3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of cobalt. 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. Section 3.2 contains a discussion of the chemical toxicity of stable cobalt; radiation toxicity associated with exposure to radioactive cobalt (primarily ^{60}Co) is discussed in Section 3.3. The chemical properties of stable and radioactive cobalt isotopes are identical and are described in Chapter 4.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

Section 3.2 discusses the chemical toxicity of stable cobalt. Radiation toxicity resulting from exposure to radioactive cobalt is discussed in Section 3.3.

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

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

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

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

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

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

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

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

Studies have shown that soluble cobalt compounds are generally more acutely toxic than insoluble cobalt compounds. When expressed in terms of the cobalt ion for the sake of comparison, however, the differences in lethality values from the available studies are within an order of magnitude and therefore do not warrant presentation in separate LSE tables and figures. Therefore, data regarding both soluble and insoluble cobalt compounds are presented in Tables 3-1, 3-2, and 3-3.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Conclusive evidence for human deaths related to inhalation exposure to cobalt has not been reported; however, results of several studies and case reports suggest a possible relationship between exposure and deaths from lung cancer and cardiomyopathy, respectively.

In general, available cohort studies in humans have not reported a significant increase in total mortality as a result of cobalt exposure. Several studies have noted increased mortality rates resulting from lung cancer following occupational exposure to cobalt, either as a mixture of cobalt compounds (Mur et al. 1987) or as hard metal, a metal alloy with a tungsten carbide and cobalt matrix (Lasfargues et al. 1994; Moulin et al. 1998). Fatal cases of hard metal disease (Figueroa et al. 1992; Ruokonen et al. 1996) and cardiomyopathy (Barborik and Dusek 1972) believed to have resulted from occupational cobalt exposure have also been reported. However, in the majority of these and other reported occupational studies, co-exposure to other substances was common, and was unable to be corrected for in the analysis.

Cobalt inhalation can be lethal in animals if exposure is sufficiently high or prolonged. The acute LC^{50} for a 30-minute inhalation exposure in rats was 165 mg cobalt/m^3 as cobalt hydrocarbonyl (Palmes et al. 1959). Exposure to 9 mg cobalt/m^3 as cobalt hydrocarbonyl for 6 hours/day, 5 days/week for

3 months resulted in 16 deaths out of 75 rats (Palmes et al. 1959). Death was reported in rats and mice exposed to 19 mg cobalt/m^3 (but not 1.9 mg cobalt/m^3) as cobalt sulfate over 16 days, but exposure to 11.4 mg cobalt/m^3 over 13 weeks was lethal only to mice and not to rats (Bucher et al. 1990; NTP 1991). Exposure to 1.14 mg cobalt/m^3 as cobalt sulfate for 104 weeks resulted in no increase in mortality in rats and mice of either sex (Bucher et al. 1999; NTP 1998). Lethal levels for each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No data were located regarding dermal effects in humans or animals after inhalation exposure to stable cobalt. Inhalation of stable cobalt by humans and/or animals resulted in respiratory, cardiovascular, hematological, hepatic, renal, endocrine, ocular, and body weight effects. For each effect, the highest NOAEL values and all reliable LOAEL values for each species and duration category are reported in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Hard metal is a metal alloy with a tungsten carbide and cobalt matrix. It is used to make cutting tools because of its hardness and resistance to high temperature. Studies (Davison et al. 1983; Harding 1950) suggest that cobalt (and not tungsten carbide) is the probable causative agent for the respiratory effects observed in hard metal workers (see Section 3.6).

The effects of chronic occupational exposure to cobalt and cobalt compounds on the respiratory system in humans are well-documented. These effects include respiratory irritation, diminished pulmonary function, wheezing, asthma, pneumonia, and fibrosis and occurred at exposure levels ranging from 0.007 to 0.893 mg cobalt/m^3 (exposure from 2 to 17 years) (Anttila et al. 1986; Davison et al. 1983; Demedts et al. 1984a, 1984b; Deng et al. 1991; Gennart and Lauwerys 1990; Gheysens et al. 1985; Hahtola et al. 2000; Hartung et al. 1982; Kusaka et al. 1986a, 1986b, 1996a, 1996b; Nemery et al. 1992; Raffn et al. 1988; Rastogi et al. 1991; Ruokonen et al. 1996; Shirakawa et al. 1988, 1989; Sprince et al. 1988; Sundaram et al. 2001; Swennen et al. 1993; Tabatowski et al. 1988; Van Cutsem et al. 1987; Zanelli et al. 1994). These effects have been observed in workers employed in cobalt refineries, as well as hard metal workers, diamond polishers, and ceramic dish painters (painting with cobalt blue dye).

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
ACUTE EXPOSURE									
Systemic									
1	Human	6 hr	Resp		0.038	(bronchial irritation, reduced FVC)			Kusaka et al. 1986b Hard Metal
2	Rat SD-Jcl	5 hr	Resp	2.72					Kyono et al. 1992 Metal
3	Rat SD-Jcl	4 d	Resp		2.12 M	(Slight damage to respiratory tissues, assessed by electron microscopy)			Kyono et al. 1992 Metal
4	Rat	30 min	Resp	7	26	(edema)	83	(severe edema)	Palmes et al. 1959 Hydrocarbonyl
INTERMEDIATE EXPOSURE									
Death									
5	Rat	16 d 5 d/wk 6 hr/d		1.9			19	(2/5 males died)	NTP 1991 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
6	Mouse	13 wk 5 d/wk 6 hr/d		3.8			11.4	(2 males died)	NTP 1991 Sulfate
	Systemic								
7	Rat	13 wk 5 d/wk 6 hr/d	Resp		0.11	(laryngial squamous metaplasia and polyps)	0.38	(chronic inflammation of larynx)	NTP 1991 Sulfate
			Cardio		11.4	(increase in severity of cardiomyopathy)			
			Hemato		1.14[b] M	(polycythemia)			
			Renal	11.4					
			Bd Wt		11.4	(15% lower body weight in males)			
8	Rat	3 mo 5 d/wk 7 h/d	Resp		9	(lung inflamm)			Palmes et al. 1959 Hydrocarbonyl
			Hemato		9[b]	(10% increase in hemoglobin)			
			Bd Wt	9					

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
9	Mouse	16d 5 d/wk 6 hr/d	Resp	0.2	1.9 (respiratory tract inflammation)	19 (necrosis)	NTP 1991 Sulfate
			Cardio	76			
			Gastro	76			
			Musc/skel	76			
			Hepatic			19 (necrosis)	
			Renal	76			
			Dermal	76			

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
10	Mouse	13 wk 5 d/wk 6 hr/d	Resp		0.11 (larynx metaplasia)	3.8 M (acute inflam of nose) 1.14[c] F (acute inflam of nose)	NTP 1991 Sulfate
			Gastro	11.4			
			Hemato	11.4			
			Musc/skel	11.4			
			Hepatic	11.4			
			Renal	11.4			
			Dermal	11.4			
			Bd Wt		11.4 (13-20% decrease in body weight)		
11	Gn Pig (Hartley)	66 d	Resp			2.4 F (Increased lung weight, increased retention of lavage fluid)	Camner et al. 1993 Chloride

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
12	Gn Pig	3 mo 5 d/wk 7 h/d	Hemato		9[b] (5% increase in hemoglobin)		Palmes et al. 1959 Hydrocarbonyl
13	Dog	3 mo 3d/wk 7h/d	Hemato	9			Palmes et al. 1959 Hydrocarbonyl
			Bd Wt		9 (wt loss)		
14	Rabbit	4 mo 5 d/wk 6 h/d	Resp		0.4 (moderate lung inflammation)	2 (severe lung inflammation)	Johansson et al. 1987
15	Rabbit	4 mo	Resp	0.5 M			Johansson et al. 1991 Chloride
16	Rabbit	4 mo	Resp		0.6 M (Histologic alterations in pulmonary tissue; altered BAL parameters)		Johansson et al. 1992 Chloride

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
17	Pig	3 mo 5d/wk 6hr/d	Resp		0.1 (decr compliance)		Kerfoot 1975 Metal
			Cardio		0.1 (EKG changes)		
			Hepatic	1			
			Renal	1			
			Bd Wt		0.1 (decr wt gain)		
	Immuno/ Lymphoret						
18	Rat	16 d 5 d/wk 6 hr/d			19 (necrosis of thymus)		NTP 1991 Sulfate
19	Mouse	13 wk 5 d/wk 6 hr/d			11.4 (lymph node hyperplasia)		NTP 1991 Sulfate
	Neurological						
20	Rat	16 d 5 d/wk 6 hr/d			19 (congestion of vessels in brain)		NTP 1991 Sulfate
21	Mouse	16 d 5 d/wk 6 hr/d			19 (congestion of vessels in brain)		NTP 1991 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
	Reproductive						
22	Rat	16 d 5 d/wk 6 hr/d				19 M (testes atrophy)	NTP 1991 Sulfate
23	Mouse	13 wk 5 d/wk 6 hr/d			1.14 M (decreased sperm motility)	11.4 (testes atrophy- increased length estrous cycle)	NTP 1991 Sulfate
	CHRONIC EXPOSURE						
	Systemic						
24	Human	occup (occup)	Resp	0.0175			Deng et al. 1991 Metal
25	Human	occup (occup)	Resp		0.1355 (Decreased FEV1 and FVC ~10%; increased cough, sputum, dyspnea)		Gennart and Lauwerys 1990 Hard-Metal
26	Human	occup (occup)	Resp	0.0053[d]	0.0151 (Decreased FEV1, FVC increased cough and upper airway irritation)		Nemery et al. 1992 Metal
27	Human	occup (occup)	Endocr		0.05 F (Decreased thyroid volume; increases in T4 and FT4I levels)		Prescott et al. 1992 Zinc-Silicate Dye

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
28	Human	occup	Resp				0.007	(asthma)	Shirakawa et al. 1988 Hard Metal
29	Human	occup	Resp				0.051	(interst lung dis)	Sprince et al. 1988 Hard Metal
30	Human	8 yr (occup)	Resp		0.125	(Dyspnoea and wheezing)			Swennen et al. 1993 Metal
			Hemato		0.125	(Decreased red cell counts ~5%; decreased total hemoglobin ~4%)			
			Endocr		0.125	(Slight (~7%) decrease in T3 levels)			
			Dermal		0.125	(Eczema and erythema)			
31	Rat (Fischer- 344)	104 wk	Resp				0.11	(Hyper- and metaplasia of respiratory tract tissues; pulmonary fibrosis)	NTP 1998 Sulfate
32	Mouse (B6C3F1)	104 wk	Resp		0.11	(Laryngial metaplasia)			NTP 1998 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
33	Hamster	life 5d/wk 7h/d	Resp			7.9 (emphysema)	Wehner et al. 1977 Oxide
			Bd Wt	7.9			
	Immuno/ Lymphoret						
34	Human	occup			0.007 (sensitization)		Shirakawa et al. 1986a Hard Metal
35	Human	8 yr (occup)			0.125 (Increased white cell count by 19%)		Swennen et al. 1993 Metal
	Cancer						
36	Rat (Fischer- 344)	104 wk				1.14 M (alveoloar/bronchiolar neoplasms) 1.14 F (pheochromocytoma) 0.38 F (alveoloar/bronchiolar neoplasms)	NTP 1998 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
37	Mouse (B6C3F1)	104 wk				1.14 M (Combined alveolar/bronchiolar adenoma/carcinoma)	NTP 1998 Sulfate
						0.38 F (Combined alveolar/bronchiolar adenoma/carcinoma)	

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

[b] An increase in hemoglobin or red blood cells (polycythemia) is not necessarily considered an adverse effect.

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

[d] Used to derive a chronic inhalation Minimal Risk level (MRL) of 0.0001 mg Co/m3., dose adjusted for intermittent exposure, and divided by an uncertainty factor of 10 (for human variability).

Bd = body weight; Cardio = cardiovascular, d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; (occup) = occupational; Resp = respiratory; wk = week(s); yr = year(s).

Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation

Acute (≤14 days)

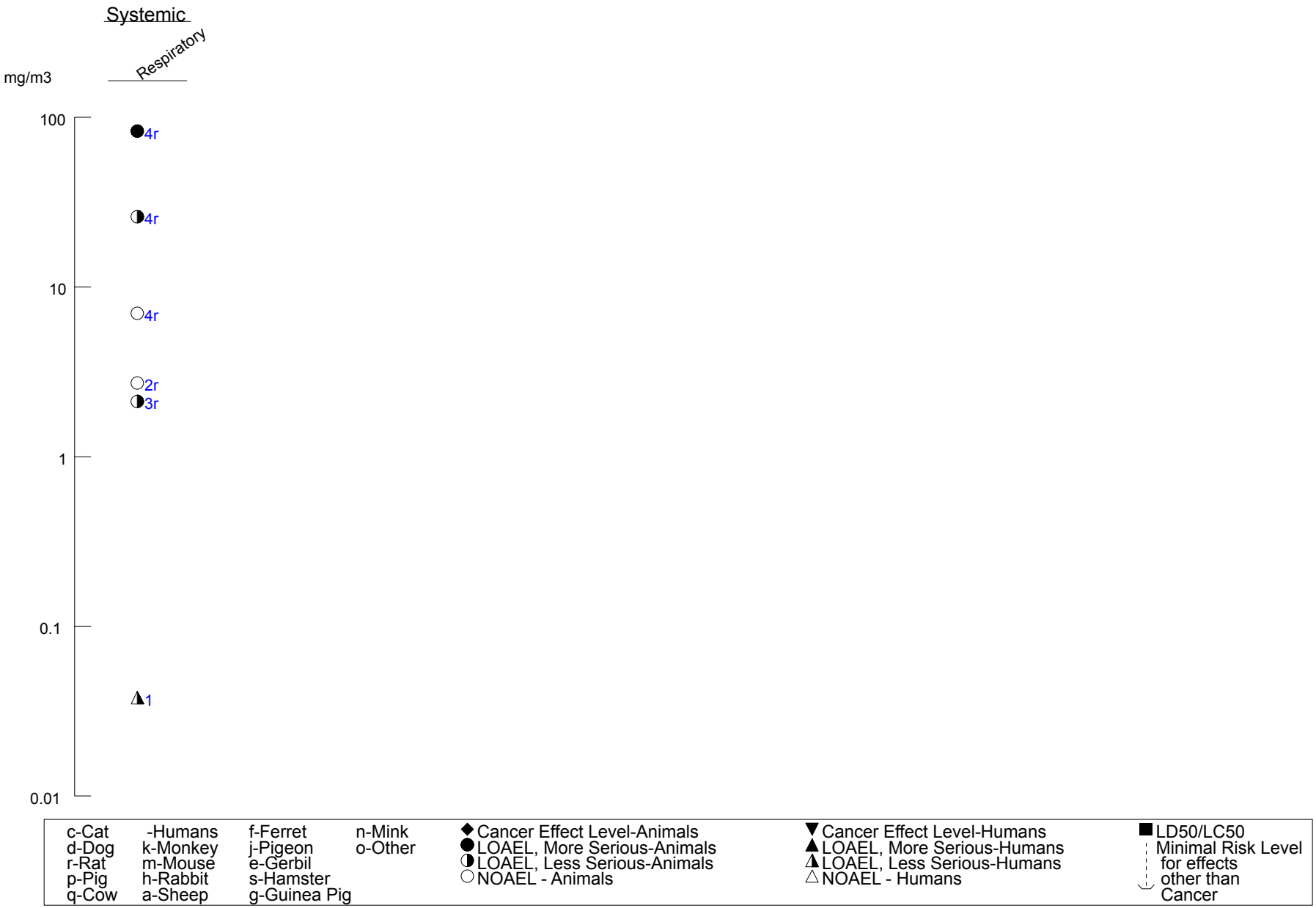


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Intermediate (15-364 days)

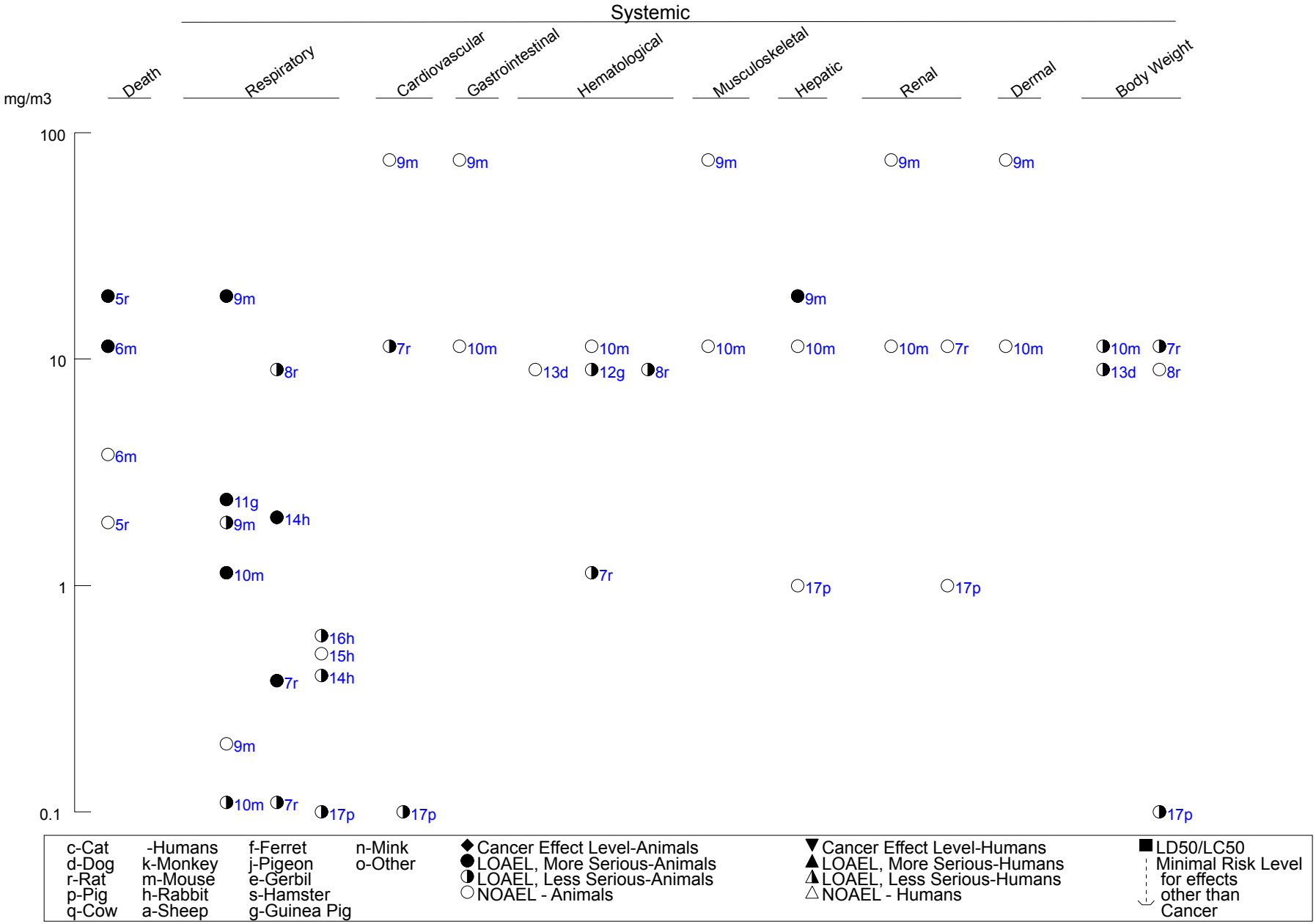


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Intermediate (15-364 days)

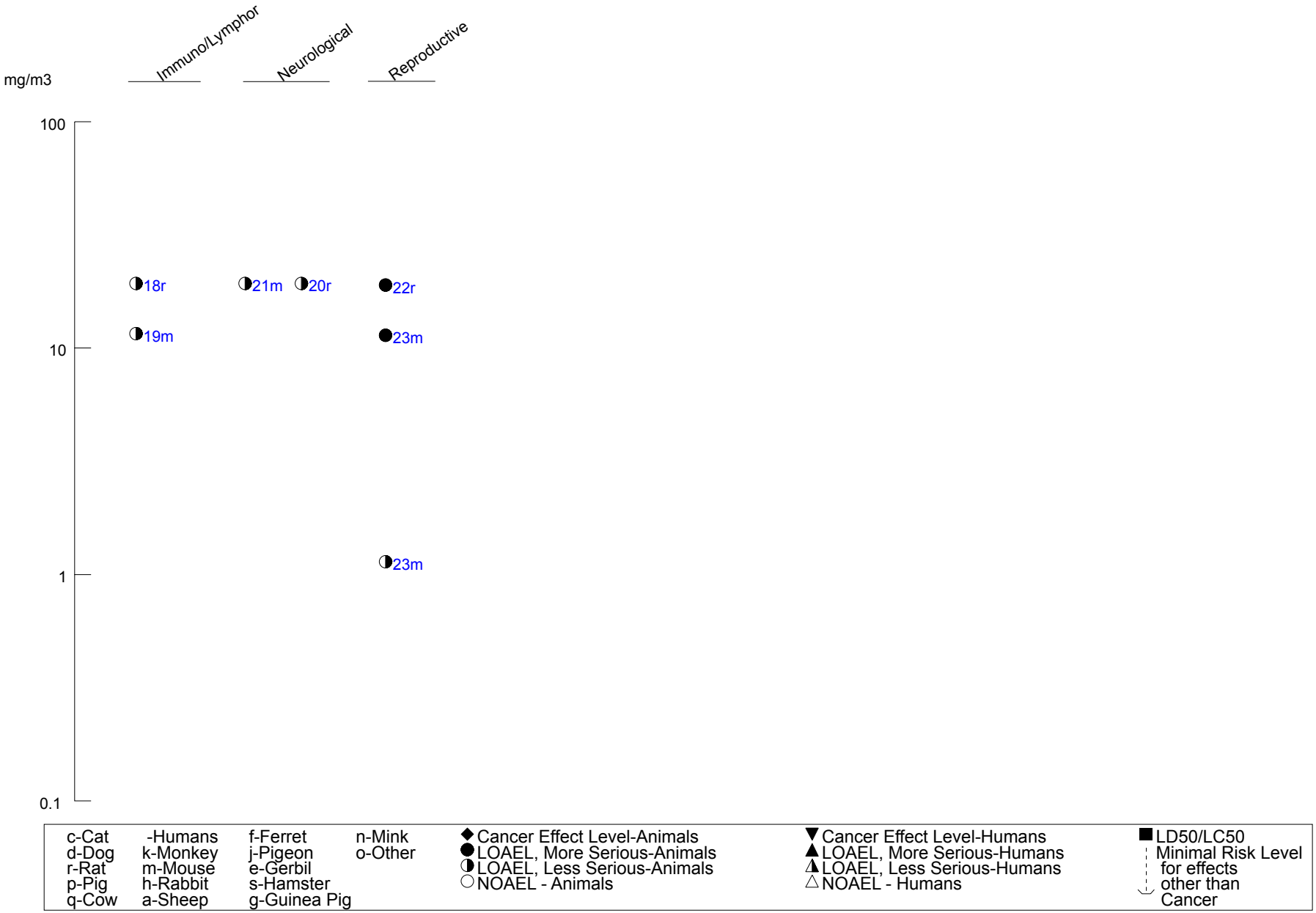
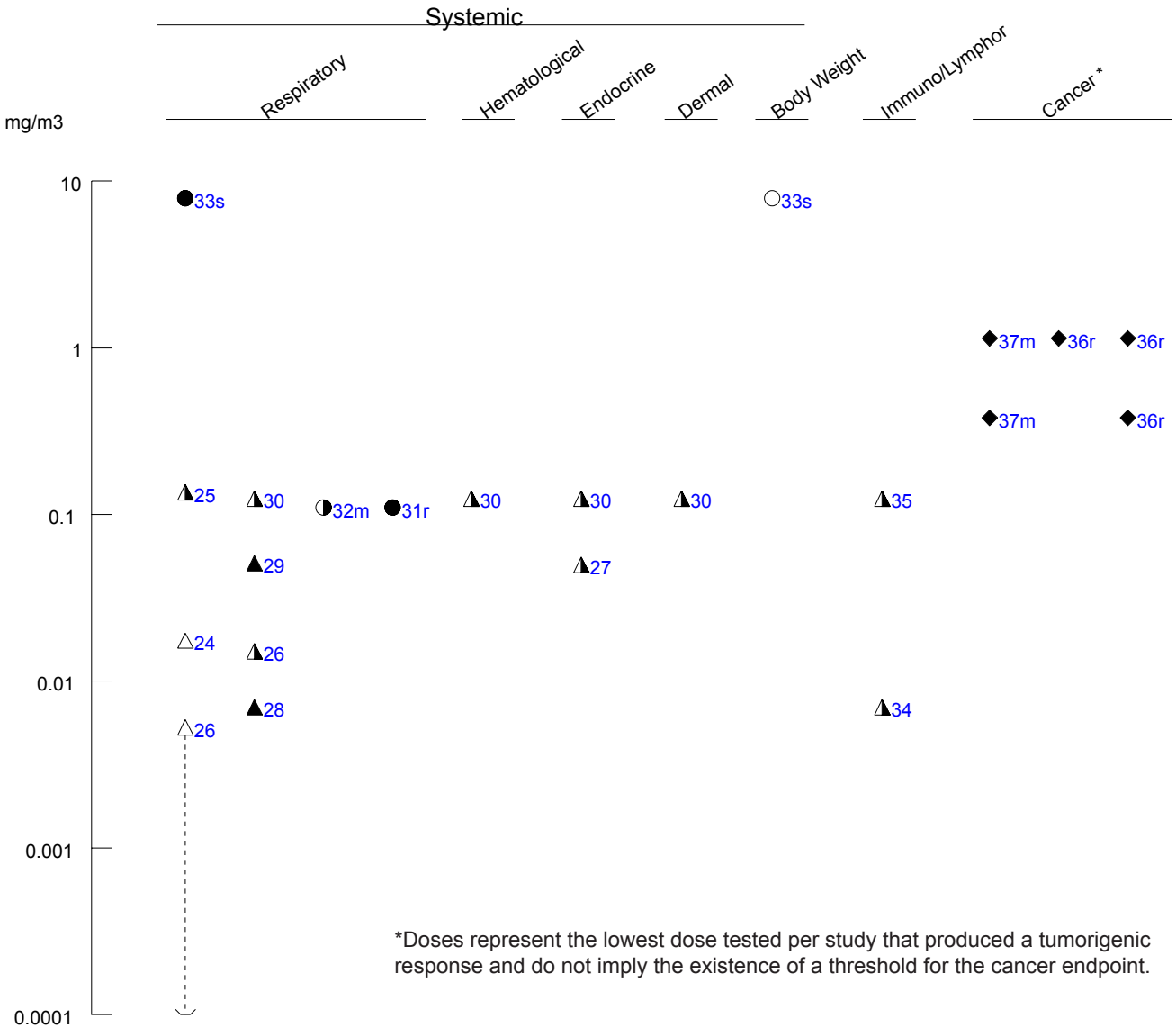


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Chronic (≥365 days)



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

Kusaka et al. (1986b) described an acute exposure of 15 healthy young men to atmospheres of hard metal dust containing 0.038 mg cobalt/m^3 for 6 hours. Forced vital capacity (FVC) was reduced, but no dose-response relation could be discerned. By contrast, 42 workers occupationally exposed to hard metal showed no decrease in ventilatory function at 0.085 mg cobalt/m^3, but significant changes in FEV_1 (forced expiratory volume in 1 second) at 0.126 mg cobalt/m^3 (Kusaka et al. 1986b). Several other studies of hard metal workers have shown respiratory effects, including decreased ventilatory function, wheezing, asthma, and fibrosis (Kusaka et al. 1996a, 1996b; Ruokonen et al. 1996; Zanelli et al. 1994), but have had less complete reports of exposure.

Swennen et al. (1993) performed a cross-sectional study on 82 workers in a cobalt refinery. Workers were examined for cobalt in blood and urine, a number of erythropoietic variables, thyroid metabolism, pulmonary function, skin lesions, and several serum enzymes. The concentrations of cobalt in blood and in urine after the shift were significantly correlated with those in air. Workers exposed to airborne cobalt metal, salts, or oxides (mean concentration 0.125 mg/m^3, range 0.001–7.7 mg/m^3) showed an increased ($p<0.05$) prevalence of dyspnea and wheezing and had significantly more skin lesions (eczema, erythema) than control workers. A dose-effect relation was found between the reduction of the FEV_1 and the intensity of the current exposure to cobalt, as assessed by measurement of cobalt in blood, air, or urine.

Gennart and Lauwerys (1990) examined the ventilatory functions of 48 diamond polishing workers, relative to 23 control workers. Exposure occurred mainly in one of two rooms, with mean airborne concentrations of 0.0152 and 0.1355 mg cobalt/m^3; control subjects worked in other areas of the facilities, where no exposure to cobalt occurred. Significant decreases in ventilatory function were found in the exposed workers relative to the control workers. Duration of exposure played a significant factor, with no significant differences in workers who had been exposed for ≤5 years; reported decreases in ventilatory function were noted in workers exposed for > 5 years. Inhalation exposure to cobalt salts (exposure levels not reported) among glass bangle workers resulted in decreases in decreased ventilatory function, generally restrictive in nature, relative to controls (Rastogi et al. 1991).

Nemery et al. (1992) conducted a cross-sectional study of cobalt exposure and respiratory effects in diamond polishers. Exposure occurred mainly from the generation of airborne cobalt resulting from the use of cobalt-containing polishing discs. The study groups were composed of 194 polishers working in 10 different workshops, and were divided into control, low-, and high-exposure groups. The low-exposure group (n=102) was exposed to an average of 0.0053 mg cobalt/m^3, based on personal sampling

measurements, while the exposure level for the high dose group (n=92) was 0.0151 mg cobalt/m^3; there was considerable overlap in the total range of concentrations for the low- and high-exposure groups. Workers in the high-exposure group were more likely than those in the other groups to complain about respiratory symptoms; the prevalence of eye, nose, and throat irritation and cough, as well as the fraction of these symptoms related to work, were significantly increased in the high-exposure group. Workers in the high-exposure group also had significantly reduced lung function compared to controls and low-exposure group workers, as assessed by FVC, FEV_1, MMEF (forced expiratory flow between 25 and 75% of the FVC) and mean PEF (peak expiratory flow rate). Results in the low-exposure group did not differ from controls. Based on the NOAEL of 0.0053 mg cobalt/m^3 for decreased ventilatory function in exposed workers, a chronic inhalation MRL of 1x10-4 mg cobalt/m^3 was calculated as described in footnote (d) in Table 3-1. It should be noted that this MRL value may not be protective for some hypersensitive individuals.

As with exposures in humans, exposures of animals to cobalt-containing aerosols have resulted in pronounced respiratory effects. Animals exposed to aerosols of cobalt oxides and cobalt sulfate developed respiratory effects that varied in severity with exposure level and duration. A single 30-minute exposure of rats to relatively high levels (26–236 mg cobalt/m^3 as cobalt hydrocarbonyl) resulted in congestion, edema, and hemorrhage of the lung (Palmes et al. 1959). Prolonged exposure (3–4 months) of rats and rabbits to mixed cobalt oxides (0.4–9 mg cobalt/m^3) resulted in lesions in the alveolar region of the respiratory tract characterized histologically by nodular accumulation of Type II epithelial cells, accumulations of enlarged highly vacuolated macrophages, interstitial inflammation, and fibrosis (Johansson et al. 1984, 1987, 1991, 1992; Kyono et al. 1992; Palmes et al. 1959). In at least one instance, the lesions appeared to regress when exposure was terminated (Palmes et al. 1959). Guinea pigs sensitized to cobalt by repeated dermal application and then exposed to 2.4 mg cobalt/m^3 as cobalt chloride showed pulmonary inflammatory changes (altered BAL fluid recovery, increased neutrophils and eosinophils in the recovered BAL fluid) that were different than those in exposed animals not sensitized to cobalt (Camner et al. 1993). Decreased lung compliance was found in pigs exposed to 0.1 mg cobalt/m^3 as cobalt dust for 3 months (Kerfoot 1975). Lifetime exposure of hamsters to 7.9 mg cobalt/m^3 as cobalt oxide resulted in emphysema (Wehner et al. 1977).

Necrosis and inflammation of the respiratory tract epithelium (nasal turbinates, larynx, trachea, bronchioles) were reported in rats exposed to 19 mg cobalt/m^3 and mice exposed to 1.9 mg cobalt/m^3 or greater as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). Exposure of rats and mice to

cobalt as cobalt sulfate for 13 weeks resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive part (Bucher et al. 1990; NTP 1991). At concentrations of ≥0.11 mg cobalt/m^3, rats and mice developed squamous metaplasia of the larynx. Histiocytic infiltrates in the lung were also reported at similar levels in both the rats and mice. In rats, chronic inflammation of the larynx was found at ≥0.38 mg cobalt/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures. In mice, acute inflammation of the nose was found at ≥1.14 mg cobalt/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures. Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (Bucher et al. 1999; NTP 1998). Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of ≥0.11 mg cobalt/m^3, with severity of the lesion increasing with increased cobalt concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of ≥0.11 mg cobalt/m^3, and in mice at concentrations of ≥0.38 mg cobalt/m^3. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe.

Cardiovascular Effects. Occupational exposure of humans to cobalt-containing dust, either as cobalt metal or as hard metal, has been shown to result in cardiomyopathy, characterized by functional effects on the ventricles (Horowitz et al. 1988) and/or enlargement of the heart (Barborik and Dusek 1972; Jarvis et al. 1992), but the exposure levels associated with cardiac effects of inhaled cobalt in humans have not been determined. Jarvis et al. (1992) reported on two patients (exposure histories not specified) who had been admitted to the emergency room for cardiac failures; these failures were believed to be associated with cobalt exposure. Barborik and Dusek (1972) reported a case of a 41-year-old man who was admitted to the hospital with cardiac failure following occupational exposure to cobalt; cobalt concentrations in heart, liver, lung, spleen, and kidney were elevated over two control patients. Horowitz et al. (1988) reported that in a cohort of 30 hard metal workers (exposure histories not specified), significant decreases in exercise right ventricular ejection fraction (EF) were seen in workers with abnormal chest x-rays relative to those with normal chest x-rays. It is possible that these effects were secondary to the respiratory effects of inhaled cobalt. It was concluded that cobalt is a weak cardiomyopathic agent following occupational exposure (Horowitz et al. 1988). Cardiomyopathy is a characteristic toxic effect of cobalt following oral exposure in both humans and animals (Section 3.2.2.2).

