

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 beryllium. 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.

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

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the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of beryllium are indicated in Table 3-1 and Figure 3-1. Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

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

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

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

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Beryllium is a lightweight metal that has many uses, including some in the aerospace industry. Beryllium is present in the earth as beryllium ores, such as beryl and bertrandite. Most beryllium compounds are poorly soluble in water. The most common compound is beryllium oxide, the solubility of which decreases in water as the temperature at which it is calcined increases. Beryllium carbonate and hydroxide are also practically insoluble in water. Beryllium chloride, fluoride, nitrate, phosphate, and sulfate (tetrahydrate) are all soluble in water. Beryllium carbonate, sulfate (tetrahydrate), and hydroxide are formed during the processing of beryllium containing ores into beryllium metal. Beryllium nitrate is used as a hardening agent for mantles on gas lanterns. Beryllium phosphate has no commercial uses. As seen in the discussions below, the solubility of beryllium compounds significantly impacts in the manifestation of toxic effects.

3.2.1 Inhalation Exposure

Most of the information regarding adverse effects in humans after inhalation exposure to beryllium or its compounds is available from studies of occupational exposure. In 1952, a Beryllium Case Registry (BCR) was established to provide a central source for cases of diagnosed beryllium poisoning (acute berylliosis or chronic beryllium disease). The criteria for entry in the BCR included either documented past exposure to beryllium or the presence of beryllium in lung tissue as well as clinical evidence of beryllium disease. Dose-response relationships are difficult to establish in the case of occupational exposure because reported workroom beryllium levels have generally ranged widely from <0.002 to $1.0 \text{ mg beryllium/m}^3$, depending on when the measurements were made. The higher beryllium levels generally have occurred in the past; improvements in industrial hygiene over the last 30–40 years have effectively reduced workroom beryllium levels. Numerous studies provide concentration-response relationships for several end points in experimental animals. However, as discussed in Section 3.5.3, an animal model has not been identified for the most sensitive health effect, chronic beryllium disease.

3.2.1.1 Death

A number of retrospective cohort studies were conducted from data taken from the Beryllium Case Registry. The mortality rate among employees who worked at a major beryllium extraction, processing, and fabricating facility between 1942 and 1968 was higher than the national average, with respect to cardiovascular and pulmonary diseases (Wagoner et al. 1980). The incidence of death due to nonneoplastic respiratory disease was higher among employees who remained in the industry for <5 years after initial exposure and were exposed prior to 1950 when strict exposure controls were initiated.

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Another retrospective cohort study of workers exposed to beryllium during 1952–1975 indicates that the overall mortality rates were significantly higher compared to the U.S. general mortality rate (Infante et al. 1980). The incidence of death due to nonneoplastic respiratory disease was significantly higher in workers exposed for ≥ 15 years and who developed acute respiratory disease. However, in workers with chronic respiratory disease, the excess number of deaths was not related to the number of years since exposure. According to case histories of 3 men and 14 women employed in the beryllium industry for an average of 17 months, 6 of the women died from pulmonary or cardiovascular disease (Hardy and Tabershaw 1946). Most of the workers reported having shortness of breath, general weakness (fatigue), and weight loss. Autopsies revealed granulomatous disease, lung fibrosis, and heart enlargement. These were the first reported cases of chronic beryllium disease.

As discussed in Section 3.2.1.2 under Respiratory Effects, exposure to beryllium can result in two types of nonneoplastic respiratory disease, acute beryllium disease and chronic beryllium disease. Both forms can be fatal. Ten fatalities occurred among 93 cases of acute beryllium pneumonitis that were documented in two beryllium refineries prior to 1950 (American College of Chest Physicians 1965). Autopsy of six of the cases revealed that the death occurred only in people with fulminating disease and resulted from massive pulmonary edema. The survival of workers diagnosed with chronic beryllium disease appears to be related to their pulmonary pathology. Patients with well-formed granulomas but with slight or absent interstitial cellular infiltration appeared to have a higher rate of survival than patients with few or absent granulomas, but with moderate to marked interstitial cellular infiltration (Freiman and Hardy 1970).

There are several studies regarding death in animals after acute inhalation exposure to beryllium compounds. Exposure to 31 mg beryllium/m³ as beryllium oxide caused death in 2 of 20 rats (Hall et al. 1950). A 50-minute exposure to an aerosol of beryllium metal at 0.8 mg beryllium/m³ resulted in the death of 20 of 74 rats 12–15 days after exposure (Haley et al. 1990). Upon necropsy, the rats had hemorrhagic lungs. All rats exposed to 4.3 mg beryllium/m³ (Stokinger et al. 1950) or 2.59 mg beryllium/m³ (Sendelbach and Witschi 1987a) as beryllium sulfate died by day 14 or 18, respectively. Three of 10 guinea pigs and 2 of 10 hamsters died when exposed to 4.3 mg beryllium/m³ as beryllium sulfate for 14 days (Stokinger et al. 1950). All monkeys exposed to ≥ 13 mg beryllium/m³ as beryllium hydrogen phosphate died after 8–10 days of exposure (Schepers 1964). Two of four monkeys exposed to 0.184 mg beryllium/m³ as beryllium fluoride died after 7–17 days of exposure. Only one of four monkeys died after 7 days of exposure to 0.198 mg beryllium/m³ as beryllium sulfate.

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The differences observed in the lethality values for certain beryllium compounds are primarily due to their various solubilities. Beryllium oxide was less toxic than beryllium sulfate, due to its relative insolubility in the lung. Based on limited comparisons among compounds and species, rats and monkeys appear to be more sensitive than hamsters and guinea pigs.

Exposure to 0.43 mg beryllium/m³ as beryllium sulfate for #100 days caused death in 23 of 47 rats (Stokinger et al. 1950). Death was reported in 15 of 23 rats exposed to 30 mg beryllium/m³ as beryllium oxide for 15 days (Hall et al. 1950). When rats, hamsters, and monkeys were exposed to 0.62 mg beryllium/m³ as beryl or 0.21 mg beryllium/m³ as bertrandite ore for 6 months, 13, 25, and 11% died, respectively (Wagner et al. 1969). Signs of toxicity included respiratory distress, anemia, and body weight depression. One of five cats and 2 of 34 guinea pigs died when exposed to 0.43 mg beryllium/m³ as beryllium sulfate for #100 days (Stokinger et al. 1950). Increased mortality was observed in mice, dogs, hamsters, and goats exposed to 2.0 mg beryllium/m³ as beryllium sulfate for #51 days. The one monkey similarly exposed also died.

Chronic exposure to 0.034 mg beryllium/m³ as beryllium sulfate for 72 weeks did not increase mortality among male rats; however, the mortality rate among exposed females was \$4 times that of controls (Reeves et al. 1967). This indicates that female rats may be more sensitive than male rats to chronic inhalation exposure to beryllium.

The LC₅₀ values and concentrations associated with increased mortality in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal or musculoskeletal effects in humans or animals after inhalation exposure to beryllium or its compounds. The respiratory, cardiovascular, hematological, hepatic, renal, and dermal, and ocular effects observed in humans or animals after inhalation exposure to beryllium and its compounds are discussed below. The highest NOAEL values and all reliable LOAEL

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
ACUTE EXPOSURE						
Death						
1	Monkey (Macacus)	7-17 d 6hr/d				Schepers 1964 BeF ₂
2	Monkey (Macacus)	8-10 d 6hr/d				Schepers 1964 BeHPO ₄
3	Monkey (Macacus)	7 d 6hr/d				Schepers 1964 BeSO ₄
4	Rat (Fischer- 344)	50 min				Haley et al. 1990 Be metal
5	Rat (Wistar)	10 d 5d/wk 6hr/d				Hall et al. 1950 BeO
6	Rat (Fischer- 344)	14 d 2hr/d				Sendelbach and Witschi 1987 BeSO ₄
7	Rat (NS)	14 d 5d/wk 6hr/d				Stokinger et al. 1950 BeSO ₄
8	Gn Pig (NS)	14 d 5d/wk 6hr/d				Stokinger et al. 1950 BeSO ₄
9	Hamster (NS)	14 d 5d/wk 6hr/d				Stokinger et al. 1950 BeSO ₄

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
ACUTE EXPOSURE							
Systemic							
10	Monkey (Macacus)	8-10 d 6hr/d	Resp			13 (emphysema)	Schepers 1964 BeHPO ₄
			Cardio		13	(enlarged heart)	
			Hepatic		13	(hepatocyte degeneration)	
			Renal	13	97	(degeneration of the nephrons)	
			Endocr		13	(hypoplasia of the adrenal gland)	
			Bd Wt			13 (severe weight loss, 8-34%)	
11	Monkey (Macacus)	7-18 d 6hr/d	Resp			0.184 (emphysema)	Schepers 1964 BeF ₂
			Cardio		0.184	(enlarged heart)	
			Hepatic		0.184	(hepatocellular degeneration)	
			Renal		0.184	(degeneration of the nephrons)	
			Endocr		0.184	(adrenal hypotrophy)	
			Bd Wt			0.184 (19-23% weight loss)	

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
ACUTE EXPOSURE							
12	Monkey (Macacus)	7 d 6hr/d	Resp			0.198 (emphysema)	Schepers 1964 BeSO ₄
			Cardio		0.198 (enlarged heart)		
			Hepatic	0.198			
			Renal		0.198 (glomerular degeneration)		
			Bd Wt			0.198 (24% average weight loss)	
13	Rat (Fischer- 344)	50 min	Resp			0.8 (acute pneumonitis progressing to chronic inflammation and necrosis)	Haley et al. 1990 Be metal
14	Rat (Wistar)	10 d 5d/wk 6hr/d	Resp	31			Hall et al. 1950 BeO
			Hemato	31			
			Musc/skel	31			
			Hepatic	31			
			Renal	31			
			Other	31			
15	Rat (Fischer- 344)	1 hr	Resp		0.447 (lung inflammation)		Hart et al. 1984 BeO

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m3)	Less Serious (mg/m3)	
ACUTE EXPOSURE						
16	Rat (Fischer- 344)	1 hr	Resp		7 (increased lactic dehydrogenase and alkaline phosphatase in bronchoalveolar lavage fluid)	Sendelbach and Witschi 1987 BeSO ₄
17	Rat (Fischer- 344)	1 hr	Resp			13 (pneumonitis) Sendelbach et al. 1986 BeSO ₄
18	Rat (Fischer- 344)	1 hr	Resp			4.05 (pneumonitis) Sendelbach et al. 1989 BeSO ₄
19	Mouse (BALB/c)	1 hr	Resp		7.2 (increased lactic dehydrogenase and alkaline phosphatase in bronchoalveolar lavage fluid)	Sendelbach and Witschi 1987 BeSO ₄
20	Mouse (BALB/c)	1 hr	Resp		13 (lung inflammation)	Sendelbach et al. 1986 BeSO ₄
21	Mouse (NS)	14 d 5d/wk 6hr/d	Bd Wt		4.3 (13% body weight loss)	Stokinger et al. 1950 BeSO ₄
22	Gn Pig (English)	10 d 5d/wk 6hr/d	Resp	31		Hall et al. 1950 BeO
			Hepatic	31		
			Renal	31		
			Bd Wt	31		

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
ACUTE EXPOSURE						
23	Dog (Beagle)	1 d	Resp			10 (granulomas in lung) Haley et al. 1989 BeO
24	Dog (Beagle)	20 min	Resp			115 (granulomatous foci, inflammation of the lung) Robinson et al. 1968 BeF ₂ , BeO BeCl ₂
			Bd Wt		115 (transient anorexia, weight loss)	
25	Rabbit (New Zealand)	10 d 5d/wk 6hr/d	Resp	31		Hall et al. 1950 BeO
			Hemato		31 (decreased erythrocyte count)	
			Hepatic	31		
			Renal	31		
			Bd Wt	31		
			Immuno/ Lymphoret			
26	Dog (Beagle)	1 d			10 (lymph node hyperplasia, lymphocyte stimulation)	Haley et al. 1989 BeO
INTERMEDIATE EXPOSURE						
Death						
27	Monkey (Macacus)	30 d 6hr/d				0.198 (1/4 died) Schepers 1964 BeHPO ₄
28	Monkey (NS)	51-100 d 5d/wk 6hr/d				2 (1/1 died) Stokinger et al. 1950 BeSO ₄

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
INTERMEDIATE EXPOSURE						
29	Monkey (Squirrel)	6 mo 5d/wk 6hr/d				0.21 (increased mortality) Wagner et al. 1969 BeO
30	Rat (Wistar)	15 d 5d/wk 6hr/d				30 (6/13 males, 9/10 females died) Hall et al. 1950 BeO
31	Rat (NS)	51-100 d 5d/wk 6hr/d				0.43 (23/47 died) Stokinger et al. 1950 BeSO ₄
32	Rat Charles River	6 mo 5d/wk 6hr/d				0.21 (increased mortality) Wagner et al. 1969 BeO
33	Mouse (NS)	51 d 5d/wk 6hr/d				2 (4/38 died) Stokinger et al. 1950 BeSO ₄
34	Gn Pig (NS)	51-100 d 5d/wk 6hr/d				0.43 (2/34 died) Stokinger et al. 1950 BeSO ₄
35	Hamster (NS)	51-100 d 5d/wk 6hr/d				2 (5/10 died) Stokinger et al. 1950 BeSO ₄
36	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d				0.21 (increased mortality) Wagner et al. 1969 BeO
37	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d				0.62 (increased mortality) Wagner et al. 1969 BeO

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
INTERMEDIATE EXPOSURE						
38	Dog (NS)	51-100 d 5d/wk 6hr/d				2 (4/5 died) Stokinger et al. 1950 BeSO ₄
39	Cat (NS)	51-100 d 5d/wk 6hr/d				0.43 (1/5 died) Stokinger et al. 1950 BeSO ₄
40	Monkey (Rhesus)	15 d 5d/wk 6hr/d	Resp	30		Hall et al. 1950 BeO
			Bd Wt		30	(marked weight loss)
41	Monkey (Macacus)	30 d 6hr/d	Resp		0.198	(emphysema) Schepers 1964 BeHPO ₄
			Hepatic	0.198		
			Renal	0.198		
			Bd Wt		0.198	(15-39% weight loss)
42	Monkey (NS)	51-100 d 5d/wk 6hr/d	Resp		0.04	(emphysema) Stokinger et al. 1950 BeSO ₄
			Bd Wt		0.43	(31% weight loss)

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
INTERMEDIATE EXPOSURE						
43	Monkey (Squirrel)	6 mo 5d/wk 6hr/d	Resp		0.21 (inflammation of lungs)	Wagner et al. 1969 BeO
			Hemato	0.21		
			Hepatic	0.21		
			Renal	0.21		
			Other	0.21		
44	Monkey (Squirrel)	6 mo 5d/wk 6hr/d	Resp		0.62 (inflammation of lungs)	Wagner et al. 1969 BeO
			Hemato	0.62		
			Hepatic	0.62		
			Renal	0.62		
			Bd Wt	0.62		
45	Rat (Wistar)	15 d 5d/wk 6hr/d	Resp			30 (respiratory distress, increased rates) Hall et al. 1950 BeO
			Bd Wt			30 (steady weight loss)
46	Rat (Wistar) (Sherman)	180 d 5-6d/wk 4-8hr/d	Resp			0.035 (metaplasia, granulomas) Schepers et al. 1957 BeSO ₄
47	Rat (Wistar)	10 wk 6hr/d	Dermal		0.5 (inflammatory reaction on skin)	Stiefel et al. 1980 Be(NO ₃) ₂

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m3)	Less Serious (mg/m3)	Serious (mg/m3)	
INTERMEDIATE EXPOSURE							
48	Rat (NS)	51-100 d 5d/wk 6hr/d	Hemato	0.04	0.43	(macrocytic anemia; leukocytosis)	Stokinger et al. 1950 BeSO ₄
			Hepatic		2	(increased serum albumin and globulin)	
			Renal	0.43	2	(proteinurea)	
			Bd Wt	2			
49	Rat Charles River	6 mo 5d/wk 6hr/d	Resp			0.21 (granuloma in lung)	Wagner et al. 1969 BeO
			Hemato	0.21			
			Hepatic	0.21			
			Renal	0.21			
			Bd Wt	0.21			
50	Rat Charles River	6 mo 5d/wk 6hr/d	Resp	0.62			Wagner et al. 1969 BeO
			Hemato	0.62			
			Hepatic	0.62			
			Renal	0.62			
			Bd Wt	0.62			
51	Gn Pig (NS)	10 wk 6hr/d	Dermal		0.5	(inflammatory reaction on skin)	Stiefel et al. 1980 Be(NO ₃) ₂

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
INTERMEDIATE EXPOSURE							
52	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d	Resp	0.62			Wagner et al. 1969 BeO
			Hemato	0.62			
			Hepatic	0.62			
			Renal	0.62			
			Bd Wt	0.62			
53	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d	Resp			0.21 (granulomas of the lung)	Wagner et al. 1969 BeO
			Hemato	0.21			
			Hepatic	0.21			
			Renal	0.21			
			Bd Wt	0.21			
54	Dog (Mongrel)	17.5 d 5d/wk 6hr/d	Resp			31 (emphysema, atelectasis, inflammation)	Hall et al. 1950 BeO
			Hemato	31			
			Hepatic	31			
			Other	31			

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
INTERMEDIATE EXPOSURE							
55	Dog (Mongrel)	15 d 5d/wk 6hr/d	Cardio		30 (decrease in arterial oxygen tension)		Hall et al. 1950 BeO
			Hemato		30 (leukocytosis)		
			Bd Wt			30 (7-14% body weight loss)	
56	Dog (Mongrel)	40 d 5d/wk 6hr/d	Resp			3.6 (emphysema)	Hall et al. 1950 BeO
			Cardio		3.6 (decrease in arterial oxygen tension)		
			Hemato		3.6 (macrocytic anemia)		
			Hepatic		3.6 (decreased serum protein)		
			Renal	3.6			
			Bd Wt			3.6 (anorexia and 25% weight loss)	

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
INTERMEDIATE EXPOSURE							
57	Dog (NS)	51-100 d 5d/wk 6hr/d	Resp			0.04 (emphysema)	Stokinger et al. 1950 BeSO ₄
			Cardio		0.04 (decreased arterial oxygen tension)		
			Hemato		0.43 (leukocytosis)		
					0.04 (macrocytic anemia)		
			Hepatic		0.04 (increased serum albumin and globulin)		
			Renal	0.04	0.43 (proteinuria)		
Bd Wt		0.04 (body weight loss)					
58	Rabbit (New Zealand)	60 d 5d/wk 6hr/d	Resp	30			Hall et al. 1950 BeO
			Hemato		30 (macrocytic anemia)		
			Bd Wt	30			
59	Rabbit (NS)	51-100 d 5d/wk 6hr/d	Resp			0.04 (atelectasis)	Stokinger et al. 1950 BeSO ₄
			Hemato	0.04	0.43 (macrocytic anemia; leukocytosis)		
			Bd Wt	2			

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
INTERMEDIATE EXPOSURE							
60	Cat (Mongrel)	15 d 5d/wk 6hr/d	Resp	30			Hall et al. 1950 BeO
			Bd Wt			30 (anorexia, severe weight loss, emaciation)	
61	Cat (NS)	51-100 d 5d/wk 6hr/d	Resp			0.04 (emphysema)	Stokinger et al. 1950 BeSO ₄
			Bd Wt			0.04 (severe weight loss)	
62	Pig (NS)	51 5d/wk 6hr/d	Bd Wt			2 (28% weight loss)	Stokinger et al. 1950 BeSO ₄
		Immuno/ Lymphoret					
63	Rat (Wistar)	10 wk 6hr/d			0.5 (increased T-cell activity)		Stiefel et al. 1980 Be(NO ₃) ₂
64	Gn Pig (NS)	10 wk 6hr/d			0.5 (increased T-cell activity)		Stiefel et al. 1980 Be(NO ₃) ₂
		Cancer					
65	Rat (Wistar) (Sherman)	180 d 5-6d/wk 4-8hr/d				0.035 (CEL: lung cancer)	Schepers et al. 1957 BeSO ₄
CHRONIC EXPOSURE							
		Death					
66	Rat (Sprague-Dawley)	72 wk 5d/wk 7hr/d				0.034 (increased mortality of females)	Reeves et al. 1967 BeSO ₄
		Systemic					
67	Human	12.6 yr average	Resp			0.0012 (breathing difficulties, scarring of the lung)	Cullen et al. 1987 mix

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
CHRONIC EXPOSURE						
68	Human	(occup)	Resp			0.00052 (chronic beryllium disease) Cullen et al. 1987 mix
69	Human	occup	Resp			0.00055 (beryllium sensitization and chronic beryllium disease) Kreiss et al. 1996 BeO
70	Monkey (Squirrel)	12-23 mo 5d/wk 6hr/d	Resp		0.62 (inflammation of lungs)	Wagner et al. 1969 BeO
			Hemato	0.62		
			Hepatic	0.62		
			Renal	0.62		
			Bd Wt	0.62		
71	Monkey (Squirrel)	12-23 mo 5d/wk 6hr/d	Resp		0.21 (inflammation of lungs)	Wagner et al. 1969 BeO
			Hemato	0.21		
			Hepatic	0.21		
			Renal	0.21		
			Bd Wt	0.21		
72	Rat (Sprague- Dawley)	72 wk 5d/wk 7hr/d	Resp		0.034 (inflammation and proliferation in lung)	Reeves et al. 1967 BeSO ₄
			Bd Wt		0.034 (decrease in body weight)	

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
CHRONIC EXPOSURE						
73	Rat (Sherman)	6-18 mo 5d/wk 6hr/d	Resp		0.0547 (inflammation and fibrosis of the lung)	Vorwald and Reeves 1959 BeSO ₄
74	Rat (Sherman)	6-18 mo 5d/wk 6hr/d	Resp		0.006 (inflammation and fibrosis of the lung)	Vorwald and Reeves 1959 BeO
75	Rat Charles River	12-17 mo 5d/wk 6hr/d	Resp			0.21 (granuloma in lung) Wagner et al. 1969 BeO
			Hemato	0.21		
			Hepatic	0.21		
			Renal	0.21		
			Bd Wt	0.21		
76	Rat Charles River	12-17 mo 5d/wk 6hr/d	Resp		0.62 (consolidation of lung)	Wagner et al. 1969 BeO
			Hemato	0.62		
			Hepatic	0.62		
			Renal	0.62		
			Bd Wt		0.62 (decreased body weight gain)	

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/m3)	Less Serious (mg/m3)		Serious (mg/m3)
CHRONIC EXPOSURE							
77	Hamster (Golden Syrian)	12-17 mo 5d/wk 6hr/d	Resp			0.21 (granulomas in the lung)	Wagner et al. 1969 BeO
			Hemato	0.21			
			Hepatic	0.21			
			Renal	0.21			
			Bd Wt	0.21			
78	Hamster (Golden Syrian)	12-17 mo 5d/wk 6hr/d	Resp	0.62			Wagner et al. 1969 BeO
			Hemato	0.62			
			Hepatic	0.62			
			Renal	0.62			
			Bd Wt	0.62			
79	Human	Immuno/ Lymphoret occup			0.00052 (increased T-cell activity)		Cullen et al. 1987 mix
80	Monkey (Rhesus)	Cancer 63 wk 5d/wk 6hr/d				0.035 (CEL: lung cancer)	Vorwald 1968 BeSO4
81	Rat (Sprague-Dawley)	72 wk 5d/wk 7hr/d				0.034 (CEL: lung cancer)	Reeves et al. 1967 BeSO4

Table 3-1 Levels of Significant Exposure to Beryllium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	
CHRONIC EXPOSURE						
82	Rat (Sherman)	6-18 mo 5d/wk 6hr/d				0.0547 (CEL: lung cancer) Vorwald and Reeves 1959 BeSO ₄
83	Rat (Sherman)	6-18 mo 5d/wk 6hr/d				0.006 (CEL: lung cancer) Vorwald and Reeves 1959 BeO
84	Rat Charles River	12-17 mo 5d/wk 6hr/d				0.62 (CEL: lung cancer) Wagner et al. 1969 BeO

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

Bd Wt = body weight; Be = Beryllium; BeCl₂ = beryllium chloride; BeF₂ = beryllium fluoride; BeHPO₄ = beryllium hydrogen phosphate; Be(NO₃)₂ = beryllium nitrate; BeO = beryllium oxide; BePO₄ = beryllium phosphate; BeSO₄ = beryllium sulfate; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minute(s); mix = beryllium oxides and ores in a refinery; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = respiratory; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation
Acute (≤ 14 days)

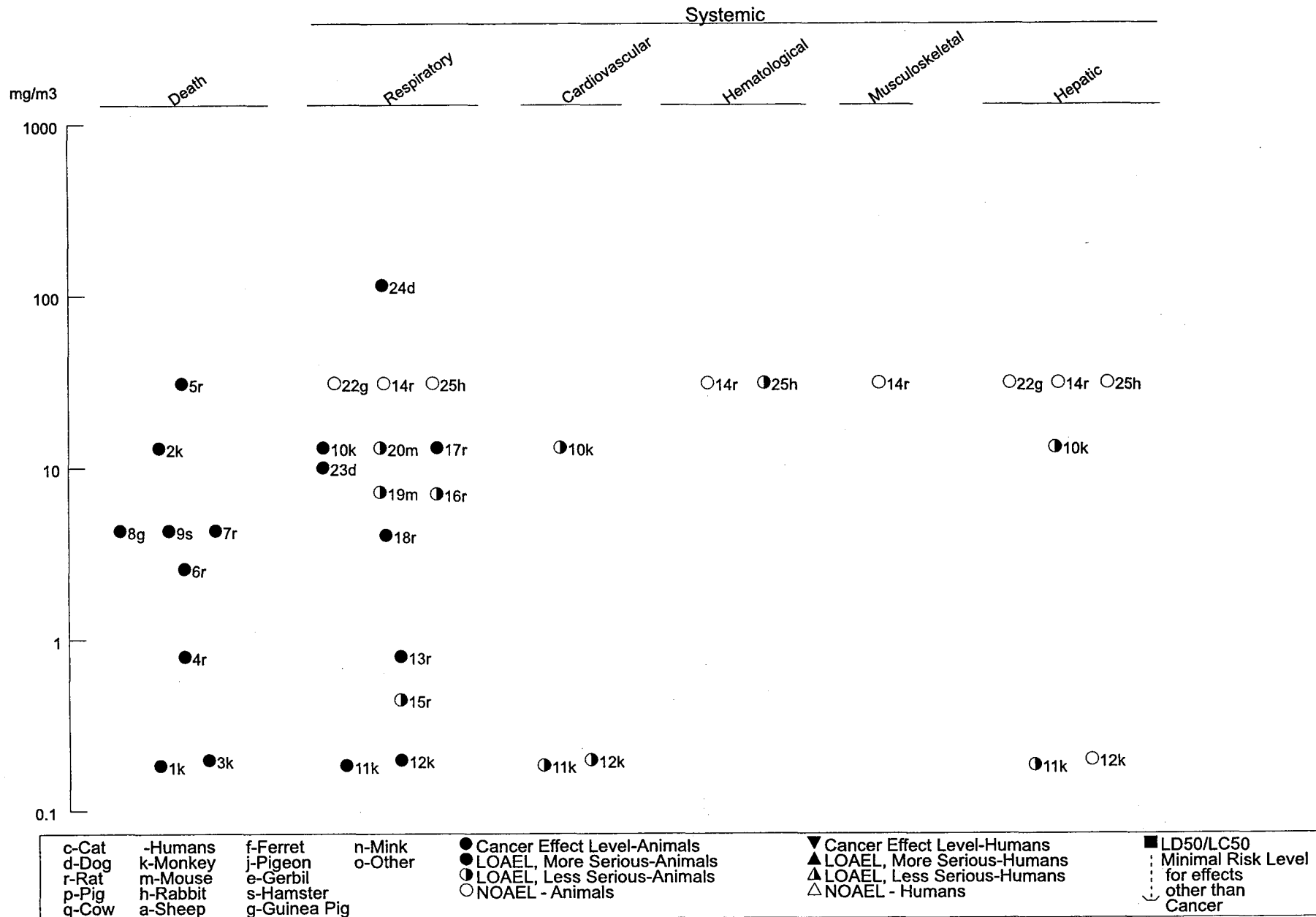


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (Continued)

Acute (≤ 14 days)

