3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of barium. 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.

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

When evaluating the health effects of barium compounds, it is important to keep in mind that different barium compounds have different solubilities in water and body fluids and therefore serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, and hydroxide) are generally highly toxic to humans and experimental animals. The insoluble barium compounds (notably sulfate) are inefficient sources of the Ba^{2+} ion and therefore are generally nontoxic. Although barium carbonate is insoluble in water, barium ions would be released from ingested barium carbonate in the acid milieu of the stomach. Throughout the following section (3.2), the health effects by route of exposure of both soluble and insoluble barium compounds are discussed.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

3.2.1 Inhalation Exposure

Studies evaluating the effects of barium following acute, intermediate, and chronic inhalation exposure are limited to several case reports of humans exposed occupationally (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988), an experimental exposure to barium in welding fumes (Zschiesche et al. 1992), and three experimental studies with animals (Cullen et al. 2000; Hicks et al. 1986; Tarasenko et al. 1977). These case reports and animal studies are not adequate for firmly establishing the health effects of barium by inhalation because of a number of significant study limitations. The case reports are generally inadequate because data were available for a limited number of exposed subjects and because exposure conditions (duration, frequency, dose) were not well characterized (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). One of the animal studies was limited in that apparently no control animals were used, an inhalation chamber providing a controlled dose and environment was not used, and there was a lack of information regarding

the vehicle used, purity of the test material, duration and frequency of exposure, and number of animals tested (Hicks et al. 1986). The second animal study consisted of several experiments, but was generally limited in that the authors provided few details regarding experimental methods, exposure conditions, and test results, and no information as to the number of animals tested, purity of the test material, or statistical methods used; furthermore, in some experiments, it was not clear whether or not control animals were used (Tarasenko et al. 1977). The third study examined a limited number of end points (Cullen et al. 2000). In view of the major limitations associated with the available case reports and studies, results from these reports should be regarded as providing only preliminary and/or suggestive evidence that acute, intermediate, and chronic inhalation exposure to barium may potentially be associated with adverse health effects. Findings from the various case reports and animal studies are briefly described below.

3.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to barium.

3.2.1.2 Systemic Effects

No studies were located regarding endocrine, dermal, or ocular effects in humans or animals after inhalation exposure to barium.

Respiratory Effects. Two reports of workers exposed chronically to dust from barium sulfate demonstrated that this exposure had a minor effect on the lungs. In one study, a benign pneumoconiosis was observed in several factory workers (Doig 1976). In a second study in which workers were exposed by mining barium sulfate, silicosis was observed but was attributed to inhalation of quartz (Seaton et al. 1986). In contrast, a study of workers chronically exposed to barium carbonate dust reported no respiratory symptoms attributable to barium exposure (Essing et al. 1976). X-ray analysis of the lungs also showed no abnormalities attributable to barium dust.

Studies regarding respiratory effects in animals following inhalation exposure to barium are limited to three reports (Cullen et al. 2000; Hicks et al. 1986; Tarasenko et al. 1977). Pulmonary lesions (perivascular and peribronchial sclerosis and focal thickening of the interalveolar septa) were observed in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust 4 hours/day, 6 days/week for 4 months (Tarasenko et al. 1977). Bronchoconstriction was reportedly noted in guinea pigs following inhalation for an unspecified period of time to 0.06 mg barium/m^3/minute as aerosolized barium chloride solution

(Hicks et al. 1986). In contrast to these finding, no adverse histological alterations were observed in the lungs of rats exposed to 44.1 mg barium/m^3 as barium sulfate for 119 days (Cullen et al. 2000).

Cardiovascular Effects. Three of 12 workers chronically exposed to barium carbonate dust had elevated blood pressure and 2 workers had ECG abnormalities (Essing et al. 1976). However, it is unknown whether this represented an increased incidence because no comparison with a control population was performed. Increased blood pressure and cardiac irregularities were reportedly observed in guinea pigs exposed by inhalation for an unspecified period of time to 0.06 mg barium/m^3/minute as aerosolized barium chloride solution (Hicks et al. 1986). Tarasenko et al. (1977) reported a 32% increase in arterial pressure and alterations in ECG readings suggestive of disturbances in heart conductivity following proserine administration in rats exposed to 3.6 mg barium/m^3 as barium carbonate; no ECG alterations were observed prior to proserine administration.

Gastrointestinal Effects. Abdominal cramps, nausea, and vomiting were experienced by a 22-year-old factory worker accidentally exposed by acute inhalation to a large but unspecified amount of barium carbonate powder (Shankle and Keane 1988). No animal studies were located regarding gastrointestinal effects in animals after inhalation exposure to barium.

Hematological Effects. Altered hematological parameters were observed in rats following inhalation for an intermediate exposure period to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). Reported changes included decreased blood hemoglobin and thrombocyte count.

Musculoskeletal Effects. After accidental exposure to a large amount of barium carbonate powder by acute inhalation, a 22-year-old factory worker developed progressive muscle weakness and paralysis of the extremities and neck (Shankle and Keane 1988); this is likely due to the low serum potassium level rather than a direct effect on muscle tissue. X-ray analysis of the bones and skeletal muscles of the pelvis and thighs of workers chronically exposed to barium carbonate dust revealed no apparent build up of insoluble barium in these tissues (Essing et al. 1976). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to barium.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to barium. Impaired detoxifying function of the liver was noted in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other details were reported.

Renal Effects. Renal failure occurred in a 22-year-old worker accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988). No studies were located regarding renal effects in animals after inhalation exposure to barium.

Body Weight Effects. A 21% decrease in body weight gain was observed in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust for 4 months (Tarasenko et al. 1977).

Metabolic Effects. Decreases in plasma potassium concentrations were observed in two groups of welders using barium-containing electrodes; the barium levels in the work environment were 4.4 and 0.3 mg/m^3 (Zschiesche et al. 1992). However, this was not observed in a third group of welders exposed to 2.0 mg barium/m^3. A low serum potassium level was also observed in a worker accidentally exposed to barium carbonate powder (Shankle and Keane 1988). Additionally, the plasma potassium concentrations were not statistically different from levels measured prior to barium exposure. Tarasenko et al. (1977) reported a decrease in urinary calcium levels and increased blood phosphorus levels in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust for an intermediate duration (Tarasenko et al. 1977). This study also reported a decrease in blood glucose levels in barium-exposed rats.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to barium.

3.2.1.4 Neurological Effects

Absence of deep tendon reflexes was observed in a 22-year-old man accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988); as noted previously, this is probably due to the barium-induced low potassium levels. No studies were located regarding neurological effects in animals after inhalation exposure to barium.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to barium. Only one limited report was available regarding reproductive effects in animals following intermediate inhalation exposure to barium carbonate (Tarasenko et al. 1977). Disturbances in spermatogenesis, including decreased number of sperm, decreased percentage of motile sperm, and decreased osmotic

resistance of sperm, were reportedly observed in male rats exposed by inhalation for one cycle of spermatogenesis to 15.8 mg barium/m^3 as barium carbonate dust. The testicles of these treated rats reportedly had an increase in the number of ducts with desquamated epithelium and a reduced number of ducts with 12^{th}-stage meiosis. The condition of the testicles of treated rats returned to normal 30 days after cessation of barium carbonate treatment (Tarasenko et al. 1977). Similar observations were noted in a second experiment in which male rats were exposed by inhalation for an intermediate period to 3.6 mg barium/m^3 as barium carbonate dust. In a third experiment by the same authors, female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust reportedly developed a shortened estrous cycle and alterations in the morphological structure of the ovaries.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to barium. Only one limited report was available regarding developmental effects in animals after intermediate inhalation exposure to barium (Tarasenko et al. 1977). Reduced survival, underdevelopment, lowered weight gain, and various hematologic alterations (erythropenia, leukocytosis, eosinophilia, neutrophilia) were reported in the offspring of female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other significant details regarding this developmental study were reported.

3.2.1.7 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to barium.

3.2.2 Oral Exposure

The majority of studies evaluating the health effects of barium are oral exposure studies. The available oral studies include numerous case reports of humans exposed orally to barium through accidental or intentional ingestion, several epidemiological and statistical investigations of humans exposed to drinking water containing barium, and various experimental animal studies involving acute, intermediate, or chronic exposure to barium either by gavage or by drinking water. Findings from the various oral studies are summarized below.

3.2.2.1 Death

Death has been reported in a number of case reports of accidental or intentional ingestion of barium salts. The cause of death was attributed to cardiac arrest, severe gastrointestinal hemorrhage, or unknown causes (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Jourdan et al. 2001; McNally 1925; Ogen et al. 1967; Talwar and Sharma 1979). Doses in these cases were not known.

In addition to case reports of death in humans, several studies have examined mortality rates in residents living in communities with elevated barium levels in the drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Two studies found no statistical correlations between barium concentrations in drinking water and total mortality and/or cardiovascular mortality rates in exposed populations (Elwood et al. 1974; Schroeder and Kraemer 1974). Interpretation of the study results are limited by the lack of information on exposure conditions (dose, duration, frequency) and the number of people exposed. Results of a third study indicated that relative to communities with little or no barium in drinking water, communities with elevated concentrations of barium in their drinking water had significantly higher mortality rates for all causes, heart disease, arteriosclerosis, and all cardiovascular disease (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981). This epidemiological study had a number of confounding variables, including possible use in the study population of home water softeners that would remove barium from the drinking water, inclusion of communities that had significant changes in population, lack of a way to control for length of time an individual lived in a community, and widely varying concentrations of other contaminants (calcium, sodium, magnesium) in the drinking water.

The LD_{50} values for barium chloride in rats range from 132 to 277 mg barium/kg (Borzelleca et al. 1988; Tardiff et al. 1980). Significant increases in mortality were observed in rats and mice exposed to 200 or 450 mg barium/kg/day as barium chloride in drinking water for 90 days (NTP 1994). Survival was not affected at 110 or 205 mg barium/kg/day in the rats or mice, respectively. No changes in mortality were observed in rats chronically exposed to doses as high as 60 mg barium/kg/day as barium chloride in the drinking water (NTP 1994). An increase in mortality, attributable to nephropathy, was observed in mice chronically exposed to 160 mg barium/kg/day as barium chloride in drinking water (NTP 1994); the number of deaths was similar to controls in mice exposed to 75 mg barium/kg/day. In male mice exposed to 0.95 mg barium/kg/day as barium acetate in drinking water, a significant decrease in longevity (defined as average lifespan of the last five surviving animals) was observed; however, no significant differences in mean lifespan were observed (Schroeder and Mitchener 1975b). Similarly, lifespan was not

significantly altered in female mice exposed to 0.95 mg barium/kg/day (Schroeder and Mitchener 1975b) or male or female rats exposed to 0.7 mg barium/kg/day as barium acetate in drinking water (Schroeder and Mitchener 1975a).

LD_{50} values and reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Limited data are available regarding respiratory effects in animals following oral barium exposure. Fluid in the trachea was observed in rats receiving a single gavage dose of 198 mg barium/kg as barium chloride (Borzelleca et al. 1988). However, this effect was not observed when rats were dosed with 198 mg barium/kg/day as barium chloride for 10 days (Borzelleca et al. 1988). No significant alterations in lung weights, gross lesions, or histopathological alterations were observed in the respiratory tracts of rats and mice exposed to doses as high as 110 or 70 mg barium/kg/day, 180 or 450 mg barium/kg/day, or 60 and 160 mg barium/kg/day for intermediate or chronic durations, respectively (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980) or lifetime exposure to 0.7 or 0.95 mg barium/kg/day, respectively, as barium acetate via drinking water (Schroeder and Mitchener 1975a).

Cardiovascular Effects. As demonstrated in numerous case reports, acute exposure to presumably high doses of barium carbonate, barium sulfate, or barium chloride can result in serious effects on heart rhythm. Barium adversely affects cardiac automaticity resulting in ventricular tachycardia and other disruptions of rhythm (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). Hypotension has also been reported in some cases (Koch et al. 2003; Talwar and Sharma 1979). The likely cause of these effects was barium-induced hypokalemia.

Several human studies have investigated a possible association between exposure to low levels of barium and alterations in blood pressure and cardiac rhythms. In a small-scale (11 subjects) study of individuals exposed to 0.1 or 0.2 mg barium/kg/day as barium chloride in drinking water for 4 weeks, no significant alterations in blood pressure or ECG readings were found (Wones et al. 1990). There was no significant

Table 3-1 Levels of Significant Exposure to Barium - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				198 (death in 15/20 rats)	Borzelleca et al. 1988 Barium chloride	
2	Rat (Sprague-Dawley)	once (GW)				269 F (LD50 in females)	Borzelleca et al. 1988 Barium chloride	
3	Rat (NS)	once (GW)				132 (LD50 adult) 220 (LD50 weanling)	Tardiff et al. 1980 Barium chloride	
Systemic								
4	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Resp	198			Borzelleca et al. 1988 Barium chloride	
			Cardio	198				
			Gastro	198				
			Hemato	198				
			Hepatic	198				
			Renal	198				
			Ocular	198				
			Bd Wt	198				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
5	Rat (Sprague-Dawley)	once (GW)	Resp	66	198	(fluid in trachea)		Borzelleca et al. 1988 Barium chloride	
			Cardio	198					
			Gastro	66	198	(inflammation of small and large intestine)			
			Hemato	198					
			Hepatic	66	198	(decreased liver/brain weight ratio; darkened liver)			
			Renal	66	198	(increased kidney/body weight ratio)			
			Ocular	66	198	(ocular discharge)			
			Bd Wt	66	198	(decreased body weight)			
			Other	198					
Immuno/ Lymphoret									
6	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		198				Borzelleca et al. 1988 Barium chloride	Evaluated weight and occurrence of gross lesions in thymus.
Neurological									
7	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		198				Borzelleca et al. 1988 Barium chloride	