In rats, exposure to 11.4 mg cobalt/m^3 as cobalt sulfate over 13 weeks resulted in a marginal increase in the severity of cardiomyopathy as compared to controls (minimal-mild in treated animals versus minimal in controls; 3/10 animals affected in either group) (Bucher et al. 1990; NTP 1991). Cardiomyopathy was not observed in mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991), nor in mice or rats exposed to up to 1.14 mg cobalt/m^3 for 2 years (Bucher et al. 1999; NTP 1998). Electrocardiogram abnormalities that may reflect ventricular impairment have been observed in miniature swine (n=5) exposed to 0.1 mg cobalt dust/m^3 for 6 hours/day, 5 days/week for 3 months (Kerfoot 1975).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to stable cobalt.

No histological lesions were reported in the esophagus, stomach, duodenum, ileum, jejunum, cecum, colon, or rectum of rats or mice of either sex exposed to 76 mg cobalt/m^3 or less as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998).

Hematological Effects. Swennen et al. (1993) reported slightly, but statistically significantly, decreased levels of red cells and total hemoglobin (~4–5% decreases) in a group of 82 workers occupationally exposed to a mean concentration of 0.125 mg cobalt/m^3 as cobalt metal dust. No other studies were located regarding hematological effects in humans after inhalation exposure to cobalt.

Increased levels of hemoglobin and increased numbers of basophils and monocytes have been observed in rats and guinea pigs, but not in dogs, exposed to 9 mg cobalt/m^3 as cobalt hydrocarbonyl for 3 months (Palmes et al. 1959). Polycythemia was reported in rats, but not mice, exposed to 1.14 mg cobalt/m^3 as cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to cobalt.

No histological lesions were reported in the sternebrae (segments of the sternum), including the bone marrow, of rats or mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg

cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998) (see the above section on respiratory effects for detailed descriptions of exposure conditions).

Hepatic Effects. Congestion of the liver was observed upon autopsy of a metal worker (exposure history not reported) who had been occupationally exposed to an unknown level of cobalt for 4 years (Barborik and Dusek 1972). The cause of death was determined to be cardiomyopathy.

Necrosis and congestion of the liver were observed in both rats and mice that died following exposure to 19 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). No histological effects on the liver were found in pigs exposed to up to 1.0 mg cobalt/m^3 as cobalt metal dust for 3 months (Kerfoot 1975).

Renal Effects. Congestion of the kidneys was observed upon autopsy of a metal worker who had been occupationally exposed to an unknown level of cobalt for 4 years (Barborik and Dusek 1972). The cause of death was determined to be cardiomyopathy.

A significant increase in the relative weight of the kidneys was reported in male rats exposed to 0.11 mg cobalt/m^3 or greater as cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991). No effects were observed upon histological examination of the kidneys in rats or mice following exposure to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998). No histological effects on the kidneys were found in pigs exposed to up to 1.0 mg cobalt/m^3 as cobalt metal for 3 months (Kerfoot 1975).

Dermal Effects. No studies were located regarding dermal effects in humans or animals after inhalation exposure to stable cobalt.

Endocrine Effects. A group of female workers occupationally exposed to a semisoluble cobalt glaze (cobalt-zinc silicate, estimated concentrations of 0.05 mg Co/m^3) showed significantly elevated levels of serum thyroxine (T4) and free thyroxine, but no change in T3 levels (Prescott et al. 1992). In contrast to this, Swennen et al. (1993) reported no significant change in serum T4 levels, but a significant reduction in serum T3 in workers occupationally exposed to cobalt oxides, cobalt salts, and cobalt metal.

Ocular Effects. Congestion of the conjunctiva was observed in a metal worker after occupational exposure to an unknown level of cobalt for 4 years (Barborik and Dusek 1972); however, due to the nature of the exposure, this effect may also have been the result of direct dermal or ocular contact. Upon autopsy, the cause of death was determined to be cardiomyopathy.

No histological lesions were reported in the eyes or on the skin of rats or mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998).

Body Weight Effects. Weight loss, measured individually from time of initial examination throughout followup, was observed in a group of five diamond polishers suffering from cobalt-induced interstitial lung disease (Demedts et al. 1984b), but the exposure level of cobalt was not reported.

Decreased body weight, relative to controls at study termination, was reported in both rats and mice exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days or to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). A 13-week exposure to 11.4 mg cobalt /m^3 resulted in ruffled fur in male rats, with no clinical signs reported in female rats or either sex of mice (Bucher et al. 1990; NTP 1991). Chronic exposure of rats and mice to up to 1.14 mg cobalt/m^3 did not result in decreased body weight (Bucher et al. 1999; NTP 1998).

Weight loss was found in dogs, but not rats or guinea pigs, exposed for 3 months to cobalt at a level of 9 mg cobalt/m^3 as cobalt hydrocarbonyl (Palmes et al. 1959). Lifetime exposure of hamsters to a similar concentration (7.9 mg cobalt/m^3 as cobalt oxide) did not result in decreased body weight gain (Wehner et al. 1977).

3.2.1.3 Immunological and Lymphoreticular Effects

Cobalt is known to function as a hapten, resulting in the generation of antibodies against cobalt-protein complexes. Although the minimum exposure level associated with cobalt sensitization has not been determined, sensitization has been demonstrated in hard metal workers with work-related asthma who have experienced prolonged occupational exposure (>3 years) to levels ranging from 0.007 to 0.893 mg cobalt/m^3 (Shirakawa et al. 1988, 1989). The lower end of this range, 0.007 mg/m^3, is reported in

Table 3-1 and plotted in Figure 3-1 as a LOAEL. The sensitization phenomenon includes the production of IgE and IgA antibodies to cobalt (Bencko et al. 1983; Shirakawa et al. 1988, 1989). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), believed to be the result of an allergic reaction within the lungs.

Necrosis of the thymus was reported in rats exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days, and hyperplasia of the mediastinal lymph nodes was found in mice exposed to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). Tests of immunological function, however, were not performed on the rats or mice.

3.2.1.4 Neurological Effects

Occupational exposure to cobalt in humans has been reported to cause several effects on the nervous system, including memory loss (Wechsler Memory Scale-Revised), nerve deafness, and a decreased visual acuity (Jordan et al. 1990; Meecham and Humphrey 1991). It should be noted, though, that both of these studies had small numbers of subjects (n=38 for Jordan et al. 1990, n=1 for Meecham and Humphrey 1991), and exposure characterization was not reported.

Congestion in the vessels of the brain/meninges was reported in rats and mice exposed to 19 mg cobalt/m^3 or greater as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991).

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to cobalt.

In animals, long-term exposure to cobalt-containing aerosols has resulted in effects on reproductive end points. Testicular atrophy was reported in rats, but not in mice, exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). Following exposure of mice to cobalt (as cobalt sulfate) for 13 weeks, a decrease in sperm motility was found at 1.14 mg cobalt/m^3, and testicular atrophy was found at 11.4 mg cobalt/m^3. A significant increase in the length of the estrous cycle was reported in female mice exposed to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). No effects on

the male or female reproductive systems were observed in rats similarly treated for 13 weeks (Bucher et al. 1990; NTP 1991), or in mice or rats exposed to up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1999; NTP 1998).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to cobalt.

3.2.1.7 Cancer

Several studies have evaluated the effects of inhalation of cobalt-containing compounds on possible carcinogenicity in humans. The mortality of a cohort of 1,143 workers in a plant that refined and processed cobalt and sodium was analyzed (Mur et al. 1987); the French national population mortality data were used as a reference population. An increase in deaths due to lung cancer was found in workers exposed only to cobalt (standardized mortality ratio [SMR] of 4.66; four cases in the exposed group versus one case in the controls). In a study within the cohort that controlled for date of birth, age at death, and smoking habits, 44% (four workers) in the group exposed to cobalt and 17% (three workers) in the group not exposed to cobalt died of lung cancer. The authors, however, indicated that the difference was not statistically significant and that the workers were exposed to both arsenic and nickel as well as cobalt. The nonneoplastic lung diseases commonly found in cobalt-exposed workers (see Section 3.2.1.2) were not reported in this group. These lung diseases may have been present in these workers, but if they were not listed as the cause of death on the death certificate, they would not have been mentioned. Inhalation was probably a prominent route of exposure to cobalt; however, oral and dermal exposure probably occurred as well. No adjustments were made for smoking habits in the larger study, and the exposure levels of cobalt were not reported for either study. However, a followup study of this cohort (Moulin et al. 1993) did not report significant increases in mortality due to respiratory or circulatory diseases. Similarly, no increase in the SMR for lung cancer was noted in exposed workers, relative to controls. While an elevated SMR for lung cancer was seen in maintenance workers (SMR=1.80, 95% confidence interval [CI]=0.78–3.55), it was not statistically significant, since the 95% confidence interval included an SMR of 1.

Lasfargues et al. (1994) reported on the mortality of a cohort of 709 male workers in a French hard metal plant, using the national rates for French males for comparison. The overall mortality did not differ from expected, but there was a significant increase in mortality due to cancer of the trachea, bronchus, and lung (SMR=2.13, 95% CI=1.02–3.93). Smoking alone did not account for the lung cancer excesses, although the influence of smoking on the observed mortality could not be entirely ruled out.

A cohort of 5,777 males and 1,682 females who were exposed occupationally to cobalt (concentrations ranging from 1 to 515 μg/m^3, means of exposure levels ranging from 39.37 to 169.0 μg/m^3) and tungsten carbide (as hard metal dust) was examined by Moulin et al. (1998). A significantly increased mortality rate (SMR=1.30, 95% CI=1.00–1.66) was seen for lung cancer in exposed workers, when compared to the national average. Within this study group, 61 cases and 180 controls were selected for a case-control study of cancer risk. When exposures during the last 10 years were ignored, presumably because cancer is a late-developing disease, a significant increase in lung cancer mortality (OR=1.93, 95% CI=1.03–3.62) relative to controls was seen among workers simultaneously exposed to cobalt and tungsten carbide. Significant trends for increasing cancer risk with increasing cumulative exposure and exposure duration were noted. Adjustments for smoking and for coexposures to other carcinogens did not change the results, though occupational risk was greatest among smokers.

A later study by the same group (Moulin et al. 2000) examined the lung cancer mortality of 4,288 male and 609 female workers employed in the production of stainless and alloyed steel from 1968 to 1992. No significant changes in mortality rate from lung cancer were seen among exposed workers (SMR=1.19, 95% CI=0.88–1.55), and a concurrent case control study identified no correlation between lung cancer excess and for exposure to cobalt (OR=0.64, 95% CI=0.33–1.25).

Wild et al. (2000) reported on a cohort of 2,216 male hard metal workers who had been employed for at least 3 months; this cohort was the same as that in Moulin et al. (2000), with some modifications. The total mortality was not increased in workers, relative to local mortality rates. However, lung cancer mortality was significantly increased (SMR=1.70, 95% CI=1.24–2.26). The risks increased with increasing exposure scores, even after adjustment for smoking and coexposure to other known or suspected carcinogens.

Inhalation exposure to 7.9 mg cobalt/m^3 as cobalt oxide intermittently for a lifetime did not increase the incidence of malignant or benign tumors in hamsters (Wehner et al. 1977).

NTP (1998) exposed groups of rats and mice of both sexes to 0, 0.11, 0.38, or 1.14 mg cobalt/m^3 as cobalt sulfate for 2 years. Increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 1.14 mg cobalt/m^3 and in female rats exposed to 0.38 mg cobalt/m^3 (Bucher et al. 1999; NTP 1998). Statistical analysis revealed that tumors occurred with significantly positive trends in both sexes of rats. Similarly, mice of both sexes exposed to 1.14 mg cobalt/m^3 showed an increase in alveolar/bronchiolar neoplasms, again with lung tumors occurring with significantly positive trends.

3.2.2 Oral Exposure

3.2.2.1 Death

In several studies, lethal cardiomyopathy was reported in people who consumed large quantities of beer containing cobalt sulfate (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969). The deaths occurred during the early to mid 1960s, at which time, breweries in Canada, the United States, and Europe were adding cobalt to beer as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969); this practice has been discontinued. Deaths occurred following ingestion of beer containing 0.04–0.14 mg cobalt/kg/day for a period of years (approximately 8–30 pints of beer each day). "Acute mortality" (death within several days of admission) accounted for 18% of the deaths (Alexander 1972). Approximately 43% of the patients admitted to the hospital with cardiomyopathy died within several years of the initial hospital visit. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse.

Treatment of both pregnant and nonpregnant anemic patients with doses of cobalt (0.6–1 mg/kg/day) that were much higher than the doses in the beer did not result in mortality (Davis and Fields 1958; Holly 1955). A 19-month-old male child who swallowed an unknown amount of a cobalt chloride solution died approximately 6.5 hours after ingestion, despite repeated induced vomiting, gastric lavage, and supportive therapy (Jacobziner and Raybin 1961).

Oral LD_{50} values for several cobalt compounds have been determined in Wistar rats (FDRL 1984a, 1984b, 1984c; Singh and Junnarkar 1991; Speijers et al. 1982). The LD_{50} values ranged from 42.4 mg cobalt/kg as cobalt chloride to 317 mg cobalt/kg as cobalt carbonate. An LD_{50} of 3,672 mg cobalt/kg was also found for tricobalt tetraoxide, a highly insoluble cobalt compound (FDRL 1984c). The exact cause of death in rats is unknown, but effects on the heart, liver, gastrointestinal tract, and kidneys have been observed. In Sprague-Dawley rats, death has been reported to occur at 161 mg cobalt/kg given by gavage as cobalt chloride (Domingo and Llobet 1984). In male Swiss mice, the LD_{50} values for cobalt chloride and cobalt sulfate have been reported to be 89.3 and 123 mg cobalt/kg, respectively (Singh and Junnarkar 1991).

Following 5 weeks of exposure to 20 mg cobalt/kg/day as cobalt sulfate by gavage, 20–25% of the guinea pigs died (Mohiuddin et al. 1970). The animals were given cobalt sulfate alone or in combination with ethanol (as part of a liquid diet) to compare the effects seen in animals to those seen in humans suffering from beer-cobalt cardiomyopathy. Although effects on the heart were found in the treated animals, alcohol did not appear to intensify the toxic effect.

The LD_{50} and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

Oral cobalt exposure in humans and/or animals resulted in respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, hypothermic, and body weight effects. For each effect, the highest NOAEL values and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. In 50 patients with beer-cobalt cardiomyopathy, pulmonary rales and pulmonary edema were observed and were attributed to cobalt-induced cardiac failure (Morin et al. 1971). These patients had ingested, over a period of years, an average of 0.04 mg cobalt/kg/day in beer containing cobalt sulfate that was added to stabilize the foam. It should be noted that these patients consumed significant quantities of alcohol, and the effect that this may have had on the symptoms seen is not known.

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	1x (GW)				161.1 (LD50)	Domingo and Llobet 1984 Chloride
2	Rat (Wistar)	1x (GW)				42.4 (LD50)	Singh and Junnarkar 1991 Chloride
3	Rat (Wistar)	1x (GW)				194 (LD50)	Singh and Junnarkar 1991 Sulfate
4	Rat (Wistar)	1 x (GO)				91 (LD50)	Speijers et al. 1982 Fluoride
5	Rat (Wistar)	1 x (GO)				187 (LD50)	Speijers et al. 1982 Phosphate
6	Rat (Wistar)	1 x (GW)				109 (LD50)	Speijers et al. 1982 Bromide
7	Rat (Wistar)	1 x (GO)				159 (LD50)	Speijers et al. 1982 Oxide

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
8	Rat (Wistar)	1 x (GW)				168 (LD50)	Speijers et al. 1982 Acetate
9	Rat (Wistar)	1 x (GW)				190 (LD50)	Speijers et al. 1982 Chloride
10	Rat (Wistar)	1 x (GW)				140 (LD50)	Speijers et al. 1982 Bromide
11	Rat (Wistar)	1 x (GW)				161 (LD50)	Speijers et al. 1982 Sulfate
12	Mouse (Swiss-Webster)	1x (GW)				123 (LD50)	Singh and Junnarkar 1991 Sulfate
13	Mouse (Swiss-Webster)	1x (GW)				89.3 (LD50)	Singh and Junnarkar 1991 Chloride
	Systemic						
14	Human	2 wk (C)	Endocr		1 (decreased Iodine uptake in thyroid)		Roche and Layrisse 1958 Chloride

[a] Key to figure

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
15	Rat	1x (GW)	Hemato		161.1[b]	(increased hematocrit 8%)			Domingo and Llobet 1984 Chloride
16	Rat	1 x (GW)	Other	110	209	(Clinical signs, including decreased activity, ataxia, diarrhea, salivation)			FDRL 1984a Sulfate
17	Rat (Sprague-Dawley)	1 x (GO)	Other		149	(Decreased activity, diarrhea)			FDRL 1984b Carbonate
18	Rat (Wistar)	1x (GW)	Renal		19.4	(Increased urinary output)			Singh and Junnarkar 1991 Sulfate
19	Rat (Wistar)	1 x (GO)	Cardio	109.6			176.6	(proliferative interstitial tissues, swollen muscle fibers, focal myocardial degeneration)	Speijers et al. 1982 Fluoride
			Hepatic	42.6			68.2	(hyperemia)	
			Renal		42.6	(swollen proximal tubules)	176.6	(degeneration of proximal tubules)	
			Other				109.6	(hypothermia)	

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
20	Rat (Wistar)	1 x (GO)	Cardio			794.5 (hemorrhage)	Speijers et al. 1982 Oxide
			Hepatic			157.3 (hyperemia)	
			Renal			157.3 (hyperemia)	
			Other			157.3 (hypothermia)	
21	Mouse (Swiss-Webster)	48 hr (W)	Hemato		76.4 M (Alteration in electrophoretic profile of serum proteins)		Bryan and Bright, 1973 Chloride
22	Mouse (Swiss-Webster)	3 mo (W)	Hemato	76.4 M			Bryan and Bright, 1973 Chloride
	Neurological						
23	Rat (Wistar)	1x (GW)			19.4 (Mild depression of spontaneous activity, muscle tone, and respiration)		Singh and Junnarkar 1991 Sulfate

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
24	Rat (Wistar)	1x (GW)			4.25 (Mild depression of spontaneous activity, muscle tone, and respiration)		Singh and Junnarkar 1991 Chloride
	Developmental						
25	Rat	Gd 6-15 (GW)		24.8			Paternian et al. 1988 Chloride
26	Mouse	Gd 8-12 (GW)		81.7			Seidenberg 1986 Chloride
	INTERMEDIATE EXPOSURE						
	Death						
27	Human	NR (W)				0.04 (death)	Morin et al. 1971 Sulfate
28	Gn Pig	5 wk (F)				20 (death)	Mohiuddin et al. 1970 Sulfate
	Systemic						
29	Human	NR (W)	Cardio			0.07 (beer-cobalt cardiomyopathy)	Alexander 1972 Sulfate

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
30	Human	1x/d 25 d (C)	Hemato		1[c] (polycythemia)		Davis and Fields 1958 Chloride
31	Human	12-32 wk (C)	Gastro		0.18 (nausea)		Duckham and Lee 1976b Chloride
			Hemato		0.18[b] (increased hemoglobin, 23-102% increase)		
32	Human	90 d (C)	Gastro		0.5 (gastric intolerance)		Holly 1955 Chloride
			Hemato	0.6			
			Hepatic	0.6			
33	Human	NR (W)	Resp		0.04 (edema)		Morin et al. 1971 Sulfate
			Cardio			0.04 (beer-cobalt cardiomyopathy)	
			Gastro		0.04 (vomiting, nausea)		
			Hepatic		0.04 (necrosis)		

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
34	Human	10-25 d 1x/d (C)	Other		0.54 (decreased Iodine uptake)		Paley et al. 1958
35	Human	12-32 wk 7d/wk (C)	Hemato		0.16[b] (increased hemoglobin)		Taylor et al. 1977 Chloride
36	Rat (Sprague-Dawley)	4 wk (F)	Bd Wt		3.79 M (45-65% reduction in body weight gain)		Chetty et al. 1979 Chloride
37	Rat	8 wk 1x/d (F)	Bd Wt		4.2 (33% decrease in body weight gain)		Clyne et al. 1988

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat	3 mo (W)	Resp		30.2 (increased lung weight 33%)		Domingo et al. 1984
			Cardio		30.2 (increased heart weight 9.4%)		
			Gastro	30.2			
			Hemato		30.2 (increased hematocrit 29%)c		
			Musc/skel	30.2			
			Hepatic	30.2			
			Renal	30.2			
39	Rat	8 wk (F)	Cardio			26 (degeneration)	Grice et al. 1969
40	Rat (Sprague-Dawley)	24 wk (F)	Cardio			8.4 M (Left ventricular hypertrophy and impaired ventricular function)	Haga et al. 1996 Sulfate

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Rat	4 mo (G)	Resp	18			Holly 1955 Chloride
			Cardio	18			
			Gastro	18			
			Hemato		18[b] (erythrocytosis)		
			Hepatic	18			
			Renal			18 (tubular necrosis)	
42	Rat	7 mo 6 d/wk (GW)	Hemato	0.05	0.5[b] (increased RBC, hemoglobin)		Krasovskii and Fridlyand 1971
			Hepatic	2.5			
43	Rat CFY	3 wk (G)	Cardio			12.4 M (Incipient, multifocal myocytolysis, with degeneration of myofibrilles)	Morvai et al. 1993 Chloride
			Bd Wt		12.4 M (Decreased body weight 8%)		

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
44	Rat	150 d 5 d/wk (GW)	Hemato		10[b] (increased hemoglobin)		Murdock 1959 Chloride
			Hepatic		10 (increased weight 17%)		
			Renal			10 (necrosis of tubular lining cells)	
			Bd Wt	10			
45	Rat (Sprague-Dawley)	8 wk	Hemato	8.4 M			Pehrsson et al. 1991 Sulfate
			Bd Wt			8.4 M (>20% decrease from appropriate control)	
46	Rat (Sprague-Dawley)	12-16 d (W)	Bd Wt	10.6 M			Saker et al. 1998 Chloride
			Metab		10.6 M (Decreased serum glucose levels in diabetic rats, but not control rats)		

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
47	Rat	6 wk 7 d/wk (C)	Hemato	0.6	2.5[b] (polycythemia)		Stanley et al. 1947 Chloride
48	Rat (Long- Evans)	3 d (F)	Bd Wt	20 M	100 M (<20% reduction of body weights)		Wellman et al. 1984 Chloride
49	Mouse Parkes	45 d (W)	Endocr			26 F (Necrosis and inflammation of thyroid)	Shrivastava et al. 1996 Chloride
50	Gn Pig	5 wk (F)	Cardio			20 (cardiomyopathy)	Mohiuddin et al. 1970
			Bd Wt	20			
51	Dog	4 wk 7 d/wk (F)	Hemato		5[b] (polycythemia)		Brewer 1940
	Immuno/ Lymphoret						
52	Rat (Sprague-Dawley)	4 wk (F)				3.79 M (Atrophy of the thymus)	Chetty et al. 1979 Chloride

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
53	Rat	7 mo 6 d/wk (GW)		0.05	0.5	(decreased phagocytic ability)			Krasovskii and Fridlyand 1971 Chloride
	Neurological								
54	Rat (Sprague-Dawley)	57 d (W)			20 M	(Increased latency during retention testing)			Bourg et al. 1985 Chloride
55	Rat	57 d (W)			20	(increased reactivity)			Bourg et al. 1985 Chloride
56	Rat	7 mo 6 d/wk (GW)		0.05	0.5	(mildly increased latent reflex)	2.5	(pronounced increase in latent reflex)	Krasovskii and Fridlyand 1971 Chloride
57	Rat (Wistar)	30 d (W)			4.96 M	(Alterations in sympathetically-induced contractility of vas deferens)			Mutafova-Yambolieva et al. 1994 Chloride
58	Rat	69 d (F)		5	20	(changes in schedule training, conditioned suppression, and mixed schedule training tests)			Nation et al. 1983

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
59	Rat (Wistar)	30 d (W)			6.44 M (Alterations in cholinergic sensitivity)		Vassilev et al. 1993 Nitrate
60	Rat (Long- Evans)	3 d (F)		20 M	100 M (Saccharin and food aversion)		Wellman et al. 1984 Chloride
	Reproductive						
61	Rat (Sprague-Dawley)	98 days (F)				20 M Pronounced histologic alteration of seminiferous tubules	Corrier et al. 1985 Chloride
62	Rat (Sprague-Dawley)	90 d (W)			30.2 M 26% decrease in testicular weight		Domingo et al. 1984 Chloride
63	Rat	98 d 7 d/wk (F)				13.25 (testicular degeneration)	Mollenhauer et al. 1985
64	Rat	69 d (F)		5		20 M (testicular atrophy)	Nation et al. 1983 Chloride

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
65	Mouse (CD-1)	13 wk (W)				43.4 M (Irreversible testicular degeneration)	Anderson et al. 1992 Chloride
66	Mouse (CD-1)	13 wk (W)				43.4 M (Testicular degeneration)	Anderson et al. 1993 Chloride
67	Mouse	13 wk (W)			23 (reversible testicular degeneration)		Pedigo et al. 1988 Chloride
68	Mouse (B6C3F1)	10 wk (W)				58.9 M (Reduced pregnant females and pups per litter; reduced fertility)	Pedigo et al. 1993 Chloride
	Developmental						
69	Human	90 d (C)		0.6			Holly 1955 Chloride

Table 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
70	Rat	Gd 14- Ld 21 (G)				5.4 (stunted pup growth)	Domingo et al. 1985 Chloride

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

[b] An increase in hemoglobin or red blood cells is not necessarily considered an adverse effect.

[c] Used to derive an intermediate oral MRL; concentration was divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability), resulting in an MRL of 0.01 mg/kg/day.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gd = gestation day; (GO) = gavage oil; (GW) = gavage-water, Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Ld = lactation day; LD50 = dose producing 50% death; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); NOAEL = no observed-adverse-effect level; NS = not specified; (W) = drinking water; wk = week(s); x = times.

Figure 3-2. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral

Acute (≤14 days)

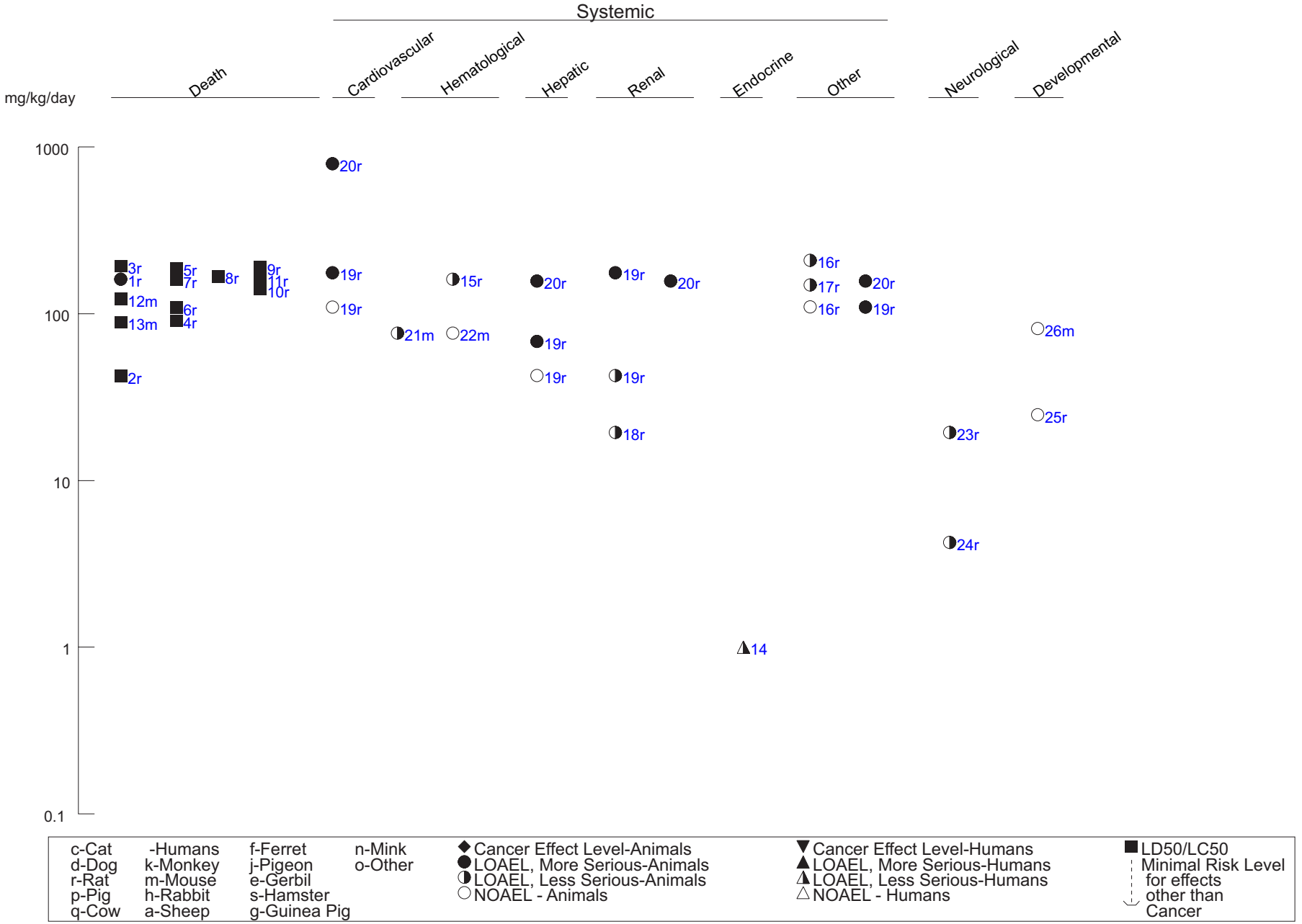


Figure 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)

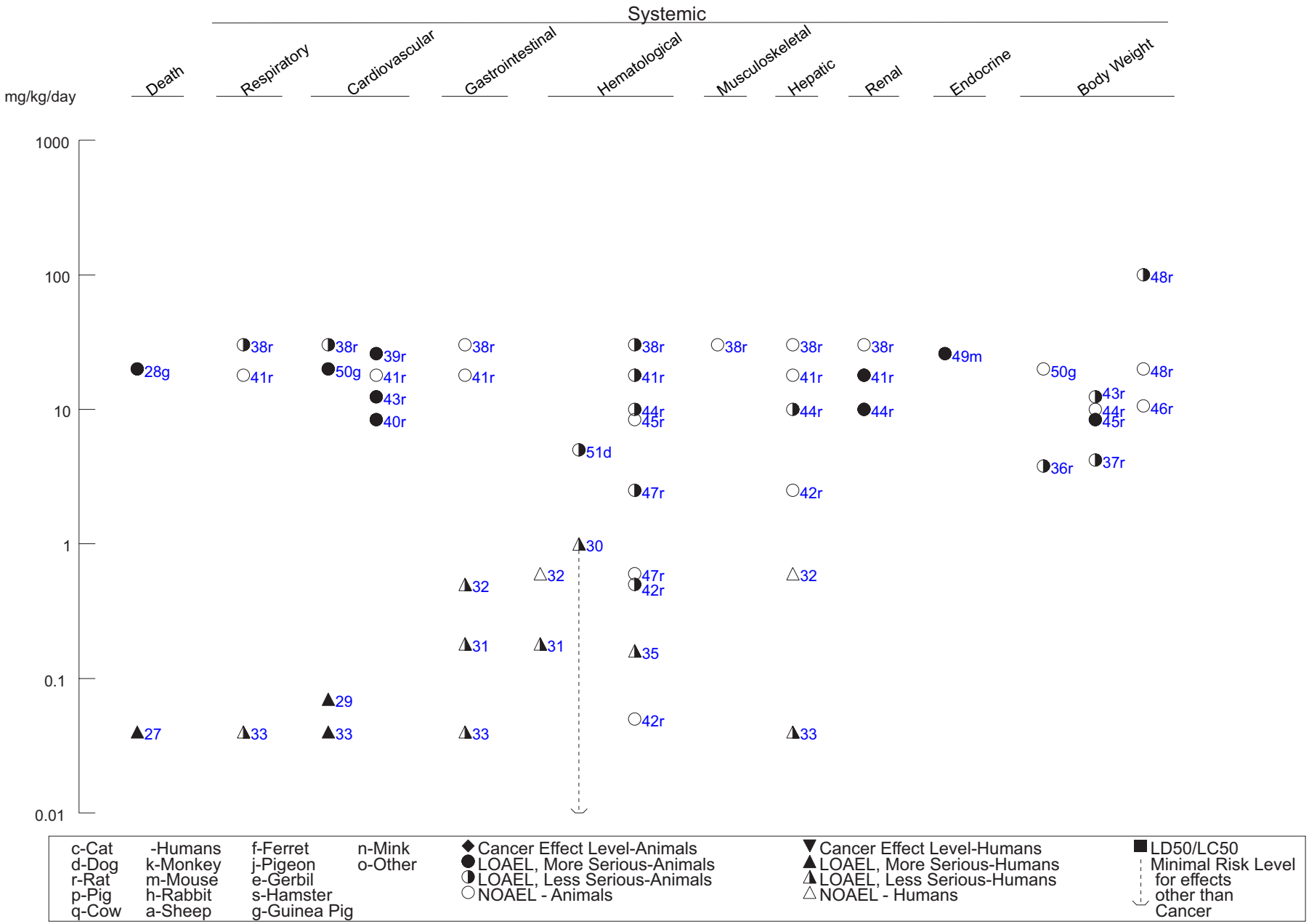
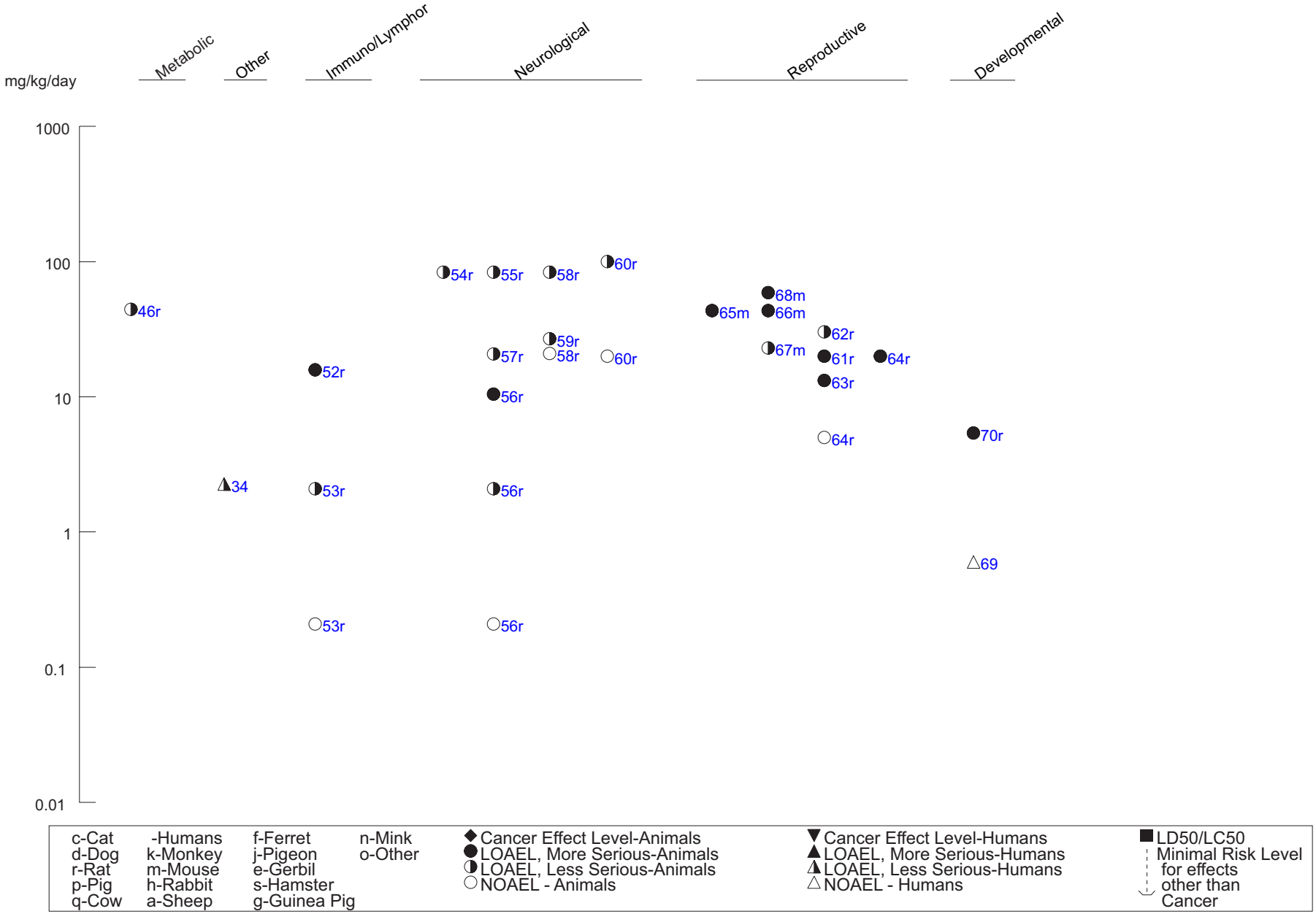


Figure 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)



A significant increase in the weight of the lungs, without morphological or histological changes, was found in rats that received 30.2 mg cobalt/kg/day as cobalt chloride in drinking water for 3 months, as compared with controls (Domingo et al. 1984). No morphological changes were seen in the lungs of rats treated with 18 mg cobalt/kg/day for 4 months (Holly 1955).