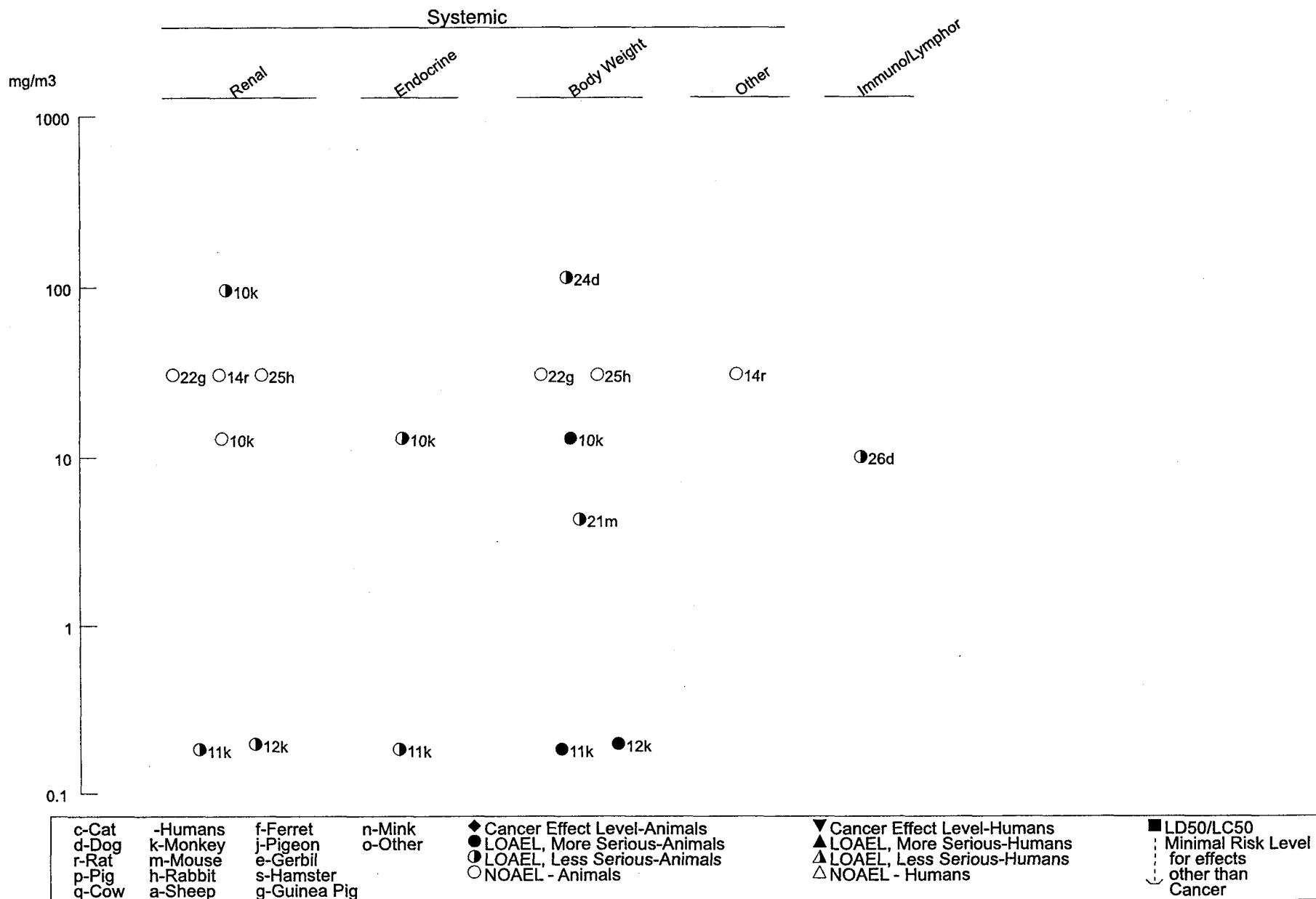


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (Continued)
Intermediate (15-364 days)

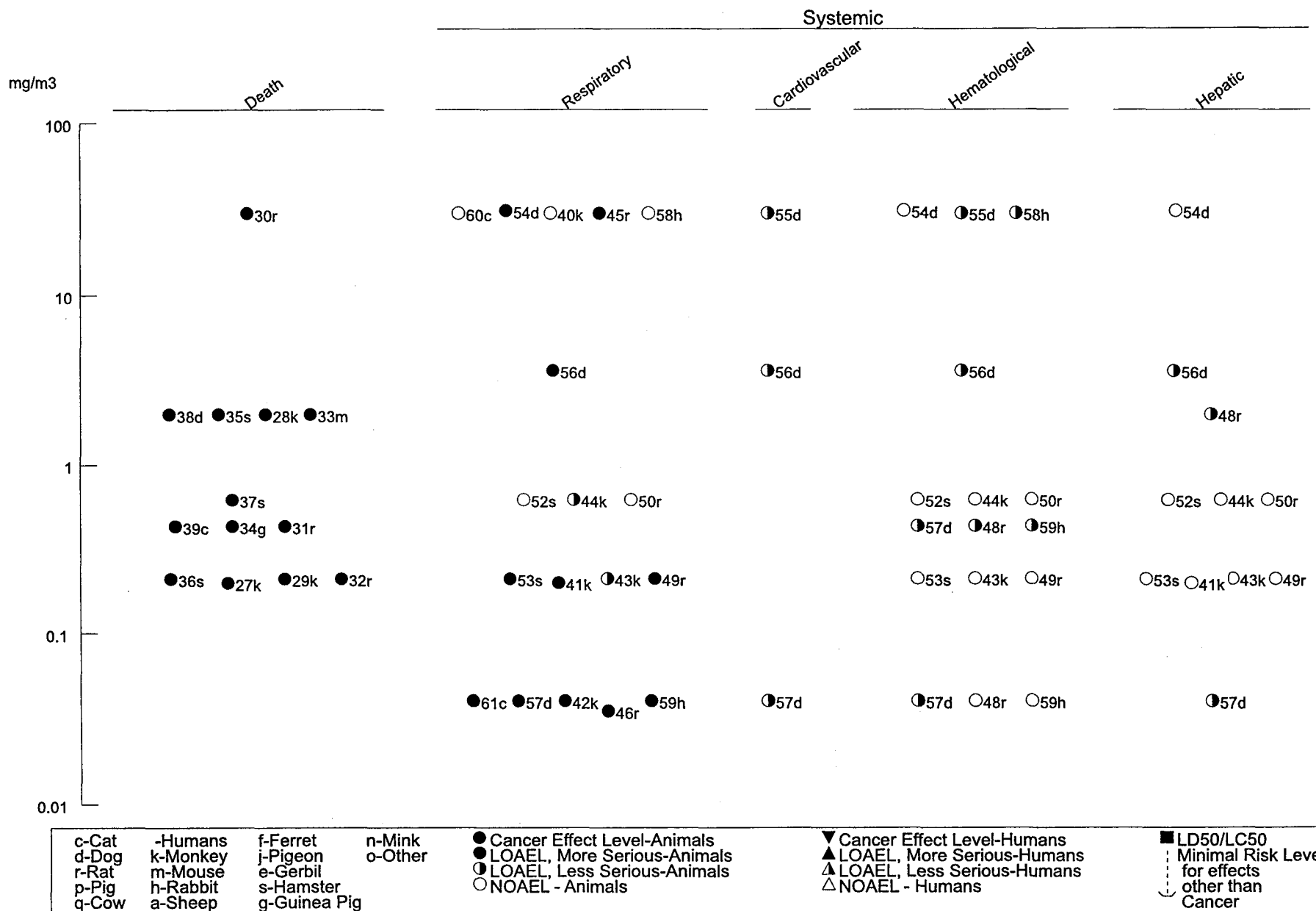
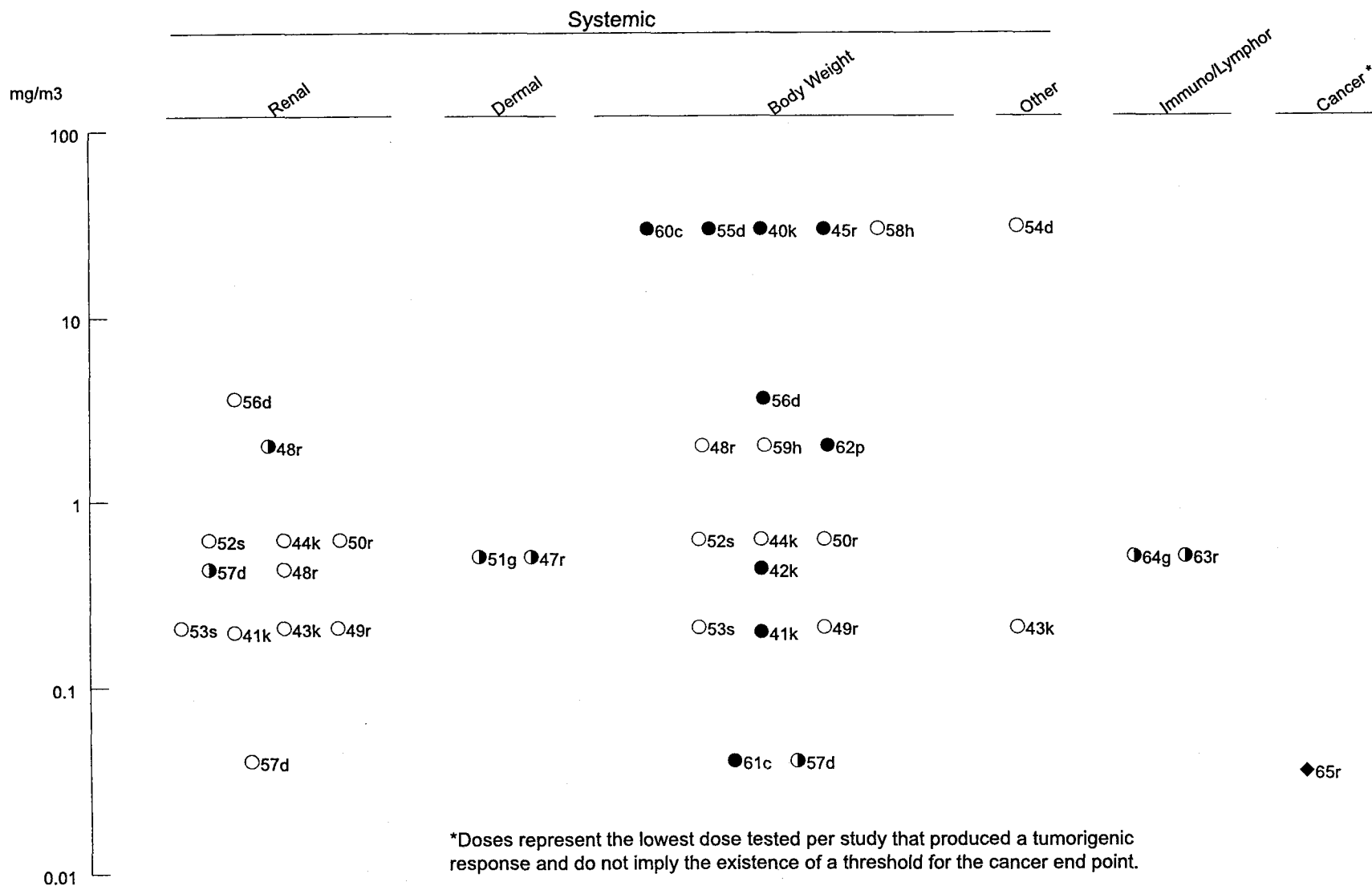


Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (Continued)
Intermediate (15-364 days)

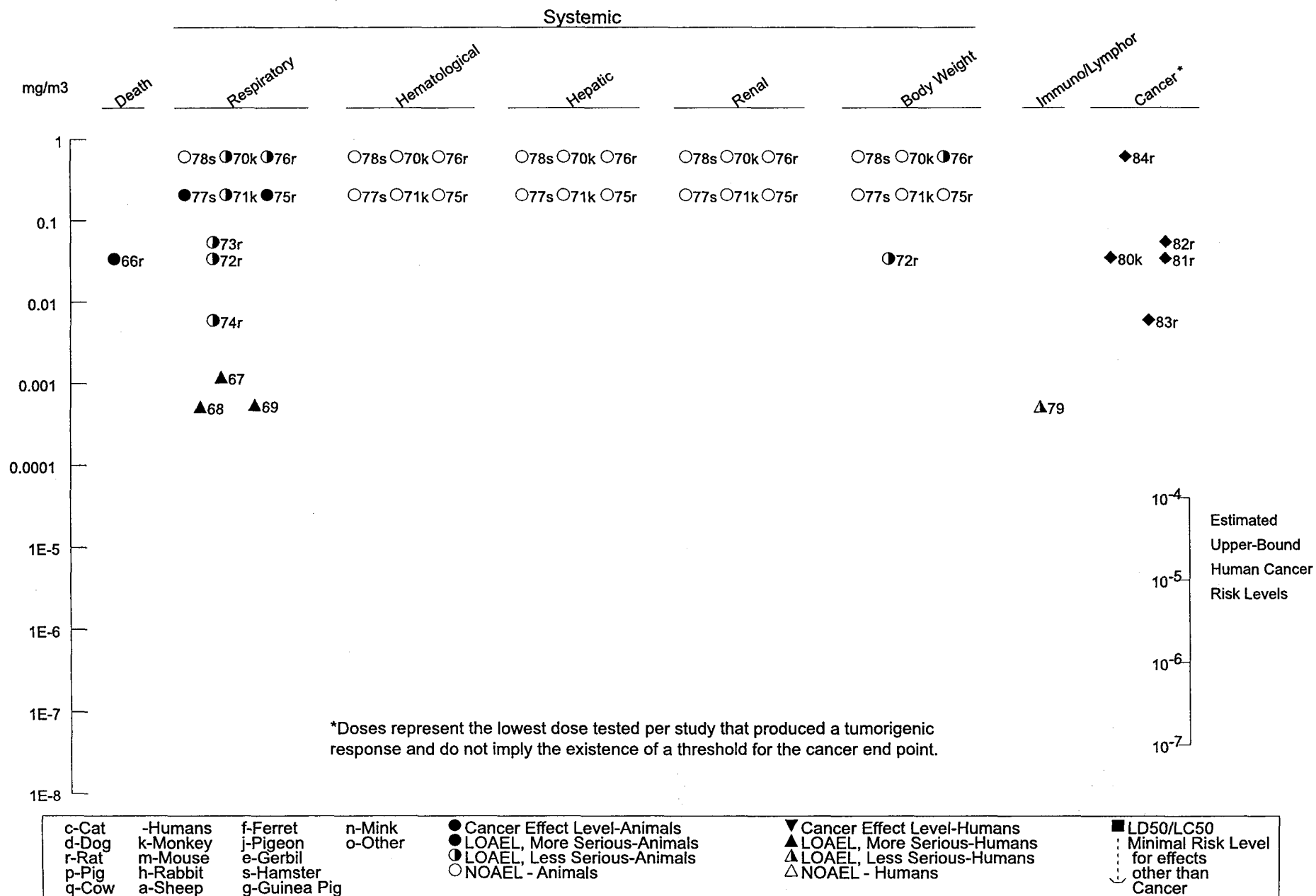


*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

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

Figure 3-1. Levels of Significant Exposure to Beryllium - Inhalation (Continued)

Chronic (≥365 days)



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values for each systemic effect in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. There is extensive evidence in humans that the respiratory tract is one of the primary targets of beryllium toxicity following inhalation exposure. In general, noncancerous respiratory effects can be divided into two categories: acute beryllium disease and chronic beryllium disease, also referred to as berylliosis or chronic berylliosis. Acute beryllium disease is a fulminating inflammatory reaction of the entire respiratory tract. The respiratory tract symptoms range from mild nasopharyngitis to a severe chemical pneumonitis, which may be fatal. Acute beryllium disease is usually associated with exposure to high concentrations of soluble beryllium compounds. VanOrdstrand et al. (1945) describe a number of cases of acute beryllium disease among workers exposed to beryllium sulfate, beryllium oxide, beryllium fluoride, and beryllium oxyfluoride. Signs and symptoms observed in the affected workers included irritation of the nasal and pharyngeal mucous membranes, sore nose and throat, weight loss, labored breathing, decreased vital capacity, anorexia, and increased fatigue. In a 1948 investigation of acute beryllium pneumonitis in three U.S. plants producing beryllium compounds from the ore and in laboratories and shops engaged in research in ceramics and metallurgy of beryllium, all cases of beryllium pneumonitis were associated with concentrations >0.1 mg beryllium/m³, primarily as beryllium sulfate or beryllium fluoride (Eisenbud et al. 1948a). The syndrome of acute beryllium disease has been virtually eliminated in workers first exposed to beryllium after 1950 (initiation of strict exposure limits), except in instances where there is accidental exposure to high levels of beryllium (Eisenbud and Lisson 1983).

Chronic beryllium disease (CBD) is an inflammatory lung disease characterized by the formation of granulomas with varying degrees of interstitial fibrosis. Chronic beryllium disease is a beryllium-specific immune response with primary manifestations in the lung. The symptoms associated with chronic beryllium disease include chest pain, cough, and/or dyspnea with relatively mild exertion. The clinical syndrome of chronic beryllium disease was first described by Hardy and Tabershaw (1946) in fluorescent lamp workers. Seventeen chronically exposed workers developed anorexia, dyspnea, cough, easy fatigue, and weakness. An autopsy on one of the workers revealed increased lung weight, diffuse fibrosis, granuloma, abnormal epithelial lining of the bronchioles, and abnormal alveoli and vasculature. Prior to the adoption of stringent industrial hygiene measures, the incidence of chronic beryllium disease among beryllium workers was high. Historically, a number of criteria were used for the diagnosis of chronic beryllium disease: evidence of beryllium exposure, evidence of lower respiratory tract disease and clinical course consistent with chronic beryllium disease, reticulonodular infiltrates on chest x-ray, obstructive or restrictive deficits in lung function or a low diffusing capacity for carbon monoxide, and pathological

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evidence of non-caseating granulomas and/or mononuclear cell interstitial infiltrates (Newman et al. 1989). Technological developments in the 1980s (e.g., fiber optic bronchoscopy and transbronchial biopsy methods, development of the beryllium lymphocyte proliferation test) now allow for the detection of subclinical cases of chronic beryllium disease and beryllium sensitization in the absence of chronic beryllium disease. Newman et al. (1989) proposed that chronic beryllium disease can be classified into three stages: (1) beryllium sensitization—consistent abnormal results for blood and/or lung BeLPT results, (2) subclinical chronic beryllium disease—sensitized individuals with histopathological evidence but no clinical signs, and (3) clinical chronic beryllium disease—sensitized individuals with histopathological evidence with respiratory symptoms, changes on chest radiographs, or altered pulmonary physiology.

Although instituting regulatory exposure limits and improved hygiene practices has decreased the number of cases of chronic beryllium disease among beryllium workers, new cases of chronic beryllium disease are still being identified in beryllium workers. Cotes et al. (1983) examined 130 workers employed at a beryllium manufacturing facility for at least 6 months during the period of 1952–1963. Based on clinical evaluation including chest x-rays and lung function tests, there were four definite cases of chronic beryllium disease and one probable case of chronic beryllium disease. Another two workers had chest x-rays consistent with chronic beryllium disease, but did not have any other alterations. Beryllium exposure levels were estimated using facility records for total airborne concentrations over the period of 1952–1960. The mean exposure levels for different job processes were 0.029–0.72 $\mu\text{g beryllium}/\text{m}^3$ in 1952 and 0.022–0.21 $\mu\text{g beryllium}/\text{m}^3$ in 1960. Two of the confirmed cases of chronic beryllium disease worked in an area of the facility where beryllium concentrations were 0.04 and 0.18 $\mu\text{g beryllium}/\text{m}^3$ in 1952 and 1960, respectively. Because these exposure levels were based on general air samples, they may not be representative of breathing zone beryllium levels.

Five cases of chronic beryllium disease were reported among workers exposed to beryllium oxide fumes at a precious metals refinery (Cullen et al. 1987). The five workers had abnormal chest x-rays, noncaseating granulomas, pulmonary fibrosis, and abnormal results for the bronchoalveolar lavage beryllium lymphocyte proliferation test (BeLPT). A health survey of 45 workers at the same facility was also conducted (Cullen et al. 1987). Eighteen workers reported lower respiratory tract symptoms (cough, dyspnea, wheezing). Among these 18 workers, 7 also had abnormal x-rays, such as focal scarring. Time weighted-average personal air samples, measured during a 2-week period in 1983, throughout the refinery ranged from 0.22 to 43 $\mu\text{g beryllium}/\text{m}^3$, with a mean of 1.2 $\mu\text{g beryllium}/\text{m}^3$. Four of the five workers with chronic beryllium disease worked in the furnace area, where the mean concentration was 0.52 μg

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beryllium/m³. This concentration is considered a LOAEL for chronic beryllium disease. However, it is possible that the air samples collected during a 2-week period may not be reflective of current or past exposure conditions.

Reversible respiratory effects were observed in a group of beryllium extraction workers examined by Sprince et al. (1978). Health surveys (including measurement of lung function and x-rays) were conducted in 1971 and 1974. When lung function test results and arterial blood gas results were compared to the 1971 values, a slight statistically significant decrease in peak expiratory flow rate, increase in alveolar-arterial O₂ tension and decrease in alveolar-arterial CO₂ tension were observed in a group of 111 workers. When workers with radiological abnormalities suggestive of interstitial disease were re-examined in 1974, nine workers had normal radiographs and nine had radiographs suggestive of interstitial disease; it should be noted that some of these workers had previous exposure to asbestos, silica, or soft coal. Improvement in hypoxia and decreased alveolar-arterial O₂ tension were observed among 13 workers diagnosed with hypoxia in 1971; no change in lung function was observed in this group. The improvement in respiratory effects corresponded to a dramatic decrease in peak air concentrations of beryllium.

Several investigators have conducted screening studies to assess the occurrence of beryllium sensitization and subclinical chronic beryllium disease among beryllium workers. Kreiss et al. (1993a) and Stange et al. (1996b, 2001) examined workers at the Rocky Flats Technology site involved in the production of nuclear weapons, Kreiss et al. (1997) and Newman et al. (2001) examined workers at other beryllium production facilities, and Deubner et al. (2001b) examined beryllium mine workers and workers at a beryllium extraction facility. In the Kreiss et al. (1993a) study, 895 current workers were examined and beryllium sensitization, defined as consistently abnormal BeLPT results, was detected in 17 workers (1.9%). All of these workers had normal chest x-rays. Sixteen of the subjects with beryllium sensitization underwent clinical evaluation (bronchoalveolar lavage BeLPT and transbronchial lung biopsy). Chronic beryllium disease (defined as having granulomas on lung biopsy and abnormal blood or bronchoalveolar lavage [BAL] BeLPT results) was diagnosed in 13 of the subjects. Forty-two subjects had abnormal chest x-rays, 40 of which underwent clinical evaluation. An additional case of chronic beryllium disease was detected in this group (this subject had inconsistently abnormal BeLPT results). Thus, the incidence of chronic beryllium disease in this population was 15/895 (1.7%; one worker refusing clinical evaluation was included in the beryllium disease group because he had ventilatory abnormalities suggestive of restrictive disease). The beryllium sensitized individuals did not significantly differ from the whole cohort in terms of gender, age, history of atopic disease, cigarette smoking status or

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pack years, prevalence of respiratory symptoms, spirometric abnormalities, or profusion of small opacities on chest x-rays.

Stange et al. (1996b) examined 4,397 current and former employees at the same facility; it is not known if any of the workers were also included in the Kreiss et al. (1993a) study. Beryllium sensitization was found in 78 of the workers (1.8%); the beryllium sensitization rate was similar in the current and former employees (1.2 versus 1.9%). Of the beryllium sensitized workers, 29 were diagnosed as having chronic beryllium disease (29/4397, 0.66%); chronic beryllium disease was defined as having histologic evidence of pulmonary granulomatous disease and a positive BAL BeLPT result. Environmental beryllium levels were measured in the main beryllium production building using fixed airhead samplers (measured for the period of 1970–1988) and personal air monitoring devices (1984–1987); the mean concentrations were 0.016 and 1.04 $\mu\text{g beryllium}/\text{m}^3$, respectively; the 1.04 $\mu\text{g beryllium}/\text{m}^3$ is considered a LOAEL because it more accurately reflected beryllium concentrations in the breathing zone. However, this value does not take into consideration beryllium levels prior to 1984 and may not be representative of historical beryllium levels.

A more recent study by this group examined 5,173 workers at the Rocky Flats facility (Stange et al. 2001). Confirmed abnormal blood BeLPT results were found in 98 workers (3.33%). Three years after the initial screening, 2,891 workers were re-examined; an additional 56 workers had abnormal blood BeLPT results. The total beryllium sensitization rate was 4.54% (154/5173). The workers with abnormal BeLPT results or with a small opacity profusion of 1/0 or greater in their chest x-ray underwent medical evaluations for chronic beryllium disease. The criteria for diagnosis of chronic beryllium disease were history of beryllium exposure, histopathologic evidence on biopsy of noncaseating granulomas or mononuclear cell infiltrates in the lung, and a positive blood or BAL BeLPT. Seventy-four cases of chronic beryllium disease were diagnosed during the initial screening period and 7 additional cases were diagnosed at the 3-year screening. Beryllium sensitization and chronic beryllium disease were found in male and female workers employed at the facility for <5 years. Increased odds ratios for beryllium sensitization were found for workers in the health physics (odds ratio=2.867; 95% confidence interval [CI]=1.12–7.36), beryllium machinist (odds ratio=3.044; 95% CI=1.95–4.77), construction trades (odds ratio=2.426; 95% CI=1.48–3.97), and general machinist (odds ratio=1.345; 95% CI=1.00–1.82) job group categories.

Viet et al. (2000) designed a case control study of workers at the Rocky Flats facility to evaluate the risks associated with various levels of historical beryllium exposure. Seventy four workers diagnosed as

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beryllium sensitive and 50 workers with chronic beryllium disease were matched by age, smoking status, gender, and race to an equal number of controls. Workers were diagnosed as beryllium sensitive if two blood BeLPT results were positive and the clinical evaluation did not reveal chronic beryllium disease; the criteria used to diagnosis chronic beryllium disease were exposure to beryllium, positive blood and lung BeLPT results and noncaseating granulomas on lung biopsy. Historical beryllium exposure levels were estimated using fixed airhead samples in one building (beryllium machine shop); annual exposure levels were estimated by averaging air samples from 2 random days each month. An individual's exposure level was estimated using annual exposure levels; the individual's work history by job location, task, and time period; and assignment of relative exposure estimates to each combination of job location, task, and time period as compared with the beryllium shop machinists. For the chronic beryllium disease cases, the mean exposure level (0.070 versus 0.025 $\mu\text{g}/\text{m}^3$), cumulative exposure level (1.35 versus 0.38 $\mu\text{g}\text{-years}/\text{m}^3$), and duration of employment (19.1 versus 14.4 years) were significantly higher than for the controls. For the beryllium sensitive cases, the mean exposure level (0.036 versus 0.026 $\mu\text{g}/\text{m}^3$) was significantly higher than for controls, but there was no significant differences for cumulative exposure level (0.54 versus 0.40 $\mu\text{g}\text{-years}/\text{m}^3$) or duration of employment (13.2 versus 14.5 years). Employment start date was not significantly different for the cases versus control comparisons. Comparisons between the chronic beryllium disease cases and beryllium sensitive cases revealed significant differences in mean exposure level (0.070 versus 0.036 $\mu\text{g}/\text{m}^3$), cumulative exposure level (1.35 versus 0.54 $\mu\text{g}\text{-years}/\text{m}^3$), duration of employment (19.1 versus 13.2 years), and employment start date (1964.9 versus 1970.2). Significant relationships between chronic beryllium disease and both cumulative and mean beryllium exposure were also found using logistic regression analysis; significant relationships were not found for beryllium sensitization. This study cannot be used to establish a LOAEL for chronic beryllium disease or beryllium sensitization because method used to assess beryllium exposure (fixed airhead samples) may not be representative of beryllium levels in personal breathing zones. The study authors note that fixed airhead sampling may underestimate breathing zone levels by a factor of 0.5–9.

Beryllium sensitization and subclinical chronic beryllium disease has also been found in workers exposed to beryllium oxide at beryllia ceramics plants. Eight cases of beryllium sensitization were found among 136 current employees at the plant (Kreiss et al. 1996). Five of these workers had consistently abnormal BeLPT results and were diagnosed with chronic beryllium disease based on the observation of granulomas. Two workers had inconsistently abnormal BeLPT results and no granulomas; however, 2 years after the initial examination, one of these workers had symptoms of chronic beryllium disease (the other refused clinical follow-up). A seventh case of chronic beryllium disease was detected in a worker

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who initially had normal BeLPT results but later developed a nonhealing granulomatous response to a beryllium-contaminated skin wound and an abnormal BeLPT result. Seven of the eight beryllium sensitized workers were machinists; the beryllium sensitization rate among the machinists was 14.3 versus 1.2% for all other workers. The beryllium exposure levels for the beryllium-sensitized workers ranged from 0.2 to 1.1 $\mu\text{g}/\text{m}^3$; the median concentration was 0.55 $\mu\text{g}/\text{m}^3$, this is a LOAEL for beryllium sensitization and chronic beryllium disease.

Additional cases of beryllium sensitization and chronic beryllium disease were identified in a follow-up to this study (Henneberger et al. 2001). This study examined 151 workers employed at a beryllium ceramics manufacturing facility; 77 of the workers were employed before 1992 (long-term workers, 76 of them participated in the first beryllium screening study [Kreiss et al. 1996]) and the remaining workers began employment at the facility after 1992 (short-term workers). Breathing zone and general area sample measurements taken from 1981 (when full production of beryllium ceramics began) to 1998 were used to estimate mean, cumulative, and peak exposure levels. The median and mean exposure levels were 0.39 and 14.9 $\mu\text{g}/\text{m}^3$, respectively, for long-term workers and 0.28 and 6.1 $\mu\text{g}/\text{m}^3$, respectively, for short-term workers. Using blood BeLPT, 15 cases of beryllium sensitization were diagnosed; 8 cases among long-term workers and 7 among short-term workers. Six of these workers were diagnosed as having chronic beryllium disease (defined as borderline or abnormal BAL BeLPT and/or characteristic granulomas on lung biopsy). Seven of the eight workers with chronic beryllium disease were long-term workers. Among long-term workers, no relationships between the prevalence of beryllium sensitization and time since first exposure, mean exposure level, or cumulative exposure level were found. However, a higher prevalence of beryllium sensitized workers was seen in the workers with the highest peak exposure levels. For the short-term workers, positive associations between prevalence of beryllium sensitization and mean, cumulative, and peak exposure levels were found.

