2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of cadmium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

The form of cadmium and the route of exposure can greatly affect the absorption and distribution of cadmium to various target sites, and therefore, the concentration at the target site and the severity of the observed effect. The mechanism of action, however, involves the cadmium cation's effect on the target site, and the cation is the same regardless of the anionic species. For inhaled cadmium compounds, the size of the cadmium particle (i.e., fume or aerosol) can also affect the absorption and distribution. The form of cadmium that is of most interest for health effects from inhalation exposure is cadmium oxide because that is the main form of airborne cadmium. For oral exposures, cadmium chloride is most often tested in animal studies because of its high water solubility and the resulting high concentrations of cadmium delivered to target sites. Studies on cadmium bound to metallothionein (MT) are also of interest because CdMT complexes may have different toxic profiles and are found in relatively high levels in organ meats (e.g., liver and kidney). Cadmium oxide and cadmium carbonate, which are relatively insoluble in water (but may dissolve at gastric pH), appear to be similar in absorption and toxicity to soluble cadmium. There are fewer studies available on other forms of cadmium including insoluble forms in water such as cadmium sulfide (a yellow pigment) and cadmium selenium sulfide (a red pigment), and a soluble form, cadmium sulfate, which is less soluble in a closed air system where there is a limited amount of dissolved carbon dioxide. Chapter 3 lists the chemical and physical properties of several cadmium compounds.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure {inhalation,

oral, and dermal); and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects).

These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observedadverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of cadmium are indicated in Tables 2-1 and 2-2, and Figures 2-I and 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-l also shows a range for the upper bound of estimated excess risks, ranging from

a risk of 1 in 10,000 to 1 in 10,000,000 ($l0^{-4}$ to $l0^{-7}$), as developed by EPA. Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for cadmium. 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.

2.2.1 Inhalation Exposure

The information in this section on health effects of inhalation exposure to cadmium in humans is derived from studies of workers exposed to cadmium fume or dusts in industries such as smelting, battery manufacturing, soldering, and pigment production. Adverse effects of human exposure to cadmium were first established among workers in a cadmium battery factory (Friberg 1950). Workers are exposed occupationally to cadmium primarily by inhalation of fumes or dust. Some gastrointestinal tract exposure may also occur when dust is removed from the lungs by mucociliary clearance and subsequently swallowed, or by ingestion of dust on hands, cigarettes, or food (Adamsson et al. 1979). In experiments with animals, some ingestion may also occur from inhalation exposures by mucociliary clearance or from animal grooming. The primary form of cadmium in occupational exposures is cadmium oxide. Experimental studies in laboratory animals have used cadmium oxide, cadmium chloride, and occasionally

other forms of cadmium such as cadmium sulfide and cadmium sulfate. In general, the different forms of cadmium have similar toxicological effects by the inhalation route although quantitative differences may exist from different absorption and distribution characteristics, particularly for the less soluble cadmium pigments such as cadmium sulfide and cadmium selenium sulfide (Buckley and Bassett 1978b; Klimisch 1993; Oldiges and Glaser 1986; Oldiges et al. 1989; Rusch et al. 1986).

Smokers inhale cadmium, but studies of cadmium exposure in the general population are considered in Section 2.2.2 because the primary route of exposure for the general population is through the diet. Also, the many other toxic compounds in cigarette smoke make it difficult at the present time to attribute specific adverse effects of smoking to the inhalation of cadmium.

2.2.1.1 Death

Numerous studies have shown that acute inhalation exposure to cadmium can cause death in humans and animals. In humans, several fatal inhalation exposures have occurred in occupational accidents. During the acute exposure, the general symptoms are relatively mild but, within a few days following exposure, severe pulmonary edema and chemical pneumonitis develop, leading to death due to respiratory failure (Beton et al. 1966; Lucas et al. 1980; Patwardhan and Finckh 1976; Seidal et al. 1993). The cadmium concentration in air was not measured in these cases of accidental death in humans. However, the lung concentrations of cadmium in the men who died from these accidental acute exposures were measured. I n micrograms of cadmium per gram wet weight (w/w) of lung tissue μg/g) Patwardhan and Finckh (1976) reported 1.5 μg/g, Beton et al. (1966) reported 2.5 μg/g, Barrett et al. (1947) reported 3.5 μg/g, and Lucas et al. (1980) reported 4.7 μg/g. Based upon estimates of the percentage of inhaled cadmium fume that would be retained in the lungs, Barrett et al. (1947) calculated an exposure of 2,500 min x mg/m^3 in air would be fatal to humans. Beton et al. (1966) used a similar technique to estimate that an exposure to CdO in air of 8.63 mg/m^3 for 5 hours led to the fatal deaths of the 5 workers with cadmium lung burdens of 2.5 μg/g. The lower lung concentrations reported by Patwardhan and Fin&h (1976) prompted Elinder (1986b) to estimate that an exposure of l-5 mg/m^3 for 8 hours could be immediately dangerous. These estimates of air concentrations, however, are based on a number of uncertain assumptions concerning the duration of exposure and the retention of cadmium in the human lung being similar to that found in animal studies (Barrett et al. 1947; Elinder 1986b). No studies on deaths in humans from intermediate inhalation exposures were found. In a study on chronic exposures, Friberg (1950) attributes the deaths of 2 workers to exposure to cadmium dust in the air averaging 6.8 mg Cd/m^3 (range 3-15 mg/m^3). One worker was

57 years old at death (after 14 years of exposure to the dust) and the other was 60 years old at death (after 25 years of exposure to the dust). A detailed post-mortem evaluation for the 60-year-old worker showed the presence of emphysema and the occurrence of hyaline casts in renal tubules, as well as slight nephrotic changes. Pneumonia was the direct cause of death as an acute complication of chronic bronchitis and pulmonary emphysema. The exposure estimate of 6.8 mg Cd/m^3 is from only 6 samples taken in 1946. The conditions in earlier years were thought to be similar, but this exposure value is, at best, a very rough approximation of the actual exposures spanning 34 years.

Acute inhalation of cadmium oxide fumes has also led to death in rats, mice, rabbits, guinea pigs, dogs, and monkeys, with the mortality rate apparently being directly proportional to the product of the duration of exposure and the concentration of inhaled cadmium (Barrett et al. 1947). The most reliable LC_{50} (lethal concentration, 50% kill) (at 7 days) established by this study was 500 min-mg CdO/m^3 for rats, equivalent to a 15minute exposure to 30 mg Cd/m^3 (Barrett et al. 1947). Rusch et al. (1986) demonstrated high mortality rates in the Sprague-Dawley rat from a 2-hour exposure to cadmium fumes at 112 mg Cd/m^3 (25 of 32 died within one week). A 2-hour exposure to a different form of cadmium, cadmium carbonate, at 132 mg Cd/m^3 resulted in considerably lower mortality (3 of 22 died by day 30). No deaths resulted from a 2-hour exposure to cadmium sulfide at 99 mg Cd/m^3 or cadmium selenium sulfide (cadmium red pigment) at 97 mg Cd/m^3. Grose et al. (1987) reported 2 out of 36 rats died from a 2-hour, nose-only inhalation exposure to only 0.45 mg Cd/m^3 of cadmium oxide dusts, but the statistical significance of this low rate of mortality was not reported. A 3-day, l-hour per day exposure to cadmium chloride aerosol at 61 mg Cd/m^3 resulted in the death of 17 of 18 rats exposed (Snider et al. 1973). In another study, no deaths were observed in rats from a cadmium yellow (CdS) pigment exposure for 10 days, 6 hours a day at 6.29 mg Cd/m^3 (Klimisch 1993). Thus, it appears that in acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium carbonate compounds are more toxic than the relatively less soluble cadmium sulfide compounds (Klimisch 1993; Rusch et al. 1986). Rusch et al. (1986) attribute this difference to higher lung absorption and retention times for the more soluble compounds, and greater mucociliary clearance for the less soluble pigments. Glaser et al. (1986), however, demonstrated that toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide in biological fluids may be greater than its solubility in water. In hamsters, Henderson et al. (1979) reported that a 30minute exposure to 10.1 mg Cd/m^3 from $CdCl_2$ resulted in the death of 3 of 30 animals by day 6 postexposure. In rabbits, Friberg (1950) reported an LC_{50} (by day 14) from a 4-hour exposure to cadmium metal dusts at 28.4 mg Cd/m^3. Barrett et al. (1947) also reported LC_{50} values for cadmium oxide fume of 940 mg Cd/m^3 for a 14minute exposure in the monkey, 46.7 mg/m^3 for a 15-minute exposure in the mouse, 204 mg

Cd/m^3 for a 15minute exposure in the guinea pig, and 230 mg Cd/m^3 for a 15-minute exposure in the dog. However, the authors report that these LC_{50} values are only approximations because of insufficiencies in the data or the small numbers of animals used.

At longer durations of exposure, lower concentrationscause lethality in rats. Cadmium oxide dust resulted in the deaths of 100% of the females at 1 mg Cd/m^3 for 20 weeks, 5 days a week for 5 hours a day (Baranski and Sitarek 1987), and of 5 of 12 female rats at only 0.105 mg Cd/m^3 for 63 days, 7 days a week for 22 hours a day (Oldiges and Glaser 1986). Continuous inhalation exposure to cadmium oxide dust at 0.105 mg Cd/m^3 (i.e., 24 hours a day) for 63 days resulted in 5 of 12 deaths in female rats (Prigge 1978a). Five of 54 males died from a cadmium chloride exposure to 1.06 mg Cd/m^3 for 62 days, 5 days a week, 6 hours a day (Kutzman et al. 1986). Kutzman et al. (1986) determined that the concentration times hours of exposure to produce 50% mortality in rats was 390 mg-hr/m^3 (males) and 489 mg-hr/m^3 (females). Takenaka et al. (1983) reported that cadmium chloride at 0.0508 mg Cd/m^3 for 18 months, 7 days a week, 23 hours a day resulted in the death of 5 of 40 male rats.

Oldiges et al. (1989) evaluated the long-term effects in rats of inhaling cadmium as either $CdCl_2$, CdS04, CdS, or CdO. Rats were exposed to aerosols in nearly continuous exposures of 22 hours a day, 7 days a week, for 18 months. An observation period of 12 months followed the exposure period. Oldiges et al. (1989) recorded mortality as exceeding 25% of the test animals during the exposure period or 75% of the test animals during the observation period. If either 25 or 75% mortality occurred, the exposure period or the observation period, respectively, was terminated. The results showed that cadmium chloride at 0.030 mg Cd/m^3 was lethal to over 75% of the male and female rats by 12 months of exposure; cadmium oxide dusts at 0.090 mg Cd/m^3 were lethal for more than 25% of the males by 7 months and 25% of the females by 11 months of exposure; cadmium oxide fume at the highest dose of 0.03 mg Cd/m^3 did not result in >25% mortality during exposure or 75% during the postexposure period; cadmium sulfate at 0.090 mg Cd/m^3 was lethal for more than 25% of the males during the exposure and for more than 75% of the females by 14 months of following exposure; and cadmium sulfide at 0.090 mg Cd/m^3 was not lethal during the exposure period but was lethal to more than 75% of the males and females by 12 months postexposure. In these chronic studies, cadmium's lethal effects differed among the chemical forms in the following order from most to least toxic: $CdCl_2 > CdSO_4 \approx$ CdO dust>CdS, but lethality still occurred from all forms of cadmium. Oldiges and Glaser (1986) report that in their chronic studies and at the doses tested, cadmium toxicity appeared to be more related to the long-term lung retention of the bioavailable amounts of cadmium than to a simple function of solubility in water. Representative LOAEL and LC_{50}

values for lethality in each species and duration category are recorded in Table 2-1 and are plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Representative NOAEL and LOAEL values for systemic effects following inhalation exposure to cadmium in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. In humans, inhalation exposure to high levels of cadmium oxide fumes or dust is intensely irritating to respiratory tissue, but symptoms can be delayed. During and immediately after (up to 2 hours) an acute exposure for 5 hours of 8.63 mg/m^3, Beton et al. (1966) reported there were few symptoms of toxicity limited to coughing and slight irritation of the throat and mucosa. From 4 to 10 hours postexposure, influenza-like symptoms began to appear, including cough, tight chest, pain in chest on coughing, dyspnea, malaise, ache, chilling, sweating, shivering, and aching pain in back and limbs. From 8 hours to 7 days postexposure, more advanced stages of pulmonary response included severe dyspnea and wheezing, chest pain and precordial constriction, persistent cough, weakness and malaise, anorexia, nausea, diarrhea, nocturia, abdominal pain, hemoptysis, and prostration. Acute, high-level exposures can be fatal (see Section 2.2.1. I), and those who survive may have impaired lung function for years after a single acute exposure. A 34-year-old worker exposed to cadmium fume from soldering for 1 hour (dose not determined) had persistent impaired lung function when examined 4 years following the exposure (Barnhart and Rosenstock 1984). Initial symptoms were dyspnea, cough, myalgia, and fever. An initial chest X-ray revealed infiltrates. Townshend (1982) reports the case of a male welder who developed acute cadmium pneumonitis from a single exposure (dose not determined). Nine years after the exposure, this worker continued to show signs of progressive pulmonary fibrosis and had no improvement in respiratory function. Precise estimates of cadmium concentrations leading to acute respiratory effects in humans are not currently available.

The initial symptoms of respiratory distress observed in the higher acute exposures do not occur following lower-level, longer-term inhalation exposures (Friberg 1950). Longer-term occupational exposure to levels of cadmium below those causing lung inflammation, however, have been reported to cause emphysema and dyspnea in humans (Bonnell 1955; Friberg 1950; Lane and Campbell 1954; Smith et al. 1960). Kjellstrom

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Human	5 hr				8.63 M (5 male workers died after a 5 hour exposure)	Beton et al. 1966 CdO fume
2	Rat (NS)	10-15 min				30 (LC_{50} at 7 days)	Barrett et al. 1947 CdO fume
3	Rat (Sprague-Dawley)	2 hr				132 (3/22 died by day 30)	Rusch et al. 1986 CdCO3
4	Rat (Sprague-Dawley)	2 hr				112 (25/32 died within 1 week)	Rusch et al. 1986 CdO fume
5	Rat (Sprague-Dawley)	3 d 1 hr/d				61.0 M (17/18 died within 3 days)	Snider et al. 1973 $CdCl_2$
6	Hamster (Golden Syrian)	30 min				10.1 (3/30 died by day 6 postexposure)	Henderson et al. 1979 $CdCl_2$
7	Rabbit (NS)	4 hr				28.4 (LC_{50} at 14 days)	Friberg 1950 Cd metal dust
Systemic							
8	Human	5 hr	Resp			8.63 M (pulmonary edema and alveolar squamous cell metaplasia)	Beton et al. 1966 CdO fume
			Renal			8.63 M (bilateral cortical necrosis of kidneys)	

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
9	Rat (Long- Evans)	1 hr	Resp			5 M (pulmonary edema, enzyme changes associated with type 2 cell hyperplasia)	Boudreau et al. 1989 $CdCl_2$
10	Rat (Wistar)	3 hr	Resp		0.4 M (mild hypercellularity at the bronchoalveolar junction and in adjacent alveoli)	4.6 M (persistent focal interstitial thickening, increased collagen, general hypercellularity)	Buckley and Bassett 1987b CdO dust
			Bd Wt	0.4 M	4.6 M (15% decreased body weight)		
11	Rat (Sprague-Dawley)	1 hr	Resp			6.5 M (severe pneumonitis)	Bus et al. 1978 $CdCl_2$
			Bd Wt		6.5 M (10.8% decreased body weight)		
12	Rat (Sprague-Dawley)	2 hr	Resp	0.45 M		4.5 M (moderate to severe pneumonitis, hemorrhage, edema)	Grose et al. 1987 $CdCl_2$
			Bd Wt			4.5 M (20% decreased body weight)	
13	Rat (Sprague-Dawley)	2 hr	Resp		0.45 M (significant increased absolute and relative lung weight)	4.5 M (severe pneumonitis, hyperplasia of type 2 cells and fibroblasts)	Grose et al. 1987 CdO dust
			Bd Wt	0.45 M			
14	Rat (Lewis)	1-6 wk 5 d/wk 3 hr/d	Resp			1.6 M (interstitial pneumonitis)	Hart 1986 CdO dust
15	Rat (Lewis)	3 hr	Resp			8.4 M (diffuse alveolitis, with hemorrhage, edema, and sheets of mononuclear cells)	Hart et al. 1989a CdO dust

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg/m3	LOAEL Less serious mg/m3	LOAEL Serious mg/m3	Reference Chemical Form
16	Rat (Wistar)	10 d 6 hr/d	Resp		0.17 M (16% increased absolute lung weights)		Klimisch 1993 $CdCl_2$
			Renal	0.17 M			
			Bd Wt	0.17 M			
17	Rat (Wistar)	10 d 6 hr/d	Resp	0.72 M	6.29 M (8% increased absolute lung weight)		Klimisch 1993 CdS
			Renal	6.29 M			
			Bd Wt	6.29 M			
18	Rat (Sprague-Dawley)	2 hr	Resp			6.0 M (alveolar type 1 cell damage and necrosis)	Palmer et al. 1986 $CdCl_2$
			Endocr	6.0 M			
			Bd Wt	6.0 M			
19	Rat (Sprague-Dawley)	2 hr	Resp			132 (rales, rapid breathing, 2-3 fold increased lung weight)	Rusch et al. 1986 *CdCO3*
			Gastro		132 (erosions of the stomach)		
			Hepatic		132 (liver discoloration)		
			Bd Wt		132 (slower rate of weight gain)		
20	Rat (Sprague-Dawley)	2 hr	Resp			112 (labored breathing, rales, discoloration of lungs)	Rusch et al. 1986 CdO fume
			Hepatic		112 (liver discoloration and congestion)		
			Bd Wt		112 (excessive weight loss, percent not reported)		
21	Rat (Sprague-Dawley)	2 hr	Resp	99			Rusch et al. 1986 CdS
			Bd Wt	99			

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
22	Rat (Sprague-Dawley)	2 hr	Resp	97			Rusch et al. 1986 CdSeS
			Renal		97 (kidney discoloration)		
			Bd Wt	97			
23	Rat (Sprague-Dawley)	5, 10, or 15 d 1 hr/d	Resp			6.1 M (emphysema)	Snider et al. 1973 $CdCl_2$
24	Rat (Sprague-Dawley)	3 d 1 hr/d	Resp			61 M (pulmonary hemorrhage)	Snider et al. 1973 $CdCl_2$
25	Hamster (Golden Syrian)	30 min	Resp		1.1 (moderate increase in PMN, 2-fold increase in acid phosphatase)	10.1 (severe pneumonitis)	Henderson et al. 1979 $CdCl_2$
26	Rabbit (New Zealand)	2 hr	Resp		4.5 M (mild, multifocal interstitial pneumonitis)		Grose et al. 1987 $CdCl_2$
27	Rabbit (New Zealand)	2 hr	Resp		0.45 M (increase in alveolar macrophages)	4.5 M (multifocal interstitial pneumonitis)	Grose et al. 1987 CdO dust
			Bd Wt		0.45 M (unspecified decrease in body weight)		
Immunological/Lymphoreticular							
28	Mouse (Swiss)	2 hr		0.110 F	0.190 F (decreased humoral immune response)		Graham et al. 1978 $CdCl_2$
29	Mouse (C57Bl/6)	60 min			0.88 F (reduction in spleen lymphocyte viability [35%], numbers, and humoral response (75%)]		Krzystyniak et al. 1987 $CdCl_2$

