CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to beryllium, but may not be inclusive of the entire body of literature.

Animal and select occupational inhalation studies are presented in Table 2-1 and Figure 2-2; animal oral studies are presented in Table 2-2 and Figure 2-3; and animal dermal data are presented in Table 2-3. Summaries of the human observational studies are presented in Tables 2-4, 2-5, and 2-8.

Levels of significant exposure (LSEs) 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 (SLOAELs) 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

endpoint 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 endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

Due to the limitations of the available occupational epidemiological studies in terms of quantitative exposure information, many of the studies identified in the literature were not included in the LSE table. Specifically, the epidemiologic studies identified generally relied on exposure data captured from a limited period of time (e.g., a year), extrapolated over the exposure time period of interest, and used a mixture of multiple exposure estimation methods (e.g., area-wide, personal monitor), often to create job-specific exposure averages. In addition, a worker's estimated exposure was often analyzed and presented as a single number (e.g., mean or cumulative exposure), while their true exposure was likely a range of concentrations. Thus, there was a large degree of uncertainty in the exact concentration workers were exposed to that would cause a health effect. These epidemiological studies are discussed in detail in the text and summarized in Tables 2-4, 2-5, and 2-8.

Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of beryllium are indicated in Table 2-1.

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

As illustrated in Figure 2-1, potential health effects associated beryllium exposure have been evaluated in epidemiological studies (primarily involving occupational exposure) and in laboratory animal studies. Most of the studies involved chronic-duration inhalation exposure. The most commonly examined endpoints are potential respiratory, immune, and cancer effects.

A number of factors influence the toxicity of beryllium; these include the exposure route, physical form and solubility of the beryllium compound, exposure level, and genetic susceptibility. The human and animal studies suggest several sensitive targets of beryllium toxicity:

- **Respiratory Effects.** Respiratory effects have been observed in humans and laboratory animals exposed to airborne beryllium. The primary respiratory effects observed in humans are acute beryllium disease (ABD) and chronic beryllium disease (CBD). ABD is an inflammatory response typically associated with short-term inhalation exposure to high levels of soluble beryllium compounds. CBD is an immune response to inhaled beryllium metal or insoluble beryllium compounds, such as beryllium oxide, which manifests as a granulomatous disorder in the lungs of genetically susceptible individuals who are sensitized to beryllium. Lung damage has also been observed in laboratory animals following inhalation exposure.

- **Gastrointestinal Effects.** Chronic-duration oral exposure to beryllium sulfate tetrahydrate resulted in ulcerative and inflammatory lesions in the stomach, small intestine, and large intestine of dogs.

- **Dermal Effects.** Dermal exposure to soluble beryllium compounds can result in an immune reaction on the skin. Observed dermal effects in workers include edematous papulovesicular dermatitis and granulomas. Granulomas and delayed hypersensitivity reactions have also been observed in laboratory animals dermally exposed to beryllium sulfate tetrahydrate.

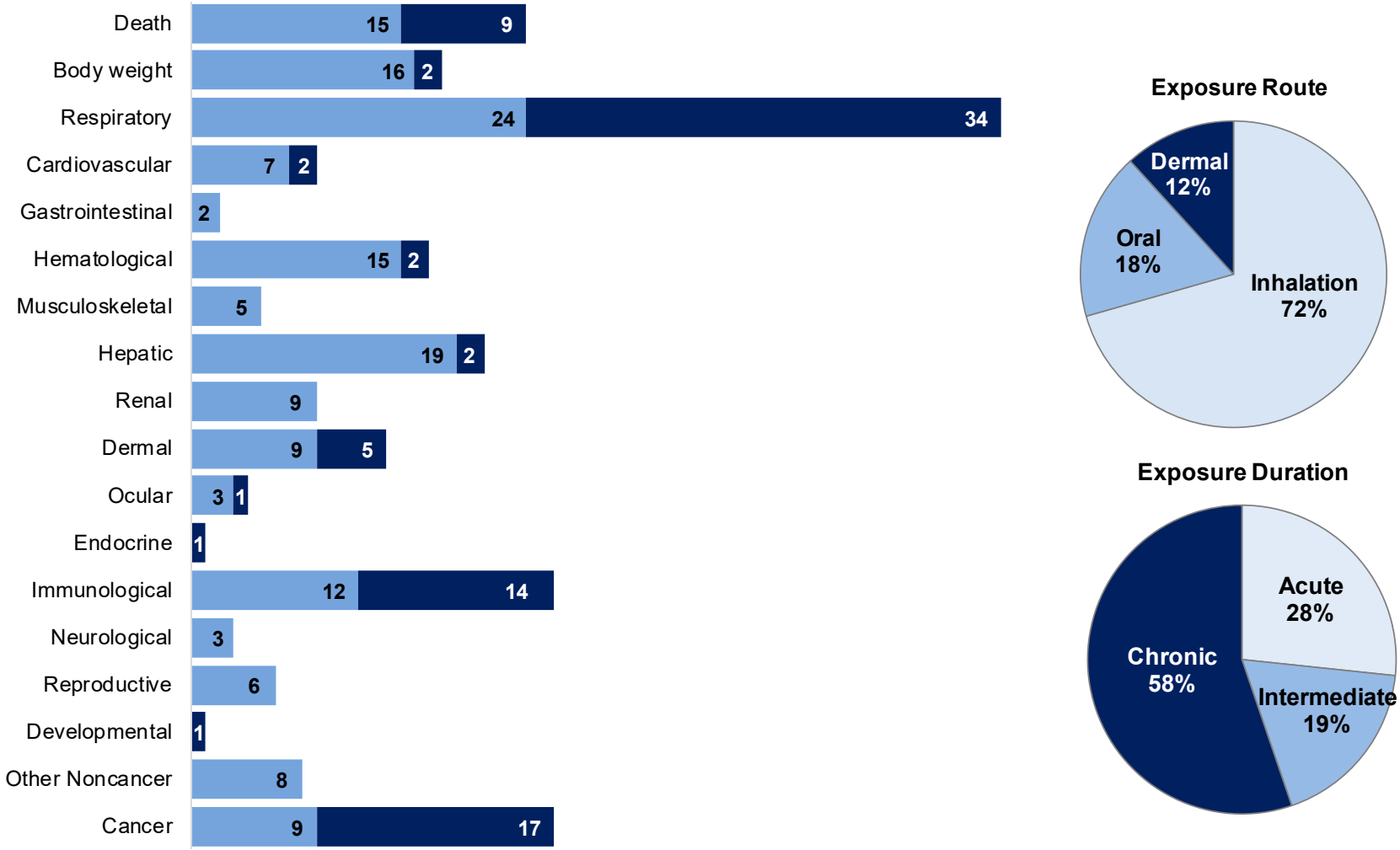
- **Immune Effects.** Beryllium sensitization, a heightened immune response to beryllium, has been observed in genetically susceptible individuals exposed to beryllium via inhalation or dermal contact exposure.

- **Cancer Effects.** Lung tumors have been reported in beryllium process workers and in laboratory animals. HHS (NTP 2021) and IARC (2012) consider beryllium to be a human carcinogen and EPA (IRIS 2002) classifies beryllium as a probable human carcinogen.

Figure 2-1. Overview of the Number of Studies Examining Beryllium Health Effects*

Most studies examined the respiratory, immunological, and cancerous effects of beryllium

Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 142 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
ACUTE EXPOSURE									
1	Monkey (*Macaca mulatta*) 4 F	8–10 days 6 hours/day	0, 1.13, 8.3	BW, OW, FI, GN, HP	Death			1.13	4/4 died
					Bd wt			1.13	Severe weight loss, 8–34%
					Resp			1.13	Emphysema
					Cardio		1.13		Enlarged heart
					Hepatic		1.13		Hepatocyte degeneration
					Renal	1.13	8.3		Degeneration of the nephrons
					Endocr		1.13		Hypoplasia of the adrenal gland
Beryllium phosphate Schepers 1964									
2	Monkey (*Macaca mulatta*) 4 F	7 days 6 hours/day	0, 0.198	BW, OW, FI, GN, HP	Death			0.198	¼ died
					Bd wt			0.198	24% average weight loss
					Resp			0.198	Emphysema
					Cardio		0.198		Enlarged heart
					Hepatic	0.198			
					Renal		0.198		Glomerular degeneration
Beryllium sulfate tetrahydrate Schepers 1964									
3	Monkey (*Macaca mulatta*) 3 F	7–13 days 6 hours/day	0, 0.184	BW, OW, FI, GN, HP	Death			0.184	2/3 died
					Bd wt			0.184	19–23% weight loss
					Resp			0.184	Emphysema
					Cardio		0.184		Enlarged heart
					Hepatic		0.184		Hepatocellular degeneration
					Renal		0.184		Nephron degeneration
					Endocr		0.184		Adrenal hypotrophy
Beryllium fluoride; pre-sensitized Schepers 1964									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
4	Rat (Fischer-344) 20 M	1 hour	0, 0.447	BI, HP	Resp		0.447 M		Increased lactate dehydrogenase, acid phosphatase, and alkaline phosphatase in lavage fluids 2 days post-exposure: lung inflammation
					Immuno		0.447 M		Reduced macrophagocytic function on days 2, 5, and 12 post-exposure
Beryllium oxide Hart et al. 1984									
5	Rat (Fischer-344) 36 M	1 hour	0, 13	HP	Resp			13	Pneumonitis
Beryllium sulfate tetrahydrate Sendelbach et al. 1986									
6	RAT (Fischer-344) 12–16 M	1 hour	0, 4.05	HP, BI	Resp			4.05	Pneumonitis
Beryllium sulfate tetrahydrate Sendelbach et al. 1989									
7	Rat (Fischer-344) 54–74 M	50 minutes	0, 0.8	BI, CS, GN, HP	Death			0.8	20/74 died
					Resp			0.8	Acute pneumonitis progressing to chronic inflammation and necrosis
Beryllium Haley et al. 1990									
8	Rat (Fischer-344) 20 M	14 days 2 hours/day	0, 2.59	LE	Death			2.6	20/20 died
Beryllium sulfate tetrahydrate Sendelbach and Witschi 1987b									
9	Mouse (BALB/c) 44 M	1 hour	0, 13	HP	Resp		13		Lung inflammation
Beryllium sulfate tetrahydrate Sendelbach et al. 1986									

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10	Dog (Beagle) 8–14 NS	1 day	0, 10	HP, BI	Resp			10	Granulomas in lung
					Immuno		10		Lymph node hyperplasia, lymphocyte stimulation
Beryllium oxide Haley et al. 1989									
INTERMEDIATE EXPOSURE									
11	Monkey (*Macaca mulatta*) 4 F	30 days 6 hours/day	0, 0.198	BW, OW, FI, GN, HP	Death			0.198	¼ died
					Bd wt			0.198	15–39% weight loss
					Resp			0.198	Emphysema
					Hepatic	0.198			
					Renal	0.198			
Beryllium phosphate Schepers 1964									
12	Monkey (*Saimiri sciureus*) 2–12 M	6 months 5 days/week 6 hours/day	0, 0.620	BI, BW, GN, HE, HP	Bd wt	0.62			
					Resp		0.62		Inflammation of lungs
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryl ore Wagner et al. 1969									
13	Monkey (*Saimiri sciureus*) 2–12 M	6 months 5 days/week 6 hours/day	0, 0.210	BI, BW, GN, HE, HP, BI	Resp		0.21		Inflammation of lungs
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
					Other noncancer	0.21			
Bertrandite ore Wagner et al. 1969									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
14	Rat (Wistar) (Sherman) 63 M, 27 F	180 days 5– 6 days/week 4–8 hours/day	0, 0.035	HP	Resp			0.035	Metaplasia, granulomas
					Cancer			0.035	CEL: lung cancer
Beryllium sulfate tetrahydrate Schepers et al. 1957									
15	Rat (Charles River) 33–60 M	6 months 5 days/week 6 hours/day	0, 0.210	BI, BW, GN, HE, HP	Bd wt	0.21			
					Resp			0.21	Granuloma in lung
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Bertrandite ore Wagner et al. 1969									
16	Rat (Charles River) 33–60 M	6 months 5 days/week 6 hours/day	0, 0.620	BI, BW, GN, HE, HP	Bd wt	0.62			
					Resp	0.62			
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryl ore Wagner et al. 1969									
17	Mouse C3H/HeJ 40 M	3 weeks 5 days/week 6 hours/day	0, 0.254	HP, IX	Immuno		0.254 M		>50% higher IFN-α, CD4+, and CD8+ T cells ($p<0.05$); 30% decrease CD19 ($p<0.05$); 77% increase IL12 ($p<0.05$)
Beryllium Muller et al. 2011									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
18	Mouse C3H/HeJ 40 M	3 weeks 5 days/week 6 hours/day	0, 0.09	HP, IX	Resp		0.09 M		Lung inflammation scores different ($p<0.05$)
					Immuno		0.09 M		40% higher IFN-α, CD4+T, and CD8+ cells ($p<0.05$); 22% decrease CD19 ($p<0.05$); >120% and 47% increase IL12 and IFN-γ, respectively ($p<0.05$)
Beryllium oxide Muller et al. 2011									
19	Mouse C3H/HeJ 40 M	3 weeks 5 days/week 6 hours/day	0, 0.06	HP, IX	Resp		0.06		Lung inflammation scores different ($p<0.05$)
					Immuno		0.06		>30% higher IFN-γ, CD4+, and CD8+; 155% increase IFN-γ
Beryllium aluminum Muller et al. 2011									
20	Hamster (Golden Syrian) 17–48 M	6 months 5 days/week 6 hours/day	0, 0.620	BI, BW, GN, HE, HP	Bd wt	0.62			
					Resp	0.62			
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryl ore Wagner et al. 1969									
21	Hamster (Golden Syrian) 33–60 M	6 months 5 days/week 6 hours/day	0, 0.210	BI, BW, GN, HE, HP	Bd wt	0.21			
					Resp			0.21	Granulomas of the lung
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Bertrandite ore Wagner et al. 1969									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
CHRONIC EXPOSURE									
22	Human 204 M, 60 F	≤6 years (median of 1.75 years) (occupational)	<0.00006 – 0.00356	CS, IX	Immuno		0.00004[b]		Beryllium sensitization observed for average lowest respirable beryllium
Beryllium Schuler et al. 2012									
23	Human 204 M, 60 F	≤6 years (median of 1.75 years) (occupational)	<0.00005– 0.00356	CS, IX	Resp			0.00017	SLOAEL: CBD cases observed for average lowest respirable beryllium
Beryllium Schuler et al. 2012									
24	Monkey (*Saimiri sciureus*) 2–12 M	12–23 months 5 days/week 6 hours/day	0, 0.210	BI, BW, GN, HE, HP	Bd wt	0.21			Inflammation of lungs
					Resp		0.21		
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Bertrandite ore Wagner et al. 1969									
25	Monkey (*Saimiri sciureus*) 2–12 M	12–23 months 5 days/week 6 hours/day	0, 0.620	BI, BW, GN, HE, HP	Bd wt	0.62			Inflammation of lungs
					Resp		0.62		
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryl ore Wagner et al. 1969									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
26	Rat (Sprague-Dawley) 75 M, 75 F	72 weeks 5 days/week 7 hours/day	0, 0.034	BW, OW, HP	Bd wt	0.034 M		0.034 F	27% decrease in body weight
					Resp		0.034		Inflammation and atypical lymphocyte proliferation with scattered dust-laden macrophages in the lung
					Cancer			0.034	CEL: lung cancer
Beryllium sulfate tetrahydrate Reeves et al. 1967									
27	Rat (Charles River) 33-60 M	12–17 months 5 days/week 6 hours/day	0, 0.620	BI, BW, GN, HE, HP	Bd wt		0.62		15% decreased body weight gain
					Resp		0.62		Consolidation of lung
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
					Cancer			0.62	CEL: lung cancer
Beryl ore Wagner et al. 1969									
28	Rat (Charles River) 33–60 M	12–17 months 5 days/week 6 hours/day	0, 0.210	BI, BW, GN, HE, HP	Bd wt	0.21			
					Resp			0.21	Granuloma in lung
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Bertrandite ore Wagner et al. 1969									
29	Hamster (Golden Syrian) 17–48 M	12-17 months 5 days/week 6 hours/day	0, 0.620	BI, BW, GN, HE, HP	Bd wt	0.62			
					Resp	0.62			
					Hemato	0.62			
					Hepatic	0.62			
					Renal	0.62			
Beryl ore Wagner et al. 1969									

Table 2-1. Levels of Significant Exposure to Beryllium–Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
30	Hamster (Golden Syrian) 17–48 M	12–17 months 5 days/week 6 hours/day	0, 0.210	BI, BW, GN, HE, HP	Bd wt	0.21			
					Resp			0.21	Granulomas in the lung
					Hemato	0.21			
					Hepatic	0.21			
					Renal	0.21			
Bertrandite ore Wagner et al. 1969									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

[b]Used to derive a chronic inhalation minimal risk level of 0.000001 mg/m^3; the LOAEL was divided by a total uncertainty factor of 30 (10 for use of a LOAEL and 3 for human variability). See Appendix A for more detailed information regarding the MRL.

Highlighted row indicates the principal study used for the MRL.

Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CBD = chronic beryllium disease; CD19 = cluster of differentiation 19; CEL = cancer effect level; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; IFN = interferon; IL12 = interleukin 12; Immuno = immunological; IX = immune function; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Resp = respiratory; SLOAEL = serious LOAEL

Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

Acute (≤14 days)

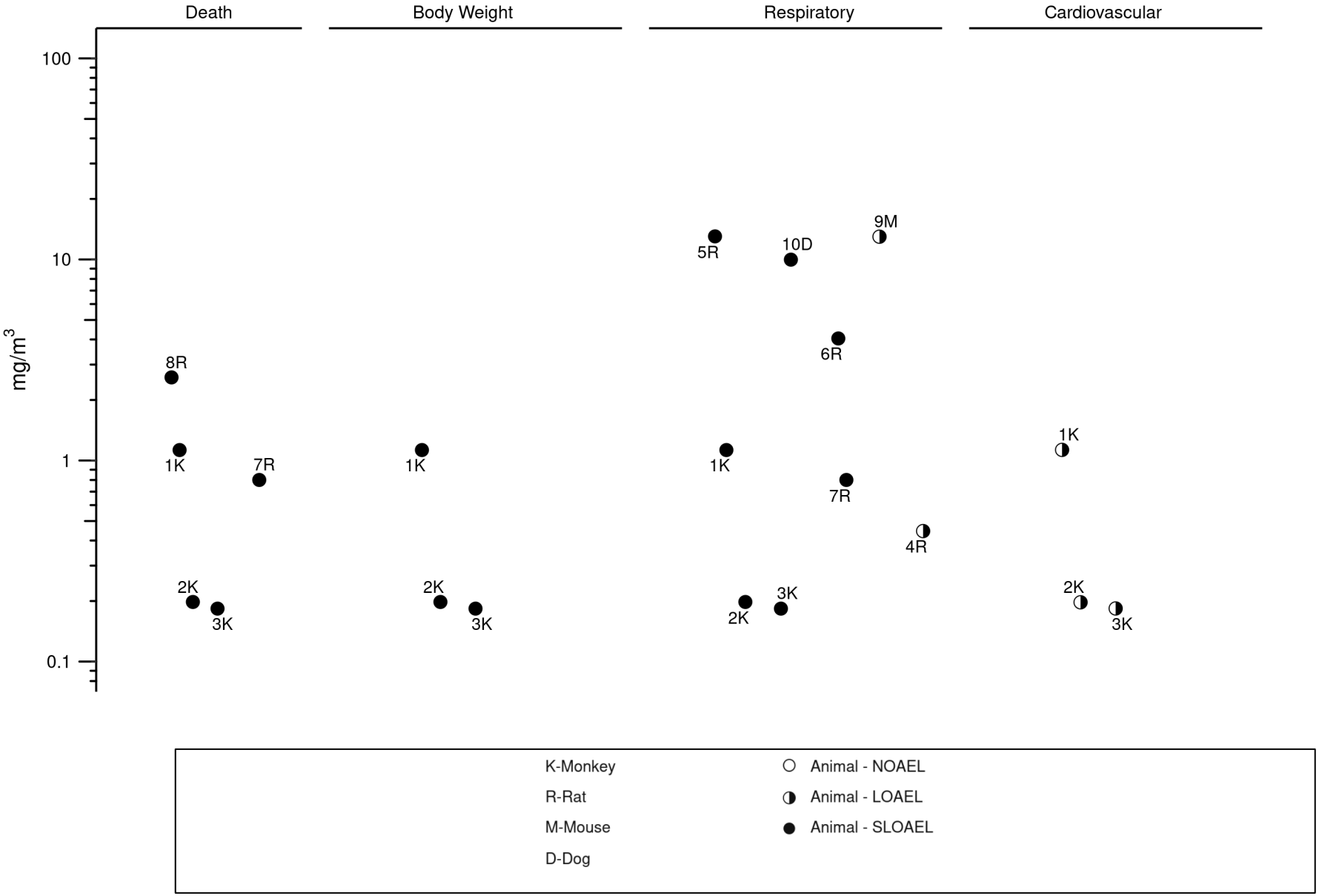


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

Acute (≤14 days)

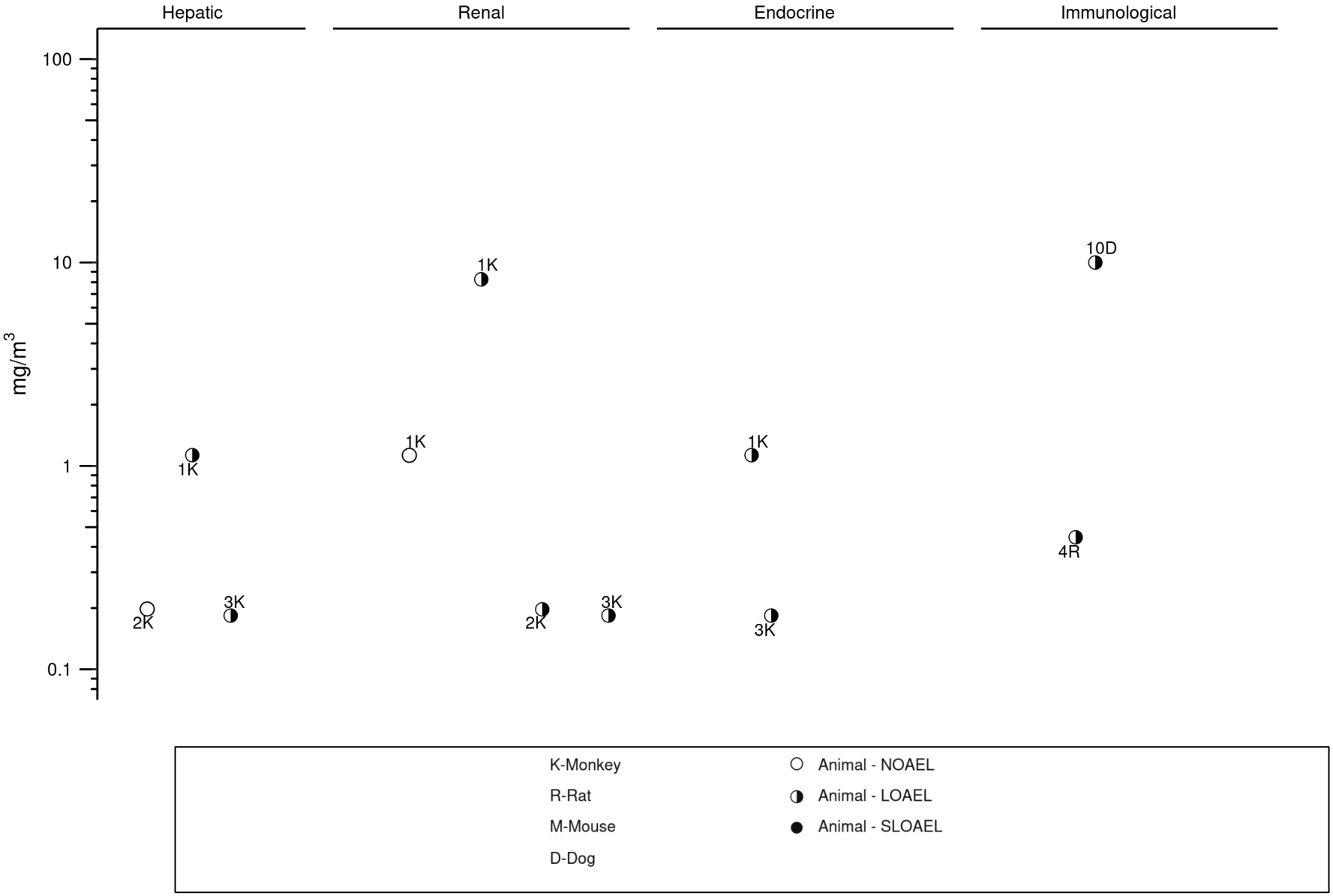


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

Intermediate (15–364 days)

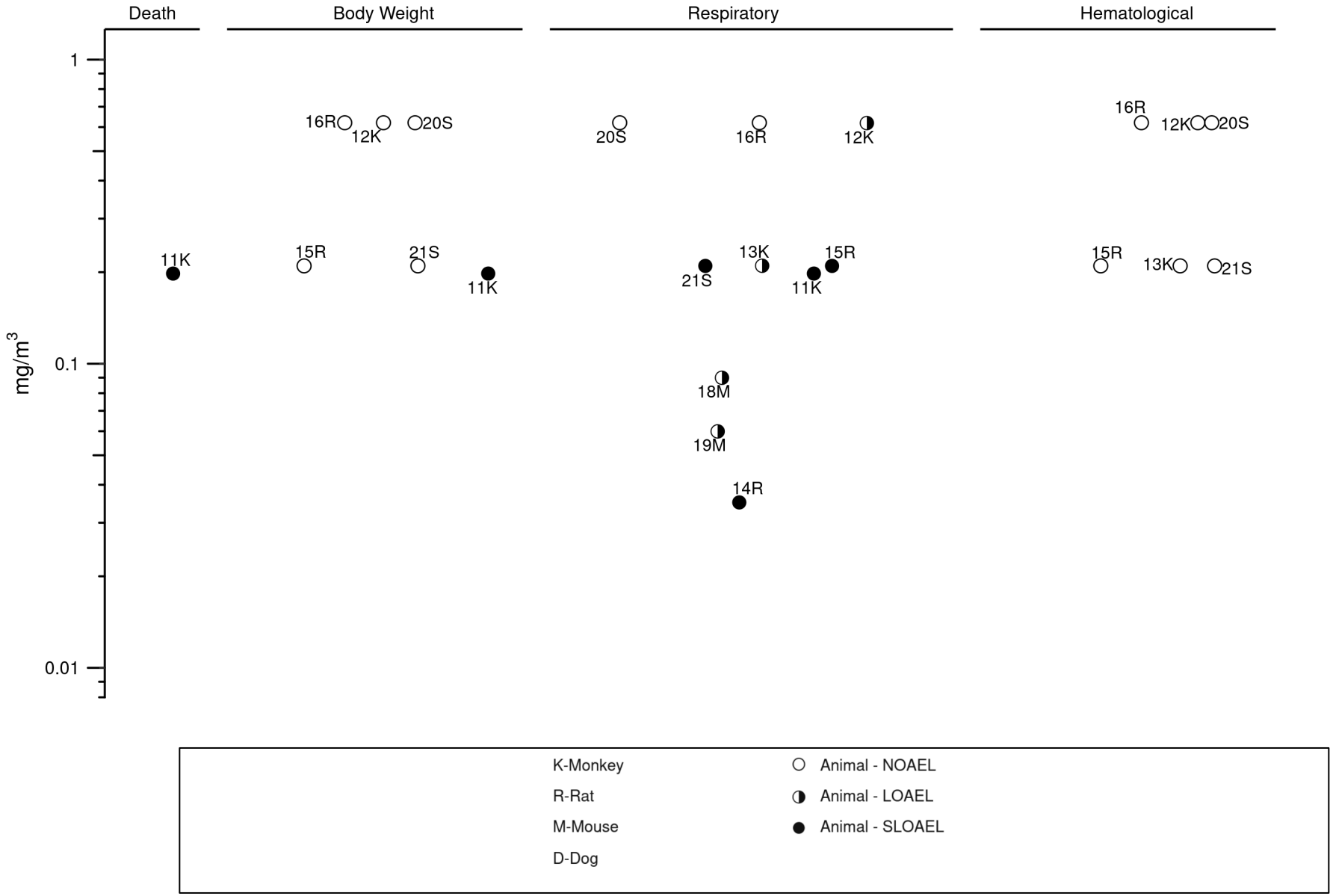


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation
Intermediate (15–364 days)

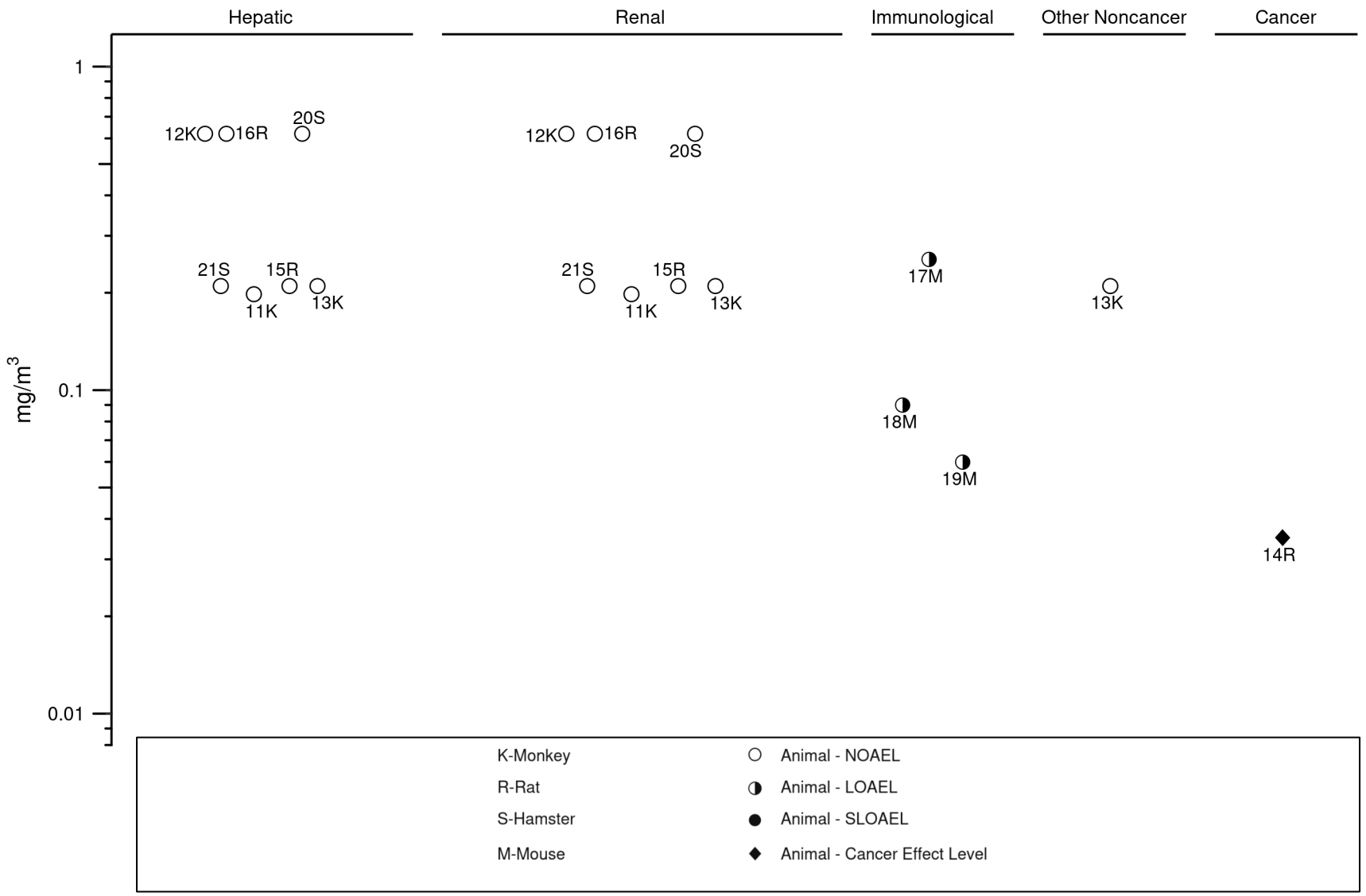


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

Chronic (≥365 days)