A study of 627 workers at a beryllium manufacturing facility found 43 cases of beryllium sensitization (6.9%) (Kreiss et al. 1997). Chronic beryllium disease was diagnosed in 24 of the beryllium sensitized workers (incidence of 4.6%). The highest incidence of chronic beryllium disease was found in ceramic workers exposed to beryllium oxide (9.0%). The only available monitoring data for this facility is historic environmental beryllium measurements taken between 1984–1993. However, these monitoring data can not be used to establish a LOAEL for chronic beryllium disease because ceramic product manufacturing (the workers with the highest disease incidence) was terminated before 1984.

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Newman et al. (2001) conducted a medical surveillance in a beryllium metal machining facility following the detection of an index case of chronic beryllium disease in 1995. All current employees were tested with the blood BeLPT between 1995 and 1997 and were retested 2 years after the initial screening. The mean age of the current workers was 39 years and the mean duration of exposure was 11.7 years. Of the 235 workers initially tested, 15 had confirmed abnormal blood BeLPT results. Eleven of these workers underwent clinical evaluation; 8 were found to have chronic beryllium disease with granulomas and/or mononuclear cell infiltrates on transbronchial lung biopsy. One worker had an abnormal BAL (bronchioalveolar lavage) BeLPT and lymphocytes in the BAL fluid, but no evidence of granulomas or infiltrates; this worker was classified as having probable chronic beryllium disease. The remaining three workers were classified as beryllium sensitized without evidence of chronic beryllium disease. During the first 2-year interval testing phase (187 workers were retested), five additional workers had consistently abnormal BeLPT results; three of these workers were diagnosed as having chronic beryllium disease and one was classified as probably having chronic beryllium disease. During the second interval testing phase, 109 workers were tested and two cases of abnormal BeLPT results were found. Both of these individuals were diagnosed as having chronic beryllium disease. Thus, the total number of beryllium-sensitized workers was 22. Of the 19 undergoing clinical evaluation, 13 workers were diagnosed with chronic beryllium disease characterized as granulomas and/or mononuclear cell infiltrates on lung biopsy, and 2 workers were diagnosed with probable chronic beryllium disease. No difference in duration of employment was found between the workers with chronic beryllium disease and the beryllium sensitized workers. The workers with chronic beryllium disease were older than the beryllium sensitized workers (41 years versus 33.5 years); three of the workers were employed for <3 months. With the exception of the index case, most of the workers with chronic beryllium disease were at the very early stages and had minimal abnormalities on pulmonary function or on exercise capacity testing.

Kelleher et al. (2001) expanded the results of the Newman et al. (2001) by examining the relationship between beryllium exposure and beryllium sensitization and chronic beryllium disease. Beryllium exposure levels for 20 of the beryllium workers with beryllium sensitization (7 workers) or chronic beryllium disease (13 workers; includes 2 workers with probable chronic beryllium disease) were compared with beryllium exposure levels for 206 workers employed at the same facility who were negative for beryllium sensitization. No significant differences in age, employment duration, or smoking status were found between the cases and controls. A significantly higher proportion of the cases worked as machinists (odds ratio=4.4; 95% CI=1.1–17.6). The median total beryllium exposure level based on personal samplers was 0.13 $\mu\text{g}/\text{m}^3$. The cases tended to have higher cumulative and median beryllium exposure levels and cumulative exposures to particle sizes of <6 or <1 μm , but the differences were not

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statistically significant. The respective mean and median cumulative exposures were 6.09 and 2.93 $\mu\text{g}/\text{m}^3$ -years for the cases and 2.27 and 1.24 $\mu\text{g}/\text{m}^3$ -years for the controls. None of the cases had lifetime-weighted average beryllium exposure levels of $<0.02 \mu\text{g}/\text{m}^3$; 60% of the cases had lifetime-weighted averages of $>0.20 \mu\text{g}/\text{m}^3$. In the control group, 11% of the workers were exposed to $<0.02 \mu\text{g}/\text{m}^3$ and 48% were exposed to $>0.20 \mu\text{g}/\text{m}^3$.

Deubner et al. (2001b) examined 75 workers at a beryllium ore mining and milling facility in Utah. The workers involved in the mining operation were primarily exposed to beryl ore or bertrandite ore and the milling operation workers were exposed to these ores and beryllium hydroxide. Three of the workers had abnormal blood BeLPT results and one had an unconfirmed positive test. The four workers were long-term employees involved in the facility's milling operations. Two of the workers with confirmed BeLPT results underwent biopsy and BAL BeLPT; one of these workers was diagnosed with chronic beryllium disease (granulomatous lung disease on biopsy). The worker with chronic beryllium disease also worked at another beryllium facility for 10 years where he was involved in beryllium metal and beryllium oxide production. General area, breathing zone, and personal lapel samples were used to estimate historical beryllium exposure. The mean general area, breathing zone, and personal lapel samples ranges were 0.3–1.1, 1.1–8.1, and 0.05–6.9 $\mu\text{g}/\text{m}^3$, respectively. Because no cases of beryllium sensitization or chronic beryllium disease were found in workers who only worked in the mines, the study author suggested that the form of beryllium may influence the risk for developing beryllium sensitization or chronic beryllium disease.

Although chronic beryllium disease is usually associated with occupational exposure to beryllium at manufacturing facilities, it has also been reported in dental technicians (Brancaleone et al. 1998; Kotloff et al. 1993), in individuals living near beryllium manufacturing facilities, and in families of beryllium workers who wore contaminated clothing at home (Chesner 1950; Dattoli et al. 1964; Eisenbud et al. 1949; Lieben and Metzner, 1959; Lieben and Williams 1969). Eisenbud et al. (1949) examined 10,000 residents living within 1 mile of a beryllium manufacturing facility. Eleven cases of chronic beryllium disease (based on radiological evidence) were initially detected; one case was eliminated due to exposure to beryllium dust on work clothes. Three more cases were detected in a follow-up study (Stern and Eisenbud 1951). The study authors estimated that the beryllium concentrations 0.75 miles from the facility were 0.01–0.1 μg beryllium/ m^3 . Because the affected residents lived within 0.75 miles of the facility, the 0.01–0.1 $\mu\text{g}/\text{m}^3$ concentration range is a NOAEL for clinical chronic beryllium disease.

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Clinical chronic beryllium disease is associated with impaired lung function. Lung function testing in individuals with chronic beryllium disease has shown reduced vital capacity and total lung capacity, increased alveolar-arterial oxygen tension difference, arterial hypoxemia, and decreased carbon monoxide diffusion capacity (Andrews et al. 1969; Johnson 1983; Rossman et al. 1988). A study by Pappas and Newman (1993) investigated whether early beryllium disease was also associated with impaired lung function. In this study, lung function test results from 21 “surveillance-identified” subjects (individuals with abnormal BeLPT results who did not seek medical attention prior to the diagnosis of beryllium sensitization) were compared with the results in 15 “clinically-identified” subjects (individuals who sought medical attention because of respiratory problems or abnormal x-rays). The lung function tests consisted of spirometry, lung volumes, diffusing capacity for carbon monoxide, arterial blood gases, and maximal exercise capacity. No alterations in spirometry, lung capacity, blood gases, or diffusing capacity were found in the surveillance-identified subjects. However, subtle alterations in exercise capacity were found in 52% of the surveillance-identified subjects, the most common effect was a rise in dead space to tidal volume ratio during exercise. In contrast, 93% of the clinically-identified subjects had alteration in lung function. The alterations included mild to moderate airway obstruction, evidence of restriction, abnormal resting blood gas analysis, and impaired exercise capacity (able to perform less work than surveillance-identified subjects).

In animals, the respiratory system is also the primary target for inhalation exposure to beryllium. Rats exposed to 1–100 mg beryllium/m³ as beryllium oxide (calcined at 1,000 EC) for 30–180 minutes had initial alveolar deposition of 1–63 µg beryllium in the lungs (Sanders et al. 1975). The exact exposure concentrations were not clearly specified. Rats developed only slight to moderate granulomatous lesions in the lungs, depending on the amount of alveolar deposition. Dust laden or degenerative macrophages and a moderate infiltration of lymphocytes were noted in the lungs of rats exposed to beryllium oxide. Hamsters, similarly exposed until an initial lung burden of 16–17 µg beryllium was achieved, developed only a few small areas of granuloma formation and degenerating macrophages. Pulmonary lavage fluid from rats exposed to 0.447 mg beryllium/m³ as beryllium oxide (calcined at 560 EC) for 1 hour was examined at various intervals for #21 days after exposure for cell populations, acid and alkaline phosphatase enzyme activity of lysozyme and lactic dehydrogenase, and biochemical analysis of protein, lipid, phosphorus, phosphatidyl choline, and sialic acid (Hart et al. 1984). Microscopic examination of the cell populations revealed inflammation characterized by increased interstitial mononuclear cells and a thickening of the alveolar septa. Increases in the lipids and proteins and levels of acid and alkaline phosphatase, lysozyme, and lactic dehydrogenase indicated cellular damage to the type II cells or the alveolar epithelium. Similar analyses of rats exposed to 3.3 mg beryllium/m³ and mice exposed to

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7.2 mg beryllium/m³ as beryllium sulfate for 1 hour and examined for #12 months indicated the occurrence of pneumonitis with thickening of the alveolar walls and inflammation of the lung (Sendelbach et al. 1986, 1989; Sendelbach and Witschi 1987b). Increased levels of acid and alkaline phosphatase, and lactic dehydrogenase in the lavage fluid of the lungs of treated rats and mice indicated damage to the cellular populations; the increase in protein indicated alveolar damage. These studies demonstrate the ability of soluble beryllium compounds to damage the lung long after exposure ceases. Dogs exposed to 10 mg beryllium/m³ as beryllium oxide calcined at 500 or 1,000 EC developed granulomas in the lung (Haley et al. 1989). Histopathology also revealed intense alveolar septal fibrosis and epithelial hyperplasia. Beryllium oxide calcined at 500 EC was associated with higher incidences of lesions, due to its greater solubility. Dogs exposed to 115 mg beryllium/m³ as a mixture of beryllium oxide, beryllium fluoride, and beryllium chloride for 20 minutes, had inflamed lungs and granulomatous foci (Robinson et al. 1968). Increased lung weight, inflammation, emphysema, and fibrosis of the lung were observed in monkeys exposed to 0.198 mg beryllium/m³ as beryllium sulfate for 7–17 days (Schepers 1964). Monkeys exposed to \$13 mg beryllium/m³ as beryllium hydrogen phosphate for 8–10 days, and 0.184 mg beryllium/m³ as beryllium fluoride for 7–18 days had severely inflamed and fibrotic lungs with granulomas. Histology revealed pleuritis, congestion, emphysema, consolidation, and edema of the lung. The severity of these effects was more notable with beryllium fluoride than with beryllium sulfate or beryllium hydrogen phosphate, partly due to the fluoride component which may form hydrofluoric acid in the lung as beryllium fluoride dissociates. Rats, rabbits, and guinea pigs exposed to 31 mg beryllium/m³ as beryllium oxide for 10 days did not have any histological evidence of lung damage (Hall et al. 1950).

Animals exposed to beryllium compounds for intermediate durations had health effects similar to those caused by acute exposure. Rats and hamsters exposed to 0.21 mg beryllium/m³ as bertrandite ore for 6 months developed granulomatous lesions composed of several large, tightly packed, dust laden macrophages and a few lymphocytes (Wagner et al. 1969). However, when the rats were exposed to 0.620 mg beryllium/m³ as beryl ore, the lungs were largely unaffected except for a few small areas of atypical alveolar wall cell proliferation. Monkeys exposed to 0.210 or 0.620 mg beryllium/m³ as bertrandite or beryl ore, respectively, had relatively minor changes in the lung. The changes observed were aggregates of dust-laden macrophages, lymphocytes, and plasma cells near respiratory bronchioles and small blood vessels. Vascular congestion, emphysema, and pneumonitis were observed during histological examination of the lungs of dogs exposed to 3.6 mg beryllium/m³ as beryllium oxide for 40 days or to 31 mg beryllium/m³ as beryllium oxide for 17.5 days (Hall et al. 1950). Epithelialization of the alveoli, focal metaplasia, and granulomas were observed in rats exposed to beryllium sulfate for

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6 months (Schepers et al. 1957); however, a nonexposure-related outbreak of pneumonia limits the interpretation of these results. Exposure of rabbits, dogs, cats, and monkeys to 0.04 mg beryllium/m³ as beryllium sulfate for 100 days caused distortion of the lung structure (Stokinger et al. 1950). The lung appeared to be severely inflamed and emphysematous, resulting in an increase in dead air space. No respiratory effects were observed in rabbits, cats, and monkeys exposed to 30 mg beryllium/m³ as beryllium oxide for 15 days; however, rats experienced respiratory distress (Hall et al. 1950).

Chronic exposure to beryllium and its compounds causes similar health effects as those observed after shorter exposure durations. Hamsters and monkeys exposed chronically to 0.210 and 0.620 mg beryllium/m³ as bertrandite or beryl ore, respectively, had relatively normal lung morphology, except that monkeys had inflamed lungs and hamsters exposed to the bertrandite ore had a few granulomatous lesions (Wagner et al. 1969). Rats exposed to 0.210 mg beryllium/m³ as bertrandite ore had bronchial lymphocytic infiltrates, abscesses, consolidated lobes, and granulomatous lesions. Inflamed lungs and areas of fibrosis and granuloma were observed in rats exposed to 0.620 mg beryllium/m³ as beryl ore. Proliferative responses of the alveolar epithelium were also observed. Although the beryllium exposure levels were fairly low in this study, the animals were exposed to 15 mg/m³ of bertrandite ore or beryl ore, which was the TLV for inert dust. Additionally, the beryllium ores contained high levels of silica (approximately 64%). It is possible that the high dust and silica exposure levels may have contributed to the observed effects; it should be noted that silicosis was not observed. Rats exposed to levels as low as 0.006 mg beryllium/m³ as beryllium oxide had inflamed lungs and some fibrosis (Vorwald and Reeves 1959). Chronic exposure of rats to other beryllium compounds caused health effects similar to those caused by beryllium oxide. Rats exposed to 0.034 mg beryllium/m³ as beryllium sulfate for 72 weeks had inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (Reeves et al. 1967). Rats exposed to 0.0547 mg beryllium/m³ as beryllium sulfate for 6–18 months had inflamed lungs and fibrosis (Vorwald and Reeves 1959).

Cardiovascular Effects. Data regarding the cardiovascular effects of beryllium and its compounds in humans are limited. Severe cases of chronic beryllium disease can result in cor pulmonale, which is hypertrophy of the right heart ventricle. In a case history study of 17 individuals exposed to beryllium in a plant that manufactured fluorescent lamps, autopsies revealed right atrial and ventricular hypertrophy (Hardy and Tabershaw 1946). An increase in deaths due to heart disease or ischemic heart disease was found in workers at a beryllium manufacturing facility (Ward et al. 1992). It is not likely that the cardiac effects are due to direct toxicity to the heart, but rather are a response to impaired lung function.

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Heart enlargement was observed in monkeys after acute inhalation exposure to $13 \text{ mg beryllium/m}^3$ as beryllium hydrogen phosphate, $0.184 \text{ mg beryllium/m}^3$ as beryllium fluoride, or $0.198 \text{ mg beryllium/m}^3$ as beryllium sulfate (Schepers 1964). Decreased arterial oxygen tension was observed in dogs exposed to $30 \text{ mg beryllium/m}^3$ beryllium oxide for 15 days, $3.6 \text{ mg beryllium/m}^3$ as beryllium oxide for 40 days (Hall et al. 1950), or $0.04 \text{ mg beryllium/m}^3$ as beryllium sulfate for 100 days (Stokinger et al. 1950). The effects of beryllium compounds on the cardiovascular system probably represent compensatory increases in cardiac musculature due to pulmonary fibrosis caused by inhalation exposure. The decrease of arterial oxygen tension reflects the reduced ability of the lung to oxygenate blood.

Hematological Effects. Information regarding the hematological effects of beryllium and its compounds in humans is limited to case histories. No difference in white blood cell counts, hematocrit, or differential white blood cell percentages was observed in a machinist with chronic beryllium disease who worked with beryllium metal (Johnson 1983). A study involving 170 case histories of beryllium workers in the Cleveland area reported few differences in erythrocyte sedimentation rates, blood counts, or blood chemistry (VanOrdstrand et al. 1945).

Acute exposure of animals to beryllium and its compounds had little effect on hematological parameters; however, intermediate-duration exposures caused anemia in several species. Hematological evaluation of rats and hamsters exposed to $1\text{--}100 \text{ mg beryllium/m}^3$ for $30\text{--}180$ minutes to achieve initial alveolar deposition of $1\text{--}63 \text{ }\mu\text{g beryllium}$ revealed no statistical difference between treated animals and controls (Sanders et al. 1975). The exact exposure concentration and duration were not clearly reported. Exposure to $31 \text{ mg beryllium/m}^3$ as beryllium oxide did not cause effects on the hematopoietic system in rats (Hall et al. 1950). No significant differences in leukocyte counts were observed in rabbits similarly exposed to beryllium oxide for 10 days. However, erythrocyte counts decreased slightly during the course of exposure.

Rabbits exposed to $307 \text{ mg beryllium/m}^3$ as beryllium oxide for 60 days developed macrocytic anemia (Hall et al. 1950). The erythrocyte counts decreased over time, and there was a tendency to develop hypochromia, indicated by transient decreases in the average mean corpuscular hemoglobin concentration. Dogs exposed to $30 \text{ mg beryllium/m}^3$ as beryllium oxide for 15 days exhibited a moderate, progressive leukocytosis, while dogs exposed to $3.6 \text{ mg beryllium/m}^3$ for 40 days developed macrocytic anemia manifested as an increased mean corpuscular volume and decreased erythrocyte count. The bone marrow was almost exhausted. Differential counting of the bone marrow smears indicated a decrease in erythroblasts and an increase in normoblasts. Exposure to the more soluble compounds of beryllium

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caused effects similar to those of beryllium oxide. Macrocytic anemia developed in rats and rabbits exposed to 0.43 mg beryllium/m³ and dogs exposed to 0.04 mg beryllium/m³ as beryllium sulfate for 100 days (Stokinger et al. 1950). Exposure to 2.0 and 0.43 mg beryllium/m³ as beryllium sulfate in rats, rabbits, and dogs caused transient leukocytosis; exposure to 2.0 mg beryllium/m³ caused mild thrombocytosis. With increasing exposure durations, dogs exposed to 0.04 mg beryllium/m³ as beryllium sulfate had decreased phospholipid and cholesterol content of the red blood cells. The changes in the biochemical constituents of the red blood cells may reflect a toxic effect on erythropoietic processes in the bone marrow.

Hematological effects were not observed in rats, hamsters, or monkeys exposed to 0.21 or 0.62 mg beryllium/m³ as bertrandite or beryl ore, respectively, for 6–23 months (Wagner et al. 1969).

Hepatic Effects. Information regarding hepatic effects in humans after inhalation exposure to beryllium and its compounds is limited. Following an accidental leakage of beryllium dust, 25 laboratory workers were exposed to an undetermined concentration of beryllium chloride over a period of 10–20 hours (Zorn et al. 1986). During a 10-month follow-up, no increase was observed in liver enzymes, serum glutamic oxaloacetic transaminase, or serum glutamic pyruvic transaminase. In another study involving case histories of 17 individuals exposed to beryllium in a plant that manufactured fluorescent lamps, autopsy revealed hepatic necrosis in one individual (Hardy and Tabershaw 1946).

Few hepatic effects have been observed in animals after inhalation exposure to beryllium and its compounds, except at lethal exposure levels. Acute exposure to 13 mg beryllium/m³ as beryllium hydrogen phosphate causes hepatocellular degeneration in monkeys (Schepers 1964). Hepatocellular degeneration was also observed in monkeys exposed to 0.184 mg beryllium/m³ as beryllium fluoride for 7–18 days. These exposure levels were lethal to monkeys. Histological examination revealed no hepatic changes in rats, rabbits, guinea pigs or hamsters following acute inhalation exposure to either beryllium oxide or beryllium sulfate (Hall et al. 1950; Sanders et al. 1975).

Intermediate-duration exposure of rats, monkeys, and hamsters to 0.210 and 0.620 mg beryllium/m³ as bertrandite or beryl ore did not result in histological evidence of hepatic damage (Wagner et al. 1969).

Decreases in serum protein concentration and the albumin/globulin ratio in the blood indicated that some liver damage occurred in dogs exposed to 3.6 mg beryllium/m³ as beryllium oxide (Hall et al. 1950). Rats and dogs exposed to 2.0 and 0.04 mg beryllium/m³ as beryllium sulfate, respectively, had increased serum

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albumin and globulin levels (Stokinger et al. 1950). Histological examination of rats exposed to 0.035 mg beryllium/m³ as beryllium sulfate for 30 days revealed no hepatic damage (Schepers et al. 1957).

No adverse hepatic effects were revealed by histological examination or liver enzyme analysis of rats, hamsters, and monkeys chronically exposed to beryllium oxide as bertrandite or beryl ore (Wagner et al. 1969).

Renal Effects. Kidney stones were observed in . 10% of the cases of chronic beryllium disease collected by the Beryllium Case Registry up to 1959 (Hall et al. 1959). In addition, an excess of calcium in the blood and urine has been seen quite frequently in patients with chronic beryllium disease. These effects are only suggestive and cannot be absolutely attributed to beryllium disease (Stoeckle et al. 1969). In a cohort mortality study of workers employed at beryllium manufacturing facilities, an increased risk of death from chronic and unspecified nephritis, renal failure, and other renal sclerosis was observed (Ward et al. 1992).

Renal effects in animals after inhalation exposure to beryllium and its compounds are minor, except at lethal concentrations. No adverse renal effects were detected by urinalysis, kidney weight measurement, or histological examination in rats, rabbits, hamsters, and guinea pigs exposed to beryllium oxide for acute durations (Hall et al. 1950; Sanders et al. 1975). Guinea pigs, mice, hamsters, and rats exposed to 4.3 mg beryllium/m³ as beryllium sulfate had protein in the urine; however, there was no protein in the urine of similarly exposed rabbits (Stokinger et al. 1950). No other measures of renal integrity were conducted in this study. Histological examination revealed glomerular degeneration in the kidneys of monkeys exposed to 0.198 mg beryllium/m³ as beryllium sulfate, 0.184 mg beryllium/m³ as beryllium fluoride, or \$13 mg beryllium/m³ as beryllium hydrogen phosphate (Schepers 1964). These concentrations were lethal to the monkeys. No histological evidence of renal damage was observed in rats exposed to 0.035 mg beryllium/m³ as beryllium sulfate.

Intermediate-duration exposure (6 months) of rats, hamsters, and monkeys to 0.210 or 0.620 mg beryllium/m³ as bertrandite or beryl ore, respectively, did not result in evidence of renal effects during histological examination or enzyme analysis (Wagner et al. 1969). No renal effects were observed in dogs exposed to 31 mg beryllium/m³ as beryllium oxide for #40 days. Urinary protein increased in dogs exposed to 0.43 mg beryllium/m³ and rats exposed to 2.0 mg beryllium/m³ as beryllium sulfate for 51–100 days (Stokinger et al. 1950).

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No renal effects were identified by histological examination or enzyme analysis in rats, hamsters, and monkeys exposed for 12–17 months to 0.21 or 0.62 mg beryllium/m³ as bertrandite or beryl ore (Wagner et al. 1969).

Endocrine Effects. Evidence of the effects of beryllium and its compounds on the endocrine system has been observed in humans and animals. One out of 17 workers exposed to beryllium in a fluorescent lamp manufacturing plant died from chronic beryllium disease (Hardy and Tabershaw 1946). Histological examination of the adrenal glands revealed marked hyperemia and vacuolization.

Effects on the adrenal gland have also been observed in animals exposed to beryllium compounds. Histological examination of monkeys exposed to 13 mg beryllium/m³ as beryllium hydrogen phosphate or 0.184 mg beryllium/m³ as beryllium fluoride revealed marked hypoplasia and hypotrophy of the adrenal gland (Schepers 1964). However, the adrenal glands of monkeys exposed to 0.196 mg beryllium/m³ as beryllium sulfate were normal. Rats and hamsters exposed to 1–100 mg beryllium/m³ as beryllium oxide for 30–180 minutes had increased adrenal weight (Sanders et al. 1975). The exact exposure concentrations were not specified.

Dermal Effects. Skin biopsies revealed granulomas containing beryllium in twins occupationally exposed to beryllium (McConnochie et al. 1988). Positive patch tests with soluble beryllium compounds were obtained in all 32 patients tested with known chronic beryllium disease, indicating that the patch test is useful in the diagnosis of chronic beryllium disease (Curtis 1959). However, the patch test using soluble beryllium compounds itself may be sensitizing and may exacerbate the condition in patients with chronic beryllium disease (Cotes et al. 1983; Epstein 1983; Stoeckle et al. 1969; Tepper 1972), contraindicating the use of patch testing in humans.

Rats and guinea pigs exposed to 0.5 mg beryllium/m³ as beryllium nitrate for 10 weeks had a typical delayed allergic reaction 24–48 hours after beryllium salts were applied to the skin (Stiefel et al. 1980).

Ocular Effects. There is limited information on the ocular toxicity of beryllium. According to a case history, twins occupationally exposed to beryllium had reduced tear secretions (McConnochie et al. 1988).

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Body Weight Effects. Effects on body weight have been observed in humans after inhalation exposure to beryllium or its compounds. Weight loss was common among workers with acute beryllium disease (VanOrdstrand et al. 1945). Weight loss was also reported in workers at a fluorescent lamp manufacturing plant with chronic beryllium disease (Hardy and Tabershaw 1946).

Weight loss, severe at times, has been observed in monkeys, rats, mice, dogs, and cats after acute-, intermediate-, and chronic-duration inhalation exposure to a variety of beryllium compounds. Due to impaired food consumption and “metabolic changes” (no additional information was provided), monkeys exposed for acute durations to 13 mg beryllium/m³ as beryllium hydrogen phosphate for 8–10 days, 0.184 mg beryllium/m³ as beryllium fluoride for 7–18 days, or 0.198 mg beryllium/m³ as beryllium sulfate for 7 days lost 8–34, 19–23, or 24%, respectively, of their original body weight (Schepers 1964). Mice exposed to 4.3 mg beryllium/m³ as beryllium sulfate for 14 days had a 13% decrease in body weight (Stokinger et al. 1950). Dogs exposed to 115 mg beryllium/m³ as beryllium fluoride, beryllium oxide, and beryllium chloride for 20 minutes had transient weight loss the first 7 days after exposure (Robinson et al. 1968). No effect on body weight was observed in rabbits exposed to 31 mg beryllium/m³ as beryllium oxide for 10 days (Hall et al. 1950).

Most of the available information on the effect of beryllium on body weight following intermediate-duration exposure comes from three studies that tested a variety of animal species. In monkeys, weight loss was seen following exposure to 0.198 mg beryllium/m³ as beryllium phosphate for 30 days (Schepers 1964), 30 mg beryllium/m³ as beryllium oxide for 15 days (Hall et al. 1950), or 0.43 mg beryllium/m³ as beryllium sulfate for 51–100 days (Stokinger et al. 1950); but not in monkeys exposed to 0.620 mg beryllium/m³ as beryllium oxide for 6 months (Wagner et al. 1969). The magnitude of weight loss ranged from 15 to 39%. A 3–9% weight loss was observed in rats exposed to 30 mg beryllium/m³ as beryllium oxide for 15 days (Hall et al. 1950); however, a series of studies by Wagner et al. (1969) did not find any alterations in body weight gain in rats exposed to 0.210 or 0.620 mg beryllium/m³ as beryllium oxide. This study also did not find body weight alterations in hamsters exposed to the same concentrations of beryllium oxide. Weight loss was also observed in dogs exposed to 3.6 or 30 mg beryllium/m³ as beryllium oxide for 40 or 15 days, respectively (Hall et al. 1950) or 0.4 mg beryllium/m³ as beryllium sulfate for 51–100 days (Stokinger et al. 1950). Severe weight loss was also observed in cats exposed to 0.04 mg beryllium/m³ as beryllium sulfate for 51–100 days (Stokinger et al. 1950) or 30 mg beryllium/m³ as beryllium oxide for 15 days (Hall et al. 1950). No effect was observed in rabbits exposed to 0.04 mg beryllium/m³ as beryllium oxide for 30 days or 2.0 mg beryllium/m³ as beryllium sulfate for 51–100 days (Stokinger et al. 1950).

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Exposure to 0.034 mg beryllium/m³ as beryllium sulfate for 72 weeks caused more severe body weight loss among female rats than among males (Reeves et al. 1967). Rats exposed to 0.62 mg beryllium/m³ as beryl ore for 17 months also had significantly reduced body weights, compared to controls (Wagner et al. 1969).

3.2.1.3 Immunological and Lymphoreticular Effects

While acute beryllium disease is a chemical pneumonitis, chronic beryllium disease appears to be an immunological disease. The evidence that chronic beryllium disease is an immunological disease is supported by the following. Beryllium can induce classic cell-mediated immune responses in humans and animals (Barna et al. 1981, 1984; Curtis 1951, 1959; Epstein et al. 1982; Haley et al. 1989; Marx and Burrell 1973; Saltini et al. 1989, 1990; Stiefel et al. 1980). Beryllium sensitized cells accumulate at sites of chronic beryllium disease, resulting in granulomas in the lungs (Rossman et al. 1988; Saltini et al. 1989, 1990). Beryllium has been identified within the granulomas of patients with chronic beryllium disease (Williams and Kelland 1986). Virtually all patients with chronic beryllium disease have a cell-mediated immune response to beryllium (Rossman et al. 1988; Saltini et al. 1989), and therapy that controls the immune response (i.e., corticosteroids) can ameliorate the disease (Aronchick et al. 1987).