Cardiovascular Effects. Beer-cobalt cardiomyopathy was observed in people who heavily consumed beer containing cobalt sulfate as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Kesteloot et al. 1968; Morin et al. 1967, 1971; Sullivan et al. 1969). The beer drinkers ingested an average of 0.04 mg cobalt/kg/day (Morin et al. 1971, n=50) to 0.14 mg cobalt/kg/day for a period of years (Alexander 1969, 1972, n=28). The cardiomyopathy was characterized by sinus tachycardia, left ventricular failure, cardiogenic shock, diminished myocardial compliance, absence of a myocardial response to exercise or catecholamine, enlarged heart, pericardial effusion, and extensive intracellular changes (changes in the myofibers, mitochondria, glycogen, and lipids). The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of beer-cobalt cardiomyopathy was very abrupt. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse. Treatment of both pregnant and nonpregnant anemic patients for 90 days with doses of cobalt (0.6–1 mg/kg/day as cobalt chloride) that were much higher than the doses in the beer did not result in effects on the heart (Davis and Fields 1958; Holly 1955).

Approximately 40–50% of the patients admitted to the hospital with cardiomyopathy died within several years of diagnosis. In a followup study of four different sites, 0–43% of the survivors, depending on the site, showed a residual cardiac disability and 23–41% had abnormal electrocardiograms (Alexander 1972).

In an experiment designed to simulate conditions leading to beer-cobalt cardiomyopathy in humans, guinea pigs were given 20 mg cobalt/kg/day as cobalt sulfate by gavage either alone or in combination with ethanol (as part of a liquid diet) for 5 weeks (Mohiuddin et al. 1970). The experiment resulted in cardiomyopathy, which was characterized by abnormal EKGs; increased heart weights; lesions involving the pericardium, myocardium, and endocardium; and disfigured mitochondria. Alcohol did not intensify the cardiac effects. Myocardia changes (proliferative interstitial tissue, swollen muscle fibers, and focal degeneration) were also found in rats following a single dose of 176.6 mg cobalt/kg administered by

gavage as cobalt fluoride or a single dose of 795 mg cobalt/kg administered as cobalt oxide (Speijers et al. 1982).

Three weeks of exposure to 12.4 mg cobalt/kg/day as cobalt chloride in male rats resulted in cardiac damage, presenting as incipient, multifocal myocytolysis, with degeneration of myofibrilles (Morvai et al. 1993). After longer-term exposure (2–3 months) of rats to 26–30.2 mg cobalt/kg/day as cobalt sulfate in the diet or as cobalt chloride in the drinking water, degenerative heart lesions (Grice et al. 1969) and an increase in heart weight were found (Domingo et al. 1984). Exposure of rats to 8.4 mg cobalt/kg/day as cobalt sulfate resulted in left ventricular hypertrophy and impaired left ventricular systolic and diastolic functions in an isolated working rat heart model (Haga et al. 1996). Clyne et al. (2001) reported that exposure of rats to 8.4 mg cobalt/kg/day, as cobalt sulfate, in the diet for 24 weeks resulted in significant reductions in a number of enzymes in cardiac tissues, including manganese-superoxide dismutase, succinate-cytochrome c oxidase, NADH-cytochrome c reductase, and cytochrome c oxidase, as well as reducing the mitochondrial ATP production rate.

Gastrointestinal Effects. The first signs of the beer-cobalt cardiomyopathy syndrome were gastrointestinal effects and included nausea, vomiting, and diarrhea (Morin et al. 1971). Signs of heart failure subsequently appeared. These individuals had ingested an average of 0.04 mg cobalt/kg/day for a period of years during which cobalt sulfate was added to beer as a foam stabilizer; however, it is likely that alcohol consumption was also a factor.

In pregnant women given cobalt supplements (alone or combined with iron) to prevent the decrease in hematocrit and hemoglobin levels commonly found during pregnancy (n=78), a small percentage of those treated complained of gastric intolerance (Holly 1955). The women were treated with 0.5–0.6 mg cobalt/kg/day as cobalt chloride for 90 days. Nausea was reported in one anemic patient following treatment with 0.18 mg cobalt/kg/day as cobalt chloride (Duckham and Lee 1976b).

No morphological changes in the gastrointestinal system were observed following exposure of 20 male rats for 3 months to 30.2 mg cobalt/kg/day as cobalt chloride in the drinking water (Domingo et al. 1984) or exposure for 4 months to 18 mg cobalt/kg/day as cobalt chloride by gavage (Holly 1955).

Hematological Effects. Cobalt has been shown to stimulate the production of red blood cells in humans. Davis and Fields (1958) exposed six apparently normal men, ages 20–47, to a daily dose of

cobalt chloride, administered as a 2% solution diluted in either water or milk, for up to 22 days. Five of the six received 150 mg cobalt chloride per day for the entire exposure period, while the sixth was started on 120 mg/day and later increased to 150 mg/day. Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell counts, hemoglobin percentage, leukocyte counts, reticulocyte percentages, and thrombocyte counts. Exposure to cobalt resulted in the development of polycythemia in all six subjects, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pretreatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. Hemoglobin levels were also increased by cobalt treatment, though to a lesser extent than the erythrocyte values, with increases of 6–11% over pretreatment values. In five of the six subjects, reticulocyte levels were elevated, reaching at least twice the pre-experiment values. Thrombocyte and total leukocyte counts did not deviate significantly from pretreatment values. From the LOAEL of 1 mg/kg-day identified by this study, an intermediate-duration oral MRL of $1x10^{-2}$ mg/kg-day was derived (for derivation, see Section 2.3 and Appendix A).

Increased levels of erythrocytes were also found following oral treatment of anephric patients (with resulting anemia) with 0.16–1.0 mg cobalt/kg/day daily as cobalt chloride for 3–32 weeks (Duckham and Lee 1976b; Taylor et al. 1977). The increase in hemoglobin resulted in a decreased need for blood transfusions. Treatment of pregnant women for 90 days with 0.5–0.6 mg cobalt/kg/day as cobalt chloride, however, did not prevent the reduction in hematocrit and hemoglobin levels often found during pregnancy (Holly 1955).

Significantly increased erythrocyte (polycythemia), hematocrit, and hemoglobin levels were found in animals treated orally with cobalt chloride as a single dose of 161 mg cobalt/kg (Domingo and Llobet 1984) or with longer-term exposure (3 weeks to 2 months) to ≥0.5 mg/kg/day (Brewer 1940; Davis 1937; Domingo et al. 1984; Holly 1955; Krasovskii and Fridlyand 1971; Murdock 1959; Stanley et al. 1947). Of particular note is an 8-week study in rats (Stanley et al. 1947), which reported dose- and time-related increases in erythrocyte number following oral administration of cobalt chloride, with an apparent NOAEL of 0.6 mg cobalt/kg/day and a LOAEL of 2.5 mg cobalt/kg/day. Changes in the levels of other blood proteins (transferrin, several haptoglobulins, and ceruloplasmin) were noted in male Swiss mice following 4, 24, and 48 hours of treatment with 76.4 mg cobalt/kg as cobalt chloride in the drinking water (Bryan and Bright 1973). Exposure for 3 weeks or 3 months to 76.4 mg cobalt/kg as cobalt chloride in the drinking water resulted in no alterations in serum proteins examined.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to cobalt.

No morphological changes were found in the skeletal muscle of rats exposed to 30.2 mg cobalt/kg/day as cobalt chloride in the drinking water for 3 months (Domingo et al. 1984). This NOAEL in rats for intermediate-duration exposure is reported in Table 3-2 and plotted in Figure 3-2.

Hepatic Effects. Liver injury was evident in patients with beer-cobalt cardiomyopathy, characterized by central hepatic necrosis accompanied by increased levels of serum bilirubin and serum enzymes (serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactate dehydrogenase [LDH]), creatine phosphokinase, ornithine carbamyl transferase, isocitric dehydrogenase, aldolase) (Alexander 1972; Morin et al. 1971). The hepatic injury may have resulted from ischemia, secondary to the cardiac effects of cobalt, and/or from excessive alcohol consumption. The cardiomyopathy resulted from the ingestion of beer containing 0.04 mg cobalt/kg/day as cobalt sulfate that had been added as a foam stabilizer (Morin et al. 1971). Liver function tests were found to be normal in pregnant women receiving up to 0.6 mg cobalt/kg/day as cobalt chloride for 90 days for treatment of the decreases in hematocrit and hemoglobin levels commonly found during pregnancy (Holly 1955).

Data from animals have also indicated that cobalt has hepatic effects. Hyperemia of the liver and cytoplasmic changes in hepatocytes (clumpy cytoplasm located along the cell membrane) were found in rats administered a single dose of 68.2 mg cobalt/kg as cobalt fluoride or a single dose of 157.3 mg cobalt/kg as cobalt oxide (Speijers et al. 1982).

Increased liver weight (17%) was found in rats exposed to 10 mg cobalt/kg/day (as cobalt chloride) for 5 months (Murdock 1959). No morphological or enzymatic changes were found in the livers of rats exposed to 2.5–30.2 mg cobalt/kg as cobalt chloride by gavage or as cobalt chloride in the drinking water for 3–7 months (Domingo et al. 1984; Holly 1955; Krasovskii and Fridlyand 1971).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to cobalt.

Acute and prolonged exposure to cobalt results in renal tubular degeneration in rats. Renal injury, evidenced by histologic alteration of the proximal tubules, was observed in rats after a single oral exposure to 42 mg cobalt/kg as cobalt fluoride (Speijers et al. 1982) and after exposure to 10–18 mg cobalt/kg/day as cobalt chloride for 4–5 months (Holly 1955; Murdock 1959). A slightly decreased urinary output was observed in rats exposed to 19.4 mg cobalt/kg as cobalt sulfate, but not in rats exposed to 4.25 mg cobalt/kg as cobalt chloride (Singh and Junnarker 1991).

Endocrine Effects. Roy et al. (1968) reported on 20 Québécois patients who died of beer drinkers' myocardosis. Of these, 14 thyroids were available for examination. Three of those were normal, and the other 11 formed the basis of the study. "Abnormal" thyroids did not show gross changes, but upon histologic examination, they showed irregular follicle morphology and decreased follicular size.

Kriss et al. (1955) reported on five patients who had been receiving cobalt therapy for sickle-cell anemia or renal amyloidosis. Three of five developed goiter, one severe, while four of five showed microscopic alterations of the thyroid gland. Two of the patients died from non-cobalt-related causes, while the other three recovered once cobalt treatment was removed. A similar study was reported by Gross et al. (1955) in which stable cobalt was used therapeutically in four cases of sickle-cell anemia. Treatment with cobalt resulted in an enlargement of the thyroid gland, which was reversible upon cessation of cobalt therapy. Similar effects on the thyroid, including enlargement, hyperplasia, and an increased firmness, have been reported in several other cases where cobalt therapy for anemia was used (Chamberlain 1961; Little and Sunico 1958; Soderholm et al. 1968; Washburn and Kaplan 1964). No other studies examining the endocrine effects of stable cobalt in humans were located.

NTP (1998; Bucher et al. 1999) reported increased incidence of pheochromocytoma, a tumor of the adrenal medulla, in female rats exposed to 1.14 mg cobalt/m^3 for 2 years, but did not measure any other endocrine effects. Female mice exposed to 26 mg cobalt/kg-day in the drinking water for up to 45 days showed histopathological changes to the thyroid gland (Shrivastava et al. 1996). Cobalt significantly stimulated serum testosterone in mice treated orally with 23 mg cobalt/kg as cobalt chloride, though no dose-response relationship was present (Pedigo et al. 1988).

Dermal Effects. Allergic dermatitis has been reported in some cobalt-sensitized people following oral challenge with cobalt. Several patients with eczema of the hands were challenged orally with 1 mg cobalt as cobalt sulfate given in tablet form once per week for 3 weeks (0.014 mg/kg/day). A flaring of the

eczema was considered to be a positive allergic response to cobalt (Veien et al. 1987). No other studies were located regarding dermal effects in humans or animals after oral exposure to cobalt.

Ocular Effects. Severe visual disturbances (optic atrophy, impaired choroidal perfusion) developed in a man who was treated with cobalt chloride for pancytopenia and hypercellular bone marrow (Licht et al. 1972). He received 1.3 mg cobalt/kg daily for four series of treatments with a total duration of 6 weeks. However, no other cases of visual disturbances due to therapeutic administration of cobalt have been reported, and no such effects have been observed in animals.

Body Weight Effects. No effects on body weight in animals were found following longer-term (1–5 months) exposure of rats to 10–30.2 mg cobalt/kg/day as cobalt chloride (Bourg et al. 1985; Domingo et al. 1984; Murdock 1959) or of guinea pigs to 20 mg cobalt/kg/day as cobalt sulfate (Mohiuddin et al. 1970). A significant decrease (33%) in body weight gain was observed following 8 weeks of exposure of rats to 4.2 mg cobalt/kg/day as cobalt sulfate (Clyne et al. 1988).

Metabolic Effects. Treatment of rats with 10.6 mg Co/kg/day as $CoCl_2$ in the drinking water for 12–16 days resulted in a significant decrease in serum glucose levels in diabetic rats, but not in control rats (Saker et al. 1998).

Other Systemic Effects. Hypothermia occurred in rats following a single oral dose of 157 mg cobalt/kg given as cobalt oxide or a single oral dose of 110 mg cobalt/kg given as cobalt fluoride (Speijers et al. 1982). The hypothermia was time- and dose-related. Hypothermia was reported as an effect during LD_{50} studies with other cobalt compounds, but the exact dose for the onset of hypothermia with these compounds was not reported (Speijers et al. 1982). Other physiological signs noted in LD_{50} studies include decreased activity, ataxia, diarrhea, and salivation (FDRL 1984a, 1984b).

3.2.2.3 Immunological and Lymphoreticular Effects

Cobalt is known to function as a hapten, resulting in the generation of antibodies against cobalt-protein complexes. Allergic dermatitis has been reported in some cobalt-sensitized people following oral challenge with cobalt. Several patients with eczema of the hands were challenged orally with 1 mg cobalt as cobalt sulfate given in tablet form once per week for 3 weeks (0.014 mg/kg/day). A flaring of the

eczema was considered to be a positive allergic response to cobalt (Veien et al. 1987). Using both the oral challenge test and dermal patch tests, it was determined that the cobalt allergy was systemically induced. The exposure level associated with sensitization to cobalt was not established. After sensitization, allergic reactivity may be independent of dose. Cobalt has been found to be a sensitizer following inhalation exposure (Section 3.2.1.3). This LOAEL value was not reported in Table 3-2 because sensitized individuals only represent a small percent of the population.

A case report of a 6-year-old boy who had ingested approximately 1.7 mg of cobalt chloride reported neutropenia by 7 hours post-exposure (Mucklow et al. 1990).

Thymic atrophy was reported in male Sprague-Dawley rats exposed to 3.79 mg cobalt/kg/day as cobalt chloride in the feed for 4 weeks (Chetty et al. 1979). A deterioration in immunological reactivity, manifested by a decline in phagocytic activity, was reported in rats following 6–7 months of treatment with 0.5 mg cobalt/kg or greater as cobalt chloride (Krasovskii and Fridlyand 1971). This value is presented in Table 3-2 and Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to stable cobalt.

Several rodent studies have identified neurological effects following cobalt exposure. In Wistar rats, a single gavage dose of 4.25 mg cobalt/kg as cobalt chloride resulted in a moderate reduction in spontaneous activity, muscle tone, touch response, and respiration, while 19.4 mg cobalt/kg as cobalt sulfate caused a mild reduction the same parameters (Singh and Junnarkar 1991). In rats exposed to 4.96 mg cobalt/kg/day as cobalt chloride for 30 days in the drinking water, cobalt led to changes in sympathetically mediated contractile activity of isolated rat vas deferens (Mutafova-Yambolieva et al. 1994). Rats exposed to 6.44 mg cobalt/kg/day as cobalt nitrate in the drinking water showed an increased sensitivity and decreased maximal response to a cholinergic agonist (Vassilev et al. 1993). In rats exposed to 20 mg cobalt/kg/day as cobalt chloride for 57 days in the drinking water, cobalt enhanced behavioral reactivity to stress (the animals were less likely to descend from a safe platform to an electrified grid) (Bourg et al. 1985). Rats exposed to the same dose in the diet for 69 days showed a slower rate of lever pressing than controls, but no change in behavioral reactivity to stress (Nation et al.

1983). Longer-term exposure of rats to cobalt chloride (7 months) resulted in a significant increase in the latent reflex period at ≥0.5 mg cobalt/kg as cobalt chloride and a pronounced neurotropic effect (disturbed conditioned reflexes) at 2.5 mg cobalt/kg (Krasovskii and Fridlyand 1971).

The NOAEL value and the LOAEL value for rats for intermediate duration are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to stable cobalt.

Testicular degeneration and atrophy have been reported in rats exposed to 13.3–58.9 mg cobalt/kg/day as cobalt chloride for 2–3 months in the diet or drinking water (Corrier et al. 1985; Domingo et al. 1984; Mollenhauer et al. 1985; Nation et al. 1983; Pedigo and Vernon 1993; Pedigo et al. 1988), or in mice exposed to 43.4 mg cobalt/kg/day as cobalt chloride for 13 weeks in the drinking water (Anderson et al. 1992, 1993).

The highest NOAEL and all reliable LOAEL values for rats in the intermediate-duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No developmental effects on human fetuses were observed following treatment of pregnant women with cobalt chloride to raise hematocrit and hemoglobin levels that are often depressed during pregnancy. Dosages up to 0.6 mg cobalt/kg/day for 90 days were given (Holly 1955). Examination of the fetuses, however, was limited to the reporting of obvious birth defects, and exposure only occurred in the final trimester.

Oral exposure of female rats to cobalt chloride at 5.4 or 21.8 mg cobalt/kg/day from gestation day 14 through lactation day 21 has been shown to result in stunted growth and decreased survival, respectively, of newborn pups (Domingo et al. 1985b). The effects on the offspring occurred at levels

that also caused maternal toxicity (reduced body weight and food consumption, and altered hematological measurements) and might therefore have been an indirect effect of maternal toxicity rather than a direct effect of cobalt on the fetus (Domingo et al. 1985b). Teratogenic effects were not observed.

Szakmary et al. (2001) reported that exposure of pregnant rats to 0–38 mg Co/kg-day as cobalt sulfate did not result in changes in fetal death rates, maternal body weigh gain, average litter size, or average fetal or placental weights; however, a dose-related trend was seen for the percent of fetuses with retarded body weights. In contrast, no effects on fetal growth or survival were found following exposure of rats to 24.8 mg cobalt/kg/day as cobalt chloride during gestation days 6–15 (Paternian et al. 1988). In mice, exposure to 81.7 mg cobalt/kg/day as cobalt chloride during gestation days 8–12 was reported to have no effect on fetal growth or mortality in mice (Seidenberg et al. 1986). In a later mouse study that exposed pregnant mice to 19 mg Co/kg-day as cobalt sulfate, no changes in litter size, postimplantation loss, or average fetal or placental weights were seen; the only difference seen was an increase in the percent of fetuses with retarded body weights (Szakmary et al. 2001). The same study reported that rabbits exposed to ≥ 38 mg Co/kg-day, as cobalt sulfate, showed nearly complete maternal lethality, and complete fetal loss. Rabbits exposed to 7.6 mg Co/kg, as cobalt sulfate, showed significant increases in mortality and fetal resorption, as well as an increase in fetuses with retarded body weight (Szakmary et al. 2001). The highest NOAEL and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

In a survey assessing the correlation between cancer mortality and trace metals in water supplies (10 basins) throughout the United States, no correlation was found between cancer mortality and the level of cobalt in the water (Berg and Burbank 1972). Cobalt levels of 1–19 µg/L, with resulting human intakes ranging from 0.03 to 0.54 µg/kg/day, were reported.

No studies were located regarding carcinogenic effects in animals after oral exposure to stable cobalt.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding lethal effects in humans after dermal exposure to cobalt.

No mortality was observed in guinea pigs dermally exposed to 51.75 mg cobalt/kg for 5 days/week as dicobalt octacarbonyl for a total of 18 applications (Kincaid et al. 1954).

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or ocular effects in humans or animals after dermal exposure to stable cobalt.

Dermal Effects. Dermatitis is a common result of dermal exposure to cobalt in humans that has been verified in a large number of studies (Alomar et al. 1985; Bedello et al. 1984; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goossens et al. 2001; Kanerva et al. 1988, 1998; Kiec-Swierczyńska and Krecisz 2002; Marcussen 1963; Minamoto et al. 2002; Pryce and King 1990; Swennen et al. 1993; Romaguera et al. 1982; Valer et al. 1967). Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt. Contact allergy was reported in 22 of 223 (9.9%) nurses who were tested with a patch test of 1.0% cobalt chloride (Kieć-Świerczyńska and Kręcisz 2000), as well as 16 of 79 (20.3%) of examined dentists (Kieć-Świerczyńska and Kręcisz 2002). Persons with body piercings showed an increased prevalence of allergy to cobalt, with the incidence of contact allergy being proportional to number of piercings (Ehrlich et al. 2001). The prevalence of sensitivity to cobalt following exposure to cobalt as a component of metal implants is low, with only 3.8% of patients developing a new sensitivity to cobalt following insertion of the implant (Swiontkowski et al. 2001). Exposure levels associated with the development of dermatitis have not been identified. It appears that the allergic properties of cobalt result mainly from exposure to the metal itself, rather than a salt, as Nielsen et al. (2000) demonstrated that daily repeated exposure to aqueous cobalt salts did not result in hand eczema in patients known to have cobalt allergy.

In animals, scabs and denuded areas were found after six doses of 51.75 mg cobalt/kg (5 days/week) as dicobalt octacarbonyl were applied to the shaved abdomens (uncovered area of approximately 50 cm^2) of guinea pigs (Kincaid et al. 1954). By the 11^{th} dose, the lesions disappeared. No adverse effects were observed in vehicle controls (methyl ethyl ketone). It is not known whether or not a similar reaction would result from metallic or inorganic forms of cobalt. This LOAEL value is reported in Table 3-3.

3.2.3.3 Immunological and Lymphoreticular Effects

Cobalt-induced dermatitis is well documented in the literature, and the studies indicate that cobalt is a sensitizer (Alomar et al. 1985; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Valer et al. 1967). Patch testing and intradermal injections were performed, but exposure levels of cobalt were not reported. Interrelationships exist between nickel and cobalt sensitization (Bencko et al. 1983; Rystedt and Fisher 1983); however, the extent of any potential interactions between the two metals on immunologic end points is not well understood. In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al. 1985), though cross-reactivity was not reported to occur.

Single or multiple dermal exposures of BALB/c mice to $CoCl_2$ in dimethylsulfoxide or in ethanol resulted in an increased cellular proliferation in the local lymph node assay in a concentration-dependant manner (Ikarashi et al. 1992a). The effect of three consecutive exposures to varying concentrations of $CoCl_2$ in DMSO on lymph node proliferation was measured in rats, mice, and guinea pigs (Ikarashi et al. 1992b). Stimulation Indices of 3 or greater, indicated by the authors as a significant response, were reported for mice exposed to 1, 2.5, or 5% $CoCl_2$, rats exposed to 2.5 or 5% $CoCl_2$, and guinea pigs exposed to 5% $CoCl_2$; these treatments resulted in dose levels of 10.8, 27, or 54.1 mg cobalt/kg/day for mice, 9.60 or 19.2 mg cobalt/kg/day for rats, and 14.7 mg cobalt/kg/day for guinea pigs.

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

Table 3-3 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
ACUTE EXPOSURE							
Immuno/ Lymphoret							
Rat (Fischer- 344)	1x/d 3d		3.84 F mg/kg/day	9.6 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
Mouse (BALB/c)	1x or 1x/d for 3 d			10.8 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992a Chloride
Mouse CBA/N	1x/d 3 d		5.4 F mg/kg/day	10.8 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
Gn Pig (Hartley)	1x/d 3 d		7.39 F mg/kg/day	14.7 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
INTERMEDIATE EXPOSURE							
Systemic							
Gn Pig (NS)	18 d 5 d/wk	Dermal		51.75 mg/kg/day	(skin lesions (scabs and denuded areas) at application site)		Kincaid et al. 1954

d =day(s); F = female; LOAEL = lowest-observed-adverse-effect level; NOAEL = no observed-adverse-effect level; wk = week(s); x = times.

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to cobalt.

3.2.4 Other Routes of Exposure

Endocrine Effects. Patients (n=12) injected with a single diagnostic dose of radioactive iodine, and then treated 48 hours later with 1 mg cobalt/kg/day as cobalt chloride for 2 weeks, resulted in a greatly reduced uptake of radioactive iodine by the thyroid in 1 week, with uptake nearing 0 by the second week (Roche and Layrisse 1956). When the cobalt treatment ended, the uptake values returned to normal. The decrease of radioactive iodine uptake found in patients administered 0.54 mg cobalt/kg/day for 10–25 days prior to iodine injection was found to result from cobalt blocking the organic binding of iodine (Paley et al. 1958).

In various species of animals, parenteral administration of cobalt resulted in cytotoxic effects on the alpha cells of the pancreas (Beskid 1963; Goldner et al. 1952; Hakanson et al. 1974; Lacy and Cardeza 1958; Lazarus et al. 1953; Van Campenhout 1955). Because this effect has never been reported in humans or animals following inhalation, oral, or dermal exposure to cobalt, the relevance of the effect to humans is not known.

Moger (1983) exposed primary cultures of mouse Leydig cells to 0–2.5 mM cobalt as cobalt for 3 hours, and measured the effects on androgen production. Cobalt exposure caused a dose-related decrease in both basal and LH-stimulated androgen production, with no effects on protein synthesis. The author suggested that these effects are the result of cobalt inhibition of calcium influx across the plasma membrane.

3.3 DISCUSSION OF HEALTH EFFECTS OF RADIOACTIVE COBALT BY ROUTE OF EXPOSURE

Section 3.3 discusses radiation toxicity associated with exposure to radionuclides of cobalt and is organized in the same manner as that of Section 3.2, first by route of exposure (inhalation, oral, and external) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing NOAELs or LOAELs reflect the actual dose (levels of exposure) used in the studies. Refer to Section 3.2 for detailed discussion of the classification of endpoints as a NOAEL, less serious LOAEL, or serious LOAEL.

Refer to Appendix B for a User's Guide, which should aid in the interpretation of the tables and figures for Levels of Significant Exposure.

3.3.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals after inhalation exposure to radioactive cobalt:

3.3.1.1 Death

3.3.1.2 Systemic Effects

3.3.1.3 Immunological and Lymphoreticular Effects

3.3.1.4 Neurological Effects

3.3.1.5 Reproductive Effects

3.3.1.6 Developmental Effects

3.3.1.7 Cancer

3.3.2 Oral Exposure

No studies were located regarding the following health effects in humans or animals after oral exposure to radioactive cobalt:

3.3.2.1 Death

3.3.2.2 Systemic Effects

3.3.2.3 Immunological and Lymphoreticular Effects

3.3.2.4 Neurological Effects

3.3.2.5 Reproductive Effects

3.3.2.6 Developmental Effects

3.3.2.7 Cancer

3.3.3 External Exposure

This section contains information regarding health effects related to external exposure to radioactive cobalt sources. Radionuclides of cobalt may emit beta particles and/or gamma rays, which may be a health hazard in living organisms because they ionize the atoms that they hit while passing through the tissues of the body (see Table 3-4 and Figure 3-3). Beta particles can travel appreciable distances in air, but travel only a few millimeters in solids. External exposure to beta particles may result in damage to skin and superficial body tissues at sufficiently high doses. Beta radiation is only a threat to internal organs if the radiation source is internalized. Gamma radiation, on the other hand, can easily pass completely through the human body and cause ionization of atoms in its path. For most radionuclides of public interest, the fraction of gamma rays that actually deposits energy and contributes to the radiation

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL			Reference Chemical Form
					Less Serious (rad)	Serious (rad)		
	ACUTE EXPOSURE							
	Death							
1	Human					2250 M	(Death)	Stavem et al. 1985
2	Mouse (BALB/c)					627	(30-day LD50 value, single exposure)	Darwezah et al. 1988
3	Mouse CBA/Ca.Lac.C	1x				1420 M	(Death)	Down et al. 1986
	Systemic							
4	Human	(occup)	Gastro	12.7				House et al. 1992
			Hemato	12.7				
5	Human		Dermal			159 M	(Severe alterations to skin of left hand)	Klener et al. 1986
			Ocular			159 M	(Progressive occlusion of vision of left eye)	

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
6	Human		Cardio			2250 M (left ventricular hypertrophy)	Stavem et al. 1985
			Gastro			2250 M (Pronounced atrophy in intestines; less severe in stomach)	
			Hemato			2250 M (>35% decrease in hemogolbin and >90% decrease in thrombocytes)	
			Renal		2250 M (Enlarged kidneys)		
7	Monkey (Rhesus)	30 min	Cardio		1000 M (Minor changes: increased heart rate; decreased blood pressure; variable cardiac output and total peripheral resistance)		Bruner 1977
8	Monkey (Rhesus)	1 hr	Cardio			10000 M (Pronounced decreases in mean arterial blood pressure and blood flow to the brain)	Cockerham et al. 1986
9	Rat (Wistar)		Cardio		2500 M (Increased brain uptake index)		Bezek et al. 1990

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
10	Rat (Sprague-Dawley)	1x	Resp			1500 M (Severe inflammation, pulmonary histopathology, fibrosis)	Lafuma et al. 1987
11	Mouse (Swiss-Webster)		Gastro		1000 M (Intestinal crypt cell damage, including necrosis and altered mitotic figures)		Devi et al. 1979
12	Mouse CBA/Ca.Lac.C	1x	Resp		1330 M (Increased breathing rate)		Down et al. 1986
			Dermal		1800 M (Mild epilation)		
13	Mouse (Swiss-Webster)	24 hr	Hepatic		1000 M (Transient decrease in total liver protein)		Mazur et al. 1991
14	Dog (Mongrel)	198 d	Cardio			4355 (Cardiac arrhythmia)	Dick et al. 1979
15	Dog (Beagle)	10.44 min	Gastro		800 (Repeated emesis)		Gomez-de-Segura et al. 1998

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
16	Rabbit (New Zealand)	1x	Dermal		1730 M (Alopecia)		Cox et al. 1981
17	Pig Large White	1x	Resp		900 F (Reversible decrease in ventilation capacity)	1090 F (Irreversible decrease in ventilation capacity, histopathology, pulmonary atrophy)	Rezvani et al. 1989
18	Pig Large White	1x	Renal			874 F (50% loss in effective renal plasma flow)	Robbins et al. 1989a
19	Pig Large White	1x	Hemato		780 F (Slight decreases in erythrocytes, hemoglobin, and hematocrit)	1190 F (Severe decreases in erythrocytes, hemoglobin, and hematocrit)	Robbins et al. 1989b
			Renal		780 F (Reversible changes in effective renal plasma flow and glomerular filtration rate)	980 F (Persistent changes in effective renal plasma flow and glomerular filtration rate)	
20	Pig Large White	1x	Renal			557 F (50% loss in effective renal plasma flow)	Robbins et al. 1989c

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
21	Pig Large White	1x	Renal			980 F (Progressive inflammatory and degenerative changes in the glomerulus)	Robbins et al. 1991
22	Baboon	3-4 wk, 1x/wk	Resp			3000 (Severe pulmonary fibrosis)	Collins et al. 1978
23	Ferret	2 hr	Gastro	49 M	77 M (Emesis with wretching)		King 1988
	Immuno/ Lymphoret						
24	Human	(occup)		12.7			House et al. 1992
25	Human				159 M (Minor reduction in white cell counts)		Klener et al. 1986
26	Human					2250 M (Pronounced decrease in lymphocytes and granulocytes)	Stavem et al. 1985