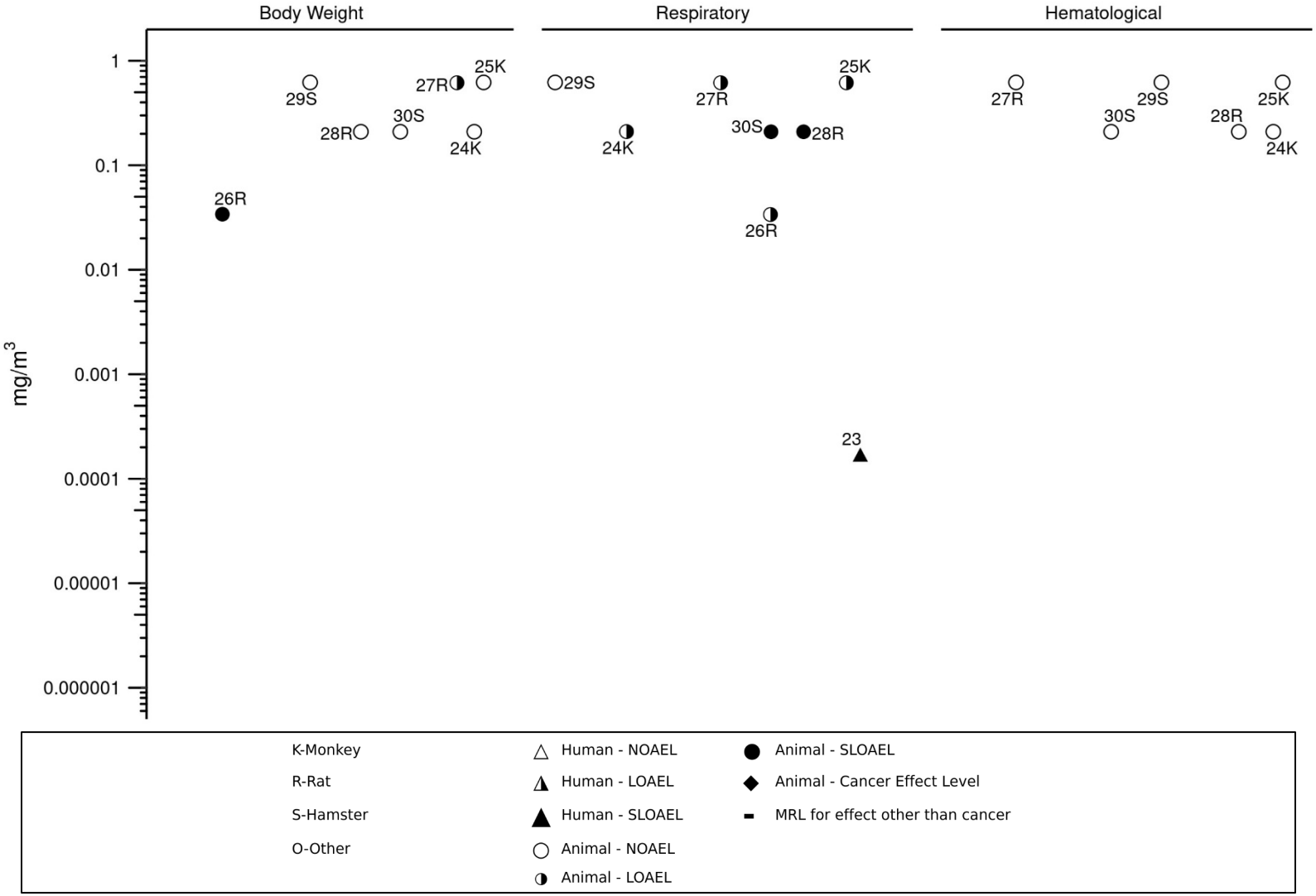


Figure 2-2. Levels of Significant Exposure to Beryllium–Inhalation

Chronic (≥365 days)

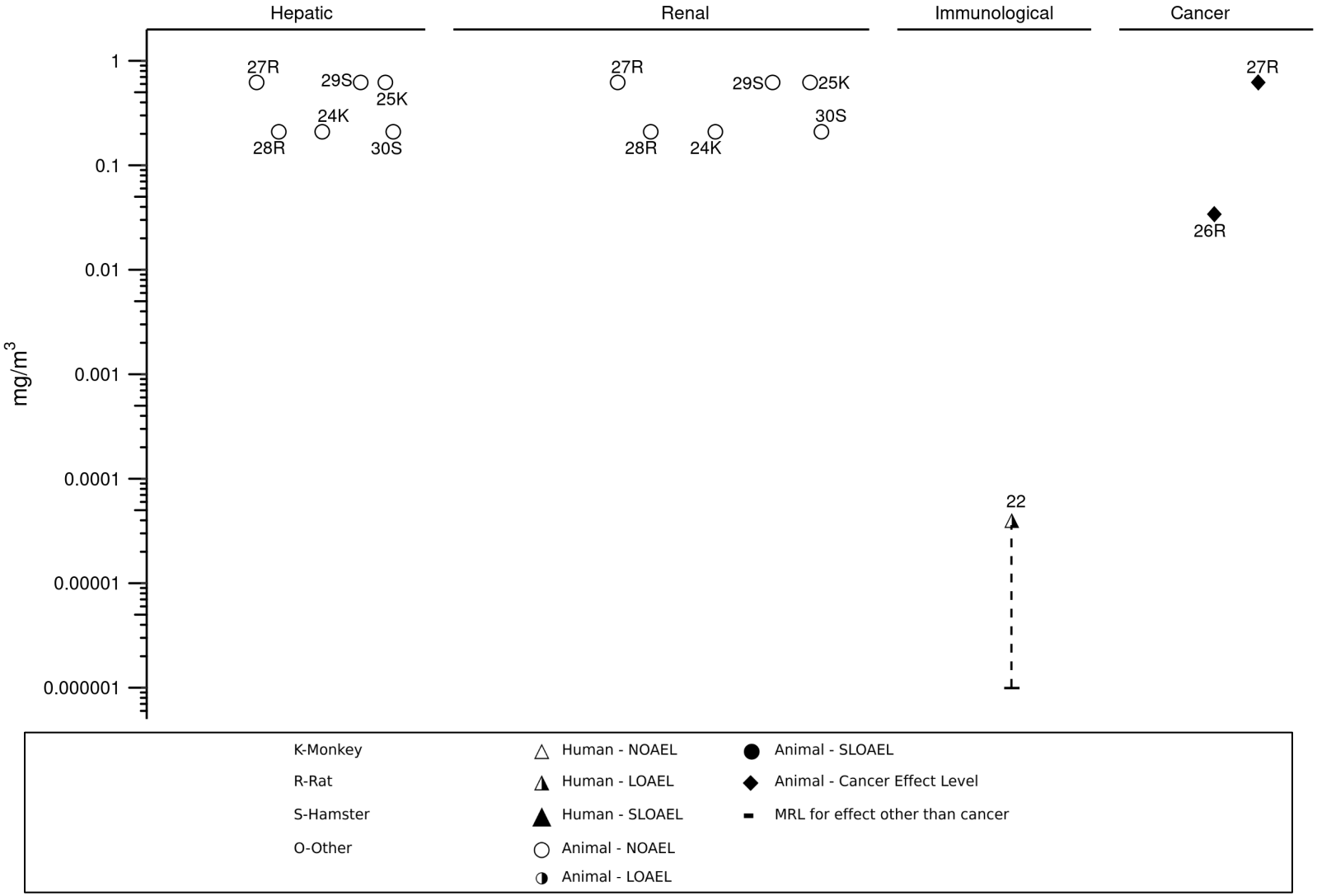


Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Wistar) 8 M	5 days (W)	0, 9.8	BI, HE	Hepatic		9.8 M		87% LDH increase, 76% protein carbonyl content increase, 38% increase MDA, 52% GSH decline; 35% CAT decrease, 40% SOD decrease with concomitant decrease in messenger RNA levels
					Neuro		9.8 M		Brain: 23% CAT decrease, 30% SOD decrease with concomitant decrease in messenger RNA levels; 96–133% increase in protein carbonyl content, MDA, and LDH
Beryllium chloride El-Beshbishy et al. 2012									
2	Rat (RccHAN: WIST) 6 F	Once (GO)	0, 2,000	BW, CS, LE	Bd wt	2000			
Beryllium Strupp 2011a									
3	Mouse (CBA) 5 M	1 d (GW)	0, 7.5, 25, 50, 70, 115, 140, 250		Death			140	LD_{50}
Beryllium sulfate tetrahydrate Ashby et al. 1990									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
INTERMEDIATE EXPOSURE									
4	Rat (Wistar) 4 NS	13–42 days (F)	0, 345	BW, FI, HP	Bd wt	345			
					Musc/skel			345	Rickets
Beryllium carbonate Jacobson 1933									
5	Rat (NS) 8 NR	21–22 days (F)	0, 70	BI, DX	Musc/skel			70	Severe rickets
					Other noncancer		70		58% decreased blood phosphate levels
Beryllium carbonate Kay and Skill 1934									
6	Rat (Wistar) 10 M	4 weeks (F)	0, 480	BI, BW	Bd wt		480		18% decrease in body weight gain
					Other noncancer		480		25% decreased serum phosphate
Beryllium carbonate Matsumoto et al. 1991									
7	Rat (Sprague-Dawley) 5 F	91d (W)	0, 0.7	BW, FI, WI	Bd wt	0.7			
Beryllium sulfate tetrahydrate Freundt and Ibrahim 1990									
8	Rat (NS) NS	24–28 days (F)	0, 35, 70, 140, 280, 840	HP	Musc/skel			35	Rickets
Beryllium carbonate Guyatt et al. 1933									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
9	Dog (Beagle) 5 M, 5 F	26–33 weeks (F)	M: 0, 12; F: 0, 17	HE, LE, GN, RX	Death			12	2/10 deaths
					Resp	12 M			
					Cardio	12 M			
					Gastro			12 M 17F	Ulceration in intestines
					Hemato		12 M		Hypoplasia in bone marrow
							17 F		Hypoplasia in bone marrow
					Musc/skel	12 M			
					Hepatic	12 M			
					Renal	12 M			
					Dermal	12 M			
					Ocular	12 M			
					Endocr	12 M			
					Repro			12 M	Testicular atrophy, testicular degeneration
Beryllium sulfate tetrahydrate Morgareidge et al. 1976									
CHRONIC EXPOSURE									
10	Rat (Wistar) 50 M, 50 F	2 years (F)	0, 0.30, 2.8, 31.0	BW, OW, FI, HP	Bd wt	31			
					Resp	31			
					Cardio	31			
					Gastro	31			
					Hemato	31			
					Musc/skel	31			
					Hepatic	31			
					Renal	31			
					Ocular	31			
					Endocr	31			
Beryllium sulfate tetrahydrate Morgareidge et al. 1975									

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
11	Rat (Long-Evans) 52 M, 52 F	3.2 years (W)	M: 0, 0.6; F: 0, 0.7	BW, HP, BC, UR	Bd wt	0.7			
					Resp	0.7			
					Cardio	0.7			
					Hepatic	0.7			
					Renal	0.7			
					Other noncancer	0.7			
Beryllium sulfate Schroeder and Mitchener 1975a									
12	Mouse (Swiss) 54 M, 54 F	898 days (W)	0, 1	BW, HP	Bd wt	1			
					Resp	1			
					Cardio	1			
					Hemato	1			
					Hepatic	1			
					Renal	1			
Beryllium sulfate Schroeder and Mitchener 1975b									
13	Dog (Beagle) 5 M, 5 F	143–172 weeks (F)	M: 0, 0.02, 0.1, 1; F: 0, 0.03, 0.2, 1	BI, BC, BW, CS, HP, GN, OW, RX, DX	Bd wt	1			
					Resp	1			
					Cardio	1			
					Gastro	1			
					Hemato	1			
					Musc/skel	1			
					Hepatic	1			
					Renal	1			
					Dermal	1			
					Ocular	1			
					Endocr	1			

Table 2-2. Levels of Significant Exposure to Beryllium–Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro	1			
					Develop	1			
Beryllium sulfate tetrahydrate									
Morgareidge et al. 1976									

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; CAT = catalase enzyme; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; (GO) = gavage in oil vehicle; GSH = glutathione; (GW) = gavage with aqueous vehicle; HE = hematology; Hemato = hematological; HP = histopathological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose, 50% kill; LDH = lactate dehydrogenase; M = male(s); MDA = malondialdehyde; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory; RNA = ribonucleic acid; RX = reproductive function; SOD = superoxide dismutase; UR = urinalysis; (W) = drinking water; WI = water intake

Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

Acute (≤14 days)

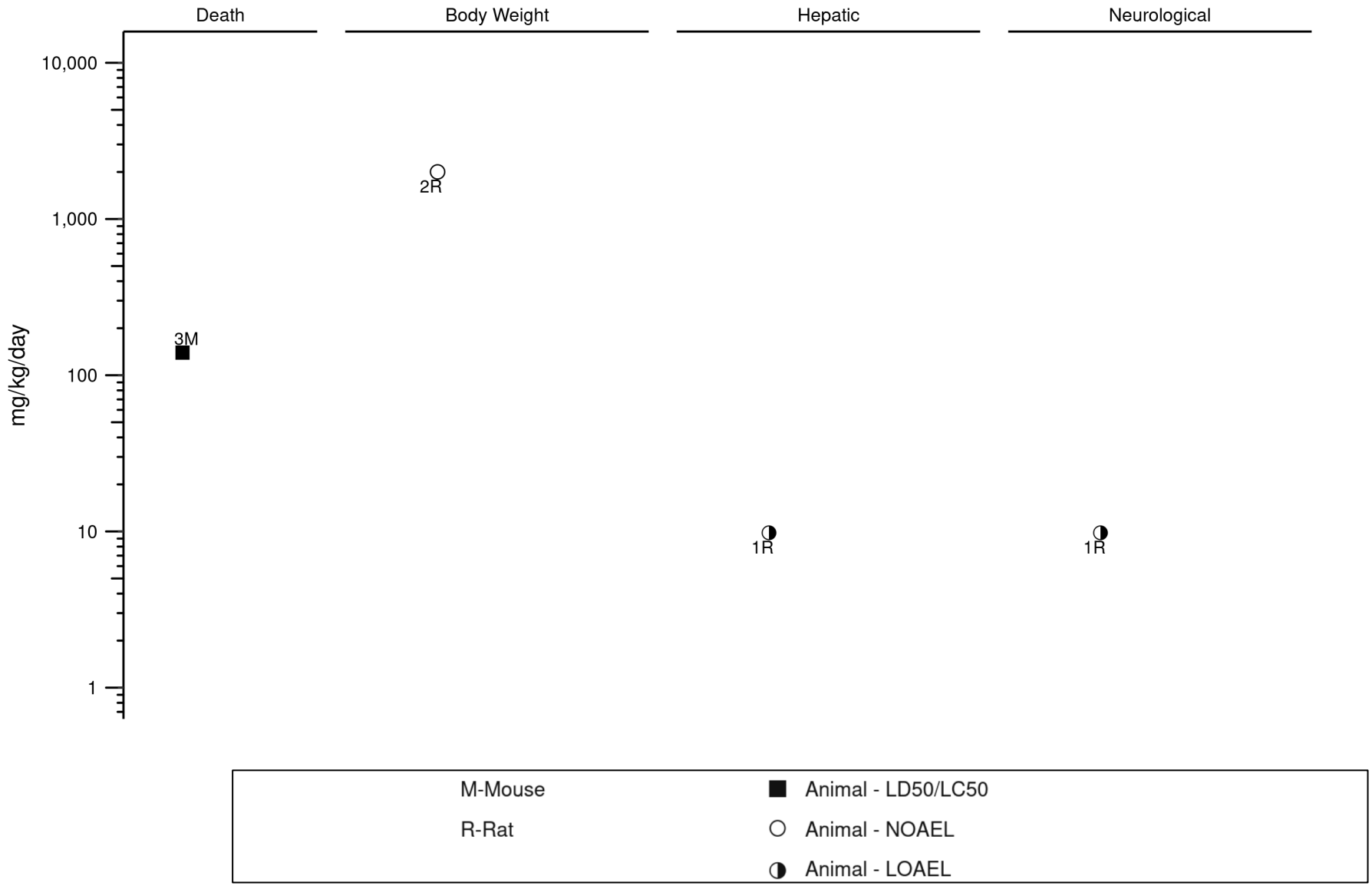


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

Intermediate (15–364 days)

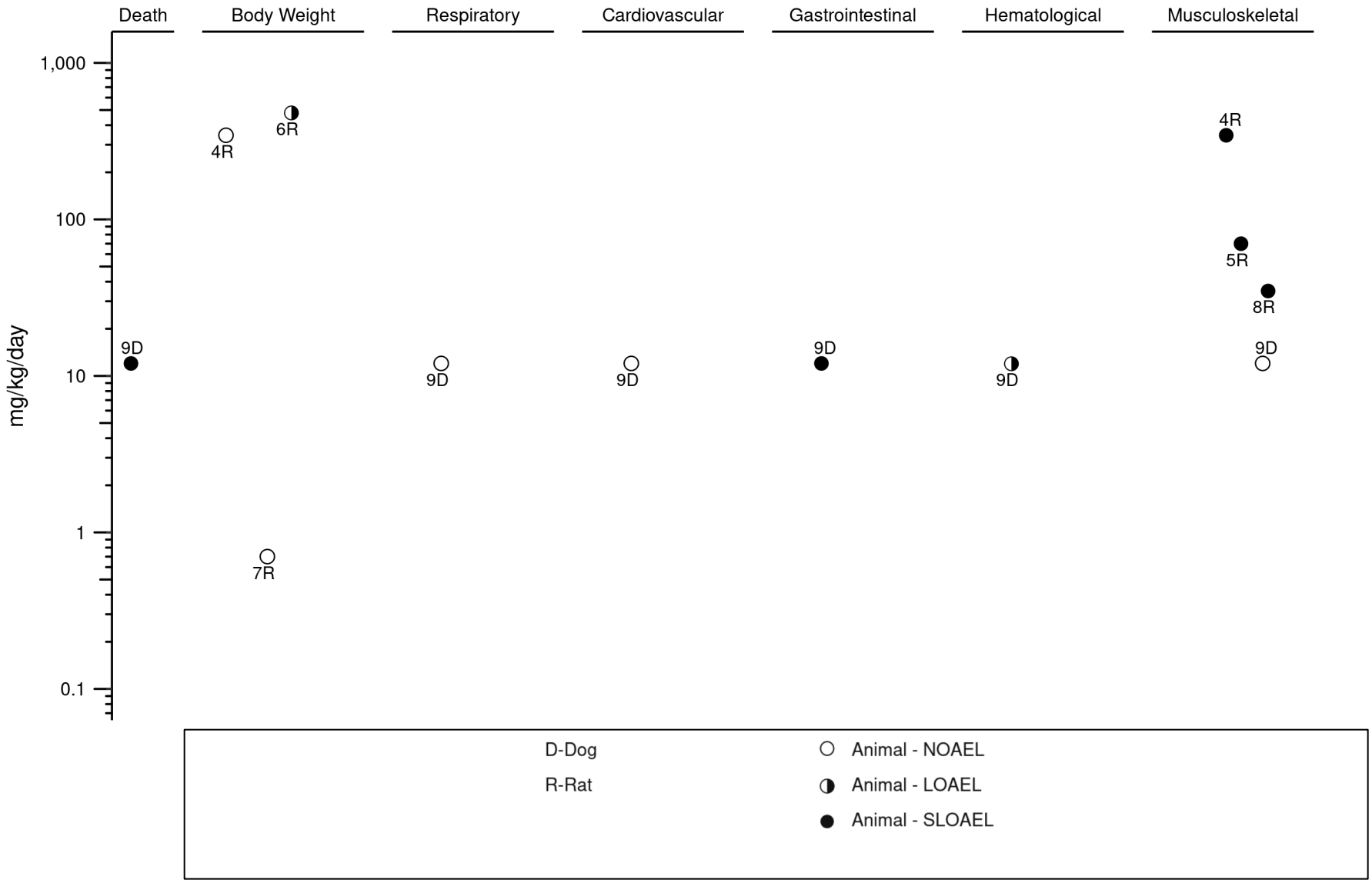


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

Intermediate (15–364 days)

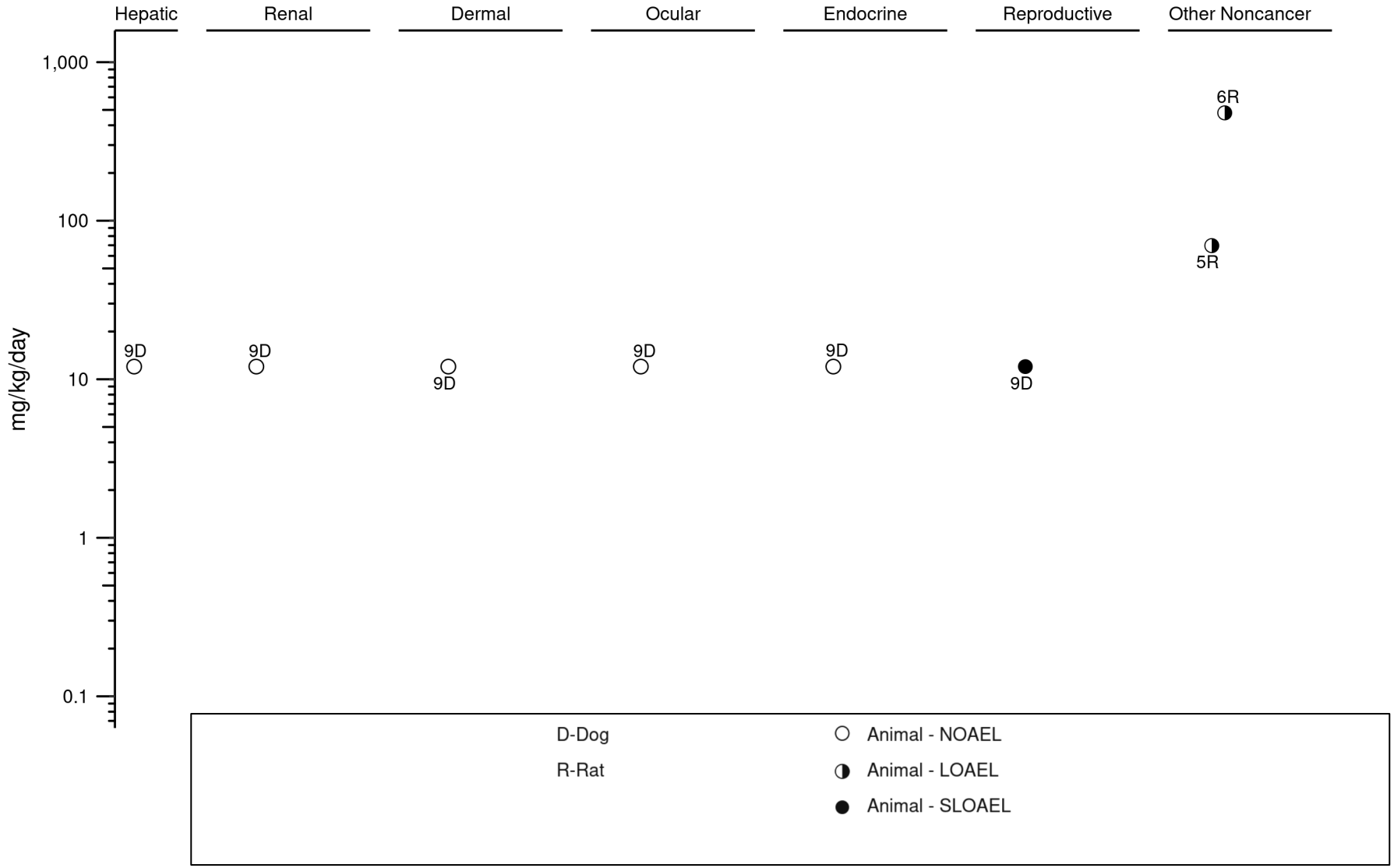


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

Chronic (≥365 days)

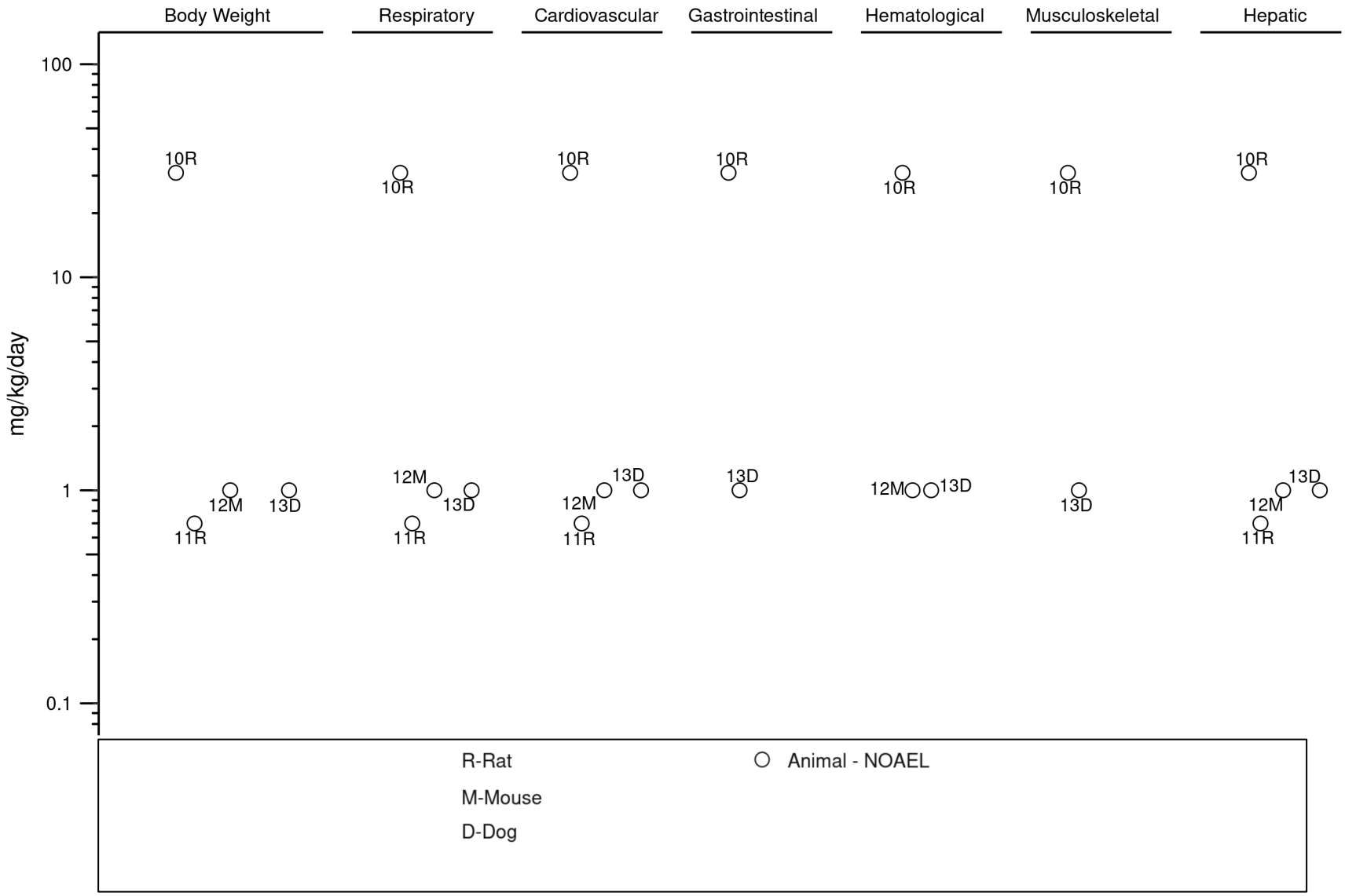


Figure 2-3. Levels of Significant Exposure to Beryllium–Oral

Chronic (≥365 days)