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
8	Rat (Sprague-Dawley)	once (GW)		198			Borzelleca et al. 1988 Barium chloride	Evaluated testes and ovary weights.
9	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		138 F	198 F (decreased ovary weight and ovaries/brain ratio)		Borzelleca et al. 1988 Barium chloride	Evaluated testes and ovary weights.
INTERMEDIATE EXPOSURE								
Death								
10	Rat (Fischer- 344)	90 d (W)				200 M (30% mortality)	NTP 1994 Barium chloride	
11	Mouse (B6C3F1)	90 d (W)				450 M (60% mortality)	NTP 1994 Barium chloride	
Systemic								
12	Human (NS)	4 wk 7 d/wk (W)	Cardio	0.2 M			Wones et al. 1990 Barium chloride	
13	Rat (Dahl)	16 wk (W)	Cardio	150			McCauley et al. 1985 NR	Study used salt resistant and salt sensitive rat strains.
			Renal	15	150 (fused podocytes and thickening of the capillary basement membrane in glomeruli)			

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	16 wk (W)	Cardio	150			McCauley et al. 1985 NR	Study used uninephrecomized rats.
			Renal	15	150 (fused podocytes and thickening of the capillary basement membrane in glomeruli)			
15	Rat (Sprague-Dawley)	36 wk (W)	Resp	37.5 M			McCauley et al. 1985 NR	
			Cardio	37.5 M				
			Gastro	37.5 M				
			Musc/skel	37.5 M				
			Hepatic	37.5 M				
			Renal	37.5 M				
			Ocular	37.5 M				
			Bd Wt	37.5 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Rat (Sprague-Dawley)	46 wk (W)	Resp	37.5 F			McCauley et al. 1985 NR	
			Cardio	37.5 F				
			Gastro	37.5 F				
			Musc/skel	37.5 F				
			Hepatic	37.5 F				
			Renal	37.5 F				
			Ocular	37.5 F				
			Bd Wt	37.5 F				
17	Rat (Fischer- 344)	15 d (W)	Resp	110			NTP 1994 Barium chloride	
			Cardio	110				
			Gastro	110				
			Hemato	110				
			Hepatic	110				
			Renal	110				
			Bd Wt	110				
			Metab	110				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Rat (Fischer- 344)	90 d (W)	Resp	180 F			NTP 1994 Barium chloride	
			Cardio	180 F				
			Gastro	180 F				
			Hemato	180 F				
			Musc/skel	180 F				
			Hepatic	180 F				
			Renal	65[b] F	180 F (dilatation of proximal renal cortex)			
					115 F (increased kidney weight)			
			Ocular	180 F				
			Bd Wt	110 M	200 M (13% lower final body weight)			
			Metab	180 F				
19	Rat (Long- Evans)	1 mo 7 d/wk (W)	Cardio	1 F	8.6 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.
20	Rat (Long- Evans)	4 mo 7 d/wk (W)	Cardio	1.2 F	11 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Rat Charles-River	13 wk 7 d/wk (W)	Resp	35			Tardiff et al. 1980 Barium chloride	
			Cardio	35				
			Hemato	35				
			Musc/skel	35				
			Hepatic	35				
			Renal	35				
			Bd Wt	35				
22	Mouse (B6C3F1)	90 d (W)	Resp	450 M			NTP 1994 Barium chloride	
			Cardio	450 M				
			Gastro	450 M				
			Hemato	450 M				
			Musc/skel	450 M				
			Hepatic	450 M				
			Renal	205 M		450 M (nephropathy)		
			Ocular	450 M				
			Bd Wt	205 M		450 M (30% lower final body weight)		
			Metab	450 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Mouse (B6C3F1)	15 d (W)	Resp	70 M			NTP 1994 Barium chloride	
			Cardio	70 M				
			Gastro	70 M				
			Hemato	70 M				
			Hepatic	70 M				
			Renal	70 M				
			Bd Wt	70 M				
			Metab	70 M				
Immuno/ Lymphoret								
24	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
25	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
26	Rat (Fischer- 344)	90 d (W)		180 F			NTP 1994 Barium chloride	Histological examination of spleen and thymus.
27	Mouse (B6C3F1)	90 d (W)		205 M	450 M (thymic and splenic atrophy)		NTP 1994 Barium chloride	Histological examination of spleen and thymus.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
28	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of brain.
29	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of brain.
30	Rat (Fischer- 344)	90 d (W)		115 F	180 F (decreased spontaneous motor activity)		NTP 1994 Barium chloride	
31	Rat (Fischer- 344)	15 d (W)		110			NTP 1994 Barium chloride	
32	Rat Charles-River	13 wk 7 d/wk (W)		35			Tardiff et al. 1980 Barium chloride	Histological examination of brain.
33	Mouse (B6C3F1)	90 d (W)		200 F	495 F (decreased forelimb grip strength)		NTP 1994 Barium chloride	
34	Mouse (B6C3F1)	15 d (W)		70 M			NTP 1994 Barium chloride	
Reproductive								
35	Rat (Fischer- 344)	M: 60 d F: 30 d (W)		200 M 180[c] F			Dietz et al. 1992 Barium chloride	

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
37	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
38	Rat (Fischer- 344)	90 d (W)		200 M 180[c] F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.
39	Rat (Fischer- 344)	15 d (W)		110			NTP 1994 Barium chloride	
40	Mouse (B6C3F1)	M: 60 d F: 30 d (W)		205 M 200[c] F			Dietz et al. 1992 Barium chloride	
41	Mouse (B6C3F1)	90 d (W)		450[c] M 495 F			NTP 1994 Barium chloride	Histological examination of reproductive tisses.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Mouse (B6C3F1)	15 d (W)		70[c] M 85 F			NTP 1994 Barium chloride	
Developmental								
43	Rat (Fischer- 344)	M: 60 d F: 30 d (W)		115 F	180 F (decreased pup body weight and nonsignificant decrease in litter size)		Dietz et al. 1992 Barium chloride	
44	Mouse (B6C3F1)	M: 60 d F: 30 d (W)		200 F			Dietz et al. 1992 Barium chloride	
CHRONIC EXPOSURE								
Death								
45	Mouse (B6C3F1)	2 yr (W)				160 M (increased mortality)	NTP 1994 Barium chloride	
Systemic								
46	Rat (Sprague-Dawley)	68 wk (W)	Resp	15 M			McCauley et al. 1985 NR	
			Cardio	15 M				
			Gastro	15 M				
			Musc/skel	15 M				
			Hepatic	15 M				
			Renal	15 M				
			Ocular	15 M				
			Bd Wt	15 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Rat (Fischer- 344)	2 yr (W)	Resp	60 M			NTP 1994 Barium chloride	
			Cardio	60 M				
			Gastro	60 M				
			Hemato	60 M				
			Musc/skel	60 M				
			Hepatic	60 M				
			Renal	60 M				
			Ocular	60 M				
			Bd Wt	60 M				
			Metab	60 M				
48	Rat (Long- Evans)	16 mo 7 d/wk (W)	Cardio	0.17 F	0.8 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.
					7.2 F (depressed rates of cardiac contraction and electrical conductivity)			

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
49	Mouse (B6C3F1)	2 yr (W)	Resp	160 M			NTP 1994 Barium chloride	
			Cardio	160 M				
			Gastro	160 M				
			Hemato	160 M				
			Musc/skel	160 M				
			Hepatic	160 M				
			Renal	75 M[d]		160 M (marked nephropathy)		
			Ocular	160 M				
			Bd Wt	75 M		160 M (weight loss)		
Immuno/ Lymphoret								
50	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
51	Rat (Fischer- 344)	2 yr (W)		60 M			NTP 1994 Barium chloride	Histological examination of spleen and thymus.
52	Mouse (B6C3F1)	2 yr (W)		75 M	160 M (lymphoid depletion in the spleen and decreased relative and absolute spleen weight)		NTP 1994 Barium chloride	Histological examination of thymus and spleen.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
53	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of brain.
54	Rat (Fischer- 344)	2 yr (W)		60 M			NTP 1994 Barium chloride	Histological examination of brain.
55	Mouse (B6C3F1)	2 yr (W)		160 M			NTP 1994 Barium chloride	Histological examination of brain.
Reproductive								
56	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
57	Rat (Fischer- 344)	2 yr (W)		60[c] M 75 F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.
58	Mouse (B6C3F1)	2 yr (W)		160[c] M 200 F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.

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

b Used to derive an intermediate duration oral minimal risk level (MRL) of 0.2 mg barium/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and modifying factor of 3 to account for database deficiencies.

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

d The chronic-duration oral MRL of 0.2 mg barium/kg/day was calculated using benchmark dose analysis. The BMDL5 of 61 mg barium/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability) and modifying factor of 3 to account for database deficiencies.

Cardio = cardiovascular; d = day; F = female; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; M = male; mo = month; Musc/skel = musculoskeletal; NS = not specified; NR = not reported; Resp = respiratory; (W) = drinking water; wk = week; x = time(s); yr = year

Figure 3-1 Levels of Significant Exposure to Barium - Oral

Acute (≤14 days)

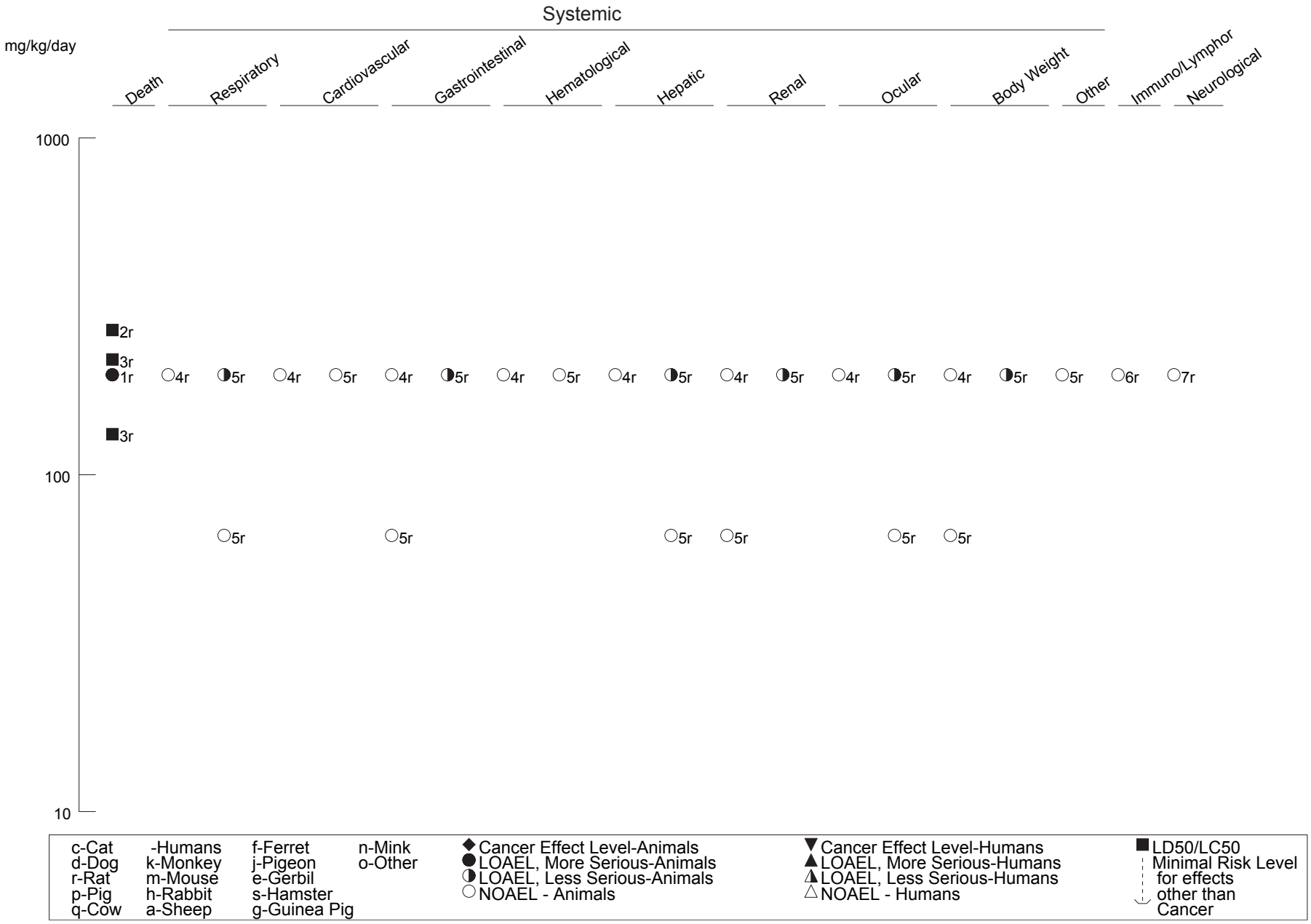
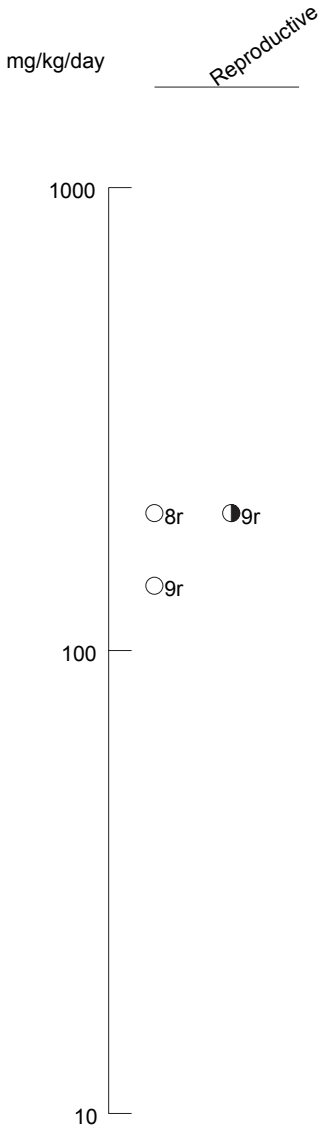


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Acute (≤14 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Intermediate (15-364 days)