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
27	Mouse (Swiss-Webster)	24 hr			1000 M (>50% decrease in spleen weight and protein; increased spleen acid phosphatase)		Mazur et al. 1991
	Neurological						
28	Rat (CD)	140 d		150 M	450 M (Reversible deficits in fixed-ratio behavior parameters)		Mele et al. 1988
29	Mouse (Swiss-Webster)	97 d		300 M	500 M (Reversible decreases in aggressive behavior)		Maier and Landauer 1989
30	Rabbit Burgundy fawn	12 hr			450 M (Altered firing rates and patterns of hippocampal neurons)		Bassant and Court 1978
	Reproductive						
31	Rat (Sprague-Dawley)	1x			330 M (Decreased testis weight and altered spermatogenesis, with some evidence of recovery)		Cunningham and Huckins 1978
32	Rat (Wistar)	1x			80 M (Reversible decrease in testicular weight)		Laporte et al. 1985

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	Developmental						
33	Monkey Squirrel	1x				100 (Developmental retardation, neurobehavioral deficits)	Brizzee et al. 1978
34	Rat (Sprague-Dawley)	1x				50 F (Defective eye development and spinal curvature)	Bruni et al. 1994
35	Rat	1x				260 (Testicular trophy; adrenal atrophy)	Inano et al. 1989
36	Rat (Wistar)	1x			260 M (Reduced NADPH cytochrome p450 reductase)		Inano et al. 1990
37	Rat (Wistar)	4d or 6d		11	16 (slightly decreased (2.6%) brain weight in offspring)	560 (decreased (13.1%) brain weight in offspring)	Reyners et al. 1992
38	Rat (Wistar)	1x				210 M (Testicular atrophy)	Suzuki et al. 1990

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)		LOAEL Serious (rad)		Reference Chemical Form
39	Mouse (Swiss-Webster)	1x		5	10	(Decreased brain weight 3-4%, significantly increased microphthalmia)	50	(Increased fetal mortality and growth retardation)	Devi et al. 1994
40	Mouse (Swiss-Webster)	1x			25	(Decreased body weight 5%, liver weight 5%, and spleen weight 12%. Decreased spleen cellularity.)			Devi et al. 1998
41	Mouse (B6C3F1)	1x					100 M	(Increased number of tumor-bearing animals after in utero exposure)	Nitta et al. 1992
42	Mouse (Swiss-Webster)	1x					200	(Atrophy or lack of development of corpus callosum)	Schmidt and Lent 1987
43	Mouse	6d					20 F	(Altered neurobehavioral parameters, growth retardation)	Want et al. 1993

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)		LOAEL Serious (rad)		Reference Chemical Form
44	Mouse LACA	1x					50	(Delayed development, altered hindlimb splay)	Zhong et al. 1996
45	Hamster (Golden Syrian)	1x					200 F	(Severe developmental abnormalities of multiple organ systems, embryo death)	Harvey et al. 1962
46	Dog (Beagle)	1x					83	(Increased risk of thyroid neoplasia)	Benjamin et al. 1997
47	Dog (Beagle)	1x					15.6	(Increased cancer-related mortality - multiple tumor types)	Benjamin et al. 1998b
48	Dog (Beagle)	1x		16	83	(Hypodontia)			Lee et al. 1989
49	Dog (Beagle)	1x					96	(Optic atrophy/degeneration)	Schweitzer et al. 1987

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	Cancer						
50	Dog (Beagle)	1x				15.6 (Increased cancer-related mortality)	Benjamin et al. 1998b
	INTERMEDIATE EXPOSURE						
	Death						
51	Human					7500 F (Death)	Roscher and Woodard 1969
	Systemic						
52	Human		Ocular			4800 F (Progressive visual impairment and blindness)	Fishman et al. 1976
53	Human	22 - 35 d teletherapy	Cardio			4623 (Persistent pericarditis)	Martin et al. 1975
54	Human	18 d	Gastro		3600 (Loose bowel movements, impaired absorption of vitamin B12)		McBrien 1973
55	Human	17 d	Dermal		4056 F (Comedones, which were resolved with treatment)		Myskowski and Safai 1981

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
56	Human		Gastro			7500 F (Severe gastrointestinal necrosis and fibrosis)	Roscher and Woodard 1969
57	Human	3 yr	Other	2400			Thibadoux et al. 1980
58	Human	7 wk	Dermal		4700 (Reversible changes in skin pigmentation)		van Oort et al. 1984
59	Rat (albino)	10 wk	Other	2400 M	4800 M (Transient alterations in incisor histopathology)	7200 M (Lasting alterations in incisor histopathology)	Sweeney et al. 1977
60	Dog (Beagle)	150-300 d	Hemato			1125 M (Aplastic anemia)	Seed et al. 1989
	Immuno/ Lymphoret						
61	Dog (Beagle)	150-300 d				1125 M (Dose- and time-related reduction in granulocytes, monocytes, and lymphocytes)	Seed et al. 1989

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	Neurological						
62	Human					4800 F (Optic nerve damage, resulting in visual impairment and blindness)	Fishman et al. 1976
63	Human	9 mo				13150 F (Neural necrosis and gliosis)	Llena et al. 1976
64	Human					5500 M (Partial paralysis secondary to radiation myelopathy) 5000 F[b] (Partial paralysis secondary to radiation myelopathy)	Sanyal et al. 1979
	Reproductive						
65	Human	47 d				6600 M (Calcification of the prostate)	Keys and Reed 1980
66	Mouse	32 wk				1282 F (Decreased offspring per litter and sterility)	Searle et al. 1980
	Cancer						
67	Human	NS				1800 F (Basal cell carcinoma)	Garcia-Silva et al. 1996
68	Human	8 mo				25150 M (Multiple basal cell carcinomas)	Wollenberg et al. 1995

[a] Key to figure

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
69	Human	3 yr	Cardio			13150 F (Endothelial hyperplasia, dysplasia, and fibrosis)	Llena et al. 1976

[a] The number corresponds to entries in Figure 3-3.

[b] Differences in levels of health and cancer effects between males and females are not indicated in Figure 3-3. Where such differences exits, only the levels of effect for the most sensitive gender are represented.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; min = minute(s); mo = month(s); NOAEL = no observed-adverse-effect level; NS = not specified; (occup) = occupational; Resp = respiratory; wk = week(s); yr = year(s).

Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation

Acute (≤14 days)

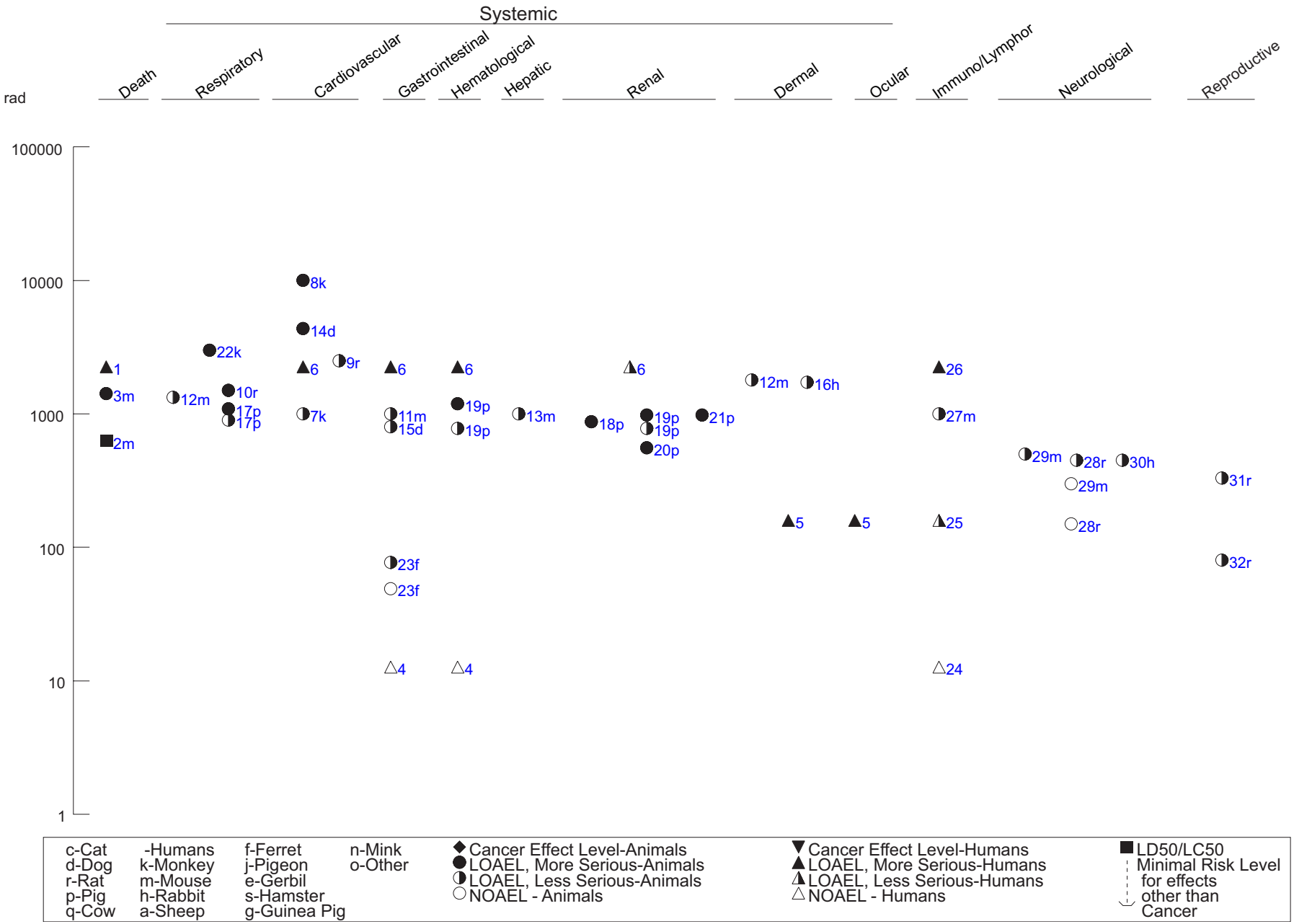


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Acute (≤14 days)

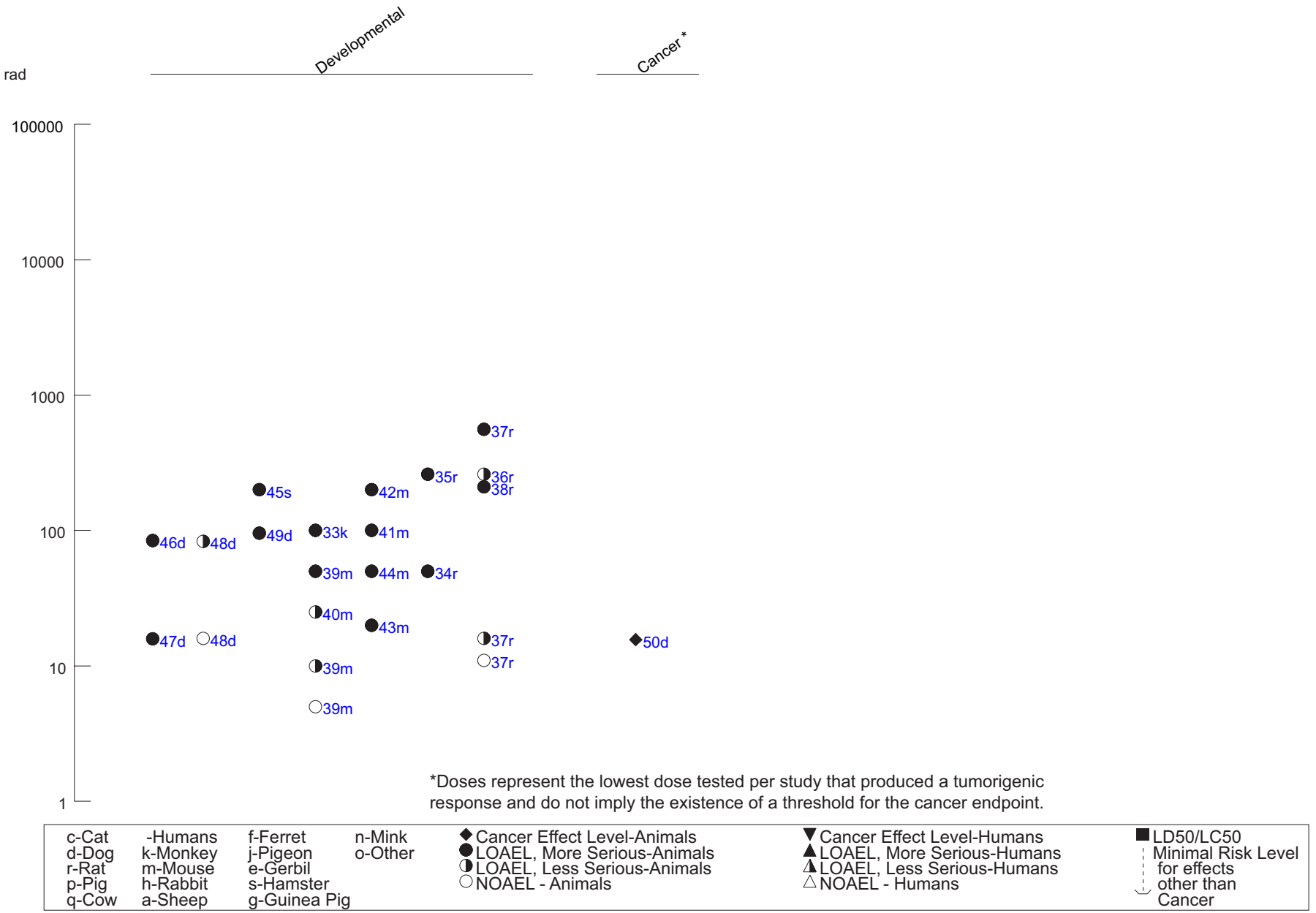


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Intermediate (15-364 days)

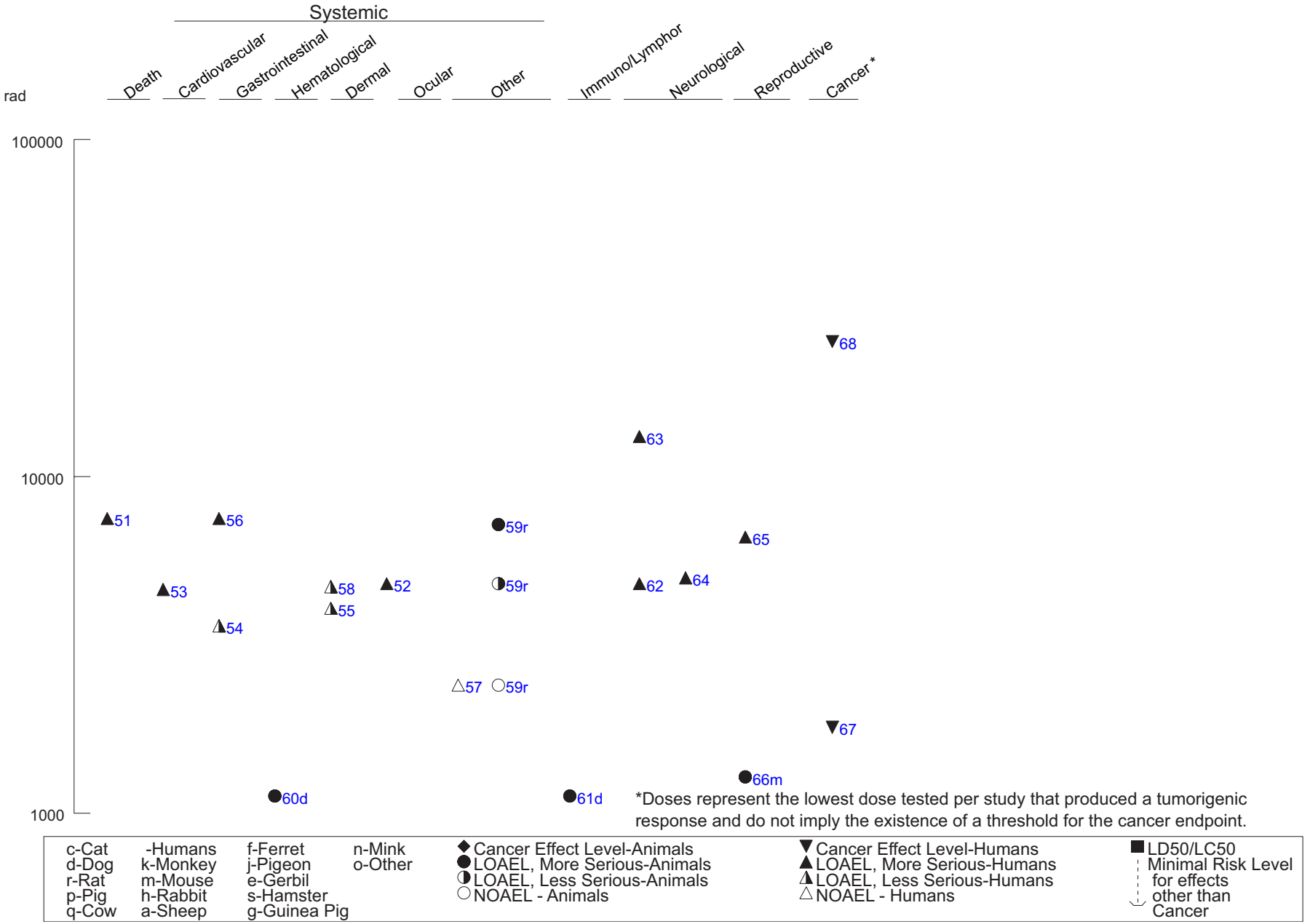
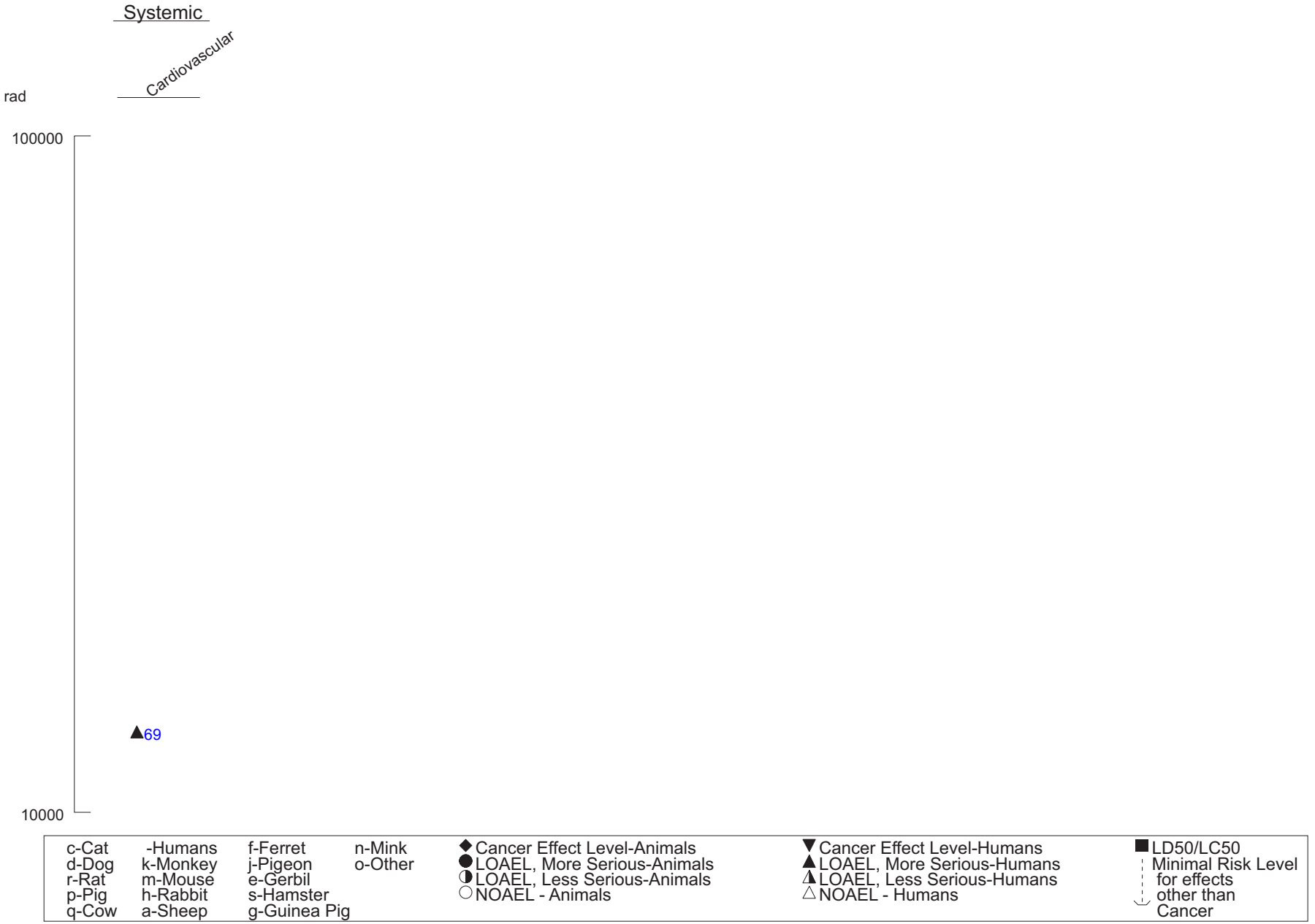


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Chronic (≥365 days)



dose increases with tissue density (resulting in a higher dose to bone than soft tissue) and decreases with energy. Several feet of concrete or a few inches of lead are typical shield thicknesses for protection from gamma rays. Because it is so highly penetrating, gamma radiation released by radionuclides such as cobalt may be a radiation hazard to internal organs (Agency for Toxic Substances and Disease Registry 1999; EPA 1997b). ^{60}Co gamma rays are commonly used for human radiotherapy. The purpose of this section is to provide information regarding health effects associated with external exposure to a radioactive cobalt source. These health effects are not specific to cobalt, but apply to any radionuclide delivering the same beta and gamma radiation dose at a comparable dose rate. Refer to Agency for Toxic Substances and Disease Registry (1999) for a detailed description of health effects from external exposure to ionizing radiation in general.

3.3.3.1 Death

Exposure to high levels of external radiation, including radiation from cobalt radionuclides, may result in mortality when the whole body dose exceeds 300 rads. Stavem et al. (1985) reported a case in which a worker was exposed to 2,250 rad (22.5 Gy) within a few minutes time, resulting in death due to acute radiation sickness (depressed leukocyte counts, vomiting, diarrhea, etc.). Complications resulting from cobalt radiotherapy resulted in the death of a patient from severe gastrointestinal complications (Roschler and Woodard 1969).

Norris and Poole (1969) reported on the mortality of dogs exposed to ^{60}Co gamma rays at a rate of 35 rad (0.35 Gy) per day for 40 days, resulting in a cumulative exposure of 1,400 rad (14 Gy). Twelve of 40 animals died prior to termination of the 40-day exposure period, 13 of 40 died within the 23-day post-exposure observation period, and 15 survived to the end of the study period, indicating an LD_{50} of <1,400 rad at 35 rad/day. Darwezah et al. (1988) reported single, whole-body exposure LD_{50} values in mice of 913 rad (9.13 Gy) and 627 rad (6.27 Gy) at 6 and 30 days post-irradiation, respectfully. Down et al. (1986) reported a slightly higher LD_{50} of 1,400–1,450 rad (14–14.5 Gy) for ^{60}Co thoracic irradiation in mice at 26 days postirradiation. Several studies have demonstrated that decreasing the dose rate or the portion of the body exposed will increase the LD_{50} for ^{60}Co gamma rays (Darwezah et al. 1988; Down et al. 1986; Hanks et al. 1966; Page et al. 1968).

3.3.3.2 Systemic Effects

Respiratory Effects. Ionizing radiation is known to exert dramatic effects on the tissue of the lung (Agency for Toxic Substances and Disease Registry 1999; Davis et al. 1992; Libshitz 1993; Roswit and White 1977), particularly at the high doses used in radiotherapy. The first phase of damage usually consists of radiation pneumonitis, which occurs between 3 and 13 weeks after irradiation and is characterized by low-grade fever, mild exertional dyspnea, congestion, and unproductive cough. The second phase is characterized by radiation-induced lung fibrosis, emphysema, and pleural thickening. Patients receiving radiotherapy treatment regimens of ≥4,000 rad (40 Gy) to the chest region almost always develop radiographic changes in the lung (Davis et al. 1992), whereas lower therapeutic doses (2,500–3,000 rad, 25–30 Gy) generally result in a lower risk of adverse pulmonary symptoms (Davis et al. 1992; Roswit and White 1977). Prophylactic protective measures may be taken, and these symptoms may be treated later if detected early enough in their progression (Roswit and White 1977).

At similar doses, studies in animals, including rats, mice, baboons, and pigs, using ^{60}Co radiation have also shown radiation pneumonitis and fibrosis, similar to effects seen in humans (Collins et al. 1978; Down et al. 1986; Lafuma et al. 1987; Rezvani et al. 1989). Other respiratory changes seen in animal experiments included an increased breathing rate, effects on the surfactant system, edema, increased pleural fluid content, pulmonary atrophy, and histologic alterations of the lung parenchyma (Bellet-Barthas et al. 1980; Collins et al. 1978; Down et al. 1986; Lafuma et al. 1987).

Cardiovascular Effects. Martin et al. (1975) reported that 24 of 81 patients who underwent ^{60}Co teletherapy for Hodgkin's disease, using an upper mantle treatment regimen of 4,000 rad (40 Gy) over 22–35 days, developed radiation-related pericarditis. In 14 of these patients, the condition was transient, while it persisted in the other 10 patients. Llena et al. (1976) presented a case wherein a 51-year-old woman who had received a localized dose of 13,150 rad (131.5 Gy) of ^{60}Co radiation between the nasopharynx and cervical lymph nodes as part of radiotherapy developed severe alterations in the endothelial cells of the brain, including proliferation, increased cytoplasmic organelles, and infoldings of the plasma membrane.

Whole-body exposure of Rhesus monkeys to 10,000 rad (100 Gy) over a 90-second period resulted in dramatic decreases in mean systemic arterial blood pressure, as well as in mean blood flow in the pons and pre-central gyrus, beginning at 10 minutes post-irradiation and persisting throughout the 60-minute

observation period (Cockerham et al. 1986). Bruner (1977) examined cardiovascular parameters in Rhesus monkeys exposed to 1,000 rad (10 Gy) at rates of 129–164 rad/minute (1.29–1.64 Gy/minute). Heart rate was elevated post-exposure, blood pressure was reduced near the end of exposure and thereafter, cardiac output increased at the end of exposure, but thereafter fell to below control levels, and total peripheral resistance to blood flow decreased at early times post-exposure, but thereafter rose to above control levels. Ten of 12 dogs irradiated with 4,355–5,655 rad (43.6–56.6 Gy), focused on the interatrial septum of the heart, developed cardiac arrhythmias (Dick et al. 1979). The permeability of the blood-brain barrier was significantly increased, particularly for hydrophillic compounds, in rats exposed to 2,500 rad (25 Gy) from a ^{60}Co source (Bezek et al. 1990).

Gastrointestinal Effects. A worker accidentally exposed to an acute whole-body dose of 2,250 rad (22.5 Gy) showed slight atrophy of the stomach glands, marked atrophy in the small intestine, and total atrophy of the glands in the large intestine (Stavem et al. 1985). Two years after a woman received ^{60}Co radiation therapy amounting to 4,000 rad (40 Gy) anteriorly and 3,500 rad (35 Gy) posteriorly over a 6-week period, she reported severe gastrointestinal difficulties, including epigastric pain, vomiting, bloody stools, and weight loss (Roschler and Woodard 1969), eventually resulting in death. Autopsy revealed dense fibrous layers around the sacrum, with severe fibrosis confirmed by microscopic examination. Cobalt radiotherapy for carcinoma of the bladder (~3,100–3,600 rad, 31–36 Gy, over 18 days) resulted in loose bowel movements and a decreased absorption of vitamin B12 following oral exposure in 8 of 14 patients (McBrien 1973). No gastrointestinal symptoms were reported in three workers who were accidentally exposed to much lower exposure levels, ranging from 2.24 to 12.7 rad (0.022–0.127 Gy) (House et al. 1992).

Exposure of male Sprague-Dawley rats to 850 rad (8.5 Gy) of ^{60}Co gamma radiation resulted in marked alterations in drug absorption, primarily due to a decrease in gastric emptying rate (Brady and Hayton 1977b). Exposure of young adult beagle dogs to 800 rad (8 Gy) of ^{60}Co radiation at a rate of 177.5 rad/minute (1.775 Gy/minute) resulted in a 100% emesis rate within 10 hours post-irradiation, with an average of 2.4 episodes per animal and an average time to emesis of 82 minutes (Gomez-d-Segura et al. 1998). King (1988a) reported a NOAEL of 49 rad (0.49 Gy) and an EC_{50} of 77 rad (0.77 Gy) for emesis and wretching following exposure of male ferrets to ^{60}Co gamma radiation. Exposure of male Swiss mice to 1,000 rad (10 Gy) of ^{60}Co radiation resulted in necrosis of the intestinal crypt cells (Devi et al. 1979).

Hematological Effects. No changes in hematologic parameters were reported in three workers who were accidentally exposed to levels ranging from 2.24 to 12.7 rad (0.022–0.127 Gy) (House et al. 1992). Hashimoto and Mitsuyasu (1967) reported that in 50 of 58 patients receiving local radiotherapy, irradiated bone marrow was more hypoplastic in the hematopoietic elements than in non-irradiated marrow in the same individual. A male worker exposed to 159 rad (1.59 Gy) showed minor reductions in leukocytes, neutrophils, and lymphocytes (Klener et al. 1986). Stavem et al. (1985) reported that a male worker exposed to 2,250 rad (22.5 Gy) showed a progressive decrease in hemoglobin and circulating thrombocytes prior to death. Autopsy showed a pronounced hypocellularity of the bone marrow.

Seed et al. (1989) exposed male Beagle dogs to 7.5 rad/day (0.075 Gy/day) gamma radiation for 150–700 days from a ^{60}Co source. The irradiated dogs initially showed a significant suppression, compared with levels from the control animals, of the five circulating types of cells studied (granulocytes, monocytes, platelets, erythrocytes, and lymphocytes), which lasted ~250 days; this was followed by a recovery phase for the remainder of the study period. Hashimoto and Mitsuyasu (1967) exposed guinea pigs to whole-body ^{60}Co radiation, and reported an initial hypoplasia of the bone marrow followed by recovery of hematopoietic activity by 3 weeks post-irradiation. Robbins et al. (1989b) reported significant reductions in erythrocyte count, hematocrit, and hemoglobin levels within 6–8 weeks of irradiation of the kidneys of female pigs with 980–1,400 rad (9.8–14 Gy) of ^{60}Co gamma rays.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following external exposure to ^{60}Co radiation. These tissues are among the most radioresistant in both humans and animals.

Hepatic Effects. No studies were located regarding hepatic effects in humans following external exposure to ^{60}Co radiation.

No changes in liver weight were seen in male Swiss mice exposed to 1,000 rad (10 Gy) of ^{60}Co radiation and examined every 4 hours for 24 hours post-irradiation (Mazur et al. 1991). Andrzejewski et al. (1980) reported increased respiration rates in rat liver mitochondria after whole-body exposure to 1,000 or 3,000 rad (10 or 30 Gy) of ^{60}Co radiation; the increase was greater and more persistent at the higher dose level.

Renal Effects. Stavem et al. (1985) reported that a 64-year-old man who accidentally received a fatal dose (2,250 rad) of cobalt radiation developed enlarged kidneys. No other studies were located regarding renal effects in humans after external exposure to cobalt radiation.

Robbins et al. (1989a, 1989b, 1989c, 1991a, 1991b) performed a series of studies in female White pigs wherein the kidneys of the animals were exposed to single doses of 780–1,400 rad (7.8–14 Gy) of ^{60}Co radiation and examined for periods up to 24 weeks postirradiation. Irradiation resulted in an initial increase in glomerular filtration rate (GFR), followed by a dose-related decrease in the GFR, beginning at 4 weeks postexposure. Effective renal plasma flow (ERPF) was also decreased in a dose-related manner beginning at 4 weeks postexposure, but did not show the initial increase seen in GFR. Some recovery of GFR and ERPF occurred by 24 weeks postirradiation, though values were still significantly reduced below controls in all groups but the 780 rad (7.8 Gy) group. Histology was performed on animals exposed to 980 rad (9.8 Gy) and killed between 2 and 24 weeks after exposure. Beginning at 2 weeks postirradiation, increased numbers of inflammatory cells were present within the glomerulus, and there was an increase in mesangial matrix and number of mesangial cells. The glomerular changes continued to progress in severity throughout the observation period, with generalized thickening of the capillary walls, extensive duplication of the basement membrane, and progressive inflammation. Tubular changes appeared to be maximal at 6 weeks, including focal degeneration and necrosis, with partial recovery at later timepoints.

Endocrine Effects. Prager et al. (1972) reported that 5 of 23 patients receiving cobalt radiotherapy (3,900–4,600 rad, 39–46 Gy) for Hodgkin's disease developed hypothyroidism, with substantial decreases in levels of T4 relative to patients with normal thyroids. Chang et al. (2001) examined the residents of ^{60}Co-contaminated buildings for effects on the thyroid. There was an increased prevalence of goiter in males of all ages and females <15 years of age, as well as a dose-related increase in the prevalence of thyroid cysts in females of all ages, and elevated tri-iodothyronine levels in males <15 years of age. No other studies examining the endocrine effects of radioactive cobalt exposure, either internal or external, in humans were located.

Whole-body acute exposure of rats to 330 rad (3.3 Gy) did not affect FSH, LH, or testosterone levels (Cunningham and Huckins 1978). Similarly, male Wistar rats exposed to a single dose of 80 rad (0.8 Gy) of testicular radiation showed no changes in FSH, LH, prolactin, or testosterone (Laporte et al. 1985). No

other studies examining the endocrine effects of radioactive cobalt exposure, either internal or external, in animals were located.

Dermal Effects. Several studies in humans have demonstrated that high-dose exposure to cobalt radiation can result in damage to the skin. Klener et al. (1986) described the accidental irradiation of a worker who was attempting to bring under control a sealed ^{60}Co source. The patient's left palm (the patient was left-handed) developed an irregular oval defect 3x4 cm with whitish edges and bleeding, as well as superficial lesions on the third and fourth finger. Considerable spontaneous pain required the administration of analgesics. The lesions showed no tendency to heal, instead spreading to the adjacent digits. After several failed skin graft attempts, the condition worsened, necessitating the amputation of fingers five through two. Walter (1980) reported that a patient who had undergone ^{60}Co radiotherapy (dose not reported) of the forehead and scalp developed a pronounced acneform reaction, characterized primarily by alopecia with multiple open comedones on the scalp and forehead, and hair loss. With treatment, the comedones were 80% cleared at 9 months post-diagnosis (13 months post-treatment), but no hair regrowth was noted. Myskowski and Safai (1981) have likewise reported localized comedones in a patient following 4,056 rad (40.6 Gy) of ^{60}Co radiotherapy. Van Oort et al. (1984) reported that patients receiving 4,700–6,000 rad (47–60 Gy) of ^{60}Co radiotherapy over a 7-week period showed significant differences in baseline color of the skin, primarily erythema, and pigmentation, beginning the third week of exposure and persisting throughout the fifth week postirradiation (study week 12). Johansson et al. (2000) reported that 86% of women who had been treated with 5,400–5,700 rad (54–57 Gy) after a radical mastectomy developed fibrosis of the skin of the treated area.