Nonspecific immunologic findings in chronic beryllium disease include an increase in serum gamma-globulin levels (Resnick et al. 1970). The existence of specific antibodies to beryllium have been reported (Clarke 1991), and further research to confirm and identify the antibodies is continuing.

While the results of peripheral blood lymphocyte proliferative responses to beryllium have been variable in patients with chronic beryllium disease (Kreiss et al. 1989; Newman et al. 1989; Saltini et al. 1989; Stokes and Rossman 1991; Williams and Williams 1983), the results of lung lymphocyte proliferative responses to beryllium have been consistently positive (Rossman et al. 1988; Saltini et al. 1989).

Lung lavage studies in patients with chronic beryllium disease have revealed that there is an accumulation of CD4⁺T cells in the lungs (Rossman et al. 1988) and that these cells are memory T cells (Saltini et al. 1989). Antibodies to Class II antigens but not Class I antigens will block the beryllium-specific proliferative response. In addition, antibodies to the IL-2 receptor will also block the beryllium proliferative response.

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Immunological effects have also been observed in animals after inhalation exposure to beryllium. Dogs exposed to 10 mg beryllium/m³ as beryllium oxide had a greater immune response to beryllium oxide calcined at 500 EC than at 1,000 EC, due to the greater solubility of the 500 EC calcined beryllium oxide (Haley et al. 1989). The dogs exposed to beryllium oxide calcined at 500 EC had higher cell counts in the bronchoalveolar lavage fluid as a result of an increased lymphocyte population. There was also a greater response of pulmonary lymphocytes *in vitro* to beryllium salts. The tracheobronchial lymph nodes had moderate cortical and paracortical lymphoid hyperplasia resulting from B and T cell activation. The lymph nodes examined 365 days after treatment were characterized by lymphoid depletion, marked congestion, and medullary fibrosis. Histological examination of monkeys exposed for 8–10 days to 13 mg beryllium/m³ or for 30 days to 0.198 mg beryllium/m³ as beryllium hydrogen phosphate revealed hypoplasia of the lymph nodes (Schepers 1964). The hypoplasia may be a result of the nutritional status of the animal since most of the monkeys lost body weight and were anorexic. Histological examination of monkeys exposed for 7–18 days to either 0.198 or 0.184 mg beryllium/m³ as beryllium sulfate or beryllium fluoride, respectively, revealed marked hyperplasia of the lymph nodes, typical of immune activation. On the other hand, exposure of rats to 0.035 mg beryllium/m³ as beryllium sulfate for <7 or 30 days did not cause histopathological changes in the suprarenal, pulmonary, or hepatic lymph nodes (Schepers et al. 1957); the high incidence on non-exposure-related pneumonia limits the interpretation of this study.

Similar immunological effects have been observed in animals exposed to beryllium for intermediate durations. Rats and guinea pigs exposed to 0.5 mg beryllium/m³ as beryllium nitrate for 10 weeks had inflammations typical of delayed hypersensitivity, as assessed by skin tests and lymphocyte proliferation tests (Stiefel et al. 1980). Lymphocytes exposed *in vitro* to beryllium salts had increased proliferation rates greater than those of the controls. Gross and histological examination of the thymus and spleen of rats, hamsters, and monkeys exposed to 0.21 or 0.62 mg beryllium/m³ as bertrandite or beryl ore, respectively, for 6–23 months revealed no pathological alterations (Wagner et al. 1969).

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

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3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after inhalation exposure to beryllium or its compounds.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to beryllium or its compounds. Male and female rats were intratracheally injected with 0.6 mg beryllium/kg as radioactive beryllium oxide and allowed to mate over a 15-month period (Clary et al. 1975). There were no consistent effects on reproductive performance as determined by the average number of pregnancies per female, live pups per litter, dead pups per litter, live pups per female, lactation index, or average weight of live pups per female.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to beryllium or its compounds. A study conducted by Selivanova and Savinova (1986) examined the developmental toxicity of 50 mg beryllium/kg as beryllium chloride and beryllium oxide administered via intratracheal injection on gestational days 3, 5, 8, or 20. An increase in fetal mortality was observed in rats dosed on gestational day 3 with beryllium oxide and in rats dosed on gestational day 5 with either beryllium compound. Exposure to beryllium oxide or beryllium chloride on gestational day 3 resulted in decreased fetal body weights and an increased percentage of pups with internal abnormalities. The latter effect was also observed in the pups of rats exposed to beryllium chloride or beryllium oxide on gestational day 5 and beryllium oxide on gestational day 8. There were no differences in the number of live births per dam or in fetal length.

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3.2.1.7 Cancer

A number of retrospective cohort mortality studies examining workers at beryllium processing facilities in Pennsylvania and Ohio have been conducted by Mancuso and Associate (Mancuso 1970, 1979, 1980; Mancuso and El-Attar 1969) and the National Institute of Occupational Safety and Health (NIOSH) (Bayliss et al. 1971; Sanderson et al. 2001a; Wagoner et al. 1980; Ward et al. 1992); many of these studies examined one or two facilities and others looked at seven facilities. One of the earliest cancer mortality studies of these workers was conducted by Mancuso and El-Attar (1969). This study examined a cohort of 3,685 Caucasian male workers employed at two beryllium facilities in Ohio and Pennsylvania from 1937 to 1948; the cohort was followed through 1966. Social Security Administration data, Beryllium Registry data, and death certificates were used to identify employees, deaths, and causes of death. A group of workers in the rubber industry were used as a control group (no additional information on this cohort was provided). The study authors note that a “slightly higher” rate of deaths from malignant neoplasms of the lung, trachea, and bronchus were observed in the beryllium workers; no statistical analyses of the data were conducted. Interpretation of these data is limited by the inclusion of nonexposed workers (no data were available on which departments the workers were employed in), lack of information on exposure characterization, incomplete reporting of deaths or cause of death, large employee turnover rate (78% of the workers were employed for <2 years), and lack of statistical analysis. An additional limitation of the study is the selection of rubber workers as the comparison group, as increased incidence of lung cancer has been found in other studies of rubber workers (Mancuso 1979).

In the second phase of the cohort mortality study (Mancuso 1970), duration of employment and age as of 1940 were considered and the observation period was extended to 1967. The small number of deaths in each duration category, as well as the limitations discussed above in the Mancuso and El-Attar (1969) study, precludes drawing conclusions from this study. A third study by this group (Mancuso 1979) restricted the cohort to workers employed during the period of 1942–1948, extended the observation period to 1974 for the Ohio cohort and 1975 for the Pennsylvania cohort, and compared mortality in the beryllium workers to mortality for the U.S. white male population (using vital statistics data for the period ending in 1967). An increase in the number of lung cancer deaths was observed in workers with a latency period of 15 years or higher (22 observed versus 9.86 expected in the Ohio cohort and 36 observed versus 22.02 expected in the Pennsylvania cohort); the study author notes that the differences are statistically significant. EPA (1987) and MacMahon (1994) have criticized this study. In particular, EPA (1987) notes that using U.S. white male lung cancer death rates for the period ending in 1967 to estimate expected cases for 1968–1975 resulted in a 10–11% underestimation of expected lung cancer deaths

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because nationwide lung cancer rates were increasing. EPA (1987) and MacMahon (1994) comment that Mancuso (1979) did not account for the potential confounding effect of cigarette smoking on lung cancer mortality.

To determine whether the increased lung cancer deaths that have been observed in the previous papers by Mancuso and Associate (Mancuso 1970, 1979; Mancuso and El-Attar 1969) were due to beryllium exposure, or the excess risk could be attributed to personal characteristics of workers having unstable employment patterns, Mancuso (1980) conducted a fourth study of the Ohio and Pennsylvania cohorts followed through 1976. Employees in the viscose rayon industry served as a comparison group. A significant increase in lung cancer deaths was observed in the beryllium workers when compared to the entire cohort of rayon workers (standardized mortality ratio [SMR]=140) or a subcohort of workers who did not transfer between departments during their employment in the viscose rayon industry (SMR=158). When the cohorts were divided into employment durations, significant increases in lung cancer deaths were observed in the workers employed for <12 months (SMRs=138 and 164 for total rayon cohort and those not transferring departments, respectively) and workers employed for >49 months (SMRs=222 and 172, respectively), but not in workers employed for 13–48 months. As with the other Mancuso studies, the design of this study has been criticized. One limitation of this study is the lack of adjustment for the potential confounding effect of smoking. EPA (1987) questioned whether there was an adjustment for potential age differences between the beryllium cohort and noted that NIOSH re-analyzed the data from this study and found “serious problems with Mancuso’s analysis”.

NIOSH studies have examined workers at the same facilities as Mancuso, as well as several other beryllium processing facilities. The study by Bayliss et al. (1971) examined workers at a number of beryllium processing facilities in Ohio and Pennsylvania. The original cohort consisted of over 10,000 male and female workers who had employment of at least a few days or longer in the beryllium industry. Removal of approximately 2,000 workers with inadequate records and all female workers (approximately 1,100 workers) resulted in a study cohort of approximately 7,000 workers. The number of deaths among the beryllium workers was lower than expected (SMR=92.2), which was attributed to a healthy worker effect. An increased number of deaths due to lung cancer was observed in the beryllium workers (SMR=105.7), but the increase was not statistically significant. Limitations of this study include lack of analysis for potential effect of latency, elimination of over 2,000 workers due to incomplete records, and the combining of populations from several different plants into one cohort (EPA 1987; MacMahon 1994).

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A subsequent study sponsored by NIOSH and the Occupational Safety and Health Administration (OSHA) (Wagoner et al. 1980) examined beryllium workers at one facility in Reading, Pennsylvania. The study cohort of 3,055 white males employed between 1942 and 1967 were followed through 1975, and mortality rates were compared to the U.S. white male population (using NIOSH vital statistics data for the period ending in 1967). A significant increase in lung cancer deaths (47 observed versus 34.29 expected) was observed in the beryllium workers. When deaths from lung cancer were segregated by latency period, significant increases in lung cancer deaths were found in workers with a latency period of at least 25 years (20 observed versus 10.79 expected); significant increases in lung cancer deaths were also observed in workers employed for <5 years and a latency period of at least 25 years (17 observed versus 9.07 expected). To assess the influence of lowering beryllium exposure concentrations, lung cancer deaths were segregated by date of initial employment. A significant increase in lung cancer deaths was observed in workers initially hired before 1950 (when strict beryllium controls were instituted) and a 25-year or higher latency period (20 observed versus 10.76 expected). An increase in lung cancer deaths was also observed in workers initially employed after 1950, across latency periods, but the difference was not statistically significant (7 observed versus 4.60 expected). The study authors note that using national mortality rates probably resulted in a 19% underestimation of cancer risk because Berks County, Pennsylvania (where 87% of the workers resided) has a lower age-adjusted lung cancer rate than the U.S. general population (31.8 per 100,000 versus 38.0 per 100,000). However, EPA (1987) notes that most of the beryllium workers residing in Berks County lived in the city of Reading, Pennsylvania with a lung cancer mortality rate 12% higher than the national rate. Thus, using the national rates may have resulted in an underestimation of expected deaths. Wagoner et al. (1980) attempted to account for the contribution of cigarette smoking to lung cancer deaths by comparing smoking histories of the beryllium cohort (obtained during a 1968 medical survey) with U.S. white male smoking history (obtained by the 1964–1965 Health Interview Survey conducted by the Public Health Service). Using these data, the study authors estimated that the smoking habits of the beryllium workers would result in a 14% higher risk of lung cancer than the comparison population. The study authors note that the frequency of cigarette smoking and the distribution of lung cancer cell type distribution support the conclusion that it is unlikely that “cigarette smoking per se could account for the increased risk of lung cancer among beryllium-exposed workers in this study.” EPA (1987), MacMahon (1994), and Bayliss (1980) have discussed a number of severe limitations of this study: (1) using male mortality data for the period of 1941–1967 resulted in a 10–11% underestimation of expected lung cancer deaths, (2) the influence of cigarette smoking was probably underestimated by the study authors, EPA estimated that differences in cigarette smoking patterns would result in a 4.6–18.8% underestimation of expected deaths, and (3) the inclusion of one individual who died of lung cancer but did not work at the beryllium facility because he

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failed the pre-employment physical. After adjusting for use of outdated mortality data and cigarette smoking, EPA (1987) estimated that the rightful omission of this worker would result in a nonstatistically significant association between beryllium exposure and lung cancer mortality (46 observed versus 41.90 expected deaths for all workers and 20 observed and 14.67 expected deaths for workers with a 2 year latency period).

In a more recent study, Ward et al. (1992) examined mortality data for a cohort of 9,225 male workers employed at seven beryllium processing facilities in Ohio and Pennsylvania for at least 2 days in the period of 1940–1969; the workers were followed through 1988. Mortality rates in the beryllium cohort were compared to the U.S. white male population. Mortality from all causes was slightly elevated among the beryllium workers (SMR=1.05; 95% CI=1.01–1.08). The elevated mortality rate was largely due to increases in respiratory tract cancer, nonmalignant respiratory disease, and deaths from ischemic heart disease. The SMRs for trachea, bronchii, and lung cancer, nonmalignant respiratory disease, and ischemic heart disease were 1.26 (95% CI=1.12–1.42), 1.21 (95% CI=1.06–1.38), and 1.08 (95% CI=1.01–1.14), respectively. Analysis of mortality data for each individual plant revealed that significant increases in lung cancer deaths were only found in two facilities: Lorain, Ohio (SMR=1.69) and Reading, Pennsylvania (SMR=1.24). To assess the effect of duration of exposure and latency on lung cancer mortality, the total cohort and the Lorain and Reading cohorts were divided into several latency and duration of employment category. For the total cohort, duration of employment was not associated with increased lung cancer deaths, but increased latency was associated with increased lung cancer deaths. In the total cohort, statistically significant increases in lung cancer deaths were observed in the >30 year latency category (SMR=1.46), workers employed for <1 year with a >30 year latency (SMR=1.52), and in the 25–30 year latency period for workers employed for <1 year. Among workers at the Lorain and Reading facilities, significant increases in cancer mortality were also observed in workers employed for <1 year with a 30-year latency (SMRs=1.68 and 1.42, respectively). The decade of hire also influenced lung cancer deaths; this was independent of potential latency. The highest cancer mortality rates were observed among workers hired before 1950. Three of the seven beryllium-processing facilities were open in the 1940s; elevated cancer risks were observed at two of the facilities: Lorain (SMR=1.69; 95% CI=1.28–2.19) and Reading (SMR=1.26; 95% CI=1.02–1.56). The cancer risk was not significantly elevated in the plants operating during the 1950s or 1960s (the Lorain plant closed in 1948). The study authors also examined the influence of geographic variation in lung cancer mortality by comparing cancer mortality in the cohort with county lung cancer data. This comparison did not change the overall conclusions of the study. As with the Wagoner et al. (1980) study, Ward et al. (1992) used smoking habit data available from a 1968 Public Health Survey (included approximately 16% of cohort and four

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facilities [including the Reading, Pennsylvania facility]) to account for this confounding variable. A smoking adjustment factor of 1.1323 was estimated using the available data on the beryllium cohort and smoking habit data for the U.S. population (obtained from the National Center for Health Statistics, 1965 and Office of Health, Research, Statistics, and Technology, 1970). The smoking-adjusted SMRs for the entire cohort, the Reading cohort, and the Lorain cohort are 1.12, 1.09, and 1.49, respectively.

As a follow-up to this study, Sanderson et al. (2001a) conducted a case control study using workers from the Reading, Pennsylvania facility. The study consisted of 142 lung cancer cases and 5 age-race matched controls for each lung cancer case. Three quantitative exposure metrics were used to estimate beryllium exposure levels: cumulative beryllium exposure, average beryllium exposure level, and maximum exposure level. Cumulative beryllium exposure was calculated by summing the products of the number of days a worker held a particular job times the estimated annual average beryllium exposure for the job on those specific days. Average beryllium exposure was calculated by dividing the cumulative exposure level by the number of days the worker was employed. The maximum exposure level was the highest time-weighted average (TWA) exposure of any job the worker held, regardless of duration. As described in a companion paper (Sanderson et al. 2001b), historical measurements were estimated using actual industrial hygiene measurements and extrapolations from existing measurements over time and across jobs. No industrial hygiene measurements were available before 1947. Data from 1947 to 1960 were used to estimate exposure during the period of 1935 to 1960 based on the assumption that exposure levels remained constant during this time period. When job-specific exposure levels were not available, measurements from other areas of the facility that were expected to have similar types of exposures were used as surrogates. No measurements were available for general laborers, maintenance workers, or salaried personnel (e.g., managers, engineers, office workers). Exposure levels for the general laborers and maintenance workers were estimated by averaging exposure estimates for a variety of jobs. For the salaried personnel, the exposure levels were estimated using measured data for janitors. The overall lung cancer mortality rate for the Reading plant through 1992 was 1.22 (95% CI=1.03–1.43), which is slightly lower than the mortality rate of this cohort through 1988 (see discussion of the Ward et al. 1992 study). Most of the cases and controls (approximately 60%) were hired during the 1940s when beryllium levels were uncontrolled. The average duration of employment was 3.7 years for the cases and 5.5 years for the controls; however, approximately 67 and 50% of the cases and controls, respectively, were employed for <1 year. The difference in employment duration was statistically significant. As compared to controls, a higher percentage of cases worked as general labor or maintenance departments where some of the highest beryllium exposures occurred; the difference was statistically significant when tenure was lagged 10 or 20 years to discount exposures that may not have contributed to causing cancer because they

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occurred after cancer induction. Cumulative, average, and maximum exposure levels were 4,606 $\mu\text{g}/\text{m}^3$ days, 22.8 $\mu\text{g}/\text{m}^3$, and 32.4 $\mu\text{g}/\text{m}^3$, respectively, for the cases and 6,328 $\mu\text{g}/\text{m}^3$ days, 19.3 $\mu\text{g}/\text{m}^3$, and 27.1 $\mu\text{g}/\text{m}^3$ for the controls; the differences between the two groups was not statistically significant. However, when the exposure was lagged 10 or 20 years, the exposure levels were significantly higher among the cases. Cumulative beryllium exposure levels were 4,057 and 2,036 $\mu\text{g}/\text{m}^3$ days for the cases and controls, respectively, when lagged 10 years and 844 and 305 $\mu\text{g}/\text{m}^3$ days, respectively, when lagged 20 years. Average exposure levels for the cases and controls were 22.6 and 12.3 $\mu\text{g}/\text{m}^3$, respectively, when lagged 10 years and 10.2 and 5.3 $\mu\text{g}/\text{m}^3$ respectively, when lagged 20 years. The maximum exposure levels were 30.8 and 16.1 $\mu\text{g}/\text{m}^3$ for the cases and controls, respectively, when lagged 10 years and 13.1 and 6.5 $\mu\text{g}/\text{m}^3$ when lagged 20 years. Significantly elevated odds ratios were observed in three highest quartiles (when compared to the first quartile) of average exposure and maximum exposure when exposure was lagged for 10 or 20 years, but not when unadjusted exposure levels were used. The odds ratios were significantly elevated in the three highest quartiles of maximum exposure when exposure was lagged 20 years and in the highest quartile of unadjusted maximum exposure. Similarly, significantly elevated odds ratios were found when the average and maximum exposure levels were divided into three categories (#2, >2-20, and >20 $\mu\text{g}/\text{m}^3$) when the exposure was lagged 10 or 20 years. In general, no significant relationship between duration of employment and cancer risk were found. Sanderson et al. (2001a) also attempted to address two potential confounding variables: cigarette smoking and exposure to other chemicals. The workers were potentially exposed to a number of other chemicals including nitric acid aerosols, aluminum, cadmium, copper, fluorides, nickel, and welding fumes. Significant odds ratios were found for copper and fluorides when exposure was lagged 10 or 20 years. Interpretation of this finding is difficult because there were no workers exposed to fluorides or copper only and exposure to fluorides and copper was highly associated with exposure to several beryllium compounds. Smoking history was only available for a small number of cases and controls. Thus, the study authors used an indirect method for assess the possible association between smoking status and cancer risk. The authors noted that in order for smoking to be a confounding variable, there would have to be an association between smoking status and beryllium exposure level; such an association was not found.

In addition to these retrospective mortality studies of beryllium workers, there are two epidemiology studies of Beryllium Case Registry enrollees (Infante et al. 1980; Steenland and Ward 1992). In the Infante et al. (1980) study, a cohort of 421 white male workers entered into the Beryllium Case Registry (BCR) between July 1952 and December 1975; the cohort consisted of workers in the beryllium extraction and smelting, metal production, and fluorescent tube production industries and individuals not exposed occupationally but living near a beryllium facility. Mortality rates were compared to the U.S.

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white male population for the period lung cancer (which includes trachea and bronchii cancers) was observed (7 observed compared to 2.81 expected), but the difference was not statistically significant. When the lung cancer rate was determined from workers with previously diagnosed respiratory problems, the number of observed deaths was 6 versus 1.91 expected ($p < 0.05$). As with the Mancuso (1979) and the Wagoner et al. (1980) studies, using lung cancer mortality data for the period ending in 1967 probably resulted in a 10–11% underestimation of the number of expected deaths. The contribution of cigarette smoking to the observed increase in lung cancer deaths was not adjusted for because no smoking data were available for the cohort; the study authors note that it is unlikely that individuals with acute beryllium illness had smoking habits of sufficient magnitude to account for the excessive lung cancer risk in this group.

A follow-up of the study by Infante et al. (1980) included female workers in the analysis and extended the follow-up period by 13 years to 1988 (Steenland and Ward 1992). The cohort consisted of 689 patients, 66% of which were men. Of the entire cohort, 34% had been diagnosed with acute beryllium disease and 64% with chronic beryllium disease (2% of the subjects had unknown disease type). The mortality rates due to specific causes were compared with that of the U.S. population after stratification by age, race, sex, and calendar time. Increases in mortality were observed among the beryllium workers; the primary cause of death was pneumoconiosis and other respiratory diseases (SMR=34.23; 95% CI=29.1–40.0), followed by deaths from beryllium poisonings (SMR=34.93; 95% CI=19.1–61.4), all cancers (1.51; 95% CI=1.17–1.91), and lung cancer (SMR=2.00; 95% CI=1.33–2.89). There were 70 deaths from all types of cancer, 28 of which were due to lung cancer. Of these, 22 lung cancer deaths occurred in men (SMR=1.76, 95% CI=1.02–2.67), and 6 occurred in women (SMR=4.04, 95% CI=1.47–8.81). No trend was found for duration of exposure or for time since initial exposure. The lung cancer excess was more pronounced among those with acute beryllium disease (SMR=2.32; 95% CI=1.35–3.72) than those with chronic beryllium disease (SMR=1.57; 95% CI=0.75–2.89). Data on smoking status were available for 141 men and 82 women, and data on amount smoked were available for 51 men and 16 women. Analysis showed that the cohort smoked less than the U.S. population, and there were more former smokers and fewer current smokers in the cohort than in the U.S. population. Thus, the study authors concluded that the lung cancer excess was probably not due to smoking; the study authors also ruled out selection bias, concluding that excess exposure to beryllium was the causative factor. It is also possible that the beryllium disease process (particularly the acute disease) contributes to the development of lung cancer.

In general, the early (prior to 1987) studies that associated beryllium exposure with lung cancer have been inadequately controlled for confounding factors such as smoking, improperly calculated expected deaths

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from lung cancer, included employees in the beryllium industry who were not actually exposed to beryllium (e.g., salesmen, clerks), or used inappropriate controls. The more recent studies by Ward et al. (1992), Steenland and Ward (1992), and Sanderson et al. (2001a) have addressed many of these issues and provide strong data on the carcinogenic potential of beryllium in humans. NTP (1999, 2002) and IARC (2001) have concluded that beryllium is a human carcinogen; EPA (IRIS 2002) classified it as a probably human carcinogen (group B1). IARC (2001) noted that several aspects of the Ward et al. (1992) and Steenland and Ward (1992) studies support the conclusion that beryllium is a human carcinogen. In particular IARC noted (a) the consistency of lung cancer excess in most of the locations, (b) greater excess cancer risk in workers hired prior to 1950 when beryllium levels were much higher than in subsequent decades, and (c) the highest risk of lung cancer in individuals with acute beryllium disease and at the facility with the greatest proportion of acute beryllium disease. However, IARC (2001) also noted a number of limitations with the existing cancer database. The limitations include poor exposure characterization, relatively low excess cancer risk, and the lack of discussion of exposure to other lung carcinogens. Additionally, several reviewers have criticized the conclusions of the Steenland and Ward (1992) and Ward et al. (1992) studies. In general, the criticism focuses on the relatively low excess of cancer risk and the inadequate adjustment for smoking habits (Eisenbud 1993, 1997; Kolanzi 2001; Kotin 1994; MacMahon 1994; Trichopoulos 2000). Using the data from the Ward et al. (1992) study, Levy et al. (n.d.) recalculated the SMRs for lung cancer using city mortality rates rather than county or U.S. rates and a different indirect method for adjusting for smoking and did not find significant increases in the incidence of lung cancer among beryllium workers. A meta-analysis of the data did find a significant increase in lung cancer risk, although the SMRs were lower than those calculated by Ward et al. (1992).

Some beryllium compounds are carcinogenic in animals exposed via inhalation. A single nose-only exposure to 410–980 mg/m³ beryllium metal aerosol for 8–48 minutes resulted in a 64% incidence of lung tumors in rats; lung tumors were first observed 14 months after exposure (Nickell-Brady et al. 1994). Rats exposed to 0.035 mg beryllium/m³ as beryllium sulfate for 180 days had increased lung cancer rates, compared to controls (Schepers et al. 1957).

Cancer incidence was not increased in hamsters exposed to 0.21 or 0.62 mg beryllium/m³ as bertrandite or beryl ore for chronic durations (Wagner et al. 1969). In addition, rats similarly exposed to bertrandite ore did not have a greater incidence of lung cancer than that observed in the controls. However, 18 of 19 rats exposed to 0.62 mg beryllium/m³ as beryl ore developed tumors that were classified as bronchial alveolar cell tumors, adenomas, adenocarcinomas, or epidermoid tumors. Primary pulmonary cancer of the bronchiole was observed at 9 months in rats exposed to 0.006 or 0.0547 mg beryllium/m³ as beryllium

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oxide (Vorwald and Reeves 1959). The rats were examined for signs of cancer at 6, 9, 12, and 18 months. Lung tumors, which appeared to be adenocarcinomas with a predominantly alveolar pattern, were observed after 13 months of exposure in 100% of rats exposed to 0.034 mg beryllium/m³ as beryllium sulfate (Reeves et al. 1967). Monkeys exposed to 0.035 mg beryllium/m³ as beryllium sulfate had tumors in the hilus and peripheral portions of the lung, and scattered throughout the pulmonary tissue, as determined by histological examination (Vorwald 1968). Moreover, there were extensive metastases to the mediastinal lymph nodes and to other areas of the body. It should be noted that many of the studies conducted in animals have been criticized because of poor documentation, being conducted at single dose levels, or failure to include controls (EPA 1987). However, collectively, the animal data indicate that beryllium is carcinogenic in animals.

The CELs in each species are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

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3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to beryllium or its compounds.

Oral LD₅₀ values in animals vary according to the compound. LD₅₀ values for beryllium sulfate were 120 mg beryllium/kg in rats (Lanchow University 1978) and 140 mg beryllium/kg in mice (Ashby et al. 1990). The LD₅₀ values for beryllium chloride in rats were 200 mg beryllium/kg (Kimmerle 1966). The LD₅₀ values for beryllium fluoride were 18–20 mg beryllium/kg in mice (Kimmerle 1966; Lanchow 1978). The LD₅₀ value for beryllium oxyfluoride was 18.3 mg beryllium/kg in rats. The additional toxicity of the fluoride ion accounted for the lower LD₅₀ value observed for beryllium fluoride and beryllium oxyfluoride. The difference in the LD₅₀ values for the other beryllium compounds is due to differences in solubility and the potential to form insoluble beryllium phosphate in the gastrointestinal tract.

Increased mortality was observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet; the likely cause of death was severe ulcerative lesions in the gastrointestinal tract (Morgareidge et al. 1976). In chronic studies, no effect on survival was observed in rats and dogs exposed to #31 or 1 mg beryllium/kg/day, respectively, as beryllium sulfate in the diet (Morgareidge et al. 1975, 1976) or in rats and mice exposed to 0.6–0.7 or 1 mg beryllium/kg/day, respectively, as beryllium sulfate in drinking water (Schroeder and Mitchener 1975a, 1975b).

The LD₅₀ values in rats and mice and doses associated with increased mortality in dogs are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal, and ocular effects in humans after oral exposure to beryllium or its compounds. The systemic effects observed in animals after oral exposure to beryllium compounds are discussed below.