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	Neurological						
30	Rat (Sprague-Dawley)	2 hr				132 (tremors)	Rusch et al. 1986 CdCO3
31	Rat (Sprague-Dawley)	2 hr			112 (reduced activity)		Rusch et al. 1986 CdO fume
	INTERMEDIATE EXPOSURE						
	Death						
32	Rat (Wistar)	20 wk 5 d/wk 5 hr/d				1.0 F (13/13 died by week 20)	Baranski and Sitarek 1987 CdO dusts
33	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d				1.06 M (5/54 males died)	*Kutzman et al.* 1986 $CdCl_2$
34	Rat (Wistar)	218-343 d 7 d/wk 22 hr/d				0.090 M (6/20 males died [CdO dust])	Oldiges and Glaser 1986 CdO dust CdO
						0.081 F (6/20 females died [CdO dust])	
35	Rat (Wistar)	6 mo 40 hr/wk				0.090 (> 75% mortality by 11-12 months postexposure)	Oldiges et al. 1989 $CdCl_2$
36	Rat (Wistar)	6 mo 40 hr/wk				0.270 (> 75% mortality by 21-23 months postexposure)	*Oldiges et al. 1989* CdS
37	Rat (Wistar)	63d 24 hr/d				0.105 F (5/12 died)	Prigge 1978a CdO dust

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Systemic							
38	Rat (Wistar)	20 wk 5 d/wk 5 hr/d	Bd Wt	0.16 F		1.0 F (30-50% decreased body weight gain)	Baranski and Sitarek 1987 CdO dusts
39	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		0.105 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 $CdCl_2$
			Hemato		0.105 M (45% increase in WBC)		
			Hepatic	105 M			
			Renal	105 M			
40	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		0.098 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdO dust
			Hemato		0.098 M (45% increase in WBC)		
			Hepatic		0.098 M (increased ALT activity)		
			Renal		0.098 M (increased urinary creatinine)		
41	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		1.034 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdS
			Hemato	1.034 M			
			Hepatic	1.034 M			
			Renal	1.034 M			
			Bd Wt	1.034 M			

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
42	Rat (Lewis)	5-6 wk 5 d/wk 3 hr/d	Resp			1.6 M (41% increased lung dry weight, type 2 cell hyperplasia)	Hart et al. 1989a CdO dust
43	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d	Resp		0.33 M (bronchiolar hyperplasia, increase in fibroblasts and some collagen deposition)	1.06 M (fibrosis with significant increase in collagen)	Kutzman et al. 1986 $CdCl_2$
			Cardio	0.33 M	1.06 M (26% increased relative heart weight)		
			Hepatic	0.33 M	1.06 M (8% increased relative liver weight)		
			Renal	0.33 M	1.06 M (22% increased relative kidney weight)		
			Bd Wt	0.33	1.06 (14% decreased body weight)	2.13 (42% (female) to 51% (male) decreased body weight)	
44	Rat (Fischer 344)	4 wks 5 d/wk 6 hr/d	Resp	0.100 M			Oberdorster et al. 1994 $CdCl_2$
45	Rat (Wistar)	63 or 90 d 24 hr/d	Resp		0.025 F (hypercellularity in the bronchoalveolar region, increased lung relative weight)	0.105 (emphysema, histiocytic cell granulomas)	Prigge 1978a CdO dust
			Hemato		0.052 F (increased hemoglobin and hematocrit)		
			Hepatic	0.105 F			
			Renal	0.105 F			
			Bd Wt		0.105 F (11% decrease in body weight)		
			Metab		0.105 F (decreased blood pH and pO2, increased pCO2)		

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
46	Rat (Wistar)	21 d Gd 1-21 24 hr/d	Resp		0.204 F (77% increased lung relative weight)	0.581 F (for nonpregnant females: emphysematous areas, 2-fold increased wet lung relative weight, mild bronchiolitis)	Prigge 1978b $CdCl_2$
			Hemato		0.204 F (8% increased hemoglobin, 5% increased hematocrit)		
			Hepatic	0.581 F			
			Renal	0.581 F			
			Bd Wt	0.394 F			
47	Rat (Wistar)	21 d Gd 1-21 24 hr/d	Resp		0.204 F (70% increased lung relative weight)	NS F (for pregnant females: emphysematous areas, 2-fold increased lung relative weight, mild bronchiolitis)	Prigge 1978b $CdCl_2$
			Hemato		0.581 F (increased hemoglobin [12%], hematocrit [12%], total biliurin [2-fold])		
			Hepatic	0.581 F			
			Renal	0.581 F			
			Bd Wt		0.394 F (12% decreased maternal weight gain)		
48	Mouse (BALB/c)	4 wks 5 d/wk 6 hr/d	Resp		0.100 M (increased neutrophils, LDH and beta-glucuronidase; pulmonary inflammation)		Oberdorster et al. 1994 $CdCl_2$
49	Rabbit (NS)	9 mo 21 d/mo 3 hr/d	Resp			4.0 (chronic pneumonia, emphysema)	Friberg 1950 Cd metal dust
			Hemato		4.0 (eosinophilia, lower hemoglobin)		
			Renal			4.0 (proteinuria)	

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
50	Rabbit (NS)	7 mo 23 d/mo 3 hr/d	Resp			5.6 (emphysema)	Friberg 1950 *Cd metal dust*
			Renal			5.6 (proteinuria in 6/10 surviving to the end of exposure)	
51	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp			0.4 M (lung interstitial inflammation, type 2 cell hyperplasia)	Johansson et al. 1984 $CdCl_2$
	Immunological/Lymphoreticular						
52	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d				1.06 M (26% increased in spleen relative organ weight, lymphoid hyperplasia, microgranulomas)	Kutzman et al. 1986 $CdCl_2$
53	Rat (Wistar)	21 d Gd 1-21 24 hr/d			0.394 F (14% increased spleen relative weight)		Prigge 1978b $CdCl_2$
	Neurological						
54	Rat (Wistar)	30 d 7 d/wk 22 hr/d		0.105 M			Glaser et al. 1986 $CdCl_2$
55	Rat (Wistar)	30 d 7 d/wk 22 hr/d		0.098 M			Glaser et al. 1986 *CdO dust*
56	Rat (Wistar)	30 d 7 d/wk 22 hr/d		1.034 M			Glaser et al. 1986 CdS
57	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d		0.33 M	1.06 M (18% increased brain relative weight)		Kutzman et al. 1986 $CdCl_2$

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Reproductive							
58	Rat (Wistar)	20 wk 5 d/wk 5 hr/d				1.0 F (increased duration of estrous cycle)	Baranski and Sitarek 1987 CdO dusts
59	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d			1.06 M (24% increased relative testes weight)		Kutzman et al. 1986 $CdCl_2$
Developmental							
60	Rat (Wistar)	4-5 mo 5 d/wk 5 hr/d			0.02 (delayed ossification; behavioral alterations)	0.16 (decreased pup viability)	Baranski 1985 CdO dusts
61	Rat (Wistar)	21 d Gd 1-21 24 hr/d			0.581 (9% decreased fetal body weight, 12% increase in fetal alkaline phosphatase)		Prigge 1978b $CdCl_2$
Cancer							
62	Rat (Wistar)	6 mo 40 hr/wk				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 $CdCl_2$
63	Rat (Wistar)	6 mo 40 hr/wk				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdO dust
64	Rat (Wistar)	6 mo 40 hr/wk				0.270 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, squamous cell carcinomas)	Oldiges et al. 1989 CdS

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
CHRONIC EXPOSURE							
Death							
65	Human	1-34 yr 5 d/wk 8 hr/d				6.8 M (2 fatalities from 14 years or 25 years of exposure to Cd dust)	Friberg 1950 Cd dust
66	Rat (Wistar)	105-409 d 7 d/wk 22 hr/d				0.254 M (3/20 died) 0.263 F (2/20 died)	Oldiges and Glaser 1986 CdS
67	Rat (Wistar)	413-455 d 7 d/wk 22 hr/d				0.095 M (6/20 died) 0.092 F (1/20 died)	Oldiges and Glaser 1986 *CdSO4*
68	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 M (> 75% mortality by 12 *months postexposure*)	Oldiges et al. 1989 $CdCl_2$
69	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (more than 25% died after 7 months [M] and 11 months [F] of exposure)	Oldiges et al. 1989 CdO dust
70	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0. 09 (>75% mortality after 12 months postexposure)	Oldiges et al. 1989 CdS
71	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 M (>25% mortality by 14 months of exposure) 0.09 F (>75% by 11 *months* postexposure)	Oldiges et al. 1989 CdSO4
72	Rat (Wistar)	18 mo 7 d/wk 23 hr/d				0.0508 M (5/40 died)	Takenaka et al. 1983 $CdCl_2$

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Systemic							
73	Human	4-24 yr 5 d/wk 8 hr/d	Resp	0.025			Edling et al. 1986 CdO fume
74	Human	30 yr 5 d/wk 8 hr/d	Renal	0.033		0.067 (pronounced proteinuria)	Elinder et al. 1985b CdO fume
75	Human	30 yr 5 d/wk 8 hr/d	Renal	0.0153 M		0.0379 M (100% incidence of proteinuria in the cohort exposed to this level for 21 years)	Falck 1983 CdO fume
76	Human	30 yr 5d/wk 8hr/d	Renal	0.017		0.023 (9.2% incidence of proteinuria)	Jarup et al. 1988 CdO dust
77	Human	30 yr 5 d/wk 8 hr/d	Renal	0.0367 M			Mason et al. 1988 form not specified
78	Human	30 yr 5 d/wk 8 hr/d	Renal	0.027			Thun et al. 1989 CdO dust or fume
79	Rat (Wistar)	413-455 d 7 d/wk 22 hr/d	Resp		0.092 (unspecified increased lung weight)		Oldiges and Glaser 1986 CdSO4
			Hepatic	0.095			
			Bd Wt	0.095			
80	Rat (Wistar)	18 mo 7 d/wk 23 hr/d	Resp			0.0134 M (adenomatous hyperplasia in the bronchoalveolar area)	Takenaka et al. 1983 $CdCl_2$
			Bd Wt	0.0508 M			

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Immunological/Lymphoreticular							
81	Rat (Wistar)	413-455 d 7 d/wk 22 hr/d			0.092 (enlarged thoracic lymph nodes)		Oldiges and Glaser 1986 CdSO4
Cancer							
82	Human	6 mo-43 yr 7d/wk 8hr/d				0.100 M (CEL: 50-111 lung cancer deaths per 1000 workers; 45 year exposure)	Stayner et al. 1992 CdO dust or
83	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 $CdCl_2$
84	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdO dust
85	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas)	Oldiges et al. 1989 CdO fume
86	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdS
87	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (CEL: lung bronchio-alveolar adenomas, adenocarcinomas, squamous cell carcinomas)	Oldiges et al. 1989 CdSO4

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
88	Rat (Wistar)	18 mo 7 d/wk 23 hr/d				0.0134 M (CEL: lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas)	Takenaka et al. 1983 $CdCl_2$

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

ALT = alanine amino transferase; AST = aspartate aminotransferase; Bd Wt = body weight; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; PMN = polymorphonuclear leukocytes; Resp = respiratory; WBC = white blood cells; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation

Acute (≤14 days)

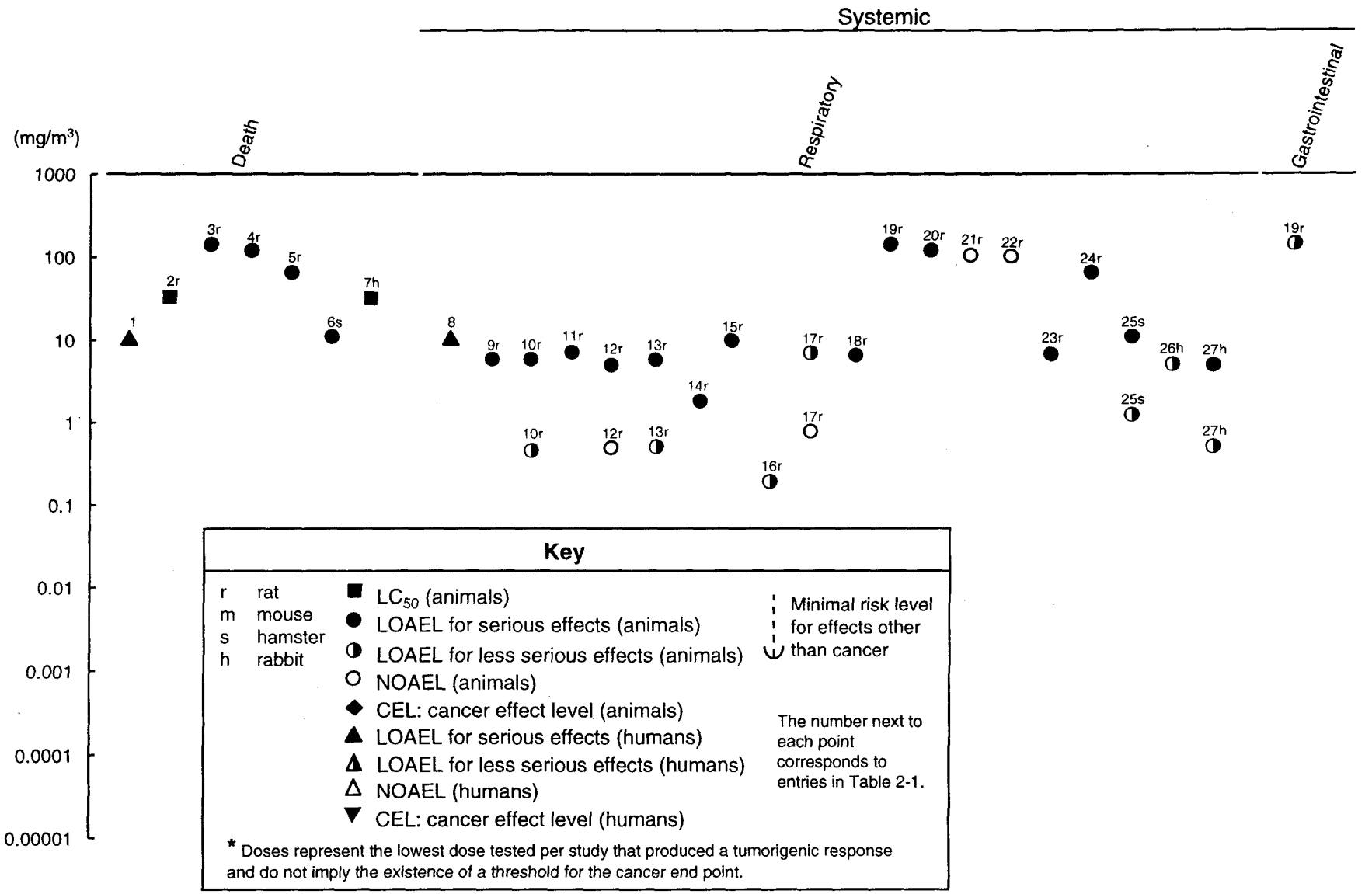


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Acute (≤14 days)

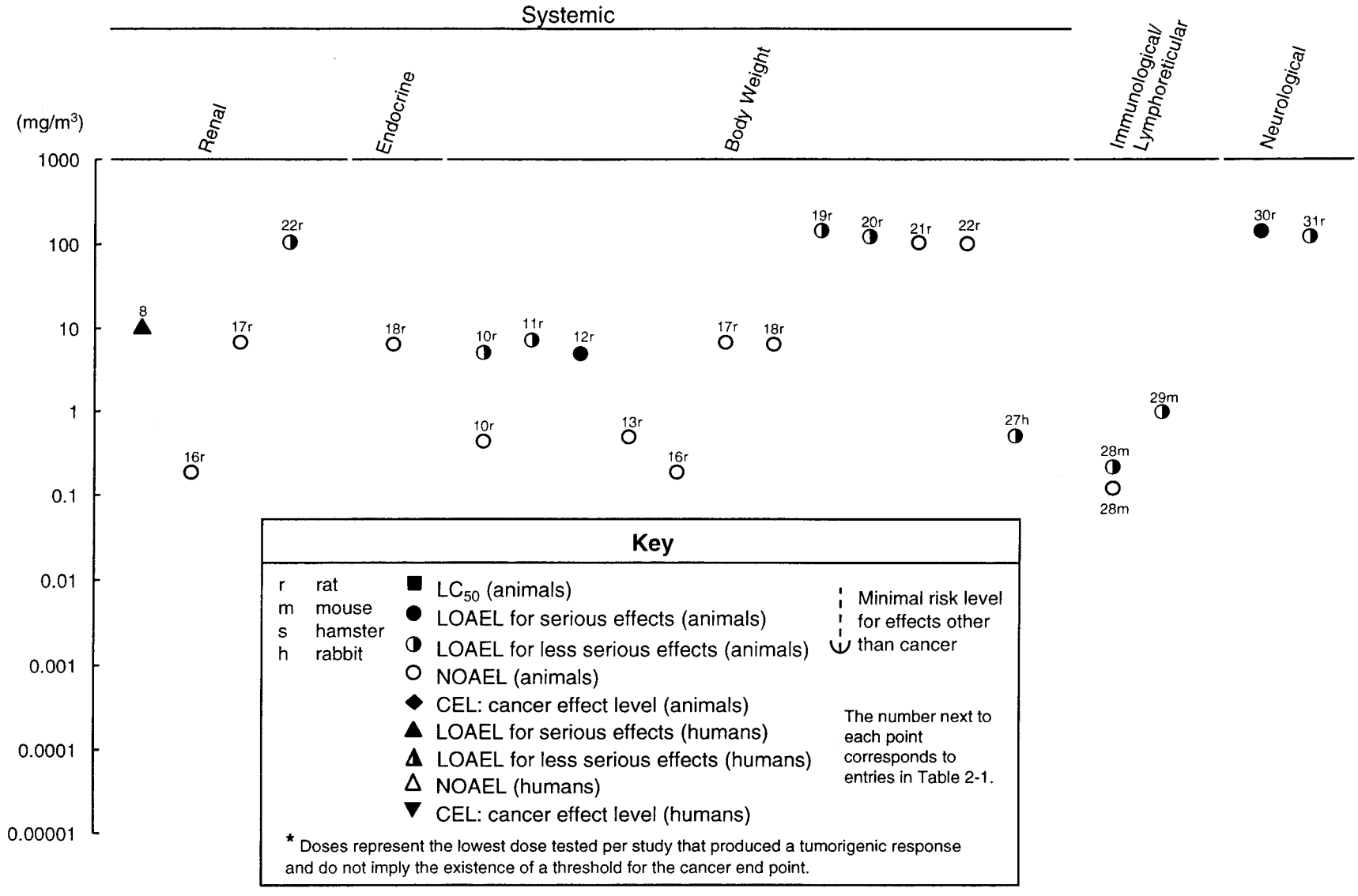


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Intermediate (15-364 days)