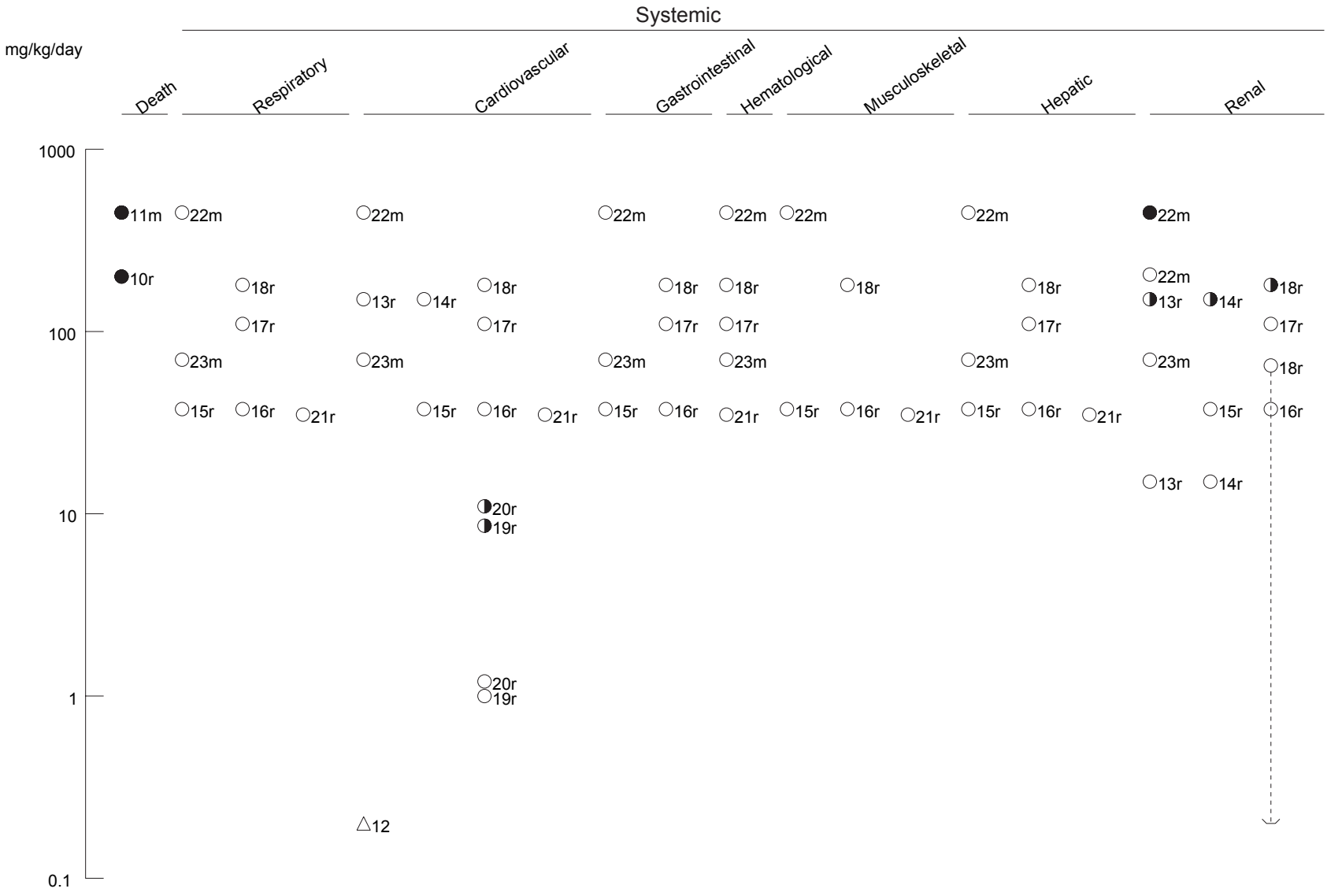


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Intermediate (15-364 days)

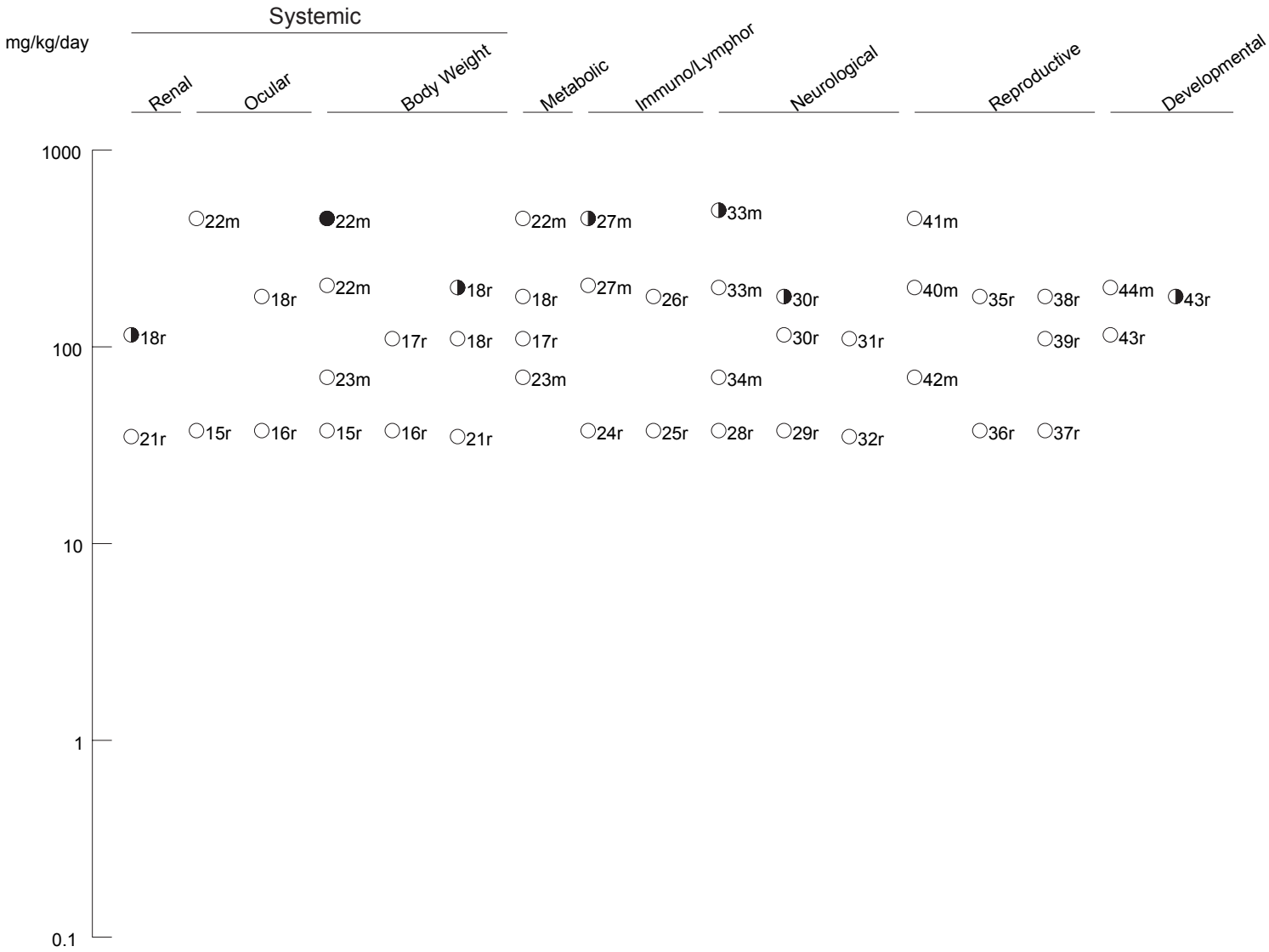
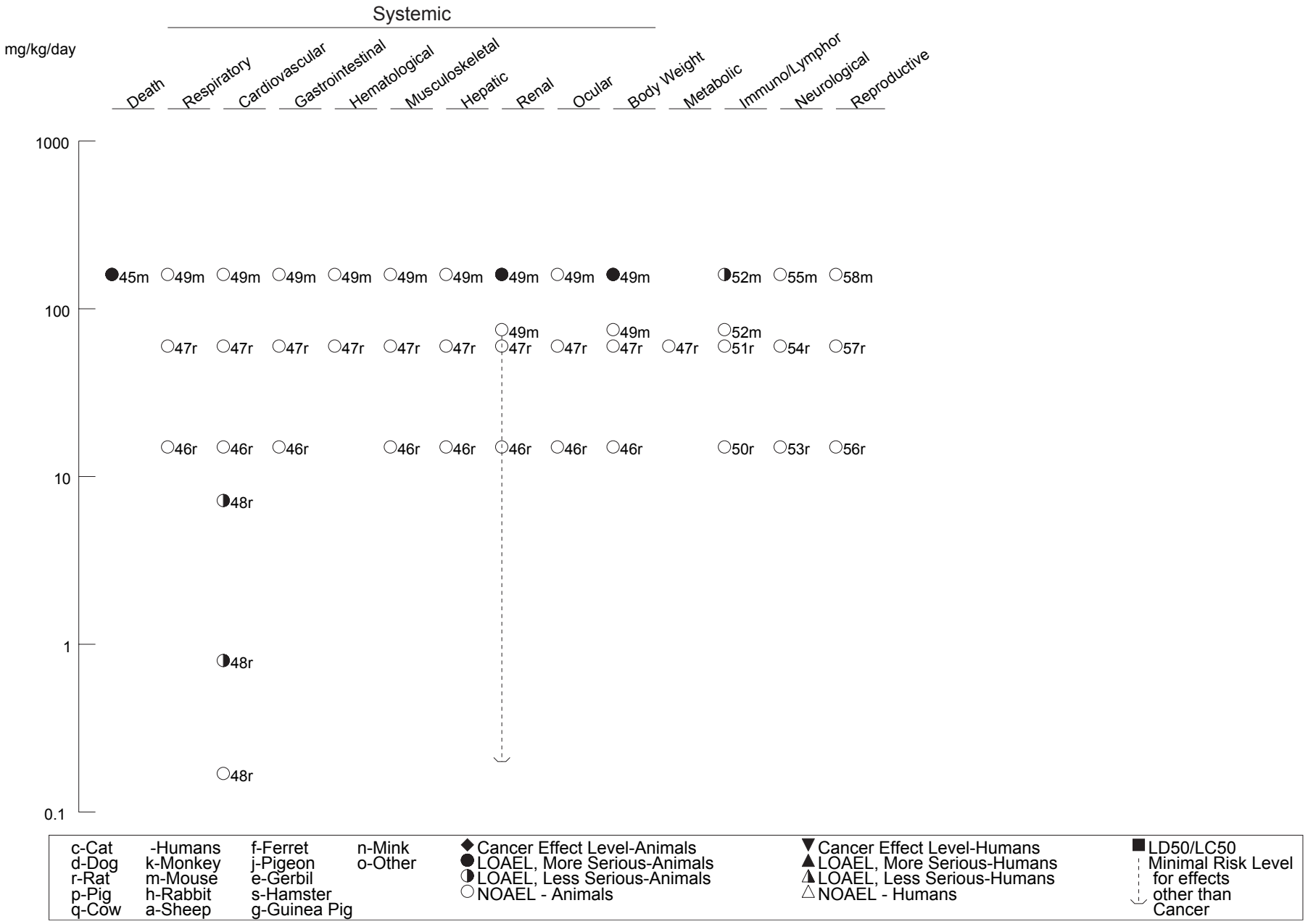


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Chronic (≥365 days)



alteration in blood pressure measurements or alterations in hypertension, heart disease, or stroke among residents of two communities with elevated (0.2 mg barium/kg/day) or low (0.003 mg barium/kg/day) levels of barium in drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). Interpretation of this study is limited by the lack of information on tap water consumption, and the fact that blood pressure was measured 3 times in a single 20-minute period and not repeatedly over a longer period, and the incidence of hypertension, stroke, and heart disease was taken from subject-completed questionnaires and not confirmed by testing or examination of medical records. Brenniman and associates (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981) also conducted a mortality study of residents living in communities with elevated or low barium levels in drinking water. Significantly higher mortality rates for cardiovascular disease and heart disease (arteriosclerosis) were found in the elevated barium communities (0.06–0.3 mg barium/kg/day) than in the low barium communities (0.006 mg barium/kg/day). The largest difference between the groups was in individuals 65 years of age and older. These results should be interpreted cautiously because the study did not control for a number of potential confounding variables such as the use of water softeners, which would reduce the amount of barium and increase sodium levels, duration of exposure, or actual barium intakes.

Several animal studies have examined potential cardiovascular end points following acute-, intermediate-, or chronic-duration exposures. No histological alterations have been observed in the hearts of rats and mice exposed to barium chloride, barium acetate, or an unspecified barium compound for intermediate or chronic durations (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a; Tardiff et al. 1980). Significant increases in systolic blood pressure were observed in rats exposed to 8.6 or 11 mg barium/kg/day for 1 or 4 months, respectively; no effect levels were 1.0 and 1.2 mg barium/kg/day (Perry et al. 1983, 1985, 1989). When the duration of exposure was longer (8–16 months), the LOAEL for increased blood pressure was 0.80 mg barium/kg/day and the NOAEL was 0.17 mg barium/kg/day (Perry et al. 1983, 1985, 1989). Depressed rates of cardiac contraction and cardiac conductivity and decreased cardiac ATP levels were observed in another group of rats exposed to 7.2 mg barium/kg/day. In contrast to the findings in the Perry study (1983, 1985, 1989), no significant alterations in blood pressure were observed in rats exposed to up to 150 mg barium/kg/day in drinking water for 16 weeks (McCauley et al. 1985); it should be noted that the McCauley et al. (1985) studies were conducted in uninephrectomized rats or Dahl salt-sensitive and salt-resistant rats. NTP (1994) also found no significant alterations in blood pressure, heart rate, or ECG readings in rats exposed to 180 mg barium/kg/day for 45 or 90 days. The low metal diet used in the Perry et al. (1983, 1985, 1989) study may have influenced the study outcome.

Gastrointestinal Effects. All cases of acute oral barium poisoning in adults exhibit gastrointestinal disturbances as the initial symptoms. These include gastric pain, vomiting, and diarrhea (Das and Singh 1970; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). In one case, severe gastrointestinal hemorrhage occurred in an adult male victim (Diengott et al. 1964).