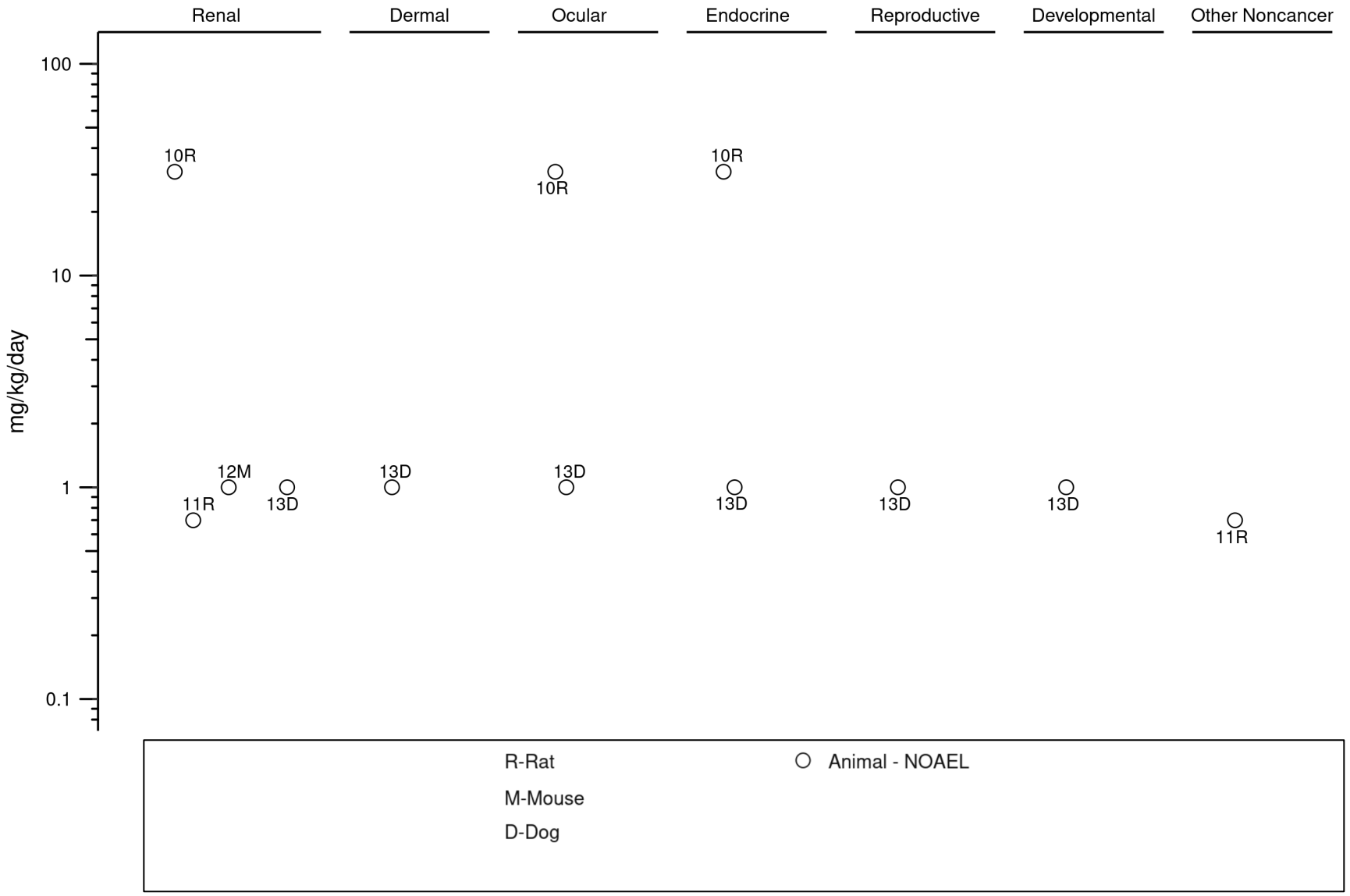


Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Human 7–10 M	48 hours	0, 0.19, 1.9, 3.8 mg/mL	CS	Dermal		0.19 mg/mL		3/10 with allergic dermatitis
Beryllium sulfate; pre-sensitized Curtis 1951								
Human 10–13 M	48 hours	0, 0.019, 0.19, 1.9, 3.8 mg/mL	CS	Dermal		0.019 mg/mL		5/13 with allergic dermatitis
Beryllium fluoride; pre-sensitized Curtis 1951								
Human 8–9 M	48 hours	0, 0.19, 1.9, 3.8 mg/mL	CS	Dermal		1.9 mg/mL		4/9 with allergic dermatitis
Beryllium nitrate; pre-sensitized Curtis 1951								
Human 16	48 hours	0, 0.019, 0.19, 0.38 mg/mL	CS	Dermal		0.38 mg/mL		8/16 with dermatitis
Beryllium fluoride Curtis 1951								
Human 16	48 hours	0, 0.019, 0.19, 0.38 mg/mL	CS	Dermal		0.38 mg/mL		2/16 with dermatitis
Beryllium chloride Curtis 1951								
Mouse CBA/Ca 4 NS	3 days	2.5, 5.0%	IX	Immuno		2.5%		Cell proliferation in lymph nodes
Beryllium sulfate tetrahydrate Basketter et al. 1999								

Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mouse C3H/HeJ or C3H/HeOuJ 10 NS	2 weeks 3 days/week	0, 0.5 Molar	IX	Immuno		0.5 M		>30-fold increase in beryllium-stimulated cell proliferation was observed in the auricular lymph node cells and blood
Beryllium sulfate; beryllium sulfate pre-sensitized Tinkle et al. 2003								
Mouse C3H/HeJ or C3H/HeOuJ NS	Once	0, 0.5 Molar	IX	Immuno		0.5 M		25–30% increase in ear thickness at 24 hours
Beryllium sulfate; beryllium oxide pre-sensitized Tinkle et al. 2003								
Guinea pig (albino) 5 M	Once	0, 0.02, 0.1 Molar	CS	Dermal		0.02 M		Delayed type hypersensitivity reaction
Beryllium fluoride Belman 1969								
Guinea pig (albino) 5 M	Once	0, 0.1 Molar	CS	Dermal		0.1 M		Delayed type hypersensitivity reaction
Beryllium chloride Belman 1969								
Guinea pig (Hartley) 4–11 NS	Once	0, 0.43 µg, 0.43 mg	HP	Resp		0.43 µg		Lung inflammation
				Dermal		0.43 µg		Delayed type hypersensitivity reaction
				Immuno		0.43 µg		Splenic hyperplasia
Beryllium sulfate Marx and Burrell 1973								
Guinea pig (Dunkin Hartley) 10–20 F	24 hours	0, 3%	CS, HP	Dermal		3%		Delayed type hypersensitivity reaction, erythema, edema
Beryllium sulfate tetrahydrate Zissu et al. 1996								

Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Guinea pig (Dunkin-Hartley) 10–20 F	24 hours	0, 50%	CS, HP	Dermal		50%		Delayed type hypersensitivity reaction, erythema, edema
Beryllium aluminum Zissu et al. 1996								
Guinea pig (Hartley) 2–4 NS	Once	0, 1.8 µg, 1.8 mg	HP	Dermal		1.8 µg		Delayed type hypersensitivity reaction
Beryllium oxide Marx and Burrell 1973								
Guinea pig (Hartley) 2 NS	Once	0, 1.8 mg	HP	Dermal	1.8 mg			
Beryllium oxide Marx and Burrell 1973								
Guinea pig (Hartley) 2 NS	Once	0, 0.48 µg, 1.9 mg	HP	Dermal		0.48 µg		Delayed type hypersensitivity reaction
Beryllium fluoride Marx and Burrell 1973								
Rabbit (New Zealand) 1 M, 2 F	4 hours	0, 500 mg	CS	Dermal	500 mg			
Beryllium Strupp 2011a								
17 Rabbit (New Zealand) 1 M, 2 F	Once	0, 100 mg	CS	Ocular	100 mg			
Beryllium carbonate Strupp 2011a								

Table 2-3. Levels of Significant Exposure to Beryllium–Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE								
Guinea pig (Hartley) 4–11 NS	24 weeks, once every 2 weeks	0, 0.86 µg		Dermal		0.86 µg		Increased macrophage inhibition factor and T cell activity
Beryllium sulfate Marx and Burrell 1973								

CS = clinical signs; F = female(s); HP = histopathological; Immuno = immunological; IX = immune function; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory

2.2 DEATH

Several retrospective cohort studies evaluating death have been conducted; these studies are summarized in Table 2-4. Retrospective mortality studies associating exposure to beryllium with death from cancer are discussed in Section 2.19. As discussed in Section 2.4, exposure to beryllium can result in two types of nonneoplastic respiratory disease, ABD and CBD. Both forms can be fatal. Many human studies indicate an increase in mortality after inhalation exposure. Furthermore, an increase in mortality is observed in animal studies after inhalation exposure. In animal studies after oral exposure, mortality was observed but was contingent on the compound being tested.

Several studies have found the pulmonary disease mortality rate among beryllium workers to be higher than the national average (Infante et al. 1980; Schubauer-Berigan et al. 2011a; Wagoner et al. 1980). In the Wagoner et al. (1980) study, 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 before strict exposure controls were initiated. Infante et al. (1980) found that the incidence of death due to nonneoplastic respiratory disease was higher in workers exposed 15 years prior and who initially developed acute respiratory disease. However, in workers classified as having chronic respiratory disease, the excess number of deaths was not related to the number of years since exposure.

Wagoner et al. (1980) also found the mortality rate due to heart disease to be higher among an occupationally exposed population when compared to the national average. Figgs et al. (2011) assessed the association between beryllium exposure and suicide among a cohort of nuclear workers and found that the likelihood of beryllium exposure was not associated with an increased risk for suicide.

Multiple retrospective cohort studies have examined all-cause mortality rates among beryllium workers, with conflicting results (Boffetta et al. 2014, 2016; Infante et al. 1980; Schubauer-Berigan et al. 2011a; Wagoner et al. 1980). Two studies found a higher all-cause mortality rate among beryllium workers than the national average, with standardized mortality ratios (SMRs) ranging from 1.04 (Schubauer-Berigan et al. 2011a) to 2.11 (Infante et al. 1980). The Boffetta et al. (2016) study examined beryllium-exposed workers from 15 different facilities, including 8 with primary exposure to insoluble beryllium and 7 with exposure to mixed soluble and insoluble beryllium compounds; the study authors found that the all-cause SMR was no different from the U.S. population's national average (SMR 1.00; 95% confidence interval [CI 0.98–1.02]) or when using state mortality data (SMR 0.98. 95% CI 0.96–1.00) in a sensitivity analysis. Although all-cause mortality is most widely reported, specific causes previously mentioned

Table 2-4. Summary of Epidemiological Studies Evaluating Mortality

Reference and study population	Exposure measurement	Death outcomes[a]	Results[b]
Boffetta et al. 2016 Retrospective cohort study; n=16,115 workers in 15 U.S. facilities (8 insoluble beryllium; 7 soluble/mixed beryllium compounds)	Mortality analyses based on national reference rates Full cohort broken into two subcohorts: • insoluble beryllium workers • soluble/mixed beryllium workers	All-cause	Full cohort: SMR 1.00 (0.98–1.02) **Insoluble beryllium: SMR 0.90 (0.86–0.94)*** **Soluble/mixed beryllium: SMR 1.05 (1.03–1.08)***
		Other nonmalignant respiratory disease	**Full cohort: SMR 1.29 (1.15–1.44)*** Insoluble beryllium: SMR 1.10 (0.85–1.40) **Soluble/mixed beryllium: SMR 1.34 (1.17–1.52)***
		COPD	Full cohort: SMR 1.00 (0.88–1.13) Insoluble beryllium: SMR 0.85 (0.65–1.09) Soluble/mixed beryllium: SMR 1.08 (0.93–1.25)
Boffetta et al. 2014 Retrospective cohort study; n=4,950 workers (79.8% male) from four U.S. insoluble beryllium manufacturing facilities	Mortality analyses based on cause-specific SMRs using combined county rates (comparing workers to general population within counties where plants are located)	All-cause	**SMR 0.947 (0.899–0.997)***
		Nonmalignant respiratory	SMR 0.90 (0.74–1.07)
Figgs et al. 2011 Retrospective cohort study; n=6,820; nuclear industry workers	Compared workers with varied history of likely beryllium exposure to workers with no beryllium exposure history	Suicide risk	HR 2.6 (0.9–7.9)
		Time-dependent model of suicide risk	HR 1.1 (0.9–1.2)
Infante et al. 1980 Retrospective cohort study from the BCR; n=421 white male workers	Mortality among cohort compared to the U.S. white male population; no smoking data available for the cohort	All-cause	**SMR 2.11[c]***
		Heart disease	SMR 1.04[c]
		Nonneoplastic respiratory disease	**SMR 16.40[c]***

Table 2-4. Summary of Epidemiological Studies Evaluating Mortality

Reference and study population	Exposure measurement	Death outcomes[a]	Results[b]
Schubauer-Berigan et al. 2011a Retrospective cohort study; n=9,199 male workers from seven beryllium processing plants; 45–65 years follow-up time subcohort from three plants with quantitative exposure measurements; n=5,436 male workers	Cumulative beryllium exposure categories (μg/m^3-day; adjusted for 5-day exposure period/week): • C1: 0–<550 • C2: 550–<2,500 • C3: 2,500–<10,300 • C4: ≥10,300	All-cause	**SMR 1.04 (1.02–1.07)***
		Categories containing CBD	**SMR 7.80 (6.26–9.60)***
		COPD	**SMR 1.23 (1.13–1.32)***
		Cor pulmonale	**SMR 1.17 (1.08–1.26)***
		Pneumoconiosis and other respiratory disease	**C3: SMR 4.58 (2.99–6.71)*** **C4: SMR 2.59 (1.58–3.99)*** *Note: C1 and C2 were not significant and thus not reported here.*
Wagoner et al. 1980 Retrospective cohort study; n=3,055 white, male workers from one beryllium extraction, processing, and fabrication facility	Compared workers to U.S. white male cause-specific mortality rates	All-cause	SMR 1.07 (p>0.05)
		Nonneoplastic respiratory disease (excluding influenza and pneumonia)	**SMR 1.65 (p<0.01)***
		Influenza and pneumonia	SMR 0.80 (p>0.05)
		Heart disease	**SMR 1.13 (p<0.05)***

[a]Many of the studies reported list many more death outcomes than those listed in this table. As beryllium exposure is most closely linked to respiratory effects, deaths related to respiratory disease are listed here, as well as all-cause and any other related death outcomes.
[b]Asterisks and bolding indicates a statistically significant (p<0.05) association with beryllium; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Confidence intervals not reported.

BCR = Beryllium Case Registry; CBD = chronic beryllium disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; SMR = standardized mortality ratio

(e.g., respiratory-related fatalities) may have a stronger relationship with beryllium exposure than all-cause mortality, since the respiratory system is the main target of beryllium exposure. Analyzing the data by beryllium form, Boffetta et al. (2016) found that the soluble/mixed beryllium cohort had a higher all-cause SMR of 1.05 (95% CI 1.03–1.08) than the national average, and the insoluble beryllium cohort had an SMR that was lower than the national average (SMR 0.90; 95% CI 0.86–0.94). The study also found that hire before 1955 (when beryllium exposure levels were higher) was associated with higher all-cause mortality compared to those hired after 1955.

Another study conducted by Boffetta et al. (2014) also found no association with all-cause mortality among workers from four insoluble beryllium manufacturing facilities (SMR 0.947; 95% CI 0.899–0.997). These studies all compared working populations to national averages rather than other workers and may thus be biased by the healthy worker effect. Regardless, the difference in mortality rates among workers exposed to soluble/mixed beryllium compared to insoluble beryllium suggests that beryllium solubility may be an effect measure modifier on the beryllium exposure and all-cause mortality relationship, although other factors, such as smoking, exposure to other compounds, or exposure in other industries, may have contributed to the overall findings.

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 CBD.

Ten fatalities occurred among 93 cases of acute beryllium pneumonitis (acute beryllium disease) 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 lung disease and resulted from massive pulmonary edema. The survival of workers diagnosed with CBD appeared 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-duration inhalation exposure to beryllium compounds. A 50-minute exposure to an aerosol of beryllium metal at 0.8 mg beryllium/m^3 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 daily to 4.3 mg beryllium/m^3 as beryllium sulfate tetrahydrate (Stokinger et al. 1950) or 2.59 mg beryllium/m^3 as beryllium sulfate tetrahydrate (Sendelbach and Witschi 1987a) died after 14 or 18 days of exposure, respectively. Three of 10 guinea pigs and 2 of 10 hamsters died when exposed to 4.3 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 14 days (Stokinger et al. 1950). All monkeys exposed to 13 mg beryllium/m^3 as beryllium hydrogen phosphate died after 8–10 days of exposure (Schepers 1964). Two of four monkeys exposed to 0.184 mg beryllium/m^3 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/m^3 as beryllium sulfate.

Exposure to 0.43 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 95 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/m^3 as beryllium oxide for 15 days (Hall et al. 1950). When rats, hamsters, and monkeys were exposed to 0.62 mg beryllium/m^3 as beryl or 0.21 mg beryllium/m^3 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 5 cats and 2 of 34 guinea pigs died when exposed to 0.43 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 95 days (Stokinger et al. 1950). Increased mortality was observed in mice, dogs, hamsters, and goats exposed to 2.0 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 51 days. The one monkey similarly exposed also died.

Chronic-duration exposure to 0.034 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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-duration inhalation exposure to beryllium. Deaths observed in the different species of animals is potentially due to the toxicity of the inhaled metal at each duration of exposure.

Oral LD_{50} values in animals vary according to the beryllium compound tested. LD_{50} values were 140 mg beryllium/kg in mice (Ashby et al. 1990) for beryllium sulfate tetrahydrate, 200 mg beryllium/kg in rats (Kimmerle 1966) for beryllium chloride, 18–20 mg beryllium/kg in mice (Kimmerle 1966) for beryllium fluoride, and 18.3 mg beryllium/kg in rats (Venugopal and Luckey 1978) for beryllium oxyfluoride. The additional toxicity of the fluoride ion accounted for the lower LD_{50} value observed for beryllium fluoride and beryllium oxyfluoride. The difference in the LD_{50} 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 tetrahydrate in the diet; the likely cause of death was severe ulcerative lesions in the gastrointestinal tract (Morgareidge et al. 1976). In chronic-duration studies, no effect on survival was observed in rats and dogs exposed to 31 mg or 1 mg beryllium/kg/day, respectively, as beryllium sulfate tetrahydrate 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).

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

2.3 BODY WEIGHT

Changes in body weight have been observed in humans and animals after inhalation and oral exposure to beryllium or its compounds. No studies were located regarding body weight effects in humans or animals after dermal exposure to beryllium or its compounds.

Weight loss was common among workers with ABD (VanOrdstrand et al. 1945). Weight loss was also reported in workers with CBD at a fluorescent lamp manufacturing plant (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/m^3 as beryllium hydrogen phosphate for 8–10 days, 0.184 mg beryllium/m^3 as beryllium fluoride for 7–18 days, or 0.198 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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/m^3 as beryllium sulfate tetrahydrate for 14 days had a 13% decrease in body weight (Stokinger et al. 1950). Dogs exposed only once to 115 mg beryllium/m^3 in a single dose 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/m^3 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/m^3 as beryllium phosphate for 30 days (Schepers 1964), 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950), or 0.43 mg beryllium/m^3 as beryllium sulfate for 95 days (Stokinger et al. 1950); but not in monkeys exposed to 0.620 mg beryllium/m^3 as beryl ore 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/m^3 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/m^3 as bertrandite ore or beryl ore, respectively. This study also did not find body weight alterations in hamsters exposed to the same concentrations of beryl ore or bertrandite ore. Weight loss was also observed in dogs exposed to 3.6 or 30 mg beryllium/m^3 as beryllium oxide for 40 or 15 days, respectively (Hall et al. 1950), or 0.4 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950). Weight loss was also observed in cats exposed to 0.04 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 51–100 days (Stokinger et al. 1950) or 30 mg beryllium/m^3 as beryllium oxide for 15 days (Hall et al. 1950). No effect was observed in rabbits exposed to 4.3 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 14 days (Stokinger et al. 1950).

Exposure to 0.034 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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/m^3 as beryl ore for 17 months also had significantly reduced body weights, compared to controls (Wagner et al. 1969).

Pregnant dams exposed to beryllium nitrate (50 mg/kg) at day 13 of gestation experienced a nearly 41% decrease in body weight compared to controls (Sharma et al. 2002).

2.4 RESPIRATORY

Human and animal studies indicate that the respiratory tract is the primary target of beryllium toxicity following inhalation exposure. Beryllium-exposed people may present with ABD from inhalation exposure to soluble beryllium compounds or CBD after inhalation exposures to soluble or insoluble beryllium or beryllium compounds. CBD is caused by immune system reactions targeting the lungs in genetically sensitive persons. ABD is caused by respiratory system irritative reactions, which can include immune effects.

Studies that examine epidemiological evidence in humans are summarized in Table 2-5. No studies were located regarding respiratory effects in humans after oral or dermal exposure to beryllium or its compounds. In general, noncancerous respiratory effects can be divided into two categories: ABD and CBD, also referred to as berylliosis or chronic berylliosis. ABD is primarily characterized by severe inflammation of the lungs and typically includes an abrupt onset of coughing and/or difficulty breathing. ABD is typically believed to be an irritative response associated with exposure to high concentrations of soluble beryllium compounds. However, Cummings et al. (2009) suggested that ABD may be an immunological response to beryllium, rather than irritative. Cummings et al. (2009) postulated that ABD may be part of the continuum of CBD; however, this theory is not completely accepted in the field and would be difficult to substantiate given that most workers are no longer exposed to such high concentrations of soluble beryllium compounds.

CBD is a beryllium-specific immune response in genetically sensitive persons with primary manifestations in the lung, characterized by the formation of granulomas with varying degrees of interstitial fibrosis. The symptoms associated with CBD include chest pain, cough, and/or dyspnea from relatively mild exertion. Lung function testing in individuals with CBD 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; CDC 1983; Rossman et al. 1988). Newman et al. (1989) provided diagnostic criteria for diseases occurring from beryllium exposure. Newman et al. (1989) identified beryllium sensitization criteria as consistent abnormal results for blood and/or lung BeLPT. Subclinical CBD criteria involved sensitized individuals with histopathological evidence of beryllium exposure but no clinical signs. A diagnosis of clinical CBD involved sensitized individuals with histopathological evidence, respiratory symptoms, changes on chest radiographs, or altered pulmonary physiology (Newman et al. 1989). Due to the overlap of methodology in epidemiological studies that look at both beryllium sensitization and CBD, these endpoints are summarized together in Table 2-5. The epidemiologic studies examining beryllium sensitization are summarized in Section 2.14. Although ABD and CBD have an immune component, they are discussed in this respiratory section because the primary organ affected is the lungs.

Historically, several criteria were used for the diagnosis of CBD: evidence of beryllium exposure, evidence of lower respiratory tract disease and clinical course consistent with CBD, reticulonodular infiltrates on chest x-ray, obstructive or restrictive deficits in lung function or a low diffusing capacity for carbon monoxide, and pathological evidence of non-caseating granulomas and/or mononuclear cell

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Nuclear facilities			
Cloeren et al. 2022	21,854 former construction workers at nuclear weapons facilities	Beryllium sensitization criteria 1 CBD diagnosis based on worker's report of a CBD claim accepted by the Department of Labor	1.2% were confirmed sensitized 17% of beryllium sensitized workers had confirmed CBD
DOE 2009	Cross-sectional study 2,773 former workers at a nuclear weapons production site (average age 63 years, 80% male) employed between 1943 and 1997 Exposure: workers exposed to beryllium (self-report or work history) were medically screened for berylliosis (also called CBD)	Medical screen included chest x-ray, spirometry and BeLPT; study does not detail specific criteria for berylliosis	3.5% of former workers had abnormal BeLPTs. 75 workers showed evidence for CBD. Limitations: incomplete site roster and databases prevented complete ascertainment of workers.
Kreiss et al. 1993a	895 current workers at a nuclear weapons assembly site	Beryllium sensitization criteria 1 CBD diagnosis criteria 1	1.9% confirmed sensitized. Beryllium sensitization was higher for machinists (4.7%) and for persons reporting measured overexposure (7.4%, OR 5.1; 95% CI 1.8, 15.0); exposure beginning before 1970 (3.6% OR 2.7; 95% CI 1.1, 7.0); consistent beryllium exposure (3.4%); and sawing (4.7%) or band sawing (6.0%). 50% of beryllium-sensitized workers were diagnosed with CBD. Several cases had minimal exposure to beryllium (employed in administrative functions).

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Mikulski et al. 2011a	1,004 former workers at a nuclear weapons assembly site; mean employment duration was 11.2 years Workers divided into three exposure categories: • virtually no exposure; lowest exposures at this facility • rare exposures; can include bystander or indirect exposure • occasional exposures; can include bystander or indirect exposures	Beryllium sensitization criteria 1; initial abnormal or borderline results were repeated within 12 months with a split test Lung function testing (FVC)	2.3% were confirmed sensitized; increased risk of sensitization in occasional exposure group (OR 4.58; 95% CI 1.09–18.13) compared to no exposure group; OR 3.83 (95% CI 1.04–14.03) after adjusting for age and smoking. No associations between beryllium sensitization and lung function.
Mikulski et al. 2011b	524 former workers at a nuclear weapons assembly site Workers divided into the same three exposure categories as Mikulski et al. (2011a)	Beryllium sensitization criteria 1; repeat samples to confirm one abnormal result or borderline or uninterpretable results Lung function testing (FVC, FEV_1)	1.5% were confirmed sensitized; increase in sensitization in workers in occasional exposure group (OR 2.64; 95% CI 0.23–29.94).
Rodrigues et al. 2008	1,786 former workers at Nevada Test Site Subcohort of 1,503 former workers; excludes females and participants with missing data Exposure potential classified by job histories and job tasks	Beryllium sensitization criteria 1; repeat sampling to confirm abnormal or borderline response with a split test Chest radiography with B-reading (used to classify pneumoconiosis), and HRCT; lung function test	1.3% were confirmed sensitized; in subcohort, sensitized workers had higher employment duration; 3% increased risk for developing sensitization for each additional year worked. Higher risk of sensitization in workers involved in clean-up and working in building where beryllium was machined: OR 2.68 (95% CI 1.10–6.56) and 2.52 (95% CI 1.02–6.19). No difference between sensitized and nonsensitized workers (after adjusting for smoking) in lung function or chest radiographs.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Sackett et al. 2004	2,381 workers involved in the cleanup (deactivation, decontamination, decommissioning, dismantling, and disposal) of beryllium-contaminated buildings and equipment at a nuclear weapons production facility Respiratory protection, protective clothing, and skin protection required; not required of workers preparing the plant for decontamination and decommissioning unless they had a legacy of known beryllium use	Beryllium sensitization criteria 2; repeat sampling to confirm abnormal response CBD diagnosis criteria 1 Chest radiographs were also performed; in participants categorized as beryllium sensitized, lung function, transbronchial lung biopsies, and BAL were conducted	0.8% were confirmed beryllium sensitized. Beryllium-sensitized workers were older, but there were no differences for sex, race, or smoking status. 1.2% of workers hired during production had abnormal BeLPT results; 0.9% of workers hired after production ceased had abnormal BeLPT results. 10.5% of the beryllium-sensitized workers were diagnosed with CBD. Limitations: although 2/19 beryllium-sensitized workers were diagnosed with CBD, only 8/19 workers underwent full clinical evaluation (i.e., 2/8 evaluated workers with beryllium sensitization were diagnosed with CBD).
Stange et al. 1996b	4,397 current and former workers at a nuclear weapons assembly site Fixed airhead sample mean concentration (for 1970–1988) 0.016 µg/m^3 Personal air monitoring mean concentration (for 1984–1987) 1.04 µg/m^3 personal air monitoring devices Questionnaire and interview administered to obtain detailed work and health histories	Beryllium sensitization diagnosis criteria 5; repeat sampling to confirm CBD diagnosis criteria 4	Overall, 2.43% prevalence rate of beryllium sensitization and CBD. 1.8% confirmed beryllium sensitization; sensitization rate was similar in current (1.2%) and former (1.9%) employees 29 confirmed CBD cases (37% of beryllium-sensitized workers). Several cases had minimal exposure to beryllium (employed in administrative functions).