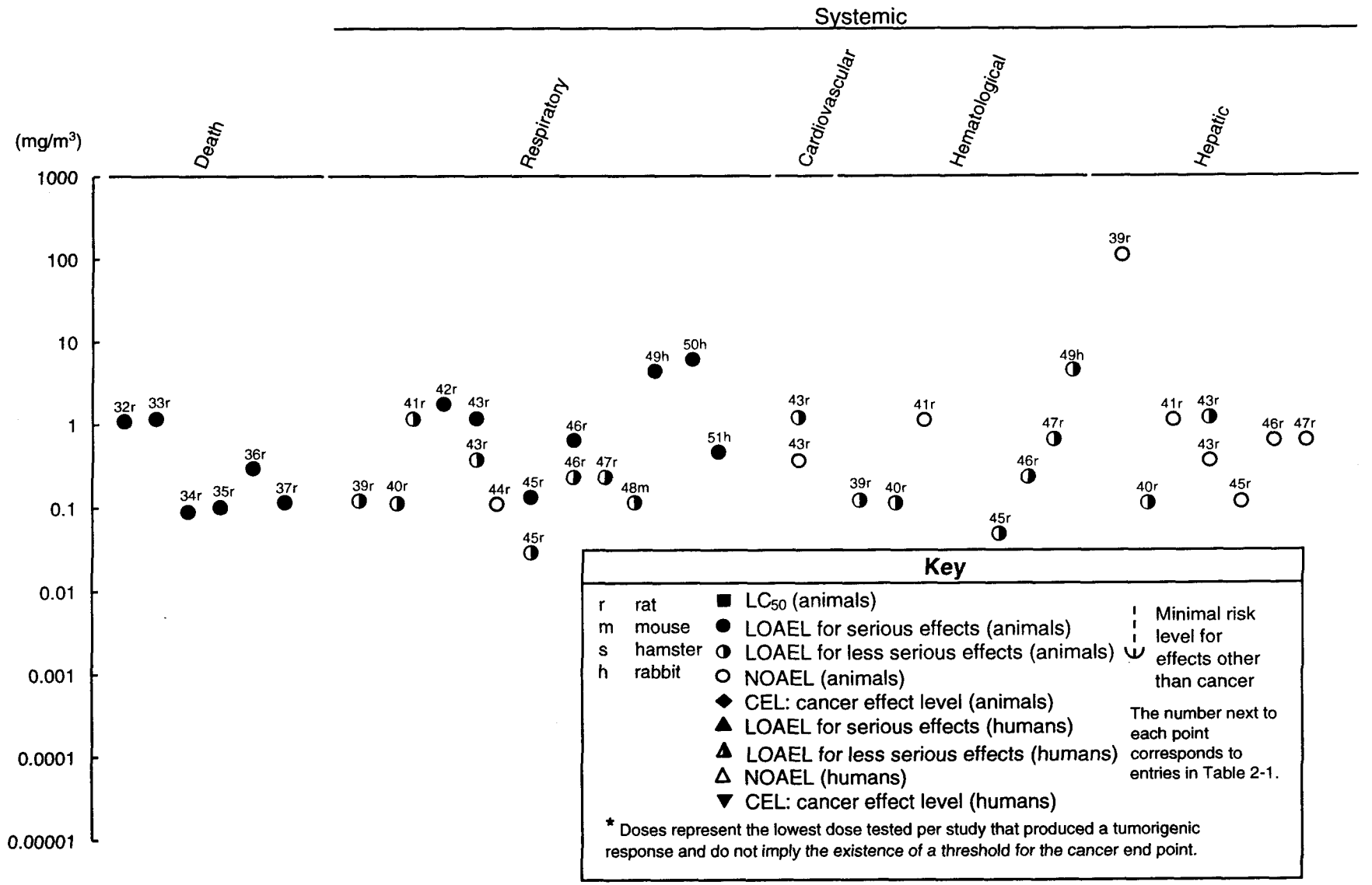


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Intermediate (15-364 days)

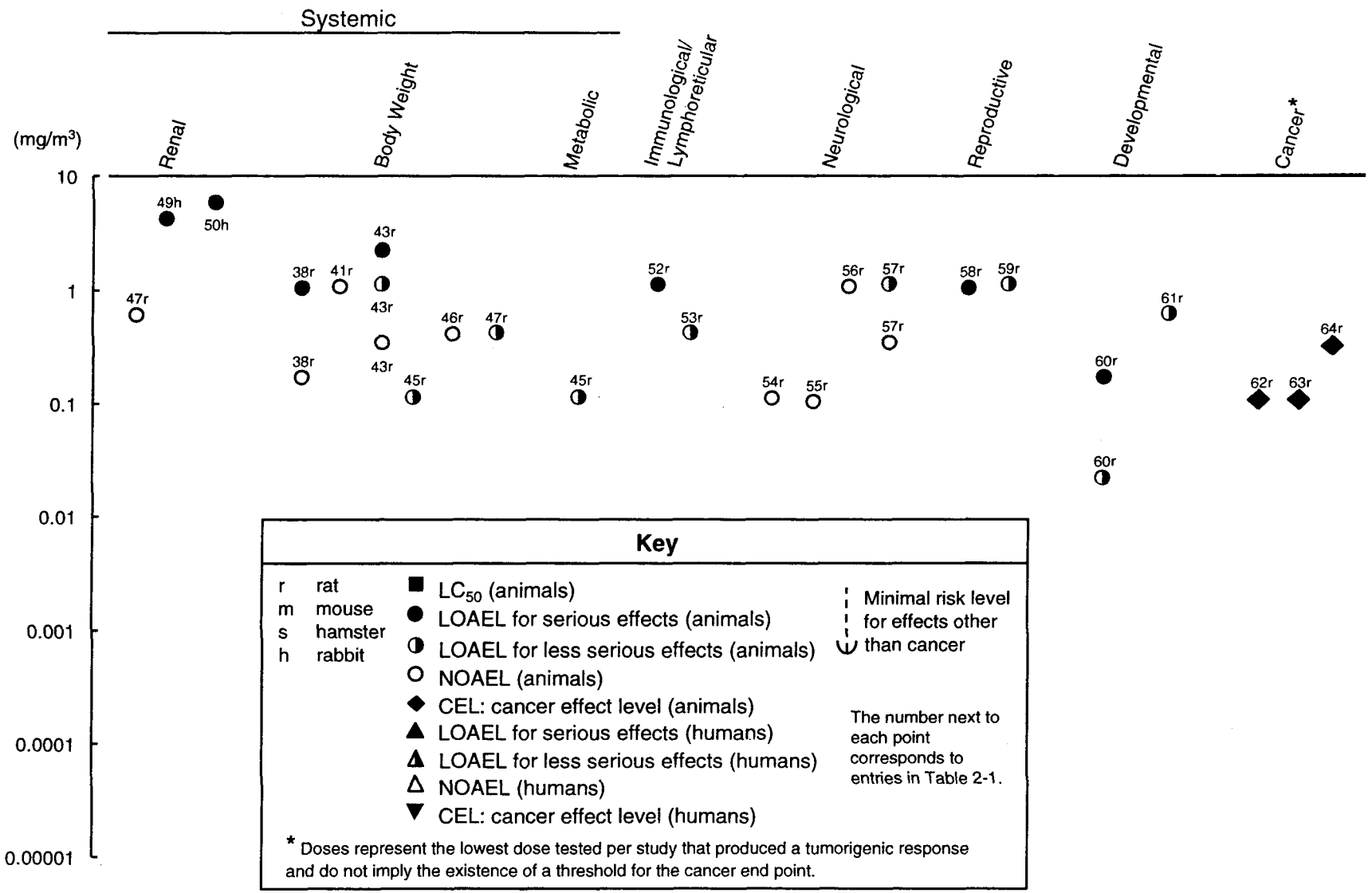
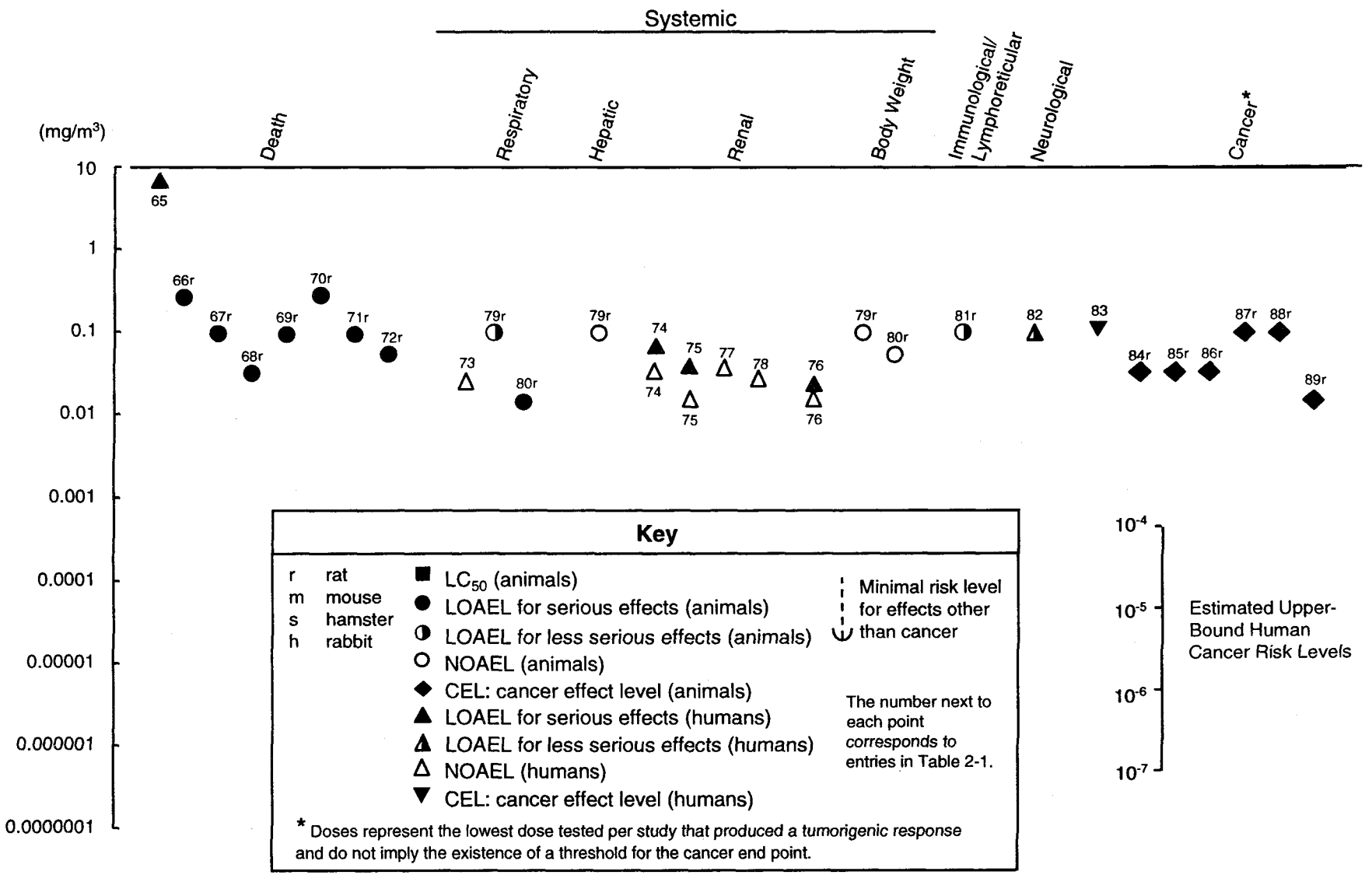


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Chronic (≥365 days)



et al. (1979) reported a significant increase in deaths due to respiratory diseases in cadmium-exposed battery factory workers exposed for longer than 5 years.

A significant, dose-dependent excess in the ratio of observed to expected deaths from bronchitis (i.e., Standardized Mortality Ratio=434) but not emphysema was found among 6,995 men occupationally exposed to cadmium for an average of 11 years (Armstrong and Kazantzis 1983). Dose level was not determined.

The earlier occupational studies did not control for the health effects of cigarette smoking. There is some evidence that cadmium may accelerate the development of emphysema in smokers. Leduc et al. (1993) report a case history of a 59-year-old male worker who smoked a pack of cigarettes per day since age 16, but had no prior history of respiratory disease in 1975 until developing emphysema in 1979 after inhaling various concentrations of cadmium (range of 0.0164-l.192 mg/m^3, mean of 0.446 mg/m^3, about nine times the threshold value of 0.050 mg/m^3) for 4 years as a furnace operator. Very high levels of cadmium in air samples at the workplace and in the patient's blood, urine, and lung tissue confirmed massive exposures. Lung-function tests declined rapidly, with a faster than usual onset of emphysema compared to other smokers. The mean concentration of cadmium in a removed section of lung was 580 μg/g dry tissue, compared to 14 μg/g in three unexposed controls matched for age, sex, and smoking habit who had also undergone resection of a bronchial carcinoma. The authors state that this case supports the hypothesis for an etiological role of cadmium fume inhalation in the development of emphysema.

More recent studies that controlled for smoking report lung impairment in cadmium-exposed workers (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976). Cortona et al. (1992) measured respiratory function parameters in 69 smoking and non-smoking male subjects (average age 45) who were exposed to concentrations of 0.008-l.53 mg/m^3 of cadmium fumes over a period of several years in a factory that produced cadmium alloys (silver-cadmium-copper). Forced Expiratory Volume (FEV), Forced Vital Capacity (FVC), Residual Volume (RV), Transfer Factor by the carbon monoxide method (TLCO), and Transfer Coefficient (KCO) were measured in these exposed individuals. The study found that there were no significant differences in the FVC, FEV, TLCO, and KCO between the workers exposed to cadmium fumes and control (non-exposed) individuals. There was a significant increase in RV of more than 8% in exposed workers; this effect was notably greater in those with higher cumulative exposures to cadmium (>l0%). It is uncertain how much of a factor on the increased RV was due to the tendency of smokers to develop an initial emphysematous alteration in lung tissue due to smoking.

Davison et al. (1988) evaluated lung function in 101 men who had manufactured copper-cadmium alloy in a plant in England for 1 or more years since 1926. The exposed men were compared to controls from the factory's other seven divisions matched for age and employment status. Smoking in exposed and control men was similar. Between 1951 and 1983, 933 measurements of airborne cadmium had been made, 697 with static samplers and 236 with personal samplers. The various sampling methods used before 1964 are no longer considered to be reliable, so estimates of air concentrations were made based on changes in production techniques, ventilation, levels of production, and discussions with occupational health physicians, industrial hygienist, the management, and the workers. Cadmium concentrations in air from 1926 to 1972 were determined to have declined from 0.6 to 0.156 mg/m^3. In 1973, concentrations were 0.085 mg/m^3; then from 1974 to 1983 concentrations ranged from 0.034-0.058 mg/m^3. The lung function of 77 of the men occupationally exposed to cadmium was significantly impaired compared to the unexposed controls, with the greatest abnormalities in the highest-dose group. Regression of the lung transfer coefficient versus cadmium exposure indicated a linear relationship with no apparent threshold.

Smith et al. (1976) studied the pulmonary function of 17 high-exposure workers, 12 low-exposure workers, and 17 controls. Cadmium air concentrations where high-exposure subjects worked were >0.2 mg/m^3. High-exposure subjects had worked at the plant a median of 26.4 years, with a maximum of 40.2 years, and low-exposure subjects had worked a median of 27.1 years, with a maximum of 34.8 years. Workers with high exposure to cadmium had significantly decreased the forced volume capacity (FVC) compared to low-exposure workers and controls. Chest X-rays indicated mild or moderate interstitial fibrosis in 29% of high exposure workers. A dose-response relationship was found between forced vital capacity and urinary cadmium, and with months of exposure to cadmium fume but not cadmium sulfate aerosol. In an analysis of the smoking habits, there was no significant difference between the two cadmium-exposed groups with respect to the proportion of present or past cigarette smokers, the intensity or duration of cigarette smoking, or cigar or pipe smoking habits. The control subjects, however, had a significantly ($p<0.05$) "higher" exposure to cigarette smoke than the cadmium exposed workers with substantially greater numbers of pack-years, cigarettes smoked per day, and years smoked. A step-down and multiple regression analyses with a dependent variable of FVC (as percent of predicted), and the independent variables, age-height, cigarette pack-years, and urinary cadmium, resulted in no indication that an interaction between the independent variables led to the observed relationship between FVC and cadmium excretion.

Other studies, however, have not shown a cadmium-related increase in impaired respiratory function. Edling et al. (1986) studied Swedish workers occupationally exposed to cadmium oxide (CdO) fume from

cadmium-containing solders. Cadmium-containing solder had been used at the plant from 1955 to 1978. The results from the lung-function analysis showed no significant difference in symptoms or lung function between the Cd-exposed and the reference group. The exposed and the reference groups were similar with respect to sex, age, and height. There was a higher percentage of smokers in the reference group (52%) than in the exposed group (42%), but the difference was not statistically significant. The authors could not explain why significant differences in effects were not seen in these workers since other studies have shown significant effects at comparable cadmium exposure levels. The authors suggest that a possible bias could have been introduced if people who had worked for more than 5 years in the plant had changed their occupation because of lung disease, so that only "healthy" workers remained. Significant effects may also have been found if the reference group included workers other than those who worked with solder, but the purpose of the study was to resolve the effects of cadmium exposure among workers with similar occupations. An analysis that factored out smoking by evaluating the data from smokers and nonsmokers separately also showed no significant impairment function between smoking exposed and smoking unexposed or nonsmoking exposed and nonsmoking unexposed. The lung impairment due to smoking was observed in that smokers in both the exposed and unexposed groups had a somewhat deteriorated closing volume and other lung function indicators in accordance with previous studies on the effects of smoking. These results support the hypothesis that the response to occupational dust exposure differs from the response to tobacco smoking.