Although gastrointestinal effects have been observed in some animal studies, most studies have not found effects. Inflammation of the intestines was noted in rats receiving a single gavage dose of 198 mg barium/kg as barium chloride (Borzelleca et al. 1988); but not in rats administered 10 doses of 198 mg barium/kg/day (Borzelleca et al. 1988). Stomach rupture, bowel obstruction, and gastrointestinal hemorrhage have been observed in rats dosed with barium sulfate; however, those adverse effects were most likely due to the massive doses of barium sulfate used in the study (25–40% of body weight) and not necessarily to barium toxicity (Boyd and Abel 1966). A 15-day exposure of male and female rats and mice to 110 or 70 mg barium/kg/day as barium chloride in drinking water, respectively, did not result in histological alterations in the gastrointestinal tract (NTP 1994). No gross or microscopic lesions of the esophagus, stomach, pancreas, small intestines, or colon were noted in several intermediate and chronic experiments in which male and female rats were exposed to doses as high as 180 mg barium/kg/day as an unspecified barium compound or barium chloride in drinking water (McCauley et al. 1985; NTP 1994) or male and female mice exposed to doses as high as 450 mg barium/kg/day as barium chloride (NTP 1994).

Hematological Effects. Results of animal studies indicate that acute, intermediate, and chronic oral exposure to barium is not associated with any adverse hematological effects. No alterations were found in rats administered 198 mg barium/kg/day as barium chloride for 10 days (Borzelleca et al. 1988) or in rats or mice exposed to 110 or 70 mg/kg/day, respectively, as barium chloride in drinking water for 15 days (NTP 1994). Intermediate and chronic oral exposure of rats to barium acetate and barium chloride in drinking water has not been associated with any significant or treatment-related changes in a variety of hematological parameters (NTP 1994; Tardiff et al. 1980). Elemental barium doses in these intermediate and chronic drinking water studies ranged from 15 to 450 mg/kg/day.

Musculoskeletal Effects. The predominant musculoskeletal effect observed in cases of barium toxicity in humans is progressive muscle weakness, often leading to partial or total paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). In severe cases, the paralysis affects

the respiratory system (Das and Singh 1970; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). The likely cause of the muscle weakness was the barium-induced hypokalemia rather than a direct effect on muscles.

Very limited animal data are available regarding the musculoskeletal effects of barium following oral exposure. No gross and microscopic lesions were observed in skeletal system of several intermediate and chronic experiments in which rats were exposed to an unspecified barium compound or barium chloride in drinking water at doses as high as 180 mg barium/kg/day for intermediate duration and as high as 60 mg barium/kg/day for chronic duration (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980); similarly, no effects were observed in mice exposed to 450 or 160 mg barium/kg/day as barium chloride in drinking water for intermediate or chronic durations, respectively (NTP 1994).

Hepatic Effects. In one case study involving accidental acute ingestion of barium carbonate in an adult female, some degeneration of the liver was noted post-mortem (McNally 1925). Adverse hepatic effects in animals following oral barium exposure have been minor or have not been observed. Decreased liver/brain weight ratio and darkened liver were observed in rats administered a single gavage dose of 198 mg barium/kg as barium chloride; however, these changes were not associated with any microscopic hepatic lesions or alterations in serum enzymes (e.g., serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], alkaline phosphatase). No histological or liver weight alterations were observed in rats dosed with 198 mg barium/kg/day as barium chloride for 1 or 10 days (Borzelleca et al. 1988) or in rats and mice exposed to 110 or 70 mg barium/kg/day, respectively, as barium chloride in drinking water for 15 days (NTP 1994). Intermediate and chronic studies involving oral exposure of rats or mice to barium in drinking water did not find significant alterations in liver weight or liver histopathology following exposure to doses as high as 180 mg barium/kg/day for rats and 450 mg barium/kg/day for mice (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b; Tardiff et al. 1980).

Renal Effects. Toxic effects on the kidneys have been observed in several adult cases of acute barium poisoning. Effects include hemoglobin in the urine (Gould et al. 1973) (which may be indicative of kidney damage), renal insufficiency (Lewi and Bar-Khayim 1964; Phelan et al. 1984), degeneration of the kidneys (McNally 1925), and acute renal failure (Wetherill et al. 1981).

Studies in animals suggest that the kidney is a critical target of barium toxicity. An increase in relative kidney weight (kidney/brain weight ratio) was observed in male and female rats receiving a single gavage

dose of 198 mg barium/kg/day as barium chloride in water (Borzelleca et al. 1988). Increases in relative kidney weight (kidney to brain weight ratio) were also observed in female rats receiving gavage doses of 66, 96, or 138 mg barium/kg/day as barium chloride in water for 10 days, but not at 198 mg barium/kg/day (Borzelleca et al. 1988). Significant reductions in blood urea nitrogen (BUN) were also observed in females exposed to 66–198 mg barium/kg/day and in males exposed to 198 mg barium/kg/day. The changes in BUN levels were not considered to be biologically significant because BUN levels are typically increased in response to kidney damage, the magnitude of change was slight (less than 15%), and there were no differences between the barium-exposed groups. The changes in relative kidney weights or BUN levels were not associated with gross or microscopic renal lesions. Studies of rats and mice did not find significant alterations in kidney weights or the incidence of renal lesions following a 15-day exposure to 110 or 70 mg barium/kg/day, respectively, as barium chloride in drinking water (NTP 1994).

Exposure of rats to doses as high as 65 mg barium/kg/day for an intermediate duration did not result in any alterations in kidney weight or the occurrence of histopathological lesions (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980). At 115 mg barium/kg/day, significant increases in absolute and relative kidney weights were observed in female rats (NTP 1994). Electron microscopy detected glomerular lesions consisting of fused podocyte processes and thickening of the capillary basement membrane in rats exposed to 150 mg barium/kg/day (McCauley et al. 1985). At slightly higher doses (180 mg barium/kg/day), minimal to mild dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in male and female rats (NTP 1994). In mice, nephropathy characterized by mild to moderate tubule dilatation, regeneration, and atrophy was observed in males and females exposed to 450 mg barium/kg/day as barium chloride, but not to 205 mg barium/kg/day (NTP 1994).

Three chronic-duration studies assessed the renal toxicity of barium. No adverse effects were observed in rats exposed via drinking water to 15 mg barium/kg/day of an unspecified barium compound for 68 weeks (McCauley et al. 1985), 60 mg barium/kg/day as barium chloride for 2 years (NTP 1994), or lifetime exposure to 0.7 mg barium/kg/day as barium acetate (Schroeder and Mitchener 1975a). In mice, exposure to 160–200 mg barium/kg/day resulted in moderate to marked nephropathy, characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, interstitial fibrosis, and glomerulosclerosis (NTP 1994); at the next lowest dose tested (75 mg barium/kg/day), the incidence of nephropathy did not differ from controls. No kidney lesions were observed in mice following lifetime exposure to 0.95 mg barium/kg/day as barium acetate (Schroeder and Mitchener 1975b).

Dermal Effects. No studies were located regarding dermal effects in humans or animals after oral exposure to barium.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to barium. In studies with Sprague-Dawley rats, ocular discharge following administration of a single gavage dose of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988); this was not reported in rats dosed for 10 days (Borzelleca et al. 1988). A nonsignificant increase in retinal dystrophy was observed in rats following intermediate and chronic oral exposure to 12–37.5 mg barium/kg/day as an unspecified barium compound (McCauley et al. 1985). Although the retinal dystrophy was statistically insignificant, a dose-related trend was observed if different duration exposure groups were combined (McCauley et al. 1985). Both ocular discharge and retinal dystrophy are commonly observed in Sprague-Dawley rats; consequently, the ocular lesions noted in these animal studies cannot necessarily be attributed to oral barium exposure. Ocular lesions were not observed in F344 rats or B6C3F1 mice exposed to barium chloride in drinking water for 90 days or 2 years to doses as high as 180 mg barium/kg/day in rats and 450 mg barium/kg/day in mice (NTP 1994).

Body Weight Effects. Body weight has been monitored in a number of acute, intermediate, and chronic studies in which rats and mice were exposed orally to barium compounds (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b; Tardiff et al. 1980). In general, body weight effects have only been observed at lethal doses. A decrease in body weight was observed in rats receiving a single gavage dose of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988), in rats exposed to 200 mg barium/kg/day as barium chloride in drinking water for an intermediate duration (NTP 1994), and in mice exposed to 450 or 160 mg barium/kg/day as barium chloride in drinking water for intermediate and chronic durations, respectively (NTP 1994).

Metabolic Effects. Hypokalemia is a common finding in cases of severe barium poisoning (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). In a group of cases examined by Deng et al. (1991), serum potassium levels ranged from 0.8 to 2.7 mEq/L; normal values range from 3.5 to 5 mEq/L. Alterations in serum potassium levels have not been reported in rats exposed to 110 or 180 mg barium/kg/day as barium chloride in drinking water for 15 or 90 days,, respectively (NTP 1994).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to barium. Several animal studies have examined potential lymphoreticular effects, particularly damage to the thymus, spleen, and lymph nodes. Acute gavage exposure of rats to doses as high as 198 mg barium/kg/day as barium chloride for 1 or 10 days was not associated with any changes in thymus weight or any gross lesions of the thymus (Borzelleca et al. 1988). Intermediate and chronic oral exposure of rats to nominal concentrations of barium in drinking water of 37.5 and 15 mg/kg/day, respectively, of an unspecified barium compound was not associated with lesions of the lymph nodes or thymus upon gross and histopathologic examination (McCauley et al. 1985). No histopathological alterations were observed in the spleen or thymus of rats exposed to 180 or 60 mg barium/kg/day for an intermediate or chronic duration, respectively (NTP 1994). In mice, thymic and splenic atrophy were observed at 450 mg barium/kg/day after intermediate exposure and lymphoid depletion in the spleen and decreased spleen weight were observed at 160 mg barium/kg/day after chronic exposure (NTP 1994). These effects were probably secondary to the severe nephropathy and weight loss observed at these doses.

No studies have assessed the potential of barium to impair immune function.

The highest NOAEL values for lymphoreticular effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

Numbness and tingling around the mouth and neck were sometimes among the first symptoms of barium toxicity in humans (Lewi and Bar-Khayim 1964; Morton 1945). Occasionally, these neurological symptoms extended to the extremities (Das and Singh 1970; Lewi and Bar-Khayim 1964). Partial and complete paralysis occurred in severe cases, often accompanied by an absence of deep tendon reflexes (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Post-mortem examination in one case of poisoning by ingestion of barium sulfide revealed brain congestion and edema (McNally 1925).

Animal studies have not found significant alterations in brain weight or histopathology following acute gavage exposure of rats for 1 or 10 days to doses as high as 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988), intermediate oral exposure of rats to doses as high as 115 mg barium/kg/day in drinking water (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980), intermediate-duration exposure of

mice to doses less than 450 mg barium/kg/day as barium chloride in drinking water (NTP 1994), or chronic exposure of rats and mice to doses greater than 60 or 160 mg barium/kg/day as barium chloride in drinking water, respectively (NTP 1994). Neurobehavioral performance (spontaneous motor activity, grip strength, tail flick latency, startle response, hindlimb foot splay) was evaluated in rats and mice exposed to barium chloride for 15 or 90 days (NTP 1994). No alterations were observed in rats or mice following a 15-day exposure to 110 or 70 mg barium/kg/day. Slight decreases in motor activity were observed in rats exposed to 10–115 mg barium/kg/day for 90 days; these changes were not considered to be biologically significant. However, in female rats exposed to 180 mg barium/kg/day, spontaneous motor activity was 30% lower than controls; this difference was considered to be biologically significant. In mice, the only alteration noted was a decrease in forelimb grip strength in females exposed to 495 mg barium/kg/day for 90 days; the investigators noted that this may have been due to debilitation. The highest NOAEL values and reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to barium. However, limited data are available from acute, intermediate, and chronic animal studies in which certain reproductive organs were weighed and examined grossly and microscopically following oral barium exposure. Gavage exposure of rats to doses of 198 mg barium/kg/day as barium chloride for 10 days resulted in decreased ovary weight and decreased ovary/brain weight ratio (Borzelleca et al. 1988); no alterations were observed after a single gavage dose with 198 mg barium/kg/day (Borzelleca et al. 1988). Neither study found changes in testicular weight, and no gross lesions of the ovaries or testes were observed at this dose. No histological alterations were observed in the reproductive tissues of male and female rats and mice exposed to 110 mg barium/kg/day (rats) or 70/85 mg barium/kg/day (mice) as barium chloride in drinking water (NTP 1994). Intermediate and chronic oral exposure of rats to barium in drinking water at doses of 200 mg barium/kg/day and lower was not associated with any gross or histopathologic lesions of the uterus, ovaries, or testes (Dietz et al. 1992; McCauley et al. 1985; NTP 1994). Similarly, no histopathological alterations were observed in reproductive tissues of mice exposed to 495 mg barium/kg/day and lower for an intermediate duration (NTP 1994) or 160 mg barium/kg/day or lower for a chronic duration (NTP 1994). Additionally, no alterations in epididymal sperm counts, sperm motility, or sperm morphology were observed in rats or mice exposed to 200 or 205 mg barium/kg/day, respectively, as barium chloride in drinking water for 60 days (Dietz et al. 1992).

There are limited data on the potential of barium to impair reproductive function. No significant alterations in pregnancy rate or gestation length were observed in rats or mice exposed to approximately 200 mg barium/kg/day as barium chloride in drinking water (Dietz et al. 1992); the males were exposed for 60 days prior to mating and the females were exposed for 30 days.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

Studies regarding developmental effects of barium following oral exposure are limited to one human study (Morton et al. 1976) and three animal studies (Dietz et al. 1992; Tarasenko et al. 1977). A statistically significant negative correlation was found between barium concentrations in drinking water and human congenital malformation rates of the central nervous system in South Wales (Morton et al. 1976). A negative correlation implies that as the barium concentration in drinking water increased, the rate of central nervous system malformations decreased. This statistical study is of limited value in identifying a NOAEL for developmental effects because exposure conditions (duration and frequency of exposure, dose, number of subjects exposed) were not characterized.

Developmental effects were reported in a study in which an unspecified animal species was orally administered a dose of barium carbonate that was equal to 1/16 of the LD_{50} for 24 days prior to conception and pregnancy (Tarasenko et al. 1977). Reported effects in offspring included increased mortality during the first 2 months, increased leukocyte count, disturbances in liver function, and increased urinary excretion of hippuric acid. This study is inadequate for evaluating developmental effects of oral barium exposure because of major study limitations. These limitations include a general lack of information provided by the authors regarding experimental methods, exposure conditions, and test results, and no information as to the species and number of animals tested, the purity of the test material, the statistical methods used, and whether or not controls were used.