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Stange et al. 2001	Cross-sectional study of 6,614 former and current workers (86.1% male, 86.5% White) at nuclear facility in Colorado	Beryllium sensitization diagnosis criteria 5 CBD diagnosis criteria 1	Overall, 4.54% prevalence rate of beryllium sensitization and CBD. Beryllium sensitization rate (11.4%) highest among machinists (OR: 3.04, 95% CI 1.48–3.97). Beryllium sensitization found in workers employed for <5 years.
Welch et al. 2004	3,842 former construction workers at three nuclear weapons facilities	Beryllium sensitization diagnosis criteria 3; repeat sampling to confirm abnormal or borderline response with a split test CBD testing (chest radiograph, chest CT scan, lung function tests, pulmonary exercise study, and bronchoscopy with lavage and/or biopsy) in beryllium-sensitized workers	1.4% confirmed beryllium sensitization with two abnormal tests of BeLPT. Five confirmed CBD cases (15% of beryllium-sensitized workers).
Welch et al. 2013	13,810 former construction workers at nuclear weapons facilities	Beryllium sensitization criteria 1; repeat sampling to confirm abnormal or borderline response with a split test only for samples collected prior to 2007 CBD testing (chest radiograph, chest CT scan, lung function tests, pulmonary exercise study, and bronchoscopy with lavage and/or biopsy) in beryllium-sensitized workers CBD diagnosis criteria 2	1.4% confirmed beryllium sensitization 15% of sensitized workers diagnosed with CBD.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Arjomandi et al. 2010	50 current and former workers with beryllium sensitization working at a nuclear weapons research and development facility	CBD testing including physical examination, chest imaging (typically radiograph and HRCT), lung function testing, and fiberoptic bronchoscopy with BAL and transbronchial biopsies CBD diagnosis criteria 3	12.5% diagnosed with CBD.
Viet et al. 2000	Case-control study of 248 workers at a nuclear weapon facility Cases: 124 workers (n=50 CBD, n=74 beryllium sensitization) Controls: negative blood LPT results and matched to controls by age (±3 years) smoking status, gender, and race Exposure: mean and cumulative exposure estimates based on job history data, job titles, and fixed airhead exposure data from one building Average employment: 13.2 years (beryllium sensitization), 19.1 years (CBD), and 14.5 years (controls)	Beryllium sensitization diagnosis criteria 4 and clinical evaluation determined no CBD CBD diagnosis criteria 2: positive and lung LPT, and noncaseating granulomas on lung biopsy	CBD cases had higher exposure levels than control (mean: 0.070 versus 0.025 µg/m^3; cumulative: 1.35 versus 0.38 µg-years/m^3). Beryllium sensitization cases had higher mean exposure levels than controls (0.036 versus 0.026 µg/m^3); no difference in cumulative exposure levels compared to controls (0.54 versus 0.40 µg-years/m^3). Strong association between the probability of CBD with increasing average exposure (OR 7.2, 95% CI 2.2–23.5) and cumulative exposure (OR 6; 9 95% CI 2.3–20.6) modeling 10-fold increase in exposure. Limitations: fixed airhead samples may not be representative of beryllium levels in personal breathing zones.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Beryllium oxide ceramics and metal refinery			
Henneberger et al. 2001	151 beryllium ceramics plant workers Exposure estimated from work history Time since first beryllium exposure: 0.25–40.1 years Median exposure: 0.55 µg/m^3 (0.2–1.1 µg/m^3) among beryllium sensitization workers	Beryllium sensitization diagnosis criteria 1 CBD diagnosis criteria 1	5.3% (8/151) overall prevalence of beryllium sensitization of which 53% (8/15) had CBD. 9.1% (7/77) CBD detected among long-term workers and 1.4% (1/74) among short-term workers. Seven out of eight beryllium sensitizations were machinists, and the sensitization rate was 14.3% among machinists versus 12.1% for other workers.
Cullen et al. 1987	Cross-sectional study of 45 workers exposed to beryllium oxide fumes at a precious metal refinery Time weighted-average personal air samples mean throughout refinery: 1.2 µg/m^3; mean in furnace area: 0.52 µg/m^3	Clinical assessment by questionnaire and review of prior radiographs and spirometry results CBD diagnosis criteria 2	40% (18/45) reported lower respiratory tract symptoms (cough, dyspnea, wheezing); 15.6% (7/45) had abnormal x-rays. Four out of five workers with CBD worked in the furnace area.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Kreiss et al. 1996	Cross-sectional study of 136 workers at a ceramics plant (62.5% males, average age 40.6 years) Exposure estimated from industrial hygiene measurements Cumulative DWA, median: 591.7 pg/m^3-days Breathing zone, median: 0.3 µg/m^3; with machinist area the highest at 63.7 µg beryllium/m^3 General area: less than detection limit (NS) Personal lapels, median: 0.20 µg/m^3	Beryllium sensitization diagnosis criteria 4, or small opacity profusion of ≥1/0 for a B-reading CBD diagnosis criteria 5	5.9% (8/136) beryllium-sensitized; 50% (4/8) beryllium-sensitized workers reported exposure to beryllium dust or mist in an accident or unusual incident 4.4% (6/136) CBD. 14.3% beryllium sensitization rate among machinists versus 1.2% employees involved with other processes at ceramics plant. Median DWA higher for machinist (0.9 µg/m^3) than all other jobs (0.3 µg/m^3).
Sawyer et al. 2005	33 current or former beryllium oxide ceramics workers Exposure mostly in the form of either fired or unfired dust	Transbronchial biopsy Secondary ion mass spectroscopy CBD diagnosis criteria 1	Beryllium levels detected in lungs were increased within the granulomas of patients with CBD compared with beryllium levels outside the granulomas. Beryllium detectable in the lungs of patients with CBD who had ceased exposure to beryllium an average of 9 years previously.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Schuler et al. 2008	136 beryllium oxide ceramics workers employed in 1992; 115 workers followed through 2003 (includes current and former workers)	Beryllium sensitization criteria 4; repeat samples to confirm one abnormal result or borderline or uninterpretable results CBD diagnosis criteria 4	The crude prevalence of beryllium sensitization was 16% (19% if workers lost to follow-up are excluded); highest rate of sensitization was found in workers involved in machining (14%); 73% of the sensitized workers ever worked in machining. The crude prevalence of CBD was 11% (13% if workers lost to follow-up are excluded); the overall mean time between hire and CBD diagnosis was 11 years.
Beryllium extraction and production			
Cotes et al. 1983	130 male workers (employed ≥6 months) at a beryllium products manufacturing factory between 1952 and 1963; 30-year follow-up Exposure estimates based on historical facility records	CBD diagnosis criteria 2	Four cases confirmed CBD and one probable; workers exposed to beryllium oxide or hydroxide. Two confirmed cases worked in areas with exposures 0.04 and 0.18 μg/m^3 in 1952 and 1960. Limitations: exposure levels based on general air samples may not be representative of breathing zone levels.
Duggal et al. 2010	72 current and former beryllium plant workers; 50 beryllium sensitization and 22 CBD diagnosed Average exposure: 15.1–18.7 years,	Beryllium sensitization diagnosis criteria 4, and no evidence of granulomas and/or mononuclear cell infiltrates on lung biopsy CBD diagnosis criteria 1 Clinical evaluation: lung function (volume and flow rate), chest x-rays	No changes in respiratory flow rates and lung volume observed. Diffusing capacity of the lungs for carbon monoxide reduced by 17.4%. 11.1% (8/72) demonstrated one or more symptoms typical of CBD.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Deubner et al. 2001b	Cross-sectional study of 75 current workers at a beryllium ore mining and milling facility in Utah Exposure: beryl ore, bertrandite, and beryllium hydroxide; average employment: 14.9–27.7 years Estimates based on historical data: General area mean: 0.3–1.1 µg/m^3 Breathing zone mean: 1.1–8.1 µg/m^3 Personal lapel mean: 0.05–6.9 µg/m^3 DWA mean: 0.1–0.4 µg/m^3	Beryllium sensitization diagnosis criteria 4 Workers with abnormal results examined by pulmonologist for BAL, BAL LPT, and trans bronchial biopsies CBD diagnosis criteria 5	Beryllium sensitization and CBD prevalence rate of 4.0% (3/75) and 1.3% (1/75), respectively; employees with beryllium sensitization worked in production area. Cumulative incidence of CBD among all 360 workers employed between the years 1969 and 1996 was 0.3%; individual with CBD worked 27.7 years at the Utah plant and an additional 10 years at another facility involved in beryllium metal and beryllium oxide production. No cases of beryllium sensitization or CBD found in workers who only worked in the mines; form of beryllium may influence the risk for developing beryllium sensitization or CBD.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Kelleher et al. 2001	Case-control study of 235 workers in a machining facility (90% male, average age 39 years); 20 cases (13 CBD and 7 beryllium sensitization) and 206 negative beryllium sensitization Median employment duration: 14.2 years (16.9 years, adjusted for machinist workday) cases, 10.5 years (12.5 years adjusted) controls Exposure: estimates based on job history, historical data, and personal samples Median personal samples: 0.13 µg/m^3 Cumulative, median: 2.93 µg/m^3-years (cases) versus 1.2 µg/m^3-years (controls)	Beryllium sensitization diagnosis criteria 4 Individuals further evaluated (bronchoscopy with BAL and trans bronchial lung biopsy) for CBD	Higher portion of cases worked as machinists (OR 4.4; 95% CI 1.1–17.6). Prevalence of 11.5% of beryllium sensitization or CBD among machinists versus 2.9% non-machinist controls. 60% (12/20) cases had LTW exposures >0.20 µg/m^3. Increased risk of beryllium sensitization and CBD among workers compared to controls.
Kreiss et al. 1997	Cross-sectional screening study of 627 workers in a beryllium metal and alloy production plant (85% male, average age 43.9 years) Exposure: historical environmental beryllium measurements between 1984 and 1993 Full shift and continuous area samples median (maximum): 0.6 (1,290) µg/m^3; general area samples median (maximum): 0.4 (2,615) µg/m^3; breathing zone samples median (maximum): 1.4 (3,750) µg/m^3; personal lapel samples median (range): 1.0 (0.1–52.6) µg/m^3	Beryllium sensitization diagnosis criteria 6 CBD diagnosis criteria 3	9.4% (59/627) had abnormal BeLPT. Overall CBD prevalence: 4.6% (29/627); highest CBD prevalence among ceramics workers exposed to beryllium oxide: 9.0%.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Madl et al. 2007	Retrospective study of 27 workers at a beryllium machining facility diagnosed with beryllium sensitization (n=9), subclinical CBD (n=16) or clinical CBD (n=2); engineering controls implemented 1996–1999 Average employment: 17. 6 years among CBD cases Employment duration prior to diagnosis: 0.2–22.1 years (beryllium sensitization), 0.2–27.5 years (subclinical CBD), 19.8–36.1 years (clinical CBD) Exposure: historical air sampling, employment year, job titles, personal lapel, and general area	Beryllium sensitization: two positive blood BeLPT; further testing of bronchoscopy with BAL and trans bronchial lung biopsy for CBD diagnosis Subclinical CBD: (1) two positive blood or one BAL BeLPT, pulmonary granulomas on lung biopsy and no physical symptoms or (2) detection of X-ray or pulmonary function changes associated with clinical CBD pathology Clinical CBD: beryllium sensitized and have histological evidence of lung granulomas, respiratory symptoms, changes on chest radiographs, and/or altered lung function	Beryllium sensitization and CBD workers exposed to >0.2 μg/m^3 (95% percentile TWA) based on highest exposed year worked adjusting for engineering controls. 90% of beryllium sensitization and CBD workers exposed to ≥0.4 μg/m^3 (upper bound, 95% percentile) within a year of employment adjusting for engineering controls. 22 out of 27 worked machining operation during employment tenure.
Mroz et al. 2009	Prospective cohort study of 229 beryllium sensitization and 171 cases CBD identified from workplace medical surveillance Comparison group: beryllium sensitization diagnosed but no pathological evidence of CBD	Beryllium sensitization diagnosis criteria 4 CBD diagnosis criteria 1	22 beryllium sensitization subjects progressed to CBD (12.6% never-smokers and 6.4% ever-smokers); conversion of beryllium sensitization to CBD estimated to be 8.8%. CBD subjects more likely to be beryllium machinist compared to subjects with beryllium sensitization (12.7%).

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Newman et al. 2001	Cross-sectional study of 235 workers at beryllium machining plant (90% males, average age 39 years Employment duration: 1–29 years, 11.7 years average	Beryllium sensitization diagnosis criteria 2, and no evidence of granulomas and/or mononuclear cell infiltrates CBD diagnosis criteria 1	9.4% (22/235) overall rate of beryllium sensitization and CBD after three rounds of screening between 1995 and 1999. 6.7% (4/60) new employees (<1 year of employment) had abnormal blood test, three underwent clinical evaluation; two workers diagnosed with CBD and one with probable CBD; new workers reported no previous exposure to beryllium.
Newman et al. 2005	Prospective cohort study of 55 beryllium sensitization mostly nuclear weapons industry workers (80%); average age 52.9 years Average employment: 24.2 years (3.6–49.5 years)	Beryllium sensitization diagnosis criteria 4 CBD diagnosis criteria 1	31% (17/55) developed CBD within follow-up period of 3.8 years (range 1.0–9.5 years). 69% (38/55) beryllium sensitization did not progress into CBD after 4.8 years average follow-up time (range 1.7–11.6 years). Beryllium sensitization to CBD more likely to have worked as machinists. Conversion rate of beryllium sensitization to CBD at rate of 6–8%/year after initial diagnosis.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Schuler et al. 2012	264 workers at a beryllium production facility with ≤6 years of employment and hired after 1993; full-shift personal air samples were used to generate a job exposure matrix	Beryllium sensitization criteria 4; repeat samples to confirm one abnormal result or borderline or uninterpretable results CBD diagnosis criteria 4	9.8% sensitized 10.3% of workers employed for <1 year were sensitized; 16.7 and 15.0% were employed for <4 or 4–8 months, respectively. A trend for increased beryllium sensitization prevalence and exposure levels was found; no cases of beryllium sensitization were found in workers exposed to average respirable beryllium levels of <0.04 μg/m^3 or exposed to the highest concentration of <0.04 μg/m^3; ORs 1.37 (95% CI 1.03–1.66) for log-transformed respirable average beryllium concentration and 1.18 (95% CI 0.95–1.49) for log-transformed cumulative respirable beryllium. Clinical evaluation for CBD was done for 22/26 beryllium sensitization workers; 27% (6/22) of sensitized workers were diagnosed with CBD (2.3% of all workers diagnosed with CBD). No cases of CBD were found in workers exposed to average respirable beryllium concentrations of <0.05 μg/m^3; ORs 0.56 (95% CI 0.86–3.49) for log-transformed average respirable beryllium concentration and 1.68 (95% CI 1.02–3.28) for log-transformed cumulative respirable beryllium concentration.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Rosenman et al. 2005, 2006	577 former employees at a beryllium processing facility in Pennsylvania operating from 1957 to 1978	Beryllium sensitization criteria 5; repeat sampling to confirm initial abnormal result; if the results were negative on repeat test, test was repeated 1 year later Definite/probable CBD testing (chest radiograph, BeLPT, EKG, and bronchoscopy with bronchial biopsy and BAL sampling) in participants with two positive BeLPT results and/or consensus chest radiograph B reading of ≥1/0 for profusion CBD diagnosis criteria 5; probable CBD diagnosis was defined as beryllium sensitization and upper lobe fibrosis	16.6% confirmed beryllium sensitized; 6.9% beryllium sensitized without CBD. 5.5% definite CBD and 2.1% probable CBD (7.6% probable or definite CBD); 52.4% of sensitized workers had probable or definite CBD. Estimated cumulative exposures were 100 and 181 μg-year/m^3; in the remaining workers, the cumulative exposures were 209 μg-year/m^3; exposures were estimated using a daily weighted average for a specific job and the amount of time spent at that job.
Bailey et al. 2010	258 workers at a beryllium processing facility employed between 1993 and 1999 (preprogram group) and 290 starting employment in 2000 or later after exposure controls were put into place (program group)	Beryllium sensitization criteria 6; repeat sampling to confirm initial abnormal, borderline, or uninterpretable results	8.9% confirmed beryllium sensitization in preprogram group and 2.1% confirmed beryllium sensitization in the program group.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Donovan et al. 2007	Approximately 2400 workers at four Brush Wellman facilities involved in mining, manufacturing, and processing Analysis included >10,000 BeLPT results collected from 1992 to 2004	Beryllium sensitization criteria 4; split analyzed at two of four laboratories; follow-up samples to confirm initial abnormal, borderline, or difficult to interpret results	Greatest positive results in workers employed for <1 year (13% in Tucson survey, 13% in Elmore survey, 15% in Reading survey); peak prevalence between 4 and 8 months (19% in Tucson survey, 19% in Elmore survey, and 38% in Reading survey); combined prevalence of 22%; the rates in workers employed >1 year were 7.4and 11% in Tucson and Reading; combined prevalence 8.8%; rate 54% greater in workers employed <1 year than for workers employed >1 year. After first year, no relationship between time of employment and prevalence of beryllium sensitization. In new employees, 2.4% had at least one abnormal BeLPT and 1.7% confirmed positive during subsequent testing; 1.1% when excluded previous occupational or take-home exposures. Reversions were noted (abnormal BeLPT followed by normal results several years later)[c].

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Beryllium alloy			
Schuler et al. 2005	153 workers at a copper-beryllium alloy facility received BeLPT Plant-wide median personal samples were 0.02 µg/m^3 and short-duration high-volume median level was 0.44 µg/m^3; in the rod and wire production area, the median level was 0.06 µg/m^3 and short-term-high volume level was 0.46 µg/m^3	Beryllium sensitization criteria 4; split analyzed at two laboratories; follow-up samples to confirm initial abnormal, borderline, or uninterpretable results CBD diagnosis criteria 4	10/153 (7%) of workers diagnosed with beryllium sensitization; workers were more likely to report incidents that may have resulted in high beryllium exposures. 6/153 (4%) diagnosed with CBD; prevalence of CBD higher among workers in the rod and wire production area. No increases in respiratory symptoms in beryllium-sensitized workers.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
Stanton et al. 2006	88 workers processing copper-beryllium alloy distribution centers Overall mean concentration: 0.05 µg/m^3 (45% below the LOD)	Beryllium sensitization criteria 4; split samples with repeat samples to confirm one abnormal result or indeterminate result Sensitized participants underwent CBD testing of BAL and transbronchial biopsies CBD diagnosis criteria 4	1.1% workers (1/88) were confirmed beryllium sensitized. 1.1% confirmed CBD. Worker with beryllium sensitization and CBD may have had unrecognized exposures that occurred during loading and unloading beryllium-contaminated trailer vans or from handling dusty aluminum-beryllium ingots (mass of metal cast into a shape).
Beryllium general exposure			
Pappas and Newman 1993	15 clinically identified subjects with beryllium disease; 22 surveillance-identified subjects with beryllium disease Clinically identified cases included five nuclear weapons plant workers, seven ceramics workers, one metal reclamation worker, one secretary from a fluorescent lamp manufacturing plant, and one wife of a beryllium-extraction plant worker	Lung function testing (spirometry, lung volumes, diffusing capacity for carbon monoxide, arterial blood gases, maximal exercise capacity) CBD diagnosis criteria 1	93% of clinically identified beryllium disease patients had one or more abnormalities, compared to 57% of surveillance-identified patients. Clinically identified patients performed less work, had more severe gas exchange abnormalities, and had higher dead space to tidal volume ratio at maximal exercise than surveillance-identified patients.

Table 2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations

Reference	Population and exposure information	Diagnosis criteria[a,b] and parameters assessed	Results
	Surveillance-identified cases were identified through two workplace screening projects: 14 nuclear weapons plant workers and 7 ceramics workers		

[a]Beryllium sensitization criteria (all tests were conducted using BeLPT with peripheral blood):
Criteria 1—beryllium sensitization defined as two abnormal BeLPTs or one abnormal and one borderline test result with repeat samples to confirm abnormal or borderline results.
Criteria 2—beryllium sensitization defined as abnormal BeLPT result on first test and abnormal or borderline result on second test.
Criteria 3—beryllium sensitization defined as abnormal BeLPT result on first test and abnormal or borderline result on second test or borderline on first test and abnormal on second test.
Criteria 4—beryllium sensitization defined as two abnormal BeLPT results.
Criteria 5—beryllium sensitization defined as two abnormal BeLPT results or abnormal BAL BeLPT result.
Criteria 6—beryllium sensitization defined as two non-normal (abnormal, borderline, or uninterpretable) BeLPT results.
[b]CBD diagnosis criteria:
Criteria 1—beryllium sensitization with mononuclear cell infiltrates and/or noncaseating granulomas or BAL lymphocytosis and abnormal BAL BeLPT.
Criteria 2—beryllium sensitization or abnormal beryllium lymphocyte transformation test on blood or lung lavage cells; lung pathology consistent with CBD and lung biopsy showing granulomas or lymphocytic process consistent with CBD, CT scan showing changes consistent with CBD, or pulmonary function study or exercise tolerance test showing pulmonary deficits consistent with CBD.
Criteria 3—beryllium sensitization and presence of granulomas or positive BAL BeLPT, and HRCT evidence of pulmonary nodules.
Criteria 4—beryllium sensitization with granulomas or other pathologic abnormalities consistent with CBD.
Criteria 5—beryllium sensitization with granulomas.
[c]The investigators hypothesized that the variability in BeLPT results over time may be due to physiological changes such as intra-individual differences in the responsiveness of circulating lymphocytes during various stages of the immune response.

BAL = bronchoalveolar lavage; BeLPT = beryllium lymphocyte proliferation test; CBD = chronic beryllium disease; CI = confidence interval; DWA = daily weighted average; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; LOD = limit of detection; LPT = lymphocyte proliferation test; NS = not specified; OR = odds ratio; TWA = time-weighted average

interstitial infiltrates (Newman et al. 1989). Screening technologies (e.g., fiber optic bronchoscopy and transbronchial biopsy methods, development of the BeLPT) allow for the detection of subclinical cases of CBD and beryllium sensitization in the absence of CBD.

Acute Beryllium Disease (ABD). Studies have described cases of ABD associated with historically high exposures to beryllium. VanOrdstrand et al. (1945) described several cases among beryllium production 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. Eisenbud et al. (1948) observed occupational ABD at concentrations >0.1 mg beryllium/m^3 as beryllium sulfate or beryllium fluoride. During a retrospective case review, Cummings et al. (2009) identified two cases of ABD in metal production workers exposed to high levels of airborne soluble beryllium fluoride in the early 1980s. The workers complained of shortness of breath, chest pain, and nonproductive cough. Pulmonary function tests showed decreases in forced vital capacity (FVC) and carbon monoxide diffusing capacity, and chest radiographs were normal. The levels of beryllium in air samples taken at the facility did not exceed 100 µg/m^3 and most were <10 µg/m^3.

Chronic Beryllium Disease (CBD). The clinical syndrome of CBD 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, granulomas, abnormal epithelial lining of the bronchioles, and abnormal alveoli and vasculature. Other case studies of CBD have described similar respiratory effects (Cullen et al. 1987).

Studies at several types of beryllium facilities have also reported cases of CBD; see Table 2-5 for summaries of the studies. In these studies, CBD was generally defined as beryllium sensitization with granulomas (or similar lesions) in the lungs and/or abnormal bronchoalveolar lavage (BAL) BeLPT results. Differences in the prevalence of sensitized workers with CBD have been found between different types of beryllium facilities, which is likely due to the differences in beryllium exposure conditions. In studies of beryllium oxide workers (ceramics and metal refineries), CBD was diagnosed in 4.4–13.0% of all workers (Cullen et al. 1987; Kreiss et al. 1996, 1997; Schuler et al. 2008). Henneberger et al. (2001) observed a higher prevalence of CBD among long-term beryllium oxide ceramics workers (9.1%) compared to short-term workers (1.4%), which may be attributed to the higher median and mean exposure levels experienced among long-term workers (0.39 and 14.9 µg/m^3, respectively) compared to short-term

workers (0.28 and 6.1 μg/m^3, respectively). Sawyer et al. (2005) also studied beryllium oxide ceramics workers and noted that beryllium levels detected in lungs were increased within the granulomas of patients with CBD compared with beryllium levels outside the granulomas. In workers at nuclear facilities, 10.5–66.7% of the beryllium-sensitized workers were diagnosed with CBD (Arjomandi et al. 2010; Cloeren et al. 2022; Kreiss et al. 1993a; Sackett et al. 2004; Stange et al. 1996b, 2001; Welch et al. 2004, 2013). The prevalence of CBD was highest among beryllium production workers, particularly among machinists. The prevalence ranged from 4 to 11% (Cotes et al. 1983; Duggal et al. 2010; Newman et al. 2001; Rosenman et al. 2005; Schuler et al. 2005, 2008). Among beryllium production workers, CBD was diagnosed in 25–64.3% of the workers with beryllium sensitization (Newman et al. 2001; Rosenman et al. 2005; Schuler et al. 2005, 2008, 2012).

Studies by Newman et al. (2005) and Mroz et al. (2009) followed beryllium-sensitized and CBD subjects over time. In the Newman et al. (2005) study, approximately 40% of the 76 beryllium-sensitized subjects were still employed and exposed to beryllium. During an average follow-up period of 4.5 years, 30.9% of the subjects developed CBD; these workers were more likely to be employed as machinists. A continual decline in lung function was observed after the initial CBD diagnosis. The study authors modeled the rate of progression from beryllium sensitization to CBD. They estimated that 13% of the subjects would progress from sensitization to CBD at 2 years of follow-up, 19% at 4 years of follow-up, and 37% at 6 years of follow-up. In a follow-up study, Mroz et al. (2009) examined the progression of beryllium sensitization to CBD among 229 subjects diagnosed with beryllium sensitization and 171 subjects with CBD between 1982 and 2002. There was a greater decline in lung function and higher levels of BAL fluid markers in the never-smoker CBD subjects compared to the never-smoker, beryllium-sensitized subjects 30 years after the initial beryllium exposure. Twenty-two subjects with beryllium sensitization developed CBD (12.6% never-smokers and 6.4% ever-smokers). CBD subjects were more likely to have been exposed to machined beryllium. Among the CBD subjects, 19.3% progressed to needing oral immunosuppressive therapy.

Several studies have examined exposure-response relationships for CBD. Madl et al. (2007) examined exposure-response relationships for cases (workers with beryllium sensitization and CBD, combined) among workers from a beryllium machining facility. Workers with beryllium sensitization and CBD were exposed to >0.2 μg/m^3 (95th percentile time-weighted average [TWA]), and 90% were exposed to concentrations >0.4 μg/m^3 (95th percentile TWA) within a given year of work history based on highest exposed year worked adjusting for engineering controls. The study authors concluded that the upper bound of worker exposures were better represented by using shorter averaging times (i.e., year versus

complete work history) (Madl et al. 2007). Viet et al. (2000) assessed exposure-response relationships in a case control study of workers at the Rocky Flats nuclear production facility. Fifty workers with CBD were matched by age, smoking status, gender, and race to an equal number of controls. For the CBD cases, the mean exposure level (0.070 versus 0.025 μg/m^3), cumulative exposure level (1.35 versus 0.38 years/m^3), and duration of employment (19.1 versus 14.4 years) were higher than controls. Comparisons between the CBD cases and beryllium sensitization cases revealed differences in mean exposure level (0.070 versus 0.036 μg/m^3), cumulative exposure level (1.35 versus 0.54 μg-years/m^3), duration of employment (19.1 versus 13.2 years), and employment start date (1964.9 versus 1970.2).

Pappas and Newman (1993) investigated whether early beryllium disease was also associated with impaired lung function. Twenty-one "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). Lung function tests included spirometry, lung volumes, diffusing capacity for carbon monoxide, arterial blood gases, and maximal exercise capacity. Physiological abnormalities in lung function were observed in 57% of the surveillance-identified subjects compared to 93% of the clinically identified subjects.

CBD in Settings Other than Manufacturing. Although CBD is usually associated with occupational exposure to beryllium at manufacturing facilities, it has also been reported in dental technicians (Brancaleone et al. 1998; Fireman et al. 2001; Kotloff et al. 1993); glassblowers, jewelry makers, and other artisans (Jamoussi et al. 2018; Naccache et al. 2003); individuals living within 1.5 miles of beryllium manufacturing facilities (Maier et al. 2008); and 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. Ten cases of CBD (based on radiological evidence) were detected, excluding para-occupationally and occupationally exposed residents. The length of exposure varied from 5 to 49 years in the residents. Three more cases were detected in a follow-up study (Sterner and Eisenbud 1951). Affected residents lived within 0.75 miles of the facility and the study authors reported that air concentrations "probably ranged between 0.01–0.1 μg beryllium/m^3." There is insufficient information about the beryllium concentrations in this study to be useful for establishing whether a health effect will occur at those levels.

Reversible Respiratory Effects. Reversible respiratory effects have been observed in several studies. Cummings et al. (2009) described two cases with ABD who had experienced decreases in FVC and carbon monoxide diffusing capacity with continued exposure. Several weeks after removal from beryllium exposure, no respiratory symptoms were noted, and pulmonary function was improved. One of the workers returned to work in the area of the facility that involved exposure to soluble beryllium compounds and redeveloped respiratory symptoms and impaired lung function within several months. The second worker returned to work in different areas of the facility that involved exposure to less soluble and insoluble beryllium compounds; the study authors did not note whether respiratory symptoms redeveloped in this worker.

Sprince et al. (1978) conducted health surveys (including measurement of lung function and x-rays) in 1971 and 1974 in beryllium workers without a diagnosis of beryllium disease. When lung function test results and arterial blood gas results were compared to the 1971 values, a slight decrease in peak expiratory flow rate, increase in alveolar-arterial O_2 tension, and decrease in alveolar-arterial CO_2 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. Improvements in hypoxia and decreased alveolar-arterial O_2 tension were observed among 13 workers diagnosed with hypoxia in 1971; no change in lung function was observed in this group. Additionally, therapy that controls the immune response (i.e., corticosteroids) can improve pulmonary function (Aronchick et al. 1987).

Donovan et al. (2007) showed a reversion of beryllium sensitization; 10 of the 18 beryllium-sensitized workers who continued to work in beryllium operations had normal BeLPT results (sent to two laboratories) 6 years later. False positive and false negative results may contribute to these “apparent” reversions (Middleton et al. 2006; Newman et al. 2001, 2005; Stange et al. 2001, 2004). However, due to methodological changes, reliability of the BeLPT has improved throughout the years. Splitting samples, increasing the number of indices with proliferative responses, and repeat sampling have increased the sensitivity (correctly identifies people potentially with CBD) and specificity (correctly identifies people potentially without disease) of the BeLPT. With these changes, the BeLPT has sensitivity estimated at 88%, with a 96% specificity (Balmes et al. 2014). Test result variability may also occur because of intra-individual differences in lymphocytes or other physiological variations (Donovan et al. 2007; Fontenot et al. 2005). While Donovan et al. (2007) noted an improvement in respiratory effects corresponding to a

dramatic decrease in beryllium exposure, it cannot be ruled out that previous methodology, physiological variations, or intra-individual differences may have influenced BeLPT results.

Respiratory Effects in Animals from Acute-Duration Inhalation Exposure to Beryllium. In animals, the respiratory system is also the primary target for inhalation exposure to beryllium. Sanders et al. (1975) studied the respiratory effects in both rats and hamsters to concentrations of 1–100 mg beryllium/m^3 as beryllium oxide (calcined at 1,000°C) (exact concentrations were not clearly specified). Rats exposed for 30–180 minutes had initial alveolar deposition of 1–63 µg beryllium in the lungs and, depending on the amount of alveolar deposition, developed slight to moderate granulomatous lesions in the lungs. Dust-laden or degenerative macrophages and a moderate infiltration of lymphocytes were also noted in the lungs of rats. Hamsters 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. Hart et al. (1984) also studied rats exposed to beryllium in the form of beryllium oxide (0.447 mg beryllium/m^3, calcined at 560°C, for 1 hour). Pulmonary lavage fluid from rats was examined at various intervals for 21 days after exposure for cell populations; acid and alkaline phosphatase enzyme activity of lysozyme and lactate dehydrogenase; and biochemical analysis of protein, lipid, phosphorus, phosphatidylcholine, 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 lactate dehydrogenase indicated cellular damage to the type II cells or the alveolar epithelium. Rats, rabbits, and guinea pigs exposed to 31 mg beryllium/m^3 as beryllium oxide for 10 days did not have any histological evidence of lung damage (Hall et al. 1950). Rats exposed to 3.3 mg beryllium/m^3 and mice exposed to 7.2 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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 and Witschi 1987b; Sendelbach et al. 1986, 1989). Increased levels of acid and alkaline phosphatase, and lactate 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/m^3 as beryllium oxide calcined at 500 or 1,000°C developed granulomas in the lung (Haley et al. 1989). Histopathology also revealed intense alveolar septal fibrosis and epithelial hyperplasia. Beryllium oxide calcined at 500°C was associated with higher incidences of lesions, due to its greater solubility. Dogs exposed to 115 mg beryllium/m^3 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/m^3 as beryllium sulfate tetrahydrate for 7–17 days (Schepers 1964). Monkeys exposed to 13 mg beryllium/m^3 as beryllium hydrogen phosphate for 8–10 days and to 0.184 mg beryllium/m^3 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.

Respiratory Effects in Animals from Intermediate-Duration Inhalation Exposure to Beryllium. Animals exposed to beryllium compounds for intermediate durations had health effects similar to those caused by acute-duration exposure. Rats and hamsters exposed to 0.21 mg beryllium/m^3 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/m^3 as beryl ore, the lungs were unaffected except for a few small areas of atypical alveolar wall cell proliferation.

Monkeys exposed to 0.210 or 0.620 mg beryllium/m^3 as bertrandite or beryl ore, respectively, had relatively minor changes in the lung (Wagner et al. 1969). 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/m^3 as beryllium oxide for 40 days or to 31 mg beryllium/m^3 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 tetrahydrate for 6 months (Schepers et al. 1957); however, a nonexposed-related outbreak of pneumonia limits the interpretation of these results. Exposure of rabbits, dogs, cats, and monkeys to 0.04 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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/m^3 as beryllium oxide for 15 days; however, similarly exposed rats experienced respiratory distress (Hall et al. 1950).

Respiratory Effects in Animals from Chronic-Duration Inhalation Exposure to Beryllium. Chronic-duration exposure to beryllium and its compounds causes similar health effects to those observed after shorter exposure durations. Wagner et al. (1969) studied intermittent daily exposure of monkeys, rats, and hamsters for periods up to 23 months to 15 mg/m^3 bertrandite or beryl ore dust (0.210 and 0.620 mg beryllium/m^3, respectively). Fifteen mg ore/m^3 of bertrandite ore or beryl ore was the threshold limit value (TLV) for inert dust. Hamsters and monkeys exposed chronically to 0.210 and 0.620 mg beryllium/m^3 as bertrandite or beryl ore, respectively, had relatively normal lung morphology, except 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/m^3 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/m^3 as beryl ore. Proliferative responses of the alveolar epithelium were also observed. 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, though silicosis was not observed (Wagner et al. 1969).

Rats exposed chronically to levels as low as 0.006 mg beryllium/m^3 as beryllium oxide or 0.0547 mg beryllium/m^3 as beryllium sulfate had inflamed lungs and fibrosis (Vorwald and Reeves 1959). Rats exposed to 0.034 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 72 weeks had inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (Reeves et al. 1967).

Respiratory Effects in Animals from Oral Exposure to Beryllium. There is limited information on the respiratory system as 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 tetrahydrate in the diet for up to 40 months (Morgareidge et al. 1976) or in rats exposed to 31 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet for 2 years (Morgareidge et al. 1975). Furthermore, chronic-duration exposure to 0.7 or 1 mg beryllium/kg/day as beryllium sulfate in drinking water did not cause lung effects in rats or mice (Schroeder and Mitchener 1975a, 1975b).

2.5 CARDIOVASCULAR

The database is not robust enough to make any conclusionary remarks concerning potential cardiovascular effects. A single monkey species and a qualitative human study have suggested heart effects. It is possible that these effects are secondary to the respiratory effects, rather than direct toxicity to the heart. No studies were located regarding cardiovascular effects in humans after oral or dermal exposure to beryllium or its compounds.

Data regarding the cardiovascular effects of beryllium and its compounds in humans by inhalation exposure are limited. Severe cases of CBD can result in cor pulmonale. Garrison et al. (2020) define cor pulmonale as "an alteration in the structure (e.g., hypertrophy or dilatation) and function of the right ventricle (RV) of the heart caused by a primary disorder of the respiratory system resulting in pulmonary hypertension." 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). The study authors stated that it is possible that the cardiac effects were not due to direct toxicity to the heart, but rather were a response to impaired lung function.