Another possible reason for differing results is that lung injury caused by high-level cadmium exposure may be partially reversible (Bonnell 1955; Chan et al. 1988), with a return towards normal several years after exposures have been significantly reduced. Chan et al. (1988) studied a cohort of 36 female and 8 male workers at a Singapore cadmium battery factory exposed to cadmium oxide dust. Cadmium concentrations in air were 0.03-0.09 mg/m^3 (geometric means). Lung function was measured using spirometry, helium dilution, tidal sampling, X-ray, and respiratory symptoms. The recovery of lung function after reduction or cessation of occupational exposure to cadmium dusts was assessed. Total lung capacity increased following reduction of exposure and, following cessation of exposure, vital capacity, FEV, and prevalence of respiratory symptoms all improved. Blood and urine cadmium concentrations were considerably lower with the reduction or cessation of exposure and were consistent with a decrease in the cadmium air levels.

Additional respiratory symptoms less frequently reported in workers occupationally exposed to cadmium are chronic rhinitis and impairment or loss of the sense of smell (Adams et al. 1969; Bonnell 1955; Friberg

1950; Liu et al. 1985; Rose et al. 1992). The cause of these effects may be chronic irritation or necrosis of the nasal membranes, as they are generally found only in individuals with high-level exposure. An increased prevalence of abnormal parasinus radiographic findings in cadmium-exposed workers compared to other published reports on non-exposed populations was reported by Shaham et al. (1993).

Studies in animals confirm that inhalation exposure to cadmium can lead to respiratory injury. Single acute exposures in rats to cadmium oxide dust, cadmium oxide fume or cadmium chloride for l-5 hours in the 5-10 mg/m^3 range resulted in moderate to severe, multifocal interstitial pneumonitis, diffuse alveolitis with hemorrhage, increased lung weight, inhibition of macrophages, focal interstitial thickening, edema, and necrosis of alveolar type 1 cells leading to type 2 cell hyperplasia and fibroblasts (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart et al. 1989a; Palmer et al. 1986). Similar results (i.e., severe pneumonitis) were seen in hamsters exposed to $CdCl_2$ at 10 mg/m^3 for 30 minutes (Henderson et al. 1979), and in rabbits exposed to CdO dusts at 4.5 mg/m^3 for 2 hours (Grose et al. 1987). Exposure to $CdCl_2$ at concentrations as low as 0.17 mg/m^3 for 6 hours a day for 10 days resulted in a 16% increase in absolute lung weight in rats (Klimisch 1993). Exposures in rats to $CdCl_2$ at 6.1 mg/m^3 1 hour a day for 5, 10, or 15 days, resulted in emphysema (Snider et al. 1973). Rats exposed to 61 mg/m^3 of $CdCl_2$ 1 hour a day for 3 days developed pulmonary hemorrhage (Snider et al. 1973). Rats exposed for 2 hours to $CdCO_3$ at the higher levels of 132 mg/m^3 developed rales, rapid breathing, and 2-3-fold increases in lung weight (Rusch et al. 1986). With the same dosing regimen, CdO fumes at 112 mg/m^3 resulted in rales, labored breathing, and lung discoloration in rats (Rusch et al. 1986).

The form of cadmium can affect its toxicity. Cadmium acetate, like cadmium chloride, produced severe respiratory effects from acute exposures in the l-5 mg/m^3 range. A single intra-tracheal instillation of cadmium acetate at 0.5 mg cadmium acetate/kg body weight (estimated to be 2.4 mg/m^3) has led to toxic lung lesions in the rat indicated by depressed levels of catalase and superoxide dismutase; increased nonprotein sulfhydryl content, glucose-6-phosphate dehydrogenase and glutathione peroxidase in lung tissue; and increases in lactate dehydrogenase (LDH) and protein in bronchoalveolar lavage fluid (BALF) (Salovsky et al. 1992). Exposure to cadmium sulfide at 6.29 mg/m^3 for 6 hours a day for 10 days resulted in an 8% increase in absolute lung weight in rats, compare to the 16% increased weight seen with only 0.17 mg/m^3 of cadmium chloride (Klimisch 1993). No respiratory effects were observed in rats exposed to cadmium sulfide at 99 mg/m^3 for 2 hours or to cadmium selenium sulfide at 97 mg/m^3 for 2 hours (Rusch et al. 1986).

Persistent damage has been reported in animal models from single acute exposure. Fibrosis caused by acute exposure was observed for at least 12 months postexposure (Dervan and Hayes 1979). Driscoll et al. (1992) evaluated rat alveolar macrophage fibronectin release, biochemical alterations in the BALF, and tumor necrosis factor (TNF) as early indicators of pulmonary inflammation in rats exposed once via intratracheal instillation to 0, 25, 100, or 400 μg $CdCl_2$/kg body weight. BALF was analyzed for LDH, total protein, and N-acetylglucosaminidase (NAG). Initial significant increases in BALF LDH, total protein, and NAG for all dose levels at day 3, and for all but LDH and NAG at the low-dose level at day 7, returned to control values by 28 days postexposure with one exception; total protein from the 400 μg/kg exposure remained elevated. The total protein response was dose-related. Neutrophils and lymphocyte numbers increased initially, but returned to control levels by days 14 and 28, respectively. In contrast, alveolar macrophage numbers increased after day 7, and remained elevated. While alveolar macrophage TNF did not change significantly, macrophage fibronectin release did significantly increase at all doses in a dose-related manner, and remained high through day 28. There was no statistically significant difference in cell viability for any of the cell populations. Hydroxyproline levels significantly increased at 100 and 400 μg/kg, but not at 25 μg/kg. Histopathological changes in the lung consisted of chronic interstitial inflammation characterized by increased alveolar wall thickening, increased number of mononuclear cells, type 2 cell hyperplasia, and at times, presence of brown pigment-laden macrophages. Alveolar spaces were variably collapsed with dilatation of some terminal bronchioles, alveolar ducts, and adjacent alveoli. The overall histopathological response was more severe at 90 days than at 28 days for the 100 and 400 μg/kg groups. Masson's trichrome-stained lung sections revealed minimally to moderately increased prominence of collagen, interpreted to reflect fibrosis in all dose groups; the response was dose related and more severe after 90 days than after 28 days.

Other studies report similar transient increases in BALF enzymes or other indicators of pulmonary pneumonitis, but also histopathological alterations that return to normal. Rats exposed to 1.6 mg/m^3 of CdO dust for 3 hours a day, 5 days a week for 1-6 weeks developed an interstitial pulmonary pneumonitis the first 2 weeks as indicated by changes in airway amounts of lactic dehydrogenase, alkaline and acid phosphatase, protein, and polymorphonuclear leukocytes. The levels of these biochemical and cytological indicators of toxicity, and the accompanying histopathological alterations, returned towards normal values during the next three weeks even though cadmium continued to accumulate in the lung. Hart (1986) suggests that the adaptive synthesis of a Cd-binding protein (i.e., presumptive metallothioneins) in the lung serves to sequester cadmium and protect the tissue from further toxicity.

Palmer et al. (1986) evaluated the role of thyroid hormone in the pulmonary repair process following $CdCl_2$-induced acute lung injury. Normal and thyroidectomized (Thyx) rats were exposed via inhalation for 2 hours to a 10 mg $CdCl_2/m^3$ aerosol. The unmodified euthyroid rats exposed to $CdCl_2$ exhibited primarily type 1 epithelial cell damage and necrosis with only minor morphological changes in type 2 cells. In contrast, thyroidectomy, followed by $CdCl_2$ exposure, produced earlier and more severe acute injury in the form of patchy alveolar edema, hemorrhage, and hyaline membrane formation on alveolar surfaces were common. Type 2 cell hyperplasia was markedly reduced compared to the euthyroid control. Type 2 cells in the Thyx rats also showed prominent cytoplasmic vacuolization, marked increase of the perinuclear space, and early nuclear alterations suggestive of pyknosis. The severity of the injury to type 2 cells in $CdCl_2$-exposed Thyx rats may account, in large measure, for the decreased DNA synthetic and proliferative ability of these cells, which would enhance the acute lung damage. Reductions in repair response were also seen in the number of lavageable lung cells (down 60% lower) and antioxidant enzyme activity (4.5-5% lower) than the normal rat response. Antioxidant enzymes were depressed especially in the early days postexposure. The authors suggest that depressed levels of T4 and increased oxidant damage may play a role in the underlying mechanism of increased damage seen in the Thyx rats. Thus, the persistence of lung damage or the development of further damage for a given level of acute exposure is probably related to the capacity of pulmonary repair mechanisms (e.g., type 2 cell hyperplasia) and to adaptive responses like the production of metal binding proteins to sequester free cadmium away from target sites.

Intermediate-duration exposure to cadmium results in similar respiratory effects as seen in the acute exposures. The level and duration of exposure determine the severity of the effects in a dose-response manner. Intermediate exposure levels in the 0.4-4 mg Cd/m^3 range generally result in serious lung damage. Kutzman et al. (1986) reported fibrosis with significant increase in collagen in rats exposed to $CdCl_2$ at 1.06 mg Cd/m^3 for 6 hours a day, 5 days a week for 62 days. Prigge (1978b) reported emphysema and bronchiolitis in pregnant rats exposed to $CdCl_2$ at 0.581 mg Cd/m^3 for 24 hours a day, for 21 days (gestational days [Gd] 1-21). Hart et al. (1989a) reported type 2 cell hyperplasia and a 41% increased lung dry weight in rats exposed to CdO at 1.6 mg Cd/m^3 for 3 hours a day, 5 days a week for 5-6 weeks. Friberg (1950) reported chronic pneumonia and emphysema in rabbits exposed to cadmium metal dust at 4 mg Cd/m^3 for 3 hours a day, 21 days a month for 9 months, and at 5.6 mg Cd/m^3 for 3 hours a day, 23 days a month for 7 months. Johansson et al. (1984) observed type 2 cell hyperplasia and lung interstitial inflammation in rabbits exposed to $CdCl_2$ at 0.4 mg Cd/m^3 for 6 hours a day, 5 days a week for 4-6 weeks. With longer exposure durations increasingly lower doses result in serious respiratory toxicity. Cadmium oxide dust, at doses as low as 0.105 mg Cd/m^3, has been shown to produce emphysema and

histiocytic cell granulomas in rats when administered for 24 hours a day for 62 days (exposure terminated due to high mortality) (Prigge et al. 1978a). At a lower dose of 0.025 mg Cd/m^3 for 24 hours a day for 90 days, CdO dust produced less severe toxicity including hypercellularity in the bronchoalveolar region and increased relative weight in the lung (Prigge et al. 1978a). Similar effects (i.e., bronchoalveolar hypercellularity) were seen for exposures to CdO dust at 0.098 mg Cd/m^3 for 22 hours a day, 7 days a week for 30 days; for exposures to $CdCl_2$ at 0.105 mg Cd/m^3 for 22 hours a day, 7 days a week for 30 days; and for exposures to CdS at 1.034 mg Cd/m^3 for 22 hours a day, 7 days a week for 30 days (Glaser et al. 1986). As with the acute exposures, cadmium sulfide is less toxic than cadmium oxide or cadmium chloride (Glaser et al. 1986).

Some tolerance to cadmium appears to develop with duration of dose so that lung lesions that developed after a few weeks of exposure are not seen to progress, sometimes even reversing after longer exposures (Hart 1986; Hart et al. 1989a). Multiple mechanisms appear to be responsible for this tolerance, including the synthesis of lung metallothionein (see Section 2.3.3) and an increase in type 2 cells (Hart et al. 1989a). With respect to differential response related to metallothionein, Oberdorster et al. (1994) compared the pulmonary responses of rats and mice to a long-term aerosol exposure of $CdCl_2$ at 100 μg Cd/m^3 6 hours a day, 5 days a week for 4 weeks. Parameters monitored included metallothionein, retained cadmium in the lung, BALF neutrophil counts, and enzyme activity (β-glucuronidase and LDH); cell proliferation measured by bromodeoxyuridine (BrdU) incorporation into lung tissues; lung morphology (histochemical staining), and induction of metallothionein concentration in lung tissue. The results showed that mice respond with significantly greater inflammatory response in their lungs after $CdCl_2$ exposure than do rats. Mice had a greater cell proliferative response, a higher baseline metallothionein level, lung metallothionein that is more inducible, and lung burdens of cadmium metallothionein that were twice as high as in rats from the same aerosol concentration of $CdCl_2$. Higher burdens are expected because of the higher respiratory rate in mice. Although the mice had increased cell proliferation, mice also responded with a significant induction of metallothionein in the epithelial cells of the conducting airways and alveolar region. Rats did not have this response. Increased metallothionein may provide more protection against the development of lung tumors in proliferating cells. The authors suggest that these enhanced responses in mice may contribute to the lack of pulmonary carcinogenicity found in mice. The authors also noted that an increased cell proliferative response (as seen in the mouse) does not necessarily lead to increased risk of tumor development, for it is the rat (with the lesser proliferative response) that is more prone to lung tumors from inhaled cadmium.

There are fewer chronic-inhalation exposure studies that specifically reported systemic respiratory effects. Oldiges and Glaser (1986) report increased lung weights (amount unspecified) in rats from exposure to either $CdSO_4$ at 0.092 mg Cd/m^3 or CdS at 0.254 mg Cd/m^3 for 22 hours a day, 7 days a week for 413-455 days. Takenaka et al. (1983) observed adenomatous hyperplasia in the bronchoalveolar region in rats from exposure to $CdCl_2$ at 0.0134 mg Cd/m^3 for 23 hours a day, 7 days a week for 18 months.

Cardiovascular Effects. Inhalation exposure to cadmium does not appear to have significant effects on the cardiovascular system. Most studies of workers occupationally exposed to cadmium have not found cadmium-related cardiovascular toxicity. In some studies, the mortality from cardiovascular disease was lower in the cadmium-exposed population. Armstrong and Kazantzis (1983) reported that a cohort of 6,995 British men occupationally exposed to cadmium for an average duration of 11 years had a significantly lower mortality from vascular disease.

Fifty-three male workers exposed to cadmium and lead and 52 male controls were examined for correlations in urine levels and blood pressure. The average duration of exposure was 12.5 years. Correlations between blood pressure and urinary cadmium in exposed workers were not significant after controlling for age or age and heart rate. Exposure to lead was a significant confounding factor (de Kort et al. 1987).

Friberg (1950) investigated the health of workers in a manufacturing plant that made cadmium-containing electrodes used in the production of batteries. Fifty-eight workers (30-50 years of age) were divided into 2 groups based on number of years at the plant. Workers were clinically examined for subjective symptoms and corresponding morphological or functional changes of the respiratory, cardiovascular, and excretory systems. The cardiovascular exam was largely unremarkable. Only a slight rise in blood pressure in a few cases was observed in Group 1. Electrocardiograms (EKG) were not significantly different from a matched control group in Group 1. Group 2 had neither increased blood pressure or altered EKGs.

Kazantzis et al. (1988) studied mortality in a cohort of 6,958 cadmium-exposed male workers with average occupational exposures of 12 years. This was a follow-up study to the work of Armstrong and Kazantzis (1983). There was a significant deficit in deaths from cerebrovascular disease among men occupationally exposed to cadmium. There was no significant excess risk from hypertensive or renal disease.

Smith et al. (1980) studied 16 male high-exposure production workers and 11 male low-exposure office and supervisory workers for renal function. Average duration of exposure was 25 years. High-exposure workers were exposed to CdO concentrations of 0.23-45.2 mg/m^3 and CdS concentrations of 0.04-l 27 mg/m^3. No difference was found in hypertension between high- and low-exposure workers, adjusted for age and weight or cigarette smoking.

Sorahan and Waterhouse (1983) examined mortality rates in a cohort of 3,025 nickel-cadmium battery workers (2,559 males and 466 females). Cadmium levels in air ranged from 0.05 to 2.8 mg/m^3, primarily as CdO. Duration of exposure ranged from 1 year to more than 6 years. No increase in mortality from diseases of the circulatory system (e.g., hypertension) were seen in cadmium-exposed workers.

Staessen and Lauwerys (1993), in a study known as the Cadmibel Study (a cross-sectional population study), evaluated 2,327 people from a random sample of the population of four Belgian districts chosen to provide a wide range of environmental exposure to cadmium. Participants completed a questionnaire regarding their medical history, current and past occupations, smoking habits, alcohol consumption, and intake of medications. Urine and blood samples were taken, and pulse rate, blood pressure, height, and weight were recorded. Exposure to cadmium was considered to be by both the oral and inhalation routes. Cadmium levels in blood and urine were significantly increased in the high-exposure areas compared to the low-exposure areas ($p<0.00l$). Blood pressure was not correlated with the urine or blood cadmium levels. The prevalence of hypertension or other cardiovascular diseases was similar in all four districts, and was not correlated with urine or blood cadmium levels. These results do not support a hypothesis that cadmium increases blood pressure, prevalence of hypertension, or other cardiovascular diseases.

One study found a statistically significant increase in blood pressure in exposed workers compared to controls (Thun et al. 1989), but mortality in this cohort was lower than expected (Thun et al. 1985). Only one study was found regarding cardiovascular effects in animals after inhalation exposure to cadmium. Kutzman et al. (1986) reported a significant increase in relative heart weight in rats exposed to 1.06 mg Cd/m^3 cadmium chloride for 62 days, 5 days a week 6 hours a day. Body weights in these rat were also significantly reduced from this exposure, and absolute organ weights were not reported, so the significance of this toxic effect on the heart is unclear.

Gastrointestinal Effects. In the cohort he studied, Friberg (1950) found no association between inhalation cadmium exposure in workers and symptoms of gastrointestinal toxicity. Symptoms that had been reported in case histories from the 1920s included pain or tenderness at the epigastrium associated with nausea and some constipation. No other human studies report any cadmium associated gastrointestinal toxicity from inhalation exposure.

In the only animal study located, Rusch et al. (1986) observed erosion of the stomach in rats from exposure to cadmium carbonate at 132 mg Cd/m^3 for 2 hours. Post-mortem evaluation was performed at 1, 3, 7, and 30 days postexposure. After the inhalation exposure in a whole-body chamber, rats were vacuumed to remove any CdCO, dust adhering to the ventral and dorsal fur. The 132 mg Cd/m^3 dose is relatively high. Three of the 10 test animals died during the 2-hour exposure so the significance of the gastrointestinal effect in this study is unclear.

Hematological Effects. The evidence concerning hematological effects following inhalation exposure to cadmium is conflicting. Lowered hemoglobin concentrations and decreased packed cell volumes have been observed in some studies of workers occupationally exposed to cadmium (Bernard et al. 1979; Friberg 1950; Kagamimori et al. 1986), but not in others (Bonnell 1955; Chan et al. 1988; Davison et al. 1988). The changes that were found often were not statistically significant (Bernard et al. 1979; Friberg 1950), and examination of bone marrow of some workers with lowered hemoglobin revealed no detectable abnormalities (Friberg 1950).