In studies by Dietz et al. (1992), male rats and mice were exposed to barium chloride in drinking water for 60 days and mated to females exposed to barium chloride for 30 days. In the rats, exposure to 180/200 mg barium/kg/day resulted in significant decreases in pup birth weights. Decreases in the live litter size at postnatal days 0 and 5 were also observed in the 180/200 mg barium/kg/day group, but the difference was not statistically significant; litter sizes were 9.0 and 9.3 pups in controls on days 0 and 5,

and 7.2 and 7.1 pups on days 0 and 5 in the 200 mg barium/kg/day group. No adverse developmental effects were observed in the mice (highest dose tested was 200 mg barium/kg/day).

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to barium. Several animal studies evaluated the induction of tumors following chronic oral exposure to barium (NTP 1994; Schroeder and Mitchener 1975a, 1975b). In studies by Schroeder and Mitchener (1975a, 1975b), rats and mice were exposed to 0.7 and 0.95 mg barium/kg/day, respectively, as barium acetate in drinking water for lifetime. No differences in the incidence of tumors were noted between treated animals and vehicle controls in either study. These studies are inadequate for evaluating the carcinogenic potential of barium because insufficient numbers of animals were used for a carcinogenicity study, it was not determined whether or not a maximum tolerated dose was achieved, a complete histological examination was not performed, the purity of the test material was not specified, and only one exposure dose was used in each study. Studies conducted by the NTP (1994) are considered adequate for carcinogenicity assessment. In rats exposed to doses as high as 60–75 mg barium/kg/day as barium chloride in drinking water, significant negative trends for mononuclear cell leukemia, adrenal medulla pheochromocytoma, and mammary gland neoplasms were found. No significant increases in malignant tumors were observed. Similarly, no increases in malignant tumor incidences were observed in mice chronically exposed to doses up to 160–200 mg barium/kg/day as barium chloride in drinking water.

3.2.3 Dermal Exposure

Limited information is available regarding the health effects of barium following dermal exposure. Barium salts would be expected to have a local effect on skin surfaces and would not likely be absorbed systematically to any great extent. Available studies include a case report of an individual exposed dermally to molten barium chloride (Stewart and Hummel 1984), a skin irritation study evaluating barium carbonate in experimental animals (Tarasenko et al. 1977), and a skin-painting study in which mice were exposed dermally to a barium hydroxide extract of tobacco leaf (Van Duuren et al. 1968). No reliable information was available from any of these dermal studies to identify study NOAELs or LOAELs for barium. In the case report (Stewart and Hummel 1984), the dermal burns that developed in the individual

exposed to molten barium chloride may potentially have contributed to some of the reported health effects, which are described briefly in Section 3.2.3.2 (Systemic Effects).

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to barium.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to barium.

Cardiovascular Effects. An abnormal electrocardiogram was observed in a 62-year-old man burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding cardiovascular effects in animals after dermal exposure to barium.

Gastrointestinal Effects. A 62-year-old man experienced vomiting after he was accidentally burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding gastrointestinal effects in animals after dermal exposure to barium.

Dermal Effects. Molten barium chloride induced burns on the skin of a 62-year-old man who was accidentally exposed through an explosion. The dermal burns, however, were very probably due to the molten nature of the material and not necessarily to barium chloride (Stewart and Hummel 1984).

The dermal effects of barium carbonate were examined in a study with rats and rabbits (Tarasenko et al. 1977). When barium carbonate in lanolin was applied to the skin, ulcers developed. These dermal lesions reportedly disappeared within a month when dermal treatment was discontinued. Although these findings suggest that barium carbonate may be a dermal irritant, these particular investigations are inadequate for establishing the dermal effects of barium because of a number of significant study limitations. The authors provided few details regarding experimental methods and results, and no information as to the concentration of barium carbonate used, the number of animals used, and whether or not controls were used.

Ocular Effects. Information on the ocular toxicity of barium is limited to a study conducted by Tarasenko et al. (1977) in rats and rabbits. When barium carbonate powder was introduced into the

conjunctival sac, purulent discharge, conjunctivitis, and slight opacity of the cornea developed. As noted in the Dermal Effects section, interpretation of these results is limited by the poor reporting of study methods and results, lack of information on barium carbonate concentration, and whether controls were used.

Metabolic Effects. A 62-year-old victim accidentally exposed to molten barium chloride had a depressed plasma potassium level when admitted to the hospital (Stewart and Hummel 1984).

No studies were located regarding the following health effects in humans or animals after dermal exposure to barium:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans after dermal exposure to barium. Dysplasia of the cervical epithelium was reportedly induced in a woman who had a barium chloride solution applied to her cervix (Ayre 1966). The use of dimethyl sulfoxide in combination with the barium chloride solution reportedly enhanced the ability of barium chloride to induce dysplasia. Dysplasia can be regarded as a potential precancerous lesion. The significance of the observations reported in this study are difficult to assess, since only one subject was exposed and because there have been no reports of similar findings in other human or animal studies. Also, the vehicle used was not specified in this study.

No studies were located regarding cancer in animals after dermal exposure to barium. However, results of one skin-painting study with mice suggest that barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent (Van Duuren et al. 1968); the purity of the barium hydroxide extract was not reported. In this study, mice were treated dermally for an unspecified period of time with either barium hydroxide extract alone, 7,12-dimethylbenz(a)anthracene (DMBA) alone (an initiating agent), or a combination of DMBA and barium hydroxide extract. After 1 year, none of the mice treated with barium hydroxide extract developed skin tumors. However, 3 out of 20 mice treated with DMBA alone and 7 out of 20 mice treated with a combination of both barium hydroxide extract and DMBA developed skin

papillomas and carcinomas. These results provide limited, but suggestive evidence that barium hydroxide extract of tobacco leaf acted as a tumor-promoting agent. However, it can not be determined whether or not this apparent positive tumorigenic response was due to barium hydroxide or some other component of the barium hydroxide tobacco leaf extract.

3.3 GENOTOXICITY

In vivo studies of barium genotoxicity are limited to a study in *Drosophila melanogaster*. In this study, positive results were found in the somatic mutation and recombination test when high levels of barium nitrate were used; the results were inconclusive at low barium nitrate levels (Yesilada 2001). *In vitro* studies were limited and summarized in Table 3-2. No significant alterations in gene mutation frequency were observed in *Salmonella typhimurium* (Monaco et al. 1990, 1991; NTP 1994) or *Escherichia coli* (Rossman et al. 1991). Similarly, barium chloride or barium nitrate did not result in deoxyribonucleic acid (DNA) damage in *Bacillus subtilis* (Kanematsu et al. 1980; Nishioka 1975). Tests of the fidelity of DNA synthesis using an avian myeloblastosis virus (AMV) DNA polymerase system showed that neither barium acetate nor barium chloride affect the accuracy of DNA replication (Sirover and Loeb 1976a, 1976b). However, studies with a DNA polymerase I system from *Micrococcus luteus*, demonstrated that concentrations of barium ion ≤0.1 mM stimulated DNA polymerase activity while concentrations greater than this inhibited polymerase activity (Korman et al. 1978). The significance of the inhibitory and stimulatory effects has not been determined. Results from an experiment designed to test the effect of barium chloride on sporulation frequency, recombination frequency, and meiotic failures in *Saccharomyces cerevisiae* demonstrated a definite inhibition of sporulation. Effects on recombination frequency and meiotic failures were ambiguous. Barium chloride may have caused a marginal increase in recombination frequency and information of diploid clones (Sora et al. 1986), but the data are inconclusive. In mammalian test systems, barium chloride did not increase the frequency of sister chromatid exchange or chromosome aberrations in Chinese hamster cells (NTP 1994). However, an increase in gene mutations was observed at the TK locus of L5178Y mouse lymphoma cells in the presence of metabolic activation, but not without metabolic activation (NTP 1994).

Table 3-2. Genotoxicity of Barium and Barium Compounds *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation frequency (with or without S9 activation)	–	Monaco et al. 1990, 1991; NTP 1994	Barium chloride
Escherichia coli WP2s(λ)	Gene mutation frequency	–	Rossman et al. 1991	Barium chloride
Bacillus subtilis	DNA damage (rec assay)	–	Kanematsu et al. 1980; Nishioka 1975	Barium chloride, barium nitrate
Eukaryotic organisms:				
Fungi				
Saccharomyces cerevesiae	Meiosis	–	Sora et al. 1986	Barium chloride
Avian myeloblastosis virus DNA polymerase	DNA synthesis	–	Sirover and Loeb 1976a, 1976b	Barium chloride, barium acetate
Mammalian cells:				
CHO cells	Sister chromatid exchange (with or without S9 activation)	–	NTP 1994	Barium chloride
CHO cells	Chromosome aberration (with or without S9 activation)	–	NTP 1994	Barium chloride
Mouse lymphoma cells	Gene mutation at TK locus With S9 activation Without S9 activation	 + –	NTP 1994	Barium chloride

– = negative result; + = positive result; CHO = Chinese hamster ovary

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption of barium in humans following inhalation exposure. Several animal studies have investigated the absorption of barium chloride or barium sulfate following inhalation, intratracheal injection, or nasal deposition. The results of these studies suggest that the rate and extent of absorption of barium from the respiratory tract depend on the exposure level, how much barium reaches the alveolar spaces, the clearance rate from the upper respiratory tract, and the solubility of the particular form of barium that was administered. Approximately 50–75% of inhaled barium chloride or barium sulfate is absorbed from the respiratory tract (Cuddihy and Griffith 1972; Morrow et al. 1968); approximately 65% of the barium chloride deposited in the nose is absorbed (Cuddihy and Ozog 1973b). Most of the barium absorption occurs within the first 24 hours (Cuddihy and Griffith 1972; Cuddihy et al. 1974). Barium chloride appears to be more rapidly absorbed than barium sulfate (Cuddihy et al. 1974), although the differences in particle size (AMADs of 2.3 and 1.0 µm for barium chloride and barium sulfate, respectively) may have influenced the absorption rate. In contrast to the rapid absorption of barium following inhalation or nasal deposition, most of the barium sulfate that is injected directly into the trachea of rats can be taken up into the epithelium membranes and remains in these membranes for at least a few weeks (Gore and Patrick 1982; Takahashi and Patrick 1987), suggesting that clearance in the upper respiratory tract is more efficient than in the trachea. Following intratracheal injection, the clearance of barium sulfate from the lungs was independent of lung burden over the range of 23.3–2,330 µg (Cember et al. 1961); this is consistent with the lack of evidence of lung overload following intermediate-duration inhalation exposure to 37.5 or 75 mg/m^3 barium sulfate (MMAD 4.3 µm, σg 1.7) (Cullen et al. 2000). Species differences in the retention of intratracheally administered radiolabelled (^{133}Ba) barium sulfate have been found. The percentages of ^{133}Ba retained in the trachea 1 week after administration were 0.41, 0.145, 0.044, and 0.043% in rats, rabbits, dogs, and monkeys, respectively (Takahashi and Patrick 1987; Takahashi et al. 1993).

3.4.1.2 Oral Exposure

The absorption of barium from the gastrointestinal tract is compound dependent. Barium sulfate is extremely insoluble and very little, if any, ingested barium sulfate is absorbed. Acid-soluble barium compounds, such as barium chloride and barium carbonate, are absorbed through the gastrointestinal

tract, although the amount of barium absorbed is highly variable. Older human studies estimated that barium was poorly absorbed; approximately 1–15% of the ingested dose was estimated to be absorbed (Harrision et al. 1956; LeRoy et al. 1966; Schroeder et al. 1972; Tipton et al. 1969). A re-examination of the methods used in these studies found a number of flaws; Leggett (1992) estimated that barium absorption in these studies was approximately 3–60%. Studies in adult rats and dogs estimated fractional absorption at 7% (Cuddihy and Griffith 1972; Taylor et al. 1962). Several unpublished animal studies discussed by Leggett (1992) found absorption rates of 1–50%. Experiments in rats have shown that younger animals (22 days old or less) absorb about 10 times more barium chloride from the gastrointestinal tract (63–84%) than do older animals (about 7%) (Taylor et al. 1962). Absorption was higher in fasted adult rats (20%) as compared to fed rats (7%). The International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is 20% in adults, 30% for children aged 1–15 years, and 60% in infants (ICRP 1993).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption of barium in humans after dermal exposure. One animal study showed that barium applied to the skin of piglets was found in the various layers of the skin (Shvydko et al. 1971). Barium is not expected to cross the intact skin because of the high polarity of the forms in which it is most commonly encountered.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Shortly after dogs were exposed to radiolabelled (^{140}Ba) barium chloride, elevated activity was found in the upper respiratory tract, stomach, and small intestine (30% of initial burden), lungs and tracheobronchial tissue (6%), and various internal organs (64%) (Cuddihy and Griffith 1972). One day post-exposure, 44% of the label was detected in the skeleton, 1% in blood, and 4% in muscle; 26% of the dose was excreted.

3.4.2.2 Oral Exposure

In humans, barium is predominantly found in bone; approximately 90% of the barium in the body was detected in the bone (Schroeder et al. 1972). Approximately 1–2% of the total body burden was found in muscle, adipose, skin, and connective tissue. This information is supported by a number of studies

(Bauer et al. 1957; Losee et al. 1974; Miller et al. 1985; Sowden 1958; Sowden and Stitch 1957; Sowden and Pirie 1958). Significant increases in the levels of barium in bone were found in rats administered barium chloride in the diet or barium as a component of Brazil nuts for 29 days (Stoewsand et al. 1988); this study did not examine other tissues. A study by McCauley and Washington (1983) in which rats were exposed to barium chloride and barium carbonate in drinking water found the following non-skeletal distribution (skeletal tissue was not examined in the study) 24 hours after ingestion: heart > eye > skeletal muscle > kidney > blood > liver.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of barium in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Human injection studies support the findings of the inhalation and oral exposure studies. Barium is rapidly cleared from the blood and distributed to bone (Bauer et al. 1957; Harrison et al. 1966, 1967; Newton et al. 1991). A long-term study of barium retention in humans injected with ^{133}Ba found that after the first couple of years, bone turnover was the most significant contributor to barium losses from the skeleton (Newton et al. 2001).