Cox et al. (1981) reported a dose-related loss of hair in rabbits exposed to 1,730–3,210 rad (17.3–32.1 Gy) ^{60}Co gamma rays, targeted at the skin near the eyes or of the ears, with recovery initially noted in animals exposed to 2,140 rad (<21.4 Gy) by day 200 postirradiation. Beginning at day 500 postirradiation, a substantial loss of hair again was seen, persisting throughout the end of the study. Mice exposed to 1,800 rad (18 Gy) of ^{60}Co radiation showed a slight increase in epilation score (Down et al. 1986).

Ocular Effects. Exposure to high-dose radiation from cobalt sources has been shown to result in effects on the eye, in particular the development of cataracts. Augsburger and Shields (1985) described 13 patients who developed cataracts following ^{60}Co plaque radiotherapy; estimated doses to the eyes ranged from 2,000 to 10,000 rad (20–100 Gy). Fishman et al. (1976) reported on two patients who

received head-only 60Co radiotherapy, in combination with chemotherapy, for the treatment of acute lymphocytic leukemia. Both patients, who received 2,400 rad (24 Gy) over an initial 16-day course of treatment followed later by either 2,400 or 2,500 rad (24 or 25 Gy) in followup therapy, developed progressively severe vision disorders, resulting in partial or total blindness. Exposure of a male worker to a whole-body dose of 159 rad (1.59 Gy) of ^{60}Co radiation resulted in a progressive deterioration of visual acuity, due to cataract development, in the left eye (which was more exposed than the right) over time (Klener et al. 1986). Chen et al. (2001) evaluated subjects that had been exposed to 120–194 mSv (range: 1.11–1493.4 mSv) for an undisclosed period of time for lenticular opacities. Subjects <20 years old showed a dose-dependent increase in the numbers of focal lens defects, while for those aged 20–40 and >40, no such statistical correlation was seen.

Other Systemic Effects. Thibadoux et al. (1980) reported that of 61 children receiving a course of 2,400 rad (24 Gy) of cranial radiotherapy, none developed significant reductions in hearing levels by the end of the third year after irradiation.

Taiwanese children (48 boys, 37 girls) who were raised in apartments contaminated with ^{60}Co were compared to 21,898 age- and sex-matched nonexposed children from a nationwide surveillance program (Wang et al. 2001). After adjusting for effects from parental heights and body mass index, clear dose-related decreases in height percentile (HP) and age-specific relative height differences (RHD) were seen in exposed boys, but not in exposed girls. Average cumulative doses were 120.8 and 129.9 mSv for the boys and girls, respectively.

Sweeney et al. (1977) examined the effects of 60Co radiation on the teeth of rats exposed to 0, 2,400, 4,800, or 7,200 rad (0, 24, 48, or 72 Gy). Animals exposed to 4,800 rad (48 Gy) showed transient effects on the incisors only, while at 7,200 rad (72 Gy), the effects lasted throughout the 10-week study period.

3.3.3.3 Immunological and Lymphoreticular Effects

A worker accidentally exposed to an acute dose of 2,250 rad (22.5 Gy) showed a rapid fall in circulating lymphocytes and granulocytes prior to death (Stavem et al. 1985). Chronic exposure to low amounts of ^{60}Co radiation in people living in a contaminated building significantly reduced the numbers of circulating CD4+ lymphocytes in the blood (Chang et al. 1997, 1999b); mean total radiation dose was estimated to be

0.169 Gy (16.9 rad) over a 2–13-year period. Similarly, children chronically-exposed to low levels (estimated dose of 0.002–0.085 Gy [0.2–8.5 rad]) of ^{60}Co radiation in a contaminated kindergarten building showed significant decreases in total leucocytes and neutrophils, but an increase in eosinophils, 5–7 years after exposure had ceased (Chang et al. 1999a).

In male Swiss mice exposed to 1,000 rad (10 Gy) of ^{60}Co radiation, significant decreases in weight of the spleen were seen as early as 1 hour post-exposure and persisted throughout the following 24 hours (Mazur et al. 1991). Spleen acid phosphatase activity, expressed as activity per gram of protein, was significantly increased in irradiated animals beginning at 13 hours post-exposure.

3.3.3.4 Neurological Effects

Exposure of both humans and animals to high doses of cobalt radiation has been shown to result in damage to nervous tissue, particularly peripheral nerves. Llena et al. (1976) presented a case wherein a 51-year-old woman who had received 13,150 rad (131.5 Gy) of 60Co radiation between the nasopharynx and cervical lymph nodes as part of radiotherapy developed focal necrosis of the brain in the frontal lobe, as confirmed by gross and microscopic examination. Fishman et al. (1976) reported on two patients who received head-only ^{60}Co radiotherapy, in combination with chemotherapy, for the treatment of acute lymphocytic leukemia. Both patients, who received 2,400 rad (24 Gy) over an initial 16-day course of treatment followed later by either 2,400 or 2,500 rad (24 or 25 Gy) in followup therapy, developed progressively severe vision disorders, resulting in partial or total blindness. Histopathology from one patient demonstrated severe alterations in the optic nerve, including severe atrophy, terminal beading, lack of myelin, and calcification. Sanyal et al. (1979) reported on five patients who received doses of 4,500–6,000 rad (45–60 Gy) ^{60}Co radiation as radiotherapy, who developed varying degrees of myelopathy, resulting in minimal to mild paralysis. In patients that had been treated with ^{60}Co radiation (total dose of 54–57 Gy, or 5,400–5,700 rad) following mastectomy, 63% developed brachial plexus neuropathy and 5% developed vocal chord paresis over the 30-year period reported by the study (Johansson et al. 2000).

Mele et al. (1988) exposed male rats to 50, 150, or 450 rad (0.5, 1.5, or 4.5 Gy) 3 times, at 43-day intervals, and examined them for changes in behavior daily for 30 days following each exposure. Rats exposed to 450 rad (4.5 Gy), but not those exposed to 150 rad (1.5 Gy) or 50 rad (0.5 Gy), showed

significant deficits in fixed-ratio response rates and running rates after each exposure, beginning the day after exposure and persisting for 4–5 days, after which both rates returned to normal. After the third exposure, all rats were exposed to 650 rad (6.5 Gy), which resulted in similar performance decrements as were seen in the 450 rad (4.5 Gy) animals, again beginning 24 hours after exposure, with previous exposure resulting in no differences in behavioral parameters. Maier and Landauer (1989) reported significant decreases in offensive behavior in mice acutely exposed to whole-body doses of 500 or 700 rad (5 or 7 Gy), but not those exposed to 300 rad (3 Gy), with changes occurring in the second week postirradiation and responses returning to normal by day 19 postirradiation. Rabin et al. (1998) reported that exposure of rats to ^{60}Co radiation (up to 30 Gy or 3,000 rad) showed a dose-related decrease in the acquisition of controlled taste aversion behavior. Bassant and Court (1978) reported that rabbits exposed to 450 rad (4.5 Gy) of ^{60}Co radiation whole-body showed an altered activity of hippocampal cells, with a slowed mean discharge rate and increased interspike variability persisting for at least 12 hours postirradiation.

3.3.3.5 Reproductive Effects

Ionizing radiation in general, and gamma-emitting isotopes in particular, is known to have profound effects on reproductive tissues, with effects seen primarily in rapidly-dividing germ cells resulting in temporary or permanent sterility in both sexes, as well as other effects (Agency for Toxic Substances and Disease Registry 1999). These effects are usually observed only at high radiation doses. Keys and Reed (1980) reported a case of a man who, as treatment for a prostate tumor, received an estimated dose of 6,600 rad (66 Gy) to the prostate over a 47-day period, and who later developed a severe prostatic calcification necessitating surgical correction.

^{60}Co radiation at high doses has been shown to elicit profound decrements in reproductive ability in animal species. Whole-body acute exposure of rats to 330 rad (3.3 Gy) decreased testicular weights beginning at 22 days postirradiation, with recovery of testicular weight beginning about day 65 (Cunningham and Huckins 1978). Histologic examination of the testes revealed destruction of the spermatogonial population, with a slow recovery as the spermatogonial population was rebuilt from the surviving stem cells. Searl et al. (1976) reported that exposure of male mice to 1,128 rad (11.3 Gy) over a 28-week period resulted in significant reductions of testis mass and epididymal sperm count. Male Wistar rats exposed to a single dose of 80 rad (0.8 Gy) to the testes showed increased tubular fluid production

and decreased testicular weight at 30 and 45 days postirradiation, but not at later time points (Laporte et al. 1985). Single doses of >100 rad (1 Gy) of ^{60}Co radiation caused decreased fertility in exposed female mice (Philippe 1975). Continuous exposure of female mice to an average daily dose of 8 or 16 rad/day (0.08 or 0.16 Gy/day) caused a decreased number of offspring per litter and decreased reproductive performance, with 100% sterility occurring at 32 weeks of exposure at 8 rad/day (0.08 Gy/day) or 20 weeks of exposure at 16 rad/day (0.16 Gy/day) (Searl et al. 1980). Female rabbits exposed to 400 rad (4 Gy) prior to implantation showed dramatic decreases in implantation (Chang et al. 1963).

3.3.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after external exposure to cobalt radiation.

In utero exposure to cobalt radiation has been extensively studied in animal species, and may elicit substantial effects across many organ systems of the developing organism. Effects have been noted following single-dose exposures as low as 10 rad (0.10 Gy) in mice (Devi et al. 1994; Wang et al. 1993), 50 rad (0.5 Gy) in rats (Bruni et al. 1994), 200 rad (2 Gy) in hamsters (Harvey and Chang 1962), 250 rad in rabbits (Chang et al. 1963), 15.6 rad (0.16 Gy) in dogs (Benjamin et al. 1998a, 1998b), and 100 rad (1 Gy) in monkeys (Brizzee et al. 1978). Organs known to be affected include the brain (Brizzee et al. 1978; Bruni et al. 1994; Devi et al. 1994; Hamilton et al. 1989; Reyners et al. 1992; Schmidt and Lent 1987), eyes (Brizzee et al. 1978; Bruni et al. 1994; Schweitzer et al. 1987), hair (Hirobe 1994; Hirobe and Zhou 1990), kidney (Benjamin et al. 1998a; Brizzee et al. 1978), liver (Devi et al. 1998), ovaries (Inano et al. 1989), pituitary (Brizzee et al. 1978), skeleton (including cleft palate, shortened digits, fused digits, and other gross abnormalities) (Bruni et al. 1994; Chang et al. 1963; Harvey and Chang 1962), spleen (Devi et al. 1998), teeth (Lee et al. 1989), testes (Inano et al. 1989; Suzuki et al. 1990), and thyroid (Benjamin et al. 1997). ^{60}Co radiation *in utero* has also shown to cause functional alterations, including postnatal growth retardation (Wang et al. 1993; Zhong et al. 1996), neurobehavioral changes (Brizzee et al. 1978; Wang et al. 1993), hormonal production (Brizzee et al. 1978; Inano et al. 1989; Suzuki et al. 1990), alterations in hepatic enzymes (Inano et al. 1990), and diabetes mellitus (Benjamin et al. 1998a). *In utero* irradiation with cobalt also leads to increased tumor incidence later in life (Benjamin et al. 1991, 1997, 1998b; Nitta et al. 1992).

Devi et al. (1994) exposed pregnant mice to a single dose of 0–50 rad (0–0.50 Gy) of ^{60}Co radiation on day 11.5 of gestation. A significant decrease in pup brain weight and an increase in the incidence of microphthalmia was seen at 10 rad (0.10 Gy), with decreases in head width, head length, body length, and body weight occurring at higher doses. A later study (Devi et al. 1998) found decreases in body weight, liver weight, and spleen weight in pups 72 hours after irradiation with 25 rad (0.25 Gy) of ^{60}Co radiation on day 17 of gestation. Male offspring, but not female offspring, of mice exposed to 50 rad (0.5 Gy) on gestation day 9 showed decreased body weights on postnatal days 0, 3, and 7, while offspring of both sexes showed delays in pinna detachment, incisor eruption, eye opening, and testes descent (Zhong et al. 1996). Wang et al. (1993) reported that mice exposed to a cumulative *in utero* dose of 10 rad (0.10 Gy) showed alterations in visual placing reflex tests, while those exposed to 20 or 40 rad (0.20 or 0.40 Gy) showed decreased mean body weight, delayed eye opening, and alterations in the air righting reflex.

Rats exposed to 50 rad (0.50 Gy) of ^{60}Co radiation on gestational day 9.5 showed histologic damage to the neuro-epithelium 4 hours post-exposure, with abnormal flexion of the embryo and abnormal flexion of the head at 48 hours post-exposure (Bruni et al. 1994). At birth, rats showed increased incidence of defective eye development, spinal curvature, and visceral anomalies. Reyners et al. (1992) reported decreased brain weight in 3-month-old rats that had been exposed to cumulative doses of 160 rad (1.6 Gy) over gestation days 12–16 or 170 rad (1.7 Gy) over gestation days 14–20. Male rats exposed to 210 rad (2.1 Gy) on day 20 of gestation showed atrophy of the testes, prostates, and seminal vesicles, as well as a complete disappearance of germinal cells within the testes, on postnatal day 70 (Suzuki et al. 1990). Inano et al. (1989) exposed rats on gestation day 20 to 260 rad (2.6 Gy) of ^{60}Co radiation. Seminiferous tubules of male offspring and ovaries of female offspring showed pronounced atrophy, and steroid hormone production was significantly altered.

Benjamin et al. (1997, 1998a, 1998b) exposed groups of pregnant Beagle dogs to 15.6–17.5 or 80.8–88.3 rad (0.15–0.175 or 0.8–0.88 Gy) of ^{60}Co radiation on day 8, 28, or 55 post-breeding. Animals were allowed to live their full life span and were observed for radiation-related illnesses and cause of death. No change in the mean age at death was seen as a result of exposure. Males exposed to either exposure level at day 55 post-breeding, but not females at any time or males exposed at days 8 or 28, showed an increase in deaths due to renal disease. High-dose females exposed on days 28 or 55 showed an increase in the frequency of diabetes mellitus. Both sexes showed an increase in malignant neoplasias in general when exposed to radiation at 8 or 55 days postcoitus, but not at 28 days, while females exposed on day 55 also showed an increase in lymphoid neoplasia. A similar exposure on day 28 or 55 postcoitus

also resulted in a dose-dependent decrease in brain weight (Hamilton et al. 1989). *In utero* radiation of dogs to higher doses (100–380 rad [1–3.8 Gy]) resulted in retinal dysplasia and atrophy (Schweitzer et al. 1987).

3.3.3.7 Cancer

The carcinogenic effects of high doses of ionizing radiation have been well documented (Agency for Toxic Substances and Disease Registry 1999), though the effects of lower doses are less clearly defined. Duncan et al. (1977) reported on a cohort of patients who had received radiotherapy for carcinoma of the cervix. Eight of 2,674 patients developed bladder tumors within 6 months to 20 years following irradiation; the incidence rate was over 57 times greater than the general female population. All eight patients had received high (therapeutic) doses of ^{60}Co irradiation, though five of the eight also received radium therapy in conjunction with ^{60}Co irradiation. Wollenberg et al. (1995) presented a case of a 55-year-old farmer who received a total of 25,150 rad (251.5 Gy) distributed over six areas of the body over an 8-month period as a ^{60}Co teletherapy treatment regimen. Twenty years after irradiation, the patient developed a total of 43 basal cell carcinomas of the skin over the treated areas, all of which were successfully removed with cryosurgery. A 2-year-old girl exposed to 1,800 rad (18 Gy) of ^{60}Co radiation as part of a treatment regimen for acute lymphoblastic leukemia L1 developed, at age 12, a basal cell carcinoma of the scalp (Garcia-Silva et al. 1996). Three patients receiving cobalt irradiation as part of a chemotherapy/radiation treatment developed basal cell carcinoma of the scalp 8–15 years after treatment in the area of radiation treatment (Dinehart et al. 1991).

3.3.4 Other Routes of Exposure

This section includes injection and *in vitro* studies that provide evidence for the biological basis of toxicity of stable and radioactive cobalt in humans and animals. Since these studies are not directly relevant to general population exposure conditions, no LSE tables have been created for this section.

3.4 GENOTOXICITY

Stable Cobalt. No studies were located regarding genotoxic effects in humans following oral or dermal exposure to cobalt. No studies were located regarding genotoxic effects in animals following inhalation exposure to cobalt.

Gennart et al. (1993) examined a cohort of 26 male workers who had been occupationally-exposed to cobalt, chromium, nickel, and iron. Analysis of variance on sister-chromatid exchange rank values revealed that exposure status (exposed vs. controls) and smoking habits had statistically significant effects. De Boeck et al. (2000) reported no significant change in the comet assay on lymphocytes from nonsmoking workers who had been occupationally exposed to cobalt or hard metal dusts; a positive association was found between hard metal exposure and increased micronucleus formation in smokers only.

Single oral exposure of male Swiss mice to 0, 4.96, 9.92, or 19.8 mg cobalt/kg as cobalt chloride resulted in significantly increased percentages of both chromosomal breaks and chromosomal aberrations in bone marrow cells, with significant linear trends toward increasing aberrations with increased exposure (Palit et al. 1991a, 1991b, 1991c, 1991d).

Results of genetic testing of cobalt are presented in Table 3-5. Several different forms of cobalt, including cobalt chloride and cobalt sulfide, were tested. No profound differences were found among the various forms.

Cobalt was found to be generally nonmutagenic in bacteria (*Salmonella typhimurium*, *Escherichia coli*) and yeast when compounds with a valence state of II were tested (Arlauskas et al. 1985; Fukunaga et al. 1982; Kanematsu et al. 1980; Kharab and Singh 1985; Ogawa et al. 1986; Singh 1983; Tso and Fung 1981). A very weak mutagenic response was found with *Bacillus subtilis* (Kanematsu et al. 1980). A mutagenic response to cobalt was found, however, when compounds with a valence state of III were tested in *S. typhimurium* and *E. coli* (Schultz et al. 1982). The authors suggested that this may be due to the formation of cobalt(III) complexes that are inert to ligand substitution, allowing optimal interaction of cobalt with genetic material (Schultz et al. 1982). Other studies have shown cobalt to be a comutagen in combination with 4-substituted pyridines in *S. typhimurium* (Ogawa et al. 1988). It has been reported that cobalt acts as an antimutagen in bacterial (*S. typhimurium*, *B. subtilis*, *E. coli*) and yeast test systems

Table 3-5. Genotoxicity of Cobalt *In Vitro*

Species (test system)	End point	Results		Reference	Valence state
		With activation	Without activation		
Stable Cobalt					
Prokaryotic organisms:					
Salmonella typhimurium (plate incorporation)	Gene mutations	No data	–	Tso and Fung 1981	II
S. typhimurium (plate incorporation)	Gene mutations	No data	–	Arlauskas et al. 1985	II
S. typhimurium (plate incorporation)	Gene mutations	No data	–	Ogawa et al. 1986	II
S. typhimurium (plate incorporation)	Gene mutations	No data	+	Schultz et al. 1982	III
Bacillus subtilis (rec assay)	Gene mutations	No data	(+)	Kanematsu et al. 1980	II
Escherichia coli (reversion assay)	Gene mutations	No data	–	Kanematsu et al. 1980	II
E. coli (repair assay)	DNA damage	No data	+	Schultz et al. 1982	III
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae (plate assay)	Reversion	No data	–	Kharab and Singh 1985	II
S. cerevisiae (plate assay)	Reversion	No data	–	Fukunaga et al. 1982	II
S. cerevisiae (plate assay)	Reversion	No data	–	Singh 1983	II
S. cerevisiae (plate assay)	Conversion	No data	+	Kharab and Singh 1985	II
S. cerevisiae (plate assay)	Conversion	No data	+	Fukunaga et al. 1982	II
S. cerevisiae (plate assay)	Conversion	No data	+	Singh 1983	II
Mammalian cells:					
Hamster ovary cells	Clastogenic effects	No data	+	Hamilton-Koch et al. 1986	II
Hamster embryo cells	Transformation	No data	+	Costa et al. 1982	II
Human lymphocytes	Sister chromatid exchange	No data	+	Andersen 1983	II
Human HeLa cells	Inhibition of DNA synthesis	No data	+	Painter and Howard 1982	II
Human diploid fibroblasts	DNA damage	No data	+	Hamilton-Koch et al. 1986	II

Table 3-5. Genotoxicity of Cobalt *In Vitro*

Species (test system)	End point	Results		Reference	Valence state
		With activation	Without activation		
Radioactive Cobalt					
Mammalian cells:					
Chinese hamster ovary cells	DNA amplification	No data	+	Luecke-Huhle et al. 1986	N/A
Hamster embryo cells	DNA amplification	No data	+	Luecke-Huhle et al. 1990	N/A
Mouse lymphosarcoma cells	Chromosomal aberrations	No data	+	Juraskova and Drasil 1987	N/A
Mouse lymphosarcoma cells	Sister-chromatid exchanges	No data	+	Juraskova and Drasil 1987	N/A
Human lymphocytes	Chromosomal aberrations	No data	+	Koksal et al. 1995	N/A
Human lymphocytes	Micronucleus formation	No data	+	Koksal et al. 1996	N/A
Human leukocytes	DNA strand breaks	No data	+	Rueff et al. 1993	N/A
Human leukocytes	Chromosomal aberrations	No data	+	Rueff et al. 1993	N/A
Human leukocytes	Chromosome breaks	No data	+	Lindahl-Kiessling et al. 1970	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1981	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1985	N/A
Human fibroblasts	DNA strand breaks	No data	+	Coquerelle et al. 1987	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1988	N/A
Human fibroblasts	Retinoblastoma gene alterations	No data	+	Endo et al. 1993	N/A
Human fibroblasts	DNA strand breaks	No data	+	Dolling et al. 1998	N/A
Human kidney cells	DNA strand breaks	No data	+	Feinendegen et al. 1977	N/A
Human kidney cells	DNA strand breaks	No data	+	Feinendegen et al. 1978	N/A

DNA = deoxyribonucleic acid; + = positive results; – = negative results; (+) = weakly positive results

(*Saccharomyces cerevisiae*) (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). A possible explanation was that cobalt acts by correcting the error-proneness of deoxyribonucleic acid (DNA) replicating enzymes by improving their performance in DNA synthesis (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). However, cobalt has also been shown to increase the frequency of genetic conversions in *S. cerevisiae* (Kharab and Singh 1985; Singh 1983). The reasons for this apparent dichotomy in yeast cells is not known.

In contrast to the results seen in bacteria, stable cobalt compounds were generally found to be genotoxic or mutagenic in mammalian assay systems. Exposure to cobalt compounds (metal, salts, or hard metal) has been shown to produce clastogenic effects in mammalian cells, including human lymphocytes (Anard et al. 1997; Hamilton-Koch et al. 1986; Painter and Howard 1982); transformation in hamster cells (Costa et al. 1982); sister chromatid exchanges in human lymphocytes (Andersen 1983); and micronucleus formation in mouse bone marrow cells (Suzuki et al. 1993) and human lymphocytes (Capomazza and Botta 1991; Olivero et al. 1995; Van Goethem et al. 1997). Hard metal is generally more genotoxic in *in vitro* tests than other cobalt compounds. Cobalt ions are also thought to inhibit DNA repair in mammalian cells by interaction with zinc-finger proteins involved in DNA excision repair (Asmuß et al. 2000; De Boeck et al. 1998; Hartwig et al. 1991; Kasten et al. 1997; Sarkar 1995).

Thirty hours following single intraperitoneal injection of cobalt(II) chloride in BALB/c mice, an increase in micronucleus formation was seen at 12.4 or 22.3 mg cobalt/kg (as cobalt chloride), but not at 6.19 mg/kg (Suzuki et al. 1993). Single injection of mg cobalt/kg (as cobalt chloride) resulted in significantly increased micronucleus formation at 24 hours post-injection, but not at 12, 48, 72, or 96 hours. Two or 10 days following intraperitoneal injection of male and female F344 rats with 3 or 6 mg cobalt/kg, increased levels of oxidatively-damaged DNA bases were noted in the liver, kidney, and to a lesser extent, the lung (Kasprzak et al. 1994).

Radioactive Cobalt. The ability of ionizing radiation to induce genotoxic damage is well-documented (Agency for Toxic Substances and Disease Registry 1999). Chang et al. (1999c) reported increased micronucleus frequency, both of single and multiple nucleates, in 48 people who had been exposed to 12–1,600 rad (0.12–16 Gy) over a 2–10-year period as a result of a building contaminated with ^{60}Co-containing steel. Subjects who had left the building showed a decrease in micronucleus formation that correlated with time since cessation of exposure. Three workers accidentally exposed to 2.2–12.7 rad (0.022–0.127 Gy) showed no elevation in frequency of chromosome alterations (House et al. 1992). Ten

children who received chemotherapy and 1,725–2,405 rad (17.25–24.05 Gy) as cobalt radiotherapy for acute lymphatic leukemia showed no clastogenic changes after chemotherapy but before irradiation. After radiotherapy, significant dose-related increases in chromosomal aberrations were seen (Rauscher and Bauchinger 1983).

Radiation from cobalt isotopes has been shown to induce numerous genetic changes, including translocations (Gilot-Delhalle et al. 1988; Grahn and Carnes 1988; Grahn et al. 1983; Searl et al. 1976), decreased DNA synthesis (Lohmann et al. 1966), dominant lethal mutations (Grahn et al. 1988; Searl et al. 1976; Zhou et al. 1986), chromosome deletions (Brooks et al. 1971b, 1974), polycentrics (Brooks et al. 1971a, 1974), and aberrations (Brooks et al. 1971a, 1971b) in exposed animals.

Radiation from cobalt isotopes was genotoxic in several assay systems in mammalian cells: DNA amplification in hamster cells (Lucke-Huhle et al. 1986, 1990); chromosomal aberrations and sister-chromatid exchanges in mouse lymphosarcoma cells (Juraskova and Drasil 1987); chromosomal aberrations and micronucleus formation in human lymphocytes (Koksal et al. 1995, 1996; Schmid et al. 2002); DNA breakage in human leukocytes (Lindahl-Kiessling et al. 1970; Reuff et al. 1993), kidney cells (Feinendegen et al. 1977), and fibroblasts (Coquerelle et al. 1987; Dolling et al. 1998); chromosomal aberrations in human leukocytes (Reuff et al. 1993); transformation of human fibroblasts (Namba et al. 1981, 1985, 1988); and retinoblastoma gene alterations in human fibroblasts (Endo et al. 1993).

3.5 TOXICOKINETICS

3.5.1 Absorption

3.5.1.1 Inhalation Exposure

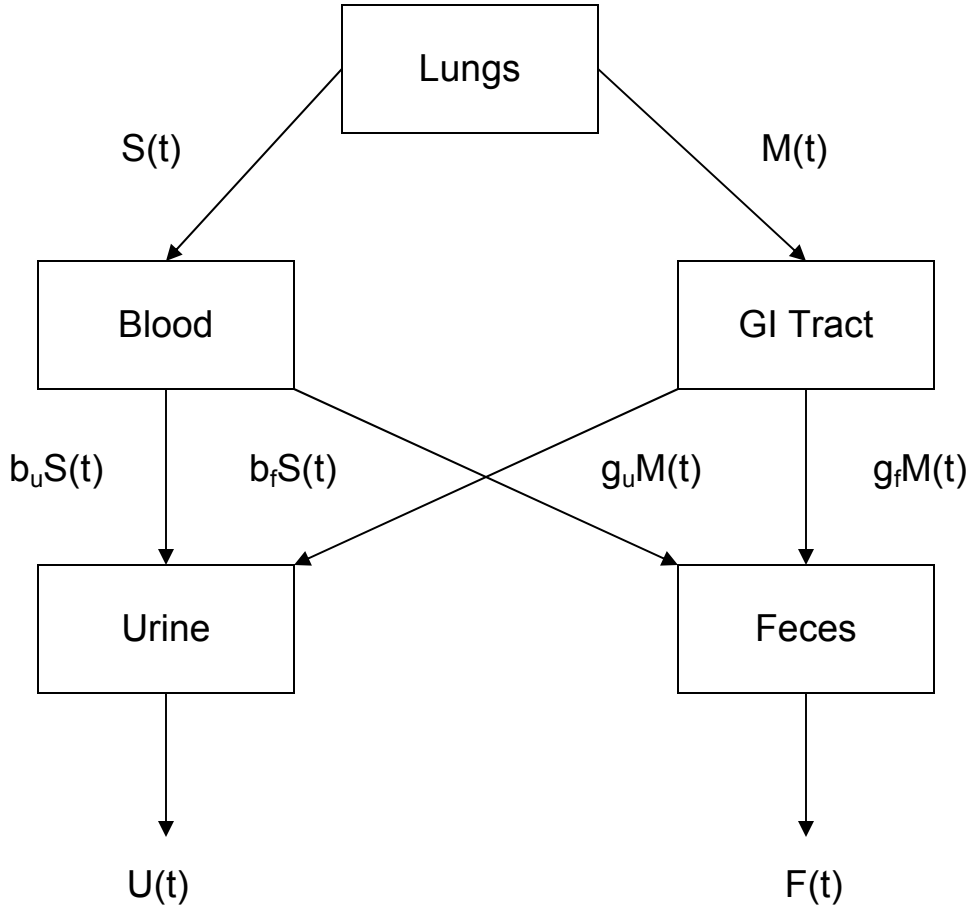
Inhaled cobalt particles are deposited in the upper and lower respiratory tract and cobalt is subsequently absorbed by several mechanisms (Casarett and Doull 1986); however, two of these mechanisms in particular appear to be most relevant. The deposition pattern in the respiratory tract is related to particle size, which determines the degree to which particles are affected by inertial impaction, sedimentation, diffusion, and electrostatic precipitation. Large particles (diameter >2 μm) tend to deposit in the upper respiratory tract where high airstream velocities and airway geometry promote inertial impaction of larger particles. Smaller particles escape inertial impaction and enter the lower respiratory tract where lower

airstream velocities and airway geometry favor the process of sedimentation, diffusion, and electrostatic precipitation of small particles. Fractional deposition can be expected to vary considerably with age, particle size, and breathing patterns (see Table 3-10). Fractional deposition of inhaled cobalt oxide particles in humans varied from approximately 50% of the inhaled dose for particles with a geometric mean diameter of 0.8 μm to approximately 75% of the inhaled dose for particles with a geometric mean diameter of 1.7 μm (Foster et al. 1989).

The transfer pathways of cobalt oxide (^{57}Co used as a tracer) from the lungs in humans and animals are shown in Figure 3-4. Particles of cobalt deposited in the respiratory tract can be absorbed into the blood after dissolution (S(t)) or mechanically transferred to the gastrointestinal tract by mucociliary action of the respiratory tract and swallowing action (M(t)). Only a portion (probably <50%) of the cobalt that enters the gastrointestinal tract will be absorbed into the body. The relative magnitude of the translocation and mechanical clearance pathways depends on the size and solubility of the cobalt particles that are inhaled. Large particles (>2 μm) will tend to deposit in the middle and upper airways where mechanical clearance mechanisms predominate over translocation. Smaller particles that enter the lower respiratory tract will tend to remain until dissolved or phagocytized by macrophages and translocation occurs. The sum of the activities of translocation and mechanical clearance determine the kinetics of absorption of inhaled cobalt. In humans, the ratio of translocation (S(t)) to mechanical clearance (M(t)) is approximately 5–1 for particle sizes ranging from 0.8 to 1.7 μm (mean geometric diameter) (Foster et al. 1989).

Data on retention of cobalt oxide (^{57}Co used as a tracer) in the respiratory tracts of humans and several animal species are summarized in Table 3-6. Considerable variability exists among species. In humans, almost one-half of the original lung burden persisted 6 months after exposure; in rats, clearance of cobalt from the lungs was nearly complete after 6 months. The elimination half-time for cobalt in the human lung increased with increasing time after exposure (Foster et al. 1989; Sedlet et al. 1958). This may reflect slower clearance of cobalt that is bound to cellular components in the lung (Kreyling et al. 1985, 1986).

Figure 3-4. Transfer Parameters for Cobalt Following Inhalation of Cobalt Oxide* (CO_3O_4) Particles, Showing the Fractions of the Lung Content, L(t), and Time, t, Cleared Per Day by Each Route**



GI tract = gastrointestinal tract;
$b_fS(t)$ = fraction of cobalt excreted in the feces after translocation;
$b_uS(t)$ = fraction of cobalt excreted in the urine after translocation;
F(t) = fecal excretion rate;
$g_fM(t)$ = fraction of cobalt excreted in the feces after mechanic clearance to the gastrointestinal tract;
$g_uM(t)$ = fraction of cobalt excreted in the urine after mechanic clearance to the gastrointestinal tract;
M(t) = rate of mechanical transport of cobalt particles from the lungs to the gastrointestinal tract;
S(t) = rate of translocation of cobalt from the lungs to the blood;
U(t) = urinary excretion rate

*Cobalt-57 tracer used
**Derived from Bailey et al. 1989

Table 3-6. Initial (Day 3) Lung Deposits of Cobalt Oxide and Summary of Lung Retention at 90 and 180 Days[a,b]

	Mean initial ^{57}Co activity in lung L(3) (kBq)		Lung retention L(90)/L(3) (%)		Lung retention L(180)/L(3) (%)	
Species (strain)	0.8 μm	1.7 μm	0.8 μm	1.7 μm	0.8 μm	1.7 μm
Human	53	42	64	75	45	56
Baboon	2,100	1,700	55	55	26	37
Beagle dog	1,150	1,450	27	45	5.5	12
Guinea pig (Harwell)	8.4	1.4	49	46	8.3	15
Rat (HMT, 1985)	10.8	4.7	5.2	20	1.3	8.0
Rat (HMT, 1986)	3.2	0.7	5.3	18	1.2	9.2
Rat (F344, SPF)	8.8	4.4	14	25	4.7	9.2
Rat (Sprague-Dawley)	0.9	0.10	8	39	1	15
Syrian hamster	4.0	1.2	21	35	3.4	12
Mouse (CBA/H)	1.8	No data	15	No data	2.8	No data

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

3.5.1.2 Oral Exposure

Gastrointestinal absorption of cobalt in humans varies considerably (18–97% of the given dose) based on the type and dose of cobalt compound given and the nutritional status of the subjects (Harp and Scoular 1952; Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). More cobalt was absorbed through the gastrointestinal tract of humans when the body was deficient in iron (31–71% in iron deficiency; 18–44% in controls) (Sorbie et al. 1971; Valberg et al. 1969). One study in humans has shown that oral exposure to cobalt chloride resulted in significantly higher urinary excretion in females relative to males (Christensen et al. 1993).