Conflicting results on the hematologic effect of cadmium after inhalation exposure have also been obtained with animal studies. Rabbits exposed to cadmium oxide dust at 4 mg/m^3 for 3 hours a day, 21 days a month for 9 months developed eosinophilia and a slightly lower hemoglobin (Friberg 1950). In contrast, rats exposed to CdO dust at 0.052 mg Cd/m^3 for 24 hours a day for 90 days had increased hemoglobin and hematocrit that were attributed to decreased lung function (Prigge 1978a). Prigge (I 978b) also reported increased hemoglobin and hematocrit in rats exposed to $CdCl_2$ at 0.204, 0.394, or 0.581 mg Cd/m^3 24 hours a day for 21 days. Other studies report no Cd-related hematological effects. A nearly continuous 30-day exposure in rats to CdS at 1.034 mg Cd/m^3 had no effect on red blood cell counts (Glaser et al. 1986). A nearly continuous 218-day exposure in rats to CdO dust or fume at 0.090 mg Cd/m^3 had no effect on a routine hematological evaluation (specific tests not reported) (Oldiges and Glaser 1986). A partial explanation for these conflicting results may be that Cd-induced anemia primarily results from

impaired absorption of iron from the diet following gastrointestinal exposure to cadmium (see Section 2.2.2.2), and the amount of gastrointestinal exposure following cadmium inhalation is variable depending on the form and dose.

Musculoskeletal Effects. Case studies indicate that calcium deficiency, osteoporosis, or osteomalacia can develop in some workers after long-term occupational exposure to high levels of cadmium (Adams et al. 1969; Blainey et al. 1980; Bonnell 1955; Kazantzis 1979; Scott et al. 1980). Effects on bone generally arise only after kidney damage has occurred and are likely to be secondary to resulting changes in calcium, phosphorus, and vitamin D metabolism (Blainey et al. 1980).

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to cadmium.

Hepatic Effects. Liver effects are not usually associated with inhalation exposure to cadmium. Friberg (1950) reported some nonspecific signs of liver disease in some workers from a group exposed to cadmium in the air for 20 years. Test results included increased serum gamma-globulin, and other indicators of abnormal serum globulins, including the flocculation test results of a positive Takata reaction and/or an elevated thymol values. These tests (the latter of which are not used today) were nonspecific indicators of cirrhosis or hepatitis. The significance of these test results with respect to cadmium exposure is questionable. Subsequent studies on workers exposed to cadmium in the air have not reported adverse liver effects (Adams et al. 1969; Bonnell 1955).

Liver effects have occasionally been found in animal studies. Cats examined within one day of inhalation exposure to an unspecified concentration of cadmium oxide fume had a variety of hepatic lesions, and liver changes from cell granulation at low doses to fatty infiltration at high doses (Prodan 1932). Increased serum alanine aminotransferase activity, indicative of liver damage, was seen in rats exposed for 30 days to 0.1 mg/m^3 cadmium, but activity had returned to normal 2 months after exposure (Glaser et al. 1986). Kutzman et al. (1986) reported an increased liver relative weight in rats from a $CdCl_2$ exposure at 1.06 mg Cd/m^3 for 6 hours a day, 5 days a week, for 62 days. Increased liver weight was not observed from a continuous $CdCl_2$ exposure at 0.029 mg Cd/m^3 for 255 days, from a continuous CdO exposure at 0.090 mg Cd/m^3 for 218 days, or from a continuous CdSO, exposure at 0.095 mg Cd/m^3 for 413 days (Oldiges and Glaser 1986). Similar negative results were reported by Prigge (1978a, 1978b) for a 21-day exposure to $CdCl_2$ at 0.581 mg Cd/m^3, and for a 63-day exposure to CdO at 0.105 mg Cd/m^3 (a dose that was very

toxic to the lungs). A continuous high-dose exposure to CdS at 2.247 mg Cd/m^3 for 105 days did result in an unspecified increase in liver weight in surviving rats (Oldiges and Glaser 1986). Cadmium accumulates in the liver as well as the kidney, the main target organ for cadmium toxicity. The resistance of the liver to toxic effects from cadmium may be related to a higher capacity of the liver to produce metallothionein that would bind to cadmium and would lower the concentrations of free cadmium ions (see Section 2.3.3).

Renal Effects. There is very strong evidence that the kidney is the main target organ of cadmium toxicity following extended inhalation exposure to cadmium. The sensitivity of the kidney to cadmium was recognized in an early investigation of workers exposed to cadmium oxide dust and cadmium fumes in a factory producing nickel-cadmium batteries (Friberg 1950). These workers suffered from a high incidence of abnormal renal function, indicated by proteinuria and a decrease in glomerular filtration rate. Similar signs of renal damage have been observed in many other studies of workers occupationally exposed to cadmium (Adams et al. 1969; Beton et al. 1966; Bernard et al. 1979; Bonnell 1955; Bustueva et al. 1994; Chia et al. 1989; Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Iwata et al. 1993; Jakubowski et al, 1987; Jarup and Elinder 1993; Jarup et al.; 1988 Kjellstrom et al. 1977a; Liu et al. 1985; Mason et al. 1988; Piscator 1966; Roels et al. 1981b; Rose et al. 1992; Smith et al. 1980; Thun et al. 1989).

The proteinuria caused by cadmium exposure is characterized by the presence of a number of low molecular-weight proteins in urine, including β_2-microglobulin, lysozyme, ribonuclease, immunoglobulin light chains, and retinol-binding protein (Piscator 1966). These low-molecular-weight proteins are all readily filtered by the glomerulus and are normally reabsorbed in the proximal tubules of the kidney. Elevated urinary excretion of these proteins is indicative of proximal tubular damage. Urinary excretion of high-molecular-weight proteins such as albumin has also been reported in occupationally exposed workers (Bernard et al. 1979; Elinder et al. 1985b; Mason et al. 1988; Roels et al. 1989; Thun et al. 1989), but there is some debate as to whether this represents glomerular damage (Bernard et al. 1979; Roels et al. 1989) or severe tubular damage (Elinder et al. 1985a; Mason et al. 1988; Piscator 1984).

The tubular proteinuria caused by cadmium exposure may be accompanied by depressed tubular resorption of other solutes such as enzymes, amino acids, glucose, calcium, copper, and inorganic phosphate (Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Mason et al. 1988). It has been suggested that the urinary concentrations of some of these solutes, particularly renal enzymes, are more sensitive than low-molecular-weight proteins for detecting tubular dysfunction in exposed humans (see Section 2.5.2).

An additional effect on the kidney seen in workers after high levels of inhalation exposure to cadmium is an increased frequency of kidney stone formation (Elinder et al. 1985a; Falck et al. 1983; Kazantzis 1979; Scott et al. 1978; Thun et al. 1989). This effect is likely to be secondary to disruption of calcium metabolism due to kidney damage.

Tubular dysfunction generally develops only after cadmium reaches a minimum threshold in the renal cortex. This threshold is often referred to as the "critical concentration." Care must be taken in its interpretation because it is not invariant, but depends on a number of variables (Foulkes 1990). The critical concentration of cadmium in the renal cortex associated with increased incidence of renal dysfunction in an adult human population chronically exposed to cadmium has been estimated to be about 200 μg/g wet weight by several investigators (Friberg et al. 1974; Kjellstrom et al. 1977a, 1984; Roels et al. 1983).

Several quantitative evaluations of kidney toxicity have been performed using cumulative dose (exposure duration times cadmium concentration) as the independent variable. For presentation in Table 2-1 and Figure 2-1, a standard exposure period of 30 years has been used to convert reported units of mg-years/m^3 to mg/m^3, based on the assumption that uptake is a linear function of concentration and time. An early study found a 10% prevalence of proteinuria at an average 30-year exposure to cadmium oxide dust of 0.017 mg Cd/m^3 (Kjellstrom et al. 1977a), but a subsequent follow-up study found only a 4% prevalence at this level of exposure (Jarup et al. 1988). The definition of proteinuria used in these studies is an excretion exceeding the 95th percentile of a normal population. Thus, a prevalence of 5% or less was considered to be unrelated to cadmium exposure. Among the workers in the follow-up study, the prevalence of proteinuria was 1.1% in the lowest exposure group with a 30-year exposure to 0.00437 mg cadmium/m^3 and 9% at 0.023 mg/m^3 (Jar-up et al. 1988). Logistic regression generated a prevalence of 4% at a 30-year exposure to 0.017 mg/m^3, which was considered to be the NOAEL for this cohort. Other recent analyses have found 30-year thresholds for proteinuria of 0.027 mg/m^3 (Thun et al. 1989), 0.033 mg/m^3 (Elinder et al. 1985b), or 0.0367 mg/m^3 (Mason et al. 1988). In another cohort, with an average 30-year exposure to cadmium fume of 0.026 mg/m^3, the average exposures of workers with and without proteinuria were 0.038 and 0.015 mg/m^3, respectively (Falck et al. 1983).

Cessation of cadmium exposure generally does not lead to a decrease in proteinuria in occupationally exposed workers (Elinder et al. 1985b; Mason et al. 1988; Piscator 1984; Thun et al. 1989), possibly because the kidney cadmium level declines very slowly after cessation of exposure. Kidney damage may

continue to worsen after exposure ceases. A progressive reduction of the glomerular filtration rate in excess of the usual age-related decline was found in 23 workers 5 years after they were removed from cadmium exposure because of proteinuria and/or albuminuria (Roels et al. 1989). End-stage renal disease is not a common cause of death among workers occupationally exposed to cadmium, but it is significantly elevated over expected values in some occupational cohorts (Elinder et al. 198%; Kazantzis et al. 1988).

To further evaluate the reversibility of proteinuria, Roels et al. (1997) studied the progression of Cd-induced renal tubular dysfunction in cadmium workers according to the severity of the microproteinuria at the time the exposure was substantially decreased. A total of 32 cadmium male workers were divided into two groups on the basis of historical records of urinary cadmium concentration (CdU) covering the period until 1984. The workers with CdU values of >l0 μg Cd/g creatinine were subdivided further on the basis of the urinary concentration of β_2-microglobulin (β_2-MG-U) measured during the first observation period (1980-1984). In each group, the tubular microproteinuria as reflected by β_2-MG-U and the concentration of retinol-binding protein in urine, as well as the internal cadmium dose as reflected by the concentration of cadmium in blood and urine, were compared between the first and second (1990-1992) observation periods. Increased microproteinuria was often diagnosed in cases with CdU values of >l0 μg Cd/g creatinine. The progression of tubular renal function was found to depend on the extent of the body burden of cadmium (as reflected by CdU) and the severity of the initial microproteinuria at the time high cadmium exposure was reduced or ceased. When cadmium exposure was reduced and β_2-MG-U did not exceed the upper reference limit of 300 μg/g creatinine, the risk of developing tubular dysfunction at a later stage was likely to be low, even in cases with historical CdU values occasionally >l0 but always < 20 μg Cd/g creatinine. When the microproteinuria was mild (β_2-MG-U >300 and ≤1,500 μg/g creatinine) at the time exposure was reduced, and the historical CdU values had never exceeded 20 μg Cd/g creatinine, there was indication of a reversible tubulotoxic effect of cadmium. When severe microproteinuria (β_2-MG-U >1,500 μg/g creatinine) was diagnosed in combination with historical CdU values exceeding 20 μg Cd/g creatinine, cadmium-induced tubular dysfunction was progressive in spite of reduction or cessation of cadmium exposure.

Early animal studies confirmed that renal damage occurs following inhalation exposure to cadmium. Rabbits developed proteinuria after a 4-month inhalation exposure to cadmium metal dust at 4 mg/m^3 for 3 hours per day, 21 days per month; histologic lesions were found after an additional 3-4 months of exposure (Friberg 1950). Friberg (1950) noted that the degree of proteinuria was not especially pronounced. Most subsequent studies using inhalation exposure have not found proteinuria (Glaser et al.

1986; Kutzman et al. 1986; Prigge 1978a, 1978b), primarily because the levels of exposure and durations of follow-up (e.g., l-5 mg/m^3 for intermediate exposures; 0.2-2 mg/m^3 for chronic exposures) that produce serious respiratory effects have not been sufficient to produce a critical concentration of cadmium in the kidney.

Dermal Effects. Dermal toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported dermal effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined dermal toxicity in humans or animals following inhalation exposure to cadmium.

Ocular Effects. Ocular toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported ocular effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined ocular toxicity in humans following inhalation exposure to cadmium.

Rats exposed to a single 2 hour inhalation exposure to about 100 mg Cd/m^3 as cadmium pigments had excessive lacrimation 4 hours after exposure (Rusch et al. 1986), but this was likely due to a direct irritation of the eyes rather than a systemic effect.

Body Weight Effects. No data were found regarding the effects of inhaled cadmium on human body weights.

In animals, cadmium has been shown to significantly reduce body weights. An acute exposure to cadmium oxide fumes at 112 mg Cd/m^3 for 2 hours (Rusch et al. 1986) and cadmium oxide dust at 4.6 mg Cd/m^3 for 3 hours (Buckley and Bassett 1978b) resulted in a significant reduction of body weight in male rats. Cadmium chloride at 6.5 mg Cd/m^3 for 1 hour or 4.5 mg Cd/m^3 for 2 hours produced significant reductions in male rat body weights (Bus et al. 1978; Grose et al. 1987). Cadmium carbonate at 132 mg Cd/m^3 for 2 hours slowed rat body weight gains (Rusch et al. 1986). NOAELs for acute cadmium chloride exposure have been reported at 0.45 mg Cd/m^3 for 2 hours (Grose et al. 1987); 0.17 mg Cd/m^3 for 10 days, 6 hours a day (Klimisch 1993); and 6 mg Cd/m^3 for 2 hours (Palmer et al. 1986). NOAELs for cadmium sulfide and

cadmium selenium sulfide were much higher at 99 mg Cd/m^3 for 2 hours and 97 mg Cd/m^3 for 2 hours, respectively (Rusch et al. 1986). Levels of cadmium that significantly reduce rat body weights when administered for an intermediate exposure duration have been reported for cadmium chloride at around 1 mg Cd/m^3 for female and male rats (Baranski and Sitarek 1987; Kutzman et al. 1986), for cadmium chloride at around 0.394 mg Cd/m^3 for pregnant female rats (Prigge 1978a), and for cadmium dusts at 0.1 mg Cd/m^3 for female rats (Prigge 1978a). NOAELs have been reported for intermediate exposures to cadmium chloride at 0.394 mg Cd/m^3 for female nonpregnant rats (Prigge 1978a), 0.33 mg Cd/m^3 for rats (Kutzman et al. 1986), and 0.0508 mg Cd/m^3 for male rats (Takenaka et al. 1983). NOVELS have been reported for intermediate exposures to cadmium oxide dust at 0.16 mg Cd/m^3 for female rats (Baranski and Sitarek 1987) and 0.45 mg Cd/m^3 for male rabbits (Grose et al. 1987); and for cadmium sulfide at 1.034 mg Cd/m^3 for male rats (Glaser et al. 1986). A NOAEL for chronic exposure in rats to cadmium sulfate has been reported as 0.95 mg Cd/m^3 (Oldiges and Glaser 1986).

Other Systemic Effects. Yellow discoloration of the teeth has occasionally been reported in workers occupationally exposed to high levels of cadmium (Friberg 1950; Liu et al. 1985). No data were located to indicate that this was related to any functional impairment.

2.2.1.3 Immunological and Lymphoreticular Effects

There is limited evidence for immunological effects following inhalation exposure to cadmium. The blood of workers exposed to cadmium for 1-14 years had a slight but statistically significant decrease in the generation of reactive oxygen species by leukocytes compared to unexposed controls (Guillard and Lauwerys 1989). The toxicological significance of this effect is unclear.

Karakaya et al. (1994) measured blood and urine concentrations of cadmium, and serum IgG, IgM, and IgA in a group of 37 males employed in zinc/cadmium smelters and a small Cd-electroplating plant. Blood cadmium concentrations were significantly higher in exposed workers compared to controls in both the urine (2.39 versus 0.69 μg/l00 mL, $p<0.001$) and the blood (5.55 versus 2.01 μg/g creatinine, $p<0.05$). No differences between the exposed and control serum concentrations of IgG, IgM, and IgA populations were observed. No changes in blood counts of white blood cells (lymphocyte, neutrophil, and eosinophil) were found between exposed and control populations, except for significantly increased monocyte counts.

No other studies were located regarding immunological effects in humans following inhalation exposure to cadmium.

Acute inhalation exposure to cadmium chloride in mice at 0.190 mg Cd/m^3 for 2 hours can affect immune function, causing suppression of the primary humoral immune response (Graham et al. 1978). The NOAEL for immunological effects from the study by Graham et al. (1978) was 0.11 mg Cd/m^3. Krzytyniak et al. (1987) reported spleen lymphocyte cytotoxicity at 0.88 mg Cd/m^3 for 1 hour.

At intermediate-duration exposures, Kutzman et al. (1986) observed increased spleen relative weights and lymphoid hyperplasia from inhalation of cadmium chloride aerosols at 1.06 mg Cd/m^3 6 hours a day, 5 days a week, for 62 days. Prigge (1978b) also observed increased relative spleen weights in pregnant females at 0.394 mg Cd/m^3 for an exposure of 24 hours a day, for 21 days during gestation. Oldiges and Glaser (1986) observed enlarged thoracic lymph nodes in dead animals in a chronic-exposure study with cadmium sulfate at 0.092 mg Cd/m^3 for 22 hours a day, 7 days a week, for 413-455 days; and in an intermediate study with cadmium oxide dust at 0.090 mg Cd/m^3 for 22 hours a day, 7 days a week, for 218 days. However, other studies have found no effect on natural killer cell activity or viral induction of interferon in mice (Daniels et al. 1987). Evidence concerning the effect of inhalation exposure to cadmium on resistance to infection is conflicting, because the same exposure decreases resistance to bacterial infection while increasing resistance to viral infection (Bouley et al. 1982). Representative NOAELs and LOAELs for immunological effects are shown in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Neurotoxicity is not generally associated with inhalation exposure to cadmium, although a few studies have specifically looked for neurological effects. Hart et al. (1989b) reported that in a group of 31 men occupationally exposed to cadmium in a refrigerator coil manufacturing plant (average exposure=14.5 years) there was a modest correlation between cadmium exposure and decreased performance on neuropsychologic tests for attention, psychomotor speed, and memory. The limited number of men studied makes it difficult to evaluate the significance of this effect.

Ijomah et al. (1993) studied an increased prevalence of dementia in elderly people living near an aluminum smelter. Dementia was defined by performance on the Anomalous Sentences Repetition Test (ASRT). Participants were selected among the patients from the general practitioners of the smelter area and the

control area. The study involved two short cognitive tests: a Delayed Recall test and an ASRT. There was no difference in the prevalence of dementia between the smelter group (25 of 168=14.9%) and the reference group (20 of 120=16.7%). There were significant elevations of plasma and red blood cell aluminum and cadmium concentrations. There were also differences in the phospholipid fatty acids of the exposed population (decreased red cell oleic acid and increased linoleic acid), that correlated with the increased aluminum and cadmium red blood cell concentrations.