Table 3-2 Levels of Significant Exposure to Beryllium - Oral

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
1	Mouse (CBA)	1 d (GW)				140 (LD50) Ashby et al. 1990 BeSO ₄
INTERMEDIATE EXPOSURE						
2	Dog (Beagle)	33 wk (F)				12 (increased mortality) Morgareidge et al. 1976 BeSO ₄
Systemic						
3	Rat (Sprague- Dawley)	91d (W)	Bd Wt	0.7		Freundt and Ibrahim 1990 BeSO ₄
4	Rat (NS)	24-28 d (F)	Musc/skel			35 (rickets) Guyatt et al. 1933 BeCO ₃
5	Rat (Wistar)	13-42 d (F)	Musc/skel			345 (rickets) Jacobson 1933 BeCO ₃ +Be(OH) ₂
			Bd Wt	345		
6	Rat (NS)	21-22 d (F)	Musc/skel			70 (severe rickets) Kay and Skill 1934 BeCO ₃
			Metab	70	(decreased blood phosphate levels)	
7	Rat (Wistar)	4 wk (F)	Bd Wt	480	(18% decrease in body weight gain)	Matsumoto et al. 1991 BeCO ₃
			Metab	480	(decreased serum phosphate and alkaline phosphatase)	

Table 3-2 Levels of Significant Exposure to Beryllium - Oral

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
8	Rat (Wistar)	2 yr (F)	Resp	31			Morgareidge et al. 1975 BeSO ₄
			Cardio	31			
			Gastro	31			
			Hemato	31			
			Musc/skel	31			
			Hepatic	31			
			Renal	31			
			Endocr	31			
			Ocular	31			
Bd Wt	31						
9	Rat (Long- Evans) (W)	3.2 yr	Resp	0.7			Schroeder and Mitchener 1975a BeSO ₄
			Cardio	0.7			
			Hepatic	0.7			
			Renal	0.7			
			Bd Wt	0.7			
			Metab	0.7			

Table 3-2 Levels of Significant Exposure to Beryllium - Oral

(continued)

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
10	Mouse (Swiss)	898 d (W)	Resp	1			Schroeder and Mitchener 1975b BeSO ₄
			Cardio	1			
			Hemato	1			
			Hepatic	1			
			Renal	1			
			Bd Wt	1			
11	Dog (Beagle)	143-172 wk (F)	Resp	12 M			Morgareidge et al. 1976 BeSO ₄
			Cardio	12 M			
			Gastro	1 ^b		12 M (ulcerative and inflammatory lesions in the gastro intestinal tract of 9/10 dogs)	
			Hemato	1	12 M (erythroid hypoplasia of bone marrow)		
			Musc/skel	12 M			
			Hepatic	12 M			
			Renal	12 M			
			Endocr	12 M			
			Dermal	12 M			
			Ocular	12 M			
			Bd Wt	1		12 M (weight loss and anorexia)	
	Reproductive						
12	Dog (Beagle)	143-172 wk (F)		1			Morgareidge et al. 1976 BeSO ₄

Table 3-2 Levels of Significant Exposure to Beryllium - Oral

(continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Developmental							
13	Dog (Beagle)	143-172 wk (F)		1			Morgareidge et al. 1976 BeSO ₄

^aThe number corresponds to entries in Figure 3-2.

^b Used to derive a chronic-duration oral minimal risk level (MRL) of 0.002 mg Be/kg/day. The MRL was calculated using a benchmark dose method; the probit model was fit to the combined male and female incidence of ulcerative lesions in the small intestine and average doses for male and female dogs to estimate a BMDL (defined as the 95% lower confidence limit on the dose corresponding to a 10% increase in the incidence of small intestine lesions compared with controls) of 0.56 mg/Be/day. The BMDL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for intrahuman variability) and a modifying factor of 3 (to account for the lack of a study which supports the gastrointestinal effects found in the Morgareidge et al. [1976] dog study and the uncertainty as to whether the benchmark dose in the NOAEL).

Bd Wt = body weight; Be = Beryllium; BeCl₂ = beryllium chloride; BeCO₃.Be(OH)₂ = beryllium carbonate; BeF₂ = beryllium fluoride; BeO = beryllium oxide; BeSO₄ = beryllium sulfate; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GW) = gavage in water; hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory; (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Beryllium - Oral
Acute (≤ 14 days)

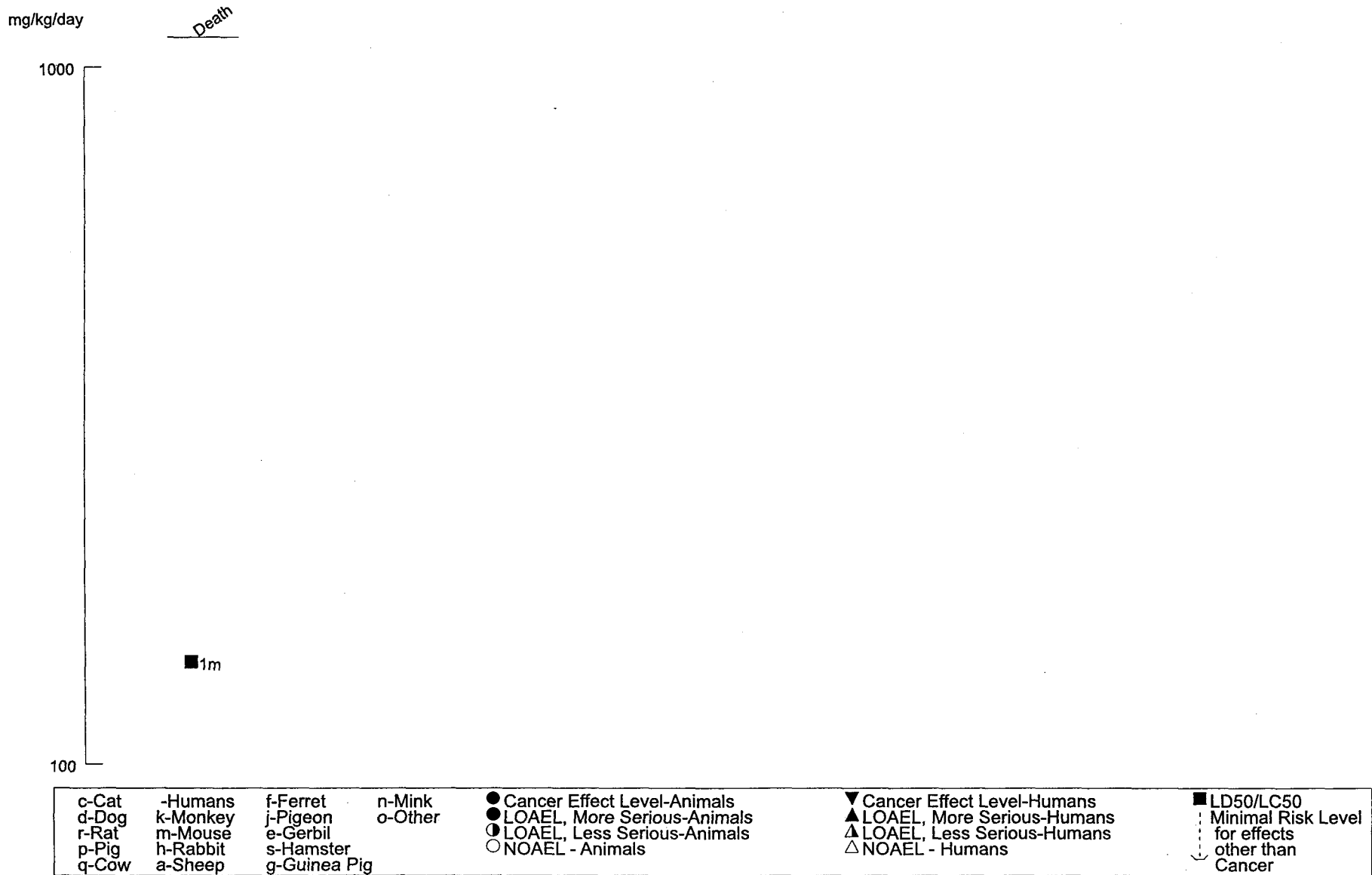


Figure 3-2. Levels of Significant Exposure to Beryllium - Oral (Continued)
Intermediate (15-364 days)

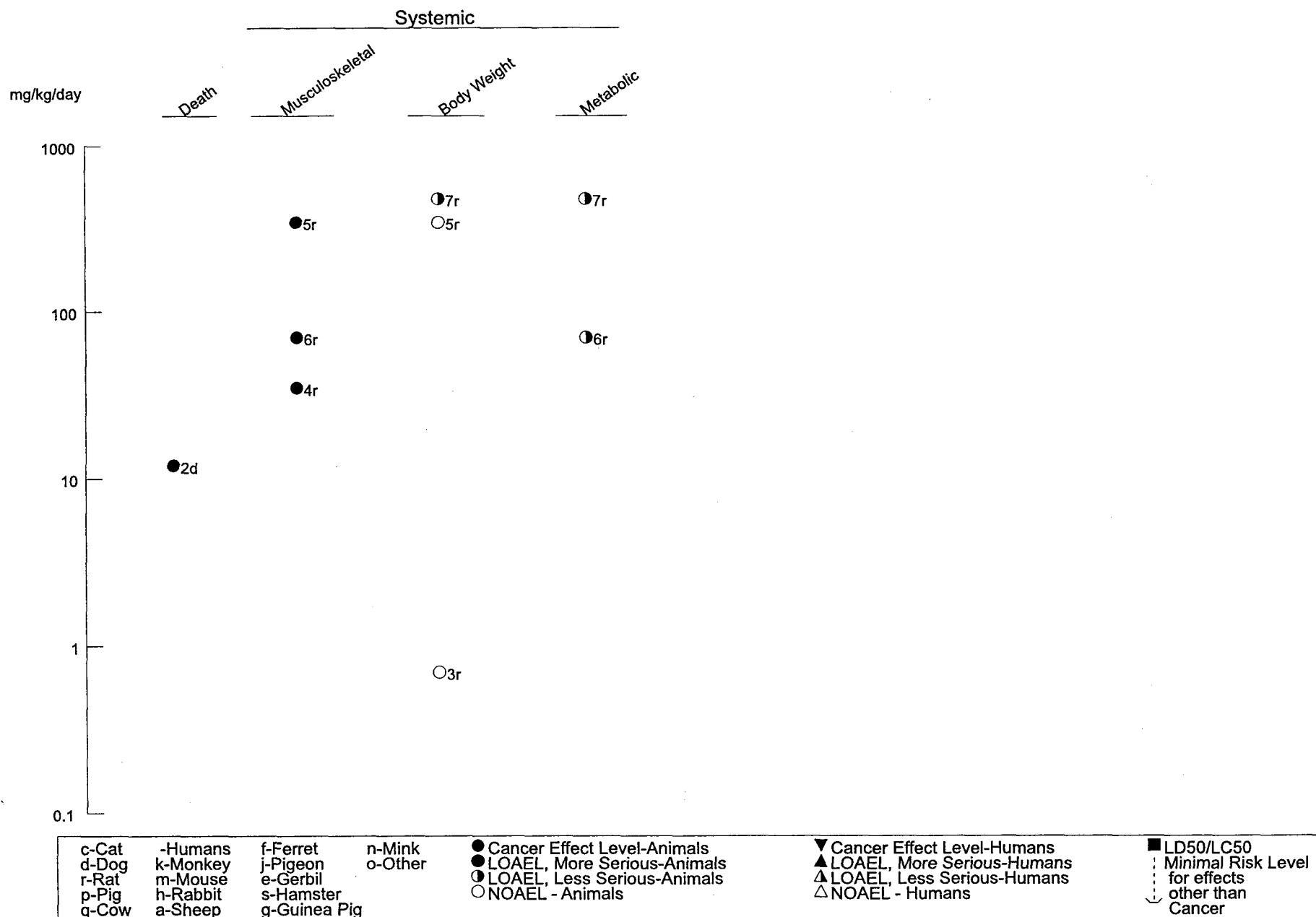
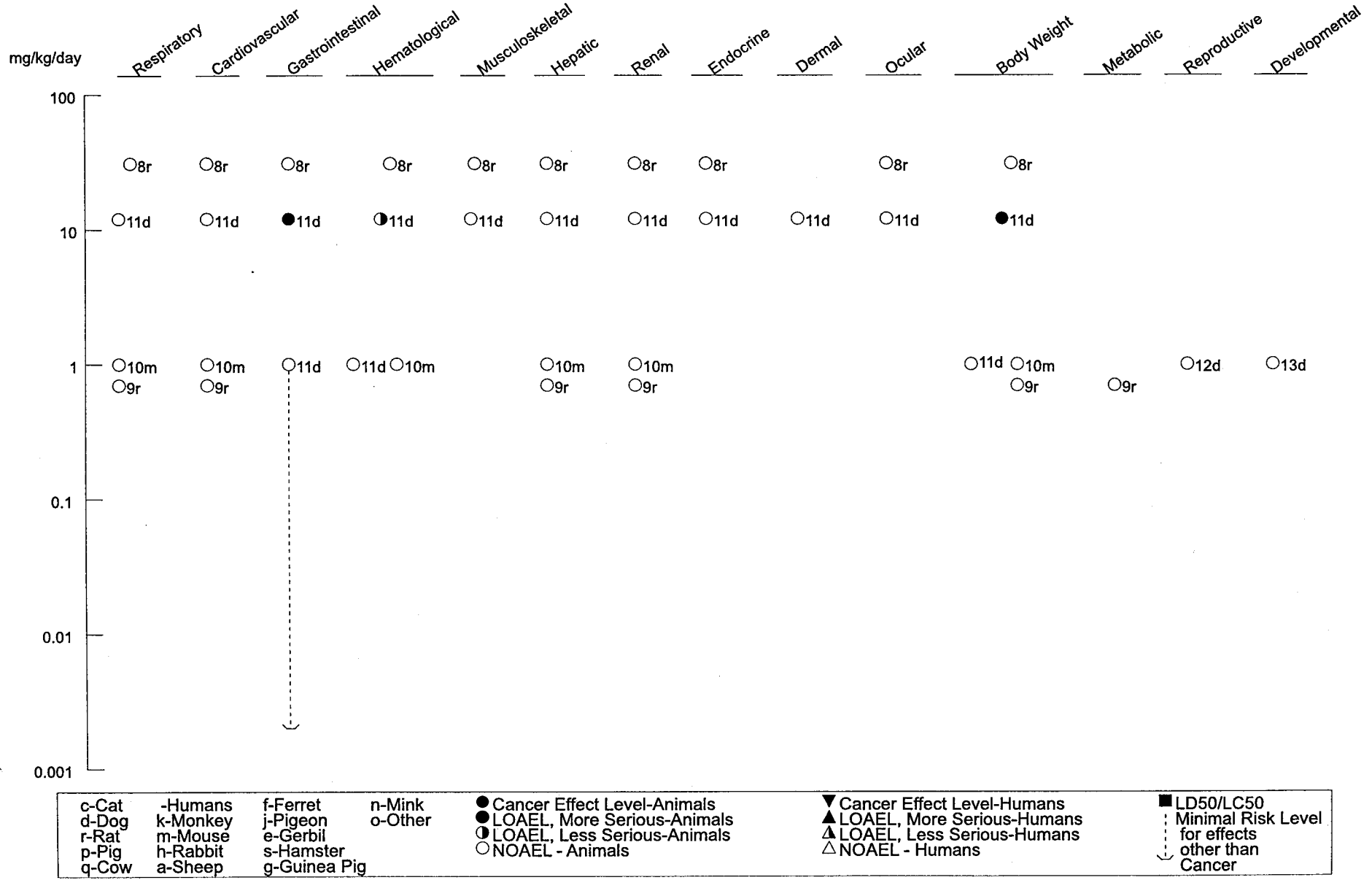


Figure 3-2. Levels of Significant Exposure to Beryllium - Oral (Continued)

Chronic (≥365 days)

Systemic



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

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

Respiratory Effects. The respiratory system does not appear to be a target of oral exposure to beryllium or its compounds. Thickening of the alveolar epithelium with areas of necrosis was observed in rats maintained on diets containing beryllium nitrate that provided 2 mg beryllium/kg every 3 days for 40 days (Goel et al. 1980). However, since the beryllium nitrate was mixed with food pellets, it is possible that the lung effects resulted from aspiration of the beryllium nitrate particulates into the lungs during feeding.

No microscopic lung abnormalities were observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks, respectively (Morgareidge et al. 1976) or in rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975). Furthermore, chronic exposure to 0.7 or 1 mg beryllium/kg/day as beryllium sulfate in the drinking water did not cause lung effects in rats and mice (Schroeder and Mitchener 1975a, 1975b).

Cardiovascular Effects. Data regarding cardiovascular effects in animals after oral exposure to beryllium or its compounds are limited. Dietary exposure to beryllium sulfate did not result in microscopic abnormalities in the heart or aorta of dogs exposed to 12 mg beryllium/kg/day for 143-172 weeks (Morgareidge et al. 1976) or rats exposed to #31 mg beryllium/kg/day for 2 years (Morgareidge et al. 1975). Histological examination revealed that chronic exposure to 0.7 or 1 mg beryllium/kg/day as beryllium sulfate in the drinking water did not cause cardiac effects in rats or mice (Schroeder and Mitchener 1975a, 1975b). The results from these studies suggest that oral exposure to beryllium is not likely to cause cardiac effects. However, other indices of cardiovascular effects, such as blood pressure determinations, were not examined.

Gastrointestinal Effects. In a chronic exposure study, extensive ulcerative and inflammatory lesions were observed in the small intestine, stomach, and large intestine of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet; similar, but less severe, lesions were observed in 1 of 10 dogs exposed to 1 mg beryllium/kg/day (Morgareidge et al. 1976). No lesions were observed in dogs exposed to 0.1 mg beryllium/kg/day. The dose-response data from this study were used to derive a chronic-duration MRL of 0.002 mg beryllium/kg/day. The only other study that examined gastrointestinal tract tissues was a chronic rat study conducted by the same group. No microscopic abnormalities of the

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stomach, small intestine, or large intestine were observed in rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975).

Hematological Effects. Two studies examined hematological end points in animals after oral exposure to beryllium sulfate. Erythroid hypoplasia of the bone marrow and slight decreases in erythrocyte, hemoglobin, and hematocrit levels were observed in dogs exposed to 12 mg beryllium/kg/day; no effects were observed at 1 mg beryllium/kg/day (Morgareidge et al. 1976). It is likely that these effects were secondary to the severe gastrointestinal hemorrhages also observed in these animals rather than a direct effect on the hematological system. No evidence of microscopic abnormalities of the bone marrow or spleen was observed in rats exposed to #31 mg beryllium/kg/day for 2 years (Morgareidge et al. 1975).

Musculoskeletal Effects. Early studies indicate that rats fed large amounts of beryllium carbonate in the diet developed rickets. Rickets were observed in rats fed diets supplemented with 35–840 mg beryllium/kg/day as beryllium carbonate (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The severity in the fragility of the bones increased with increasing concentrations of beryllium. These “beryllium rickets” are likely due to impaired gastrointestinal phosphate absorption rather than a direct effect of beryllium on bone. Following ingestion of beryllium carbonate, the beryllium in the gut binds to soluble phosphorus compounds and forms an insoluble beryllium phosphate; the rickets are a result of the decreased phosphorus levels. Although there are a number of methodological deficiencies in these studies, such as small numbers of animals per group and lack of statistical analysis, collectively, the studies suggest a relationship between beryllium carbonate ingestion and the occurrence of rickets. No bone effects were observed in dogs chronically exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1976). Chronic exposure to #31 or #12 mg beryllium/kg/day as beryllium sulfate did not cause morphological abnormalities in the muscle tissue of rats (Morgareidge et al. 1975) or dogs (Morgareidge et al. 1976), respectively.

Hepatic Effects. Oral exposure to beryllium compounds causes few effects, if any, on the liver of animals. Biochemical analysis of the lipid and protein contents of liver homogenates from rats exposed to 0.2 mg beryllium/kg/day as beryllium sulfate did not reveal any hepatic damage (Reeves 1965), however, histological examination was not performed.

Dogs fed 12 mg beryllium/kg/day as beryllium sulfate for 143-172 weeks (Morgareidge et al. 1976) and rats fed #31 mg beryllium/kg/day as beryllium sulfate for 2 years (Morgareidge et al. 1975) did not

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develop morphological abnormalities of the liver or changes in liver weight. Rats given 0.7 mg beryllium/kg/day as beryllium sulfate in drinking water for 3.2 years had transient increases in serum cholesterol (Schroeder and Mitchener 1975a). Histological examination of the livers of the exposed rats did not provide evidence of morphological alterations. In mice exposed to beryllium sulfate via a similar regimen, no changes in serum cholesterol or morphological abnormalities were observed (Schroeder and Mitchener 1975b).

Renal Effects. Oral exposure to beryllium compounds causes few renal effects, if any, in animals. Histological examination of rats fed #31 mg beryllium/kg/day as beryllium sulfate for 2 years established no evidence of morphological damage to kidney tissue; however, kidney weight increased slightly (Morgareidge et al. 1975). No significant alterations in kidney weight or histological examinations were observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143- 172 weeks (Morgareidge et al. 1976). Morphological alterations of the kidney were not observed in either sex of rats or mice exposed to 0.6–1 mg beryllium/kg/day as beryllium sulfate, respectively (Schroeder and Mitchener 1975a, 1975b). Female rats, however, developed a transient glucosuria (Schroeder and Mitchener 1975a).

Endocrine Effects. There is limited information on potential endocrine effects following oral exposure to beryllium. No adverse effects were observed in the adrenal, thyroid, pituitary, or pancreas of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976) or in rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975).

Dermal Effects. Information regarding dermal effects in animals after oral exposure to beryllium or compounds is limited. Histological examination of the skin of rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976) did not indicate morphological changes.

Ocular Effects. Two studies examined the eyes of animals repeatedly exposed to beryllium sulfate in the diet. No ocular effects were observed in rats exposed to #31 mg beryllium/kg/day for 2 years (Morgareidge et al. 1975) or dogs exposed to 12 mg beryllium/kg/day for 143-172 weeks (Morgareidge et al. 1976).

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Body Weight Effects. In general, exposure to beryllium sulfate in the diet or drinking water does not adversely affect body weight gain. Intermediate-duration exposure to high doses of beryllium carbonate in the diet (480 mg beryllium/kg/day) resulted in an 18% decrease in body weight gain in rats (Matsumoto et al. 1991). At lower doses (0.7 mg beryllium/kg/day), no body weight effects were observed (Freundt and Ibrahim 1990). Anorexia and weight loss was observed in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet; no effects on body weight gain were observed in dogs exposed to #1 mg beryllium/kg/day (Morgareidge et al. 1976). The weight loss observed at the highest dose was probably secondary to the ulcerative gastrointestinal lesions present in these animals. No alterations in weight gain were observed in rats (Morgareidge et al. 1975) chronically exposed via the diet to 31 mg beryllium/kg/day, or in rats (Schroeder and Mitchener 1975a) and mice (Schroeder and Mitchener 1975b) exposed via drinking water to 0.7 or 1 mg beryllium/kg/day, respectively.

Metabolic Effects. There are very limited data on metabolic effects in animals following oral exposure to beryllium or its compounds. Decreases in serum phosphate levels and alkaline phosphatase activity were observed in rats exposed to \$70 mg beryllium/kg/day as beryllium carbonate in the diet (Kay and Skill 1934; Matsumoto et al. 1991). As discussed under Musculoskeletal Effects, it is likely that these effects are due to beryllium binding to soluble phosphorus compounds causing a decrease in phosphorus absorption.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to beryllium or its compounds.

No histopathological lesions were observed in the spleen, lymph nodes, or thymus of rats chronically exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976). More sensitive tests of the immune function were not conducted.

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3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to beryllium or its compounds.

No changes in brain weight and no histopathological lesions were observed in the brain, nerve, or spinal cord of rats chronically exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate in the diet for 143-172 weeks (Morgareidge et al. 1976). This information is insufficient to conclude that beryllium does not cause neurological effects because more sensitive neurological or neurobehavioral tests were not performed.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to beryllium or its compounds.

There is limited information available on beryllium effect on reproduction. In a chronic duration dog study conducted by Morgareidge et al. (1976), male and female dogs were housed together at the time of the second heat, were allowed to mate and wean their pups; the study authors reported that there were no significant alterations in the number of pregnancies, number of pups, or number of live pups observed at doses of #1 mg beryllium/kg/day as beryllium sulfate in the diet. The result of this study should be interpreted with caution because very few study details were provided. Rats maintained for 2 years on diets containing beryllium sulfate had a significantly decreased average testes-to-body weight ratio at concentrations of 0.3 and 2.8 mg beryllium/kg/day, but not at #31 mg beryllium/kg/day (Morgareidge et al. 1975). Histological examination of the testes, prostate, seminal vesicles, and epididymis did not reveal any abnormalities. No decrease in ovary weight was observed in female rats similarly exposed. Furthermore, histological examination of the ovaries, uterus, and oviducts did not reveal any abnormalities (Morgareidge et al. 1975). The absence of further evidence of adverse effects of reproductive organs and of a positive dose relationship makes the toxicological significance of the decreased testes-to-body weight ratio unclear.

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3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to beryllium or its compounds.

There is limited information on beryllium's potential to induce developmental effects in animals following oral exposure. As discussed under Reproductive Effects, the Morgareidge et al. (1976) chronic dog study co-housed males and females, allowed them to mate, and wean their pups. Pups in the first litter were examined for gross and skeletal malformations. No significant alterations in the occurrence of gross or skeletal malformations, number of live pups, pup body weights, or pup survival were observed at 1 mg beryllium/kg/day; however, stillborn or cannibalized pups dying within the first few postnatal days were not examined.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to beryllium or its compounds.

Beryllium has not been found to cause cancer in animals after oral exposure. This could be due to the poor absorption of beryllium compounds from the gastrointestinal tract. Nonsignificant increases in the number of lung reticulum cell carcinomas were observed in male rats exposed to 0.3 or 2.8 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years; the incidences were 10/50, 17/50, 16/50, and 5/50 in males and 5/50, 7/50, 7/50, and 5/50 in females in the 0, 0.3, 2.8, and 31 mg beryllium/kg/day groups, respectively (Morgareidge et al. 1975). No differences in the number of reticulum cell carcinoma bearing rats were observed in the beryllium-exposed rats (18/50, 16/50, and 13/50 for males and 11/50, 7/50, and 8/50 for females in the 0.3, 2.8, and 31 mg beryllium/kg/day groups, respectively) compared to controls (12/50 and 8/50 for males and females, respectively). The incidence of tumors in rats or mice exposed chronically to 1 mg beryllium/kg/day as beryllium sulfate in the drinking water was not significantly altered, although the incidence of total tumors in treated male rats (9/33) was slightly increased, compared to controls (4/26) (Schroeder and Mitchener 1975a, 1975b). The incidence of neoplasms was not significantly increased in dogs exposed to 12 or 1 mg beryllium/kg/day as beryllium sulfate in the diet for 33 or 172 weeks, respectively (Morgareidge et al. 1976).

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3.2.3 Dermal Exposure**3.2.3.1 Death**

No studies were located regarding death in humans or animals after dermal exposure to beryllium or its compounds.

3.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans or animals after dermal exposure to beryllium or its compounds.

Most of the available information on the systemic toxicity of beryllium following dermal exposure comes from a series of studies conducted by Marx and Burrell (1973). In these studies, guinea pigs were sensitized via 12 biweekly intradermal injections of beryllium sulfate and/or received a single intradermal injection of beryllium oxide or a single intradermal injection of beryllium oxide, beryllium sulfate, and beryllium fluoride. Another group of guinea pigs received two intraperitoneal injections of beryllium sulfate. The study authors note “a number of guinea pigs which were being sacrificed were examined for evidence of any systemic involvement of the disease state.” No additional information was provided as to which group(s) of animals were examined; however, an assumption can be made that it was animals receiving intradermal doses. The observed effects are described below, but are not presented in the LSE table or figure.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to beryllium or its compounds.

Several respiratory effects were described in the Marx and Burrell (1973) study; the observed effects included mild to moderate interstitial fibrosis of the alveolar wall, mild to moderate emphysema with dilatation of the respiratory bronchioles, hypertrophy of smooth muscle, and mucosal hypertrophy of the terminal bronchioles.

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Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to beryllium or its compounds.

Splenic effects were observed in the guinea pigs examined by Marx and Burrell (1973). The observed effects in the spleen included follicular hyperplasia and focal hematopoietic tissue hyperplasia and large deposits of hemosiderin in the medullary area.

Dermal Effects. Dermatological abnormalities due to beryllium exposure were reported in the case histories of 42 workers exposed to beryllium sulfate, beryllium fluoride, or beryllium oxyfluoride (VanOrdstrand et al. 1945). The dermatological manifestations were characterized as edematous, papulovesicular dermatitis. Ulceration occurred only after the skin was accidentally abraded. These ulcers began as small indurated papules surrounded by an area of erythema which later underwent necrosis. Conjunctivitis occurred only as a splash burn or in association with contact dermatitis of the face. Granuloma formation was reported in the case histories of 26 beryllium workers with skin lesions resulting from cuts and abrasions sustained at work (Williams et al. 1987). Skin biopsies of six workers showed that the granulomatous lesions of the skin contained beryllium. Eight other workers had skin lesions only. Twelve of the workers had nonspecific inflammation of the skin without granuloma (Williams et al. 1987). An allergic contact dermatitis can occur and is most frequently caused by beryllium fluoride (Curtis 1951) (see Section 3.2.3.3).

Delayed hypersensitivity reactions, as described under Immunological and Lymphoreticular Effects, were observed in beryllium-sensitized guinea pigs dermally exposed to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride (Belman 1969; Marx and Burrell 1973).