In animal studies, many factors have been shown to influence the absorption of cobalt compounds following oral exposure. In several studies in rats (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Schade et al. 1970; Taylor 1962), soluble cobalt chloride was absorbed in the range of 13–34%, whereas physiologically insoluble cobalt oxide particles have been shown to be poorly absorbed, in the range of 1–3% (Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989). The particle size of the given dose of cobalt oxide had no significant effect on gastrointestinal absorption (Table 3-7). Administration of cobalt chloride labeled with radioactive 58Co and complexed with histidine, lysine, glycylglycine, ethylenediaminetetraacetic acid (EDTA), casein, or glycine resulted in decreased gastrointestinal absorption of cobalt; administration of cobalt chloride (with 58Co tracer) in cows' milk permitted a significantly greater (about 40%) absorption through the gastrointestinal tract (Taylor 1962). The same study found that while there was no difference in the chlorides of cobalt(II) and cobalt(III), a cobalt(II) glycine complex was absorbed in greater quantities than a cobalt(III) glycine complex. Other studies have also demonstrated that the chemical form of the cobalt compound can affect the absorption of cobalt following oral exposure (Deka et al. 1981; Firriolo et al. 1999; Inaba et al. 1980; Kinoshita and Fujita 1972), with more water-soluble compounds generally showing greater absorption.

Iron deficiency led to increased absorption of cobalt from the gastrointestinal tract, and simultaneous administration of cobalt and iron reduced the amount of cobalt absorbed (Reuber et al. 1994; Schade et al. 1970). Increasing oral doses of cobalt resulted in decreased fractional absorption (Houk et al. 1946; Kirchgessner et al. 1994; Taylor 1962), and more soluble forms of cobalt were better absorbed than less soluble compounds (Kreyling et al. 1986). Absorption is 3- to 15-fold greater in younger animals (rats and guinea pigs examined from days 1–60 of life) than in adult (200 days of age) animals (Naylor and

Table 3-7. Summary of Measurements of Retention and Excretion After Intragastric Administration of Cobalt Oxide (Co_3O_4) Particles (Mean Percentage of Recovered Activity at 7 Days After Administration)[a,b]

Species (strain)	Cumulative fecal excretion		Whole body retention		Cumulative urinary excretion		Absorption	
	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm
Baboon	97.8	98.4	0.12	0.20	2.0	1.4	2.6	1.9
Guinea pig	98.7	97.6	0.16	0.66	1.1	1.9	1.3	2.3
Rat (HMT)	96.3	99.4	0.09	0.02	2.8	0.6	3.9	1.0
Rat (F-344)	99.6	99.7	0.04	0.03	0.4	0.3	0.4	0.3
Hamster	96.0	96.3	0.50	0.18	3.5	3.5	5.1	5.1
Mouse (CBA/H)	99.1	No data	0.3	No data	0.6	No data	0.8	No data

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

Harrison 1995). Species differences in absorption of cobalt oxide do not appear to exist (Bailey et al. 1989), but absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; van Bruwaene et al. 1984).

3.5.1.3 Dermal Exposure

Four humans who placed their right hands into a box filled with hard metal dust (~5–15% cobalt metal, 95–85% tungsten carbide) for 90 minutes showed an increase in urinary cobalt levels by an order of magnitude in the post-exposure samples, remaining elevated for as long as 48–60 hours (Scansetti et al. 1994). Similarly, cobalt was detected in the fingernails of three volunteers who placed their fingers in cobalt solution 10 minutes/day for 7 days (Nielsen et al. 2000), even after the cessation of exposure. These findings demonstrate that cobalt from these metal dusts can be absorbed through the skin. The absorption of $2.2x10^{-5}$ mg ^{60}Co/kg as cobalt chloride in 1.4N HCl through 1 cm^2 of intact or abraded skin of guinea pigs was examined by Inaba and Suzuki-Yasumoto (1979). Absorption through intact skin was very small (<1%), while absorption through abraded skin was almost 80% 3 hours after exposure. A study in hamsters (Lacy et al. 1996) also reported a low amount of absorption of cobalt through unabraded skin.

3.5.1.4 Other Routes of Exposure

No studies were located regarding absorption of cobalt in humans or animals after other routes of exposure.

3.5.2 Distribution

As a component of vitamin B_{12}, cobalt is an essential element and, therefore, is found in most body tissues. It has been identified in liver, muscle, lung, lymph nodes, heart, skin, bone, hair, stomach, brain, pancreatic juice, kidneys, plasma, and urinary bladder of nonexposed subjects, with the highest cobalt concentration found in the liver (Collecchi et al. 1986; Forbes et al. 1954; Hewitt 1988; Ishihara et al.

1987; Muramatsu and Parr 1988; Teraoka 1981; Yamagata et al. 1962; Yukawa et al. 1980) (see Chapter 6 for more information). Tissue levels reflected exposure from all routes. The total body content of cobalt has been estimated at 1.1–1.5 mg (ICRP 1979; Yamagata et al. 1962); about 0.11 mg was found in the liver (ICRP 1979).

In patients with laryngeal carcinoma, levels of cobalt in the tumor were significantly higher ($p<0.001$) than levels in the nonmalignant tissues around the tumor (68.7 ng/g tissue versus 39.6 ng/g) (Collecchi et al. 1986). The mean cobalt concentrations in plasma (18.3 ng/mL) were also significantly higher in these patients than in the comparison population (0.73 ng/mL). The clinical significance of these findings is not known.

3.5.2.1 Inhalation Exposure

In workers occupationally exposed to airborne cobalt, increased cobalt levels were found in tissues at death. Significant increases in cobalt in the lung have been found in copper smelter and metal workers and coal miners occupationally exposed to cobalt (Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Teraoka 1981). No increase in liver or kidney cobalt levels were found in the copper smelter workers as compared to controls (Gerhardsson et al. 1984). In metal workers, increased cobalt levels were also found in the lymph nodes, liver, spleen, and kidneys (Hillerdal and Hartung 1983; Teraoka 1981).

The tissue distribution of cobalt in animals is similar to that in humans, with marked increases in the concentration of cobalt in the lungs following inhalation exposure (Barnes et al. 1976; Brune et al. 1980; Collier et al. 1991; Kreyling et al. 1986; Kyono et al. 1992; Patrick et al. 1989; Talbot and Morgan 1989). Histologically, the particles of cobalt in the lung are found in macrophages within the bronchial wall or in the interstitium close to the terminal bronchioli (Brune et al. 1980). Significant concentrations of cobalt have been found in the liver, kidney, trachea, spleen, bones, and heart (Barnes et al. 1976; Brune et al. 1980; Kerfoot 1975; Kreyling et al. 1986; Wehner and Craig 1972), with the greatest concentrations in the liver and the kidney (Kerfoot 1975; Wehner and Craig 1972).

3.5.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to cobalt.

In animals, the cobalt absorbed through the gastrointestinal tract was primarily retained in the liver (Ayala-Fierro et al. 1999; Greenberg et al. 1943; Simesen 1939). Appreciable levels were also found in the kidneys, heart, stomach, and intestines (Ayala-Fierro et al. 1999; Persson et al. 1992; Simesen 1939). Following a single oral dose of cobalt napthenate, appreciable levels of cobalt were found in the heart, liver, and kidney, but not in the spleen or testes (Firriolo et al. 1999). Following oral exposure to pregnant rats, a dose-dependent increase in cobalt levels in fetal blood and amniotic fluid was seen (Szakmary et al. 2001).

Following longer-term exposure (8 weeks) to cobalt sulfate in the diet, exposed rats showed a 30-fold increase in the cobalt concentration in the myocardium, a 26-fold increase in the concentration in the soleus muscle, and a 100-fold increase in the concentration in serum compared with nonexposed controls (Clyne et al. 1988; Pehrsson et al. 1991). Long-term oral exposure of rats to cobalt chloride resulted in significantly increased levels of cobalt in the liver, kidney, muscle, brain, and testes of treated rats (Barnaby et al. 1968; Bourg et al. 1985; Thomas et al. 1976).

3.5.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to cobalt.

3.5.2.4 Other Routes of Exposure

Following intravenous injection of cobalt chloride (as a combination of radioactive $^{55}CoCl_2$ and $^{56}CoCl_2$) in two humans, the liver and bladder contained the highest portions of cobalt (Jansen et al. 1996).

Distribution in animals after an intravenous dose appears to be similar to what we know of cobalt distribution in humans following injection of cobalt compounds. Two hours after intravenous injection of cobalt chloride (with a radioactive ^{57}Co tracer) in rats, accumulation was found in the liver (22.8% of the dose), kidneys (10.2%), and intestines (3.16%) (Gregus and Klaassen 1986). Similar results (29% liver,

10% kidneys, 4.6% intestines) were found following intracardiac injection of cobalt nitrate in rats (Patrick et al. 1989) or intravenous injection of a combination of radioactive $^{55}CoCl_2$ and $^{56}CoCl_2$ in rats (exact percentages were not provided) (Jansen et al. 1996). One hundred days after intravenous injection of $^{60}CoCl_2$ in rats, the greatest concentrations were found in spleen>heart>bone, while liver and kidney, initially the highest in cobalt, contained comparatively low amounts of cobalt (Thomas et al. 1976). Similar results were seen 132 days following an intraperitoneal injection of $^{60}CoCl_2$ in rats (Barnaby et al. 1968). Intramuscular injection of cobalt mesoporphyrin in rats yielded the greatest levels of cobalt in liver and blood, followed by kidney, lung, spleen, adrenal glands, and heart at 7 days post-injection and later (Feng et al. 1998). Four weeks after subcutaneous administration of cobalt protoporphyrin, the greatest tissue levels of cobalt occurred in the kidney, followed by spleen, liver, lung, thymus, and gonads (Rosenberg 1993). When cobalt (with a ^{57}Co tracer) encapsulated in liposomes was intravenously injected into rats, decreased distribution to the heart (40% less than animals receiving cobalt chloride), kidneys, and carcass, and increased distribution to the spleen and bones were found (Szebeni et al. 1989).

3.5.3 Metabolism

Cobalt is essential in the body because it is a component of cyanocobalamin (vitamin B_{12}) (Vouk 1986). Vitamin B_{12} acts as coenzyme in many enzymatic reactions, most notably a methyl transfer reaction that converts homocysteine to methionine and for a separate reaction that converts L-methylmalonylcoenzyme A (CoA) to succinyl-CoA (Institute of Medicine 2000). Vitamin B_{12} is also a part of some enzymes involved in hematopoiesis; deficiency can lead to pernicious anemia (Domingo 1989). No other essential function of cobalt has been reported. The Recommended Dietary Allowance (RDA) for vitamin B_{12} for adults is 2.4 μg/day, which contains 0.1 μg of cobalt (Institute of Medicine 2000).

3.5.4 Elimination and Excretion

3.5.4.1 Inhalation Exposure

No data are available on the clearance of soluble cobalt particles in humans. Following exposure of humans to physiologically insoluble cobalt compounds (cobalt metal, cobalt oxides), clearance from the body, assessed by both urinary/fecal clearance and a reduction in whole-body retention, appears to follow

three-phase kinetics. The first phase, likely representing mucociliary clearance of particles deposited in the tracheobronchial region, has a half-time on the order of 2–44 hours (Apostoli et al. 1994; Mosconi et al. 1994b). The second phase, with a half-time on the order of 10–78 days, may represent macrophage-mediated clearance of cobalt particles from the lung (Beleznay and Osvay 1994; Mosconi et al. 1994b). The third clearance phase, representing long-term clearance from the lungs, has a half-time on the order of years (Bailey et al. 1989; Beleznay and Osvay 1994; Mosconi et al. 1994b; Newton and Rundo 1971). Following a controlled aerosol exposure in humans, about 40% of the initial lung burden of inhaled cobalt oxide (with a 57Co tracer) was retained for a period of 6 months after exposure (Foster et al. 1989). Within the first week, about 17% of the initial lung burden was eliminated, with the majority (about 90%) mechanically cleared to the gastrointestinal tract and excreted in the feces (Foster et al. 1989). Six months after exposure, a cumulative elimination of 33% of the initial lung burden was found in the urine and 28% was found in the feces (Foster et al. 1989). The ratio of peak absorption rate to average mechanical clearance rate (Figure 3-4 and Table 3-8) was about 5 to 1. The elimination of cobalt following inhalation exposure was affected by the time after exposure (urinary excretion increases as time increases) and particle size (more cobalt is initially mechanically cleared to the gastrointestinal tract when the aerosol consists of bigger particles) (Bailey et al. 1989; Foster et al. 1989).

In animals, the solubility of the cobalt compound appears to greatly affect its long-term clearance. Studies with cobalt oxides have shown that the more soluble CoO is cleared from the lungs at a greater rate than the less soluble Co_3O_4 (Barnes et al. 1976; Kreyling 1984a). More soluble cobalt compounds are absorbed into the blood at a greater rate, and excreted in the urine and, to a lesser extent, the feces (Barnes et al. 1976). The rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1986, 1989; Patrick et al. 1989; Talbot and Morgan 1989). Following an initial high rate of fecal clearance, urinary excretion was the primary route of cobalt elimination after a single inhalation exposure (2 weeks of observation) (Palmes et al. 1959) or 3 months of exposure (Kerfoot 1975; Palmes et al. 1959). In several species of animals, most of the inhaled Co_3O_4 (with a ^{57}Co tracer) following a single exposure was cleared from the lungs by 6 months after exposure (Table 3-6) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). The peak translocation and average mechanical clearance of cobalt from the lungs for different species are reported in Table 3-8, with the rate (high to low) following as mouse > rat > hamster > guinea pig > baboon, human > beagle dog.

Table 3-8. Peak Translocation and Average Mechanical Clearance Rates After Inhalation of Cobalt Oxide[a,b]

	Percent of lung content cleared per day				
	Translocation at peak				Average mechanical clearance[c]
Species (strain)	0.8 µm	Peak day	1.7 µm	Peak day	
Human	0.45	180	0.5	180	0.1
Baboon	0.6	180	0.2	d	0.1
Beagle dog	2.1	85	1.7	180	0.03
Guinea pig	2.1	180	1.0	75	0.3
Rat HMT	2.4	40	0.6	d	0.9
Rat (F-344)	1.1	10	0.4	d	1.0
Hamster	1.8	180	0.7	180	0.8
Mouse	1.7	180	No data	No data	1.05

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer
[c]Clearance rates were virtually identical in both particle size groups
[d]Constant value over 180 days

3.5.4.2 Oral Exposure

In humans orally exposed to cobalt, fecal elimination, which is the primary route of elimination, varies considerably (3–99% of the dose) and depends on the amount and type of cobalt given and on the nutritional status of the subjects (Section 3.5.1.2) (Harp and Scoular 1952; Paley et al. 1958; Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). Within days after oral exposure, 10 times more cobalt was excreted in feces than in the urine (Paley et al. 1958). Less cobalt was eliminated in the feces (more was absorbed) in subjects with an iron deficiency (Sorbie et al. 1971; Valberg et al. 1969).

Fecal elimination of cobalt is the primary route of elimination in animals following oral exposure and depends mainly upon the particle solubility (decreasing fecal clearance with increasing solubility) of the cobalt compound. The cumulative urinary and fecal elimination in several species following oral administration of Co_3O_4 (with a ^{57}Co tracer) is reported in Table 3-7 (Bailey et al. 1989). Following oral administration in several species, very little Co_3O_4 was absorbed through the gastrointestinal tract and most (>96%) was quickly eliminated in the feces. No significant differences in elimination of Co_3O_4 were found among species of animals (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). For the more soluble cobalt(II) chloride, reported fecal elimination levels have ranged from 70 to 83% of the administered dose for rats, with urinary excretion accounting for the majority of the remainder of the dose (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971). In lactating dairy cows, about 97% of an oral dose of cobalt chloride was recovered in the feces by day 70 post-exposure, while the urine and milk contained 0.26 and 0.012% of the dose, respectively (van Bruwaene et al. 1984). Following a single exposure in beagle dogs, more Co_3O_4 (physiologically insoluble) was eliminated in the feces (90% in the feces and 5% in the urine) than following an exposure to cobalt nitrate (soluble) (70% in the feces and 25% in the urine) (Kreyling et al. 1986).

As is the case for absorption of cobalt compounds, the iron status of the animal also appears to affect the elimination of cobalt compounds. Following oral exposure, iron-deficient rats eliminated less of a given dose in the feces than normal rats, while co-administration of iron compounds resulted in an increased fecal excretion of cobalt compounds (Reuber et al. 1994; Schade et al. 1970).

3.5.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to cobalt.

Lacy et al. (1996) reported that the majority of the absorbed dose of $CoCl_2$ was excreted in the urine 48 hours after a single dermal exposure in Syrian hamsters. No other studies were located regarding excretion in animals after dermal exposure to cobalt.

3.5.4.4 Other Routes of Exposure

Following intravenous injection of cobalt chloride in humans, about 30% of the dose was excreted in the urine within 24 hours (Smith et al. 1972), 56–73% was excreted within 48 hours (Paley et al. 1958), and 57% was excreted within 2 weeks (Kent and McCance 1941).

Following intravenous injection of cobalt nitrate (with a 57Co tracer) in various species of animals, most of the injected dose was excreted in the urine; about 80% of the given dose was excreted in the urine within 21 days (Table 3-9) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). Other investigators have also found that the urine is the primary route of cobalt excretion following intravenous administration (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Gregus and Klaassen 1986; Kreyling et al. 1986; Onkelinx 1976; Thomas et al. 1976). Most of the remaining cobalt (5–30% of the total dose) after intravenous exposure was excreted in the feces, with the majority of studies reporting very little long-term retention. Excretion of cobalt (about 2–7% of the injected dose) in the bile was also reported (Cikrt and Tich 1981; Gregus and Klaasen 1986; Sheline et al. 1945). Elimination following intraperitoneal injection is similar to that seen following intravenous exposure, with urinary excretion being the major route of elimination, and fecal excretion accounting for the majority of the remainder of the dose (Barnaby et al. 1968; Hollins and McCullough 1971; Talbot and Morgan 1989), though long-term clearance may be more balanced between the two (Hollins and McCullough 1971). Following subcutaneous injection, both $CoCl_2$ and $Co(NO_3)_2$ were cleared rapidly from the body (Rosenberg 1993; Talbot and Morgan 1989), with the urine being the major route of clearance (Talbot and Morgan 1989).

Table 3-9. Summary of Measurements of Retention and Excretion of Cobalt Following Injection of Cobalt Nitrate $Co(NO_3)_2$ Solution (Mean Percent Recovery)[a,b]

Species (strain)	Whole body retention on day			Cumulative urinary excretion on day			Cumulative fecal excretion on day		
	1	7	21	1	7	21	1	7	21
Baboon	No data	No data	No data	57	74	80	5	17	20
Beagle dog	No data	No data	No data	71	86	87	3.4	4.4	4.9
Guinea pig	34	8	3.5	64	82	85	2.2	10	12
Rat (HMT)	18	4.2	1.9	64	72	74	18	24	24
Rat (F-344)	No data	No data	2.9	No data	No data	80	No data	No data	18
Hamster	27	4.3	1.9	55	68	69	17	28	29
Mouse	23	2.9	1.1	59	71	72	18	26	27

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

Following injection, studies have shown that the chemical form of the cobalt compound can affect its elimination. Subcutaneous injection of cobalt protoporphyrin in rats, in which the cobalt atom is chelated within the porphyrin ring, resulted in a slower elimination from the body than cobalt chloride, with significant cobalt levels (~20% of initial injection) still present in the body 14 days after exposure (Rosenberg 1993). Likewise, intramuscular injection of cobalt mesoporphyrin resulted in primarily in fecal excretion, with a high systemic retention (Feng et al. 1998). It therefore appears that a greater solubility leads to fast elimination, mainly in the urine, while a less soluble compound will be retained for longer periods and eliminated to a greater extent in the feces.

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

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

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

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

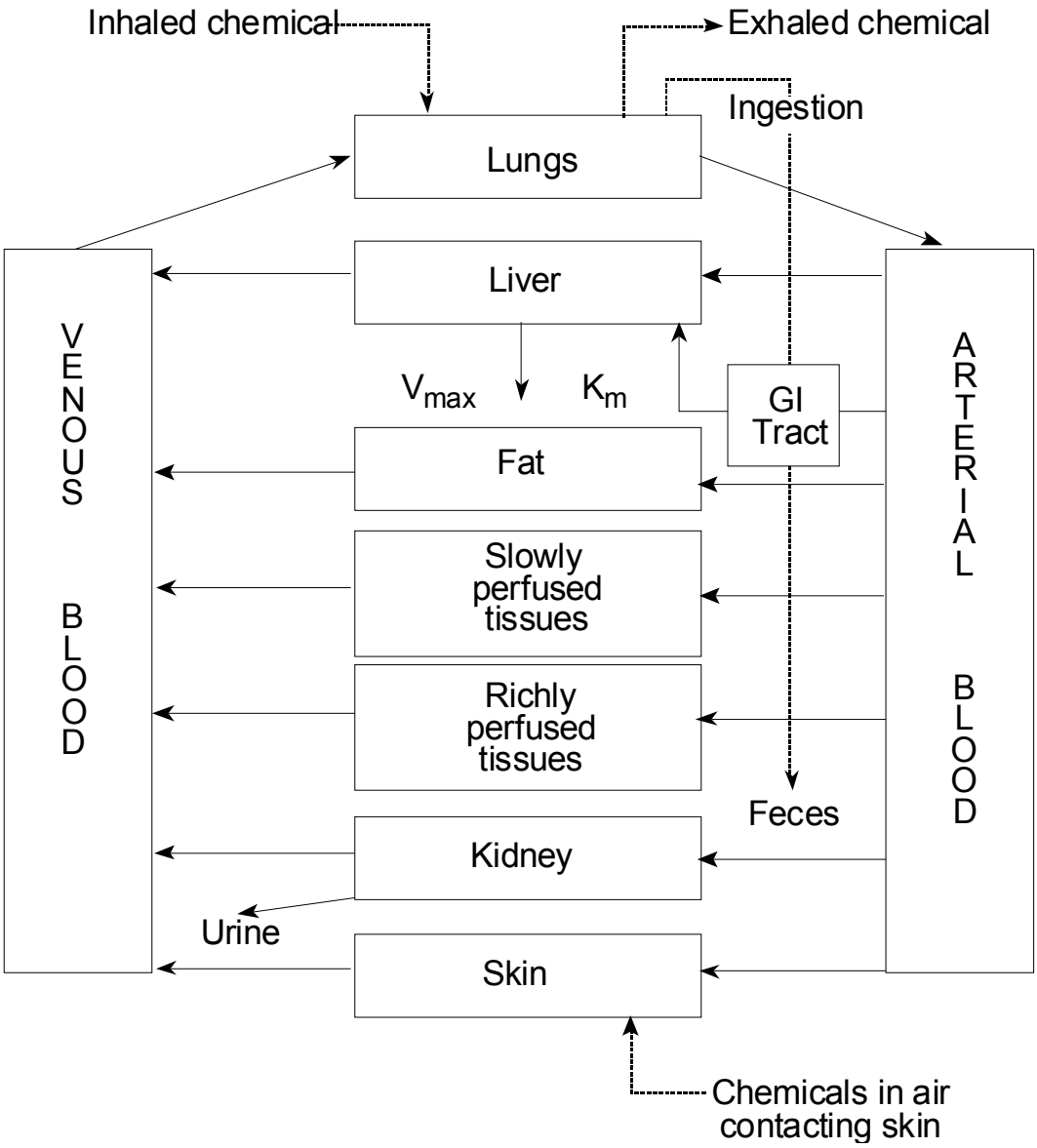
toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters.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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). Similar models have been developed for radionuclides. These PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model. Figures 3-6 through 3-9 show models for radionuclides in general or specifically for cobalt.

The ICRP (1995) developed a Human Respiratory Tract Model for Radiological Protection, which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to particulate aerosols of cobalt compounds. The ICRP (1993) also developed a 3-compartment biokinetic model for human oral exposure that applies to cobalt. EPA (1998) has adopted the ICRP (1993, 1995) models for assessment of radiologic cancer risks from cobalt exposures. The National Council on Radiation Protection and Measurement (NCRP) has also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

ICRP model for calculating doses for radiation workers and the general public. Readers interested in this topic are referred to NCRP Report No. 125; *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances* (NCRP 1997). In the appendix to the report, NCRP provides the animal testing clearance data and equations fitting the data which supported the development of the human model for cobalt

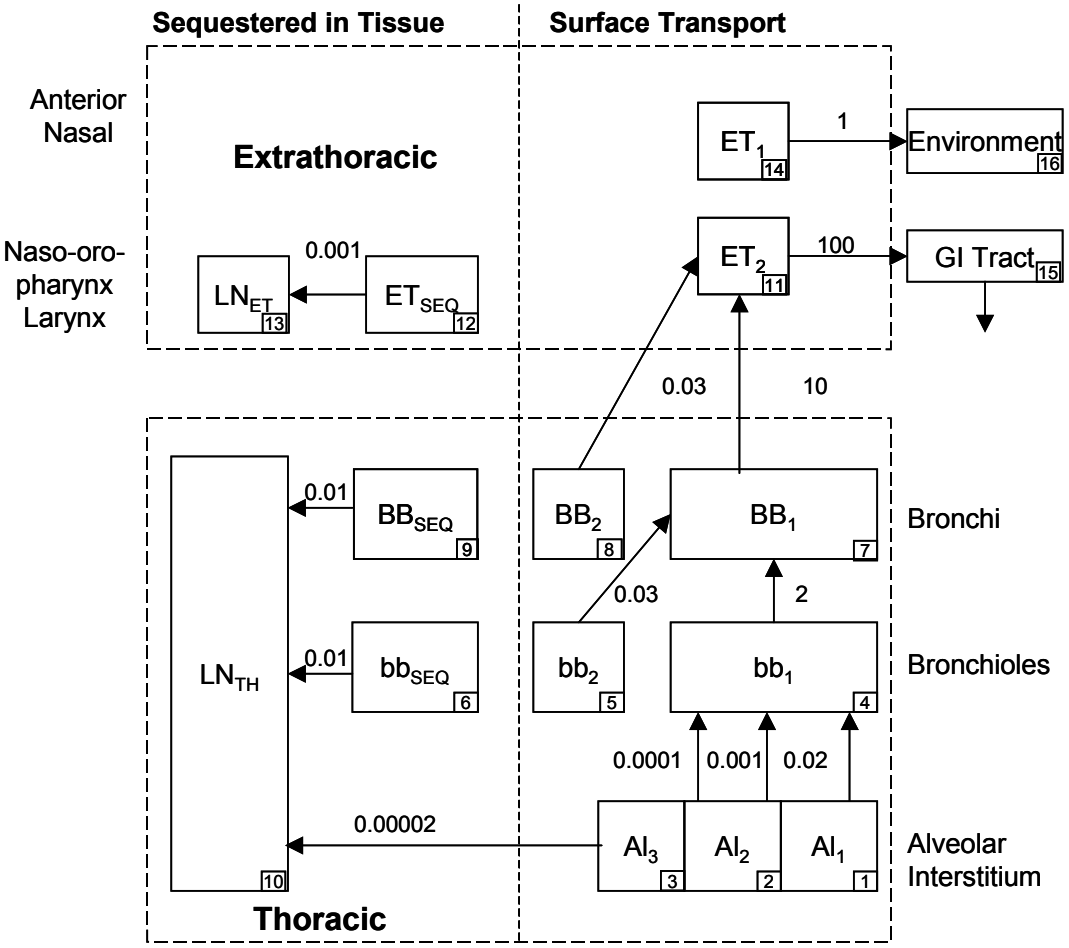
Human Respiratory Tract Model for Radiological Protection (ICRP 1994).

Respiratory Tract Deposition. The ICRP (1994) has developed a physiologically-based pharmacokinetic model for behavior of aerosols and vapors in the respiratory tract. ICRP (1994) provides inhalation dose coefficients that can be used to estimate the committed equivalent and the effective doses to organs and tissues throughout the body based on a unit intake of radioactive material and the anticipated distribution and retention of the material, its radioactive decay, and the energy of the radiationemitted from the material and absorbed by tissues. The model applies to three levels of particle solubility, a wide range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values that can be adjusted for various segments of the population (e.g., sex, age, level of physical exertion). This model also allows one to evaluate the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. It is applicable to particulate aerosols containing cobalt, and was developed for a wide variety of radionuclides and their chemical forms.

The ICRP deposition model estimates the fraction of inhaled particle mass that initially deposits in each compartment (Figure 3-6). The model was developed with 5 compartments: (1) the anterior nasal passages (ET_1); (2) all other extrathoracic airways (ET_2) (posterior nasal passages, the naso- and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar interstitium (AI). Particles deposited in each of the regions may be removed from each region and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

For extrathoracic deposition of particles, the model uses experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similarly to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition

Figure 3-6. Compartment Model to Represent Particle Deposition and Time-Dependent Particle Transport in the Respiratory Tract*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations are presented in Table 3-11.

Source: ICRP 1994b

was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-10 provides reference respiratory values for the general Caucasian population under several levels of activity.

Deposition of inhaled gases and vapors is modeled as a partitioning process, which depends on the physiological parameters noted above as well as the solubility and reactivity of compound in the respiratory tract (Figure 3-7). The ICRP (1994) model defines three categories of solubility and reactivity: SR-0, SR-1, and SR-2:

- Type SR-0 compounds include insoluble and nonreactive gases (e.g., inert gases such as H2, He). These compounds do not significantly interact with the respiratory tract tissues and essentially all compound inhaled is exhaled. Radiation doses from inhalation of SR-0 compounds are assumed to result from the irradiation of the respiratory tract from the air spaces.

- Type SR-1 compounds include soluble or reactive gases and vapors that are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues, as well as the solubility and reactivity of the compound.

- Type SR-2 compounds include soluble and reactive gases and vapors that are completely retained in the extrathoracic regions of the respiratory tract. SR-2 type compounds include sulfur dioxide (SO2) and hydrogen fluoride (HF).

Respiratory Tract Mechanical (Particle) Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various chemical materials. The compartmental model is linked to the deposition model (see Figure 3-6) and to reference values presented in Table 3-11. This table provides deposition fractions and clearance rates for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction of the deposit per day and also as clearance half-time. ICRP (1994) also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

The clearance of deposited particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers

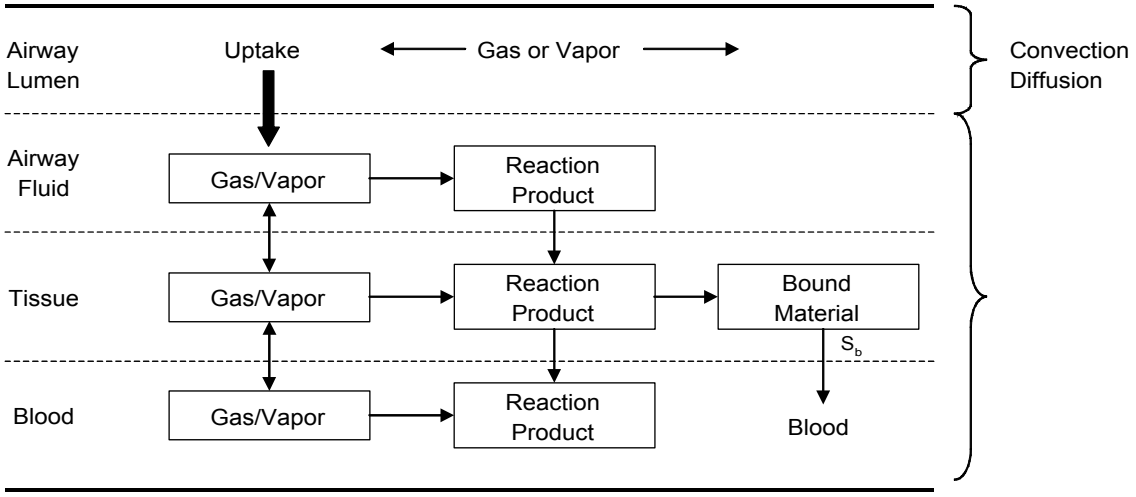
Table 3-10. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity[a]

Activity:		Resting (sleeping)			Sitting awake			Light exercise			Heavy exercise		
Maximal workload:		8%			12%			32%			64%		
Breathing parameters[b]		V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})
Age	Sex												
3 months		0.04	0.09	38	N/A	N/A	N/A	0.07	0.19	48	N/A	N/A	N/A
1 year		0.07	0.15	34	0.1	0.22	36	0.13	0.35	46	N/A	N/A	N/A
5 years		0.17	0.24	23	0.21	0.32	25	0.24	0.57	39	N/A	N/A	N/A
10 years	Male:										0.841	2.22	44
	Female:										0.667	1.84	46
	Both:	0.3	0.31	17	0.33	0.38	19	0.58	1.12	32			
15 years	Male:	0.50	0.42	14	0.533	0.48	15	1.0	1.38	23	1.352	2.92	36
	Female:	0.42	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
Adult	Male:	0.63	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	Female:	0.44	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

[a]See Annex B (ICRP 1994) for data from which these reference values were derived.
[b]V_T = Tidal volume, B = ventilation rate, f_R = respiration frequency

h = hour; L = liter(s); min = minute(s); N/A = not applicable

Figure 3-7. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



Source: ICRP 1994b

Table 3-11. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance rates for insoluble particles

Pathway	From	To	Rate (d^{-1})	Half-time[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	0.0001	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	0.00002	—
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

See next page for Part B

Table 3-11. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B

Partition of deposit in each region between compartments[b]		
Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment[c]
ET_2	ET_2	0.9995
	ET_{seq}	0.0005
BB	BB_1	0.993-f_s
	BB_2	f_s
	BB_{seq}	0.007
bb	bb_1	0.993-f_s
	bb_2	f_s
	bb_{seq}	0.007
AI	AI_1	0.3
	AI_2	0.6
	AI_3	0.1

[a]The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of day^{-1}. A half-time is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment AI_3 is determined by the sum of the clearance rates from it.
[b]See paragraph 181, Chapter 5 (ICRP 1994) for default values used for relating f_s to d_{ae}.
[c]It is assumed that f_s is size-dependent. For modeling purposes, f_s is taken to be:

$$f_s = 0.5 \text{ for } d_{ae} \le 2.5\sqrt{\rho/\chi}\ \mu m \text{ and}$$

$$f_s = 0.5e^{0.63(d_{ae}\sqrt{\rho/\chi}-2.5)} \text{ for } d_{ae} > 2.5\sqrt{\rho/\chi}\ \mu m$$

where:

f_s	=	fraction subject to slow clearance
d_{ae}	=	aerodynamic particle diameter/(µm)
ρ	=	particle density (g/cm^3)
χ	=	particle shape factor

AI = alveolar-interstitial region; BB = bronchial region; bb = bronchiolar region; BB_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region; bb_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region; ET = extrathoracic region; Et_{seq} = compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages; LN_{ET} = lymphatics and lymph nodes that drain the extrathoracic region; LN_{TH} = lymphatics and lymph nodes that drain the thoracic region

Source: ICRP 1994

of particles (acute exposure), transport rates change as particles are cleared from the various regions. Physical and chemical properties of deposited material determine the rate of dissolution and as particles dissolve; absorption rates tend to change over time. By creating a model with sub-compartments of different clearance rates within each region (e.g., BB_1, BB_2, BBseq), the ICRP model overcomes problems associated with time-dependent functions. Each compartment clears to other compartments by constant rates for each pathway.