Rose et al. (1992) studied the presence and severity of olfactory impairment in workers chronically exposed to cadmium fumes generated during a brazing operation. Detailed occupational history, medical history, and smoking history, and symptoms were collected for 55 workers. Body burden was estimated using urinary cadmium levels, and renal damage was assessed by urinary β_2-microglobulin levels. Olfactory test scores from these workers were compared to a reference group of 16 male subjects that were selected according to the following criteria:1) no history of taste or smell complaints, 2) no history of surgery to the upper respiratory tract, 3) no upper respiratory tract infection within 2 days of testing, and 4) no history of having been tested. The dose of the CdO fume received by the workers being evaluated in this study was not reported or estimated. For both the exposed workers and the reference group, 38% were smokers. A significant olfactory impairment was observed in the workers compared to the reference group ($p<0.003$). Thirteen percent of the workers were either moderately or severely hyposmic compared to none in the reference group, 44% of the workers were mildly hyposmic compared to 31% of the reference group, and only 44% of workers were normosmic. Although the odor-identification test findings for workers were similar to those of the reference group, butanol detection threshold scores were significantly lower in the worker population ($p<0.005$). The workers with both higher urinary cadmium levels and tubular proteinuria had the most significant olfactory dysfunction, with a selective defect in odor threshold. The results suggest that chronic occupational cadmium exposure sufficient to cause renal damage is also associated with impairment in olfactory function. Some limitations of the study are that historical exposure to other confounders cannot be ruled out, the classification for nephrotoxicity is based on a single 24-hour urine β_2-microglobulin level, and the smoking history of the reference group was unknown. No other human neurological studies from inhaled cadmium were found.

In rats, cadmium carbonate produced tremors from exposure to 132 mg Cd/m^3 for 2 hours, and cadmium fumes produced reduced activity at 112 mg Cd/m^3 for 2 hours (Rusch et al. 1986). Studies on continuous exposure to cadmium for 30 days have shown no neurological effects at 0.105 mg Cd/m^3 for cadmium chloride, 0.098 mg Cd/m^3 for cadmium dusts, or 1.034 mg Cd/m^3 for cadmium sulfide (Glaser et al. 1986).

Cadmium chloride had no neurological effects at 0.33 mg Cd/m^3 for 5 days a week, 6 hours a day, for a total of 62 daily exposures, but did significantly increase relative brain weight at 1.034 mg Cd/m^3 (Kutzman et al. 1986). No other studies were located regarding neurological effects in adult animals after inhalation exposure to cadmium. Neurological effects in offspring of rats exposed to cadmium by inhalation during gestation are discussed in Section 2.2.1.5. NOAELs and LOAELs from the above studies are listed in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

Evidence is insufficient to determine an association between inhalation exposure to cadmium and reproductive effects.

Gennart et al. (1992) studied male reproductive effects of cadmium in 83 occupationally exposed bluecollar Belgian workers in 2 smelting operations. The workers were exposed to cadmium in dust and fumes. Information was recorded on age, residence, education, occupational and health history, actual and previous occupations, smoking habits, and coffee and alcohol consumption. Fertility parameters included dates of birth of wife and husband, date of marriage, and the number of children born alive and their dates of birth. Blood and urine samples were also collected from each worker. Some cadmium workers had been excessively exposed; 25% of them already had signs of kidney dysfunction as evidenced by microproteinuria and/or a serum creatinine level above 13 mg/L. No effects were observed on male fertility as evidenced by no significant influence of cadmium on the probability of a live birth. The limitation of this study, as described by the authors, included the fact that the wives were not interviewed and, therefore, factors that could have influenced their reproductive ability were not considered.

Men occupationally exposed to cadmium at levels causing renal damage had no change in testicular endocrine function, as measured by serum levels of testosterone, luteinizing hormone, and follicle stimulating hormone (Mason 1990). Noack-Fuller et al. (1992) measured concentrations of cadmium, lead, selenium, and zinc in whole semen and seminal fluid of 22 unexposed men (13 were smokers) to evaluate intra-individual variability and to examine the statistical association between element concentrations and semen characteristics and sperm motion parameters. None of the men had any known occupational exposure to cadmium.

Concentrations of cadmium were similar in semen and seminal plasma (0.40±0.23 and 0.34±0.19 μg/L, respectively). Sperm motility ($p<0.02$), linear velocity ($p<0.001$), and curvilinear velocity (CV) ($p<0.002$) were significantly correlated with semen cadmium levels. Intra-individual coefficients of variation for sperm count (CV=46±4%) and sperm concentration (CV=37±6%) showed the highest variability. No positive correlation was found between cadmium concentration in semen and sperm density. The smokers had slightly elevated levels of cadmium. The concentrations of cadmium in semen of these volunteers was very low. Additional studies are needed (preferably with larger sample sizes) to evaluate the robustness of this association between cadmium (at the low levels detected) and sperm motion parameters. Saaranen et al. (1989) measured cadmium, selenium, and zinc in seminal fluid and serum in 64 men, half of whom were smokers. Smokers had significantly higher serum cadmium concentration than nonsmokers. Seminal fluid cadmium was also elevated in smokers, and was higher than serum cadmium in smokers consuming more than 20 cigarettes daily. Semen quality was measured for volume, sperm density, morphology, motility, and number of immature germ cells. No differences were found in semen quality or fertility between smokers and nonsmokers. There was no significant correlation between seminal fluid cadmium levels and semen quality or fertility.

Xu et al. (1993a) measured trace elements in blood and seminal plasma and their relationship to sperm quality in 221 Singapore men (age range 24-54; mean 34.8) who were undergoing initial screening for infertility. Men with significant past medical history and those who had been occupationally exposed were excluded. Parameters monitored included semen volume and sperm density, motility, morphology, and viability. Graphite furnace atomic absorption was used to determine cadmium concentration in blood and semen. No differences were observed in sperm quality (density, motility, morphology, volume, and viability) of the 221 men compared to a cohort of 38 fertility proven men (wives had recently conceived). Cadmium levels in blood did have a significant inverse relationship with sperm density ($r=-0.15$, $p<0.05$) in oligospermic men (sperm density below 20 million/ml), but not in normospermic men. There was a significant reduction in sperm count in men with blood cadmium of >1.5 μg/L. Also, there was a weak negative correlation between defective sperm and concentration of cadmium in semen ($r=-0.21$, $p<0.05$). The volume of semen was inversely proportional to the cadmium concentration in semen ($r=-0.29$, $p<0.05$). These findings suggest that cadmium may have an effect on the male reproductive system. Limitations of the study include lack of control for potential confounding factors such as the lower levels of zinc in seminal plasma, and the validity of using infertile men as the study group (i.e., again because of confounding factors that may be affecting both cadmium levels and sperm levels).

A post-mortem study of men occupationally exposed to cadmium who died from emphysema found high levels of cadmium in their testes, but no histologic lesions other than those attributable to terminal illness (Smith et al. 1960)

Russian women occupationally exposed to cadmium concentrations up to 35 mg/m^3 had no irregularities in their menstrual cycles (Tsvetkova 1970). Fertility and other indices of reproductive function were not measured. No studies were located that showed reproductive effects in women following inhalation exposure to cadmium.

In rats, exposure to cadmium oxide dusts at 1 mg Cd/m^3 for 5 hours a day, 5 days a week, for 20 weeks, increased the duration of the estrous cycle (Baranski and Sitarek 1987). Male and female rats exposed to cadmium concentrations of 1 mg/m^3 for 6 hours a day, 5 days a week, for 62 days and subsequently mated with unexposed controls showed no loss in reproductive success measured by viable embryos and preimplantation losses, but males did have an increased relative testes weight (Kutzman et al. 1986). Tsvetkova (1970) studied rats exposed to cadmium sulfate aerosols at 2.8 mg Cd/m^3 before and during pregnancy. A lengthening of the estrous cycle was observed 2 months after the start of exposure in onehalf of the exposed animals. By the fourth month, diestrus was 6.2 days in the exposed group compared to 1.2 days in controls. No other studies were found on reproductive effects in animals. NOAELs and LOAELs from the above studies are listed in Table 2-1 and plotted in Figure 2-l.

2.2.1.6 Developmental Effects

Russian women occupationally exposed to cadmium at concentrations ranging from 0.02 to 35 mg/m^3 had offspring with decreased birth weights compared to unexposed controls, but without congenital malformations (Tsvetkova 1970). No association was found between birth weights of offspring and length of maternal cadmium exposure. Moreover, no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight (Tsvetkova 1970). A nonsignificant decrease in birth weight was found in offspring of women with some occupational exposure to cadmium in France; however, no adverse effects were documented in these newborns (Hue1 et al. 1984). Hue1 et al. (1984) used hair samples to estimate exposure, and this method is limited without controls to distinguish between exogenous and endogenous sources. No other studies were located regarding developmental effects in humans after inhalation exposure to cadmium.

Developmental toxicity in offspring of female rats exposed to cadmium oxide at 0.02 mg Cd/m^3 for 5 hours a day, 5 days a week, for 4-5 months prior to mating and during the first 20 days of gestation was manifest by delayed ossification, decreased locomotor activity, and impaired reflexes in offspring (Baranski 1985). Decreases in weight gain, osteogenesis, and viability were also noted at concentrations of 0.16 mg/m^3 (Baranski 1985). Maternal weight gain and fetal weight were reduced in pregnant rats exposed to cadmium chloride aerosols during gestation at concentrations of 0.204, 0.394, or 0.581 mg/m^3 (Prigge 1978b). The decrease in fetal weight was statistically significant only at 0.581 mg/m^3 (Prigge 1978b). LOAELs from these studies are listed in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

Examination of lymphocytes from workers occupationally exposed to both cadmium and. lead have shown statistically significant increases in chromosomal aberrations (Bauchinger et al. 1976; Deknudt and Leonard 1975; Deknudt et al. 1973), but not in men exposed primarily to cadmium (Bui et al. 1975; O'Riordan et al. 1978).

No studies were located regarding genotoxic effects in animals after inhalation exposure to cadmium. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

The relationship between occupational exposure to cadmium and increased risk of cancer (particularly lung and prostate cancer) has been explored in a number of epidemiologic studies. The data and some of the analyses for lung cancer are conflicting, and controls for confounding factors such as co-exposure with other metal carcinogens and smoking have occurred in only a few of the studies. Overall, the results provide little evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium. Initial studies indicated an elevation in prostate cancer among men occupationally exposed to cadmium (Kipling and Waterhouse 1967; Kjellstrom et al. 1979; Lemen et al. 1976), but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant (Elinder et al. 1985c; Kazantzis et al. 1988; Sorahan 1987; Thun et al. 1985). Based on an analysis of the mortality data from a 5-year update of the cohort from 17 plants in England and a review of

the other epidemiological evidence, Kazantzis et al. (1992) concluded that cadmium does not appear to act as a prostatic carcinogen.

Evaluations of occupationally exposed cohorts in countries other than the United States have found some increases in lung cancer, but no clear relationship between level and duration of cadmium exposure and increased risk of lung cancer. Cigarette smoking was also a confounding factor. These cohorts came from an English zinc-lead-cadmium smelter (Ades and Kazantzis 1988), from 17 different manufacturing or processing facilities involving cadmium in England (Kazantzis et al. 1988), from a nickel-cadmium battery plant in Sweden (Elinder et al. 1985c), and from a nickel-cadmium battery plant in England (Sorahan 1987). The most recent report comes from Sorahan et al. (1995) on mortality rates (lung cancer and nonmalignant respiratory diseases) in 347 copper cadmium alloy workers in the United Kingdom. The authors state that the study results are consistent with the hypothesis that exposure to cadmium oxide fumes increases the risk of mortality from chronic non-malignant diseases of the respiratory system, but do not support the hypothesis that exposure increases the risks of mortality for lung cancer.

An increased risk of lung cancer from cadmium exposure was reported in studies on the only U.S. cohort (workers in a cadmium recovery plant in Globe, Colorado) (Thun et al. 1985; Stayner et al. 1992), but subsequent studies have attributed the increase to either arsenic exposure and/or smoking (Lamm et al. 1992, 1994; Sorahan et al. 1997). These studies and the conflicting results are discussed in detail below.

A statistically significant, 2-8-fold excess risk of lung cancer was reported in the highest exposure group (cumulative exposures >8 years x mg/m^3), and the dose-response trend over the three exposure groups was highly significant (Thun et al. 1985). Confounding factors included possible exposure to the heavy metals, arsenic (Thun et al. 1989; Kazantzis et al. 1992) and nickel (Sorahan 1987), which are known human lung carcinogens. The data in the U.S. cohort supported an analysis that controlled for the effects of smoking.

Stayner et al. (1992) used data from a retrospective study on lung cancer mortality in the United States to further evaluate the lung cancer risk associated with cadmium exposure in the U.S. cohort. The analysis controlled for smoking and for ethnicity (i.e., Hispanic and non-Hispanic workers). Lung cancer mortality rates are lower for Hispanics compared to non-Hispanics. The cohort included 606 male Hispanic and non--Hispanic workers with 16,898 person-years of combined work history. Medical records were use to examine death rates and occurrences of lung cancer which were then compared with length of exposure and exposure dose of cadmium. Vital status was successfully determined for approximately 98% of this

of cadmium. Vital status was successfully determined for approximately 98% of this cohort. A total of 162 deaths were identified, including eight additional lung cancers through December 31, 1984, that were not included in the Thun et al. (1985) analysis. Workers were sorted into 4 groups by cumulative exposure (<584, 585-1,460, 1,461-2,920, and >2,921 mg-days/m^3) and by number of years since the first exposure (<10, 10-19, >20 years). The findings were analyzed using a modified life-table analysis to estimate standardized mortality ratios (SMR), and various functional forms (i.e., exponential, power, additive relative rate, and linear) of the Poisson and Cox proportional hazards models to examine the dose-response relationship. Estimates of working lifetime risks (45 years) were developed using an approach that corrects for competing causes of death. The mortality rate for white U.S. males was used in this analysis as the referent rate for both the Hispanic and non-Hispanic workers. Lung cancer mortality was significantly elevated among non-Hispanics and less than expected among Hispanics (as would be predicted from the use of the white male referent rate). The lung cancer SMR increased with cumulative cadmium exposure and was nearly significant for the entire cohort (SMR=149, 95% CI=95, 222; p=0.076, two-tails). The SMR was significantly elevated in the highest exposure group (>2,921 mg-days/m^3) for the combined cohort (SMR=272,95% CI=123,513), and for the three highest exposure groups for the non-Hispanic groups. A significant excess of lung cancer mortality was also observed among workers in the longest time-since-firstexposure category (>20 years) for the combined cohort (SMR=161, 95 % CI= 100, 248) and for non-Hispanics (SMR=233, 95% CI=141, 365). A statistically significant dose-response relationship was evident in nearly all of the regression models evaluated. Based on this analysis, the lifetime excess of lung cancer at the previous OSHA standard for cadmium fume of 100 μg/m^3 would be approximately 50-l 1 lung cancer deaths per 1,000 workers exposed to cadmium for a working lifetime (45 years). At the current OSHA standard of 5 μg/m^3 (OSHA 1992), the lifetime risk of lung cancer was predicted to be approximately 2.6-6 lung cancer deaths per 1,000 workers exposed to cadmium for 45 years (Stayner et al. 1992).

Stayner et al. (1992) also performed an indirect assessment of confounding effects of exposure to arsenic. No direct arsenic exposure data were available, so an indirect assessment consisted of a comparison of SMRs for populations employed before and after 1940, a date prior to which arsenic exposure was reportedly high (i.e., the plant was an arsenic smelter prior to 1926). The authors propose that the levels of arsenic declined substantially after 1940. Among non-Hispanics hired before 1940, a clear dose-response trend was evident, and a significantly elevated SMR (SMR=381, 95% CI=l00248) was observed within the highest exposure group (>2,921 mg-days/m^3). For those non-Hispanic individuals hired during or after 1940, a significantly elevated SMR was observed among workers in the 585-1,460 mg-days/m^3

(SMR=281) and 1,461-2,920 mg-days/m^3 (SMR=470) exposure groups. This analysis indicates that there was no significant effect on lung cancer mortality from cumulative cadmium exposure because of year of hire; in fact, the authors report that their dose-response analysis demonstrated a greater dose-response relationship for workers hired after 1939.

Lamm et al. (1992, 1994) used nearly the same data set for the U.S. cohort as Stayner et al. (1992) in a nested case-control analysis that used the period of hire as a surrogate for arsenic exposure. Based on this analysis as a means to control for the confounding factor of arsenic exposure, Lamm et al. (1992, 1994) reported no residual association of lung cancer with cadmium in the Globe, Colorado, cohort. They also reported that cases were more than eight times more likely to have been cigarette smokers than were controls. Lamm et al. (1992, 1994) conclude that arsenic exposure and cigarette smoking were the major determinants of lung cancer risk, not cadmium exposure.

The reasons for these conflicting conclusions based on the same cohort data are unclear. Doll (1992) suggested some possible reasons including: (1) that the total number of cases was small (n=25) and that only 21 of these cases were included in both studies (i.e., each study included some cases that were not included in the other study); (2) that Stayner et al. (1992) used national rather than regional mortality rates; (3) that the Lamm et al. (1992, 1994) control series was overmatched, although the matching by date of hire was necessary to control for arsenic exposure; and (4) that there are some concerns about the validity (i.e., biologica1 relevance) of the dose-response-models used by Stayner et al. (1992). In a response to Doll (1992), Stayner et al. (1993) reported that use of regional mortality rates would increase rather than decrease support for their conclusion, and that the nested case-control analysis of Lamm et al. (1992) used overmatched controls. Stayner et al. (1993) provided additional analyses including the use of the Arrnitage-Doll multistage model to support the conclusion of an increased risk of cancer from cadmium exposure.

Sorahan and Lancashire (1994) subsequently raised concerns about inconsistencies and inaccuracies in the NIOSH job history data used in these studies on the U.S. cohort. Sorahan and Lancashire (1997) then conducted further analyses, based on detailed job histories extracted from time sheet records, to better resolve the potential confounding affects of arsenic. Poisson regression was used to investigate risks of mortality from lung cancer in relation to four concentrations of accumulative exposure to cadmium (<400, 400-999, 1000-1999, and >2000 mg-days/m^3). After adjustment for age attained, year of hire, and Hispanic ethnicity; Sorahan and Lancashire (1997) report a significant positive trend ($p<0.05$) between

cumulative exposure to cadmium and risks of mortality from lung cancer. However, when the exposure to cadmium was evaluated with or without concurrent exposure to arsenic, a significant trend for lung cancer was only found for exposure to cadmium received in the presence of arsenic trioxide. Since there were only 21 deaths from lung cancer, Sorahan and Lancashire (1997) state that it is impossible to determine which of the following three hypotheses is the correct one: (1) cadmium oxide in the presence of arsenic trioxide is a human lung carcinogen, (2) cadmium oxide and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulphide are not (i.e., cadmium sulphate and cadmium sulphide were the main cadmium compounds of exposure when arsenic was not present), or (3) arsenic trioxide is a human carcinogen and the three cadmium compounds are not carcinogenic.