3.2.3.3 Immunological and Lymphoreticular Effects

Thirteen patients with dermatitis as a result of occupational dermal contact with beryllium fluoride, ground metallic beryllium, or water drippings from overhead pipes coated with dust of various compounds were evaluated with patch tests using different beryllium compounds to determine whether the dermatitis was due to an immune response (Curtis 1951). Positive patch tests were obtained in 5 of 13 patients challenged with 0.019 mg beryllium/mL as beryllium fluoride. The incidence and severity of positive reactions increased with increasing concentrations of test substance. The relative ability of the compounds to elicit reactions was as follows: beryllium fluoride > beryllium sulfate=beryllium chloride > beryllium nitrate.

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Sensitization of guinea pigs with 12 biweekly intradermal injections of 0.0019 or 0.0005 mg beryllium as either beryllium fluoride or beryllium sulfate increased the amount of macrophage inhibition factor and lymphotoxin when the lymphocytes were cultured with beryllium salts (Marx and Burrell 1973). The sensitivity of the lymphocytes to beryllium salts, as noted by the increase in lymphokine levels, could be passively transferred from a sensitized donor to a naive recipient. Delayed hypersensitivity reactions also developed in guinea pigs tested with beryllium fluoride or beryllium chloride after dermal or intracutaneous sensitization with beryllium fluoride (Belman 1969) and in guinea pigs tested with beryllium sulfate or metallic beryllium after intradermal sensitization with beryllium sulfate (Zissu et al. 1996). The LOAEL values for immunological effects in each species and duration category are recorded in Table 3-3.

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

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Animal models of chronic beryllium disease have increased our understanding about the potential pathogenesis of chronic beryllium disease in humans. Hartley guinea pigs that were injected intratracheally with 16 mg beryllium/kg as beryllium oxide calcined at 560 EC developed slight edema and had focal interstitial lymphomononuclear infiltration at 1 week after injection (Barna et al. 1981). Granulomatous lesions were found at 2 weeks after injection and became progressively more severe at 4–6 weeks, with the level of severity persisting up to the end of the observation period (6 months). *In vitro* blood lymphocyte transformation tests in response to beryllium sulfate challenge were consistently positive with cells from beryllium oxide injected guinea pigs and consistently negative in cells from controls. Treatment of the guinea pigs with immunosuppressive agents (prednisone, L-asparaginase,

Table 3-3 Levels of Significant Exposure to Beryllium - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Immuno/ Lymphoret						
Human	48 hr			0.19 mg/ml	(allergic dermatitis)	Curtis 1951 BeSO ₄
Human	48 hr			0.19 mg/ml	(allergic dermatitis)	Curtis 1951 BeCl ₂
Human	48 hr			0.019 mg/ml	(allergic dermatitis)	Curtis 1951 BeF ₂
Human	48 hr			0.19 mg/ml	(allergic dermatitis)	Curtis 1951 Be(NO ₃) ₂
Gn Pig (albino)	1 x			0.1 M	(delayed type hypersensitive reaction)	Belman 1969 BeCl ₂
Gn Pig (albino)	1 x			0.02 M	(delayed type hypersensitive reaction)	Belman 1969 BeF ₂
Gn Pig (Hartley)	1 d			0.25 ug	(delayed hypersensitive reaction, splenic hyperplasia, lung inflammation)	Marx and Burrell 1973 BeSO ₄
Gn Pig (Dunkin Hartley)	24 hr			3 Percent (%)	(delayed type hypersensitivity)	Zissu et al. 1996 beryllium sulfate

Table 3-3 Levels of Significant Exposure to Beryllium - Dermal

(continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
INTERMEDIATE EXPOSURE						
Immuno/ Lymphoret						
Gn Pig (Hartley)	24 wk 1x/2wk			0.0005 ug	(increased macrophage inhibition factor and T-cell activity)	Marx and Burrell 1973 BeSO ₄

BeCl₂ = beryllium chloride; BeF₂ = beryllium fluoride; Be(NO₃)₃ = beryllium nitrate; BeSO₄ = beryllium sulfate; Gn pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s); x = times

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cytoxin) decreased the severity of beryllium oxide-induced lung disease. Pretreatment with beryllium sulfate prior to beryllium instillation delayed the development and reduced the severity of lung granuloma and also suppressed the delayed skin reactions to beryllium sulfate injected intradermally in guinea pigs intratracheally exposed to beryllium oxide. These experiments demonstrate that the development of granulomas in response to beryllium involves cell-mediated immune mechanisms. Similar studies with strain 2 and strain 13 guinea pigs demonstrated that strain 2 guinea pigs consistently developed chronic beryllium disease, while strain 13 guinea pigs did not, indicating that the immune mechanisms are genetically controlled in guinea pigs, and may explain the low prevalence of chronic beryllium disease in humans (Barna et al. 1981, 1984). In an attempt to develop a murine model for chronic beryllium disease, A/J (H-2^a haplotype) mice received intratracheal injections of beryllium sulfate or beryllium oxide calcined at 550 or 1,100 EC (Huang et al. 1992). In mice that received beryllium oxide, no histological differences or differences in bronchoalveolar lavage cells were found from the control mice until 8 months after instillation. At 8 months, there were moderate infiltrates and diverse microgranulomatous lesions, but these were apparently resolved at 10 months. The mice that received beryllium sulfate intratracheally were preimmunized with beryllium sulfate subcutaneously. Nonspecific inflammatory cells plus perivascular areas of lymphocytic infiltrates were seen at 2 weeks after beryllium sulfate instillation; numerous active areas containing macrophages, microgranulomas, and fibrosis were seen at 4 weeks; more severe granulomas and fibrosis were seen at 8 weeks, but at 20 weeks the lungs were generally normal. Results of tests on cells obtained by bronchoalveolar lavage showed increases in lymphocytes that corresponded with the time course of pathological changes. At 2 weeks, . 30% of the lymphocytes expressed the γ/σ T lymphocyte receptor. Most of the lymphocytes at 4 weeks were Thy1+, LdT4+ (CD4+), and expressed the α/β T lymphocyte receptor. Significant *in vitro* proliferation of bronchoalveolar lavage lymphocytes from preimmunized mice in response to beryllium sulfate was observed. During the acute phase (2 weeks), macrophage activation antigens were expressed, while at later times beyond the acute inflammatory phase, monocyte-macrophage antigens were expressed. Similar effects could not be induced in BALB/c (H-2_d haplotype) or C57BL/6 (H-2_b haplotype) mice, suggesting that genetic differences at the H-2 major histocompatibility complex gene complex may account for the differential responses to beryllium sulfate. Another cellular mechanism by which beryllium is thought to induce toxicity is by interaction with the cell lysosome (Witschi and Aldridge 1968). It has been postulated that beryllium destroys the integrity of the lysosomal membrane and releases lysosomal enzymes, which are injurious to the cell (Reeves and Preuss 1985).

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3.3 GENOTOXICITY

Genotoxic Effects. No studies were located regarding genotoxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. CBA mice were exposed by gavage to 117 and 71 mg/kg as beryllium sulfate corresponding to 80 and 50% of the LD₅₀ values, respectively (Ashby et al. 1990). The number of micronucleated polychromatic erythrocytes was not exceptional 24, 48, and 72 hours after dosing. *In vitro* studies are summarized in Table 3-4. The results of genotoxicity assays of soluble beryllium compounds are inconsistent; however, the carcinogenicity of beryllium is supported by the positive mutagenic potential reported in some of these studies. The inconsistencies may have been due to the physical/chemical properties of beryllium; in particular the binding of beryllium to phosphate, hydroxide, or proteins in the culture media. Beryllium nitrate was not mutagenic in the *Salmonella typhimurium* reverse mutation assay (Ames test) (Arlauskas et al. 1985). Beryllium sulfate was mutagenic in the forward mutation assay in *Bacillus subtilis* (Kanematsu et al. 1980) but was not mutagenic in the Ames test, regardless of the presence of microsomal fractions (Ashby et al. 1990; Rosenkranz and Poirier 1979; Simmon 1979b). Beryllium chloride was mutagenic in the reverse mutation assay in *Photobacterium fischeri* (Ulitzur and Barak 1988). Beryllium chloride was not mutagenic in the forward mutation assay with *Escherichia coli* (Zakour and Glickman 1984). Beryllium sulfate did not cause gene mutations in *Saccharomyces cerevisiae* (Simmon 1979b). Gene mutations were induced in whole mammalian cell cultures by the addition of either beryllium sulfate or beryllium chloride (Hsie et al. 1979; Miyaki et al. 1979). According to one study, beryllium sulfate induced chromosomal aberrations in mammalian cells (Larramendy et al. 1981); however, other studies indicate that beryllium sulfate did not induce chromosomal aberrations in cultured mammalian cells (Ashby et al. 1990; Brooks et al. 1989). Beryllium sulfate did not affect deoxyribonucleic acid (DNA)-repair in mammalian cells (Williams et al. 1989). Differences in the positive and negative results depend on the assay conditions, the concentrations of the beryllium compounds *in vitro*, and the differences among bacterial strains. Thus, soluble beryllium compounds appear to be weakly genotoxic.

Table 3-4. Genotoxicity of Beryllium and Its Compounds *In Vitro*

Species (test system)	End point	With activation	Without activation	Reference	Compound
Prokaryotic organisms:					
<i>Salmonella typhimurium</i>	Gene mutation	—	—	Arlaukas et al. 1985; Ashby et al. 1990; Rosenkranz and Poirer 1979; Simmon et al. 1979; Simmon 1979a	Beryllium sulfate
<i>S. typhimurium</i>	Gene mutation	No data	—	Arlauskas et al. 1985	Beryllium nitrate
<i>Bacillus subtilis</i>	Gene mutation	No data	+	Kanematsu et al. 1980	Beryllium sulfate
<i>Escherichia coli</i>	Gene mutation	No data	—	Zakour and Glickman 1984	Beryllium chloride
<i>Photobacterium fischeri</i>	Gene mutation	No data	+	Ulitzur and Barak 1988	Beryllium chloride
Eukaryotic organisms:					
Fungi:					
<i>Saccharomyces cerevisiae</i>	Gene mutation	No data	—	Simmon 1979b	Beryllium sulfate
Mammalian cells:					
Chinese hamster ovary K1-BH4 cell	Gene mutation	No data	+	Hsie et al. 1979	Beryllium sulfate
Chinese hamster ovary cell	Chromosomal aberration	No data	—	Brooks et al. 1989	Beryllium sulfate
Chinese hamster CHL cells	Chromosomal aberration	—	—	Ashby et al. 1990	Beryllium sulfate
Chinese hamster V79 cells	Gene mutation	No data	+	Miyaki et al. 1981	Beryllium chloride
Human lymphocytes	Chromosomal aberration	No data	+	Larramendy et al. 1981	Beryllium sulfate
Rat hepatocytes	DNA-repair	No data	—	Williams et al. 1989	Beryllium sulfate
Syrian hamster cells	Chromosomal aberration	No data	+	Larramendy et al. 1981	Beryllium sulfate

— = negative result; + = positive result; CHL = Chinese hamster lungs; DNA = deoxyribonucleic acid

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3.4 TOXICOKINETICS**3.4.1 Absorption****3.4.1.1 Inhalation Exposure**

Beryllium compounds are absorbed primarily through the lungs, but sufficient information to determine the rate and extent of absorption was not located. Due to an accidental leakage of beryllium dust in a laboratory, 25 people were exposed to an undetermined concentration for 10–20 hours (Zorn et al. 1986). The day after exposure, serum beryllium levels were 3.5 ± 0.47 ppb beryllium, compared to 1.0 ppb in unexposed controls. Six days later, the serum level decreased to 2.4 ± 0.3 ppb beryllium, and 2–8 weeks after exposure the serum levels returned to normal. The biological half-time of beryllium was calculated to be 2–8 weeks. In eight men accidentally exposed to .8 ng beryllium/m³ as beryllium chloride for 4–6 hours/day for 10 days, the beryllium levels in urine and blood increased 4-fold above the levels of .1 ng beryllium/g of either blood or urine in unexposed individuals (Stiefel et al. 1980).

Rats exposed to 0.034 mg beryllium/m³ as an aerosol of beryllium sulfate 7 hours/day, 5 days/week for 72 weeks achieved steady state concentrations in the lungs in .36 weeks of exposure (Reeves and Vorwald 1967). The beryllium concentration in tracheobronchial lymph nodes peaked between 36 and 52 weeks, and decreased thereafter. In guinea pigs and rats exposed to 2–40 mg beryllium/m³ as beryllium nitrate for 16 hours, steady-state concentrations in the blood were reached after 8–12 hours of exposure (Stiefel et al. 1980).

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to beryllium or its compounds.

Beryllium and its compounds are poorly absorbed from the gastrointestinal tract in animals. Urinary excretion data from rats treated by gavage with radioactive beryllium chloride indicate that the cumulative excretion of beryllium in the urine and feces was 0.11 and 104.7% of the total dose, respectively (Furchner et al. 1973). In mice, dogs, and monkeys similarly exposed, the urinary output was 0.24, 0.38, and 3.71% of the total dose, respectively, while most of the radiolabel was excreted in the feces. Therefore, although intestinal absorption of beryllium varies somewhat among species, beryllium was

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poorly absorbed in these animals. Mice exposed to radioactive beryllium retained beryllium in the gastrointestinal tract (LeFevre and Joel 1986). The amount found in the tissues other than intestinal was <0.1%.

Urinary excretion accounted for #0.5% of the total dose of beryllium sulfate administered to rats as 0.019 and 0.190 mg beryllium/kg/day in drinking water for 24 weeks (Reeves 1965). The percent absorption, determined as the percentage of the dose that could be recovered from the total body load and excreta, was #0.9% in the 0.019 mg beryllium/kg/day group and #0.2% in the 0.190 mg beryllium/kg/day group. Rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in drinking water for 2 years excreted very little beryllium via the urine (Morgareidge et al. 1975). Oral absorption of beryllium and its compounds may be reduced by the formation of beryllium phosphate precipitates in the alkaline environment of the intestine (Reeves 1965).

3.4.1.3 Dermal Exposure

It is unlikely that beryllium is absorbed through intact skin. Skin ulceration in workers exposed to beryllium occurred only after the skin was accidentally cut or abraded (Williams et al. 1987).

Only small amounts of beryllium were absorbed through the tail skin of rats after exposure to an aqueous solution of beryllium chloride (Petzow and Zorn 1974). Beryllium has been demonstrated to bind to alkaline phosphatase and nucleic acids in guinea pig epidermis *in vitro* (Belman 1969). This binding could account for the inefficient transfer of beryllium from the epidermis to the blood.

3.4.2 Distribution

Average concentrations of beryllium were measured in human organs as follows: 0.21 ppm in lungs; 0.08 ppm in brain; 0.07 ppm in both the kidney and spleen; 0.04 ppm in each of liver, muscle, and vertebrae; 0.03 ppm in heart; and 0.02 in bone (Meehan and Smythe 1967). Further information regarding the nature of exposure (e.g., environmental or occupational) or the source of the organ samples (e.g., autopsy or biopsy) was not provided. A study by Krachler et al. (1999a) provides evidence that beryllium is transferred across the placenta and excreted via breast milk. The levels of beryllium in umbilical cord serum and in colostrum were higher than in maternal serum.

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3.4.2.1 Inhalation Exposure

In eight men exposed to .8 ng beryllium/m³, 4–6 hours/day for 10 days due to an accidental leak of beryllium chloride, 60–70% of the beryllium found in the blood was bound to two classes of serum proteins, prealbumins and γ -globulins (Stiefel et al. 1980).

Beryllium is widely distributed to the organs of animals, as a result of pulmonary absorption.

Immediately after rats were exposed to radioactive beryllium (beryllium sulfate and beryllium chloride) for 3 hours, the percentage of total body radioactivity in tissues was 60% in lungs, 0.9% in the liver, 1.5% in the kidney, 0.1% in the spleen, 0.4% in the heart, 1.4% in the brain, 9.5% in the muscle, 13.5% in the skeleton, 5.0% in the blood, and 10% in the excreta (Zorn et al. 1977). After 408 hours, the liver, spleen, heart, brain, and muscle had concentrations <0.0005%; concentrations in the kidneys, skeleton, blood, and excreta were 0.0005, 6.8, 0.05, and 92.0%, respectively. The beryllium concentrations in the bone increased until 96 hours after exposure and then decreased. Dogs exposed to beryllium oxide calcined at 500EC had higher beryllium concentrations in the extrapulmonary tissue, principally the liver and skeleton, than dogs exposed to beryllium oxide calcined at 1,000 EC, due to the greater solubility of the 500 EC calcined product (Finch et al. 1990). The translocation of beryllium to the tracheobronchial lymph nodes increased and by day 64 accounted for a higher concentration than found in the lung. Beryllium was also detected in the liver, skeleton, and blood.

Distribution studies in rats and guinea pigs exposed to 2–40 mg beryllium/m³ as beryllium nitrate for 16 hours report that 60–70% of the beryllium in the blood was bound to prealbumins and γ -globulins (Stiefel et al. 1980). Rats and hamsters exposed to beryllium oxide did not have detectable beryllium concentrations in the liver, skeleton, or urine 7 days after exposure (Rhoads and Sanders 1985; Sanders et al. 1975). At 63 days after exposure, 1.7% of the initial alveolar deposit was present in the pulmonary lymph nodes in rats. Exposure to 0.04 mg beryllium/m³ as beryllium sulfate for 90–100 days resulted in the following concentrations (in μ g beryllium/g fresh tissue) of beryllium in rabbits: 1.6 in the lungs, 0.02 in the femur, 0.01 in the spleen, 0.004 in the liver, and 0.003 in the kidney (Stokinger et al. 1950). Dogs similarly exposed had the highest concentrations in the pulmonary lymph node (0.7), followed by lung (0.6), femur (0.03), spleen (0.01), liver (0.01), and kidney (0.003). In monkeys, the pulmonary lymph nodes (1.3) also had the highest concentrations followed by lung (1.2), spleen (0.5), femur (0.1), and kidney (0.01). In cats, the concentrations of beryllium from greatest to least were lung (0.08), femur (0.03), liver (0.02), spleen (0.01), and kidney (0.01). In rats, hamsters, and monkeys exposed to 0.21 or 0.62 mg beryllium/m³ as bertrandite or beryl ore, concentrations were highest in the lung followed by

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bone or liver, and kidney (Wagner et al. 1969). The greater degree of distribution of beryllium sulfate, compared with beryllium oxide or the ores, reflects its greater solubility and absorption rate.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure of beryllium or its compounds.

Beryllium is poorly absorbed from the gastrointestinal tract in animals; however, that which is absorbed is distributed to the organs and tissues. Beryllium was found in the liver, large intestine, small intestine, kidneys, lungs, stomach, and spleen in hamsters given beryllium sulfate, beryllium oxide, or beryllium metal in the diet for 3–12 months (Watanabe et al. 1985). In mice given a radioactive dose of beryllium chloride by gavage, the accumulation of radioactivity was greatest in the liver followed by the kidney, mesenteric lymph nodes, lungs, blood, and carcass, 3 hours after exposure (LeFevre and Joel 1986). The pattern of beryllium distribution to tissues and organs in rats given beryllium sulfate indicated that as the exposure duration increases, accumulation levels also increase (Reeves 1965). In tissue, beryllium concentrations were highest in the gastrointestinal tract (with contents), followed by bone, blood, and liver. Other studies indicate that in animals, high levels of beryllium accumulate in bone tissue as a result of oral exposure to the chemical or its compounds. In rats treated by gavage with radioactive beryllium chloride, the greatest accumulation (other than that in the gastrointestinal tract) was detected in the bone, followed by viscera, pelt, and muscle (Furchner et al. 1973). Beryllium accumulation in the bones of rats exposed for 2 years to dietary concentrations of the chemical was proportional to the administered dose (Morgareidge et al. 1975).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to beryllium or its compounds. The lack of data is expected because beryllium is poorly absorbed after dermal exposure (see Section 3.4.1.3).

3.4.2.4 Other Routes of Exposure

In rats receiving a single intravenous injection of radiolabelled beryllium sulfate, circulating beryllium was found almost exclusively in the plasma (Vacher and Stoner 1968). Two fractions of plasma

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beryllium were identified. The smaller fraction was presumably bound to plasma organic acids. In the larger fraction, the beryllium sulfate was converted to beryllium phosphate, which formed aggregates associated with plasma globulins, presumably α -globulin. The size of the aggregates appeared to increase with increasing beryllium sulfate doses.

3.4.3 Metabolism

Beryllium and its compounds are not biotransformed, but soluble beryllium salts are partially converted to less soluble forms in the lung (Reeves and Vorwald 1967).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

In eight men accidentally exposed to . 8 ng beryllium/m³ as beryllium chloride 4–6 hours/day for 10 days, urinary levels were four times higher than the average levels of . 1.0 ng beryllium/g in unexposed individuals (Stiefel et al. 1980). Accidental exposure of 25 individuals to beryllium dust for 10–20 hours increased serum levels to 3.5 ppb beryllium 1 day after exposure, compared to . 1 ppb for unexposed individuals (Zorn et al. 1986). Serum levels returned to normal 2–8 weeks after exposure. The biological half-life was estimated to range from 2 to 8 weeks.

Beryllium oxide deposited in the lungs of rats was cleared in a biphasic manner (Rhoads and Sanders 1985). In the first phase, 30% of the total lung burden was cleared; the half-life was 2.5 days. In the second phase, the remaining 70% of the beryllium in the lung was cleared with a half-life of 833 days. The whole body clearance yielded a single-phase exponential curve with a half-life of 356 days. Rats exposed to beryllium oxide were able to clear 12 and 21% (female and male, respectively) of the alveolar lung burden within 63 days of exposure (Sanders et al. 1975). Hamsters, however, cleared 38 and 45% (female and male, respectively) of the beryllium in the alveoli. The study indicates that male rats are better able to clear beryllium particles from the lungs than female rats are. The biological half-life for beryllium oxide in the rat lung was estimated to be . 6 months. Approximately 95% of the beryllium was excreted through the feces. Rats and guinea pigs exposed to 2–40 mg beryllium/m³ as beryllium nitrate for 16 hours had increased concentrations of urinary beryllium (300 ng beryllium/g), compared to normal concentrations (2.1 ng beryllium/g) (Stiefel et al. 1980). Rats exposed to radioactive beryllium compounds excreted 92% of the dose in 408 hours (Zorn et al. 1977). In dogs exposed only via nose to

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10 mg beryllium/m³ as beryllium oxide calcined at 500 or 1,000 EC (the solubility of beryllium oxide decreases as the temperature at which it is calcined increases) for sufficient durations to result in low (. 5 µg beryllium/kg) initial lung burdens and high (36–64 µg beryllium/kg) initial lung burdens, there were no differences in whole-body retention with regard to initial lung burdens (Finch et al. 1990). Whole-body clearance after exposure to beryllium oxide calcined at 500 EC was described by a two-component, negative exponential function. The short-term component accounted for 59% of the initial lung burden and had a half-life of 54 days. The long-term component accounted for 41% of the initial lung burden and had a half-life of >1,000 days. The long-term component may have represented beryllium that dissolved from beryllium oxide particles and bound to extrapulmonary compartments, such as, bone and liver. Whole-body clearance after exposure to beryllium oxide calcined at 1,000 EC was described by a single-component negative exponential function with a half-life of 310 days. Clearance from the lung was more rapid and greater amounts were translocated to the liver, blood, and skeleton in the dogs exposed to beryllium calcined at the lower temperature than in dogs exposed to beryllium calcined at the higher temperature. However, lung clearance of both was described by a single-component negative exponential function. Clearance half-lives were 64 days for 500 EC calcined beryllium oxide and 240 days for 1,000 EC calcined beryllium oxide. Fecal excretion predominated at early times after exposure to either beryllium oxide aerosols, and at all times for 1,000 EC calcined beryllium oxide. Dogs exposed to beryllium oxide calcined at 500 EC excreted a significantly ($p < 0.05$) greater total percentage of the initial lung burden of beryllium than dogs exposed to beryllium calcined at the higher temperature by 180 days. Thus, beryllium oxide calcined at 500 EC was cleared more rapidly than beryllium oxide calcined at 1,000 EC. This is consistent with the fact that more soluble beryllium compounds are cleared faster than relatively insoluble beryllium compounds because the solubility of beryllium oxide decreases as the temperature at which it is calcined increases. Although clearance of beryllium oxide calcined at the lower temperature was relatively fast during the first few days after exposure due to mucociliary clearance, later clearance may result from slow translocation of tracheobronchial lymph nodes, macrophage clearance from the pulmonary to the tracheal regions, and pulmonary solubilization of beryllium followed by mobilization through blood to liver and bone or excretion in urine. Beryllium decreased the clearance rate of radioactive plutonium oxide from the lungs of rats 60 and 90 days after exposure to beryllium oxide (Sanders et al. 1975). Inhalation exposure to beryllium may decrease the overall rate of lung clearance by damaging alveolar macrophages.

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3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to beryllium or its compounds.

Animals exposed to oral doses of beryllium or its compounds excrete the greatest percentage of the dose via the feces, which indicates that beryllium is poorly absorbed by the gastrointestinal tract. Analysis of the excreta of rats exposed to 0.019 and 0.190 mg beryllium/kg/day as beryllium sulfate in the drinking water indicated that 99% of the dose was excreted in the feces and <0.5% was excreted in the urine (Reeves 1965). The excretion pattern of beryllium in the feces reached steady-state after 9 weeks (Reeves 1965). Similarly, excretion of beryllium occurred mainly via the feces of rats exposed to 0.3, 2.8, and 31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years (Morgareidge et al. 1975). The feces contained 10.7 ppm and the urine 29.7 ppb of the 0.3 mg beryllium/kg/day dose, and a similar pattern was observed with the other doses. Rats, monkeys, mice, and dogs orally exposed to radioactive beryllium chloride excreted 98% of the dose via the feces (Furchner et al. 1973).

3.4.4.3 Dermal Exposure

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

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 (Clewel and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.

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1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

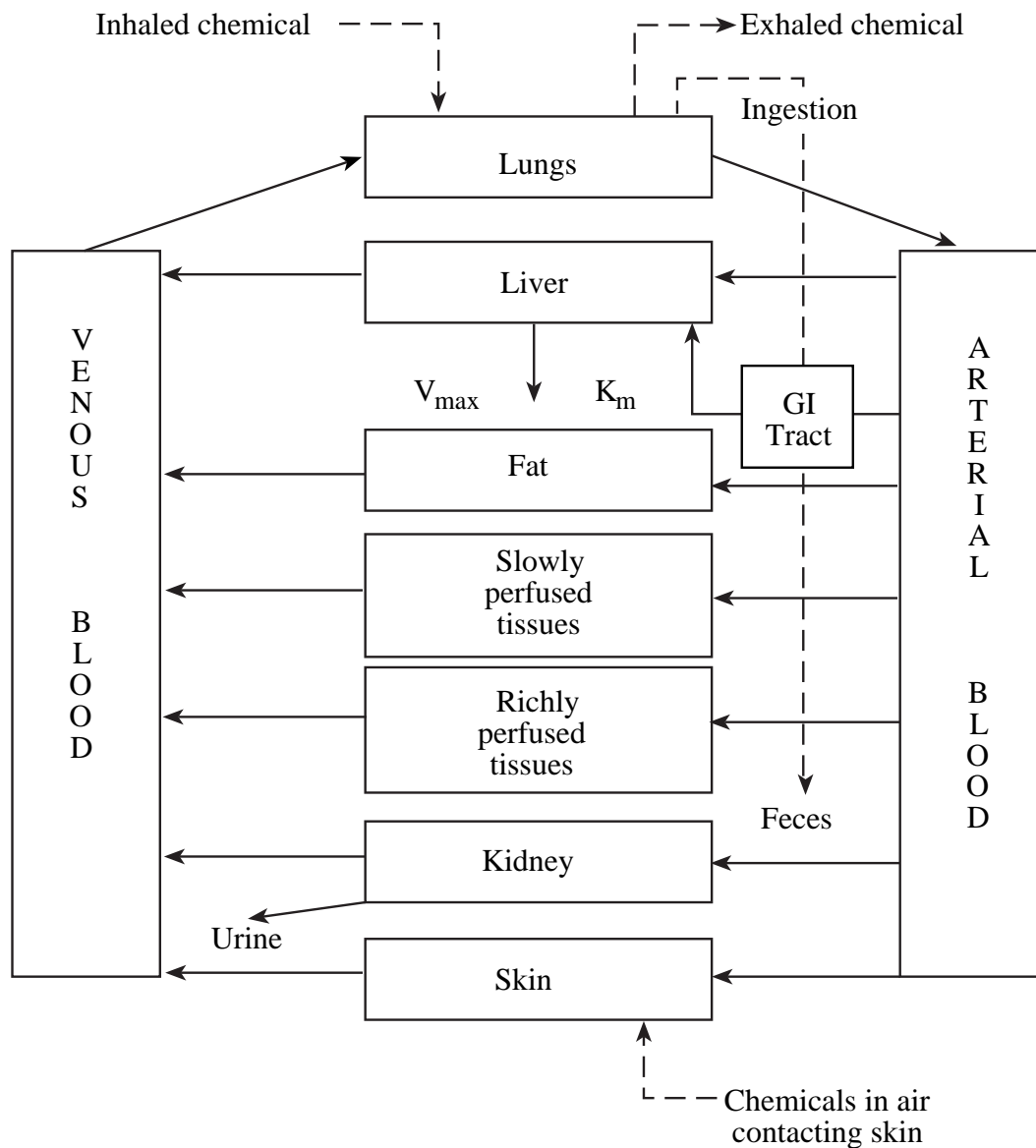
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical 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) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

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

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



Source: adapted from Krishnan et al. 1994

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

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No PBPK modeling studies were located for beryllium.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The absorption of inhaled beryllium depends on a number of factors, including physical and chemical properties of the particles (e.g., size, solubility) and the activity of alveolar macrophages. Following deposition, beryllium is slowly cleared from the lung; clearance half-lives range from days to years in animals. Beryllium clearance from the lungs is biphasic, the initial phase is rapid and involves clearance via the mucociliary escalator. Approximately 30% of the total lung burden was cleared during the first phase with a half-life of 2.5 days (Rhoads and Sanders 1985). The second phase is slower, involving translocation to the tracheobronchial lymph nodes, alveolar macrophage clearance, and solubilization. The half-life for this phase was 833 days (Rhoads and Sanders 1985). Beryllium is poorly absorbed through the gastrointestinal tract; <1% of the dose is absorbed (Furchner et al. 1973; Reeves 1965). It is also poorly absorbed through intact skin (Petzow and Zorn 1974; Williams et al. 1987).