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles end up being swallowed. In the front part of the nasal passages (ET_1), nose blowing, sneezing, and wiping remove most of the deposited particles. Particles remain here for about a day. For particles with AMADs a few micrometers or greater, the ET_1 compartment is probably the largest deposition site. The majority of particles deposited at the back of the nasal passages and in the larynx (ET_2) are removed quickly by the fluids that cover the airways. In this region, particle clearance is completed within 15 minutes. Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucocilliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles are cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The “slow” action of the cilia may remove as many as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly the closer to the alveoli it is. For the faster compartment, it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment (BB_2 and bb_2) is assumed to have fractions of the inhaled particles, depending on the particle size, deposited in BB_2 and bb_2; both have clearance half-times estimated at 20 days. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BBseq and bbseq).

If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the alveolar surface or move into the lymph nodes. The one mechanism by which particles are physically resuspended and removed from the AI region is coughing. For modeling purposes, the AI region is divided into three subcompartments to represent different clearance rates, all of which are slow.

Particle clearance from the alveolar-interstitial region has been measured in human subjects. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time, and

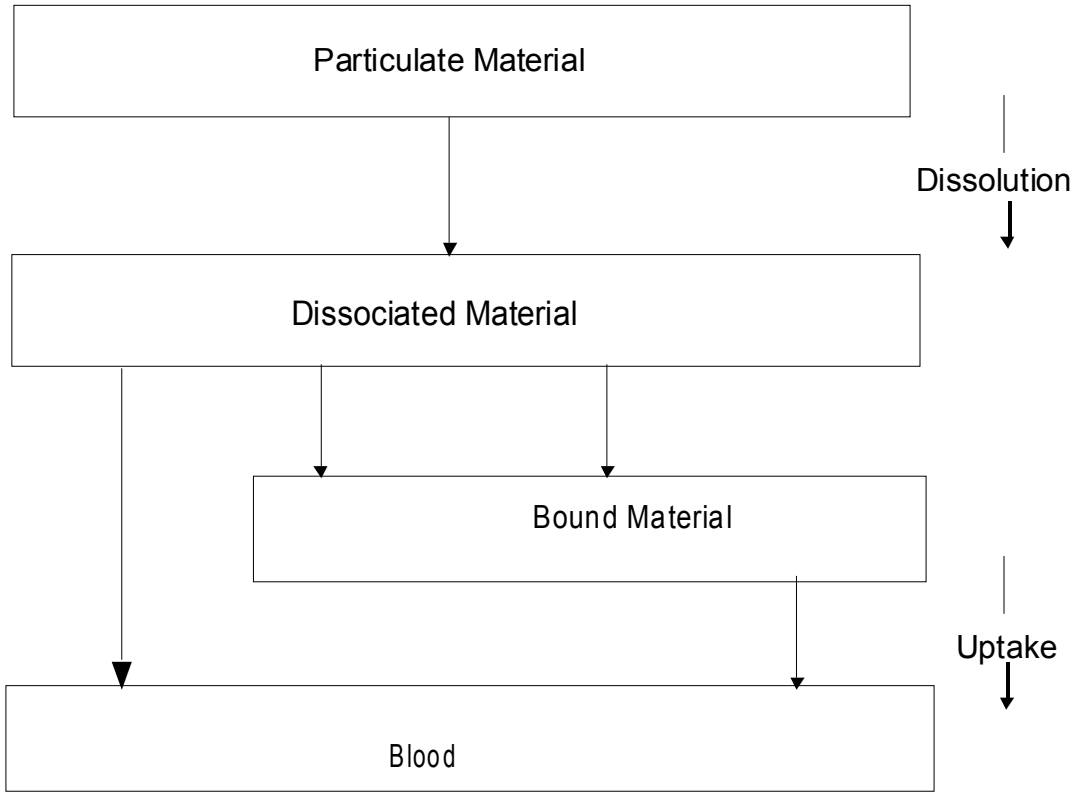
the remaining 70% are given a half-time of several hundred days. Over time, the AI particle transport rate falls and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 3-8. First, there is a dissociation (dissolution) of particles; then, the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of data for specific compounds, the model uses the following default absorption rate values for those compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET_2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET and 50% for mouth breathing.
- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET_2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing.
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually.
- For Type V, complete absorption (100%) is considered to occur instantaneously.

ICRP (1995) considers the experimental and human data to support the following classifications: cobalt chloride and nitrate, Type F; cobalt oxides, Type M or S; cobalt in fused aluminosilicate or polystyrene, Type S; cobalt in mineral dusts such as fly ash and volcanic ash, Type M; cobalt metal and metal alloys, M or S. ICRP (1995) recommends assigning all cobalt aerosols to Type M in the absence of specific information supporting an alternative classification.

Figure 3-8. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994

ICRP (1993) Cobalt Biokinetics Model.

Description of the model.

ICRP (1979, 1993) developed a 3-compartment model of the kinetics of ingested cobalt in humans that is applicable to infants, children, adolescents, and adults. Absorption of ingested cobalt is assumed to be 60% in infants up to 3 months of age, 30% from 3 months to 15 years of age, and 10% after age 15 years. Absorbed cobalt is assumed to distribute as follows: 50% is excreted (urine and feces combined in a 6:1 ratio), 5% is transferred to the liver, and 45% is transferred to other tissues (Figure 3-9). Elimination from tissue compartments is described by three first order rate constants representing slow, medium, and fast elimination pools with half-times of 6, 60, and 800 days, respectively. The elimination half-times are assumed to be independent of age.

Validation of the model.

The extent to which the ICRP model has been validated is not described in ICRP (1993).

Risk assessment.

The model has been used to establish radiation dose equivalents (Sv/Bq) of ingested ^{57}Co, ^{58}Co, and ^{60}Co for ages 3 months to 70 years (ICRP 1993).

Target tissues.

The model can be used to estimate the radiation dose from cobalt radionuclides to all major organs and can be applied to environmental and occupational exposures.

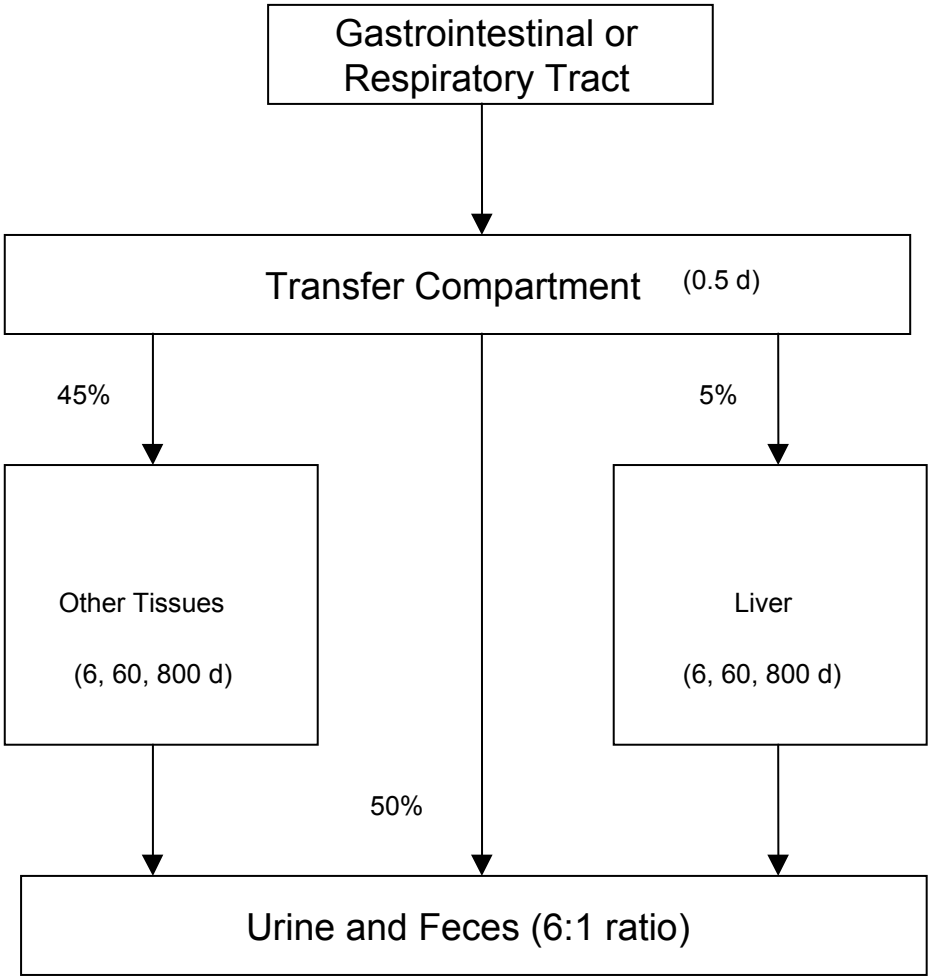
Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

*Inter*route extrapolation.

The model is designed to simulate oral exposures to cobalt and cannot be applied to other routes of exposure without modification.

Figure 3-9. ICRP Biokinetics Model for Cobalt



Absorbed cobalt enters a virtual transfer compartment from which unidirectional transfer to tissues is assumed to occur. Percentages shown are of the initial amounts absorbed. Numbers in parentheses are elimination half-times to urine and feces combined (d=days. Liver other tissues are assumed to have fast, medium, and slow elimination pools.

3.6 MECHANISMS OF ACTION

3.6.1 Pharmacokinetic Mechanisms

Absorption. Following inhalation exposure, the absorption of deposited cobalt compounds seems to be related to their biological solubility. Cobalt compounds deposit in the lungs based on their aerosol characteristics. Physiologically insoluble cobalt particles are generally cleared by phagocytosis and/or mucociliary transport, and thus, have a low systemic absorption. To some extent, cobalt particles may be dissolved within alveolar macrophages (Kreyling et al. 1990). More soluble forms of cobalt may enter the bloodstream through the alveolar or bronchial walls.

Following oral exposure, the absorption of cobalt varies with the amount given, with a greater dose leading to 4- to 20-fold greater fractional absorption (Smith et al. 1972). Nutritional status also seems to be an important factor in cobalt absorption, with both overnight fasting and iron deficiency resulting in increased cobalt absorption (Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). It has been suggested that cobalt and iron share a common absorptive pathway in the intestines, though the cobalt absorption takes place without ferritin (Reuber et al. 1994; Schade et al. 1970; Thomson et al. 1971). Solubility of the cobalt compound is also an important factor regarding the absorption following oral exposure, with increasing solubility resulting in increasing absorption (Christensen et al. 1993). One study in humans showed that oral exposure to cobalt resulted in significantly higher urinary excretion in females relative to males (Christensen et al. 1993), but these results have not been verified by other studies. A complex, specific pathway exists for the absorption of vitamin B_{12}, whereby the molecule interacts with several factors in the stomach and intestine to facilitate absorption (for review, see Russel-Jones and Alpers 1999).

Dermal absorption of cobalt compounds depends greatly on whether the skin is intact or damaged. Absorption through intact skin is comparatively low, while absorption through damaged skin is much higher (Inaba and Suzuki-Yasumoto 1979; Lacy et al. 1996).

Distribution. As a component of vitamin B_{12}, cobalt is found in most body tissues. Absorbed cobalt is transported throughout the body in the blood, with greatest levels found in the liver, followed by the kidney (Ayala-Fierro et al. 1999; Greenberg et al. 1943; Gregus and Klaassen 1986; Patrick et al. 1989).

Following inhalation exposure, significant levels of cobalt are found in the lungs of exposed humans and animals (Barnes et al. 1976; Brune et al. 1980; Collier et al. 1991; Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Kreyling et al. 1986; Kyono et al. 1992; Patrick et al. 1989; Talbot and Morgan 1989; Teraoka 1981). Within the lung, physiologically insoluble cobalt particles tend to be located within macrophages within the bronchial wall or in the interstitium close to the terminal bronchioli (Brune et al. 1980).

Excretion. Following inhalation exposure, the rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kerfoot 1975; Kreyling et al. 1986, 1989; Palmes et al. 1959; Patrick et al. 1989; Talbot and Morgan 1989). Likewise, the majority of absorbed cobalt following oral exposure is rapidly removed from the body by excretion in the urine, and to a lesser extent in the bile and feces, with fecal elimination being the primary method of excretion for physiologically insoluble cobalt compounds in both humans and animals (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Harp and Scoular 1952; Paley et al. 1958; Patrick et al. 1989; Smith et al. 1972; Sorbie et al. 1971; Talbot and Morgan 1989; Valberg et al. 1969). The primary route for excretion following dermal exposure is the urine (Lacy et al. 1996; Scansetti et al. 1994).

3.6.2 Mechanisms of Toxicity

Stable Cobalt. The exact mechanisms by which cobalt exerts its effects on cells are not completely understood. However, a number of potential mechanisms have been identified. Several studies have demonstrated that hard metal, a metal alloy with a tungsten carbide and cobalt matrix, is considerably more toxic than either cobalt or tungsten carbide alone. A mechanism by which hard metal may exert its effects has been proposed by a group of Belgian researchers (Lasfargues et al. 1995; Lison et al. 1995, 1996). In this proposed mechanism, tungsten carbide, which is a very good conductor of electrons, facilitates the oxidation of cobalt metal to ionic cobalt (presumably Co^{2+}) by transferring electrons from the cobalt atom to molecular oxygen adjacent to the tungsten carbide molecule. The result is an increased solubility of cobalt, relative to cobalt metal alone, and the generation of active oxygen species. The cobalt ions formed may be absorbed into the blood and transported throughout the body, where they may elicit effects by the above mechanisms. *In vitro* evidence for this mechanism includes the ability of hard

metal particles, but neither cobalt nor tungsten carbide alone, to generate substantial levels of oxidant species and cause significant lipid peroxidation (Lison et al. 1995; Zanetti and Fubini 1997). Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS), a gene responsive to oxidant stress (Rengasamy et al. 1999).

Another potential mechanism for cobalt toxicity is through oxidant-based and free radical-based processes. Exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage (Hoet et al. 2002; Kasprzak et al. 1994; Lewis et al. 1991; Zhang et al. 1998a); hydrogen peroxide appears to be a necessary cofactor for cobalt-induced oxidative DNA damage (Ivancsits et al. 2002). Cobalt has been shown to generate oxygen radicals, including superoxide, both *in vitro* and *in vivo* (Kadiiska et al. 1989; Kawanishi et al. 1994; Moorhouse et al. 1985), through what may be a Fenton-type mechanism (Lloyd et al. 1997). *In vivo* exposure to cobalt in rats and guinea pigs resulted in increased lipid peroxidation in the liver (Christova et al. 2001, 2002; Sunderman and Zaharia 1988), as well as changes in reduced glutathione and hepatic levels of superoxide dismutase, catalase, heme oxygenase, and glutathione peroxidase (Christova et al. 2001, 2002). Exposure to cobalt results in accumulation in cardiac tissues, and is thought to stimulate carotid-body chemoreceptors, mimicking the action of hypoxia (Di Giulio et al. 1990, 1991; Hatori et al. 1993; Morelli et al. 1994). Cobalt administration to a neuroblastoma/glioma cell line resulted in an upregulation of opioid delta receptors, through a mechanism similar to that of hypoxia (Mayfield et al. 1994). Exposure to cobalt also elicits effects on a number of genes known to be sensitive to oxidant status, including hypoxia-inducible factor 1, erythropoietin, vascular endothelial growth factor, catalase, and monooxygenase enzymes (Bunn et al. 1998; Daghman et al. 1999; Dalvi and Robbins 1978; Di Giulio et al. 1991; Goldberg et al. 1988, 1994; Ho and Bunn 1996; Hoet et al. 2002; Ladoux and Frelin 1994; Legrum et al. 1979; Semenza et al. 1994; Yasukochi et al. 1974), and may also lead, through these genes or other pathways, to the induction of apoptosis (Zou et al. 2001).

Soluble cobalt has also been shown to alter calcium influx into cells, functioning as a blocker of inorganic calcium channels (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). This mechanism has been linked to a reduction of steroidogenesis in isolated mouse Leydig cells (Moger 1983). Additionally, soluble cobalt has been shown to alter the inorganic calcium influx in liver cells after exposure to glucagon (Yamatani et al. 1998), and calcium influx into pancreatic β cells (Henquin et al. 1983) and

isolated rat islets (Henquin and Lambert 1975). Cobalt may also affect neuromuscular transmission though antagonism with calcium (Weakly 1973).

Another potential mechanism of cobalt toxicity is relevant to cobalt cardiomyopathy. As mentioned previously, cobalt accumulated in the heart of beer drinkers. Microscopic analysis revealed fragmentation and degeneration of myofibers and aggregates of abnormal mitochondria (Ferrans et al. 1964). These mitochondrial changes are indicative of disturbances in energy production or utilization possibly related to cobalt effects on lipoic acid. Cobalt irreversibly chelates lipoic acids under aerobic conditions (Webb 1982). Lipoic acid is a required cofactor for oxidative decarboxylation of pyruvate to acetyl CoA and of α-ketoglutarate to succinate (Lehninger 1982). In the myocadrium of rats treated with cobalt, oxidation of pyruvate or fatty acids is impaired (Wiberg 1968).

A number of investigators have reported that cobalt ions can result in increased damage to DNA when co-exposed with oxidants *in vitro*, such as UV radiation or H_2O_2 (De Boeck et al. 1998; Hartwig et al. 1991; Nackerdien et al. 1991). It is believed that cobalt acts by inhibition of DNA repair, particularly the incision and polymerization steps (Asmuß et al. 2000; Kasten et al. 1997), accomplishing this through interaction with zinc finger DNA repair proteins (Asmuß et al. 2000; Sarkar 1995).

Another potentially important mechanism by which cobalt may exert effects is through its effects on heme and heme-containing enzymes. Cobalt is thought to inhibit heme synthesis *in vivo* by acting upon at least two different sites in the biosynthetic pathway: synthesis of 5-aminolevulinate and conversion of 5-aminolevulinate into heme (de Matteis and Gibbs 1977). This inhibitory activity might result in the formation of cobalt protoporphyrin rather than heme (Sinclair et al. 1979). Cobalt treatment also stimulates heme oxidation in many organs, due to the induction of heme oxygenase (for review, see Sunderman 1987). Effects on heme synthesis may potentially affect a wide variety of heme-containing proteins, including monooxygenase enzymes (i.e., cytochromes P450) and catalase (Legrum et al. 1979; Yasukochi et al. 1974). Conversely, cobalt acts, through a mechanism believed to involve a heme-containing protein, to increase erythropoietin, which stimulates the production of red blood cells (Di Giulio et al. 1991; Goldberg et al. 1988; Smith and Fisher 1973). The regulatory mechanisms behind this apparent dichotomy have not been fully elucidated.

Another potential mechanism by which cobalt may exert its effects is through interactions with the immune system. Exposure of humans to cobalt by the inhalation and dermal routes have resulted in

sensitization to cobalt (Alomar et al. 1985; Bencko et al. 1983; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Shirakawa et al. 1988, 1989; Valer et al. 1967). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), suggesting cobalt sensitization as one mechanism by which cobalt-induced asthma may be produced. IgE and IgA antibodies specific to cobalt have been reported in humans (Bencko et al. 1983; Shirakawa et al. 1988, 1989). There is evidence that cobalt sensitivity in humans may to be regulated by T-lymphocytes (Katsarou et al. 1997). A human helper T-lymphocyte cell line specific for cobalt (CoCl2) has been established (Löfström and Wigzell 1986). Cobalt may also interact directly with immunologic proteins, such as antibodies or Fc receptors, to result in immunosensitization (Cirla 1994). *In vitro*, cobalt(II) has been shown to reduce the proliferation of both B and T lymphocytes, as well as the release of the cytokines IL-2, IL-6, and IFN-Gamma (Wang et al. 1996). Interrelationships exist between nickel and cobalt sensitization (Bencko et al. 1983; Rystedt and Fisher 1983); however, the extent of any potential interactions between the two metals on immunologic end points is not well understood. In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al. 1985), though cross-reactivity was not reported to occur.

Cobalt has been shown to have a number of effects on glucose metabolism. Treatment of animals with cobalt results in a depression of serum (Eaton and Pommer 1973; Ybarra et al. 1997) or tissue (Wiberg 1968) glucose levels. In rats made diabetic by pretreatment with streptozotocin, this depression was persistent, whereas it was transient in normal rats (Ybarra et al. 1997). Many of the effects of cobalt on glucose metabolism are thought to result from alterations in the expression of the glut family of glucose transport proteins, a family of facilitative Na+-independent transport proteins thought to mediate non-insulin-dependent transport of glucose. Exposure to soluble cobalt results in increased expression of these genes, particularly GLUT1, in cells of the liver, kidney cortex, myocardium, skeletal muscle, and cerebrum (Behrooz and Ismail-Beigi 1997; Ybarra et al. 1997). Cobalt also reduces the amount of glucose produced in liver cells following stimulation with glucagon (Eaton and Pommer 1973; Yamatani et al. 1998), as well as reducing insulin release in isolated rat islets (Henquin and Lambert 1975).

Radioactive Cobalt. Due to the nature of its ionizing radiation, radioactive cobalt can present a health hazard. Highly-penetrating gamma emissions are the major source of damage to tissues and internal organs following external exposure to radioactive cobalt isotopes. If radioactive cobalt is internalized, nearby tissues are at highest risk for damage due to the release of beta particles. In either case, exposure to ionizing radiation results in an increased risk of cellular damage. Both beta and gamma radiations are

capable of producing ionization events when they hit cellular molecules, including DNA, RNA, or lipids. Ionized molecules within irradiated cells may be repaired quickly to prevent further damage. On the other hand, irreparable damage may be imposed on cellular materials, such as DNA, which might ultimately result in either cell death or the formation of cancerous tumors. Very large acute radiation doses can damage or kill enough cells to cause the disruption of organ systems, resulting in acute radiation syndrome or even death. Human and animal data indicate that sufficiently high exposures to cobalt radiation can result in adverse effects such as reduced fertility, abnormal development, genotoxicity, pulmonary fibrosis, gastrointestinal atrophy and fibrosis, hematological and lymphoreticular disorders, cancer, and death (Chang et al. 1999b; Davis et al. 1992; Dinehart et al. 1991; Hashimoto and Mitsuyasu 1967; Klener et al. 1986; Libshitz 1993; Myskowski and Safai 1981; Rauscher and Bauchinger 1983; Roschler and Woodard 1969; Roswit and White 1977; Stavem et al. 1985; Van Oort et al. 1984). For a more complete discussion of the mechanisms associated with the toxic effects of ionizing radiation, refer to Chapter 5 of the Toxicological Profile for Ionizing Radiation (Agency for Toxic Substances and Disease Registry 1999).

3.6.3 Animal-to-Human Extrapolations

Bailey et al. (1989) reported a wide variation across species, including man, in the retention and clearance of inhaled physiologically insoluble 57Co particles (see Table 3-8), noting that this variation illustrates the potential difficulty of extrapolating the results of animal lung retention experiments to human even qualitatively. Species differences in absorption of physiologically insoluble cobalt oxide following oral exposure do not appear to exist (Bailey et al. 1989), although humans were not examined. Absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; van Bruwaene et al. 1984).

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate

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

The available human and animal data suggest that the endocrine system, particularly the thyroid gland, may be a target of stable and radioactive cobalt toxicity. These effects are discussed in Sections 3.2 and 3.3 under Systemic Effects.

3.8 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential

effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

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

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

have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Though human data are lacking, animal studies have suggested several differences in pharmacokinetic behavior of cobalt compounds between children and adults. Following inhalation exposure to Co_3O_4, deposition tended to increase with age, though no significant differences were reported (Collier et al. 1991). The youngest animals exposed (3 weeks postnatal) had the lowest fractional retention 182 days postexposure, though no differences were seen at day 7 or 83. The authors attributed this to a faster rate of translocation of cobalt from the lung to the blood, which could enhance subsequent excretion. Naylor and Harrison (1995) reported that in rats and guinea pigs, fractional absorption of cobalt following oral exposure was highest at 1 day after birth, and diminished rapidly with time thereafter. Collier et al. (1991) reported no difference in absorption of cobalt nitrate following oral exposure to animals aged 3–46 weeks, which is in agreement with the results of the later portion of the Naylor and Harrison (1995) study. No PBPK models specific for cobalt exposures to children were located. However, the ICRP Human Respiratory Tract Model is applicable to children, and may be used for children if the appropriate values for the parameters are used.

Once in the bloodstream, soluble cobalt compounds have been shown, in animal studies, to cross the placenta and enter the fetus. Twenty-four hours after intravenous injection of cobalt chloride in rats, 0.14% of the dose was found in the fetus, 0.19% in the chorioallantoic placenta, and 0.22% in the yolk sac (Zylicz et al. 1975). Several other rat studies (Nishimura et al. 1978; Zylicz et al. 1975, 1976) have demonstrated that the amount of cobalt crossing the placenta following intravenous injection is greater in later gestation stages, though the percent of the maternal dose reaching the fetus is still relatively low (in <1% of the maternal dose). The fetal uptake of cobalt following intravenous administration to the mother was increased when the cobalt was given as cyanocobalmin, relative to cobalt chloride (~5% of the maternal dose for cyanocobalmin, compared to <1% for cobalt chloride) (Nishimura et al. 1978), indicating that the form of the cobalt compound may affect its availability to the fetus.

Cobalt has been detected in human breast milk (Byczkowski et al. 1994; Kratchler et al. 1998). In general, physiological concentrations of cobalt in breast milk are very low, on the order of parts per billion (Byczkowski et al. 1994). Animal studies are in agreement with this observation. By day 70 post-exposure in lactating dairy cows orally exposed to cobalt chloride, the milk contained 0.012% of the dose (van Bruwaene et al. 1984). One to two percent of cobalt given intravenously to mother rats as cyanocobalmin was transferred to offspring via the breast milk (Nishimura et al. 1978).

Health Effects from Exposure to Stable Cobalt. Available data have not clearly defined whether children are at greater risk from exposure to stable cobalt than adults. Studies in adult humans have identified several health effects of cobalt compounds following inhalation, oral, or dermal exposure. Data on effects of cobalt in children following inhalation exposures are lacking. Jacobziner and Raybin (1961) reported on two cases of children who had accidentally ingested unknown amounts of cobalt chloride; a 19-month-old male died approximately 6.5 hours after ingestion, whereas a 3-year-old male was given medical treatment and showed no symptoms after ingestion. Several studies (Chamberlain 1961; Little and Sunico 1958; Sederholm et al. 1968; Washburn and Kaplan 1964) have reported enlarged thyroid glands in children given cobalt chloride for treatment of anemia; removal of cobalt therapy resulted in a return to normal thyroid size. Patch testing of children aged 4–14 years revealed a 13.3% dermal sensitization rate to cobalt chloride (Romaguera and Vilaplana 1998). More girls reacted positively than boys, which the authors attributed to the wearing of costume jewelry, which often contains cobalt, and the resulting exposure.

Offspring of mice intravenously injected with approximately 1.2 mg cobalt/kg at day 8 of gestation, but not at day 3, showed a significant increase in the number of skeletons with delayed ossification (Wilde 1984). Other studies, however, have not shown developmental effects of stable cobalt compounds, or have shown effects only at maternally toxic doses (Domingo et al. 1985b; Paternian et al. 1988; Seidenberg 1986).

Health Effects from Exposure to Radioactive Cobalt. Taiwanese children (48 boys, 37 girls) who were raised in apartments contaminated with ^{60}Co were compared to 21,898 age- and sex-matched non-exposed children from a nationwide surveillance program (Wang et al. 2001). After adjusting for effects from parental heights and body mass index, clear dose-related decreases in height percentile (HP) and age-specific relative height differences (RHD) were seen in exposed boys, but not in exposed girls. Average

cumulative exposures were 120.8 and 129.9 mSv (equivalent to ~12.1 or 13 rad) for the boys and girls, respectively.

No other studies of human children exposed to radioactive cobalt or cobalt radiation were located. As rapidly-dividing cells are more sensitive to radiation, the developing fetus and growing children are expected to be more sensitive to cobalt radiation than adults.

Animal studies have shown that exposures to external radiation from cobalt isotopes (as low as 10 rad [0.1 Gy] in mice) may have a dramatic effect on the developing fetus (see Section 3.2.4.6 and Agency for Toxic Substances and Disease Registry 1999). Exposure duration, gestational day, and dose all influence the effect of cobalt radiation on the developing organism. Radiation exposure to very young dogs (80 rad [0.8 Gy] on day 2 or 70 postpartum) has resulted in an increased incidence of diabetes mellitus, renal disease, and cancer (Benjamin et al. 1998a, 1998b).

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cobalt are discussed in Section 3.9.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cobalt are discussed in Section 3.9.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11 "Populations That Are Unusually Susceptible".

3.9.1 Biomarkers Used to Identify or Quantify Exposure to Cobalt

Biomonitoring data exist that demonstrate a positive correlation between occupational exposure levels of cobalt and the levels of cobalt in both the urine and blood (Table 3-12) (Alexandersson 1988; Ichikawa et al. 1985; Lison et al. 1994; Nemery et al. 1992; Scansetti et al. 1985). Available studies of unexposed humans have reported cobalt blood levels of 0.05–0.19 µg/dL and urinary cobalt levels of 0.04–2 µg/dL (Alexandersson 1988; Ichikawa et al. 1985). Figure 3-10 graphically presents the cobalt exposure data and cobalt in blood data presented in Table 3-12 (Ichikawa et al. 1985). The highest excretion rate of cobalt in urine occurs during the first 24 hours after short-term exposure; therefore, subjects should be tested quickly to assess whether cobalt exposure has occurred (Alexandersson 1988). Occupational exposure to 0.1 mg/m^3 cobalt resulted in blood levels of cobalt ranging (95% CI) from 0.57 to 0.79 µg/dL, compared to 0.19 µg/dL in unexposed workers, and urinary levels from 59 to 78 µg/L, compared to 2 µg/L in unexposed workers (Ichikawa et al. 1985). Correlations between recent exposure and cobalt levels in the blood or urine are more consistent for soluble cobalt compounds (metal, salts, and hard

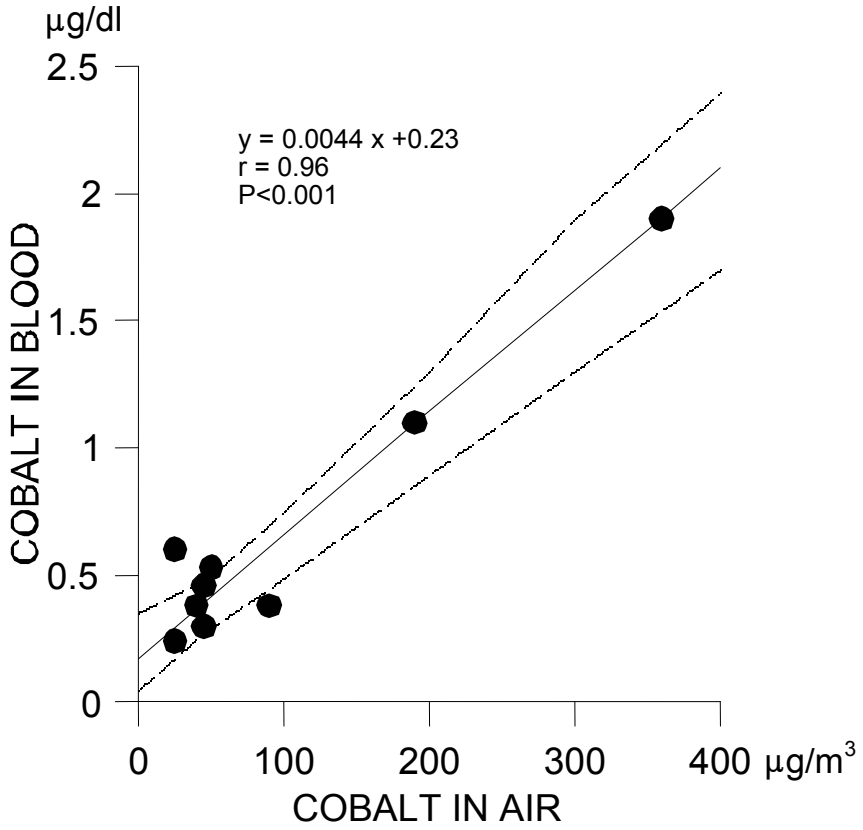
Table 3-12. Cobalt Exposure Concentrations and Amounts in the Blood and Urine of Subjects Examined[a]

Subjects	Number	Cobalt in air[b] mean±SD µg/m^3		Cobalt in blood[b] mean±SD µg/dL		Cobalt in urine[b] mean±SD µg/L	
Powder handlers	2	186±108	(110–262)	1.08±0.28	(0.88–1.28)	148±13	(138–158)
Rubber press operators	6	367±324	(92–859)	1.87±1.96	(0.40–5.30)	235±182	(41–392)
Automatic press operators	11	56±60	(9–210)	0.57±0.53	(0.10–0.95)	34±43	(4–73)
Shapers (lathing)	7	33±15	(15–62)	0.67±0.44	(0.14–1.34)	33±30	(11–95)
Shapers (sawing)	21	50±35	(8–144)	0.52±0.31	(0.15–1.15)	41±60	(6–266)
Sintering workers	21	28±30	(4–145)	0.26±0.10	(0.09–0.45)	10±10	(2–46)
Wet grinders							
A	27	44±48	(4–227)	0.42±0.31	(0.10–1.30)	35±34	(2–180)
B	18	45±50	(3–161)	0.33±0.10	(0.16–0.52)	19±15	(2–67)
C	12	92±92	(15–291)	0.43±0.39	(0.12–1.90)	68±87	(3–265)
D	25	44±54	(3–205)	0.35±0.20	(0.10–1.00)	17±16	(1–69)
Workers using respirators	25	317±307	(7–1,203)	0.65±0.86	(0.20–3.90)	26±30	(1–119)
Office workers	20	No data		0.19±0.11	(0.08–0.40)	2±1	(1–4)

[a]Adapted from Ichikawa et al. 1985
[b]The range of each value is given in parentheses.