3.4.3 Metabolism

Barium is not metabolized in the body, but it may be transported or incorporated into complexes or tissues.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies have been located regarding excretion of barium following inhalation exposure in humans. Studies in animals demonstrate that the fecal excretion of barium exceeds urinary excretion (Cember et al. 1961; Cuddihy and Griffith 1972; Cuddihy et al. 1974). In dogs, 30% of the total barium excretion was accounted for by urine (Morrow et al. 1964).

3.4.4.2 Oral Exposure

A study of two humans ingesting a normal diet found that fecal excretion of barium was 2–3 times higher than urinary excretion over a 30-day period (Tipton et al. 1966). A 29-day rat study also demonstrated that the feces was the primary route of excretion following exposure to barium chloride in the diet or barium from brazil nuts (Stoewsand et al. 1988).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of barium in humans or animals after dermal exposure.

3.4.4.4 Other Routes of Exposure

Several human studies have examined the excretion of barium following parenteral administration. These studies confirm the findings of the inhalation or oral exposure studies that barium is primarily excreted in the feces. In a study, one subject receiving an intravenous injection of ^{133}Ba, 84% of the radiolabelled barium was excreted within the first 6 days, primarily in the feces (75% of total dose) (Harrison et al. 1967; Newton et al. 1977). The ratio of fecal to urinary barium excretion in six subjects injected with ^{133}Ba ranged from 6 to 15 for the first 2 weeks (Newton et al. 1991).

A study in rats (Edel et al. 1991) found that biliary excretion did not significantly contribute to the total amount of barium excreted in the feces, suggesting that other physiological routes were responsible for fecal barium. A study of rabbits administered an intravenous injection of radiolabelled barium also found that barium was primarily excreted in the feces. After the first day, fecal excretion was approximately twice as high as urinary excretion. The barium was primarily excreted in the first 5 days after exposure; after 9 days, approximately 50% of the dose was excreted (Liniecki 1971).

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

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

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-2 shows a conceptualized representation of a PBPK model.

If PBPK models for barium 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.

No information on available PBPK models for barium has been identified.

3.5 MECHANISMS OF ACTION

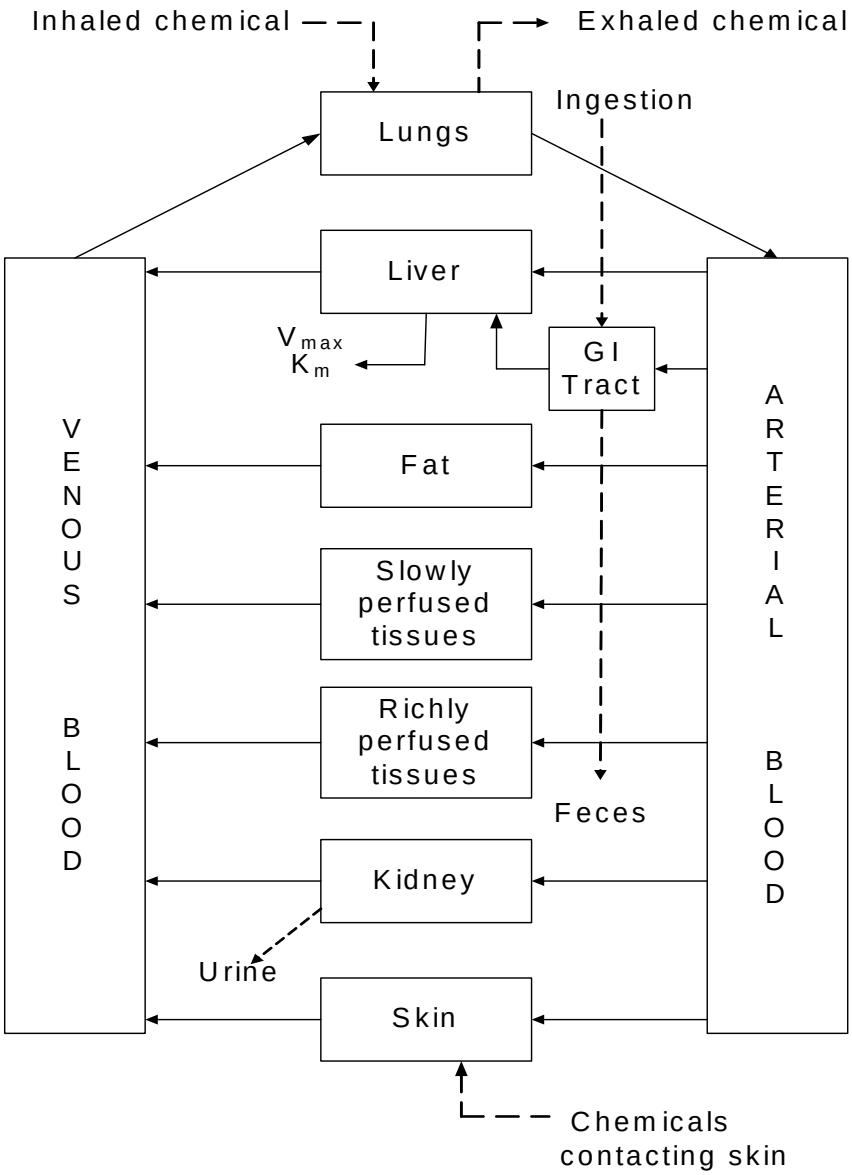
3.5.1 Pharmacokinetic Mechanisms

No studies were located for animals or humans that describe observed mechanisms for barium absorption across the skin, lung, or gut or barium distribution, metabolism, or excretion.

3.5.2 Mechanisms of Toxicity

The mechanism of barium toxicity has not been fully elucidated. Presumably, high-dose exposure to barium consistently results in a number of effects including ventricular tachycardia, hypertension and/or hypotension, and muscle weakness and paralysis (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Talwar and Sharma 1979; Wetherill et al. 1981). There is strong evidence that many of these effects result from increases in intracellular potassium levels. Barium is a competitive potassium channel antagonist that blocks the passive efflux of intracellular potassium, resulting in a shift of potassium from extracellular to intracellular compartments (Roza and Berman 1971). The intracellular translocation of potassium results in a decreased resting membrane potential, making the muscle fibers electrically unexcitable and causing paralysis (Koch et al. 2003). Hypokalemia (serum potassium levels below 3.5 mEq/L) has been reported in a number of individuals exposed to high doses of barium (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). Intravenous infusion of potassium often relieves many of the symptoms of barium toxicity (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). However, there is also evidence that some of these effects may be due to barium-induced neuromuscular blockade and membrane depolarization (Phelan et al. 1984; Thomas et al. 1998). Two investigators (Phelan et al. 1984; Thomas et al. 1998) have shown an apparent direct relationship

Figure 3-2. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

Source: adapted from Krishnan and Andersen 1994

between serum barium levels and the degree of paralysis or muscle weakness in two individuals orally exposed to barium.

3.5.3 Animal-to-Human Extrapolations

Most of the available data in humans comes from case reports involving acute oral exposure to presumably high doses of barium; the primary effects noted were gastrointestinal distress and effects associated with hypokalemia (e.g., ventricular tachycardia, hypo or hypertension, paralysis). Only one human exposure study (Wones et al. 1990) provided reliable information on exposure level; this study did not find any significant alterations in blood pressure in subjects exposed to relatively low doses of barium. The available data in laboratory animals suggest that toxicity of ingested barium is similar across species. Studies conducted by the NTP (1994) in rats and mice found similar targets of toxicity; although some differences in sensitivity were found between the species. Following intermediate-duration exposure, renal effects were observed at lower doses in rats (115 mg barium/kg/day) than in mice (450 mg barium/kg/day). However, NTP (1994) concluded that rats and mice were equally sensitive to the barium-induced renal effects because adverse effect levels when estimated on a per unit surface area basis were similar for the two species. In the absence of contrary data, it is assumed that humans and animals would have similar targets of toxicity and equal sensitivity.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active

chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in human and/or animals after exposure to barium; additionally, *in vitro* studies were not located.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage

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

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There is limited information on age-related differences in the toxicity of barium in humans or animals. Deng et al. (1991) and Lewi and Bar-Khayim (1964) reported cases from two food poisoning incidents that involved exposure of adults and children. Both reports noted that children did not seem to be affected by the barium carbonate exposure; however, these data should be interpreted cautiously because neither involved examination of exposed children and no information is available on barium carbonate intake. There are limited data on the developmental toxicity of barium in laboratory animals. The body weights of the offspring of rats exposed to barium chloride prior to mating were significantly lower than

control pup body weights. A decrease in litter size was also observed, although the difference was not statistically significant (Dietz et al. 1992). No developmental effects were observed in the offspring of mice exposed to barium chloride prior to mating (Dietz et al. 1992). Reduced survival and decreased body weight were observed in the offspring of rats exposed to barium carbonate dust (Tarasenko et al. 1977); however, poor reporting of the study methods and results limits the interpretation of the Tarasenko et al. (1977) study.

There are some data suggesting possible age-related differences in toxicokinetic properties of barium. A higher rate (about 10 times higher) of absorption was found in younger rats compared to older rats (Taylor et al. 1962). A study of cadmium and mercury also found higher permeability in the jejunum of immature rats as compared to mature animals (Foulkes and Bergman 1993). An unpublished study by Della Rosa summarized by ICRP (1993) found higher barium retention in dogs aged 43 (2.3% retained) or 150 (2.0%) days, compared to dogs aged 250 days (0.8%) or adult dogs (0.4–0.6%). Information on biomarkers, interactions, and methods for reducing toxic effects of barium (discussed in Sections 3.8, 3.10, and 3.11) comes from studies in adults and mature animals; no child-specific information was identified. In the absence of data to the contrary, it is assumed that this information will also be applicable to children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental

conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to barium are discussed in Section 3.8.1.

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 barium are discussed in Section 3.8.2.

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

At present, there are no well-established biomarkers of exposure and effect for barium. Data suggesting possible biomarkers are presented below.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Barium

Barium can be measured in bone, blood, urine, and feces. It has been shown to be sequestered in bone and teeth and excreted in feces and urine. Background levels of barium in bone are approximately 2 µg/g wet weight (ICRP 1974; Schroeder et al. 1972). Background levels of barium in blood, urine, and feces will vary with daily intake of barium. However, the following levels have been reported: bone, 2 ppm (ICRP 1974; Schroeder et al. 1972); feces, 690–1,215 µg/day (ICRP 1974; Schroeder et al. 1972; Tipton et al. 1969); and urine, 17–50 µg/day (ICRP 1974; Schroeder et al. 1972; Tipton et al. 1969). In the United States, the geometric mean concentration of barium in the urine is approximately 1.5 µg/L (CDC 2005). There are no data correlating bone, blood, urine, or feces levels of barium with specific exposure levels. For more detailed information on the toxicokinetics of barium, see Section 3.4.

3.8.2 Biomarkers Used to Characterize Effects Caused by Barium

Reports of individuals exposed to high levels of barium suggest that cardiovascular, nervous, and gastrointestinal systems are targets of barium toxicity (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). The likely cause of most of these effects is barium induced hypokalemia. Gastrointestinal disturbances are usually the first symptoms of acute barium exposure. Hypokalemia, hypertension, and abnormalities in heart rhythm frequently occur shortly afterwards. General muscle weakness is a frequent symptom, sometimes followed by paralysis. Nerve conduction is often affected, resulting in numbness and tingling of the mouth, neck and extremities. Loss of deep tendon reflexes may also occur. Not all symptoms appear in every case of acute barium poisoning. Although the observation of hypokalemia and gastrointestinal upset may be indicative of exposure to high doses of barium, other toxicants and disease states can produce these effects.

Animal studies also suggest that the kidney is a target of barium toxicity; the observed nephropathy is not specific to barium and would not be a sensitive biomarker of effect.

3.9 INTERACTIONS WITH OTHER CHEMICALS

There are no data regarding the interaction between barium and various chemicals potentially found at hazardous waste sites. However, there are data that suggest that barium may interact with other cations and certain prescription drugs. Drug interactions are of relevance because individuals exposed to barium by living or working near hazardous waste sites contaminated with this substance may also be taking prescription drugs.

The cations potassium, calcium, and magnesium also interact with barium. Barium exposure, for example, may cause a buildup of potassium inside the cell resulting in extracellular hypokalemia, which is believed to mediate barium-induced paralysis. In fact, potassium is a powerful antagonist of the cardiotoxic and paralyzing effects of barium in animals (Foster et al. 1977; Jaklinski et al. 1967; Roza and Berman 1971; Schott and McArdle 1974) and is used as an antidote in cases of acute barium poisoning. Calcium and magnesium suppress uptake of barium by pancreatic islets *in vitro*. Conversely, barium, in low concentrations, stimulates calcium uptake in these cells. Although the data are insufficient to

determine the significance of these findings to human health effects, displacement of calcium may be the mechanism by which barium stimulates insulin release (Berggren et al. 1983).

Among the drugs that are known to interact with barium, the barbiturates sodium pentobarbital and phenobarbital, were found to have an increased depressive effect on the hearts of rats exposed to barium (Kopp et al. 1985; Perry et al. 1983, 1989). This hypersensitivity of the cardiovascular system to anesthesia was not observed in similarly treated animals that were anesthetized with xylazine plus ketamine. Results of the study indicated that the hypersensitivity was specific to the barbiturates and not a generalized effect of anesthesia (Kopp et al. 1985).

Other medically prescribed drugs interact with barium. Experiments with mice indicated that atropine significantly antagonized antinociception and death induced by intracerebroventricular injection of barium chloride (Segreti et al. 1979; Welch et al. 1983). These same studies also found that naloxone, a narcotic antagonist, inhibited the lethal toxicity of barium (Segreti et al. 1979; Welch et al. 1983). Propranolol had no effect on barium-induced paralysis in rats (Schott and McArdle 1974). Verapamil rapidly abolished cardiac dysrhythmias in rabbits injected with barium chloride (Mattila et al. 1986). In the same study, pretreatment with the tricyclic antidepressant, doxepin, was found to offer some protection against barium-induced dysrhythmias (Mattila et al. 1986). Ouabain, which is an inhibitor of Na^+-K^+ ATPase, while not widely prescribed, has been shown to rapidly reverse the paralyzing effects of barium. It has been hypothesized that ouabain works by reducing barium-induced hypokalemia by allowing some intracellular potassium to escape. However, this hypothesis has not yet been proved or disproved because of the complexity of the mechanism involved (Schott and McArdle 1974).