Absorbed beryllium is distributed throughout the body via blood, with the highest concentrations in the liver and skeleton (Finch et al. 1990; Furchner et al. 1973; Morgareidge et al. 1975; Stokinger et al. 1950). Beryllium has been detected in breast milk (Krachler et al. 1999a), but the relationship between beryllium exposure and breast milk levels has not been established.

The primary routes of elimination of absorbed beryllium is urine and feces. In rats and dogs, whole body clearance of inhaled beryllium follows a single-phase exponential curve with a half-life of 300–400 days (Finch et al. 1990; Rhoads and Sanders 1985).

3.5.2 Mechanisms of Toxicity

The respiratory tract is the primary target of beryllium toxicity following inhalation exposure. In humans, chronic beryllium disease and lung cancer are the principal effects observed. In animals, the respiratory tract effects include emphysema, pneumonitis, and lung cancer. Chronic beryllium disease begins as a sensitizing cell-mediated response to beryllium antigen that progresses to noncaseating granulomatous lung disease. Although the mechanism has not been fully elucidated, a number of recent studies using bronchoalveolar lavage (BAL) fluid from individuals with chronic beryllium disease provide information

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on some of the components of the toxic sequence. Beryllium, acting as a hapten, interacts with antigen presenting cells in the lungs (i.e., alveolar macrophages) resulting in a beryllium-peptide becoming physically associated with a major histocompatibility (MHC) class II molecule (Newman 1996b; Saltini et al. 1989). The MHC class II-beryllium-peptide complex is recognized by the T lymphocyte receptor, with the help of CD4⁺ molecules. This interaction triggers CD4⁺ T lymphocyte activation and proliferation. There is evidence to suggest that there is a selective expansion of certain CD4⁺ lymphocyte subsets. In a study by Fontenot et al. (1998), a number of individuals with chronic beryllium disease had an increase in the percentage of T cell receptor (TCR) variable β 3 regions (V β 3). Further work by this group showed that in four of five individuals with chronic beryllium disease, expansions within the V β 3 region resulted in homologous or identical CDR3 amino acid sequences (Fontenot et al. 1999). The expansion of the CDR3 motif appeared to be unique to chronic beryllium disease.

The antigen-specific inflammatory response to beryllium is a cell-mediated process orchestrated by cytokines. The results of several studies support the role of cytokines in chronic beryllium disease. Using alveolar macrophages present in BAL fluid from individuals with chronic beryllium disease, Bost et al. (1994) found elevated mRNA levels for tumor necrosis factor α (TNF- α) and interleukin (IL)-6 cytokines, as compared to levels in normal subjects. Additionally, TNF- α levels in the BAL fluid were higher. Another study found that the addition of beryllium to a culture of BAL cells from chronic beryllium disease patients, resulted in increases in the TNF- α , IL-6, IL-2, and interferon-gamma (IFN- γ) (Tinkle et al. 1996). Although for many inflammatory diseases IL-10 inhibits antigen-induced T lymphocyte proliferation, it does not play a role in chronic beryllium disease (Tinkle et al. 1996a). In chronic beryllium disease, as in other delayed-type hypersensitivity diseases, IL-2 plays an important role in the T lymphocyte proliferation and the regulation of IFN- γ (Tinkle et al. 1997). BAL cells from control subjects did not show any measurable spontaneous or beryllium sulfate-stimulated release of IL-2, α -sIL-2R (α subunit of the soluble IL-2 receptor), IL-4, or IFN- γ . Beryllium sulfate stimulation of BAL cells from chronic beryllium disease subjects resulted in the production of IL-2, α -sIL-2R, and IFN- γ , but not IL-4. In the absence of beryllium sulfate stimulation, the response was the same as in controls. Although IL-2 has a dose-dependent role in T lymphocyte proliferation, T lymphocyte proliferation is only partially dependent on it. Beryllium sulfate stimulated T lymphocyte proliferation remained elevated in the presence of anti-IL-2 antibodies. INF- γ levels were also decreased in the presence of anti-IL-2 antibodies suggesting that it is also partially dependent on IL-2.

There appears to be a genetic factor associated with susceptibility to chronic beryllium disease. The MHC class II molecules play a critical role in the T lymphocyte proliferation and the development of

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chronic beryllium disease; thus, MHC class II genes (human leukocyte antigen, HLA-DR, DQ, DP) probably play a role in susceptibility to the disease. Analysis of the MHC class II genes shows a biased usage of the HLA-DPB1 gene alleles in individuals with chronic beryllium disease (Richeldi et al. 1993, 1997; Wang et al. 1999). Genetic susceptibility to chronic beryllium disease is discussed in greater detail in Section 3.10.

3.5.3 Animal-to-Human Extrapolations

As reviewed in EPA (1998) and Finch et al. (1996), a number of animal models of human chronic beryllium disease have been developed, but none of the models to date mimic all aspects of the human disease. Numerous studies in dogs, monkeys, and rats have reported granulomatous inflammation in the lungs. However, the lung lesions do not histopathologically resemble chronic beryllium disease in humans, the effects are transient, or are not consistently associated with beryllium-specific immune responses. Recent studies in mice (Huang et al. 1992; Nikula et al. 1997) suggest that mice may be an appropriate model. In the model developed by Huang et al. (1992), mice were preimmunized with beryllium sulfate and then administered a single intratracheal dose of beryllium sulfate. A number of aspects of this model mimicked chronic beryllium disease, influx of CD4⁺ T lymphocytes into the lungs, sensitization of T lymphocytes to beryllium, interstitial inflammation, and granuloma formation. However, these effects were observed at 8 months and were resolved by 10 months. The study by Nikula et al. (1997), in which mice received a 90-minute nose-only exposure to beryllium metal, also found many similarities between effects observed in mice and human chronic beryllium disease. The study authors concluded that this mouse model can be used to study the influence of dose, exposure pattern, and physicochemical form of beryllium on the development of chronic beryllium disease. A comparison of the histologic characteristics of beryllium-induced disease in humans and mice is presented in Table 3-5.

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

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Table 3-5. Histologic Characteristics of Beryllium-induced Disease in Mice and Humans^a

Histologic findings	Mice	Humans
Interstitial cellular infiltration of macrophages, lymphocytes, and variable numbers of plasma cells	Mild to moderate	Moderate to marked
Granulomas	Present; poorly formed	Variable; absent to poorly formed to well formed
Giant cells	Numbers variable; may be scattered or associated with granulomas	Numbers variable; may be scattered or associated with granulomas
Cholesterol clefts	Numerous and often seen within giant cells	Numerous and often seen within giant cells
Interstitial fibrosis	Present in 75% of cases; minimal to mild	Present in large percentage of cases; minimal to mild in 50% and moderate to marked in 50%
Calcific inclusions	Absent	Present in approximately 55% of cases
Hyalinized nodules	Absent	Present in lung or hilar lymph nodes of 40% of cases
Interstitial compact aggregates of lymphocytes	Present	Not described
Beryllium	Metal evident in H&E sections	Increased tissue levels found by spectrographic and chemical analysis

^aTaken from Nikula et al. (1997)

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terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (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), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

There are no data to assess whether exposure to beryllium will adversely affect the endocrine system.

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.

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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

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

Data on the toxicity of beryllium in children is limited to a case report of a child diagnosed with chronic beryllium disease (Eisenbud et al. 1948b). The child lived near a beryllium manufacturing facility. The only available studies on young animals are the beryllium carbonate dietary studies that found beryllium rickets in young rats (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The observed skeletal effects are not due to a direct effect of beryllium on the bone, but rather an interaction between beryllium carbonate and dietary phosphorus. The potential of beryllium to induce developmental effects has not been adequately investigated. A chronic study did not find developmental effects (gross and skeletal malformations, fetal survival, and fetal body weights were examined) in dogs exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). However, intratracheal and intravenous exposure studies have found increases in fetal/neonatal mortality, internal abnormalities, and behavioral abnormalities in rat and mouse offsprings (Bencko et al. 1979; Mathur et al. 1987; Selivanova and Savinova 1986; Tsujii and Hoshishima 1979). More details about these studies can be found in Chapter 2 and Section 3.2.2.6.

No human or animal data were located that examined possible age-related differences in the toxicokinetics of beryllium. There are no data on the toxicokinetic properties of beryllium in children or immature animals. The results of a study by Krachler et al. (1999a) suggests that beryllium is transferred across the placenta and via maternal milk. Beryllium levels in the umbilical cord sera and in colostrum were higher than maternal sera levels.

Subsequent sections of this chapter (Sections 3.8, 3.10, and 3.11) discuss the available information on biomarkers, interactions, and methods for reducing toxic effects. The available information is from adults and mature animals; no child-specific information was identified. It is likely 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

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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 or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to beryllium 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 beryllium are discussed in Section 3.8.2.

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Beryllium

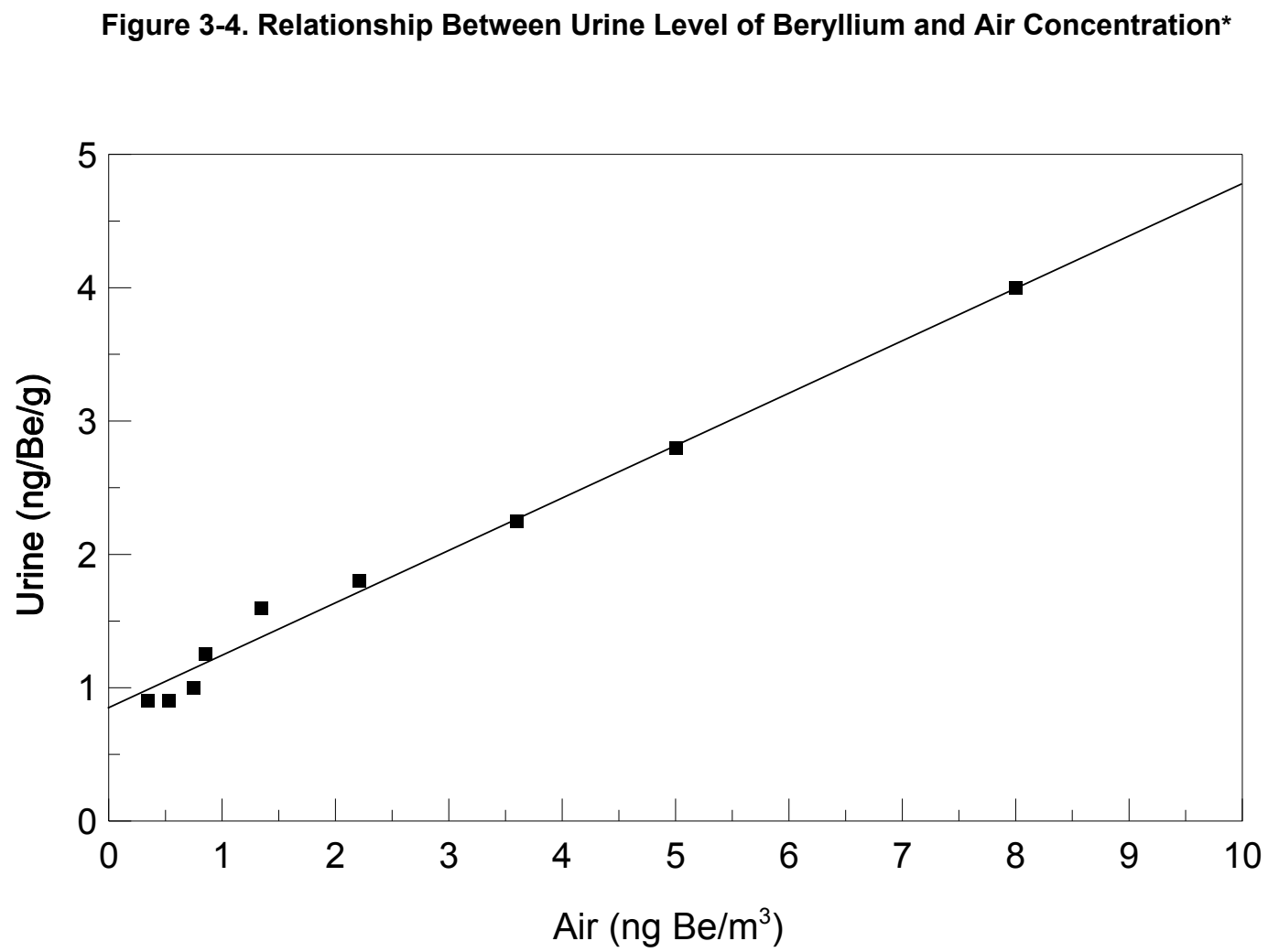
There are several tests for measuring beryllium in biological fluids and tissues (Frame and Ford 1974; Foreman et al. 1970; Hurlburt 1978; IARC 1980; Martinsen and Thomassen 1986; Paschal and Bailey 1986; Shan et al. 1989). These include measurement of beryllium levels in the blood and urine. Information regarding normal background levels of beryllium and tissue levels associated with exposure

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levels are limited or unreliable. Normal background levels of 1 ng beryllium/g (1 ppb) for blood (Stiefel et al. 1980; Zorn et al. 1986), 0.28–1 µg/L for urine (Paschal et al. 1998; Stiefel et al. 1980), and of 0.02 µg beryllium/g (0.02 ppm) for lung tissue (Kanarak et al. 1973) have been reported. Average beryllium levels in human tissues have been measured as follows: 0.21 ppm in lungs; 0.08 ppm in brain; 0.07 ppm in both kidney and spleen; 0.04 in each of liver, muscle, and vertebrae; 0.03 ppm in heart; and 0.02 in bone (Meehan and Smythe 1967). However, it was not clear whether these organ samples were obtained at biopsy or autopsy or whether the subjects had been exposed occupationally or environmentally in the compilation by Meehan and Smythe (1967).

Background urinary levels of beryllium were determined to be . 1.0 µg beryllium /L using flameless atomic absorption spectroscopy (Stiefel et al. 1980). Beryllium levels in urine were analyzed in eight laboratory workers and compared to the levels of beryllium in the laboratory atmosphere for 30 days after an accidental leakage of beryllium chloride. Figure 3-4 represents urinary levels versus atmospheric levels. The urinary levels appear to be directly proportional to atmospheric levels at #8 ng/m³. Based on serum levels of beryllium in workers accidentally exposed, the biological half-life was estimated to be 2–8 weeks (Zorn et al. 1986). These are the only available data that associate airborne beryllium levels with urinary levels in humans. A sampling of 500 urine samples collected during the NHANES III study, suggested that background levels of beryllium in the urine may be lower; the mean urinary level was 0.28 µg beryllium/L (Paschal et al. 1998). Nonetheless, urinary excretion of beryllium is irregular and not useful for diagnostic purposes (Reeves 1986).

Biopsy tissue has been analyzed to determine beryllium concentrations in the body. Lung tissue of two employees of a beryllium extraction and processing plant, where beryllium concentrations exceeded the recommended standards of 2 µg beryllium/m³ for an 8-hour day and 25 µg beryllium/m³ for a 30-minute



*Source: Stiefel et al. 1980

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maximum level, contained 0.18 and 0.65 μg beryllium/g dry weight compared to the normal level of 0.02 μg beryllium/g (Kanarek et al. 1973). The subject with the higher beryllium level did not have lung lesions; however, the subject with the lower beryllium level had granulomas. Thus, beryllium levels in lung biopsies indicate exposure to beryllium but may not confirm the presence of chronic beryllium disease. The presence of beryllium in lung tissue also will not indicate how recently the exposure occurred because the clearance of beryllium from the lungs depends upon the solubility of the beryllium compound (see Section 3.3.4.1). Biomarkers of oral or dermal exposure to beryllium were not located, probably because very little beryllium is absorbed after exposure by these routes (see Section 3.4.1).

3.8.2 Biomarkers Used to Characterize Effects Caused by Beryllium

The lung is the most sensitive target organ of beryllium exposure. As a consequence of long term exposure to beryllium, lung function decreases. This decrease has been measured by spirometry, such as forced expiratory volume in 1 second, maximum breathing capacity, maximum mid-expiratory flow, and vital capacity (Andrews et al. 1969; Kriebel et al. 1988a, 1988b). Blood gases such as carbon dioxide tension, oxygen tension, alveolar oxygen tension, alveolar carbon dioxide tension, and carbon monoxide diffusion capacity have also been analyzed.

Radiographic examinations revealed opacities in the lung following chronic exposure to beryllium (Kanarek et al. 1973). X-rays have been used to determine three stages of chronic beryllium poisoning: a fine diffuse granularity in the lungs, followed by a diffuse reticular pattern, followed by the appearance of distinct nodules. However, x-ray results cannot distinguish between chronic beryllium disease and sarcoidosis. A patch test using soluble beryllium salts was evaluated in 32 patients with known chronic beryllium disease (Curtis 1959). The patch test was positive in all 32 patients and negative in 16 of 18 patients with lung diseases other than chronic beryllium disease, indicating that the patch test may be useful in the diagnosis of chronic beryllium disease. However, the patch test using soluble beryllium compounds itself may be sensitizing and may exacerbate the condition in patients with chronic beryllium disease (Cotes et al. 1983; Epstein 1983; Stoeckle et al. 1969; Tepper 1972). Therefore, this method is not recommended as a diagnostic tool. Analysis of secretions and cells of the lower respiratory tract obtained by bronchoalveolar lavage is useful for detecting granulomatous lung disease; however, it alone cannot distinguish chronic beryllium disease from sarcoidosis (James and Williams 1985). The presence of beryllium in the bronchoalveolar fluid, however, would aid the diagnosis.

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Because chronic beryllium disease is caused by an immune reaction to beryllium, several tests have been developed to assess beryllium hypersensitivity. The most commonly used test is the beryllium lymphocyte proliferation test (BeLPT). This test, originally referred to as the lymphocyte blast transformation test (LTT or LBTT), measures cell proliferation via thymidine incorporation in cultured cells in the presence or absence of beryllium salts. Both peripheral blood cells and bronchioalveolar lavage cells can be used in the BeLPT. In early studies, abnormal blood BeLPT results were found in 100% of the subjects with chronic beryllium disease (Williams and Williams 1982, 1983), normal results in all individuals who were suspected of having chronic beryllium disease (Williams and Williams 1983), and abnormal results in approximately 2% of the healthy beryllium workers (Williams and Williams 1983). Despite these results, the blood BeLPT test was not widely used because it was very difficult to perform and not very reproducible. Refinement of the test methodology resulted in a more reproducible test that could be used as a screening tool (Newman 1996a). A number of large-scale screening studies have utilized this test for identifying beryllium sensitized workers (Kreiss et al. 1993a, 1996, 1997; Newman et al. 2001; Stange et al. 2001). In these studies, the majority (53–86%) of the workers with consistently abnormal blood BeLPT results were also diagnosed as having chronic beryllium disease. Using the blood BeLPT to screen workers for beryllium sensitization and chronic beryllium disease is not foolproof; Kreiss et al. (1993a, 1996) found a small percentage of workers with chronic beryllium disease and normal or inconsistent blood BeLPT results. Deubner et al. (2001a) assessed the predictive value of the blood BeLPT as a screening tool for chronic beryllium disease among 129 beryllium workers. The incidences of chronic beryllium disease among workers with a single unconfirmed abnormal blood BeLPT result, workers with confirmed abnormal blood BeLPT results, and workers with first-time double abnormal blood BeLPT results were 7/19 (37%), 34/75 (45%), and 17/35 (49%), respectively. One limitation of the blood BeLPT is high inter- and intra-laboratory variability. Using split blood samples, Stange et al. (1996b) found an 85–96% agreement rate among three laboratories; however, the agreement rate was only 21–33% for positive blood BeLPT results. Similarly, Deubner et al. (2001a) found poor to moderate agreement in blood BeLPT results among three laboratories.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Mortality rates were lower if rats exposed to 2.59 mg beryllium/m³ as beryllium sulfate were injected daily with ferric ammonium citrate beginning 4 days prior to beryllium exposure (Sendelbach and Witschi 1987a). The protective action of ferric ammonium citrate may be related to the ability of beryllium to form a complex with citrate (Reeves 1986). In addition, the protective action of iron on beryllium toxicity may be related to the ability of iron to increase ferritin synthesis, making more ferritin

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available to bind with beryllium (Lindenschmidt et al. 1986). Ferritin chelates with beryllium to protect against the inhibition of phosphoglucomutase (Joshi et al. 1984).

Ingested soluble beryllium compounds may interact with phosphate to form insoluble beryllium phosphate particles that are sequestered in Kupffer cells of the liver (Tepper 1972). Diffusion of beryllium from the deposited particulates may cause damage to these cells and necrosis of the liver.

Intravenous injection of rats or mice with the ammonium salt of aurine tricarboxylic acid increased the survival of both species that were injected intravenously with lethal doses of beryllium sulfate (White et al. 1951). The protective effect was observed when the aurine tricarboxylic acid was administered from 1 hour before to 8 hours after injection of beryllium sulfate. The protective effect was attributed to the ability of aurine tricarboxylic acid to complex with the beryllium ion, thereby reducing the amount of beryllium ion available to induce tissue injury.

Co-exposure of Chinese hamster ovary cells to beryllium sulfate and x-rays resulted in an increased rate of chromatid-type exchanges compared to the rates resulting from exposure to beryllium sulfate or x-rays alone (Brooks et al. 1989). The increase was multiplicative rather than additive. Experiments on cell cycle kinetics suggested that the multiplicative interaction occurs only in cells in the S and G₂ stages.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to beryllium than will most persons exposed to the same level of beryllium 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 beryllium, or compromised function of organs affected by beryllium. Populations who are at greater risk due to their unusually high exposure to beryllium are discussed in Section 6.7, Populations With Potentially High Exposures.

There are strong data to suggest that there is genetic susceptibility factor that may predispose certain individuals to development of chronic beryllium disease. A human leukocyte antigen (HLA) class II marker has been strongly associated with chronic beryllium disease. Studies conducted by Fontenot et al. (2000) and Lombardi et al. (2001) suggest that the HLA-DP allele, in particular alleles with HLA-DP containing Glu at DP69, are involved in the presentation of beryllium to CD⁴⁺ T cells, which are involved in the pathogenesis of chronic beryllium disease. Richeldi et al. (1993) found a higher frequency of

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allelic variants of the HLA-DP gene coding for a glutamate in position 69 of HLA-DPB1 chain (HLA-DPB1 Glu⁶⁹) among individuals with chronic beryllium disease than in beryllium-exposed individuals without the disease. The HLA-DPB1 Glu⁶⁹ DNA marker was found in 5 of 6 beryllium workers with chronic beryllium disease, 0 of 2 beryllium-sensitized individuals without disease and 36 of 119 (30%) unsensitized beryllium-exposed individuals (Richeldi et al. 1997).

Further analysis by Wang et al. (1999) found the Glu⁶⁹ marker on the HLA-DPB1 gene was not very predictive of chronic beryllium disease (predictive value of 0.36). However, the presence of the relatively rare HLA-DP allele, HLA-non*0201 DPB1 Glu⁶⁹, had a predictive value of 0.57. Wang et al. (1999) also found a higher percentage of homozygous Glu⁶⁹ carriers in the chronic beryllium disease group as compared to controls. The study authors estimated that carriers of the Glu⁶⁹/Glu⁶⁹ markers or non-*0201Glu⁶⁹ allele accounted for 85% of the chronic beryllium disease cases and only 16% of unaffected beryllium-exposed individuals. Additional studies by this group found that most beryllium sensitized individuals without chronic beryllium disease also carried rare HLA-non*0201 Glu⁶⁹ DPB1 alleles (Wang et al. 2001).

Stubbs et al. (1996) also found allelic differences in the DR isotype of class II HLAs. The HLA-DRB1 alleles associated with beryllium sensitization were *0103, *09, *1302, *0403, and *0302. It is likely that chronic beryllium disease is a multigenetic disease with a number of genetic factors contributing to the development of an immune response to beryllium.

A case control study by Maier et al. (1999) was designed to assess whether polymorphisms in the angiotensin converting enzyme (ACE) were associated with chronic beryllium disease and chronic beryllium disease severity. No statistically significant associations between ACE genotype and chronic beryllium disease were found in the comparisons of individuals with chronic beryllium disease to beryllium-exposed controls or nonberyllium exposed controls.

Animal data support the human data that genetically determined cellular immune mechanisms may be involved in chronic beryllium disease, as indicated by studies in different strains of guinea pigs and mice. Intratracheal instillation of beryllium oxide (calcined at 560 EC) resulted in the development of granulomatous lung disease in outbred Hartley and in strain 2 guinea pigs, but not in strain 13 guinea pigs (Barna et al. 1981; 1984). Granulomatous lung disease also was produced in the F₁ offspring of mated strain 2 and strain 13 guinea pigs, but the severity was milder in the hybrid strain than in the strain 2 guinea pigs (Barna et al. 1984). In addition, when guinea pigs exposed intradermally or intratracheally

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to beryllium oxide were challenged by dermally applied beryllium sulfate, the strain 2 and the F₁ guinea pigs showed positive skin tests for delayed-type hypersensitivity, while strain 13 guinea pigs did not. Granulomatous lung disease was also induced in strain A/J (H-2_a haplotype) mice, but not in BALB/c (H-2_d haplotype) or C57BL/6 (H-2_b haplotype) mice, after intratracheal injection of beryllium sulfate, suggesting that genetic differences at the H-2 major histocompatibility gene complex may account for the differential responses to beryllium sulfate in mice (Huang et al. 1992). These results suggest that genetically determined factors may make some humans more susceptible to chronic beryllium disease.

Animal data indicate that females may be more susceptible than males to the effects of beryllium. Female rats exposed to 0.034 mg beryllium/m³ as beryllium sulfate for 72 weeks had higher mortality rates and more severe weight loss than males (Reeves et al. 1967). Female rats exposed to #31 mg beryllium/kg/day as beryllium sulfate in the diet for 2 years developed a transient glucosuria; renal effects were not observed in males (Morgareidge et al. 1975). The distribution of beryllium in body tissue in female (bred and nonbred) and male rats exposed intratracheally to 0.6 mg beryllium/kg as radioactive beryllium oxide revealed the highest concentrations (other than in the lung) in the liver of female rats and in the kidney of male rats (Clary et al. 1975). This corroborates the findings of Clary et al. (1972) which suggest that translocation of beryllium from bone to liver eventually causes a systemic disease characterized by weight loss and liver necrosis. The study involves intratracheal exposure of guinea pigs and mice to radioactive beryllium oxide after hormone biosynthesis is inhibited by metyrapone injection. The results indicate that altered adrenal hormone synthesis shifts beryllium concentrations from bone to liver, causing weight loss. Therefore, any adverse effect on the adrenal gland may profoundly affect the course of beryllium disease, and a combination of adrenal dysfunction and compromised liver function could exacerbate beryllium disease. Therefore, people with lowered adrenal and/or liver functionality may be unusually susceptible to the effects of beryllium.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

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Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. Second Edition. Baltimore, MD: Williams & Wilkins, 1546-1548.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. *Clinical Management of Poisoning and Drug Overdose*. Third Edition. Philadelphia, PA: WB Saunders, 792.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to beryllium and its compounds occurs by inhalation, ingestion, or dermal contact. The inhalation route is of greatest concern for systemic effects because beryllium and its compounds are poorly absorbed after ingestion and dermal contact. General recommendations for reducing absorption of beryllium following acute exposure have included removing the individual from the contaminated area and removing contaminated clothing. Although beryllium is poorly absorbed from the gastrointestinal tract, administration of milk or water has been suggested to reduce the possibility of stomach irritation (HSDB 2000). Chronic granulomas observed following dermal exposure are surgically removed (HSDB 2000). Thorough washing of the skin or eyes is indicated in the case of dermal or ocular exposure, especially to irritating beryllium compounds, such as beryllium fluoride.

3.11.2 Reducing Body Burden

Beryllium is widely but slowly distributed following inhalation exposure. The highest concentration of beryllium was found in bone (13.5%) of rats following 3 hours of exposure to beryllium sulfate or beryllium chloride (Zorn et al. 1977). The percentage of beryllium in the bone was still high (6.8%) compared with other tissues following 408 hours of exposure. After inhalation exposure, beryllium that is not absorbed into the bloodstream is retained in the lung (see Section 3.4.4.1). Insoluble beryllium compounds, such as beryllium oxide, are retained in the lungs longer than soluble compounds and are associated with chronic beryllium disease. Although beryllium compounds are poorly absorbed from the gastrointestinal tract (see Section 3.4.1.2), the portion that is absorbed appears to preferentially accumulate in bone (Furchner et al. 1973; Morgareidge et al. 1975; Reeves 1965). In addition, relatively high levels of beryllium accumulated in the spleen and liver of rats after intravenous injection of beryllium sulfate (Lindenschmidt et al. 1986).

