitive changes in orally-exposed adult rats and mice (Bilkei-Gorzo 1993; Bowdler et al. 1979; Commissaris et al. 1982; Connor et al. 1988; Dixon et al. 1979; Domingo et al. 1987b; Florence et al. 1994; Golub et al. 1989, 1992b, 1995; Gomez et al. 1986; Jope and Johnson 1992; La1 et al. 1993; Oteiza et al. 1993; Thorne et al. 1986; Varner et al. 1993, 1994, 1998). Research issues related to neurodevelopmental effects of aluminum are discussed in the Data Needs section on Developmental Toxicity. Some of that discussion also pertains to the neurotoxicity database in adult animals, particularly the need for additional information on bioavailability of different forms and ingested amounts of aluminum to better assess its neurotoxic potential, as well as more low-dose studies in which levels of aluminum in the base diet are adequately characterized. Additional low-dose neurotoxicity data are desirable because the NOAEL for the effect on which the MRL is based (reduced spontaneous motor activity) is uncorroborated, in part due to a lack of total dose information in most existing low-dose studies (i.e., experimental doses were often reported with no data on aluminum in the base diet). Additional studies could also confirm that motor activity is the most sensitive and appropriate neurotoxic end point for risk evaluation of aluminum because other no other neurotoxicity end points were tested in the MRL study (Golub et al. 1989).

Numerous mechanistic studies of aluminum neurotoxicity have been performed, but the main sites of action have not been discerned as discussed in Section 2.4.2 and by Strong et al. (1996). Additional studies could help identify a single unifying mechanism that can explain and reconcile the wide variety of pathological, neurochemical, and behavioral effects of aluminum induced by oral exposure and in various model systems (e.g., intracerebral and intracisternal administration), but these kinds of studies are unlikely to better characterize neurotoxicity NOAELs and LOAELs relevant to MRL assessment. The relationship between aluminum exposure and neurotoxicity is an active area of research.

Epidemiological and Human Dosimetry Studies. Some studies have been conducted in the workplace on people who have been exposed by the inhalation route, but the exposure levels have not been well quantified. People with chronic renal failure may be at higher risk for developing aluminum-related neurological disorders (Alfrey 1993b). A number of studies have examined the possible association between Alzheimer's disease and aluminum exposure in air (Salib and Hillier 1996), drinking water (Forster et al. 1995; Martyn et al. 1989, 1997; McLachlan et al. 1996; Michel et al. 1990; Wettstein et al. 1991), and use of aluminum-containing antiperspirants/deodorants (Graves et al. 1990). These studies have found 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. Results from these studies could also be used to identify what are potentially unhealthy exposure levels for individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. Reliable methods for determining tissue and plasma levels of aluminum exist. The nlechanism 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 serum (Alfrey et al. 1980; Arieff et al. 1979; Ganrot 1986), urine (Gorsky et al. 1979; Greger and Baier 1983b; Kaehny et al. 1977; Mussi et al. 1984; Reeker et al. 1977; Sjögren et al. 1985, 1988), and feces (Greger and Baier 1983b), 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. Because of the great human variability in aluminum tissue and plasma levels following exposure, it is doubtful if additional studies will provide better models of aluminum exposure.

Effect. The mechanisms of action for aluminum toxicity is not known. Aluninum has a number of subcellular effects, such as affecting cation protein interactions or microtubule structure and effects on cellular signaling mechanisms, which can be observed *in vitro.* Further information would be useful in indicating whether these subcellular effects lead to disease processes. 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 0.1-0.3% in humans, although absorption of particularly bioavailable forms such as aluminum citrate can be on the order of 1% (Day et al. 1991; DeVoto and Yokel 1994; Ganrot 1986; Greger and Baier 1983b; Jones and Bennett 1986; Nieboer et al. 1995; Priest 1993). 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). Although the range of fractional absorption is low compared to many other chemicals, aluminum uptake can significantly increase following oral exposure depending on conditions, including long-term ingestion, the presence of certain dietary components (e.g., citrate), and when large quantities are ingested (e.g., during use of antacids). The apparent lo-fold range in aluminum absorption has not been systematically documented using a variety of aluminum compounds and the most suitable analytical techniques. Few estimates of aluminum absorption have been determined using isotopic tracer techniques because [26]Al (the only isotope with a biologically usable half-time) is not readily available, is expensive in the quantities necessary for radiochemical detection, and requires the use of a sophisticated analytical technique (accelerator mass spectrometry) (Day et al. 1991; Priest et al. 1996). 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). Only one [26]Al study (Priest et al. 1996) has assessed bioavailability using different forms of aluminum and this study is limited by testing of only two compounds (aluminum citrate and aluminum hydroxide), a minimal number (two) of human subjects, and lack of data on effects of diet on absorption (e.g., comparison of empty versus full stomach conditions). 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.