Other substances can affect barium pharmacokinetics. One study showed that sodium alginate could reduce retention of orally administered barium, possibly by inhibiting absorption in the gut (Sutton et al. 1972). This could be useful in treating cases of acute barium ingestion. Lysine and lactose increase absorption of barium and could increase the toxic effects of oral exposure (Lengemann 1959).

A human study involving one adult female was performed by applying barium chloride, alone and in combination, with dimethyl sulfoxide to the cervical epithelium. Dimethyl sulfoxide significantly enhanced the ability of barium chloride to induce dysplasia with unusual cell formation in the cervical epithelium (Ayre 1966). The significance of this is difficult to determine since there was only one subject, there were no controls, and few details of the experiment were provided.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

The limited data available suggest that certain subgroups of the population may be more susceptible to barium exposure than the general population. These include people with cardiovascular problems or lung disease, those taking certain prescription drugs, children, pregnant women, and smokers.

Animal studies suggest that the kidney may be a sensitive target of barium toxicity; thus, individuals with impaired renal function may have a higher risk of developing barium-induced kidney damage. There is suggestive evidence that barium may affect blood pressure. Therefore, humans with hypertension could be at increased risk from either chronic, intermediate, or acute barium exposure. Barbiturates have been shown to have an enhanced depressant effect on the heart in barium-exposed animals (Kopp et al. 1985; Perry et al. 1983, 1989). Individuals on this type of medication may experience an increased risk of heart problems on exposure to barium.

Since exposure to high doses of barium has been repeatedly demonstrated to significantly decrease serum potassium in both humans and animals (Foster et al. 1977; Gould et al. 1973; Phelan et al. 1984; Roza and Berman 1971), individuals taking diuretics may have a more severe hypokalemic reaction to barium toxicity.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to barium. 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 barium. 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 barium:

Dreisbach RH, Robertson WO, eds. 1987. Handbook of poisoning: Prevention, diagnosis and treatment. 12th ed. Norwalk, CT: Appleton & Lange, 119-120.

Haddad LM, Winchester JF, eds. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: WB Saunders Company, 1129.

3.11.1 Reducing Peak Absorption Following Exposure

The general population is typically exposed to barium through consumption of food and drinking water; workers may also be exposed to barium via inhalation or dermal contact. General recommendations for reducing absorption of barium following exposure have included removing the exposed individual from the contaminated area and removing contaminated clothing, followed by washing with mild soap and water. If the eyes and skin were exposed, they are flushed with water. Lavage or emesis has also been suggested; however, high concentrations of barium cause nausea and emesis should not be induced in cases where substantial vomiting has already occurred (Haddad and Winchester 1990). Furthermore, there is a risk of aspiration of vomitus during emesis. Administration of soluble sulfates orally will also limit absorption of barium by causing precipitation of an insoluble form of barium (barium sulfate) (Dreisbach and Robertson 1987; Haddad and Winchester 1990). However, intravenous administration of sulfate salts should be avoided because barium precipitate in the kidneys will cause renal failure (Dreisbach and Robertson 1987; Koch et al. 2003).

3.11.2 Reducing Body Burden

Barium is primarily distributed to the bone and teeth; it is not known if the barium distributed to these tissues would result in toxicity. A method for reducing the levels of barium in bone and teeth has not been identified. Removal of barium from the bloodstream may be facilitated by infusing with saline and inducing saline diuresis (Dreisbach and Robertson 1987). As described in several case reports of barium poisoning (Bahlmann et al. 2005; Koch et al. 2003; Thomas et al. 1998; Wells and Wood 2001), hemodialysis resulted in significant decreases in the levels of barium in the blood and improved clinical signs.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Hypokalemia is commonly seen in cases of acute barium toxicity and may be responsible for some of the symptoms of barium poisoning (Proctor et al. 1988). Plasma potassium should be monitored and hypokalemia may be relieved by intravenous infusion of potassium (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988).

3.12 ADEQUACY OF THE DATABASE

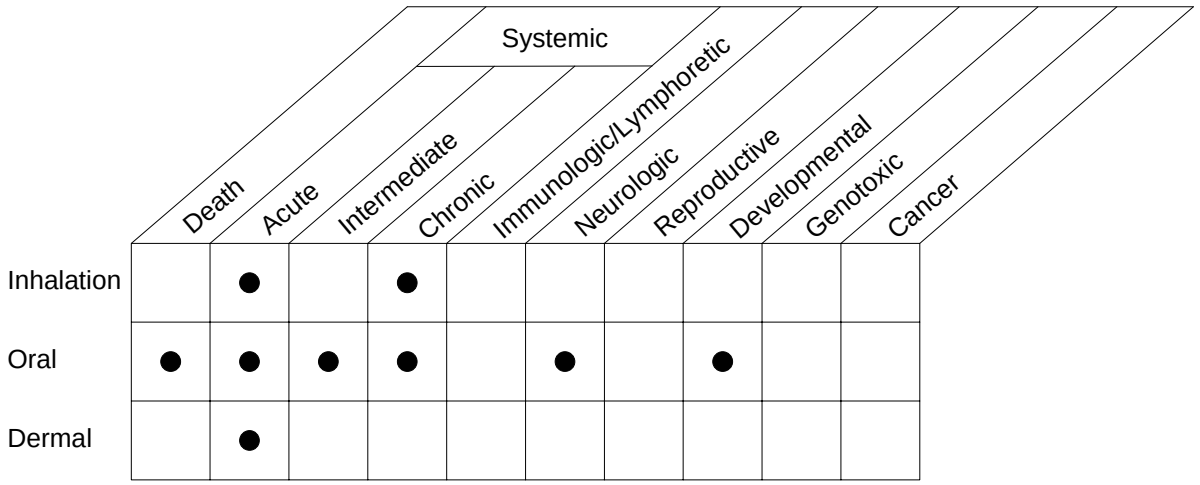
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium and compounds is available. Where adequate information 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 barium and compounds.

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

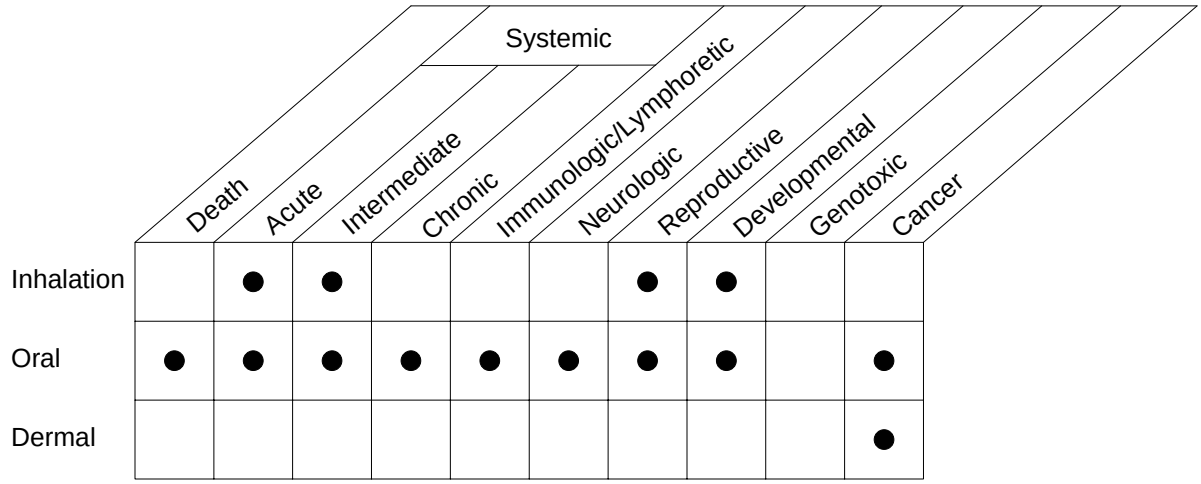
3.12.1 Existing Information on Health Effects of Barium and Barium Compounds

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

Figure 3-3. Existing Information on Health Effects of Barium and Barium Compounds



Human



Animal

● Existing Studies

There is little information regarding health effects in humans following inhalation, oral, or dermal exposure to barium and barium compounds (Figure 3-3). Inhalation studies are limited to several case reports of individuals exposed acutely or chronically through occupational exposure (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). A number of case reports of acute oral exposure to high doses of barium have been identified (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). Additionally, there is information from a single intermediate-duration experimental study (Wones et al. 1990) and several human epidemiological studies or statistical studies examining mortality and morbidity rates in communities having exposure to barium through drinking water supplies (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Dermal studies are limited to one case report of an exposed individual (Stewart and Hummel 1984).

The majority of studies conducted on animals have been oral exposure studies (Figure 3-3). Available inhalation studies with experimental animals (Hicks et al. 1986; Tarasenko et al. 1977) can only suggest information on the health effects of barium because these studies have a number of limitations and deficiencies; a third inhalation study (Cullen et al. 2000) is limited to the examination of the respiratory tract. The available oral studies have examined a number of end points, although most studies focused on various systemic effects for acute (Borzelleca et al. 1988; Boyd and Abel 1966; Tardiff et al. 1980), intermediate (Dietz et al. 1992; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tarasenko et al. 1977; Tardiff et al. 1980), and chronic exposure (Kopp et al. 1985; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b). Dermal studies with experimental animals are limited to one skin irritation study (Tarasenko et al. 1977) and one study evaluating the tumor-promoting activity of barium (Van Duuren et al. 1968).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are limited data on the acute toxicity of barium following inhalation, oral, or dermal exposure. Data on the toxicity of inhaled barium are limited to a human experimental study in which welders were exposed to fumes from barium-containing electrodes (Zschiesche et al. 1992), a case of a worker exposed to a large amount barium carbonate dust (Shankle and Keane 1988), and a study in which guinea pigs were exposed to a single concentration of barium chloride for unspecific amount of time (Hicks et al. 1986). Although none of these studies are suitable for derivation of an MRL, the Hicks et al. (1986) study does identify two potential end points (increased

blood pressure and bronchoconstriction). Additional inhalation studies are needed to fully evaluate the toxicity of barium and establish concentration-response relationships.

Most of the available information on the acute toxicity of barium comes from human case reports involving oral exposure to soluble barium compounds and oral toxicity studies in animals. There are a number of case reports of individuals accidentally or intentionally ingesting large doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). In general, dose levels were not reported; based on the severity of the observed effects, it is likely that the doses were very high. The observed effects included effects associated with hypokalemia (cardiac arrest, ventricular tachycardia, muscle weakness, and paralysis), gastrointestinal distress (vomiting, gastric pain, and diarrhea), and kidney damage (hemoglobin in the urine, renal insufficiency, degeneration, and acute renal failure). Several studies in experimental animals have examined the acute oral toxicity of barium chloride (Borzelleca et al. 1988; Tardiff et al. 1980). These studies have determined LD_{50} values and evaluated potential systemic, neurological, and reproductive end points. These studies have not consistently identified targets of toxicity or adverse effect levels. The available data were considered inadequate for derivation of an acute oral MRL. Human data consistently identify the gastrointestinal tract as a target of barium toxicity; most case reports of individuals ingesting soluble barium compounds report vomiting, diarrhea, and/or abdominal pain as one of the early signs of toxicity. However, none of the animal studies have adequately investigated this end point; rodents are not a good model for examining gastrointestinal irritation. Animal studies are needed to identify the critical targets of barium toxicity and establish dose-response relationships; these studies should include a more appropriate animal model for investigating potential gastrointestinal effects.

Two studies have examined the dermal toxicity of barium. One is a case report on an individual burned with molten barium chloride (Stewart and Hummel 1984); extrapolation of the results of this study to environmental exposure scenarios is complicated by the thermal burns. Tarasenko et al. (1977) examined the dermal and ocular toxicity of barium carbonate in several animal species. Poor reporting of the experimental design and results limits the interpretation of the study. Additional dermal toxicity studies are needed for several barium compounds to confirm the Tarasenko et al. (1977) study findings that barium is a local irritant and to establish the existence of remote toxicity.

Intermediate-Duration Exposure. No human studies have examined the toxicity of barium in humans following intermediate-duration inhalation exposure. Two animal studies have been identified

(Cullen et al. 2000; Tarasenko et al. 1977). The Tarasenko et al. (1977) study examined systemic, reproductive, and developmental end points. However, interpretation of the results is limited by poor reporting of the study design and results. The Cullen et al. (2000) study only examined the respiratory tract. As these studies were considered inadequate for development of an inhalation MRL, additional studies examining a variety of end points are needed to identify the critical targets of barium toxicity and to establish concentration-response relationships.

One human experimental study examined the cardiovascular toxicity of barium (Wones et al. 1990) following oral exposure; no adverse effects were found. Several animal studies also examined the oral systemic toxicity (McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tardiff et al. 1980), neurotoxicity (NTP 1994), reproductive toxicity (Dietz et al. 1992), and developmental toxicity (Dietz et al. 1992; Tarasenko et al. 1977) of barium. The results of these studies suggest that the kidney is the most sensitive target of toxicity following intermediate-duration oral exposure. An intermediate-duration oral MRL based on kidney effects in rats exposed to barium chloride for 13 weeks (NTP 1994) has been derived.

Information on the oral toxicity of barium following intermediate-duration exposure comes from a human experimental study examining cardiovascular toxicity (Wones et al. 1990) and several animal studies examining systemic toxicity (McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tardiff et al. 1980), neurotoxicity (NTP 1994), reproductive toxicity (Dietz et al. 1992; NTP 1994), and developmental toxicity (Dietz et al. 1992). The human study did not find significant alterations in blood pressure or ECG readings in adults exposed to fairly low doses (Wones et al. 1990). Effects observed in the animal studies include increased blood pressure (Perry et al. 1983, 1985, 1989), kidney damage (glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane and mild to moderate nephropathy) (McCauley et al. 1985; NTP 1994), and developmental toxicity (decreased pup birth weight) (Dietz et al. 1992). The increase in blood pressure was observed at the lowest adverse effect level; however, two other studies (McCauley et al. 1985; NTP 1994) did not find significant alterations in blood pressure or ECG readings in rats exposed to higher doses of barium. The low-mineral diet used in the Perry et al. (1983, 1985, 1989) studies may have influenced the results. The calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995). Additional studies are needed to support this hypothesis. The results of the McCauley et al. (1985) and NTP (1994) studies suggest that the kidney is the most sensitive target of toxicity in rats and mice following intermediate-duration oral

exposure; an intermediate-duration oral MRL was derived based on kidney effects observed in rats exposed to barium chloride for 13 weeks (NTP 1994).