Heart enlargement was observed in monkeys after acute inhalation exposure to 13 mg beryllium/m^3 as beryllium hydrogen phosphate, 0.184 mg beryllium/m^3 as beryllium fluoride, or 0.198 mg beryllium/m^3 as beryllium sulfate tetrahydrate (Schepers 1964). Decreased arterial oxygen tension was observed in dogs exposed to 30 mg beryllium/m^3 beryllium oxide for 15 days, 3.6 mg beryllium/m^3 as beryllium oxide for 40 days (Hall et al. 1950), or 0.04 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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.

Data regarding cardiovascular effects in animals after oral exposure to beryllium or its compounds are limited. Dietary exposure to beryllium sulfate tetrahydrate 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-duration 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.

2.6 GASTROINTESTINAL

It is unclear whether gastrointestinal effects result from oral exposure to beryllium, as only two animal species have been tested and have conflicting results. Effects observed in dogs were at a non-environmentally relevant dose level (a higher level than found in the general environment). No studies were located regarding gastrointestinal effects in humans or animals after inhalation or dermal exposure to beryllium or its compounds.

In an exposure study, extensive ulcerative and inflammatory lesions were observed at 26–33 weeks in the small intestine, stomach, and large intestine of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet; similar, less severe lesions were observed in 1 of 10 dogs exposed to 1 mg beryllium/kg/day (Morgareidge et al. 1976) for 143–172 weeks. No lesions were observed in dogs exposed to 0.1 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 stomach, small intestine, or large intestine were observed in rats exposed to 31 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet for 2 years (Morgareidge et al. 1975).

2.7 HEMATOLOGICAL

Potential hematological effects from beryllium exposure in humans have not been well studied. Anemia was observed in animals after inhalation and oral exposure. No studies were located regarding hematological effects in humans after oral or dermal exposure to beryllium or its compounds.

No differences in white blood cell counts, hematocrit, or differential white blood cell percentages were observed in a machinist with CBD who worked with beryllium metal (CDC 1983). A study involving 170 case histories of beryllium workers in the Cleveland area reported normal erythrocyte sedimentation rates, blood counts, and blood chemistry (VanOrdstrand et al. 1945).

Inhalation and oral duration animal studies of beryllium and its compounds suggest hematotoxic potential. Although a few reported studies observed no effect (Hall et al. 1950; Sanders et al. 1975; Wagner et al. 1969), the majority of studies located were consistent with hematological effects; for example, hemoglobin, blood count, and hematocrit levels were altered due to beryllium exposure (El-Beshbishy et al. 2012; Hall et al. 1950; Mathur et al. 1987a; Nirala et al. 2008; Sharma and Shukla 2000).

Acute-duration exposure of animals to beryllium and its compounds had little effect on hematological parameters in some studies; other reports have shown that intermediate-duration exposures caused anemia in several species. However, hematological evaluation of rats and hamsters exposed to 1–100 mg beryllium/m^3 for 30–180 minutes to achieve initial alveolar deposition of 1–63 µg beryllium revealed no statistical difference between treated animals and controls (Sanders et al. 1975). The exact exposure concentration and duration were not clearly reported. Hematological effects were not observed in rats, hamsters, or monkeys exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore, respectively, for 6–23 months (Wagner et al. 1969).

Exposure to 31 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 for the duration of exposure. Rabbits exposed to 307 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 mg beryllium/m^3 as beryllium oxide for 15 days exhibited a moderate, progressive leukocytosis, while dogs exposed to 3.6 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 caused effects like those of beryllium oxide. Macrocytic anemia developed in rats and rabbits exposed to 0.43 mg beryllium/m^3 and dogs exposed to 0.04 mg beryllium/m^3 as beryllium sulfate tetrahydrate for 95 and 100 days, respectively (Stokinger et al. 1950). Exposure to 2.0 and 0.43 mg beryllium/m^3 as beryllium sulfate tetrahydrate in rats, rabbits, and dogs caused transient leukocytosis; exposure to 2.0 mg beryllium/m^3 caused mild thrombocytosis. With increasing exposure durations, dogs exposed to 0.04 mg beryllium/m^3 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.

Several studies examined hematological endpoints in animals after oral exposure to beryllium. 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 as beryllium sulfate tetrahydrate; 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 as beryllium sulfate tetrahydrate for 2 years (Morgareidge et al. 1975).

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.

Male Wistar rats exposed to beryllium orally as 86 mg/kg body weight of beryllium chloride (equivalent to experimental LD_{50}) for 5 days elicited significant decreases in red blood count, hemoglobin levels, and hematocrit percentages compared to controls. In an *in vitro* study, beryllium chloride at concentrations of 2.5, 5.0, and 10.0 µg/mL resulted in increased platelet reactivity leading to thromboxane production and platelet aggregation (Togna et al. 1997).

Following intermediate-duration exposure to beryllium parenterally administered to rats as 1.0 mg/kg of beryllium nitrate for 6 days/week for 3 weeks, hemoglobin was reduced by 12%, and zinc protoporphyrin (ZPP) increased by 82%, suggesting anemia. Further, blood aminolevulinic acid dehydratase (ALAD) activity (that produces heme) was inhibited by 18%, and urinary 5-aminolevulinic acid (ALA; coenzyme in energy production) excretion increased but only transiently (Mathur et al. 1993). Exposure to beryllium as 1.0 mg/kg of beryllium nitrate for 28 days intraperitoneally caused significant depletion of hemoglobin by 20% and serum albumin by 41% (Nirala et al. 2008). Rats exposed once intramuscularly to beryllium as 50 mg/kg beryllium nitrate were characterized as having macrocytic anemia and exhibited significant decreases in hemoglobin percentage over the observed days (Sharma and Shukla 2000).

2.8 MUSCULOSKELETAL

Irregularities in bone morphologies were observed in rats after oral exposure to beryllium carbonate (30–345 mg/kg/day). However, dog and rat studies using beryllium sulfate (1–31 mg/kg/day) did not find any musculoskeletal effects. No effects were observed in humans. No studies were located regarding musculoskeletal effects in humans or animals after inhalation or dermal exposure to beryllium or its compounds.

Early studies indicate that rats fed large amounts of beryllium carbonate in the diet developed rickets. Rats exposed to 35–840 mg beryllium/kg/day as beryllium carbonate for an intermediate duration developed rickets (Gorlin 1951; Guyatt et al. 1933; Jacobson 1933; Kay and Skill 1934). The fragility of the bones increased with increasing concentrations of beryllium. Although there are several methodological deficiencies in these studies (e.g., 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.

Beryllium rickets are thought to be secondary to phosphorus deficiency rather than a direct effect on the bone. Beryllium in the gut can bind to soluble phosphorus compounds to form insoluble beryllium phosphate, thus decreasing the amount of soluble phosphorus compounds available for absorption (Kay and Skill 1934).

No bone effects were observed in dogs chronically exposed to 12 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet (Morgareidge et al. 1976). Chronic-duration exposure to 31 or 12 mg beryllium/kg/day as beryllium sulfate tetrahydrate did not cause morphological abnormalities in the muscle tissue of rats (Morgareidge et al. 1975) or dogs (Morgareidge et al. 1976), respectively. However, Drolet-Vives et al. (2009) nose-only exposed groups of C3H/HeJ mice to filtered air (n=7) or 250 μg/m^3 beryllium metal with a fine (mass median aerodynamic diameter [MMAD] 1.5 μm; n=40) or large (MMAD 4.1 μm; n=35) particle size for 6 hours/day, 5 days/week for 3 weeks, resulted in beryllium accumulation in bone. Those exposed to finer particles and those exposed for longer time periods had more accumulation in bone.

2.9 HEPATIC

Limited human studies and conflicting results in animal studies for hepatic effects from beryllium exposure preclude conclusive remarks regarding hepatic effects. No studies were located regarding hepatic effects in humans after oral or dermal exposure to beryllium or its compounds.

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 via serum glutamic oxaloacetic transaminase (also called aspartate aminotransferase or AST), or serum glutamic pyruvic transaminase (also called alanine aminotransferase or ALT). 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).

Acute-duration exposure to 13 mg beryllium/m^3 as beryllium hydrogen phosphate caused hepatocellular degeneration in monkeys (Schepers 1964). Hepatocellular degeneration was also observed in monkeys exposed to 0.184 mg beryllium/m^3 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/m^3 as bertrandite or beryl ore did not result in histological evidence of hepatic damage (Wagner et al. 1969). However, 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/m^3 as beryllium oxide (Hall et al. 1950). Histological examination of rats exposed to 0.035 mg beryllium/m^3 as beryllium sulfate tetrahydrate 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, or monkeys chronically exposed to beryllium oxide as bertrandite or beryl ore (Wagner et al. 1969). Evidence of hepatic effects from oral exposure to beryllium compounds is mixed. A few studies indicated that beryllium exposure has few, if any, effects on the liver, while other studies reported observations to the contrary.

Biochemical analysis of the lipid and protein contents of liver homogenates from rats exposed to 0.2 mg beryllium/kg/day as beryllium sulfate tetrahydrate for 6–24 weeks did not reveal any hepatic damage (Reeves 1965); however, histological examination was not performed. Other studies suggest that intermediate-duration exposure to beryllium alters hepatic enzymes. Oral exposure of beryllium as 1 mg/2 mL/kg of beryllium nitrate daily for 28 days caused significant increases in AST, ALT, lactate dehydrogenase (LDH), and gamma-glutamyl transpeptidase levels after beryllium administration; however, serum alkaline phosphatase was decreased. Substantial alteration of the ultra-morphology of the liver was observed as well (Nirala and Bhadauria 2008).

Similar observations were reported by Sharma and Shukla (2000). Beryllium administered once as 50 mg/kg of beryllium nitrate intramuscularly induced changes in AST and ALT levels, as much as 51 and 62%, respectively, and in combination with severe lesions in the liver. Histopathology examination revealed hypertrophy of hepatocytes including vacuolization, swollen Kupffer cells, deformed nuclei, and increased chromatin (Sharma and Shukla 2000).

Acute-duration exposure to beryllium as 86 mg/kg of beryllium chloride administered orally increased AST and ALT serum levels 1.9 and 1.5 times greater than controls, respectively, indicating liver damage. Liver LDH enzyme levels were also elevated 1.9 times as much as controls and the measurement of the reaction of carbonyl groups with dinitrophenylhydrazine suggest oxidative damage to liver proteins, which may lead to functional damage (El-Beshbishy et al. 2012). Dogs fed 12 mg beryllium/kg/day as beryllium sulfate tetrahydrate for 143–172 weeks (Morgareidge et al. 1976) and rats fed 31 mg beryllium/kg/day as beryllium sulfate tetrahydrate for 2 years (Morgareidge et al. 1975) did not 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).

Other available animal studies where beryllium was administered intraperitoneally, intravenously, or intramuscularly suggest beryllium has hepatotoxic potential.

Rats exposed to beryllium as 1.0 mg/kg beryllium nitrate daily for 28 days had AST and ALT levels elevated by 77 and 90%, respectively, marking damage to the liver (Nirala et al. 2008). Other hepatic enzymes, including alkaline phosphatase have been observed to decrease between 28 and 68%, indicating damage to the liver (Mathur et al. 1993, 2004). With altered enzymatic levels, Mathur et al. (1993) also observed severe lesions and hepatocytes exhibiting cytoplasmic granulation and debris accumulation. Sharma et al. (2000) reported in an intermuscular injection study similar alkaline phosphatase activity where decreases between 29 and 48% were observed 3 and 7 days post exposure, respectively.

Intravenous injection studies have shown a correlation between the rise in acid phosphatase and beryllium concentration in the liver (Mathur et al. 1987a; Witschi and Aldridge 1968). Acid phosphatase levels of rats acutely exposed to beryllium as 50 mg/kg of beryllium nitrate increased on days 2–30 after exposure (Mathur et al. 1987a; Sharma et al. 2000). Changes in levels of acid phosphatase may indicate the initial start of damage or disease processes in the liver.

Levels of hepatic glutathione (GSH) (Mathur et al. 1993; Nirala and Bhadauria 2008) and lipid peroxidation (Mathur et al. 1993) were reported to increase; however, other studies such as Nirala et al. (2008) showed increases in hepatic lipid peroxidation but decreased levels in reduced GSH. The rise in levels of lipid peroxidation indicate cell injury leading to the generation of cytotoxic products, which can induce structural and functional changes in the cell (Nirala et al. 2008). GSH is an antioxidant that aids in preventing cell damage caused by reactive oxygen species including heavy metals. Altered GSH levels after beryllium administration indicate severe oxidative stress on the target organ.

The liver is responsible for the synthesis and metabolism of cholesterol. Acute-duration exposure to beryllium as beryllium nitrate disturbed lipid profiles, elevating triglycerides and cholesterols in the liver significantly, pointing to alterations in the metabolism function of the liver (Mathur et al. 1987a; Nirala and Bhadauria 2008; Nirala et al. 2008). Beryllium was noted to cause hypoalbuminemia (Nirala et al. 2008).

2.10 RENAL

Monkeys that were acutely exposed had renal effects from high amounts of inhaled beryllium ($\geq$8.3 mg/m^3) or from the combination of pre-sensitization and lower dose exposure ($\geq$0.184 mg/m^3). Intermediate- and chronic-duration exposure at doses up to 0.62 mg beryllium/m^3 did not result in renal effects for monkeys, rats, or hamsters. Limited human studies showed potential renal effects. No studies

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

Kidney stones were observed in 10% of the cases of CBD collected by the Beryllium Case Registry up to 1959 (Hall et al. 1959). 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 have been studied. No adverse renal effects were detected by urinalysis, kidney weight measurement, or histological examination in rats, rabbits, hamsters, or 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/m^3 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 beryllium sulfate tetrahydrate or beryllium fluoride at very low levels (0.198 or 0.184 mg beryllium/m^3, respectively) for 6 hours/day with durations of 7–16 days. Schepers (1964) also observed monkeys with glomerular degeneration when exposed to 13 mg beryllium/m^3 as beryllium hydrogen phosphate for 6 hours/day and 8–30 days. These concentrations were lethal to the monkeys. No histological evidence of renal damage was observed in rats exposed up to 6 days/week for 8 hours/day and 180 days to 0.035 mg beryllium/m^3 as beryllium sulfate tetrahydrate (Schepers et al. 1957).

Intermediate-duration exposure (6 months) of rats, hamsters, and monkeys to 0.210 or 0.620 mg beryllium/m^3 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/m^3 as beryllium oxide for 40 days. Urinary protein increased in dogs exposed to 0.43 mg beryllium/m^3 and rats exposed to 2.0 mg beryllium/m^3 as beryllium sulfate for 51–100 days (Stokinger et al. 1950). 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/m^3 as bertrandite or beryl ore (Wagner et al. 1969).

Few renal effects have been observed after oral exposure to beryllium. Histological examination of rats fed 31 mg beryllium/kg/day as beryllium sulfate tetrahydrate 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 tetrahydrate in the diet for 143–172 weeks (Morgareidge et al. 1976). Morphological alterations of the kidney were not observed in either sex of rats exposed to 0.6 mg beryllium/kg/day as beryllium sulfate daily for 3.2 years or of mice exposed to 1 mg beryllium/kg/day as beryllium sulfate daily for 898 days, respectively (Schroeder and Mitchener 1975a, 1975b). Female rats, however, developed a transient glucosuria (Schroeder and Mitchener 1975a).

Other available animal studies where beryllium was administered intraperitoneally or intramuscularly reported altered biochemical indices. Observed effects include acid phosphatase, alkaline phosphatase, and lipid peroxidation and decreased protein and glycogen levels in the kidney (Mathur et al. 2004; Nirala and Bhadauria 2008; Nirala et al. 2008; Sharma et al. 2000, 2002). These may be indicative of damage and oxidative stress induced by beryllium at the cellular level. Histopathology examination by Nirala and Bhadauria (2008) revealed renal damage characterized by deformed ultrastructural integrity (loosely arranged mitochondria, cytoplasmic condensation, and vacuolation). It should be noted these studies did not examine other renal endpoints aside from biochemical indices.

2.11 DERMAL

Occupational studies indicate dermal eruptions from beryllium exposure; however, the studies often have multiple exposure routes (e.g., inhalation, dermal) and therefore cannot be attributed to just one route. No studies were located regarding dermal effects in humans after oral exposure to beryllium or its compounds. Skin lesions were observed in humans and animals after dermal exposures (Table 2-3).

Several case studies involving dermal occupational exposure to beryllium have documented dermal effects. Two studies conducted skin biopsies among beryllium workers and have documented granulomas containing beryllium (McConnochie et al. 1988; Williams et al. 1988). In the Williams et al. (1988) study, 26 beryllium workers had documented skin lesions resulting from cuts and abrasions sustained at work. 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. 1988).

Dermatological abnormalities (i.e., contact dermatitis and skin ulcers) due to beryllium exposure were also reported in the case histories of 42 workers exposed to beryllium sulfate, beryllium fluoride, or

beryllium oxyfluoride (VanOrdstrand et al. 1945). The contact dermatitis cases were characterized as an edematous, papulovesicular dermatitis. Conjunctivitis occurred only as a splash burn or in association with contact dermatitis of the face. Ulceration occurred only after the skin was accidentally abraded and was predominantly seen in beryllium sulfate workers. These ulcers began as small, indurated papules surrounded by an area of erythema which later underwent necrosis.

Schuler et al. (2005) also found that beryllium oxide ceramics workers with CBD were more likely to report ulcers or small craters in the skin, compared to employees without CBD. Specifically, workers with CBD were among the 5 who reported ulcers or small craters, compared to 4 employees with CBD among 135 with no reported ulcers or craters. An allergic contact dermatitis can also occur and is most frequently caused by beryllium fluoride (Curtis 1951) (see Section 2.14). Cummings et al. (2009) reviewed cases through a survey of workers at a beryllium manufacturing plant; two workers reported dermal and respiratory symptoms and a significant decline in pulmonary function. One reported a rash and skin ulcers on their wrists and forearms within 2 weeks of beginning work in the metal production operation, and the other complained of a rash within a year of being hired; both improved upon cessation of exposure. In both cases, the rash and skin ulcers were associated with exposure to soluble beryllium compounds, particularly beryllium fluoride. Haberman et al. (1993) examined the use of beryllium dental materials that may cause allergic contact dermatitis in some patients. Signs and symptoms consistent with gingivitis, oral lichen planus, leukoplakia, aphthous ulcers, and pemphigus were observed with exposure to beryllium in dental alloys (Haberman et al. 1993).

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 tetrahydrate in the diet for 2 years (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet for 26–33 weeks (Morgareidge et al. 1976) did not indicate morphological changes.

Strupp (2011a) examined the effects of beryllium metal particle size on skin sensitization in guinea pigs and skin irritation in rabbits. No skin sensitization was observed in guinea pigs exposed intradermally to beryllium metal powder suspended in Freund's complete adjuvant. No skin irritation was observed in rabbits exposed dermally to 0.5 g of beryllium metal powder for 4 hours (Strupp 2011a). Delayed hypersensitivity reactions, as described in Section 2.14, 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; Polak et al. 1968; Zissu et al. 1996). Rats and guinea pigs also had delayed

hypersensitivity reactions upon airborne exposure with information provided in the immunological effects section.

2.12 OCULAR

There is limited information on ocular effects in humans and animals. Conjunctivitis has been noted to occur after a splash burn or in association with contact dermatitis of the face (VanOrdstrand et al. 1945). No studies were located regarding ocular effects in humans after oral exposure to beryllium or its compounds. According to a case history, twins occupationally exposed to beryllium had reduced tear secretions (McConnochie et al. 1988).

No studies were located regarding ocular effects in animals after inhalation or dermal exposure to beryllium or its compounds. 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 as beryllium sulfate tetrahydrate for 2 years (Morgareidge et al. 1975) or dogs exposed to ≤1 mg beryllium/kg/day as beryllium sulfate tetrahydrate for 143–172 weeks (Morgareidge et al. 1976). One study evaluated the effects of beryllium exposure in rabbits. Rabbits exposed to beryllium as 0.1 g of beryllium metal powder applied to the conjunctival sac of the eye showed slight redness, but after 7 days, no signs of irritation were present (Strupp 2011a).

2.13 ENDOCRINE

There are limited studies on the potential endocrine effects from beryllium exposure. A single occupational study and monkey studies observed adrenal gland changes after beryllium inhalation exposure. No effects were observed in the endocrine system after oral exposure in humans or animals. No studies were located regarding endocrine effects in humans or animals after dermal exposure to beryllium or its compounds.

One out of 17 workers exposed to beryllium in a fluorescent lamp manufacturing plant died from CBD (Hardy and Tabershaw 1946). Histological examination of the adrenal glands revealed marked hyperemia and vacuolization of cortical cells. Examination of the pancreas revealed marked hyperemia. Another worker exhibited bilateral lobe enlargement of the thyroid gland, which contained a cystic mass the size of a silver dollar.

Effects on the adrenal glands have also been observed in animals exposed to beryllium compounds. Histological examination of monkeys acutely exposed to 1.13 mg beryllium/m^3 as beryllium hydrogen phosphate or 0.184 mg beryllium/m^3 as beryllium fluoride revealed hypoplasia and hypotrophy of the adrenal glands (Schepers 1964). However, the adrenal glands of monkeys exposed to 0.196 mg beryllium/m^3 as beryllium sulfate were normal. Rats and hamsters exposed to 1–100 mg beryllium/m^3 as beryllium oxide for 30–180 minutes had increased adrenal weights (Sanders et al. 1975). The exact exposure concentrations were not specified. There were no studies available for intermediate- or chronic-duration inhalation exposures.

There is limited information on potential endocrine effects following oral exposure to beryllium. No adverse effects were observed in the adrenal glands, thyroid, pituitary, or pancreas of dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet for 26–33 weeks (Morgareidge et al. 1976) or in rats exposed to 31 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet for 2 years (Morgareidge et al. 1975).

2.14 IMMUNOLOGICAL

Alterations in lymphocytes and inflammatory responses were consistently observed in humans and animals after inhalation exposure to beryllium and its compounds. Potential immune effects from oral beryllium exposure have not been addressed. Dermal beryllium studies also indicate immune responses for humans and animals (Table 2-3).

Beryllium-sensitized cells accumulate at sites of CBD, 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 CBD (Williams and Kelland 1986). Patients with CBD 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 and improve pulmonary function (Aronchick et al. 1987; Marchand-Adam et al. 2008; Sood 2009). A retrospective cohort study of 48 subjects observed that inhalation of corticosteroids in workers with CBD showed improvements in symptoms of coughing by 58% (compared to 17% in controls), and dyspnea improved in 26% of the workers (Mroz et al. 2018).

CBD and beryllium sensitization have similar etiologies so epidemiological studies tend to look at both endpoints, and these are therefore discussed in Section 2.4 (see Table 2-5). However, the findings are highlighted in this section. Studies specifically looking at patch testing are also covered in this section.

Patch testing indicates beryllium hypersensitivity, though using soluble beryllium compounds may be sensitizing and may exacerbate the condition in patients with CBD (Cotes et al. 1983; Epstein 1983; Stoeckle et al. 1969; Tepper and VanOrdstrand 1972), contraindicating the use of patch testing in humans. The BeLPT is now the preferred test.

Beryllium Sensitization. A number of epidemiological studies have evaluated the prevalence of beryllium sensitization among workers at several types of facilities (see Table 2-5); a common limitation of most of these studies is a lack of exposure monitoring data, although some studies attempted to estimate average and/or cumulative exposure levels based on work histories and monitoring data. Beryllium sensitization is a beryllium-specific cell-mediated immune response. T-lymphocytes recognize beryllium as an antigen triggering cell proliferation, release of inflammatory mediators, and accumulation of inflammatory cells in the target organ. Beryllium sensitization can occur in the absence of CBD and in the absence of symptoms (Kreiss et al. 1989). Studies have found that the rates of beryllium sensitization vary by the type of beryllium exposure (discussed further in the cancer section).

The highest rates of beryllium sensitization were found in beryllium production workers; rates ranged from 7 to 19% (Bailey et al. 2010; Donovan et al. 2007; Henneberger et al. 2001; Kreiss et al. 1996, 1997; Newman et al. 2001; Rosenman et al. 2005; Schuler et al. 2005, 2008, 2012). Several studies have found that beryllium sensitization and disease can occur within the first year of exposure or less (Donovan et al. 2007; Newman et al. 2001; Schuler et al. 2005, 2012). Newman et al. (2001) found that 6.7% of new employees (worked in the plant for <1 year) were sensitized; all had worked for <3 months when tested and reported no previous beryllium exposure. Donovan et al. (2007) found the prevalence in workers from three facilities ranged from 13 to 15% in workers employed <1 year compared to 7.4–11% in workers employed for >1 year. Within the first year of exposure, the prevalence peaked between 4 and 8 months; the overall prevalence in workers employed for 4–8 months was 22%. No relationship between prevalence and duration of employment was found after the first year of employment. As with the Donovan et al. (2007) study, a study of rod and wire production workers found the highest prevalence of beryllium sensitization among workers with ≤1 year of exposure (13 compared to 7% overall) (Schuler et al. 2005). A study of beryllium production workers found higher prevalence in workers exposed for <4 months (16.7%) or 4–8 months (15.0%) compared to 9.8% overall (Schuler et al. 2012). Duggal et al. (2010) followed the same population as Donovan et al. (2007) for 7.4±3.1 years; no significant changes in flow rates and lung volumes were observed from baseline among the 72 current and former beryllium-sensitized workers, but diffusing capacity of the lungs for carbon monoxide dropped to 17.4% of

predicted capacity. Eight subjects (11.1%) developed symptoms typical of CBD at follow-up after 7.4±3.1 years.

Several studies provided some estimates of exposure levels associated with beryllium sensitization. Kelleher et al. (2001) expanded the results of Newman et al. (2001). The respective mean and median cumulative exposures were 6.09 and 2.93 μg/m^3-years for the cases (beryllium sensitization or CBD) and 2.27 and 1.24 μg/m^3-years for the controls. None of the cases had estimated lifetime-weighted average beryllium exposure levels of <0.02 μg/m^3; 60% of the cases had lifetime-weighted averages of >0.20 μg/m^3. In the control group, 11% of the workers were exposed to <0.02 μg/m^3, and 48% were exposed to >0.20 μg/m^3. In another study of this facility, Madl et al (2007) noted that Kelleher and associates likely underestimated historical exposures because a small number of samples were collected for each job category, contemporaneous data were not used to estimate historical exposures, and the upper end distribution of exposures were not captured.

Kreiss et al. (1996) found the highest beryllium sensitization rate among the machinists at the Rocky Flats Technology site (14.3 versus 1.2% for all other workers), where beryllium exposure levels were higher (median daily weighted average for machinists was 0.9 versus 0.3 μg/m^3 for all other jobs). Viet et al. (2000) studied the same population at the Rocky Flats facility and found that exposure to beryllium was significantly higher among the beryllium sensitization cases compared to controls (0.036 versus 0.026 μg/m^3), but there were no significant differences for cumulative exposure level (0.54 versus 0.40 μg-years/m^3) or duration of employment (13.2 versus 14.5 years).

Schuler et al. (2005) showed that the highest prevalence of beryllium sensitization was in workers in the rod and wire production area, where beryllium levels were more likely to exceed 0.2 μg/m^3. Rosenman et al. (2005, 2006) created a task exposure (amount of time spent at a task) and job exposure (daily weighted average exposure) matrix and estimated that the mean average exposure for workers at a beryllium processing facility with beryllium sensitization was 1.6 μg/m^3. Using personal air sampling data, Schuler et al. (2012) found no incidences of beryllium sensitization in workers exposed to average or peak exposure respirable beryllium levels of <0.04 μg/m^3 and that the prevalence of beryllium sensitization increased with increasing beryllium levels.

A relationship between beryllium exposure level and beryllium sensitization is supported by a study of workers at a beryllium processing facility that initiated a program to control beryllium exposure (Bailey et al. 2010). Beryllium sensitization was confirmed in 8.9% of the workers employed between 1993 and

1999, compared to 3.1% of workers employed after additional exposure controls were put into place in 2000.

Deubner et al. (2001b) examined beryllium mine and milling workers at a beryllium extraction facility and found the prevalence of beryllium sensitization to be 4%. 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 μg/m^3, respectively. CBD was not detected among workers only exposed at the mine to beryllium ore.

A relatively low prevalence (1.3–3.3%) of beryllium sensitization was found among workers in nuclear facilities (a weapons assembly site and at the Nevada Test Site) or construction workers at nuclear weapons facilities who were exposed to beryllium while on the job (Cloeren et al. 2022; Kreiss et al. 1993a; Mikulski et al. 2011a, 2011b; Rodrigues et al. 2008; Sackett et al. 2004; Stange et al. 1996b, 2001; Welch et al. 2004, 2013). A study by Rodrigues et al. (2008) found an association between employment duration and increased risk of beryllium sensitization. Although none of the studies provided exposure monitoring data, Mikulski et al. (2011a), Rodrigues et al. (2008), and Stange et al. (2001) noted that the risk of sensitization was significantly higher in workers involved in beryllium machining (odds ratio [OR] 3.83; 95% CI 1.04–14.03 [adjusted for age and smoking], OR 2.52; 95% CI 1.02–6.19 and OR 3.04; 95% CI 1.95–4.77, respectively) compared to workers who were not involved in beryllium machining. A similar rate of beryllium sensitization (1.1%) was found in beryllium alloy workers (Stanton et al. 2006).

Low prevalences (0.27–0.47%) of beryllium sensitization were reported in studies of aluminum smelter workers exposed to beryllium in bauxite (Nilsen et al. 2010; Taiwo et al. 2008, 2010). Beryllium concentrations measured via personal monitoring devices ranged from <0.01 to 13.00 μg/m^3 in the Taiwo et al. (2008, 2010) studies; Nilsen et al. (2010) estimated beryllium air concentrations of 0.1–0.3 μg/m^3. The investigators noted that the smelter workers wore respiratory protection, which may have decreased beryllium exposure (Nilsen et al. 2010; Taiwo et al. 2008, 2010).

Thirteen individuals with dermatitis because of occupational dermal contact with beryllium fluoride, inhalation of 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 test results were reported for pre-sensitized individuals following exposure to beryllium fluoride (5 of 13 individuals), beryllium nitrate (4 of 9 individuals), beryllium sulfate (3 of 10 individuals), or beryllium chloride (3 of

10 individuals) at a dose of 0.19 mg beryllium/mL. Nonsensitized individuals exposed to either beryllium fluoride (8 of 16 individuals) or beryllium chloride (2 of 16 individuals) developed dermatitis when exposed to 0.38 mg beryllium/mL (Curtis 1951). This demonstrated that patch testing could potentially sensitize individuals to beryllium. Negative patch test results were found for the insoluble compounds such as elemental beryllium and beryllium oxide.

Yoshifuku et al. (2012) reported that beryllium patch testing with beryllium nitrate may result in an active sensitization. The study authors reported that initial patch testing results were negative for beryllium in two cases. However, on day 10, skin reactions in the form of an erythematous lesion appeared in the area where a 1% aqueous beryllium nitrate solution had been applied. Six months later, the skin patch testing was repeated, using concentrations of 0.01, 0.1, and 1% beryllium nitrate. Both cases had positive reactions appear for the 1% solution but not the 0.01 or 0.1% solutions. Due to the potential for an active sensitization, the study authors recommended that beryllium patch testing be performed only when previous exposure is strongly suspected.