A series of studies by Mathur and associates have examined the effectiveness of several agents in reducing beryllium body burden following parenteral exposure (no additional information on exposure route was provided). Decreases in blood, liver, kidney, and/or spleen beryllium levels were observed in rats administered a single or repeated doses of beryllium followed by a 2- to 10-day exposure to Liv-52,

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an alternative medicine (Mathur et al. 1994) or 5 days of N-(2-hydroxyethyl)ethylene diamine triacetic acid (HEDTA) (Mathur et al. 1993), calcium disodium ethylenediamine tetraacetic acid (CaNa-EDTA) (Mathur et al. 1993), 4,5-dihydroxy-1,3-benzene disulfonic acid (tiron) (Shukula et al. 1998) *meso*-2,3-dimercaptosuccinic acid (DMSA) (Flora et al. 1995), or 2,3-dimercaptopropane 1-sulfonate (DMPS) (Flora et al. 1995), but not after calcium trisodium diethylene triamine pentaacetic acid (CaNA-DTPA) (Mathur et al. 1993) or succinic acid (Shukula et al. 1998). For absorbed beryllium, administration of chelating agents such as aurine tricarboxylic acid increases the urinary excretion of beryllium in animals (Venugopal and Luckey 1978). However, metal chelating agents available for use in human clinical medicine have not been shown to be effective in reducing the toxicity of beryllium (Hall and Rumack 1992). Since chronic berylliosis is associated with the retention of unabsorbed beryllium compounds in the lungs, enhancing the clearance of beryllium from the lungs, perhaps by bronchoalveolar lavage, might prevent or reduce the severity of chronic beryllium disease. However, at this time there are no established methods for reducing the lung burden.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

As discussed in Section 3.9, pretreatment of rats with ferric ammonium citrate reduces mortality rates following inhalation exposure to beryllium (Sendelbach and Witschi 1978a). This protective effect has been attributed to sequestering of beryllium either through formation of a beryllium-citrate complex (Reeves 1986), or by induced ferritin (Lindenschmidt et al. 1986). Aurine tricarboxylic acid may reduce mortality by a similar mechanism (White et al. 1951). Neither of these treatments has undergone clinical trial in humans.

Parenteral administration of beryllium nitrate results in decreased hemoglobin, blood glucose, and serum protein levels, decreased serum alkaline phosphatase levels, increased serum transaminase activities, and degeneration and necrosis in the liver, kidney, and spleen. Administration of Liv-52, HEDTA, CaNa-EDTA, tiron or DMPS resulted in an improvement of these effects (Flora et al. 1995; Mathur et al. 1993, 1994; Shukula et al. 1998). The effectiveness of these treatments at lower body burdens or in humans is not known. As discussed in Section 3.2.1.2, the respiratory tract can be severely affected by inhalation of dust containing beryllium compounds. Inhalation exposure to high concentrations of soluble beryllium compounds may lead to acute chemical pneumonitis. Prolonged inhalation of low concentrations of less soluble forms are more often associated with chronic beryllium disease. Chronic beryllium disease may involve the induction of hyperplasia and hypertrophy of histiocytes (Policard 1950). Mitogenic effects may be the result of interactions of beryllium ions with lymphocyte membranes

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(Price and Skilleter 1985, 1986). Hypersensitivity may be due to the formation of a beryllium-protein complex that is antigenic. Beryllium stimulates a population of CD4+ T cells, and this reaction can be blocked by antibodies to HLA Class II molecules and by antibodies to the IL-2 receptor (Saltini et al. 1989). In some cases, the manifestations of chronic beryllium disease may be reversed by corticosteroid therapy (Aronchick et al. 1987; Finkel 1983; Hardy and Stoeckle 1959). Although corticosteroids are used to control the clinical manifestations of chronic beryllium disease and to prevent further progression of the disease, steroid therapy is not without its own risks.

Ingested soluble beryllium compounds may interact with phosphate to form insoluble beryllium phosphate particles that are sequestered in Kupffer cells of the liver (Tepper 1972). Diffusion of beryllium from the deposited particulates may cause damage to these cells and necrosis of the liver. Beryllium may also be taken up by lysosomes and cause release of lysosomal enzymes, and beryllium may interfere with DNA synthesis in the nucleus.

It has been established that beryllium inhibits DNA synthesis (Witschi 1968, 1970). Magnesium failed to influence the inhibitory effect of beryllium, although it had been shown that magnesium partly neutralizes the toxic effects of beryllium on fibroblasts or yeast cells (Lieben et al. 1964; Wainer 1972).

Because of the variety of effects noted for beryllium and possible mechanisms of action for those effects, it is difficult to speculate regarding therapies that will interfere with specific mechanisms of action such that net toxic effects are reduced. Given the variety of effects possible for absorbed beryllium, the most effective strategy for reducing toxic effects may be to reduce the amount of free beryllium ion through sequestering or complexing reactions as discussed in Section 3.11.2.

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 beryllium 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 beryllium.

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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 Beryllium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to beryllium are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of beryllium. 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.

Studies regarding adverse health effects in humans after exposure to beryllium or its compounds are limited (Figure 3-5). No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in humans following inhalation exposure to beryllium or its compounds. Studies regarding death were limited to chronic inhalation exposure. An accidental leakage of beryllium did not cause respiratory, hepatic, or immunological effects. Most of the human data concerns respiratory effects

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Figure 3-5. Existing Information on Health Effects of Beryllium

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

Human

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

Animal

- Existing Studies

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and lung cancer as a result of occupational exposure to beryllium or its compounds. Immunological data indicate that beryllium induces a T-cell lymphocyte-mediated immune response in the lung and skin. No studies were located regarding any effects in humans following oral exposure to beryllium. Since beryllium is poorly absorbed through the gastrointestinal wall, effects from this route of exposure are unlikely. For dermal exposure, only skin effects (ulcerations) were reported.

The database for animals is more complete. LC_{50} values have been reported for a number of beryllium compounds. Systemic effects of acute, intermediate, and chronic exposure via inhalation include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular effects. Immunological and carcinogenic effects were observed in various species after inhalation exposure to beryllium. No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in animals after inhalation exposure to beryllium or its compounds. Oral LD_{50} values were reported for many of the beryllium compounds. No other oral exposure studies were located regarding acute effects in animals exposed to beryllium or its compounds. Immunological, neurological, reproductive, genotoxic, and carcinogenic effects due to ingestion of beryllium are reported in the available literature.

No dermal studies were located regarding death, neurological, developmental, reproductive, genotoxic, or carcinogenic effects in animals. Acute dermal studies report dermatological effects of beryllium on sensitized animals. Since beryllium is a T-cell activator, exposure can cause immunological effects on the skin.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The lung is the main target organ of inhaled beryllium and its compounds in humans (Eisenbud et al. 1948a; Van Ordstrand et al. 1945) and animals (Haley et al. 1989; Hart et al. 1984; Robinson et al. 1968; Sanders et al. 1975; Schepers 1964; Sendebach and Witschi 1987b; Sendebach et al. 1980, 1989); however, the heart, liver, kidney, adrenal (Schepers 1965), skin (Stiefel et al. 1980), and the hematopoietic tissue (Hall et al. 1950) in animals have also been identified as target organs of beryllium exposure. The effects of occupational exposure to beryllium or its compounds include acute pneumonitis as a result of inhalation exposure to more soluble beryllium compounds or chronic beryllium disease as a result of inhalation of soluble and less soluble beryllium compounds (e.g., beryllium oxide) (Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1948a; Rossman et al. 1988). Because an animal model that mimics all aspects of chronic beryllium disease has not been

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identified, it is inappropriate to use animal data to derive an acute-duration inhalation MRL. No human acute-duration studies were identified; thus, an acute-duration inhalation MRL was not identified. No data were located regarding effects in humans after acute oral exposure to beryllium. No acute oral MRL can be derived because the only acute oral data in animals involves lethality (Ashby et al. 1990; Kimmerie 1966; Lanchow University 1978; Venugopal and Luckey 1977). The target organs of acute oral exposure of animals to low levels of beryllium are not known, but beryllium compounds are poorly absorbed from the gastrointestinal tract (Furchner et al. 1973; Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965). In humans and animals sensitized to beryllium, contact with beryllium and its soluble and insoluble compounds can cause dermatitis and skin granulomas (Belman 1969; Curtis 1951; Marx and Burrell 1973; Williams et al. 1987). In general, the more soluble the compound the greater the sensitizing potential. Dermal effects usually occur on abraded skin. Dermal absorption of beryllium is assumed to be poor and would not likely cause further systemic effects. Dermal studies would be helpful to determine the amount and duration of exposure necessary for human sensitization. Additional human exposure studies that examine the potential of beryllium to cause beryllium sensitization and chronic beryllium disease after a <2 weeks of exposure would be useful for establishing an acute-duration inhalation MRL. The information regarding beryllium toxicity is useful to the general population and to populations residing at or near hazardous waste sites, who might be subject to acute exposure.

Intermediate-Duration Exposure. No studies were located regarding effects in humans after intermediate-duration inhalation exposure to beryllium or its compounds. The available occupational exposure studies provide sufficient evidence that beryllium sensitization and chronic beryllium disease would be the most sensitive end points following intermediate-duration inhalation exposure to beryllium; however, no intermediate-duration studies were identified. Several studies indicate that the lung is the main target organ in animals for intermediate exposure to soluble and insoluble beryllium compounds via inhalation (Hall et al. 1950; Schepers 1964; Schepers et al. 1957; Stokinger et al. 1950; Wagner et al. 1969). Other target organs in animals include the heart, liver, kidney, skin, and hematopoietic tissue (Hall et al. 1950; Stiefel et al. 1980; Stokinger et al. 1950). Derivation of an intermediate-duration inhalation MRL is precluded because there are no human intermediate-duration studies and an animal model that mimics all aspects of chronic beryllium disease has not been identified, thus making it inappropriate to derive an MRL from animal data. There are limited data on the toxicity of ingested beryllium following intermediate-duration exposure. The available animal data suggest that rickets is a critical end point following ingestion of beryllium carbonate (Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The rickets do not appear to be due to a direct effect of beryllium on the bone. Rather, the rickets are due to a phosphorus deficiency, which results from the binding of beryllium to dietary phosphorus in the gut.

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Thus, the available data are insufficient for derivation of an intermediate-duration oral MRL. Additional studies involving exposure to low concentrations of several beryllium compounds would be useful for identifying critical targets of toxicity and establishing dose-response relationships. According to one study, guinea pigs were sensitized to beryllium via intradermal administration of beryllium compounds, with the sensitizing potential increasing with increasing solubility (Marx and Burrell 1973).

Chronic-Duration Exposure and Cancer. Health effects in humans and animals after chronic exposure to beryllium and its compounds are reported in the available literature. The lung is the main target organ in human (Andrews et al. 1969; Cullen et al. 1987; Eisenbud and Lisson 1983; Hardy and Tabershaw 1946; Kreiss et al. 1993a, 1996, 1997; Rossman et al. 1988; Stange et al. 1996b) and animals (Reeves et al. 1967; Vorwald and Reeves 1959; Wagner et al. 1969) after inhalation exposure to beryllium and its compounds. Occupational exposure to soluble and insoluble beryllium compounds caused delayed granulomatous disease of the lung, known as chronic beryllium disease or berylliosis (Cotes et al. 1983; Cullen et al. 1987; Eisenbud and Lisson 1983; Eisenbud et al. 1949; Kreiss et al. 1993a, 1996, 1997; Stange et al. 1996b). Acute lung inflammation was also observed after occupational exposure to soluble beryllium compounds (Eisenbud et al. 1948a). These serious respiratory effects in humans were found even at the lowest occupational exposure concentrations, which were lower than concentrations used in chronic inhalation experiments in animals. Therefore, NOAELs for respiratory effects due to occupational exposure or chronic inhalation exposure in animals have not been determined. An environmental exposure study did identify a NOAEL for chronic beryllium disease (Eisenbud et al. 1949); however, technology available at the time of the study did not allow for the detection of beryllium sensitization or subclinical chronic beryllium disease and it is not known if the identified NOAEL would be protective for these effects. Hence, derivation of a chronic inhalation MRL is precluded. Data were not located regarding effects in humans after chronic oral exposure to beryllium. The results of a chronic dog study suggests that the gastrointestinal tract is a target of beryllium sulfate toxicity (Morgareidge et al. 1976). This study is the basis for a chronic-duration oral MRL for beryllium. The MRL was derived using a benchmark dose approach and the dose-response data for small intestinal lesions in dogs (Morgareidge et al. 1976). Data regarding the effects of chronic dermal exposure to beryllium were limited to findings of dermatitis in occupationally exposed individuals (Curtis 1951; Van Ordstrand et al. 1946; Williams et al. 1987). Studies regarding inhalation and dermal exposure to low concentrations of beryllium for chronic durations would be useful for determining the respective NOAELs for respiratory and dermal effects. Studies in dogs exposed to beryllium oxide by inhalation (Finch et al. 1990) and in guinea pigs (Barna et al. 1981, 1984) and in mice (Huang et al. 1992) exposed to beryllium oxide intratracheally have been performed to identify an appropriate model to elucidate the pathogenesis of

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chronic beryllium disease in humans. However, an animal model that exactly mimics chronic beryllium disease in humans has not been found. Further inhalation studies conducted in several species of animals designed to identify the most appropriate animal model that mimics chronic beryllium disease in humans would be useful to for determining mechanisms for induction and treatment of chronic beryllium disease. This work is in progress (see Section 3.12.3). This information would be useful to the general population and to populations residing at or near hazardous waste sites.

Data regarding occupational exposure to beryllium and its compounds appear to indicate an increased incidence of lung cancer (Infante et al. 1980; Mancuso 1970, 1979, 1980; Sanderson et al. 2001a; Steenland and Ward 1992; Wagoner et al. 1980; Ward et al. 1992). However, the quality of some of these studies has been severely criticized (EPA 1987). Animal studies indicate increases in lung cancer due to inhalation exposure to beryllium or its soluble and insoluble compounds (Nickell-Brady et al. 1994; Reeves et al. 1967; Vorwald 1968; Vorwald and Reeves 1959; Wagner et al. 1969), but these studies are also flawed. Nevertheless, these data and studies conducted by intratracheal, intravenous, and intramedullary routes taken as a whole support the carcinogenic potential of beryllium, and inhaled beryllium is considered a human carcinogen (IARC 2001; NTP1999, 2002); EPA considers beryllium to be a probable human carcinogen (IRIS 2002). A well-conducted chronic inhalation study in rats and mice using several exposure levels would add confidence to the database and eliminate uncertainties due to the flaws in the existing studies. Beryllium has not been found to cause cancer in animals after oral exposure (Morgareidge et al. 1975, 1976; Schroeder and Mitchener 1975a, 1975b); although, as previously noted, these studies may not have been adequate to assess carcinogenic potential. Beryllium and its compounds are poorly absorbed from the gastrointestinal tract. Therefore, conducting oral studies at doses high enough to affect plausible target organs would be difficult.

Genotoxicity. Genotoxicity data regarding exposure to beryllium or its compounds are contradictory. Forward and reverse mutation bacterial assays yielded both positive (Kanematsu et al. 1980; Ulitzur and Barak 1988) and negative (Arlauskas et al. 1985; Ashby et al. 1990; Rosenkranz and Poirier 1979; Simmon et al. 1979) results for the same compounds. The results are also contradictory for chromosomal aberrations induced by beryllium in mammalian cell cultures (Ashby et al. 1990; Brooks et al. 1989; Hsie et al. 1979; Larramendy et al. 1981; Miyaki et al. 1979; Williams et al. 1989). Studies to examine the mechanism of mutagenic activity of beryllium would be useful. Studies regarding the genotoxic potential of beryllium in occupationally exposed workers also would be useful, especially if exposure levels were related to genotoxic effects. In addition, studies regarding the *in vivo* genotoxic potential of beryllium in animals, particularly by the inhalation route, would be helpful.

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Reproductive Toxicity. No studies were located regarding reproductive toxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. A chronic duration study that allowed continuous mating did not find any adverse reproductive effects in dogs exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). A study involving histological examination of rats exposed to beryllium sulfate in drinking water for 2 years reported no alterations of the reproductive organs (Morgareidge et al. 1975); beryllium compounds are not well absorbed by the gastrointestinal tract. Another study involving intratracheal injection of beryllium oxide in rats reported no effects on reproductive function (Clary et al. 1975). Additional inhalation studies should examine reproductive organs in order to determine whether the potential for reproductive effects due to beryllium exposure exists.

Developmental Toxicity. No studies were located regarding developmental toxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. No developmental effects were observed in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976); although the usefulness of this study in establishing the potential developmental toxicity of ingested beryllium is limited by the nonconventional study design. No inhalation or dermal exposure studies examining developmental toxicity in animals were identified. Rats injected intravenously with beryllium nitrate during gestation delivered pups that died soon after birth (Mathur et al. 1987). Increased fetal mortality and fetal weight and increased abnormalities were observed after pregnant rats were injected intratracheally with beryllium oxide or beryllium chloride (Selivanova and Savinova 1986). Other studies in which beryllium salts were injected into pregnant mice indicated that beryllium can penetrate the placenta and reach the fetus and cause behavioral abnormalities in the offspring (Bencko et al. 1979; Tsujii and Hoshishima 1979). Additional animal studies would be useful to determine if developmental effects may occur after inhalation or oral exposure to beryllium.

Immunotoxicity. While beryllium has not been shown to be toxic to the immune system, beryllium and the soluble and insoluble compounds can be sensitizing and induce a cell-mediated immune response to beryllium (Cullen et al. 1987; Johnson 1983; Rossman et al. 1988; Saltini et al. 1989). This heightened immune response to beryllium is the cause of chronic beryllium disease and certain skin lesions (Williams et al. 1987). Granuloma formation and dermatitis are the principal immunological effects caused by exposure to beryllium. Although beryllium is not well absorbed by the gastrointestinal tract, studies evaluating the immunological effects of beryllium exposure to the associated lymphoid tissue would be useful to determine the local immunological reaction. Intermediate-duration studies designed to characterize the effects on the immune system would be helpful. The elucidation of the molecular

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mechanisms of the immune response to beryllium and the identification of the specific T-cell families that are reactive to beryllium would aid in the identification and treatment of patients with chronic beryllium disease. In addition, identification of potential differences in allelic phenotypes between people with chronic beryllium and people exposed to beryllium but without chronic beryllium disease might help identify potentially susceptible populations based on genetic differences.

Neurotoxicity. No studies were located regarding neurotoxicity in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. Histological examination of rats and dogs chronically exposed to beryllium sulfate in drinking water did not reveal any abnormalities in nerve tissues (Morgareidge et al. 1975, 1976). Beryllium is not well absorbed by the gastrointestinal tract or after dermal exposure; therefore, neurological effects are not expected to occur as a result of oral or dermal exposure. Inhalation studies involving low-level exposure to beryllium would be useful for determining its neurotoxicity.

Epidemiological and Human Dosimetry Studies. The general population is exposed to beryllium through contaminated air, water, and food. The highest exposure levels are incurred by workers in beryllium ore processing, manufacturing, or fabricating plants (Eisenbud and Lisson 1983). Few studies correlate beryllium exposure with effects on the respiratory system. Epidemiology data have been criticized for using inappropriate cohorts and including nonexposed workers. Studies that correlate occupational exposure to beryllium with cancer and other health effects would be useful and would offset the limitations of the now available studies.

Biomarkers of Exposure and Effect. There are several tests for detecting beryllium in biological fluids and tissues (Frame and Ford 1974; Foreman et al. 1970; Hurlburt 1978; IARC 1980; Martinsen and Thomassen 1986; Paschal and Bailey 1986; Shan et al. 1989). Increased levels of beryllium in urine and blood indicate exposure (Stiefel et al. 1980; Zorn et al. 1986). Beryllium has also been measured in granulomas in the lung tissue of individuals with chronic beryllium disease (Kanarek et al. 1973) and in the skin of beryllium sensitive individuals (Williams et al. 1987). Laser ion mass analysis for beryllium is the most sensitive test for identifying beryllium on histological sections from lung or skin granulomas of patients with chronic beryllium disease (Williams and Kelland 1986). A lymphocyte proliferation test has also been used to identify workers with chronic beryllium disease; positive test results rarely occur in workers who are not exposed to beryllium or its compounds (James and Williams 1985; Stokes and Rossman 1991).

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Chronic exposure to beryllium can result in decreased lung function (Andrews et al. 1969; Johnson 1983). This decrease can be measured by spirometry such as forced expiratory volume in 1 second or forced vital capacity (Andrews et al. 1969; Kriebel et al. 1988a,b). Measurements of lung function cannot distinguish between chronic beryllium disease and sarcoidosis, and lung opacities are not definitively captured by x-rays (Kanarek et al. 1973). Lymphocyte proliferation assays on cells obtained from individuals by bronchoalveolar lavage are sensitive in confirming chronic beryllium disease in symptomatic individuals (James and Williams 1985; Rossman et al. 1988). The lymphocyte proliferation test also distinguishes between chronic beryllium disease and sarcoidosis. A less invasive method of determining sensitivity to beryllium would be useful, especially for monitoring health effects in individuals living at or near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. Beryllium and its compounds are absorbed primarily through the lungs in humans and animals (Finch et al. 1990; Reeves and Vorwald 1969; Stiefel et al. 1980; Zorn et al. 1986), but the available information is not sufficient to determine the rate and extent of pulmonary absorption. Soluble compounds are absorbed more readily than insoluble compounds (Finch et al. 1990). Information from animal studies indicates that beryllium is poorly absorbed from the gastrointestinal tract, with the majority of the dose excreted in the feces (Furchner et al. 1973; Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965). Dermal absorption is also poor (Petzow and Zorn 1974). Studies regarding the rate and extent of beryllium absorption via the lungs would be useful.

The only study on the distribution of beryllium and its compounds in humans was conducted on tissue taken from autopsies (Meehan and Smythe 1967); distribution studies in animals exposed to beryllium via inhalation were more available (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Stokinger et al. 1950; Wagner et al. 1969; Zorn et al. 1977). The target organs identified in these studies were the lung, lymph nodes, kidney, liver, and bone. Distribution of beryllium is more widespread for the soluble compounds, reflecting the degree of absorption (Finch et al. 1990). Rats and guinea pigs achieved steady state concentrations in the lungs 36 weeks after initial exposure to beryllium sulfate (Reeves and Vorwald 1969). Steady state concentrations in the blood were reached after 8–12 hours (Stiefel et al. 1980). After oral exposure to beryllium metal, beryllium sulfate, or beryllium oxide, beryllium was distributed primarily to the liver and then to the kidneys, lymph nodes, blood, and bone (Le Fevre and Joel 1986; Morgareidge et al. 1975; Reeves 1965; Watanabe et al. 1985). Studies investigating distribution patterns of dermally absorbed beryllium would be useful to determine if sensitization to beryllium can occur after dermal exposure.

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Beryllium is not biotransformed in the body. Studies involving the conversion of soluble beryllium compounds to insoluble compounds would be useful to determine the residence time of the compounds in the gastrointestinal tract. Studies investigating the binding of beryllium to proteins or nucleic acids would be useful in determining the antigenic forms of beryllium, as well as a possible mechanism for genotoxicity.

Information regarding the clearance of beryllium from serum in humans (Stiefel et al. 1980; Zorn et al. 1986) and animals (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Zorn et al. 1977) after inhalation exposure to beryllium compounds is reported in the available literature. Beryllium compounds are poorly absorbed by the gastrointestinal tract, and primarily eliminated in the feces (Furchner et al. 1973; Morgareidge et al. 1975; Reeves 1965). Studies regarding excretion after dermal exposure to beryllium and its compounds were not located in the available literature.

Comparative Toxicokinetics. Studies in cats, rats, monkeys, and dogs indicate quantitative and qualitative differences in the distribution of inhaled beryllium to the lung, bone, spleen, and lymph nodes (Finch et al. 1990; Rhoads and Sanders 1985; Sanders et al. 1975; Stiefel et al. 1980; Stokinger et al. 1950; Wagner et al. 1969; Zorn et al. 1977). No studies were located comparing the differences in inhalation exposures among species with respect to absorption or excretion. Since beryllium is not well absorbed by the gastrointestinal tract or after dermal exposure, comparative studies for these routes of exposure would not be particularly valuable. Additional comparative toxicokinetics studies regarding distribution, absorption, and excretion of inhaled beryllium would be helpful to determine the use of the appropriate animal model to study acute and chronic beryllium disease.

Methods for Reducing Toxic Effects. Beryllium is poorly absorbed after oral and dermal exposure, obviating the need to develop methods to reduce absorption following these routes. While beryllium is absorbed by the lungs, the major effects of inhalation exposure to beryllium are acute chemical pneumonitis, which is associated with soluble beryllium compounds and chronic berylliosis, which is associated with retention of unabsorbed less soluble beryllium compounds in the lungs (Finch et al. 1990). Testing of bronchoalveolar lavage to enhance beryllium clearance from the lungs might prevent or reduce the severity of berylliosis. The chelating agent, aurine tricarboxylic acid, by combining with beryllium ions, increases the urinary excretion of beryllium in animals (Venugopal and Luckey 1978). However, metal chelating agents available for use in human clinical medicine have not been shown to be effective in reducing the toxicity of beryllium (Hall and Rumack 1992). Effects of soluble beryllium compounds (liver necrosis due to sequestration of insoluble beryllium phosphate formed from

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the interaction with phosphate, acute pneumonitis, immunological effects) are probably due to beryllium ions (Price and Skilleter 1985, 1986). Further studies on the influence of chelating agents on beryllium-induced effects would aid in establishing effective strategies for preventing or reducing the severity of these effects. Absorbed beryllium appears to preferentially accumulate in bone, and beryllium may substitute for calcium in bone, resulting in rickets or osteoporosis (Guyatt et al. 1933; Jacobson 1933). Studies could be performed to determine whether a high calcium diet would be effective in preventing the replacement of calcium by beryllium in bone.

Children's Susceptibility. No information on the toxicity of beryllium in children has been located. Studies that examine sensitive end points such as the lung, immune, and gastrointestinal effects in young animals would be useful for assessing whether children will be unusually susceptible to beryllium toxicity. The available animal data are inconclusive to determine whether the developing organism is sensitive to beryllium toxicity. As discussed in Chapter 2 and in Section 3.2.2.6, the only available oral study did not find developmental effects in the offspring of dogs chronically exposed to beryllium sulfate in the diet (Morgareidge et al. 1976). However, injection studies have found developmental effects (fetal/neonatal mortality, internal abnormalities, and behavioral effects) (Bencko et al. 1979; Mathur et al. 1987; Selivanova and Savinova 1986; Tsujii and Hoshishima 1979). Data needs relating to development are discussed in detail in the Developmental Toxicity subsection above. There are some data to suggest that beryllium can cross the placenta and be transferred to an infant via breast milk (Krachler et al. 1999a).

The available toxicokinetic data did not evaluate the potential differences between adults and children. Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of beryllium would be useful in assessing children's susceptibility to beryllium toxicity. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. Research in adults on methods for reducing beryllium toxic effects or body burdens would also be applicable to children.

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

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3.12.3 Ongoing Studies

Ongoing studies pertaining to beryllium have been identified and are shown in Table 3-6.

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Table 3-6. Ongoing Studies on Beryllium

Investigator	Affiliation	Research description	Sponsor
Albertini, RJ	University of Vermont	Biomarkers for beryllium sensitization	EM
Marian, B	University of California, Los Alamos National Laboratory	Screening of beryllium worker cohorts using the immun.-flow lymphocyte proliferation test	NCR
Newman, L	University of Colorado	Immunopathogenesis of beryllium disease	NCR
Rossmann, M	University of Pennsylvania	Examination of exposure-response relationship for various measures of beryllium exposure	NCR
Kotzin, BL	University of Colorado	Examination of T-cell clones in individuals with CBD and beryllium sensitized individuals	NHLBI
King, TE	National Jewish Medical and Research Center	Prevention of pulmonary fibrosis in individuals with granulomatous inflammation	NHLBI
Newman, L	National Jewish Medical and Research Center	Role of T-cells and mast cells in the development of pulmonary fibrosis	NHLBI
Mason, RJ	National Jewish Medical and Research Center	Immunologic regulation of pulmonary fibrosis	NHLBI
Warren, JS	University of Michigan	Study of oxidant-induced β -chemokines in granuloma formation	NHLBI
Fontenot, AP	University of Colorado	Pathogenic cells in beryllium-induced lung disease	NHLBI
LA Maier	National Jewish Medical and Research Center	Local angiotensin system in lung fibrogenesis	NHLBI
Bell, J	Fayetteville State University	Mutagenic effects of beryllium on the fidelity of DNA synthesis	NIGMS
Newman, L	National Jewish Medical and Research Center	Cytokine regulation in CBD	NIEHS
Finch, GL	Lovelace Biomedical and Environmental Research Institute	Mechanisms of granulomatous disease from inhaled beryllium	USDOE

CBD = chronic beryllium disease; NCR = National Center for Research Resources; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health and Science; NIGMS = National Institute of General Medical Sciences; USDOE = U.S. Department of Energy