Studies in rats provide strong evidence of the lung carcinogenic potential of chronically inhaled cadmium. Oldiges et al. (1989) reported a clear dose response increase in lung tumors in male and female rats from an 18-month continuous exposure to either cadmium chloride, cadmium oxide dusts, cadmium oxide fume, cadmium sulfate, or cadmium sulfide. In the cadmium chloride study at 30 $\mu g/m^3$, the observation period in the males had to be shortened to 30 months (rather than 31) because of mortality in excess of 75%. No lung tumors were observed in control rats after 31 months of observation. A high incidence of nodules and tumors was seen in 30 $\mu g/m^3$ exposures to $CdCl_2$ in both males and females. Results showed lung nodules in 18 of 20 males and 15 of 18 females and primary lung tumors in 15 of 20 males and 13 of 18 females. Tumor incidence as bronchioalveolar adenomas, adenocarcinomas, squamous cell carcinomas, or combined were 2, 12, 0, and 1 for males; and 4, 7, 0, and 2 for females, respectively. Increased lung tumors in males and females were also observed with chronic exposures to cadmium oxide dust or fume at 30 $\mu g/m^3$, to cadmium sulfate at 90 $\mu g/m^3$, and to cadmium sulfide at 90 $\mu g/m^3$ (Oldiges et al. 1989). Cadmium sulfate produced by photolysis of cadmium sulfide under the experimental conditions may have contributed to some of the response observed with cadmium sulfide (Konig et al. 1992).

Takenaka et al. (1983) also demonstrated cadmium carcinogenicity in male rats exposed to cadmium chloride aerosols at 0.0134, 0.0257, and 0.0508 mg Cd/m^3 for 18 months. The exposure produced a dose related increase in lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas starting at 20 months. No other type of tumor was observed to increase with increasing dose.

In a protocol similar to the studies by Oldiges et al. (1989), Heinrich et al. (1989) did not observe an increase in lung tumors in male or female Syrian golden hamsters from chronic inhalation exposure to either CdO dust or fumes, $CdCl_2$, $CdSO_4$, or CdS. In female mice, lung tumor incidence increased at all

dose levels, but incidence in the controls was also high, and the cadmium-induced increases were not statistically significant. Lung tumors in the cadmium-treated mice also did not increase in a dose responsive manner except for a weak increase from exposure to the cadmium oxide fumes (Heinrich et al. 1989).

The Environmental Protection Agency (EPA) has classified cadmium as a probable human carcinogen by inhalation (Group Bl), based on limited evidence of an increase in lung cancer in humans (Thun et al. 1985) and sufficient evidence of lung cancer in rats (IRIS 1996; Takenaka et al. 1983). EPA has calculated an inhalation unit risk (the risk corresponding to lifetime exposure to 1 $\mu g/m^3$) of $1.8x10^{-3}$ (IRIS 1996). A range of concentrations that correspond to upper bound lifetime excess risks of 10^{-4} to 10^{-7} is shown in Figure 2-1. The National Toxicology Program (NTP) has classified cadmium and certain cadmium compounds as substances that are reasonably anticipated to be carcinogens, based on limited evidence for carcinogenicity from studies in humans and sufficient evidence for carcinogenicity in humans (NTP 1994). In contrast, the International Agency for Research for Research on Cancer (IARC) has classified cadmium as carcinogenic to humans (Group l), based on sufficient evidence for carcinogenicity in both human and animal studies (IARC 1993). The differences in conclusions about the adequacy of the human carcinogenicity data are further discussed in Section 2.5, Relevance to Public Health.

2.2.2 Oral Exposure

Information on health effects of oral exposure to cadmium in humans is derived mainly from studies of residents living in cadmium-polluted areas. Cadmium exposure in these populations is often estimated by blood or urinary cadmium levels (see Section 2.7.1). Exposure in these cases occurs primarily through the diet, but smokers in these cohorts are also exposed to cadmium by inhalation. Smoking, however, is treated as a confounding variable, not as an exposure route because of the large number of toxic compounds (in addition to cadmium) present in cigarette smoke, and because the primary concern is effects attributable to cadmium. Cadmium is more readily found in the free ionic form in water; while in food, the cadmium ion generally exists in a complex with a variety of ligands, including proteins such as metallothionein (Crews et al. 1989; Groten et al. 1990; Nordberg et al. 1986). Experimental studies in animals have generally used soluble salts of cadmium (such as cadmium chloride) for food, drinking water, and gavage exposures. The toxicological properties of the cadmium ion do not appear to depend on the counter ion, although absorption may be significantly affected by protein complexes (see Section 2.3.1.2).

2.2.2.1 Death

Intentional ingestion of cadmium has been used as a means of suicide, causing death due to massive fluid loss, edema, and widespread organ destruction (Buckler et al. 1985; Wisniewska-Knypl et al. 1971). The doses ingested in two known fatal cases were estimated to be 25 mg Cd/kg from cadmium iodide (Wisniewska-Knypl et al. 1971) and 1,840 mg Cd/kg from cadmium chloride (Buckler et al. 1986). Time to death after cadmium iodide ingestion was 7 days (Wisniewska-Knypl et al. 1971) and 33 hours after ingestion of the cadmium chloride (Buckler et al. 1986).

In rats and mice, acute oral LD_{50} (lethal dose, 50% kill) values for cadmium range from about 100 to 300 mg/kg (Baer and Benson 1987; Basinger et al. 1988; Kostial et al. 1978; Kotsonis and Klaassen 1978; Shimizu and Morita 1990). The lowest dose causing death (2 of 20 animals) was 15.3 mg/kg in Sprague-Dawley rats (Borzelleca et al. 1989). Very young animals have lower LD_{50} values than adult animals (Kostial et al. 1978, 1989a); this effect may be related to the greater fractional absorption of ingested cadmium in the immature organism (see Section 2.3.1.2).

Deaths related to cadmium exposure have been reported in only two of the intermediate exposure studies found. In a study in Wistar rats exposed to cadmium chloride by gavage at 40 mg Cd/kg daily, 5 days a week, for up to 14 weeks; 4 of 13 female Wistar rats died by 8 weeks (Baranski and Sitarek 1987). In mice, Blakley (1986) studied the effect of cadmium on chemical- and viral-induced tumor production. Female albino Swiss mice (8 weeks old, N=41) were administered $CdCl_2$ in the drinking water for 280 days at doses of 0, 5, 10, or 50 ppm. These mice have a high incidence of spontaneous lymphocytic leukemia of thymic origin. A significant 33% increase ($p=0.0228$, chi-square analysis) in deaths from virally induced leukemia was observed from exposure to 1.9 or 9.5 mg Cd/kg/day. The deaths were attributed to cadmium-impaired immunosurveillance mechanisms that control expression of the murine lymphocytic leukemia virus.

Representative LOAEL values for lethality after acute oral exposure to cadmium are recorded in Table 2-2 and plotted in Figure 2-2.

Table 2-2. Levels of Significant Exposure to Cadmium - 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	Human	once (IN)				1840 F (fatal human dose within 1-2 days)	Buckler et al. 1986 $CdCl_2$
2	Human	once (IN)				25 M (fatal human dose within 7 days)	Wisniewska-Knypl et al. 1971 CdI2
3	Rat (Sprague-Dawley)	10 d 1 x/d (GW)				15.3 (2/10 males, 1/10 females died)	Borzelleca et al. 1989 $CdCl_2$
4	Rat (Sprague-Dawley)	once (GW)				15.3 (1/10 males, 1/10 females died)	Borzelleca et al. 1989 $CdCl_2$
5	Rat (NS)	once (G)				29 (LD_{50} at 8 days; 2 wk old)	Kostial et al. 1978 $CdCl_2$
						129 F (LD_{50} at 8 days; 6 wk old)	
						104 F (LD_{50} at 8 days; 18 wk old)	
6	Rat (Sprague-Dawley)	once (GW)				225 M (LD_{50} at 14 days)	Kotsonis and Klaassen 1977 $CdCl_2$
7	Rat (Sprague-Dawley)	2 wk (W)				42 M (7/9 died within 2 weeks)	Kotsonis and Klaassen 1978 $CdCl_2$
8	Rat (Sprague-Dawley)	once (GW)				327 M (LD_{50} at 24 hours; fed rats)	Shimizu and Morita 1990 $CdCl_2$
						107 M (LD_{50} at 24 hours; fasted rats)	

Table 2-2. Levels of Significant Exposure to Cadmium - 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
9	Mouse (CBA/Bom)	once (GW)				30.4 M (2/54 died within 10 days)	Andersen et al. 1988 $CdCl_2$
10	Mouse (Swiss-Webster)	once (GW)				95.5 M (LD_{50} at 96 hours)	Baer and Benson 1987 $CdCl_2$
11	Mouse (ICR)	once (GW)				112 M (5/10 died within 8 days)	Basinger et al. 1988 $CdCl_2$
	Systemic						
12	Human	once (IN)	Cardio			25 M (rhythmic disturbance, ventricular fibrillation)	Wisniewska-Knypl et al. 1971 $CdCl_2$
			Gastro			25 M (hemorrhagic gastroenteritis)	
			Renal			25 M (hypoalbuminemia, anuria)	
			Metab		25M (metabolic acidosis, hyperthermia)		
13	Rat (Wistar)	10 d Gd 7-16 once (GW)	Bd Wt	2 F	12 F (14% decreased maternal body weight)		Baranski 1985 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
14	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Hemato	31.3 M	65.6 M (increased hemoglobin, hematocrit, erythrocytes)		Borzelleca et al. 1989 $CdCl_2$
				138 F			
			Hepatic	65.6 M		138 M (focal necrosis of hepatocytes)	
			Renal			15.3 (focal necrosis of tubular epithelium)	
			Bd Wt		15.3 M (18% decreased body weight)	31.3 M (23% decreased body weight)	
				31.3 F	65.6 F (18% decreased body weight)		
15	Rat (Sprague-Dawley)	10 d (W)	Hepatic	13.9			Borzelleca et al. 1989 $CdCl_2$
			Renal	13.9			
			Bd Wt	13.9			
				1.1 M	7.8 M (14% decreased body weight)	11.2 M (25% decreased body weight)	
16	Rat (Sprague-Dawley)	once (GW)	Cardio	150 M			Kotsonis and Klaassen 1977 $CdCl_2$
			Hemato	150 M			
			Hepatic	150 M			
			Renal		25 M (50% decrease in urine flow for first 2 days)		
			Bd Wt	100	150 M (initial 12% decreased body weight)		

Table 2-2. Levels of Significant Exposure to Cadmium - 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
17	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (GW)	Gastro	6.13 F		61.32 F (intestinal necrosis, hemorrhage, ulcers)	Machemer and Lorke 1981 $CdCl_2$
			Bd Wt	1.84 F	6.13 F (transient 27% decrease in body weight gain during treatment)	18.39 F (persistent 50% decrease in maternal body weight gain)	
18	Rat (Long- Evans)	10 d Gd 6-15 (F)	Gastro	12.5 F			Machemer and Lorke 1981 $CdCl_2$
			Bd Wt	3.5 F	12.5 F (transient 19% decrease in maternal body weight gain during treatment)		
19	Rat (Wistar)	12 d (W)	Hemato			12 M (anemia)	Sakata et al. 1988 $CdCl_2$
20	Rat (Sprague-Dawley)	once (GW)	Hepatic		75M (focal degeneration and necrosis of parenchymal cells)		Shimizu and Morita 1990 $CdCl_2$
21	Mouse (CBA/Bom)	once (GW)	Gastro	15.7 M	30.4 M (gastritis and enteritis)	88.8 M (severe gastric necrosis)	Andersen et al. 1988 $CdCl_2$
			Hepatic	15.7 M	30.4 M (fatty infiltration of liver cells, occasional hepatocellular necrosis)		
			Renal	59.6		88.8 M (tubular necrosis and casts)	
22	Mouse (ICR)	once (GW)	Gastro			112 M (glandular stomach epithelial necrosis)	Basinger et al. 1988 $CdCl_2$
			Hepatic			112 M (extensive hepatocellular coagulative necrosis)	
			Renal	112 M			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
	Immunological/Lymphoreticular						
23	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		31.3 F 65.6 M	65.6 F (increased leukocyte counts)		Borzelleca et al. 1989 $CdCl_2$
	Neurological						
24	Rat (Sprague-Dawley)	once (GW)		25 M	50M (decreased motor activity)		Kotsonis and Klaassen 1977 $CdCl_2$
	Reproductive						
25	Rat (Wistar)	once (GW)		50 M		100 M (testicular necrosis)	Bomhard et al. 1987 $CdCl_2$
26	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		138 F		65.6 M (testicular atrophy and loss of spermatogenic elements)	Borzelleca et al. 1989 $CdCl_2$
27	Rat (Sprague-Dawley)	once (GW)		25 M			Dixon et al. 1976 $CdCl_2$
28	Rat (Sprague-Dawley)	once (GW)		50 M		100 M (testicular necrosis; decr. spermatogenesis; decr. # females producing pups)	Kotsonis and Klaassen 1977 $CdCl_2$
29	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (GW)		18.39 F		61.32 F (decreased percent fertilized and percent pregnant)	Machemer and Lorke 1981 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (F)		12.5 F			Machemer and Lorke 1981 $CdCl_2$
31	Mouse (CBM/ Bom)	once (GW)		30.3 M		59.6 M (testicular necrosis)	Andersen et al. 1988 $CdCl_2$
	Developmental						
32	Rat (Wistar)	10 d Gd 7-16 once (GW)			2 F (delayed ossification of the sternum and ribs)	40 (fused lower limbs, absent limbs, decreased number of live fetuses, increased number of resorptions)	Baranski 1985 $CdCl_2$
33	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (GW)		6.13		18.39 (malformations including dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis)	Machemer and Lorke 1981 $CdCl_2$
34	Rat (Long- Evans)	10 d Gd 6-15 (F)		12.5			Machemer and Lorke 1981 $CdCl_2$
	INTERMEDIATE EXPOSURE						
	Death						
35	Rat (Wistar)	14 wk 5 d/wk (GW)				40 F (4/13 died by week 8; 7/13 by week 14)	Baranski and Sitarek 1987 $CdCl_2$
36	Mouse (Swiss)	280 d (W)				1.9 F (24/41 died by 280 days)	Blakley 1986 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
	Systemic								
37	Monkey (Rhesus)	10 wk (F)	Bd Wt	5 M					Chopra et al. 1984 $CdCl_2$
38	Rat (Wistar)	21 d Gd 1-20 (W)	Bd Wt		9.6	(37% decreased maternal weight gain)			Baranski 1987 $CdCl_2$
			Other		9.6	(decreased water [18%] and food [30%] intake)			
39	Rat (Wistar)	14 wk 5 d/wk (GW)	Bd Wt	4 F			40 F	(29% decreased maternal body weight)	Baranski and Sitarek 1987 $CdCl_2$
40	Rat (Sprague-Dawley)	2-10 mo (W)	Renal				30 F	(B_2-microglobulinuria)	Bernard et al. 1988a $CdCl_2$
41	Rat (Sprague-Dawley)	4 or 7 mo (W)	Renal				15.2 F	(albuminuria, transferrinuria, B_2-microglobulinuria)	Cardenas et al. 1992a $CdCl_2$
42	Rat (Sprague-Dawley)	190 d (W)	Cardio		1.4 M	(20% increase in diastolic blood pressure)			Carmignanti and Boscolo 1984 Cd acetate
			Bd Wt	2.8 M					

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
43	Rat (Sprague-Dawley)	12 wk (W)	Hepatic			8.58 (hepatic necrosis of central lobules)	Cha 1987 $CdCl_2$
			Renal			8.58 M (necrosis of proximal tubular epithelial cells and cloudy swelling)	
			Bd Wt		8.58 M (23% decreased in body weight gain; 9% total body weight decrease)		
44	Rat (Wistar)	170 d (W)	Bd Wt	56 F			Cifone et al. 1989a $CdCl_2$
45	Rat (Sprague-Dawley)	3 mo (W)	Hemato			2.0 (anemia)	Decker et al. 1958 $CdCl_2$
			Bd Wt		2.0 F (15% decreased body weight)	2.0 M (25% decreased body weight)	
46	Rat (Wistar)	4-60 wk (W)	Renal		1.18 (vesiculation of proximal tubules)		Gatta et al. 1989 $CdCl_2$
47	Rat (Wistar)	15 d 1 x/d (GW)	Hepatic		10M (increased lipid peroxidation)		Gill et al. 1989b $CdCl_2$
			Renal		10M (increased lipid peroxidation)		
			Bd Wt	10			
48	Rat	4 wk (F)	Hemato			2.5 M (anemia)	Groten et al. 1990 $CdCl_2$
			Hepatic		2.5 M (increased ALT and AST activities)		
			Renal	2.5 M			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
49	Rat (Wistar)	120 d (W)	Hemato			3.6 M (anemia)	Itokawa et al. 1974 $CdCl_2$
			Musc/skel			3.8 M (osteomalacia in Ca deficient animals)	
			Renal			3.6 M (tubular necrosis and casts, glomerular adhesions)	
50	Rat (Sprague-Dawley)	7 wk (F)	Cardio			2.5 M (congested myocardium, separation of muscle fibers)	Jamall et al. 1989 $CdCl_2$
			Renal	2.5 M			
			Bd Wt	2.5 M			
51	Rat (Wistar)	90 d (W)	Hemato			8 F (anemia)	Kawamura et al. 1978 $CdCl_2$
			Musc/skel			8 F (osteomalacia changes)	
			Renal			8 F (decreased renal clearance)	
			Endocr	8 F			
			Bd Wt		8 F (12% decreased body weight)		
52	Rat (Sprague-Dawley)	22 days Gd 0-21 (W)	Hemato		1.5 F (slight anemia)		Kelman et al. 1978 form not specified
			Musc/skel	3.8 F			
53	Rat (albino)	10 wk (W)	Bd Wt	4.8			Kostial et al. 1993 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
54	Rat (Sprague-Dawley)	24 wk (W)	Resp	8.0 M			Kotsonis and Klaassen 1978 $CdCl_2$
			Cardio	8.0 M			
			Gastro	8.0 M			
			Hemato	8.0 M			
			Musc/skel	8.0 M			
			Hepatic	8.0 M			
			Renal	1.2 M		3.1 M (proteinuria, slight focal tubular necrosis)	
			Endocr	8.0 M			
			Bd Wt	8.0 M			
55	Rat	1 or 2 mo (W)	Musc/skel			3.8 F (reduced bone accretion; osteoporosis in Ca deficient rats)	Larsson and Piscator 1971 form not specified
56	Rat (Wistar)	3 mo (F)	Cardio	3.0			Loeser and Lorke 1977a $CdCl_2$
			Hemato	3.0			
			Hepatic	3.0			
			Renal	3.0			
			Endocr	3.0			
			Bd Wt	3.0			
57	Rat (Sprague-Dawley)	6-16 wk (W)	Resp			2.4 (lung fibrosis)	Miller et al. 1974b $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
58	Rat (Sprague-Dawley)	6 wk 5 d/wk 1 x/d (GW)	Hepatic	0.25 M			Muller et al. 1988 Cd acetate
			Bd Wt	0.25 M			
59	Rat (NS)	4 wk (W)	Hemato			0.8 F (decreased hematocrit and hemoglobin)	Ogoshi et al. 1989 $CdCl_2$
			Musc/skel		0.8 F (decreased bone strength in young animals)		
			Bd Wt	0.8	1.6 F (10% decreased body weight gain)		
60	Rat (Long- Evans)	5 mo (W)	Cardio		0.0081 F (15 mmHg increase in systolic blood pressure)		Perry et al. 1989 $CdCl_2$
			Bd Wt	0.0081 F			
61	Rat (NS)	200 d (W)	Resp	0.6 M	1.2 M (reduced static compliance, lung lesions)		Petering et al. 1979 $CdCl_2$
62	Rat (Sprague-Dawley)	120 d (W)	Resp			3.62 M (emphysema)	Petering et al. 1979 $CdCl_2$
63	Rat (Sprague-Dawley)	111 d (90 d prior to Gd 1 through Gd 21) (W)	Hemato	5.23 F			Petering et al. 1979 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
64	Rat (Long- Evans)	14 wk (W)	Hepatic	5.8 M			Pleasants et al. 1992 $CdCl_2$
			Hemato		2.9 M (decreased neutrophils and monocytes, increased lymphocytes)		
			Musc/skel			2.9 M (osteoporosis)	
			Bd Wt	2.9 M	5.8 (21% increased relative kidney weight)		
			Bd Wt	2.9 M		5.8 M (22% decreased body weight gain)	
65	Rat (Long- Evans)	14 wk (W)	Hemato			11.6 M (decreased hematocrit and erythrocyte counts)	Pleasants et al. 1993 $CdCl_2$
			Hepatic	11.6 M			
			Renal		11.6 M (increased relative kidney weight)		
			Bd Wt			11.6 M (44% decreased body weight gain)	
66	Rat (Sprague-Dawley)	21-25 d Gd 1-Ld 1 (F)	Bd Wt			19.7 F (77-80% decreased maternal weight gain)	Pond and Walker 1975 $CdCl_2$
67	Rat (Wistar)	90 d (W)	Resp	16 F			Prigge 1978a $CdCl_2$
			Hemato		4 F (23% decreased serum iron, 21% decreased serum alkaline phosphatase)		
			Renal	4 F		8 F (35% increase in urine protein)	
			Bd Wt	8 F			