Bircher (2011) used skin patch testing to test for allergic responses to a series of metals, including beryllium sulfate. Three of the 87 people from a clinic in Switzerland had a positive response to beryllium, and only 1 of the 3 had an occupational exposure. One person who had a negative initial patch test was retested 2 years later and had a positive patch test for beryllium, despite not having additional exposure to beryllium during the 2-year period. Bircher (2011) suggested that this person was sensitized to beryllium during the initial patch test and does not recommend use of skin patch testing for beryllium, as there is the potential for inadvertent sensitization from the patch test.

Skin patch testing in three individuals with CBD with beryllium sulfate resulted in strongly positive reactions that were characterized by erythema, induration (tissue hardening), and vesicles (Fontenot et al. 2002). Mild to moderate spongiosis involving the lower layers of the epidermis and focal edema of the papillary epidermis were observed in skin biopsy samples obtained 96 hours after exposure. A second skin biopsy taken from the three individuals 2–5 weeks post exposure showed the presence of a noncaseating granuloma; the spongiosis and edema had resolved.

Toledo et al. (2011) reported 12 cases of positive results of skin patch testing with beryllium chloride, all of which were delayed responses. The study authors suggested that due to the delayed reaction, readings should be taken on day 7 or later, in order to ensure accurate results (Toledo et al. 2011). Chaudhry et al. (2017) subjected 87 individuals to skin patch testing with an aqueous solution of 1% beryllium sulfate

tetrahydrate and noted that 3 of the 87 individuals had no reaction at day 5 but did react by day 7 or later; 1 had a strong reaction and 2 had weak reactions. The results reported by Toledo et al. (2011) and Chaudhry et al. (2017) suggest that delayed readings may help to identify reactions to beryllium that may be missed by earlier readings.

In lymphocyte proliferation studies, 0.5 M beryllium sulfate (Tinkle et al. 2003) and 2.5% beryllium sulfate tetrahydrate (Basketter et al. 1999) resulted in increases in beryllium-stimulated cell proliferation in the lymph node cells and/or peripheral blood mononuclear cells of beryllium-exposed mice. In another experiment (Tinkle et al. 2003), beryllium oxide in petrolatum was applied to the backs of mice for 24–30 hours; 6 days later, all mice were challenged with a single application of beryllium sulfate applied to the ear. The challenge test resulted in increased murine ear thickness, as compared to the control group.

Studies have quantified the levels of T cells in lungs of patients exposed to beryllium and observed that beryllium induces an immune response in the lungs and suggests a high degree of compartmentalization of lymphocytes in the lungs (Fontenot et al. 2002; Rossman et al. 1988; Saltini et al. 1989). No histopathological lesions were observed in the spleen, lymph nodes, or thymus of rats chronically exposed to 131 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet (Morgareidge et al. 1975) or in dogs exposed to 12 mg beryllium/kg/day as beryllium sulfate tetrahydrate in the diet for up to 33 weeks (Morgareidge et al. 1976).

Kim et al. (2013) evaluated the effects of short-term exposure to beryllium on the immune system of workers in a Korean manufacturing plant. T-lymphocytes, B cells, and tumor necrosis factor α (TNF-α) levels were measured in serum samples collected from 43 exposed workers. The exposure time for the workers was <3 months, and the mean ambient beryllium levels varied depending on type of work: molding (3.4 $\mu g/m^3$), grinding (112.3 $\mu g/m^3$), and sorting (2.3 $\mu g/m^3$). After a process change, ambient levels were <0.1 $\mu g/m^3$. Decreased CD95 lymphocyte levels were found in workers, as compared to controls, although after controlling for age, sex, smoking, and drinking, no alterations were found. However, beryllium exposure did affect the total lymphocyte levels. Limitations of this study, including the small sample size and a relatively small range of beryllium exposures, potentially precluded finding a correlation between exposure and immune response. The study authors suggested that short-term exposure to beryllium may not result in an immune response.

Immunological effects have also been observed in animals after inhalation exposure to beryllium. Beagle dogs were exposed to beryllium oxide calcined at either 500 or 1,000°C to achieve either high or low

initial lung burdens. There were 14 dogs at each calcination temperature for the low initial lung burden and eight dogs in the high initial lung burden for each calcination temperature. There were also four controls. Dogs exposed to 10 mg beryllium/m^3 as beryllium oxide had a greater immune response to beryllium oxide calcined at 500°C than at 1,000°C, due to the greater solubility of the 500°C calcined beryllium oxide (Haley et al. 1989). The dogs exposed to beryllium oxide calcined at 500°C had higher cell counts in the BAL 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 1.13 mg beryllium/m^3 or for 30 days to 0.198 mg beryllium/m^3 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 7–10 days to either 0.198 or 0.184 mg beryllium/m^3 as beryllium sulfate or beryllium fluoride, respectively, revealed marked hyperplasia of the lymph nodes, typical of immune activation.

Similar *in vivo* and *in vitro* immunological effects have been observed in other animals exposed to beryllium. Rats and guinea pigs exposed to 0.5 mg beryllium/m^3 as beryllium nitrate for 10 weeks had inflammation typical of delayed hypersensitivity, as assessed by skin tests and BeLPTs (Stiefel et al. 1980). When lymphocytes from naïve controls and beryllium-exposed animals were exposed *in vitro* to beryllium salts, they showed increased proliferation rates greater than those of the controls (Stiefel et al. 1980). Gross and histological examination of the thymus and spleen of rats, hamsters, and monkeys exposed to 0.21 or 0.62 mg beryllium/m^3 as bertrandite or beryl ore, respectively, for 6–23 months revealed no pathological alterations (Wagner et al. 1969).

Salehi et al. (2009) reported significantly higher CD4 and CD8 counts in splenic mononuclear cells in exposed mice than in the control group, a lower percentage of CD19 (a marker for B cells), increased expression of cytotoxic $CD8^+$ T cells and $CD4^+$ T helper cells, and an increase in interferon-gamma (IFN-γ) in mice exposed for three weeks to fine (285±32 μg/m^3) or inhalable (253.3±31 μg/m^3) beryllium metal particles. However, the statistical significance of these results is questionable, as the number of mice sacrificed does not match with the number of mice reported in the results, and the study authors did not provide an explanation for the discrepancy in the number of reported mice. Therefore, this study is

not included in the LSE tables. Although significant differences in the results of BeLPT testing were found between the beryllium-exposed mice and controls, the concentration (100 µmol) of beryllium sulfate used in the BeLPT test proved toxic to most of the murine cell cultures, indicating that murine cell cultures may not be a good model for human toxicity.

Both IRSST (2012) and Muller et al. (2011) reported significant increases in the expression of IFN-γ, $CD4^+$, and $CD8^+$ and a decrease in CD19 expression in splenic mononuclear cells in mice exposed, nose only, to beryllium metal, beryllium oxide, or beryllium aluminum for 3 weeks. Except for IFN-γ, which was greater in beryllium-oxide-exposed mice compared to beryllium-metal-exposed mice, there were no differences between the beryllium groups. Significantly higher percentages of $CD4^+$ and $CD8^+$ lymphocytes were observed in mice exposed to fine beryllium aluminum particles compared to mice exposed to larger beryllium aluminum particles. This study is not included in the LSE tables due to discrepancies in the total reported number of tissue samples.

Muller et al. (2010) also nose-only exposed groups of 30 C3H/HeJ mice to HEPA filtered air (same control group as fine particle study described above), beryllium metal (MMAD of 1.50±0.12 µm), beryllium oxide (MMAD of 0.41±0.03 µm), or beryllium aluminum (MMAD 4.40±1.64 µm) intermittently for 3 weeks. The study also involved exposure to fine particles. The measured beryllium concentration was 252 $\mu g/m^3$. The mice (30/group) were sacrificed 1 week after exposure termination, and histological examinations of the lungs were conducted. Lung inflammation was observed in all three beryllium groups (Table 2-6). Comparing these results to those obtained in mice exposed to fine particles (Muller et al. 2010) suggests that exposure to fine particles resulted in more severe lung damage than exposure to larger particles. This is potentially due to dosimetric differences in delivery versus an inherent difference between the toxicity of the two types of particles.

Table 2-6. Lung Inflammation Severity Scores in Mice Exposed to Beryllium Metal, Beryllium Oxide, or Beryllium Aluminum

Sacrificed 1 week post-exposure	No inflammation	Mild inflammation	Moderate inflammation
Controls	95.5%	4.5%	0%
Beryllium metal	0%	54.5%	45.5%
Beryllium oxide	22.7%	63.6%	13.6%
Beryllium aluminum	44.4%	55.6%	0%

Table 2-6. Lung Inflammation Severity Scores in Mice Exposed to Beryllium Metal, Beryllium Oxide, or Beryllium Aluminum

Sacrificed 3 weeks post-exposure	No inflammation	Mild inflammation	Moderate inflammation
Beryllium metal	0%	29.4%	70.6%
Beryllium oxide	0%	75.0%	25.0%
Beryllium aluminum	0%	77.8%	22.2%

Source: Muller et al. 2010, 2011

2.15 NEUROLOGICAL

No studies were located regarding neurological effects in humans after oral, inhalation, or dermal exposure to beryllium or its compounds. No studies were located regarding neurological effects in animals after dermal or inhalation 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 tetrahydrate in the diet (Morgareidge et al. 1975) or in dogs exposed to ≤1 mg beryllium/kg/day as beryllium sulfate tetrahydrate 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.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to beryllium or its compounds. No studies were located regarding reproductive effects in animals after dermal or inhalation exposure to beryllium or its compounds. Available animal studies are unclear and inconsistent on the effects of oral beryllium exposure on reproduction.

Pregnant rats acutely exposed to beryllium as beryllium nitrate (50 mg/kg) on day 13 of gestation were found to have a 71% decrease in live fetuses per litter, reduced fetal weight by 33%, and nearly 3 times more post-implantation losses than the control groups (Sharma et al. 2002). In a study where female albino rats were exposed to beryllium as 0.031 mg/kg beryllium nitrate once on days 14, 16, 18, and 20 post coitum, fetus and placenta mean weight were reduced by half. Dams were found to have

decreased body weight (Mathur and Mathur 1994). The study authors postulated that beryllium disrupts enzymes responsible for energy metabolism.

Two rodent studies evaluated the effects of beryllium on male reproductive organs. Groups of five male mice were administered 0, 93, 75, 188, or 375 mg/kg beryllium chloride via gavage for 5 days and were sacrificed (Fahmy et al. 2008). At all doses tested, there were significant increases in the percentage of abnormal sperm. Rats maintained for 2 years on diets containing beryllium sulfate tetrahydrate 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 epididymides 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.

Testicular atrophy was observed in male dogs exposed to beryllium sulfate tetrahydrate doses of 12 mg beryllium/kg/day for 26–33 weeks (Morgareidge et al. 1976). Dogs exposed to lower doses (≤1 mg/kg/day) for a longer duration (>365 days) were mated, and the pups were weaned; 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 tetrahydrate in the diet. This was conducted in a small sample of animals (five per sex per dose group).

2.17 DEVELOPMENTAL

Developmental effects of beryllium in humans are limited to cross-sectional studies or case studies after occupational exposure to beryllium or its compounds. A single oral study in dogs looked for developmental effects and found none. No studies were located regarding developmental effects in animals after inhalation or dermal exposure to beryllium or its compounds.

An infant was clinically diagnosed with Bartter syndrome, and a fecal test revealed elevated levels of beryllium among other heavy metals. His mother was occupationally exposed to beryllium-copper alloy through lead soldering for 14 years. This case study suggests that beryllium may be transferred to the infant *in utero* or through lactation (Crinnion and Tran 2010). This observation is supported by findings

from Sharma et al. (2002), who observed offspring with beryllium accumulation when pregnant rats were exposed to a single dose of beryllium as 50 mg/kg beryllium nitrate.

Shirai et al. (2010) investigated the association between maternal exposure to heavy metals during pregnancy and birth size including birth weight, length, and head circumference. Single spot urine samples were collected from 78 pregnant females. The geometric mean of beryllium was measured at 0.031 µg/g creatinine. No association was determined between beryllium and birth size; however, this absence of evidence should be interpreted cautiously. This was a cross-sectional study and limited by small sample size.

There is limited information on beryllium's potential to induce developmental effects in animals following oral exposure. As discussed in Section 2.16, the Morgareidge et al. (1976) chronic-duration dog study co-housed males and females and 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 as beryllium sulfate tetrahydrate; however, stillborn, or cannibalized pups dying within the first few postnatal days were not examined.

2.18 OTHER NONCANCER

There are 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 in Section 2.8, it is likely that these effects are due to beryllium binding to soluble phosphorus compounds causing a decrease in phosphorus absorption.

Changes in metabolic activity including energy metabolism and enzyme activity due to beryllium exposure have been reported. Mathur et al. (1987a) observed substantial decreases in blood sugar level in rats 2–10 days post-exposure to beryllium as 0.316 mg/kg beryllium nitrate. Changes in glucose and enzyme activity responsible for energy metabolism were observed for glucose-6-phosphatase, adenosine triphosphatase, and succinic dehydrogenase in pregnant and nonpregnant rats when exposed to between 0.031 and 50 mg/kg of beryllium as beryllium nitrate (Mathur and Mathur 1994; Sharma et al. 2000, 2002). Messer et al. (2000) reported beryllium ions at 0.75–12 ppm increased mitochondrial nicotinamide adenine dinucleotide (NADH) reductase activity *in vitro*. This increase in mitochondrial

function may be a compensatory response to maintain normal cellular function. No changes in succinate dehydrogenase activity were reported.

Various measures of cellular damage including lipid peroxidation and oxidative stress have been observed by El-Beshbishy et al. (2012). Catalase, responsible for the breakdown of hydrogen peroxide and the antioxidant superoxide dismutase (SOD), were found to significantly decrease in both liver and brain tissue after exposure to beryllium. Significant increases in m*alondialdehyde* (MDA), a measure of lipid peroxidation, were observed as well.

An *in vitro* study by Dobis et al. (2008) supports the oxidative damages caused by beryllium. Comparing blood mononuclear cells from subjects with CBD, subjects with beryllium sensitization, and non-beryllium exposed individuals, Dobis et al. (2008) found beryllium to significantly increase levels of oxidative stress by depleting available thiol antioxidants and generating reactive oxygen species (ROS).

2.19 CANCER

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

2.19.1 Cancer in Humans

Numerous retrospective cohort mortality studies examining workers at beryllium processing facilities have been conducted and are summarized in Table 2-7. The populations studied all have some degree of overlap, as described in Table 2-8, and many were reevaluations of earlier studies.

Table 2-7. Beryllium Facilities Included in Studies Evaluating Cancer Endpoints

Reference	Lorain, Ohio	Reading, Pennsylvania	Luckey, Ohio	Perkins (Cleveland, Ohio)[b]	St. Claire (Cleveland, Ohio)[b]	Elmore, Ohio	Hazelton, Pennsylvania	Shoemakersville, Pennsylvania	Tucson, Arizona	Chester, Pennsylvania	Delta, Utah	Four distribution centers
Bayliss et al. 1971	✓	✓	✓	✓	✓	✓	✓					
Boffetta et al. 2014		✓		✓	✓			✓	✓			
Boffetta et al. 2016	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Levy et al. 2002, 2009	✓	✓	✓	✓	✓	✓	✓					
Mosquin and Rothman 2017		✓				✓	✓					
Sanderson et al. 2001a, 2001b		✓										
Schubauer-Berigan et al. 2008		✓										
Schubauer-Berigan et al. 2011a	✓	✓[a]	✓	✓	✓	✓[a]	✓[a]					
Schubauer-Berigan et al. 2011b, 2017		✓				✓[a]	✓[a]					
Wagoner et al. 1980		✓										
Ward et al. 1992	✓	✓	✓	✓	✓	✓	✓					

[a]Facility/facilities were included in a separate/sub-analysis.
[b]Perkins and St. Claire facilities are often combined into one “Cleveland” cohort.

✓ = facility was included in the cohort for the study listed in the left-hand column.

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
Bayliss et al. 1971[c] Retrospective cohort study; n=6,818 male workers; employed during 1942–1967	Cause-specific mortality among workers compared to mortality rates for the United States	Lung cancer Digestive cancer	SMR 1.06 SMR 0.75
Boffetta et al. 2016 Retrospective cohort study from 15 facilities (8 insoluble beryllium; 7 soluble/mixed beryllium); n=16,115; employed during 1925–2008; followed until 2011	Cause-specific mortality among workers compared to mortality rates for the United States	All cancer Lung cancer	SMR • **Whole cohort: 0.93 (0.89–0.98)[a]** • Insoluble beryllium: 0.94 (0.86–1.02) • **Soluble/mixed beryllium: 0.94 (0.89–0.99)[a]** SMR • Whole cohort: 1.02 (0.94–1.10) • Insoluble beryllium: 0.88 (0.75–1.03) • Soluble/mixed beryllium: 1.09 (0.99–1.19)
Boffetta et al. 2014 Retrospective cohort study from four U.S. insoluble beryllium manufacturing facilities; n=4,950 workers (3,912 men; 1,038 women); followed through 2009	Cause-specific mortality among workers compared to mortality rates for the United States (all facilities combined) or regional mortality rates	All cancer Lung cancer Uterine cancer (females only)	SMR 1.00 (0.90–1.10) SMR: 0.96 (0.80–1.14) **SMR: 3.02 (1.22–6.23)[a]**
Levy et al. 2002, 2009 Retrospective cohort study from 7 beryllium production facilities; n=9,225 male workers; employed during 1940–1969; vital status ascertained as of 12/31/1988 (reanalyses of Ward et al. 1992)	2002: lung cancer mortality among workers compared to mortality rates from the city within which each plant is located, county rates, and U.S. rates 2009: calculated univariate and multivariate lung cancer HRs to adjust for smoking in a different way than original study (Ward et al. 1992)	Lung cancer	SMR, Lorain plant • **Compared to United States: 1.69 (1.28–2.19)[a]** • **Compared to county: 1.60 (1.21–2.07)[a]** • Compared to city: 1.14 (0.86–1.48) SMR, Reading plant • **Compared to United States: 1.24 (1.03–1.48)[a]** • **Compared to county: 1.42 (1.18–1.70)[a]** • Compared to city: 1.07 (0.89–1.28) HR, Lorain plant • Univariate: 1.36 (0.92–2.02) • Multivariate: 1.26 (0.80–1.99)

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
			HR, Reading plant • Univariate: 0.98 (0.69–1.38) • Multivariate: 1.00 (0.69–1.48)
Levy et al. 2007 Case-control study; n=142 cases; 200 matched controls within 3 years of age (reanalyses of Sanderson et al. 2001a, 2001b)	See Sanderson et al. (2001a, 2001b)	Lung cancer	OR • Cumulative: 0.99 (0.91–1.08) • Average: 1.11 (0.95–1.31) • Maximum: 1.06 (0.92–1.22)
Infante et al. 1980 Retrospective cohort study from the BCR; n=421 white male workers Subcohorts: S_{ABD}=workers entered into BCR with a diagnosis of ABD S_{CBD}=workers entered into BCR with a diagnosis of CBD	Lung cancer mortality among cohort compared to the U.S. white male population; no smoking data available for the cohort	All cancer Lung cancer	**SMR 1.53[a,c]** SMR[c] • All: 2.12 • **S_{ABD}: 3.14[a]** • S_{CBD}: 0.72
Mosquin and Rothman 2017 Retrospective cohort study from three beryllium processing plants in Ohio and Pennsylvania; n=5,436 male workers (reanalysis of Schubauer-Berigan et al. 2011a)	Beryllium exposure quartiles (μg/m^3-day [cumulative] and μg/m^3 [maximum]; adjusted for 5-day exposure period/week) Cumulative beryllium exposure: • C1 (referent): 1–<550 • C2: 550–<2,500 • C3: 2,500–<10,300 • C4: ≥10,300 Maximum beryllium exposure:	Lung cancer	SRR for cumulative exposure (no lag)[c] C2 / C3 / C4 All workers: 0.90 / 0.94 / 1.13 Tenure <1 year: 0.98 / 0.90 / 1.16 Tenure ≥1 year: 1.16 / 1.68 / 1.97 SRR for cumulative exposure (lagged 10 years)[c] C2 / C3 / C4 All workers: 0.98 / 0.94 / 1.17

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
	• M1 (referent): <10 • M2: 10–<25 • M3: 25–<70 • M4: ≥70 SRR compared to C1 or M1		Tenure <1 year | 1.01 | 0.94 | 1.18 Tenure ≥1 year | 1.58 | 1.70 | 2.16 SRR for maximum exposure (no lag)[c] | | M2 | M3 | M4 All workers | 1.87 | 1.91 | 1.59 Tenure <1 year | 1.63 | 2.24 | 1.56 Tenure ≥1 year | 2.18 | 1.39 | 1.72 SRR for maximum exposure (lagged 10 years)[c] | | M2 | M3 | M4 All workers | 1.89 | 1.92 | 1.57 Tenure <1 year | 1.64 | 2.28 | 1.57 Tenure ≥1 year | 2.17 | 1.39 | 1.68
Sanderson et al. 2001a, 2001b Case control study; n=142 lung cancer cases; 710 age-race-matched controls; follow-up through 1992	Beryllium exposure quartiles (μg/m^3-day [cumulative] and μg/m^3 [mean and maximum]; adjusted for 5-day exposure period/week) Cumulative beryllium exposure: • $Q1_{Cumu}$ (referent): ≤1,425 • $Q2_{Cumu}$: 1,426–5,600 • $Q3_{Cumu}$: 5,601–28,123 • $Q4_{Cumu}$: >28,123 Lag | Cases | Controls No lag | 4,606 | 6,328	Lung cancer	**SMR: 1.22 (1.03 to 1.43)[a]** OR for cumulative (μg/m^3-days) exposures (quartiles): Lag | Q2 | Q3 | Q4 No lag | $Q2_{Cumu}$ | $Q3_{Cumu}$ | $Q4_{Cumu}$ OR | 0.73 | 0.85 | **0.57[a]** 10 years | 809–3,970 | 3,971–20,996 | >20,996 OR | 1.38 | 1.38 | 0.92 20 years | 21–2,195 | 2,196–12,376 | >12,376 OR | **2.18[b]** | **1.89[a]** | **1.89[a]**

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects

10 years[a] | **4,057** | **2,036**

20 years[a] | **844** | **305**

Mean beryllium exposure:
- $Q1_{Mean}$ (referent): ≤11.2
- $Q2_{Mean}$: 11.3–24.9
- $Q3_{Mean}$: 25.0–34.0
- $Q4_{Mean}$: >34.0

Lag	Cases	Controls
No lag	22.8	19.3
10 years[b]	**22.6**	**12.3**
20 years[b]	**10.2**	**5.3**

Maximum beryllium exposure:
- $Q1_{Max}$ (referent): ≤17.0
- $Q2_{Max}$: 17.1–25.0
- $Q3_{Max}$: 25.1–71.5
- $Q4_{Max}$: >71.5

Lag	Cases	Controls
No lag	32.4	27.1
10 years[b]	**30.8**	**16.1**
20 years[b]	**13.1**	**6.5**

OR for mean (μg/m^3) exposures (quartiles):

Lag	Q2	Q3	Q4
No lag	$Q2_{Mean}$	$Q3_{Mean}$	$Q4_{Mean}$
OR	1.61	**1.75[a]**	1.27
10 years	9.6-23.6	23.7-32.8	>32.8
OR	**2.39****	**2.71****	**1.83[a]**
20 years	1.1-19.3	19.4-25.5	>25.5
OR	**1.92[a]**	**3.06****	1.70

OR for mean (μg/m^3) exposures (three categories):

	<2	>2–20	>20
No lag	1.00	2.10	2.23
10 years	1.00	**4.07[b]**	**4.17[b]**
20 years	1.00	**2.30[b]**	**2.19[b]**

OR for maximum (μg/m^3) exposures (quartiles):

Lag	Q2	Q3	Q4
No lag	$Q2_{Max}$	$Q3_{Max}$	$Q4_{Max}$
OR	**1.82[a]**	1.08	1.14
10 years	10.1–25.0	25.1–70.0	>70.0
OR	**3.34[b]**	**2.19[a]**	**1.92[a]**
20 years	1.1–23.0	23.1–56.0	>56.0
OR	**1.95[a]**	**2.89[b]**	1.67

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

<table>
<tr><th>Reference and study population</th><th>Exposure or comparison population information</th><th>Cancer outcomes</th><th>Effects</th></tr>
<tr><td></td><td></td><td></td><td>OR for maximum (µg/m^3) exposures (three categories):
<table>
<tr><td></td><td><2</td><td>>2–20</td><td>>20</td></tr>
<tr><td>No lag</td><td>1.00</td><td>1.85</td><td>2.22</td></tr>
<tr><td>10 years</td><td>1.00</td><td>3.89[b]</td><td>4.58[b]</td></tr>
<tr><td>20 years</td><td>1.00</td><td>2.09[a]</td><td>2.34[b]</td></tr>
</table></td></tr>
<tr><td>Schubauer-Berigan et al. 2008

Case control study; n=142 lung cancer cases; 710 age-race-matched controls; follow-up through 1992 (reanalyses of Sanderson et al. 2001a, 2001b)</td><td>See Sanderson et al. (2001a, 2001b)

ORs adjusted by birth year (BY) and by age-at-hire (AH)

BY categories: <1899, 1900–1910, 1911–1920, >1921

AH categories: <24.99, 25.0–34.99, 35.0–44.99, >45.0</td><td>Lung cancer</td><td>OR for cumulative (µg/m^3-days) exposures (quartiles):
<table>
<tr><td>Lag</td><td>Q2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>No lag</td><td>Q2$_{Cumu}$</td><td>Q3$_{Cumu}$</td><td>Q4$_{Cumu}$</td></tr>
<tr><td>OR (BY-adjusted)</td><td>0.77</td><td>0.89</td><td>0.61</td></tr>
<tr><td>OR (AH-adjusted)</td><td>0.75</td><td>0.85</td><td>0.56[a]</td></tr>
<tr><td>10 years</td><td>809–3,970</td><td>3,971–20,996</td><td>>20,996</td></tr>
<tr><td>OR (BY-adjusted)</td><td>1.27</td><td>1.23</td><td>0.83</td></tr>
<tr><td>OR (AH-adjusted)</td><td>1.24</td><td>1.18</td><td>0.78</td></tr>
<tr><td>20 years</td><td>21–2,195</td><td>2,196–12,376</td><td>>12,376</td></tr>
<tr><td>OR (BY-adjusted)</td><td>1.46</td><td>1.29</td><td>1.30</td></tr>
<tr><td>OR (AH-adjusted)</td><td>1.37</td><td>1.21</td><td>1.18</td></tr>
</table>
OR for mean (µg/m^3) exposures (quartiles):
<table>
<tr><td>Lag</td><td>Q2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>No lag</td><td>Q2$_{Mean}$</td><td>Q3$_{Mean}$</td><td>Q4$_{Mean}$</td></tr>
</table></td></tr>
</table>

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects			
			OR (BY-adjusted)	1.68	**2.02[a]**	1.33
			OR (AH-adjusted)	1.55	**1.80[a]**	1.21
			10 years	9.6–23.6	23.7–32.8	>32.8
			OR (BY-adjusted)	**2.04[a]**	**2.47[a]**	1.59
			OR (AH-adjusted)	**2.05[a]**	**2.38[a]**	1.54
			20 yrs	1.1–19.3	19.4–25.5	>25.5
			OR (BY-adjusted)	1.29	**2.14[a]**	1.19
			OR (AH-adjusted)	1.24	2.05	1.11
Schubauer-Berigan et al. 2011a Retrospective cohort study from seven beryllium processing plants in Ohio and Pennsylvania; n=9,199 male workers; 45–65 years of follow-up time; follow-up through 2005 (follow-up study to Ward et al. 1992) Subcohort from three plants with quantitative exposure measurements; n=5,436 male workers	Beryllium exposure quartiles (μg/m^3-day; adjusted for 5-day exposure period/week) Cumulative beryllium exposure: • C1 (referent): 0–< 550 • C2: 550–<2,500 • C3: 2,500–<10,300 • C4: ≥10,300 Maximum beryllium exposure: • M1 (referent): <10 • M2: 10–<25 • M3: 25–<70 • M4: ≥70 • M_{all} ≥10 SMR compared to U.S. population	Lung cancer	SMR • **Whole cohort: 1.17 (1.08–1.28)[a]** • **Lorain: 1.45 (1.17–1.78)[a]** • **Reading: 1.20 (1.04–1.37)[a]** SMR of subcohort (lagged 10 years): • **C4: 1.31 (1.03–1.65)[a]** • C4 (excluding short-term workers): 1.26 (0.97–1.61) • **C4 (excluding workers exposed to other occupational carcinogens ≥1 year): 1.48 (1.05–2.03)[a]** • **C4 (excluding professional workers): 1.30 (1.02–1.64)[a]** SMR of subcohort (unlagged 10 years): • M1: 0.83 (0.67–1.02) • **M_{all}: 1.40 (1.21–1.61)[a]** • **M_{all}: (excluding short-term workers): 1.32 (1.04–1.65)[a]** • **M_{all}: (excluding workers exposed to other occupational carcinogens ≥1 year):**			

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
			1.46 (1.24–1.71)[a] • **M_{all}: (excluding professional workers): 1.39 (1.20–1.60)[a]**
		Nervous system cancer	SMR whole cohort: 0.87 (0.58–1.24)
Schubauer-Berigan et al. 2011b Retrospective cohort study from 3 plants with quantitative exposure measurements; n=5,436 male workers (same population as subcohort of Schubauer-Berigan et al. 2011a)	Mean DWA exposure category ($\mu g/m^3$): • D1 (referent): <0.6 • D2: 0.6–<2.0 • D3: 2.0–<8.0 • D4: 8.0–<12 • D5: 12–<50 • D6: ≥50 HR compared to D1	Lung cancer	HR for all workers: • **D2: 2.29 (1.29–4.30)[a]** • **D3: 2.84 (1.54–5.49)[a]** • **D4: 5.68 (2.66–12.4)[a]** • **D5: 4.88 (2.64–9.62)[a]** • **D6: 4.13 (2.14–8.41)[a]** **Exposure-response coefficient: 0.155 (p<0.0001)[a]** HR for workers excluding asbestos-exposed and professionals: • D2: 1.30 (0.59–3.11) • **D3: 2.41 (1.06–5.82)[a]** • **D4: 7.22 (2.62–21.4)[a]** • **D5: 6.68 (2.81–18.0)[a]** • **D6: 4.80 (1.74–14.2)[a]** **Exposure-response coefficient: 0.231 (p=0.0001)[a]**

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
Schubauer-Berigan et al. 2017 Retrospective cohort study from 3 plants with quantitative exposure measurements; n=5,436 male workers; Follow-up through 2005 Two-plant cohort (plants 6 and 7) excluded plant 2; Plants 6 and 7 handled higher percentage of soluble beryllium	Mean beryllium exposure ($\mu g/m^3$–tertiles of case distribution): • $T1_{Mean}$ (referent): 0–<0.88 • $T2_{Mean}$: 0.88–<1.85 • $T3_{Mean}$: ≥1.85 Cumulative beryllium exposure ($\mu g/m^3$-days tertiles of case distribution): • $T1_{Cumu}$ (referent): 0–723 • $T2_{Cumu}$: 723–<4,211 • $T3_{Cumu}$: ≥4,211 Two-plant cohort compared to full three-plant cohort described in Schubauer-Berigan et al. 2011b	Lung cancer	HR mean beryllium exposure: • $T2_{Mean}$: 1.18 (0.63–2.19) • $T3_{Mean}$: 1.72 (0.92–3.24) Exposure-response coefficient: 0.270 (p=0.61) HR cumulative beryllium exposure: • $T2_{Cumu}$: 1.34 (0.67–2.68) • $T3_{Cumu}$: 1.68 (0.78–3.63) **Exposure-response coefficient: 0.170 (p=0.033)[a]**
Steenland and Ward 1991 Retrospective cohort study from the BCR; n=689; entry into BCR 1952-1980; followed through 1988 Subcohorts: S_{AP}=workers entered into BCR with a diagnosis of acute pneumonitis S_{CBD}=workers entered into BCR with a diagnosis of CBD	Cancer mortality rates compared to U.S. male and female population (all races)	Lung cancer	SMR • **All: 2.00 (1.33–2.89)[a]** • **Men: 1.76 (1.02–2.67)[a]** • **Women: 4.04 (1.47–8.81)[a]** • **S_{AP}: 2.32 (1.35–3.72)[a]** • S_{CBD}: 1.57 (0.75–2.89)

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
Wagoner et al. 1980[d] Retrospective cohort study; n=3,055 white male workers employed between 1942 and 1967; followed through 1975	Cancer mortality rates compared to the U.S. white male population Lung cancer mortality rates calculated for the cohort overall, by interval since onset of employment, and by duration of employment	All cancer	SMR: 1.05
		Lung cancer	SMR • **All: 1.37**[a] SMR by onset of employment (years) • <15: 0.95 • 15–24: 1.28 • **≥25: 1.85**[b] SMR by duration of employment (years) • **<5: 1.40**[a] • ≥5: 1.23
		Digestive cancer	SMR: 0.95
Ward et al. 1992 Retrospective cohort study; n=9,225 male workers employed between 1940 and 1969; followed through 1988	No occupational history data, beyond starting and ending dates of employment Lung cancer mortality rates compared to county lung cancer rates	Lung cancer	SMR: • **All: 1.26 (1.12–1.42)**[a] • **Lorain: 1.69 (1.28–2.19)**[a] • **Reading: 1.24 (1.03–1.48)**[a] • Luckey: 0.82 • Cleveland (Perkins and St. Claire): 1.08 • Elmore: 0.99 • Hazelton:1.39 SMR pre-1950 (Lorain, Reading, and Cleveland): • **All: 1.42**[b] • **Lorain: 1.69 (1.28–2.19)**[b] • **Reading: 1.26 (1.02–1.56)**[a] • Cleveland: 1.06

Table 2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints

Reference and study population	Exposure or comparison population information	Cancer outcomes	Effects
			SMR after smoking adjustment factor of 1.1323 (Lorain and Reading): • All: 1.12 • Lorain: 1.49 • Reading: 1.09

[a]p<0.05.
[b]p<0.01.
[c]CIs not reported.
[d]Study received criticism for using male mortality data for the period of 1941–1967, which may have resulted in a 10–11% underestimation of expected lung cancer deaths.