SD = standard deviation

Figure 3-10. Relation Between Mean Cobalt Exposure and Mean Blood Concentration of Cobalt in Exposed Workers*



*Adapted from Ichikawa et al. 1985

metals), while blood and/or urinary cobalt levels are less reflective of recent exposure for less soluble compounds (cobalt oxides) (Lison et al. 1994).

Sensitive serum protein responses were found in animals exposed to cobalt at levels below those necessary to produce hematopoietic effects (Stokinger and Wagner 1958). These serum protein responses included an increase in alpha globulin fractions of serum proteins and associated serum neuraminic acid. The responses were observed in rabbits and dogs following both inhalation and injection of cobalt. The authors indicated that this increase was a unique response to cobalt exposure. The characteristics of the response were similar to those of the erythropoietic response found following exposure to higher levels of cobalt; the response is delayed, does not occur in all animals within a given exposure group, is not of great magnitude, and is not persistent (Stokinger and Wagner 1958).

Biomarkers specific for exposure to cobalt radioisotopes have not been reported.

3.9.2 Biomarkers Used to Characterize Effects Caused by Cobalt

Sensitization to cobalt results in cobalt-specific changes in serum antibodies (IgE and IgA) that may be monitored to determine if sensitization, or additional exposure, to cobalt has occurred (Bencko et al. 1983; Shirakawa et al. 1988, 1989).

No biomarkers specific for effects of radioactive cobalt isotopes have been reported. Biomarkers for response to ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999).

3.10 INTERACTIONS WITH OTHER CHEMICALS

A major medical use of cobalt is in combination with bleomycin, an antineoplastic antibiotic, as a tumor-localizing and therapeutic agent (Goodwin and Meares 1976; Hansen et al. 1976; Kapstad 1978, 1979). The anti-tumor effects of the two agents are amplified when given in combination with each other. The complex, wherein cobalt is coordinately bound to the bleomycin molecule, is intravenously injected and acts by binding to and cleaving the DNA in the tumor cells (Kakinuma and Orii 1982).

The interaction of cobalt with various chelators has been investigated in animals for mitigation of the toxicity of cobalt (Baker et al. 1987; Domingo et al. 1983; Llobet et al. 1988). Glutathione, N-acetyl-L-cysteine (NAC) and diethylenetriaminepentaacetic acid (DTPA), administered to rats previously exposed to cobalt, significantly increased urinary excretion of cobalt, while EDTA, NAC, and 2,3-di-mercaptosuccinic acid (DMSA) increased fecal excretion. NAC was the most effective chelator because it increased both urinary and fecal excretion of cobalt while decreasing its levels in liver and spleen (Llobet et al. 1988). Cysteine, also acting as a chelator, mitigated the toxicity of cobalt when both chemicals were given to chicks in the feed (Baker et al. 1987).

A number of studies have suggested an association between cobalt ions and calcium ions. Soluble cobalt has also been shown to alter calcium influx into cells, functioning as a blocker of inorganic calcium channels (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). This mechanism has been linked to a reduction of steroidogenesis in isolated mouse Leydig cells (Moger 1983). Additionally, soluble cobalt has been shown to alter the inorganic calcium influx in liver cells after exposure to glucagon (Yamatani et al. 1998), and calcium influx into pancreatic β cells (Henquin et al. 1983) and isolated rat islets (Henquin and Lambert 1975). Cobalt may also affect neuromuscular transmission through antagonism with calcium (Weakly 1973).

Hard metal, consisting of 5–10% cobalt with the balance being tungsten carbide, has been shown to be considerably more toxic than cobalt alone, resulting from interactions between particles of cobalt metal and tungsten carbide particles. The mechanisms responsible for this interaction are discussed in Section 3.6.2.

An interrelationship between cobalt and nickel sensitization has been reported in individuals exposed to the two metals (Rystedt and Fisher 1983; Veien et al. 1987), as well as in animal studies (Wahlberg and Lidén 2000). It was concluded that the combination of nickel sensitivity and irritant eczema resulted in a high risk for developing an allergy to cobalt. Studies of cultured alveolar type II cells showed a synergistic (greater than additive) response to co-exposure to cobalt and nickel chlorides (Cross et al. 2001).

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Individuals who are already sensitized to cobalt may be unusually susceptible because cobalt exposure may trigger asthmatic attacks (Shirakawa et al. 1988, 1989). Sensitization to cobalt results in cobalt-specific changes in serum antibodies (IgE and IgA) (Bencko et al. 1983; Shirakawa et al. 1988, 1989). Potolicchio et al. (1997, 1999) have suggested that individuals with a polymorphism in the HLA-DP gene (presence of glutamate 69 in the β chain) may be more susceptible to hard metal lung disease. Individuals with ongoing respiratory illness may also be more susceptible to the effects of inhaled cobalt. Following oral exposure, individuals with iron deficiency may at greater risk, as animal studies have shown an increased absorption of cobalt compounds in iron-deficient animals (Reuber et al. 1994; Schade et al. 1970). Studies of beer-cobalt cardiomyopathy have suggested that individuals with high alcohol consumption may be more susceptible to health effects of cobalt (Alexander 1969, 1972; Morin et al. 1971).

Ionizing radiation has greater effects on rapidly-dividing cells than on those that divide at a slower rate. The most sensitive population to exposure to cobalt radiation is likely to be the developing fetus, as even moderate exposures to cobalt radiation have been shown to cause dramatic effects on the developing fetus in animal studies (see Section 3.2.4.6), Likewise, growing children are likely to be more susceptible to cobalt radiation than adults, and people who are immunocompromised, have existing lung diseases, or who have defects in genetic repair enzymes would be expected to show an increased susceptibility to cobalt radiation. A detailed discussion on the effects of ionizing radiation in children can be found in Agency for Toxic Substances and Disease Registry (1999).

3.12 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams & Wilkins, 1682–1723.

Goldfrank, LR, Flomenbaum, NE, Lewin, NA, et al., eds. 1998. Toxicological emergencies. 6th edition. Connecticut: Appleton & Lange, 481t, 489, 490t, 1338–1339.

REAC/TS. Radiation Emergency Assistance Center/Training Site. www.orau.gov/reacts/.

3.12.1 Reducing Peak Absorption Following Exposure

Methods for reducing peak absorption are similar for both the stable and radioactive forms of cobalt. General management and treatment of patients following acute exposure to cobalt includes removal of the victim from the contaminated area, and removal and isolation of contaminated clothing, jewelry, and shoes (Bronstein and Currance 1988; Stutz and Janusz 1988). The excess solid contaminant is gently brushed away, and excess liquids are blotted with absorbent material. If the victim is in respiratory distress, ventilation assistance is provided and oxygen is administered. Measures that are appropriate to the route of exposure are then taken to remove cobalt from the body. Following ocular exposure, the eyes are immediately flushed thoroughly with water. Skin is washed immediately with soap or mild detergent and water. Some evidence has been presented that the use of cheating creams on the skin can reduce the occurrence of symptoms in allergic persons (Wöhrl et al. 2001). Following ingestion of cobalt, two conflicting forms of treatment have been recommended. Stutz and Janusz (1988) recommend that victims over 1 year old be given ipecac, followed by activated charcoal (after vomiting). A cathartic, such as magnesium sulfate in water, is then administered to adults and children. Bronstein and Currance (1988) recommend that the victim be given water for dilution of the cobalt; however, they recommend that emetics not be administered. Following all routes of exposure, victims are monitored for pulmonary edema, circulatory collapse, and shock, and treated as necessary.

3.12.2 Reducing Body Burden

Chelation therapy with EDTA or dimercaprol can be effectively used if necessary (Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988). Animal studies have investigated the effectiveness of various chelating agents for mitigating the toxicity of cobalt (Baker et al. 1987; Domingo et al. 1983; Llobet et al. 1988). NAC was found to be the most effective chelator because it increased both urinary and fecal excretion of cobalt as well as decreased the levels of cobalt in the liver and spleen (Llobet et al. 1988). These chelators react chemically with cobalt, so they are effective for both stable and radioactive cobalt isotopes. For more complete information on treatment of specific symptoms, refer to Bronstein and Currance (1988) and Stutz and Janusz (1988).

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

No studies were located in humans or animals regarding interfering with the mechanism of action of stable or radioactive cobalt compounds.

3.13 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cobalt.

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

3.13.1 Existing Information on Health Effects of Cobalt

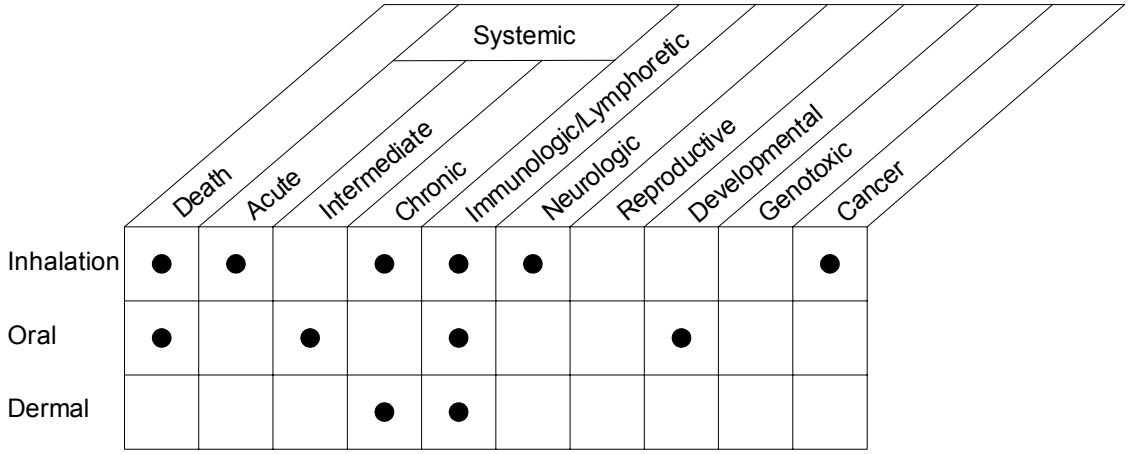
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals are summarized in Figure 3-11 for stable cobalt and in Figure 3-12 for radioactive cobalt. The purpose of these figures is to illustrate the existing information concerning the health effects of cobalt. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figures 3-11 and 3-12 represent studies conducted with all forms of cobalt. The effects of cobalt have been studied in humans following both inhalation and oral exposure. Human dermal studies designed to investigate nondermal systemic effects of cobalt have been reported. Similarly, the effects of cobalt in animals have been studied following inhalation and oral exposure. Few dermal studies are available.

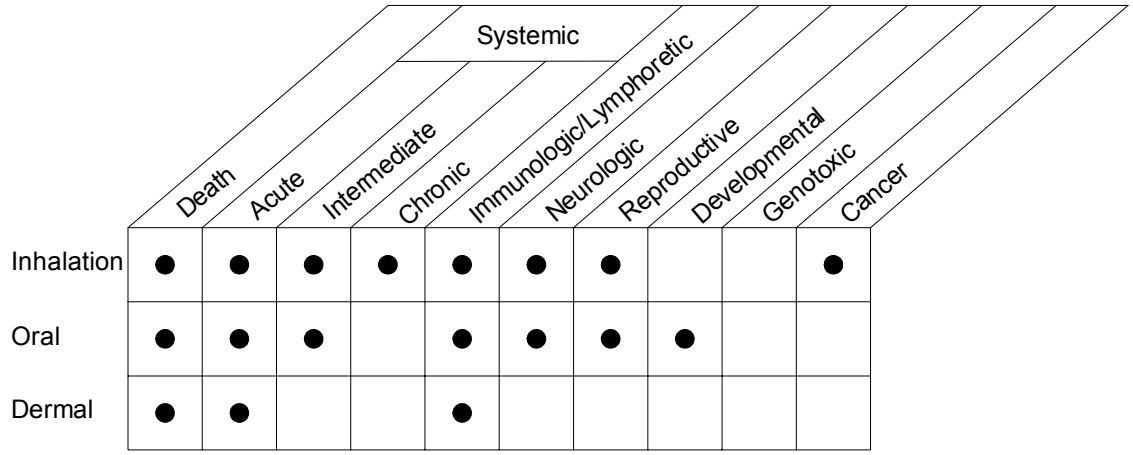
3.13.2 Identification of Data Needs

Stable Cobalt. Effects in humans following acute inhalation, oral, and dermal exposures to cobalt have been reported. In humans, the primary targets following acute exposure to cobalt include the respiratory system following inhalation exposure (Kusaka et al. 1986a), the thymus following oral exposure (Roche and Layrisse 1956), and the immunological system following dermal exposure (Alomar et al. 1985; Fischer and Rystedt 1983; Kanerva et al. 1988). Acute oral studies in animals have also identified the cardiovascular and hematopoietic systems as targets of cobalt toxicity (Domingo and Llobet 1984; Speijers et al. 1982). Although acute exposure levels associated with some of these effects in humans have been reported, the minimal acute exposure levels required to produce these effects are not known because few acute human studies exist. The results of animal studies of the acute toxicity of cobalt have been used to determine dose levels that produce death and respiratory effects following inhalation exposure, death and various systemic effects following oral exposure, and dermal and immunological effects following dermal exposure.

Figure 3-11. Existing Information on Health Effects of Stable Cobalt



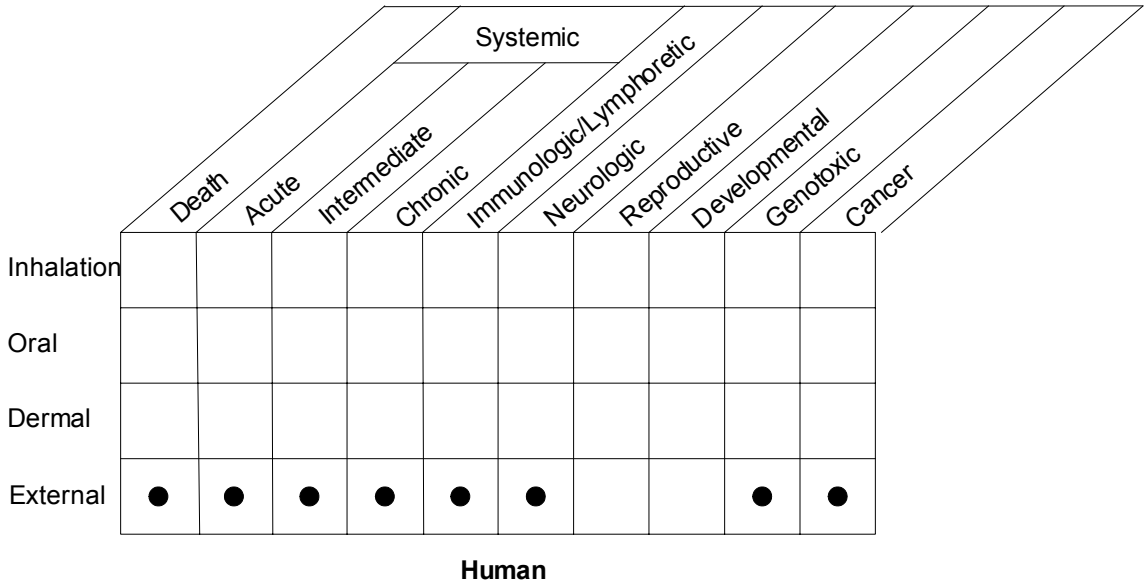
Human



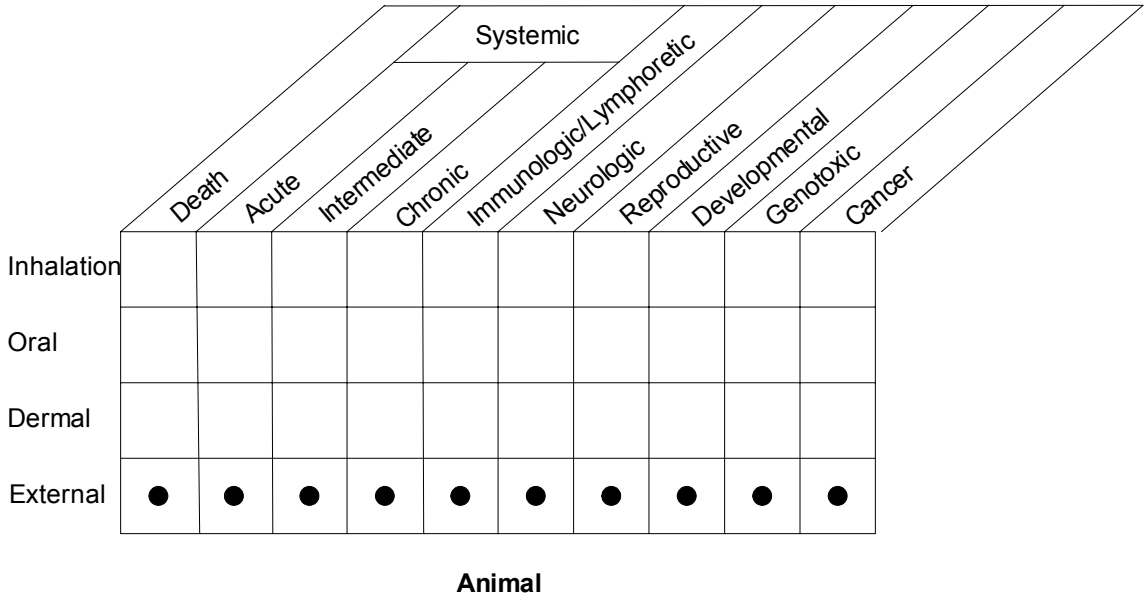
Animal

● Existing Studies

Figure 3-12. Existing Information on Health Effects of Radioactive Cobalt



Human



Animal

● Existing Studies

There were insufficient data for derivation of inhalation or oral acute MRLs because reported effects were severe and occurred at levels above those reported in the few human studies. Animal studies that identify minimally effective inhalation and oral exposure levels for the various cobalt compounds would be useful in estimating acute MRLs for each cobalt compound. Acute dermal studies would enable the determination of hazardous levels for this route of exposure. Because a small portion of the cobalt taken into the body is retained for a relatively long time, studies on the long-term consequences of acute exposure on the heart, respiratory tract, hematological system, and immune response could provide information about the potential for chronic effects of acute exposures in humans. Knowledge about the acute toxicity of cobalt is important because people living near hazardous waste sites might be exposed for brief periods.

Radioactive Cobalt. Data on health effects following acute exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because all cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. A number of health effects have been seen following cases of accidental acute exposure to high levels of external cobalt radiation in humans, including death, gastrointestinal disorders, hematological alterations, and dermal lesions (Klener et al. 1986; Stavem et al. 1985). Acute-exposure animal studies have shown pronounced effects, including death, cardiovascular changes, gastrointestinal effects, kidney effects, and neurobehavioral changes (Brady and Hayton 1977b; Bruner 1977; Cockerham et al. 1986; Darwezah et al. 1988; Down et al. 1986; Gomez-d-Segura et al. 1998; Hanks et al. 1966; King 1988a; Mele et al. 1988; Page et al. 1968; Robbins 1989a, 1989b, 1989c, 1991a). The most pronounced effects in animals following acute exposure to cobalt radiation have been reproductive and developmental effects (see Sections 3.2.4.5 and 3.2.4.6). Agency for Toxic Substances and Disease Registry (1999) has derived an acute MRL for external exposure to ionizing radiation, which is applicable to external exposures to cobalt radiation, so additional data for the derivation of an MRL are not needed.

Intermediate-Duration Exposure.

Stable Cobalt. Information on oral exposure of humans to cobalt, in the form of cobalt chloride added to beer as a foam stabilizer, provides the only human data available for exposure of intermediate duration (Alexander 1969, 1972; Morin et al. 1971). Inhalation and dermal data in humans were not located for this duration of exposure. The cardiac and hematopoietic systems are the primary targets in humans following oral exposure to cobalt. Some exposure levels associated with cardiomyopathy have been

reported following oral exposure, but the minimal exposure level required to produce this effect in humans is not known (Alexander 1969, 1972; Morin et al. 1971). Oral studies in animals reported dose levels associated with death, various systemic and neurological effects, and effects on reproduction and development (Domingo et al. 1984, 1985b; Krasovskii and Fridlyand 1971; Mohiuddin 1970; Mollenhauer et al. 1985; Pedigo et al. 1988). Intermediate-duration inhalation studies in animals reported that the respiratory tract is the target of the toxicity of inhaled cobalt (Bucher et al. 1990; Johansson et al. 1987; Kerfoot 1975; NTP 1991; Palmes et al. 1959). Animal studies were insufficient for derivation of an intermediate-duration MRL for oral exposure, since the reported effects were severe and the effects occurred at levels above those reported in the few human studies. Dermal data in animals were not located. Animal studies that investigate the possible toxic interaction between cobalt and alcohol may be helpful in understanding the role of cobalt in the cardiomyopathy reported in the heavy beer drinkers (Alexander 1969, 1972; Morin et al. 1971). One such study in guinea pigs already exists (Mohiuddin et al. 1970), but this study used a single, high dose of cobalt. Studies using a series of lower doses, both with and without alcohol preexposure, would be helpful in determining the threshold for the cardiac effects. Intermediate-duration dermal studies would enable determination of hazardous levels for this route of exposure. Intermediate-duration toxicity information is important because people living near hazardous waste sites might be exposed for corresponding time periods.

Radioactive Cobalt. Data on health effects following acute exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Substantial human data exist concerning intermediate-duration exposure to external radiation, as radiotherapy treatment regimens fall into this duration category. Animal data from intermediate-duration external exposure also exist, but are less numerous. Additional intermediate-duration studies are not likely to provide substantial additions to our knowledge of radiation-induced toxic effects.

Chronic-Duration Exposure and Cancer.

Stable Cobalt. Chronic inhalation exposure levels in humans associated with respiratory effects have been reported (Gennart and Lauwerys 1990; Nemery et al. 1992; Shirakawa et al. 1988; Sprince et al. 1988). In humans, the respiratory system is the primary target following chronic inhalation exposure. A chronic-duration inhalation MRL was derived from a NOAEL for decreased ventilatory function in exposed workers (Nemery et al. 1992). Wehner et al. (1977) reported no adverse effects in hamsters

exposed chronically to cobalt oxide. NTP (1998; Bucher et al. 1999) exposed rats and mice to cobalt sulfate for 2 years, reporting pronounced effects on the respiratory tract, including hyperplasia, inflammation, fibrosis, and metaplasia; an increased incidence of cancer was also reported. Chronic oral or dermal studies have not been reported in either humans or animals. Animal studies that identify minimally effective chronic oral exposure levels would be useful for estimating a chronic MRL. Chronic dermal studies would enable determination of hazardous levels for this route of exposure. Chronic toxicity information is important because people living near hazardous waste sites might be exposed to cobalt for many years.

Several studies of hard metal exposure in humans have reported increases in lung cancer mortality from occupational inhalation exposure to hard metal (Lasfargues et al. 1994; Moulin et al. 1998; Wild et al. 2000). In humans, cancer has not been reported following exposure to cobalt by the oral or dermal routes. An increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 1.14 mg cobalt/m^3 and in female rats to 0.38 mg cobalt/m^3 as cobalt sulfate, with tumors occurring in both sexes with significantly positive trends (Bucher et al. 1999; NTP 1998). Similarly, mice of both sexes exposed to 1.14 mg cobalt/m^3 showed an increase in alveolar/bronchiolar neoplasms, again with lung tumors occurring with significantly positive trends. Parenteral exposure to cobalt has been found to induce tumors (Gilman 1962; Gilman and Ruckerbauer 1962; Heath 1956, 1969; Heath and Daniel 1962; Shabaan et al. 1977). Further chronic exposure studies by the oral and dermal routes may determine the actual carcinogenic potential of cobalt. Also, studies examining the effect of cobalt speciation (i.e., cobalt metal vs. cobalt sulfate) would add to our understanding of the carcinogenic potential of cobalt.

Radioactive Cobalt. Data on health effects following chronic exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Limited data exist on chronic exposure to cobalt radiation in humans, with genotoxicity, immunologic effects, and cancer being the primary end points examined. Animal data are similarly limited. Additional human or animal data following chronic exposure to external cobalt radiation would be useful in further identifying possible long-term health effects or susceptible populations. Agency for Toxic Substances and Disease Registry (1999) has derived a chronic-duration MRL for external radiation exposure, which is applicable to external exposures to cobalt radiation, so additional data for the derivation of an MRL are not needed.

Genotoxicity.

Stable Cobalt. Gennart et al. (1993) reported an increase in sister-chromatid exchanges in workers exposed to a mixture of cobalt, chromium, nickel, and iron. De Boeck et al. (2000) reported no significant change in the comet assay on lymphocytes from nonsmoking workers who were occupationally exposed to cobalt or hard metal dusts; a positive association was found between hard metal exposure and increased micronucleus formation in smokers only.

Data regarding the mutagenic action of cobalt in bacterial cell lines and mammalian cell lines have been reported in the literature (Hamilton-Koch et al. 1986; Kharab and Singh 1985; Ogawa et al. 1986). *In vivo* mutagenicity studies in animals following inhalation, oral, or dermal exposure to cobalt would be helpful in ascertaining its true mutagenic potential. Further studies examining the differences in genotoxicity between different valence states of cobalt would also be useful.

Radioactive Cobalt. Data on genotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Several studies have demonstrated genotoxic effects in humans exposed to external cobalt radiation (Chang et al.1999c; House et al. 1992; Rauscher and Bauchinger 1983). Numerous data from animal studies exist demonstrating the genotoxic effects of ionizing radiation, including cobalt radiation.

Reproductive Toxicity.

Stable Cobalt. No studies were located regarding the reproductive effects of cobalt in humans following exposure by any route. Inhalation and oral studies in male animals have demonstrated adverse effects on reproductive organs (Anderson et al. 1992, 1993; Bucher et al. 1990; Corrier et al. 1985; Domingo et al. 1985b; Mollenhauer et al. 1985; NTP 1991; Pedigo et al. 1988). One study also reported effects on the estrous cycle in mice following inhalation exposure (Bucher et al. 1990; NTP 1991). Multigenerational studies would be helpful in assessing the significance of these effects on reproductive performance.

Radioactive Cobalt. Data on reproductive effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human data on reproductive effects following external exposure to cobalt radiation are lacking,

but are sufficiently understood for gamma radiation. Available animal studies are limited, but have demonstrated radiation-induced deficits on reproductive ability in both genders (Cunningham and Huckins 1978; Laporte et al. 1985; Searl et al. 1976, 1980). Additional data in humans and animals would be helpful in refining minimal effective doses for radiation effects on reproduction.

Developmental Toxicity.

Stable Cobalt. No developmental effects were observed in the children of 78 women given cobalt chloride orally during pregnancy for treatment of anemia (Holly 1955); however, only a limited examination of offspring was reported, and details of examined end points were not reported. No studies of developmental effects by other routes of exposure in humans were located. Developmental effects in animals following oral exposure during gestation, however, have been observed (Domingo et al. 1985b). Further developmental studies in animals by all relevant routes of exposure (inhalation, oral, dermal) may clarify the potential developmental effects of cobalt in humans.

Radioactive Cobalt. Data on developmental effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. No human studies describing developmental effects of exposure to external cobalt radiation were located. Extensive data from animal studies have shown that even acute exposures to small amounts of cobalt radiation may elicit profound effects on the developing organism (see Section 3.2.4.6). The effects of ionizing radiation on the developing organism are also described in the Agency for Toxic Substances and Disease Registry Toxicological Profile for Ionizing Radiation (1999).

Immunotoxicity.

Stable Cobalt. Humans have been shown to develop sensitivity to cobalt following occupational exposure (Bencko et al. 1983; Shirakawa et al. 1988, 1989). No immunological effects were observed following oral exposure of humans to cobalt. Similar evidence of sensitization has been reported in animals (Lammintausta et al. 1985). Studies examining the mechanism of sensitization might be helpful in fully understanding and treating this effect in humans. A battery of immune function tests would further assess the immunotoxicity of cobalt in humans and animals.

Radioactive Cobalt. Data on immunotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Following external exposure to cobalt radiation, above levels normally encountered except for medical procedures, decreases in white blood cell counts have been seen in both humans and animals. Further studies on the immunotoxic effects of external cobalt radiation would be useful in refining the minimum effective dose.

Neurotoxicity.

Stable Cobalt. No studies were located regarding neurotoxic effects of cobalt in humans following oral or dermal exposure. Two occupational inhalation exposure studies have reported memory deficits, optic atrophy, or nerve deafness in humans exposed to cobalt (Jordan et al. 1990; Meecham and Humphrey 1991). In animals, alterations in several neurologic parameters were found following oral exposure (Bourg et al. 1985; Krasovskii and Fridlyand 1971; Mutafova-Yambolieva et al. 1994; Nation et al. 1983; Singh and Junnarkar 1991; Vassilev et al. 1993; Wellman et al. 1984). Additional studies in animals would assist in determining whether these neurological effects have any relevance to potential effects in humans.

Radioactive Cobalt. Data on neurotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human data following cobalt radiotherapy have demonstrated effects believed to result from neurological damage, but data are limited, doses were extreme, and effects have not been well-characterized. Several animal studies have shown neurobehavioral or neurophysiological changes following exposure to cobalt radiation (Bassant and Court 1978; Maier and Landauer 1989; Mele et al. 1988).

Epidemiological and Human Dosimetry Studies.

Stable Cobalt. Epidemiological studies relating to cobalt exposure are available in the literature. Studies of persons exposed to cobalt occupationally are available (Kusaka et al. 1986a, 1986b; Shirakawa et al. 1988, 1989; Sprince et al. 1988), dietetically (beer drinkers) (Alexander 1969, 1972; Morin et al. 1971), and medically (cobalt given to alleviate anemia) (Davis and Fields 1958; Holly 1955; Taylor et al. 1977).

Further studies assessing the cause/effect relationship between cobalt exposure and human health effects would be helpful in monitoring individuals living near a hazardous waste site to verify that documented exposure levels are not associated with adverse health effects.

Radioactive Cobalt. Epidemiological data on exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human external exposures to cobalt radiation have been documented in the literature. Radiotherapy exposures, though to extremely high radiation doses, are generally well-controlled and documented, whereas environmental and accidental workplace exposures are less frequent and less well-documented.

Biomarkers of Exposure and Effect.

Exposure.

Stable Cobalt. Information is available on the monitoring of cobalt exposure by the quantification of cobalt in urine and blood (Alexandersson 1988; Ichikawa et al. 1985; Scansetti et al. 1985). A portion of inhaled cobalt is rapidly excreted in the feces, and the amount retained in the body tends to be steadily excreted over time. Levels in body fluids, therefore, can be monitored up to several days after exposure. Many different methods for the detection of cobalt in body fluids have been reported (Section 7.1).

Radioactive Cobalt. No information is available regarding biomarkers specific for exposure to cobalt radionuclides by the inhalation, oral, dermal, or external exposure routes. Biomarkers for exposure to ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999). Personal dosimeters (film or luminescent) are an artificial surrogate to measure the amount of exposure to external beta or gamma radiation, though these are not specific for radiation from cobalt radionuclides.

Effect.

Stable Cobalt. Alterations in serum proteins and changes in serum antibodies have been found that are specific for cobalt exposure (Stokinger and Wagner 1958). These changes may be the earliest indication of the effects of cobalt exposure. Further studies may reveal other cobalt-specific biomarkers that, in

combination with these changes, may alert health professionals to cobalt exposure before serious toxicological effects occur.

Radioactive Cobalt. While in many cases radioactive cobalt itself can be measured following exposure, no information is available regarding biomarkers specific for effects of cobalt radionuclides following exposure by the inhalation, oral, dermal, or external exposure routes. Biomarkers for effects of ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999), and include changes in levels of formed elements of the blood as some of the most sensitive indicators. These biomarkers are believed to be suitable for monitoring exposure to cobalt radiation.

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetic data in humans indicate that cobalt is absorbed through the lungs (Foster et al. 1989) and the gastrointestinal tract (Harp and Scoular 1952; Sorbie et al. 1971; Valberg et al. 1969), that cobalt is well distributed in the body with the highest concentration being found in the lungs following inhalation (Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Teraoka 1981), and that some of the inhaled or ingested cobalt is rapidly excreted in the feces, with the amount retained in the body being excreted slowly, primarily in the urine (Foster et al. 1989; Paley et al. 1958; Smith et al. 1972). Pharmacokinetic studies in animals following inhalation and oral exposure have demonstrated similar responses (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Foster et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). Few data exist regarding the pharmacokinetics of cobalt following dermal exposure, though what data are available demonstrate that cobalt can be absorbed in small quantities through human (Scansetti et al. 1994) and animal (Inaba and Suzuki-Yasumoto 1979; Lacy et al. 1996) skin, with greater absorption occurring through damaged than intact skin.

Comparative Toxicokinetics. Several inhalation and oral studies have compared the toxicokinetics of cobalt in several different species of animals, including humans (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Foster et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). No comparative pharmacokinetic studies following dermal exposure were located. These studies would be useful because humans are exposed via the skin in the workplace and may potentially be exposed via this route at waste sites.

Methods for Reducing Toxic Effects.

Stable and Radioactive Cobalt. Chelation therapy is expected to apply equally well to stable and radioactive cobalt isotopes. EDTA or British anti-lewisite (BAL) has been shown to effectively mitigate the toxicity of cobalt in humans (Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988). In animal studies examining the effectiveness of various chelators, n-acetyl cysteine (NAC) was shown to be the most effective (Llobet et al. 1988). It would be useful to determine the effective dose of NAC in humans. Studies examining the effectiveness of other chelating agents may be helpful in determining the most effective chelation therapy for humans.

Children's Susceptibility.

Stable Cobalt. Data comparing the susceptibility of children to cobalt compounds are limited. Animal studies have suggested that absorption following inhalation or oral exposure may be greater in very young animals, resulting in increased systemic dose. Data are not available on the differences between children and adults following dermal exposure. Further studies on the susceptibility of young animals relative to adult animals may be useful in determining whether children are at greater risk from exposure to cobalt in the environment than adults.

Radioactive Cobalt. No data are available on whether children are more susceptible to the effects of radioactive cobalt compounds than adults. Animal studies have shown that exposure *in utero* to even moderate amounts of cobalt radiation can cause dramatic effects in the developing organism. It would be expected that children would be more susceptible to the effects of external cobalt radiation, due to the greater percentage of rapidly-dividing cells during growth.

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

3.13.3 Ongoing Studies

Relevant ongoing studies were not located for cobalt.