Oral bioavailability of aluminum compounds appears to generally parallel water solubility, but current knowledge does not allow a straight extrapolation from solubility in water to bioavailability. Studies of aluminum speciation in the stomach and intestines, including mathematical modeling, would be useful because they could enable such an extrapolation by helping to resolve the critical role of speciation in making aluminum available to uptake mechanisms.

Adequate data are available on the retention of aluminum following various durations of exposure. Metabolism of the element does not occur (Ganrot 1986), and excretion routes are known (Gorsky et al. 1979; Greger and Baier 1983b; Kaehny et al. 1977; Reeker 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. Although the interpretation of the human data is limited by poor exposure characterization, the occupational exposure studies suggest that neurotoxicity is also a sensitive end point following inhalation exposure (Htinninen et al. 1974; Hosovski et al. 1990; Rifat et al. 1990; Sim et al. 1997; Sjögren et al. 1996; White et al. 1992). The toxicokinetic properties of aluminumhave been extensively studied in human and animals. The results of these studies suggest that the absorption, distribution, and excretion properties of aluminum are similar across species.

Methods for Reducing Toxic Effects. The mechanism of absorption and distribution of aluminum have not been established. Studies which 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; however, the clinical

usefulness of DFO is limited by a variety of toxic effects. Studies which 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.

2.11.4 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 2-5 (FEDRIP 1998).

2. HEALTH EFFECTS

Table 2-5. Ongoing Studies for Aluminum Toxicity

Investigator	Study Topic	Institution	Sponsor
Swyt CR	Aluminum in Alzheimer's Disease	NCRR, NIH	National Center for Research Resources
Sakhaee K	Aluminum absorption - effects of calcium citrate on aluminum-containing antacids	University of Texas SW Med. Center	National Center for Research Resources
Bondy SC	Aluminum ion-induced interactions and neurological disease	University of California Irvine	National Institute of Environmental Health Science
Banks WA	Aluminum blood-brain barrier permeability	Department of Veterans Affairs Medical Center	USA
Berlyne GM	Aluminum handling in kidney and gut	Department of Veterans Affairs Medical Center	USA
NA	Aluminum in brain diseases	Atom Sciences Inc.	HHS
Dunn MA	Effects of dietary aluminum on vitamin D-dependent calcium absorption	University of Hawaii	U.S. Dept. Of Agriculture Competitive Research Grant Office
Fanti P	Effects of aluminum on bone cells in culture	Dept. of Veterans Affairs Medical Center	Dept of Veterans Affairs Research and Development
Castro CE Johnson NE	Interactive effects of dietary aluminum and zinc deficiency on nuclear chromatin structure and function	University of Hawaii	U.S. Dept. Of Agriculture Cooperative State Res. Ser.
Melethil SK	Mechanism of blood-brain transport of aluminum in rats	University of Missouri Kansas	National Institute of Environmental Health Sciences
Yokel R	Bioavailability of ^{26}Al from drinking water	University of Kentucky Medical Center	EPA
Golub MS	Mouse model for chronic oral aluminum toxicity	University of California Davis	National Institute of Environmental Health Sciences

Table 2-5. Ongoing Studies for Aluminum Toxicity *(continued)*

Investigator	Study Topic	Institution	Sponsor
Coburn JW	Studies of aluminum absorption in man	Department of Veterans Affairs Medical Center	USA

NA = not available

Source: FEDRIP 1998