ABD = acute beryllium disease; AH = age-at-hire; BCR = Beryllium Case Registry; BY = birth year; CBD = chronic beryllium disease; CI = confidence interval; DWA = daily weighted average; HR = hazard ratio; OR = odds ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio

Bayliss et al. (1971) examined 6,818 male workers at several beryllium processing facilities in Ohio and Pennsylvania. There was a slight increase in deaths due to lung cancer in the beryllium workers (SMR 1.06). Limitations of this study include lack of analysis for potential effect of latency, elimination of over 2,000 workers due to incomplete records (e.g., date of birth), and combination of populations from several different plants into one cohort (EPA 1987; MacMahon 1994).

A subsequent study (Wagoner et al. 1980) examined 3,055 white male beryllium workers at one facility in Reading, Pennsylvania. An increase in lung cancer deaths was observed (47 versus 34.29 expected) in the beryllium workers. Increases in lung cancer deaths were found in workers with a latency period of at least 25 years (20 observed versus 10.79 expected). Increases in lung cancer deaths were also observed (17 versus 9.07 expected) in workers employed for <5 years and a latency period of at least 25 years. To assess the influence of lowering beryllium exposure concentrations, lung cancer deaths were segregated by date of initial employment (Wagoner et al. 1980). An increase in lung cancer deaths was observed in workers initially hired before 1950 (before strict beryllium controls were instituted in 1950) and a ≥25-year latency period (20 observed versus 10.76 expected). A slight increase in lung cancer deaths was also observed in workers initially employed after 1950, across latency periods (7 observed versus 4.60 expected). The study authors noted 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) noted 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) accounted 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, although 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) and MacMahon (1994) have discussed limitations of the Wagoner et al. (1980) study. Specifically, EPA (1987) noted that using male mortality data for the period of 1941–1967 resulted in a 10–11% underestimation of expected lung cancer deaths because nationwide lung cancer rates were increasing. EPA (1987) and MacMahon (1994) commented that the influence of cigarette smoking may

have been underestimated by the study authors, and EPA estimated that differences in cigarette smoking patterns would result in a 4.6–18.8% underestimation of expected deaths. EPA (1987) also asserted that one individual who died of lung cancer but did not work at the beryllium facility because he failed the pre-employment physical should not have been included in analyses. After adjusting for use of outdated mortality data and cigarette smoking, EPA (1987) estimated that the rightful omission of this worker would result in no 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 12-year latency period).

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. The SMR for trachea, bronchi, and lung cancer was 1.26 (95% CI 1.12–1.42). Analysis of mortality data for each individual plant revealed that 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 categories. 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, 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 (Ward et al. 1992). Among workers at the Lorain and Reading facilities, 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 elevated in the plants operating during the 1950s or 1960s (the Lorain plant closed in 1948). Ward et al. (1992) 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 (which included approximately 16% of the cohort and four 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. The smoking adjusted SMRs for the entire cohort, the Reading cohort, and the Lorain cohort are 1.12, 1.09, and 1.49, respectively.

In a study sponsored by Brush Wellman, Levy et al. (2002) used data from the Ward et al. (1992) study to recalculate 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; the incidence of lung cancer among beryllium workers was not substantially increased. A meta-analysis of the data indicated an increase in lung cancer risk, although the SMRs were lower than those calculated by Ward et al. (1992). IARC (2012) noted that there are several potential methodological limitations of this reanalysis (e.g., the city mortality rates used for these calculations were not published, whereas Ward et al. [1992] used only published rates).

In a similar study sponsored by industry, Levy et al. (2009) re-evaluated the lung cancer mortality data from the Ward et al. (1992) study by calculating hazard ratios (HRs) using Cox proportional regression analysis to examine potential confounders. Unlike the Ward et al. (1992) study, Levy et al. (2009) did not find substantial differences in HRs between the exposed cohorts and the reference cohorts. Additionally, no differences in the HRs between the different dates of hires (which are considered a surrogate for exposure concentration) were found.

The National Institute for Occupational Safety and Health (NIOSH) sponsored a study by Schubauer-Berigan et al. (2011a), which extended follow-up from the Ward et al. (1992) study to 2005. Lung cancer mortality was examined among 9,199 workers at seven facilities, and beryllium exposure data were assessed in four of these seven facilities (exposure data were available for 5,436 of the 9,199 workers). Beryllium exposure was assessed by estimating maximum and cumulative daily weighted average exposures for specific job operations and using these data and the amount of time each worker spent in that task to create job-exposure matrices. Elevated SMRs were found for lung cancer in workers at two of the facilities (SMR 1.45; 95% CI 1.17–1.78 at the Lorain facility and SMR 1.20; 95% CI 1.04–1.37 at the Reading facility) and all facilities combined (SMR 1.17; 95% CI 1.08–1.28). At some facilities, the lung cancer mortality rate was 64% higher than the U.S. population.

In the subcohort of workers in the facilities with monitoring data (5,436 workers), Schubauer-Berigan et al. (2011a) examined lung cancer rates for both cumulative and maximum beryllium exposure. For cumulative exposure, the lung cancer rates were higher than the U.S. population only for cumulative beryllium exposure of ≥10,300 $\mu g/m^3$-days; however, there was no increase in trend with cumulative exposure observed in the standardized rate. When short-term workers (<1 year) were excluded, the SMR

in the lowest exposure group decreased and yielded a positive trend ($4.28x10^{-8}$ lung cancer deaths per $\mu g/m^3$-day·person-year) in the standardized rate with increasing cumulative exposure (p=0.012). Trends for cumulative exposure were stronger when stratified by plant: $6.99x10^{-8}$ (p<0.0001) at the Reading plant, $3.57x10^{-7}$ (p<0.0001) at the Elmore plant, and $1.10x10^{-7}$ (p=0.13) at the Hazelton plant. Adjusting for a smoking bias factor did not substantially alter the results. For maximum exposure, lung cancer SMRs were not elevated for those within the <10 $\mu g/m^3$ exposure group but were elevated for higher exposure groups. For example, all exposure groups combined with ≥10 $\mu g/m^3$ maximum exposure demonstrated a 40% (CI 21–61%) increased risk of lung cancer compared to the general population. Maximum daily weighted average exposure ≥10 $\mu g/m^3$ was associated with a 72% increased lung cancer rate (95% CI 32–124%) compared to receiving <10 $\mu g/m^3$ exposure.

Schubauer-Berigan et al. (2011a) also examined nervous system cancers and urinary tract cancers. Findings related to these two types of cancers excluded workers employed for <1 year. No relationship between nervous system cancer and cumulative or maximum beryllium exposure were found. Associations (increased SMR and standardized rate ratio [SRR] values) between beryllium exposure and urinary tract cancer were observed in workers with maximum beryllium exposures of ≥10 $\mu g/m^3$.

Mosquin and Rothman (2017) conducted a reanalysis of the Schubauer-Berigan et al. (2011a) study, with funding provided by Materion Corporation. This reanalysis used standardization and Poisson regression to evaluate the effect of cumulative and maximum exposure, unlagged and lagged 10 years, adjusting for plant, employment tenure, and date of hire. The study authors found a modest increase in risk in the full cohort by duration of tenure, and within most subgroups defined by plant and date of hire. The study authors noted that the regression-based, point-wise confidence bands did not clearly separate risk for low versus high exposure groups, but the study authors did not report any CIs in the paper.

To address criticisms of the Ward et al. (1992) and Schubauer-Berigan et al. (2011a, 2011b) studies, NIOSH funded another study by Schubauer-Berigan et al. (2017) to evaluate whether cohort members who were exposed to lower levels of mainly insoluble forms of beryllium demonstrated an increased risk of lung cancer. The study consisted of employees from three plants (Reading, Elmore, and Hazelton) for which quantitative exposure estimates were available. From these three plants, a two-plant cohort was created (Elmore and Hazelton), which removed the larger and higher exposed plant (Reading). The exposure-years to insoluble-only beryllium were 50, 64, and 67% for Reading, Elmore, and Hazelton, respectively. After adjustment for confounders, there was a monotonic increase in lung cancer mortality across exposure categories within the two-plant cohort. The exposure-response coefficients (per ln

increase in estimated exposure) were 0.278 for mean exposure and 0.170 for cumulative exposure in the two-plant cohort, compared with 0.155 ($p<0.001$) and 0.094 ($p=0.0017$) in the full cohort, respectively. As with other studies, interpretation of the results is limited by the lack of smoking data for the full cohort and the use of an annually averaged job exposure matrix to estimate exposure.

As a follow-up to the Ward et al. (1992) 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 that 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 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 1935–1960 based on the assumption that exposure levels remained constant during this time period. However, this may have resulted in an under- or over-estimation of beryllium exposures. 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. The overall lung cancer mortality rate for the Reading plant through 1992 was 1.22 (95% CI 1.03–1.43) (Sanderson et al. 2001b), which is similar to the mortality rate of this cohort through 1988 (Ward et al. 1992). 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 (Sanderson et al. 2001b).

Sanderson et al. (2001b) found that compared to controls, a higher percentage of cases worked as general labor or in maintenance departments, where some of the highest beryllium exposures occurred; there were differences in lung cancer mortality rate when tenure was lagged 10 or 20 years to discount exposures that may not have contributed to causing cancer because they occurred after cancer induction. Exposure levels were not substantially different between cases and controls, respectively, with cumulative (4,606 versus 6,328 $\mu g/m^3$ days), average (22.8 versus 19.3 $\mu g/m^3$), and maximum exposure levels

(32.4 versus 27.1 μg/m^3), within the same order of magnitude. When the exposure was lagged 10 or 20 years, exposure levels were higher among the cases. Cumulative beryllium exposure levels were 4,057 and 2,036 μg/m^3 days for the cases and controls, respectively, when lagged 10 years and 844 and 305 μg/m^3 days, respectively, when lagged 20 years. Average exposure levels for the cases and controls were 22.6 and 12.3 μg/m^3, respectively, when lagged 10 years and 10.2 and 5.3 μg/m^3, respectively, when lagged 20 years. The maximum exposure levels were 30.8 and 16.1 μg/m^3 for the cases and controls, respectively, when lagged 10 years and 13.1 and 6.5 μg/m^3, respectively, when lagged 20 years (Sanderson et al. 2001b). Elevated ORs were observed in the 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 ORs were 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, elevated ORs were found when the average and maximum exposure levels were divided into three categories (>2, >2–20, and >20 μg/m^3) and lagged 10 or 20 years (Sanderson et al. 2001a, 2001b). In general, no relationship between duration of employment and cancer risk was found.

Sanderson et al. (2001b) also attempted to address two potential confounding variables: cigarette smoking and exposure to other chemicals. The workers were potentially exposed to several other chemicals including nitric acid aerosols, aluminum, cadmium, copper, fluorides, nickel, and welding fumes. Elevated ORs 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 assessing the possible association between smoking status and cancer risk. The study authors noted that for smoking to be a confounding variable, there would have to be an association between smoking status and beryllium exposure level; no such association was found.

In another industry-sponsored study, Levy et al. (2007) reanalyzed the data from the nested case-control study by Sanderson et al. (2001a) and criticized the log-transformation of the exposure metrics and the use of a value of 0.1 assigned to subjects having no exposure during the latency period. Using untransformed exposure metrics, Levy et al. (2007) did not find associations between lung cancer mortality and any of the exposure metrics. Levy et al. (2007) also noted that the mean ages at death, first employed, and termination were higher in the controls, as compared to the cases.

Following letters and critiques of the Sanderson et al. (2001b) study (Deubner and Kent 2007; Deubner et al. 2001a; Sanderson et al. 2001c), NIOSH funded a reanalysis of the study (Schubauer-Berigan et al. 2008). This reanalysis evaluated whether adjusting for age-at-hire and birth year (that may account for known differences in smoking rates by birth year) influenced the association between beryllium exposure and lung cancer mortality; the study also evaluated the choice of the exposure value used during the latency period (because exposure metrics were log transformed, a value of zero could not be used to account for no exposure during the latency period). Increases in the risk of lung cancer were associated with average exposure using a 10-year lag; cumulative exposure was not associated with lung cancer mortality when adjusted for birth cohort. Using a small value to avoid taking the log of zero did not reduce the magnitude of the findings.

Boffetta et al. (2014) conducted a retrospective mortality study (funded by Materion Brush, Inc.), which evaluated lung cancer in 4,950 workers (3,912 males, 1,038 females) exposed to insoluble forms of beryllium at four U.S. manufacturing facilities. Cause-specific mortality among the workers was compared to mortality rates for the United States (all facilities combined) or regional mortality rates. In the whole cohort, there were no increases in deaths from all cancer types (SMR 1.00; 95% CI 0.90–1.10) and lung cancer (SMR 0.96; 95% CI 0.80–1.14), even when the workers were divided by latency and/or start date. An increase in deaths from uterine cancer was found. Seven uterine cancer deaths were observed: two cervical cancers and five corpus cancers. The study authors noted that these cancers have very different molecular and clinical characteristics and do not have overlapping known risk factors.

In a retrospective mortality study sponsored by Materion Brush Inc., Boffetta et al. (2016) evaluated the relationship between the solubility of beryllium exposures and cancer outcomes. The cohort included 16,115 workers employed during 1925–2008 in 15 facilities (some of which have not been included in other investigations); 8 of the facilities involved exposure to insoluble beryllium, and 7 of the facilities involved exposures to soluble/mixed beryllium compounds. There were no increases in deaths from all cancer types and lung cancer when using national reference rates or state reference rates in sensitivity analyses. The study found a significant interaction between the period of hire and type of beryllium and lung cancer deaths. Lung cancer deaths were increased in workers hired prior to 1955 in soluble/mixed beryllium facilities.

In addition to these retrospective mortality studies and case-control studies of beryllium workers, NIOSH funded two studies (Infante et al. 1980; Steenland and Ward 1991). In the Infante et al. (1980) study, 421 white male workers entered the cohort between July 1952 and December 1975. The cohort included

workers in beryllium extraction and smelting, metal production, and fluorescent tube production. Mortality rates were compared to the U.S. white male population for the same period, and lung cancer (which includes trachea and bronchi cancers) was observed (7 observed compared to 2.81 expected). 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 ($p<0.05$). However, Infante et al. (1980) may have underestimated the number of expected U.S. deaths for the 1968–1975 time period by using mortality rates for 1965–1967. In an analysis of the Wagoner et al. (1980) study (described earlier) using a similar method, EPA (1987) stated that using male mortality data for the period of 1941–1967 resulted in a 10–11% underestimation of expected lung cancer deaths because nationwide lung cancer rates were increasing. The contribution of cigarette smoking to the observed increase in lung cancer deaths was not adjusted for in the NIOSH studies because no smoking data were available for the cohort. The study authors noted 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. This hypothesis suggests that an increased acute dose may be more important in whether an individual gets cancer than the length of time a person is exposed, especially to lower doses.

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 1991). The cohort consisted of 689 individuals, 66% of whom were men. Of the entire cohort, 34% had been diagnosed with ABD and 64% with CBD (2% of the subjects had unknown disease type). The mortality rates were compared with that of the U.S. population after stratification by age, race, sex, and calendar time. Increases in lung cancer mortality were observed among the beryllium workers (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 ABD (SMR 2.32; 95% CI 1.35–3.72) than those with CBD (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 ABD) contributes to the development of lung cancer. In his review of the Steenland

and Ward (1991) study, MacMahon (1994) disagreed with the investigators that the adjustments made to account for the smoking confounding factor were adequate.

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 from lung cancer, included employees in the beryllium industry who were not actually exposed to beryllium (e.g., salesmen, clerks), or used inappropriate controls. Studies by Ward et al. (1992), Steenland and Ward (1991), Sanderson et al. (2001a), and Schubauer-Berigan et al. (2008, 2011a, 2011b) have addressed many of these issues and provide strong data on the carcinogenic potential of beryllium in humans. It is noted that most of the occupational exposure studies did not consider possible differences in the carcinogenic potential of different beryllium compounds (i.e., exposure to insoluble beryllium and soluble/mixed beryllium). HHS (NTP 2021) and IARC (2012) have concluded that beryllium is a human carcinogen. EPA (IRIS 2002) classified inhaled beryllium as a probable human carcinogen (group B1) and that the carcinogenic potential of ingested beryllium cannot be determined. IARC (2012) noted that several aspects of the Ward et al. (1992), Sanderson et al. (2001b), Steenland and Ward (1991), and Schubauer-Berigan et al. (2008) studies support the conclusion that beryllium is a human carcinogen. In particular, IARC (2012) noted: (1) the consistency of lung cancer excess in most of the locations; (2) greater excess cancer risk in workers hired prior to 1950 when beryllium levels were much higher than in subsequent decades; and (3) the highest risk of lung cancer in individuals with ABD and at the facility with the greatest proportion of ABD. In addition, the nested case-control studies found evidence for an exposure-response relationship that was strongest when using the 10-year lag average-exposure metric.

2.19.2 Cancer in Animals

Some beryllium compounds are carcinogenic in animals exposed via inhalation. A single nose-only exposure to 410–980 mg/m^3 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/m^3 as beryllium sulfate tetrahydrate 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/m^3 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/m^3 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 mg beryllium/m^3 as beryllium oxide or at 12 months in rats exposed to 0.0547 mg beryllium/m^3 as anhydrous beryllium sulfate (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/m^3 as beryllium sulfate tetrahydrate (Reeves et al. 1967). No increases in neoplastic lesions were observed in the lungs of dogs and monkeys exposed for three 30-minute monthly exposures to 3.30–4.38 mg beryllium/m^3 as beryllium oxide (Conradi et al. 1971). 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).

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 cell carcinomas were observed in male rats exposed to 0.3 or 2.8 mg beryllium/kg/day as beryllium sulfate tetrahydrate 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 cell carcinomas 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 tetrahydrate in the diet for up to 33 or up to 172 weeks, respectively (Morgareidge et al. 1976).

2.20 GENOTOXICITY

The genotoxicity of beryllium has been studied in *in vivo* animal models and *in vitro* cultures of microorganisms and mammalian cells. A summary of the genotoxic activities is provided in Table 2-9. The results of genotoxicity assays of soluble beryllium compounds are inconsistent. Negative results were reported for beryllium nitrate using *Salmonella typhimurium* (Arlauskas et al. 1985; Endo et al. 1991; Kuroda et al. 1991). On the other hand, beryllium sulfate was found to be mutagenic using *Bacillus subtilis* (Kanematsu et al. 1980), but results were negative when mutagenicity was evaluated

using *S. typhimurium* (Ashby et al. 1990; Rosenkranz and Poirier 1979; Simmon 1979; Yamamoto et al. 2002) and in *Saccharomyces cerevisiae* (Simmon 1979).

Table 2-9. Genotoxicity of Beryllium and Its Compounds *In Vitro*

Species (test system)	Endpoint	With activation	Without activation	Reference	Compound
Prokaryotic organisms					
Salmonella typhimurium	Gene mutation	–	–	Arlauskas et al. 1985; Ashby et al. 1990; Endo et al. 1991; Kuroda et al. 1991; Rosenkranz and Poirier 1979; Simmon 1979; Strupp 2011a; Yamamoto et al. 2002	Beryllium sulfate Beryllium nitrate Beryllium chloride Beryllium oxide Beryllium metal
S. typhimurium	Gene mutation	No data	–	Arlauskas et al. 1985; Tso and Fung 1981	Beryllium ion Beryllium nitrate
Bacillus subtilis	Gene mutation	No data	+	Kanematsu et al. 1980	Beryllium sulfate
Escherichia coli	Gene mutation	No data	+	Taylor-McCabe et al. 2006; Zakour and Glickman 1984	Beryllium chloride Beryllium sulfate
Photobacterium fischeri	Gene mutation	No data	+	Ulitzur and Barak 1988	Beryllium chloride
Eukaryotic organisms					
Fungi					
Saccharomyces cerevisiae	Gene mutation	No data	–	Simmon 1979	Beryllium sulfate
Mammalian cells					
Chinese hamster ovary K1-BH4 cell	Gene mutation	No data	+	Hsie et al. 1978	Beryllium sulfate
Chinese hamster V79 cells	Gene mutation	No data	+	Miyaki et al. 1979	Beryllium chloride
Chinese hamster V79 cells	Gene mutation	–	–	Strupp 2011a	Beryllium metal
Rat hepatocytes	DNA-repair	No data	–	Williams et al. 1989	Beryllium sulfate
Chinese hamster ovary cell	Chromosomal aberrations	No data	–	Brooks et al. 1989	Beryllium sulfate
Chinese hamster CHL cells	Chromosomal aberrations	–	–	Ashby et al. 1990	Beryllium sulfate tetrahydrate
Human lymphocytes	Chromosomal aberrations	No data	+	Larramendy et al. 1981	Beryllium sulfate
Syrian hamster cells	Chromosomal aberrations	No data	+	Larramendy et al. 1981	Beryllium sulfate
Syrian hamster embryo cells	Micronuclei formation	No data	+	Fritzenschaf et al. 1993	Beryllium sulfate

Table 2-9. Genotoxicity of Beryllium and Its Compounds *In Vitro*

Species (test system)	Endpoint	With activation	Without activation	Reference	Compound
Human lymphocytes	Sister chromatid exchange	No data	–	Andersen 1983	Beryllium sulfate
Human P388D$_1$ cells	Sister chromatid exchange	No data	+/–	Andersen 1983	Beryllium sulfate

– = negative result; + = positive result; +/– = weak result; CHL = Chinese hamster lungs; DNA = deoxyribonucleic acid

Ulitzur and Barak (1988) reported positive results for mutagenicity of beryllium chloride when evaluating *Photobacterium fischeri* using a reverse mutation assay. Furthermore, while beryllium chloride and beryllium sulfate were found to be mutagenic, the dose-response relationship was weak when the compounds were tested with *Escherichia coli* (Taylor-McCabe et al. 2006; Zakour and Glickman 1984).

In mammalian cell culture, beryllium sulfate and beryllium chloride induced gene mutation (Hsie et al. 1978; Miyaki et al. 1979) and were found to be weak mutagens by themselves, but strong comutagens when used in conjunction with 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) when tested in *E. coli* (Taylor-McCabe et al. 2006).

Beryllium metal was not found to be mutagenic or clastogenic *in vitro* in bacterial (*S. typhimurium* and *E. coli*) or mammalian gene mutation assays, with and without metabolic activation (Strupp 2011a). Overall, soluble beryllium compounds appear to be weakly genotoxic. It should be noted that differences in the positive and negative results depend on the assay conditions, concentrations of the beryllium compounds *in vitro*, and differences among bacterial strains. Inconsistent findings may be due to the physical/chemical properties of beryllium.

A chromosome aberration assay of beryllium was evaluated. Beryllium sulfate and chloride were reported to induce chromosomal aberrations in mammalian cells (Larramendy et al. 1981; Talluri and Guiggiani 1967), while other studies of beryllium sulfate gave negative results (Ashby et al. 1990; Brooks et al. 1989; Paton and Allison 1972). A study using beryllium ions observed chromosome aberrations in mammalian cells *in vitro* (Talluri and Guiggiani 1967), while other studies reported negative results (Paton and Allison 1972). Beryllium alone does not produce chromosomal aberrations, but in conjunction with x-rays, it produces a response in Chinese hamster ovary cells (Brooks et al. 1989). In

mice administered a single dose of 2187.5 mg/kg beryllium chloride via gavage, significant increases in chromosomal aberrations were observed in the bone marrow and spermatocytes; no significant alterations were observed at 93.75 mg/kg. Repeated exposure for 1, 2, or 3 weeks resulted in significant increases in chromosomal aberrations in bone marrow and spermatocytes at 293.75 mg/kg/day. The study authors noted that the percentage of induced chromosomal aberrations was dose- and duration-related (Fahmy et al. 2008). Treatment of human primary lymphocytes with beryllium metal extracts in a mammalian cell chromosome aberration assay did not reveal a genotoxic potential, neither in the presence nor in the absence of metabolic activation (Strupp 2011a).

No deoxyribonucleic acid (DNA) damage was observed when human T-lymphocyte cells were exposed to 50–5,000 µM beryllium chloride *in vitro* (Caicedo et al. 2008). No significant DNA damage or micronucleus frequencies were observed in a human B lymphoblast cell line exposed to 17.2±5.9 µg/L (17.2±5.9 ppm) beryllium metal extracts of nickel-chromium-beryllium-based dental alloy (Zhihong et al. 2011); however, dental alloys containing beryllium were found to be cytotoxic (Elshahawy et al. 2009). Significant increases in DNA strand breaks and micronuclei formation were observed in the bone marrow of mice administered >11.5 mg/kg/day beryllium chloride via gavage for 7 days; exposure to 5.75 mg/kg/day did not result in significant alterations (Attia et al. 2013).

Beryllium and its compounds were associated with significant alterations in the ability to repair damaged DNA. An unscheduled DNA synthesis assay did not induce DNA repair synthesis, indicating that beryllium metal may not directly damage DNA. A cell-transforming potential and a tendency to inhibit DNA repair when the cell is severely damaged by an external stimulus were observed (Strupp 2011a). Thus, beryllium may inhibit the repair of DNA damage and act in a cooperative manner to enhance the genotoxicity of other agents (Snow 1992). Beryllium sulfate was not found to affect DNA repair in mammalian cells (Williams et al. 1989); however, it increases misincorporation in cell-free DNA synthesis *in vitro* (Sirover and Loeb 1976). Additionally, *in vitro* studies of beryllium sulfate induced morphological transformation of mammalian cells in culture (DiPaolo and Casto 1979; Dunkel et al. 1981; Pienta et al. 1977) and enhanced viral-induced transformation of hamster embryo cells (Andersen 1983; Casto 1981; Casto et al. 1979).

Beryllium and its compounds were associated with significant alterations in gene expression associated with DNA damage repair. Beryllium appears to interfere with gene expressions associated with DNA repair. Gene expression analysis on the bone marrow cells from beryllium chloride-exposed mice showed significant alterations in genes associated with DNA damage repair. Therefore, beryllium chloride may

cause genetic damage to bone marrow cells due to the oxidative stress. The induced unrepaired DNA damage is probably due to the downregulation in the expression of DNA repair genes, which may lead to genotoxicity and eventually cause carcinogenicity (Attia et al. 2013).

Mitochondrial ribonucleic acid (RNA) expression of catalase and superoxide dismutase genes were found to significantly decline in male Wistar rats treated orally with 86 mg beryllium chloride/kg body weight for 5 consecutive days. Beryllium induced oxidative stress led to functional damages in the liver and brain and hematological abnormalities in rats (El-Beshbishy et al. 2012). The ability of beryllium to interfere with gene expression may be related to its ability to induce genotoxicity (Perry et al. 1982).

Beryllium may induce carcinogenesis by activating or inhibiting cellular enzymes, or by interfering with gene expression by inhibiting protein phosphorylation (Snow 1992). Beryllium may also decrease the reliability of DNA replication by mimicking magnesium and may reduce editing activity of DNA polymerase (Luke et al. 1975). Snow (1992) suggested that beryllium's ability to adversely impact cellular metabolism and DNA repair along with the immune response may be sufficient to result in carcinogenesis.

The differential display reverse-transcription polymerase chain reaction method was used to detect differences in expressed genes in peripheral blood monocytes from patients with CBD after stimulation with beryllium sulfate. Beryllium sulfate was found to cause mean changes of 32.5–37.4% in the gene sequencing of four berylliosis patients after examining 1,663 sequence tags. Alterations associated with beryllium sulfate were detected at 1.4–4.5%, and an exclusive association with beryllium sulfate was found in 2.6–5.7% of the analyzed sequence tags (Gaede et al. 2005). The study authors speculated that monocyte/macrophage lineage in berylliosis patients does not act in a typical beryllium-induced manner but acts in a way that might be common for various granuloma inductors.

Gene expression profiling was conducted on human peripheral blood mononuclear cells, and nearly 450 differentially expressed genes were relevant to the immunopathogenesis of CBD. A gene enrichment analysis identified the Janus kinase (JAK) signal transducer and activator of transcription (STAT) set of genes to be overly represented, so they may be associated with CBD. It should be noted that CBD shares similar pathogenic genes/pathway with sarcoidosis. The top shared pathways included cytokine-cytokine receptor interactions, and toll-like receptor, chemokine and JAK-STAT signaling pathways (Li et al. 2016).