No studies have examined the toxicity in humans or animals following intermediate-duration dermal exposure. Studies are needed to assess the potential toxicity of various barium compounds and to establish whether dermal exposure would result in remote toxicity.

Chronic-Duration Exposure and Cancer. The toxicity of barium following chronic-duration inhalation exposure is limited to three occupational exposure studies (Doig 1976; Essing et al. 1976; Seaton et al. 1986). These studies focused on potential respiratory tract effects and are limited by co-exposure to other compounds, small number of tested workers, and/or lack of a comparison group. Well-designed studies examining a number of potential end points are needed to identify the critical targets of barium toxicity and establish concentration-response relationships. These studies would be useful for deriving a chronic-duration inhalation MRL for barium.

Three groups of investigators have examined the effect of living in a community with elevated barium levels in the drinking water and the risk of mortality and cardiovascular effects (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). These studies are limited by a number of factors including the lack of information on barium ingestion levels and the possible use of water softeners, which may have removed barium from the drinking water and increased the sodium content of the water. Several studies in rats and mice have examined the chronic toxicity of barium (NTP 1994; Perry et al. 1989; Schroeder and Mitchener 1975a, 1975b). The Perry et al. (1989) study found significant increases in systolic blood pressure in rats fed a relatively low concentration of barium in the diet; however, the contribution of the low mineral basal diet to the observed effect is not known. Several rat studies did not find adverse effects at the highest doses tested (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a). Marked renal nephropathy was observed in mice (NTP 1994); this study and effect were the basis of the chronic-duration MRL for barium. The available toxicokinetic data suggest that barium accumulates in bone; it is not known if this accumulation would result in adverse effects. Studies designed to test the possible association between high levels of barium in bone and adverse bone effects would be useful.

Data on the dermal toxicity of barium are limited to a skin tumor promotion study using barium hydroxide extract from tobacco plants (Van Duuren et al. 1968); the study did not examine noncancerous

end points. Additional dermal exposure studies are needed to evaluate whether various barium compounds are irritants and can cause remote-site toxicity.

No studies assessing the carcinogenicity of barium following chronic inhalation exposure were identified. The carcinogenicity of ingested barium has been assessed in several long-term oral exposure studies in rats and mice (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b). These studies did not find significant increases in the incidence of neoplastic lesions in either species. Although a study by Van Duuren et al. (1968) provided evidence suggesting that barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent when applied with a tumor initiating agent, there are no studies to assess barium's potential to be a complete carcinogen following dermal exposure. Based on the results of the oral study, it can be predicted that inhalation or dermal exposure to barium would not result in remote site carcinogenicity; however, it is not known if long-term exposure would result in respiratory tract cancer following inhalation exposure or skin cancer following dermal exposure. Inhalation and dermal exposure cancer studies are needed to address these questions.

Genotoxicity. The genotoxicity of barium has not been well characterized. One study used an *in vivo* assay to assess genotoxic potential (Yesilada 2001); increases in somatic mutations were observed in *D. melanogaster* following exposure to high levels of barium nitrate. The available data utilizing *in vitro* assays have not found significant alterations in gene mutation frequency or DNA damage in non-mammalian systems (Kanematsu et al. 1980; Monaco et al. 1990, 1991; Nishioka 1975; NTP 1994; Rossman et al. 1991; Sirover and Loeb 1976a, 1976b). In mammalian test systems, barium did not have clastogenic effects (NTP 1994), but did increase the frequency of gene mutation (NTP 1994). The available data are inadequate to thoroughly assess the genotoxic potential of barium; additionally studies, particularly *in vivo* assays, are needed.

Reproductive Toxicity. The reproductive effects of barium have not been thoroughly studied. There are no studies regarding reproductive effects in humans following barium exposure. Several animal studies have examined potential end points of reproductive toxicity. In the only inhalation exposure study (Tarasenko et al. 1977), a number of adverse effects were reported, including disturbances in spermatogenesis, shortened estrus cycle, and histological damage to the testes and ovaries. However, limited reporting of the study design and results and the lack of incidence data and statistical analysis limit the interpretation of the study results. Although a 10-day gavage study found significant decreases in relative and absolute ovary weights (Borzelleca et al. 1988), other oral exposure studies have not found alterations in organ weights or histological alterations in reproductive tissues following acute-,

intermediate-, or chronic-duration exposure (McCauley et al. 1985; NTP 1994). Additionally, no alterations in sperm morphology, motility, or counts were observed in rats or mice exposed to barium in drinking water for 60 days (Dietz et al. 1992). Only one oral study evaluated reproductive function (Dietz et al. 1992) and found no alterations in pregnancy rate or gestation length in rats or mice. A two-generation study would be useful for further evaluating the potential reproductive toxicity of barium. No dermal exposure studies examining reproductive end points were identified; based on available toxicokinetic data. Additional studies are needed to further assess if reproductive toxicity is an end point of concern for barium.

Developmental Toxicity. The developmental effects of barium have not been studied extensively in either humans or animals. One limited statistical study evaluated the degree of correlation between barium concentrations in drinking water and human congenital malformation rates of the central nervous system (Morton et al. 1976). Results of the study indicated there was a negative statistical correlation between these parameters, implying that a lower risk of congenital abnormalities was found in populations with higher barium levels. Two animal studies evaluated the potential developmental toxicity of barium. Reduced survival, underdevelopment, lowered body weight, decreased lability of the peripheral nervous system, and various blood disorders were reportedly noted in the offspring of rats following inhalation to barium for an intermediate exposure period (Tarasenko et al. 1977). The investigators also noted increased mortality and systemic toxicity in the offspring of rats orally exposed to barium during conception and pregnancy. As noted previously, interpretation of the results from the Tarasenko et al. (1977) studies are limited because the studies were poorly reported and no incidence data or statistical analysis were reported. In a mating study involving oral exposure to barium chloride prior to mating (Dietz et al. 1992), decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in rats; no adverse effects were observed in mice. It is not known if the decrease in body weight observed in the rat offspring was secondary to maternal toxicity or was a direct effect on the fetus. Additional developmental toxicity studies, particularly studies involving oral exposure during gestation and lactation, would be useful to confirm the results of the Tarasenko et al. (1977) and Dietz et al. (1992) studies. Developmental toxicity studies via dermal exposure are also needed because this end point has not been evaluated for this route of exposure.

Immunotoxicity. The effect of barium on the immune system has not been well studied. No studies were available regarding immunological effects in humans or animals following inhalation, oral, or dermal exposure to barium. Several oral exposure studies in animals examining lymphoreticular end points such as thymus and lymph node histopathology have not reported adverse effects at nonlethal

doses (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994). Screening studies are needed to evaluate the potential immunotoxicity of barium following inhalation, oral, or dermal exposure.

Neurotoxicity. Exposure to high oral doses of barium is associated with numbness and tingling around the mouth and neck (Lewi and Bar-Khayim 1964; Morton 1945); higher doses can result in partial or complete paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Absence of a deep tendon reflex has been reported in an individual exposed to airborne barium carbonate powder (Shankle and Keane 1988). Oral exposure of rats and mice to barium has not been associated with changes in brain weight or gross or microscopic lesions of the brain (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Tardiff et al. 1980). NTP (1994) evaluated neurobehavioral performance in rats and mice exposed to barium chloride in drinking water for acute or intermediate durations. Decreases in spontaneous motor activity were observed in rats exposed for an intermediate duration. Decreased grip strength was also observed in mice; however, this was likely due to debilitation rather than neurotoxicity. The human data demonstrate that at presumably high doses, barium affects action potentials of muscles and nerve cells by increasing cellular potassium levels. However, oral studies are needed to establish a dose-response relationship for these neurological effects. No data were available regarding neurological effects in animals following inhalation exposure or humans and/or animals following dermal exposure. Additional studies would be useful to further evaluate the neurotoxic potential of barium.

Epidemiological and Human Dosimetry Studies. A limited number of epidemiological and human dosimetry studies evaluating the health effects of barium are available (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974; Wones et al. 1990). These studies have primarily focused on the potential of barium to adversely affect cardiovascular function by altering blood pressure or increasing the risk of death due to cardiovascular disease; consistent results have not been found. However, all of the available human studies on barium have limitations and/or confounding variables that make it difficult to draw firm conclusions regarding the health effects of barium (see Sections 3.2.2.1 and 3.2.2.2 for discussions on the specific limitations associated with available epidemiological and human dosimetry studies). Several human studies have also examined the potential toxicity of inhaled barium to the respiratory tract or cardiovascular system (Doig 1976; Essing et al. 1976; Seaton et al. 1986). As with the oral studies, limitations in the study reporting or confounding variables preclude using the studies to establish causal relationships. In addition to these epidemiological or experimental studies, there are numerous case reports of individuals ingesting large doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995;

Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981) or exposed to airborne barium carbonate (Shankle and Keane 1988). In general, these studies reported serious health effects such as death, ventricular tachycardia, and paralysis. Animal studies provide evidence that the kidney is a sensitive target of toxicity; there is also some evidence that the cardiovascular and neurological systems and the developing organisms are targets of barium toxicity (Dietz et al. 1992; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989). Additional epidemiological and/or human dosimetry studies would be useful to determine the effects of low doses of barium on these end points. Studies of workers exposed to airborne barium would also be useful for establishing the toxicity of barium to the respiratory tract.

Biomarkers of Exposure and Effect.

Exposure. There are no established biomarkers of exposure for barium. Analytical methods exist for measuring barium in blood, urine, feces, and biological tissues (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987); however, there are no data correlating levels of barium in these tissues and fluids with exposure. Studies associating barium levels in biological media (such as blood or urine) with exposure concentrations or doses would be useful for establishing biomarkers of exposure.

Effect. Symptoms of barium toxicity, such as hypokalemia, gastrointestinal upset, hyper- or hypotension, ventricular tachycardia, and numbness and tingling around the mouth and neck (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981) are well documented. However, there are no quantitative studies correlating these effects with dose and these effects are not specific to barium toxicity. For purposes of facilitating medical surveillance, studies to determine useful biomarkers of effect for barium, particularly effects associated with low doses of barium, would be useful.

Absorption, Distribution, Metabolism, and Excretion. The database on absorption, distribution, metabolism, and excretion of barium is limited. Existing studies indicate that barium is absorbed from the respiratory tract (Cuddihy and Griffith 1972; Cuddihy and Ozog 1973b; Morrow et al. 1968) and gastrointestinal tract (Cuddihy and Griffith 1972; Harrison et al. 1956; Leggett 1992; LeRoy et al. 1966; Schroeder et al. 1972; Taylor et al. 1962;Tipton et al. 1969), primarily deposited in the bones and teeth (Bauer et al. 1957; Cuddihy and Griffith 1972; Losee et al. 1974; Miller et al. 1985; Sowden 1958;

Sowden and Pirie 1958; Sowden and Stitch 1957), and excreted mostly in feces and urine (Cuddihy and Griffith 1972; Tipton et al. 1966). Deposition in bones and teeth and excretion in feces and urine appear to be independent of the route of exposure. Essentially no data exist on absorption, distribution, or excretion following dermal exposure; however, this route is not considered to be a significant source of exposure to barium. No significant data exist on the metabolism of barium compounds in the body. Additional studies evaluating the binding and/or complexing of barium and barium compounds with biological macromolecules or organic molecules in the body would be useful. Studies quantifying the extent of absorption following inhalation, oral, and dermal exposure also would be useful because of limited absorption data. A wide variety of individual differences in absorption efficiencies have been detected in the available human studies; studies examining factors influencing barium absorption would be useful.

Comparative Toxicokinetics. Based on available data, there do not appear to be significant differences in the toxicokinetics of barium between species (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983), although there is some indication that a larger percentage of absorbed barium is excreted in the feces of humans compared to that of experimental animals. However, there are not enough similar studies on different species to determine this with certainty. Studies on different species would increase confidence in the reliability of the existing database.

Methods for Reducing Toxic Effects. Methods have been reported for limiting oral and dermal absorption of barium compounds (Bronstein and Currance 1988; Dreisbach and Robertson 1987; Haddad and Winchester 1990) and for counteracting the hypokalemia that is produced by barium in acute high-level exposure situations (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). Contradictions exist in the literature regarding the efficacy or desirability of administering emetics (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Additional studies clarifying this issue would be helpful. Also, studies directed at finding a more efficient way to remove barium from the body would be useful. It is unclear whether mechanisms other than hypokalemia contribute to the toxic effects produced in acute high-level exposure situations. Additional information on the mechanisms responsible for the toxic effects of barium could aid in the development of effective treatments. Magnesium has been reported to antagonize the neuromuscular effects (Dreisbach and Robertson 1987). Additional studies examining the efficacy of administering soluble magnesium salts to antagonize the effects of barium would also be helpful. No information was located on treatment strategies for long-term low-level exposures. Research on procedures for mitigating such chronic exposure situations would be helpful.

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

There is very little information on the toxicity of barium in children. Two reports of food poisonings with barium carbonate (Deng et al. 1991; Lewi and Bar-Khayim 1964) provide some suggestive information that children may not be as sensitive as adults to barium carbonate toxicity; however, the lack of detailed examination of the exposed children and lack of exposure information limits the interpretation of these data. No human or animal toxicity studies have been designed to assess possible differences in the toxicity of barium. There is some information suggesting that infants and young children may have a higher barium absorption rate than adults (ICRP 1993; Taylor et al. 1962). Other potential toxicokinetic differences have not been thoroughly investigated. Additional studies are needed to evaluate potential age-specific differences in toxicity and toxicokinetics.

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

3.12.3 Ongoing Studies

No ongoing studies were reported in the FEDRIP (2006) database.