Many DNA methylation and gene expression changes associated with CBD and sarcoidosis were tested in lung cells obtained by BAL from individuals with CBD, beryllium sensitization, sarcoidosis, and additional progressive sarcoidosis and remitting sarcoidosis. There were extensive, genome-wide, significant DNA methylation changes in those with CBD (52,860 CpGs with nominal $p<0.005$ and false discovery rate (FDR)-adjusted $q<0.05$), but not those with sarcoidosis. Genomic alterations in DNA methylation in CBD were substantial compared with those with beryllium sensitization. DNA methylation and gene expression in sarcoidosis were more genetically variable, perhaps due, at least in part, to disease status and state, such as disease progression versus remission. These data demonstrate that CBD and sarcoidosis have many similarities in DNA methylation. Analysis of progressive versus remitting sarcoidosis demonstrated that DNA methylation markers of disease progression changes are more subtle. CBD-associated epigenetic marks affect gene expression in BAL cells, suggesting the significance of epigenetic markers in lung immune response in granulomatous lung disease (Yang et al. 2019).

The carcinogenicity of beryllium sulfate was evaluated using *in vitro* mammalian cell culture. Keshava et al. (2001) reported that after 72 hours of varying concentrations of beryllium sulfate (50–200 μg), there was a concentration-dependent 9–41-fold increase in the frequency of cell morphological changes observed. In this study, beryllium sulfate induced morphological cell transformation in mammalian cells, and those cells are potentially tumorigenic. Cell transformation induced by beryllium sulfate may be attributed, in part, to the gene amplification of K-ras and c-jun, and some beryllium sulfate-induced transformed cells possess neoplastic potential resulting from genomic instability (Keshava et al. 2001).

2.21 MECHANISM OF ACTION

Beryllium can transport across the cell membranes with ease and target enzymes and receptors in the nucleus (Witschi 1970). Beryllium exposure is predominantly through inhalation, and the respiratory tract is the primary target where it evokes an immune response and affects the expression of numerous receptors, thus altering normal physiology. Genes associated with receptors like estrogen receptor α (ER) and $p16^{INK4a}$ genes were examined to evaluate whether they potentially contributed to the development of lung cancer associated with exposure to particulate beryllium metal. In this study, lung tumors were induced in F344/N rats by beryllium metal at all exposure concentrations after a single, nose-only exposure to four different exposure levels of aerosol leading to lung burdens of 40, 110, 360, and 430 μg (Belinsky et al. 2002). Methylation of the p16 and ER genes were found to be common (80 and 50%, respectively) in beryllium-induced lung tumors; both genes were methylated in 40% of the tumors.

Sequencing revealed dense methylation (~80% of all CpG sites) throughout exon 1 of the ER gene. The methylation was reported to have inhibitory effects on gene transcription; p16 genes were found to be less expressed by 30–60-fold when compared to unmethylated tumors. Therefore, beryllium-induced tumors can be, in part, explained through inactivation of the p16 and ER genes. Furthermore, the inactivation of the p16 gene by exposure to beryllium metal supports a possible role for oxidative stress and inflammation in the etiology of human lung cancer (Belinsky et al. 2002).

Gene profiling was conducted to better elucidate the molecular mechanism of cell transformation and tumorigenesis induced by beryllium. Cell lines were derived from tumors developed in nude mice injected subcutaneously with BALB/c-3T3 cells morphologically transformed with beryllium sulfate. The expression profiles of 1,176 genes, belonging to several different functional categories, were examined in the tumor cells as well as in the non-transformed control cells. It was found that expression of the cancer-related genes was upregulated; expression of genes involved in DNA synthesis, repair, and recombination were downregulated in the tumor cells when compared with the control cells. As a result, it appears that beryllium-induced cell transformation and tumorigenesis are concomitant and possibly a result of alterations in gene expression related to cancer and DNA synthesis, repair, and recombination. These alterations in gene expression may be responsible for conferring the proliferative advantage resulting in cell transformation and tumorigenesis (Joseph et al. 2001).

Because beryllium sulfate was found to be weakly mutagenic, a proteomic study was conducted to better elucidate the proteins regulated by beryllium. Thirty-two proteins were identified that were differentially regulated by beryllium sulfate and/or MNNG in the *E. coli* test system. Furthermore, a regulation of proteins involved in glycolysis, the citric acid cycle (CAC), and the pentose phosphate pathway (PPP) was observed. PPP and CAC cycle effects can be linked to oxidative stress reactions due to beryllium exposure, providing insight into beryllium's mode of action. Because the identified *E. coli* model has human homologs, this system may be helpful in identifying the mechanisms of beryllium's effect in humans (Taylor-McCabe et al. 2006).

Beryllium has been observed to behave as an inducer of premature senescence in cells causing proliferation arrest with early expression of the primary senescence markers (p53, p21, p16, and SA-β-gal) after young human fibroblasts were treated with beryllium sulfate. Chromatin immunoprecipitation experiments showed that Be^{2+} caused p53 to associate with the promoter region of the CDKN1A gene, suggesting that Be^{2+} may affect p53 activation in a manner similar to that seen during senescence. Therefore, Be^{2+} may be characterized as a potential pharmacological inducer of premature

senescence (Coates et al. 2007). Beryllium sulfate may also inhibit the growth of cancer cells with a pathway distinct from the DNA damage response (Gorjala and Gary 2010).

The role of p53, the tumor-suppressing transcription factor, in mediating beryllium-induced cytostasis was evaluated in A172 cells treated at 10 μM beryllium sulfate. Beryllium sulfate was found to cause a 300% increase in CDKN1A messenger RNA (mRNA) and a 90% reduction of CCNE2 mRNA. Upregulation of CDKN1A (cyclin-dependent kinase inhibitor p21) and downregulation of CCNE2 (cyclin E2) were associated with the p53-dependent cytostatic response. The regulation of mRNA levels for each of these two-cell cycle regulatory genes during cytostatic response requires p53 function (Gorjala et al. 2016). Beryllium fluoride at low concentrations was found to exert mitogenic effects in peritoneal macrophages by elevating $[Ca^{2+}]_{©}$, which triggers the activation of $p21^{ras}$-dependent mitogen activated protein kinases signaling cascades (Misra et al. 2002).

Glycogen synthase kinase 3β (GSK-3β) is a key regulator in signaling networks that control cell proliferation, metabolism, development, and other processes. Many investigators have noted connections between GSK-3β signaling, p53, and cellular senescence. Beryllium chloride was shown to inhibit purified recombinant GSK-3β *in vitro* (Ryves et al. 2002). Beryllium sulfate inhibits endogenous GSK-3β in cultured human cells. Exposure to Be^{2+} was about 1,000-fold more potent in producing a decrease in GSK-3β kinase activity than classical inhibitor, Li^{+}, when treating intact cells. Treating cells by adding Be^{2+} to the extracellular medium caused inhibition of GSK-3β activity in cells that express endogenous GSK-3β at normal levels. This inhibitory effect was seen in normal human fibroblasts and in glioma tumor cells (Mudireddy et al. 2014).

2.21.1 Mechanisms of Toxicity Associated with Respiratory Effects

The respiratory tract is the primary target of beryllium toxicity following inhalation exposure. In humans, CBD and beryllium sensitization are the primary noncancer effects observed. Lung cancer has also been observed in beryllium workers. In animals, the respiratory tract effects include emphysema, pneumonitis, and lung cancer.

In susceptible persons, CBD requires immune sensitization and may result in a subsequent inflammatory response due to beryllium exposure. The disease may appear after removal from exposure and can have a long latency of ≥20 years (Clayton et al. 2014; Kriebel et al. 1988a; Schubauer-Berigan et al. 2017). Sensitization is a cell-mediated response in the presence of beryllium and is currently measured by the

BeLPT. Sensitization precedes the development of clinical and subclinical CBD. Although the mechanism has not been fully elucidated, a number of studies using BAL fluid from individuals with CBD provide information on some of the components of the immune sequence. Beryllium interacts with antigen-presenting cells in the lungs (alveolar macrophages) and becomes 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 a selective expansion of certain $CD4^+$ lymphocyte subsets (Fontenot et al. 1999).

Studies in animals support a mechanism where beryllium compounds are taken up by alveolar macrophages and participate in a hypersensitivity immune response to a beryllium-containing antigen (Eidson et al. 1991). Duckett et al. (2000) reported that once beryllium sulfate is injected (subcutaneously) into the lung, it passes through the vascular wall and into the surrounding pulmonary tissues, where it is then phagocytized by macrophages resulting in acute vasculitis. Noncaseating granulomas were present in the vascular wall of the lung.

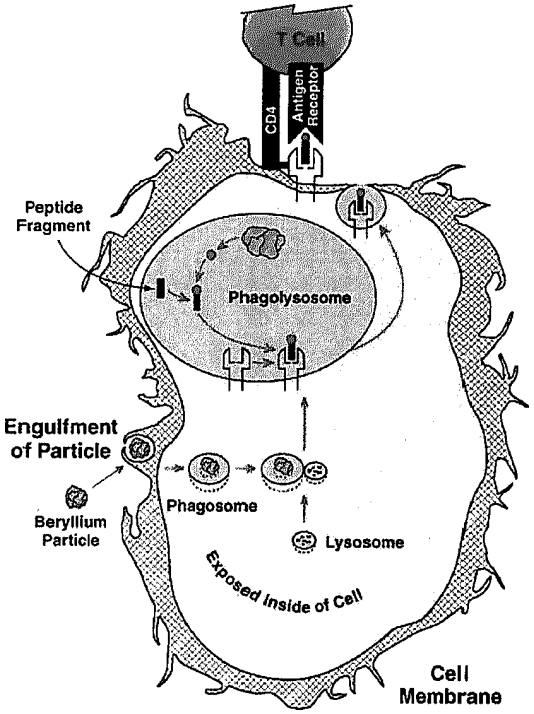
Inhalation exposure to beryllium may decrease the overall rate of lung clearance by damaging alveolar macrophages, indicating an important role of alveolar macrophages in beryllium-induced granulomatous disease as well as the rapid impairment of alveolar macrophage function by phagocytized beryllium oxide (Sanders et al. 1975).

Using the human monocyte cell line THP-1, Ding et al. (2009) studied cellular beryllium uptake and its related biological effects. A considerable amount of beryllium was incorporated into THP-1 macrophages, with amounts varying based on administered concentration, compound solubility, and exposure duration. There was a greater uptake of particulate beryllium oxide than soluble beryllium sulfate (Ding et al. 2009).

Beryllium was found to increase the $CD14^{dim}$CD16+ cells in the lung of CBD subjects. Beryllium stimulates the compartmentalization of a more mature CD16+ macrophage phenotype, and in turn, these macrophages are a source of Th1 cytokines and chemokines that perpetuate the beryllium immune response in CBD (Li et al. 2015). Using both a human and murine model of CBD, Falta et al. (2021) demonstrated that beryllium exposure resulted in a cycle of innate and adaptive immune activation. This cycle was characterized by an innate induction of inflammatory chemokine production resulting in an adaptive immune response to these chemokines presenting as neoantigens in the lung (Falta et al. 2021).

Day et al. (2005) demonstrated a mechanism of bioavailability for beryllium where the macrophage behaves both as a phagocytic and antigen-presenting cell. In this model, particles deposited in the alveolar region of the lung are phagocytized by macrophages and sequestered within phagolysosomes. Macrophages not cleared by mechanical processes remain in the alveoli, enter the lymphatic system, or are sequestered in the alveolar interstitium. Dissolved beryllium in the macrophages may then be available and drive a cell-mediated immune response (Figure 2-4). While Day et al. (2005) postulated that beryllium interacted with antigens, it is now thought that beryllium may bind to MHC molecules (Dai et al. 2010). Canine alveolar macrophages indicate similar results (Day et al. 2005).

Figure 2-4. Hypothesized Pathway for Cellular Processing of Beryllium-Containing Particles from Phagocytosis to Antigen Presentation



Source: Day et al. 2005; reprinted by permission of Taylor & Francis Ltd.

An *in vivo* study exposed mice to soluble or crystalline forms of beryllium in the trachea, which resulted in the promotion of alveolar macrophage death impacting the mobilization of immunogenic dendritic cells (Wade et al. 2018). Pulmonary exposure to beryllium sulfate and $Be(OH)_2$ promoted the release of IL-1α and DNA into the lung and neutrophil influx. These act as damage-associated molecular patterns to enhance dendritic cell function during beryllium sensitization.

Skin exposure to soluble beryllium compounds causes systemic sensitization in humans and animals. Duckett et al. (2000) and Redlich and Herrick (2008) suggest a greater research focus on the role of skin exposure in promoting beryllium sensitization and CBD. Penetration of poorly soluble particles through intact skin has been proposed as a mechanism for beryllium sensitization. Tinkle et al. (2003) suggested that the beryllium oxide particle penetrates through the outer stratum corneum layer of the epidermis to the inner immunologically active layer of the epidermis thereby starting the sensitization process. The concept of particle penetration through intact skin is controversial, as it appears that surface coatings and skin motion are important factors (Tinkle et al. 2003). The release of ions from beryllium particulate compounds through dissolution in sweat on the skin surface may be an alternative pathway for inducing beryllium sensitization in exposed individuals.

Beryllium was found to stimulate the TNF-α pathway in CBD macrophages by a transcription factor-independent mechanism and a mechanism involving an IFN-γ-induced AP-1 upregulation (Hamada et al. 2000). The antigen-specific inflammatory response to beryllium is a cell-mediated process involving cytokines. The role of cytokines in CBD has been reported in several studies.

Using alveolar macrophages that are present in BAL fluid from individuals with CBD, Bost et al. (1994) found increased levels of mRNA levels for TNF-α and interleukin (IL)-6 cytokines. TNF-α levels in the BAL fluid were also found to be elevated. Tinkle et al. (1996) reported similar results using BAL cells from CBD patients in that there were elevated levels in TNF-α, IL-6, IL-2, and IFN-γ when exposed to beryllium; IL-4 and IL-7 were not increased in these studies (Tinkle et al. 1996, 1997). The proportion of IL-10 and IL-6 release and the correlated p45 phosphorylation are factors in determining the beryllium-mediated immune response in healthy individuals (Chaudhary et al. 2004).

In CBD, as in other delayed-type hypersensitivity diseases, IL-2 is involved with the proliferation and regulation of T-lymphocyte and IFN-γ, respectively (Tinkle et al. 1997). BAL cells from subjects with CBD were reported to produce IL-2, α-sIL-2R, and IFN-γ, but not IL-4 when stimulated with beryllium sulfate. However, in the absence of beryllium sulfate stimulation, the response was the same as in controls and showed no measurable levels of IL-2, α-sIL-2R, IL-4, or IFN-γ release. While 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 was found to remain elevated in the presence of anti-IL-2 antibodies. Additionally, INF-γ levels were also decreased in the presence of anti-IL-2 antibodies, suggesting that it is also partially dependent on IL-2. Beryllium also stimulates

IL-18, and beryllium cytokine responses are nitric oxide sensitive. Nitric oxide may have a potent dampening effect on the capacity of beryllium to induce IFN-γ responses in CBD lavage cells and to stimulate lavage cell IL-18 (Barna et al. 2002).

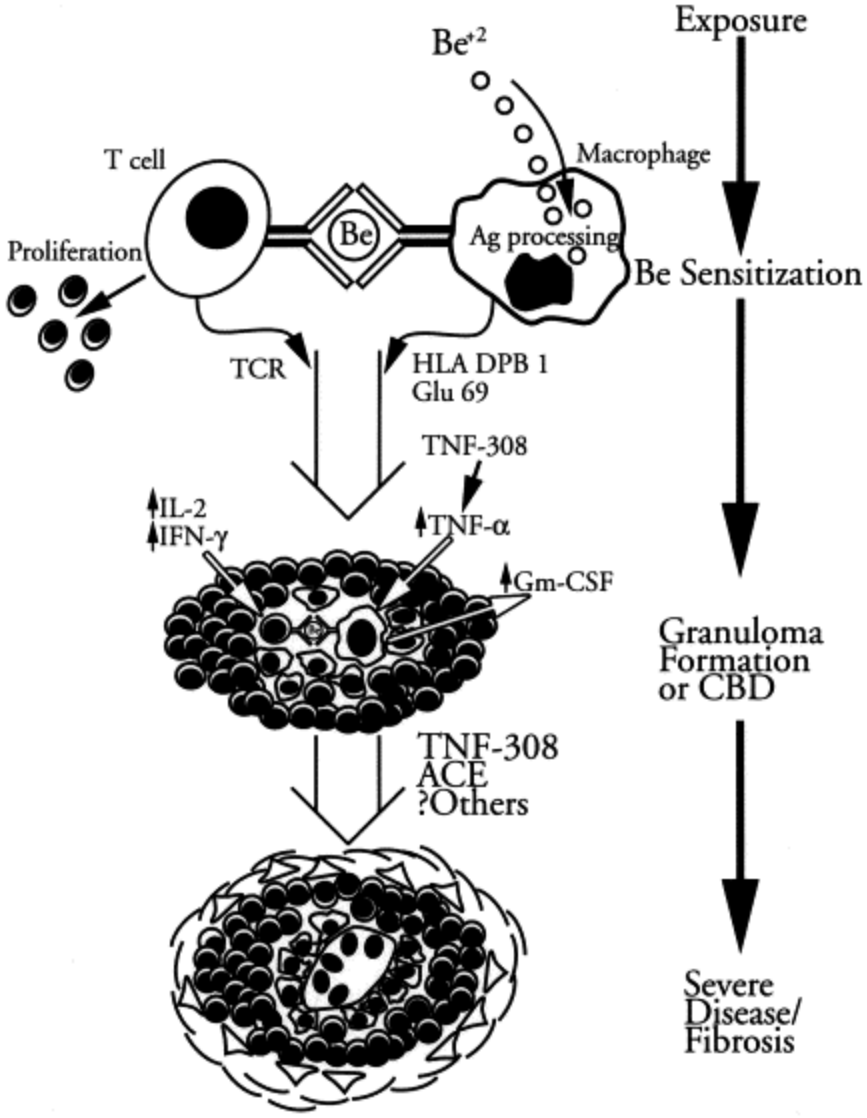
TNF-α and cytokine/chemokine genes are likely to contribute to beryllium sensitization and CBD pathogenesis. The JAK pathway and the JAK2 gene contribute most significantly to ongoing inflammation in the lung in response to beryllium. A JAK2 inhibitor significantly decreased the proliferation of peripheral blood mononuclear cells (PBMCs) in the blood BeLPT after both 10 and 100 μM beryllium sulfate treatment for 4 days; it was also found to decrease TNF-α and IFN-γ production (Li et al. 2016).

There appears to be a genetic factor associated with susceptibility to CBD. Because MHC class II molecules play a critical role in the T-lymphocyte proliferation and the development of CBD, genes related to the MHC class II (e.g., human leukocyte antigen [HLA], HLA-DPDR, DQ, DP) probably play a role in susceptibility to the disease. Analysis of the MHC class II genes shows the presence of specific HLA-DP DPB1 alleles in individuals with CBD (Richeldi et al. 1993, 1997; Wang et al. 1999). Genetic susceptibility to CBD is discussed in greater detail in Section 3.2.

Several studies have examined the mechanisms of beryllium toxicity; most of the studies focused on CBD. Figure 2-5 shows that numerous genes interact with the environment in the development of beryllium sensitization, the progression from beryllium sensitization to CBD, and its development to a more severe disease state (Maier 2002).

Several papers have extensively reviewed mechanistic data (Amicosante and Fontenot 2006; Dai et al. 2013; Falta et al. 2010; McCleskey et al. 2009; Sawyer and Maier 2011). The following discussion is taken from these reviews, supplemented with data from the primary studies; primary sources were also evaluated to verify the accuracy of the reviews.

Figure 2-5. Steps and Genetic Variants in the Development of Beryllium Sensitization, CBD, and More Severe Forms of Disease[a]



[a]This drawing outlines the steps in the development of beryllium sensitization, CBD, and more severe forms of disease, along with the potential genetic variants associated with each of these steps. Some individuals who are exposed to beryllium develop sensitization after beryllium is internalized and then processed and presented in the context of class II MHC to T cells with appropriate T cell receptors. These T cells respond by proliferating to beryllium. The class II MHC DPB1 with a glutamic acid at position 69 (Glu69) is a risk factor for sensitization. Following the development of sensitization, some individuals develop an inflammatory response to beryllium in the lung, characterized by IFN-γ, IL-2, and TNF-α production along with the formation of granulomas. Beryllium-stimulated TNF-α production is associated with the -308 A TNF-α promoter variant.

CBD = chronic beryllium disease; IFN = interferon; IL = interleukin; MHC = major histocompatibility; TNF = tumor necrosis factor

Source: Maier 2002; reprinted with permission from Elsevier

CBD is a granulomatous lung disease that is characterized by an accumulation of beryllium-specific, $CD4^+$ T cells. Originally, beryllium was believed to behave like a traditional hapten (Clayton et al. 2014). However, Clayton et al. (2014) reported that this is not the case, as beryllium binds in an MHC complex and changes the peptide binding properties of this immune response molecule. The changes in this complex caused by beryllium binding allow it to be recognized by T cell receptors (TCRs) and initiate a hypersensitivity response (Clayton et al. 2014; Dai et al. 2013). The binding takes place with glutamic acid at codon 69 of the HLA-DP gene or at position 71 of the HLA-DPDR and forms an antigen-presenting complex (APC) (Falta et al. 2010). Bill et al. (2005) also observed that beryllium recognition was dependent on the glutamic acid at position 69 of the HLA-DP protein and position 71 of the HLA-DR protein; therefore, it was speculated that changes in this position can modify binding and affect beryllium sensitivity. Polymorphisms in this position and their impact on sensitivity to beryllium sensitization and CBD are discussed in Section 3.2.

HLA-DP alleles have also been strongly associated with CBD inflammatory T-cell-mediated lung disease caused by hypersensitivity to beryllium. Soluble HLA-DP molecules expressing βGlu69 but not HLA-DP molecules with a lysine can bind beryllium in vitro with high affinity, suggesting susceptibility to CBD (Amicosante et al. 2001; Fontenot et al. 2006).

The TCR-activated beryllium-specific $CD4^+$ T cells proliferate and secrete Type 1 helper T (Th1) cytokines such as IL-2, IFN-γ, and TNF-α. The release of Th1-type cytokines initiates macrophage activation, accumulation, and aggregation, and the development of granulomatous inflammation. A study showed that HLA-DP Glu69- and HLA-DR Glu71-expressing molecules can induce beryllium-specific proliferation and IFN-γ expression by lung $CD4^+$ T cells (Bill et al. 2005). $CD4^+$ T cells from the lungs of individuals with active CBD displayed a phenotype that demonstrated expansion of TCRs that are specific to beryllium and are compartmentalized in the lungs (Clayton et al. 2014). Most beryllium-specific $CD4^+$ T cells in blood and lung of patients with beryllium sensitization and CBD expressed an effector memory phenotype, regardless of IFN-γ or IL-2 production. The proliferation ability of $CD4^+$ T cells after exposure to beryllium depends on several factors including the maturation state of the memory T cell; this is well correlated with how severely the lungs are inflamed as mediated by the $CD4^+$ T cells (Fontenot et al. 2005). The frequency of beryllium-specific, cytokine-secreting $CD4^+$ T cells in blood was found to be significantly greater in CBD patients (Pott et al. 2005). Furthermore, Falta et al. (2013) identified peptides that can form a complex that is recognized by $CD4^+$ T cells in CBD patients. These peptides act to bind to the MCHII and beryllium.

There is also evidence to indicate beryllium-specific $CD4^+$ T cells may use a pathway other than the APC for activation. Two beryllium-specific T cells have been observed in the BAL fluid of CBD patients: cells that have the co-stimulatory CD28 molecule and cells that are CD28 negative. Beryllium-specific $CD28^+$ $CD4^+$ T cells in the blood have been reported to be sequestered in the CBD lung where CD28 expression is downregulated. The absence of CD28 molecules results in increased IFN-γ expression and decreased IL-2 secretion. $CD28^-$ $CD4^+$ T cells exhibit HLA-DP and LFA-1 co-stimulatory surface molecules and can present beryllium to other T cells. This allows for the T cell to activate and proliferate in the absence of APCs. It also appears that APCs are involved in the early stages of establishing sensitization and responding to re-exposure to beryllium (Chain et al. 2013).

Among CBD subjects with beryllium-specific CF4+ T cells in their lungs, programmed-death 1 (PD-1) protein has been found to be upregulated. PD-1 was found to be increased in BAL $CD4^+$ T cells and was also found to be highly expressed in beryllium-specific T cells in beryllium sensitization and CBD subjects. The PD-1 pathway appears to be involved in regulating the proliferation of beryllium-induced T cells. However, this pathway is not sufficient by itself to downregulate T cell function (Palmer et al. 2008).

Available data suggest that beryllium increases oxidative stress in the lungs of those with CBD by directly generating reactive oxygen species (ROS) and depleting thiol antioxidants. As a result, the elevated levels of ROS result in induced macrophage apoptosis via caspases (3-, 8-, and 9-).

Based on these mechanistic data, Sawyer and Maier (2011) proposed a pathogenic mechanism that explained the development of lung inflammation and granuloma formation in CBD, which occur during beryllium exposure and after termination. Upon exposure, macrophages and dendritic cells in the skin and respiratory tract endocytose beryllium. The HLA-DP-beryllium antigen complexes are produced as a response to the beryllium particles. In the regional lymph nodes, the APCs activate naïve T cells through a mechanism that is dependent on B7/CD28 co-stimulation proliferating to become beryllium-specific T effector memory cells. In the lungs, the $CD28^+$ T effector memory cells, along with APCs, form interstitial mononuclear cell infiltrates. Next, CD28 is downregulated, and HLA-DP and LFA-1 expression are upregulated in the beryllium-specific $CD4^+$ T cells, allowing them to self-present the beryllium antigen within the granuloma.

Persistent levels of beryllium are present in CBD lung granulomas. Even after termination of beryllium exposure, beryllium in the lung is endocytosed by granuloma macrophages, which consequently undergo ROS and caspases mediated apoptosis. Beryllium-induced, human lung-adherent macrophage apoptosis could contribute to the host's continued re-exposure to beryllium leading to chronic granulomatous inflammation (Kittle et al. 2002). These apoptotic macrophages are endocytosed by other healthy macrophages, which in turn release beryllium in a manner that promotes presentation to beryllium-specific $CD28^-$ $CD4^+$ T cells. As a result, the activated $CD4^+$ T cells further proliferate to generate increased levels of cytokines. The cytokines sustain chronic inflammation by incorporating blood mononuclear phagocytes and beryllium specific $CD4^+$ T effector memory cells into the granuloma (Sawyer and Maier 2011).

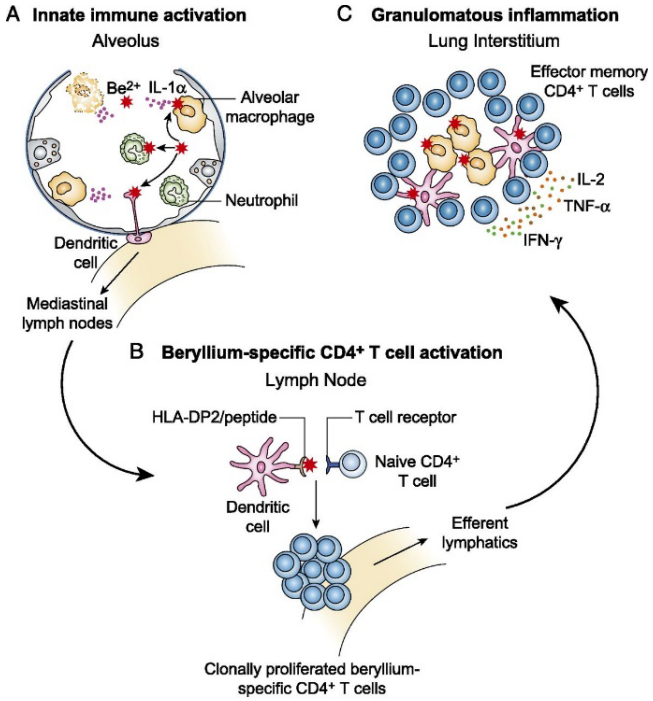
Mack et al. (2010, 2014) proposed an additional mechanism that would explain the continued lung damage after exposure to beryllium terminated. These studies found a relationship between the percentage of $CD4^+$ regulatory T cells expressing forkhead box P3 (FoxP3) in the BAL fluid and the severity of CBD disease. The study authors proposed that the dysfunction of FoxP3-expressing $CD4^+$ regulatory T cells enhanced development and perpetuation of an exaggerated immune response in the lungs (Mack et al. 2010, 2014).

Fontenot et al. (2016) reviewed the recent advances in understanding of T cell recognition of beryllium including the interaction between environmental exposure and genetic susceptibility of granulomatous inflammation. The development of CBD due to susceptibility and the interaction between the gene and environment can be explained by the latest understanding of the adjuvant properties of beryllium, the unique features of HLA-DP2, the stimulatory peptides that capture and coordinate beryllium, and structural changes caused by the formation of beryllium to the MHCII-peptide complex. Beryllium is coordinated by amino acid residues derived from the HLA-DP2 β-chain and peptide (Amicosante et al. 2009). Beryllium-specific TCR recognizes a beryllium-loaded HLADP2- peptide complex with charge and conformational changes. Findings by Clayton et al. (2014) provide a structural basis for the development of CBD. Beryllium binds internally to HLA-DP2-peptide complexes, leading to structural and biophysical changes and the creation of neoantigens. Post-translational modifications can change the formation of the peptide binding to the MHCII molecule, and this may potentially alter T cell recognition (Fontenot et al. 2016).

The study authors further reviewed the interaction between innate and adaptive immunity in the development of CBD and the generation of an inappropriate immune response in genetically susceptible

individuals. Beryllium exposure activates the innate immune system through the pattern-recognition receptors, which leads to cell death, and activation and migration of DCs to lung-draining lymph nodes. The cascade of events results in the development of an adaptive immune response that is characterized by beryllium-specific, T-helper type 1 polarized, $CD4^+$ T cells and granuloma formation in the lung. The binding of beryllium to HLA-DP molecules that possess the glutamic acid at position 69 generates a structural change to the HLA-DP peptide complex, which increases the susceptibility of CBD developing (Dai et al. 2010; Fontenot 2018). Figure 2-6 illustrates the pathogenesis of CBD.

Figure 2-6. Pathogenesis of CBD*



*(A) Beryllium exposure results in cellular death and the release of DNA and IL-1a into the lung, followed by IL-1R-dependent expression of keratinocytes and neutrophil recruitment. Ingestion of beryllium also results in dendritic cell activation and trafficking to lung-draining lymph nodes.
(B) Dendritic cells expressing HLA-DP molecules with a glutamic acid at amino acid position 69 of the b-chain present beryllium (red stars) to CD4+ T cells, resulting in T cell activation, proliferation, and trafficking to the lung.
(C) Clonally expanded CD4+ T cells in the lung are CD28 independent, express an effector memory T cell phenotype, and secrete Th1-type cytokines, including IFN-γ, IL-2, and TNF-α. The release of IFN-γ and TNF-α promotes macrophage accumulation, activation, and aggregation, resulting in the development of granulomatous inflammation. Within granulomas, HLA-DP-expressing antigen-presenting complexes present the beryllium-peptide complex to antigen-experienced CD4+ T cells.

DNA = deoxyribonucleic acid; HLA = human leukocyte antigen; IFN = interferon; IL = interleukin; TNF = tumor necrosis factor

Source: Fontenot et al. 2016

ABD is usually observed at high soluble beryllium exposure levels, has a short period of induction, and is usually resolved within a couple of months after exposure. A review by the National Research Council elaborates on the animal models of pulmonary immunotoxicity and sensitization, where the study authors concluded that the animal models are inadequate when it comes to replicating the symptoms and effects observed in human CBD (NRC 2008).