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
68	Rat (Wistar)	12, 26, 50, or 100 d (W)	Hemato			12 M (iron deficient anemia)	Sakata et al. 1988 $CdCl_2$
69	Rat (Sprague-Dawley)	2-6 wk 5 d/wk 1 x/d (G)	Bd Wt	0.250 M			Stacey et al. 1988a Cd acetate
70	Rat (Sprague-Dawley)	6 wk (W)	Bd Wt	0.4 M			Stacey et al. 1988a $CdCl_2$
71	Rat (ITRC)	15-60 d (F)	Hepatic		5M (reduced glycogen, increased G6PD and FDP)		Tewari et al. 1986b $CdCl_2$
			Renal		5M (reduced AST and ALT activity, increased G6PD and FDP activity)		
72	Rat (Sprague-Dawley)	7-12 mo (W)	Renal	13 F			Viau et al. 1984 $CdCl_2$
			Bd Wt	13 F			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
73	Rat (NS)	100 d (F)	Cardio		2.79 M (muscle hypertrophy, increased weight, some fibrous tissue)		Wilson et al. 1941 $CdCl_2$
			Hemato			2.79 M (severe anemia)	
			Hepatic		2.79 M (focal necrosis with some fibrous tissue)		
			Renal		2.79 M (slight tubular epithelial swelling and casts)		
			Endocr		2.79 M (pancreatic atrophy and pancreatitis)		
			Bd Wt		2.79 M (12% decreased body weight)	5.58 M (33% decreased body weight)	
74	Mouse (C57BL/6)	3-11 wk (W)	Bd Wt			12.5 M (63% decreased body weight gain)	Malave and de Ruffino 1984 $CdCl_2$
75	Mouse (B6C3F1)	16-46 wk (W)	Bd Wt			232 M (45% decreased body weight)	Waalkes et al. 1993 $CdCl_2$
76	Mouse (QS/CH)	Gd 1-19 (W)	Hemato	4.8 F		9.6 F (anemia)	Webster 1978 $CdCl_2$
			Bd Wt	4.8 F	9.6 F (14% decrease in maternal weight gain)		
77	Dog (Beagle)	3 mo (F)	Cardio	0.75			Loeser and Lorke 1977b $CdCl_2$
			Hemato	0.75			
			Hepatic	0.75			
			Renal	0.75			
			Bd Wt	0.75			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
78	Rabbit (New Zealand)	9 mo (W)	Cardio		1.6 M (increased aortic resistance, reduced contractility)		Boscolo and Carmignani 1986 $CdCl_2$
			Renal	1.6 M			
			Bd Wt	1.6 M			
79	Rabbit (New Zealand and Belgian Giant)	200 d (W)	Hemato			14.9 M (anemia)	Stowe et al. 1972 $CdCl_2$
			Hepatic			14.9 M (focal hepatic fibrosis and biliary hyperplasia)	
			Renal			14.9 M (tubular necrosis, glomerular and interstitial fibrosis)	
			Endocr	14.9			
			Bd Wt		14.9 M (11% decrease in body weight)		
80	Rabbit (New Zealand)	34 d (W)	Cardio			0.07 F (hypertension: increased arterial pressure (>50 mmHg) and increased ventricular mass)	Tomera and Harakal 1988 Cd acetate
			Bd Wt	0.07 F			
	Immunological/Lymphoreticular						
81	Monkey (Rhesus)	10 wk (F)			5 M (increased cell-mediated immune response)		Chopra et al. 1984 $CdCl_2$
82	Rat (Wistar)	170 d (W)			28 F (biphasic decrease then increase in natural killer cell activity)		Cifone et al. 1989a $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
83	Rat (Wistar)	3 mo (F)		3.0			Loeser and Lorke 1977a $CdCl_2$
84	Rat (Long- Evans)	14 wk (W)		5.8 M			*Pleasants et al.* 1992 $CdCl_2$
85	Rat (Sprague-Dawley)	2-6 wk 5 d/wk 1 x/d (G)			0.250 M (increased blastogenesis)		Stacey et al. 1988a Cd acetate
86	Rat (Sprague-Dawley)	6 wk (W)			0.4 M (increased blastogenic activity)		Stacey et al. 1988a $CdCl_2$
87	Mouse (BDF1)	3 wk (W)		1.4 F	2.8 F (decreased humoral immune response)		*Blakley 1985* $CdCl_2$
88	Mouse (Swiss)	280 d (W)				1.9 F (greater susceptibility to murine lymphocytic leukemia virus)	*Blakley 1986* $CdCl_2$
89	Mouse (BDF1)	26 d (W)		12.5 F			Blakley 1988 $CdCl_2$
90	Mouse (Swiss-Webster)	30 d (W)		22 M			Bouley et al. 1984 Cd acetate
91	Mouse (Swiss-Webster)	10 wk (W)		57 M			Exon et al. 1986 $CdCl_2$, Cd acetate

Table 2-2. Levels of Significant Exposure to Cadmium - 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
92	Mouse (C57BL/6N)	12-16 wk (W)		19 F	57 F (reduced number of SRBC-activated, plaque-forming cells)		Krzystyniak et al. 1987 $CdCl_2$
93	Mouse (C57BL/6)	3-11 wk (W)			12.5 M (decreased suppressor cell activity)		Malave and de Ruffino 1984 $CdCl_2$
94	Mouse (ICR)	10 wk (W)			0.75 M (induction of anti-nuclear autoantibodies)		Ohsawa et al. 1988 $CdCl_2$
	Neurological						
95	Rat (Wistar)	14 wk 5 d/wk (GW)		4 F	40 F (aggressive behavior)		Baranski and Sitarek 1987 $CdCl_2$
96	Rat (Sprague-Dawley)	3-24 wk (W)		1.2 M	3.1 M (decreased motor activity)		Kotsonis and Klaassen 1978 $CdCl_2$
97	Rat (Wistar)	90 d (W)			24 M (increased brain dopamine levels; decreased 5-HT, SDH, MAO, and ATPase levels)		Murthy et al. 1989 Cd acetate
98	Rat (Sprague-Dawley)	55 d (F)		1 M	5 M (increased passive avoidance)		Nation et al. 1984 $CdCl_2$
99	Rat (Sprague-Dawley)	60 d (F)			9 M (decreased motor activity)		Nation et al. 1990 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
100	Mouse (QS)	22 wk (W)		0.2 F		1.4 F (necrosis of choroid plexus epithelial cells)	Valois and Webster 1989 $CdCl_2$
	Reproductive						
101	Rat (Wistar)	20 d Gd 1-20 (W)		28.8 F			Baranski 1987 $CdCl_2$
102	Rat (Wistar)	14 wk 5 d/wk (GW)		4 F		40 F (increased duration of estrus cycle)	Baranski and Sitarek 1987 $CdCl_2$
103	Rat (Wistar)	11 wk 5 d/wk (GW)		4 F			Baranski et al. 1983 $CdCl_2$
104	Rat (Wistar)	10 wk 1 x/wk (GW)		5 M			Bomhard et al. 1987 $CdCl_2$
105	Rat (Sprague-Dawley)	12 wk (W)				8.58 M (necrosis and atrophy of seminiferous tubule epithelium)	Cha 1987 $CdCl_2$
106	Rat	4 wk (F)		2.5			Groten et al. 1990 $CdCl_2$
107	Rat (Sprague-Dawley)	22 d Gd 0-21 (W)		3.8 F			Kelman et al. 1978 form not specified
108	Rat (albino)	4 wk (W)		4.8 F			Kostial et al. 1993 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
109	Rat (Sprague-Dawley)	24 wk (W)		8.0 M			Kotsonis and Klaassen 1978 $CdCl_2$
110	Rat (Wistar)	3 mo (F)		3.0			Loeser and Lorke 1977a $CdCl_2$
111	Rat (Sprague-Dawley)	60 d prior to Gd 1 or Gd 1-Gd 21 (W)		2.61 F			Petering et al. 1979 $CdCl_2$
112	Rat (Sprague-Dawley)	111 d (90 d prior to Gd 1 through Gd 21) (W)		5.23 F			Petering et al. 1979 $CdCl_2$
113	Rat (Long- Evans)	14 wk (W)		2.9 M	5.8 M (28% increased relative testes weight)		Pleasants et al. 1992 $CdCl_2$
114	Rat (Long- Evans)	14 wk (W)			11.6 M (64% increased relative weight of testes)		Pleasants et al. 1993 $CdCl_2$
115	Rat (Sprague-Dawley)	21-25 d Gd 1-Ld 1 (F)		19.7 F			Pond and Walker 1975 $CdCl_2$
116	Rat (NS)	120 d (W)				12.6 M (decreased sperm count and motility, seminiferous tubular damage)	Saxena et al. 1989 Cd acetate

Table 2-2. Levels of Significant Exposure to Cadmium - 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
117	Rat (Sprague-Dawley)	9 wk 7 d/wk 1 x/d (GW)		1.0		10	(>50% fewer copulating and pregnant females, 50% reduction in number of live fetuses)	Sutou et al. 1980 *form not specified*
118	Rat (Long- Evans)	70-80 d (W)		4.64 M				Zenick et al. 1982 $CdCl_2$
119	Mouse (CD)	6 mo (W)				2.5	(reproductive failure)	Schroeder and Mitchener 1971 Unspecified Cd
120	Dog (Beagle)	3 mo (F)		0.75				Loeser and Lorke 1977b *$CdCl_2$*
	Developmental							
121	Rat (Wistar)	21 d Gd 1-21 (W)				0.706	(delayed development of sensory motor coordination reflexes; increased motor activity)	*Ali et al. 1986* Cd acetate
122	Rat (Wistar)	20 d Gd 1-20 (W)				9.6	(decreased fetal body weight [12%], body length [7%], and hematocrit [13%])	Baranski 1987 $CdCl_2$
123	Rat (Wistar)	11 wk 5 d/wk 1 x/d (GW)			0.04 (pup behavioral alterations)			Baranski et al. 1983 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
124	Rat (Wistar)	11-94 d Gd 5-15 Ld 2-28 1 x/d ppd 1-56 5 d/wk 1 x/d (GW)				14.0 M (decr. horizontal ambulation and rearing activity; incr. frequency of somatosensory, visual, and auditory electrocorticogram; prolonged latency and duration of evoked potentials)	Desi et al. 1998 $CdCl_2$
125	Rat (Druckery)	42 d Gd 0- Ld 21 (W)				5.0 (decreased pup brain and body weight at 7, 14, and 21 days)	Gupta et al 1993 Cd acetate
126	Rat (Sprague-Dawley)	21 d Gd 0-20 (W)				1.5 (12% decreased hematocrit)	Kelman et al. 1978 form not specified
127	Rat (albino)	10 wk (W)			4.8 (12% decrease in pup body weight at weaning)		Kostial et al. 1993 $CdCl_2$
128	Rat (Wistar)	approx. 49 d 4 wks of age thru mating 7 d/wk 1 x/d addt. 49 days gestation thru parturition 5 d/wk (GO)				7.0 M (alterations in ambulation behavior; prolonged latency and duration of somatosensory evoked potentials)	Nagymajtenyi et al. 1997 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
129	Rat (Sprague-Dawley)	60 d prior to Gd 1 or Gd 1-21 (W)			2.61 (decreased live birth weight)		Petering et al. 1979 $CdCl_2$
130	Rat (Sprague-Dawley)	111 d (90 d prior to Gd 1-21) (W)			0.56 (reduction in neonate copper levels)		Petering et al. 1979 $CdCl_2$
131	Rat (Sprague-Dawley)	22 d Gd 1-Ld 1 (F)			19.7 (13-19% decreased pup birth weight)		Pond and Walker 1975 $CdCl_2$
132	Rat (ITRC)	21 d Gd 0-20 (W)		21			Saxena et al. 1986 Cd acetate
133	Rat (Sprague-Dawley)	15 d Gd 6-20 (W)		0.63	4.7 (8% decreased fetal body weight)		Sorell and Graziano 1990 $CdCl_2$
134	Rat (Sprague-Dawley)	9 wk 1 x/d (GW)		1.0	10 (delayed ossification, decreased body weight)		Sutou et al. 1980 form not specified
135	Mouse (CD)	6 mo (W)				2.5 (malformation-sharp angulation of the distal third of the tail; increased mortality)	Schroeder and Mitchener 1971 Unspecified Cd
136	Mouse (QS/CH)	19 d Gd 1-19 (W)				2.4 (decreased fetal body weight; severe anemia)	Webster 1978 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
137	Mouse (Wistar)	3.5 mo (W)		5.7	14.25 (increased lipid peroxide in brain, liver, and heart of 7-day old pups)		Xu et al. 1993b form not specified
	Cancer						
138	Mouse (Swiss)	280 d (W)				1.9 F (CEL: small increase in mammary tumors in leukemia prone mice)	Blakley 1986 $CdCl_2$
	CHRONIC EXPOSURE						
	Systemic						
139	Human	NS lifetime (F)	Renal	0.0021 [b]			Nogawa et al. 1989 form not specified
140	Human	>25 yr lifetime (environ)	Hemato	0.0078			Shiwen et al. 1990 Cd metal
			Musc/skel	0.0078			
			Renal			0.0078 (renal tubule interstitial lesions)	
141	Monkey (Rhesus)	9 yr (F)	Cardio	0.53 M	1.71 M (increased blood pressure during the first 1.5 years)		Akahori et al. 1994 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
142	Monkey (Rhesus)	9 yr (F)	Resp	4.0 M			Masaoka et al. 1994 $CdCl_2$
			Hemato			4.0 M (anemia)	
			Musc/skel			4.0 M (marked decrease in body length)	
			Renal	0.4 M		4.0 M (proteinuria, glucosuria)	
			Bd Wt	0.12 M	0.4 M (decreased body weight from decreased food intake)	4.0 M (markedly decreased growth rate)	
143	Rat (Sprague-Dawley)	18 mo (W)	Renal			13 F (loss of glomerular polyanion charge barrier, proteinuria)	Bernard et al. 1992 $CdCl_2$
144	Rat (Wistar)	72 wk (F)	Renal	3.5		17.5 (8 to 9-fold increase in LDH and GST starting at 13 weeks)	Bomhard et al. 1984 $CdCl_2$
145	Rat (Sprague-Dawley)	12 mo (W)	Hemato	0.79			Decker et al. 1958 $CdCl_2$
			Bd Wt	0.79			
146	Rat (Sprague-Dawley)	M: 92 wk F: 84 wk (W)	Cardio	4.01			Fingerle et al. 1982 $CdCl_2$
			Renal	0.8		1.51 (proximal tubule lesions)	
			Bd Wt	4.01			
147	Rat (Long- Evans)	18 mo (W)	Cardio			0.01 F (hypertension, 20% increase in systolic pressure)	Kopp et al. 1982 Cd acetate
			Hepatic	0.65 F			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
148	Rat (Sprague-Dawley)	6, 12, or 18 mo (W)	Cardio	2.281 F			Mangler et al 1988 $CdCl_2$
			Hepatic	2.281 F			
			Renal			2.337 F (cloudy swelling of tubular cells)	
			Bd Wt	2.281 F			
149	Rat (Wistar)	31 mo (W)	Musc/skel			3.6 (muscle atrophy)	Sato et al. 1978 $CdCl_2$
			Bd Wt	3.6			
150	Rat (Wistar)	2 yr (W)	Renal	2.6 M			Shaikh et al. 1989 $CdCl_2$
151	Rat (Wistar)	77 wk (F)	Bd Wt	3.5 M	7.0M (10% decreased body weight)		Waalkes and Rehm 1992 $CdCl_2$
152	Mouse (CBA/H)	12 mo (W)	Hemato			57 (anemia and bone marrow hypoplasia)	Hays and Margaretten 1985 form not specified
			Renal	57			
			Bd Wt			57 (21% decreased terminal body weight)	
	Neurological						
153	Rat (Wistar)	31 mo (W)				3.6 (peripheral neuropathy)	Sato et al. 1978 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
	Cancer							
154	Rat (Wistar)	77 wk (F)				3.5 M	(CEL: increased rates of prostatic adenomas)	Waalkes and Rehm 1992 $CdCl_2$

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

[b]Used to derive a chronic-duration oral minimal risk level (MRL) of $2x10^{-4}$ mg/kg/day based upon kidney effects. A threshold of lifetime intake of 110 µg/g (2,000 mg Cd for a 50-year lifetime) was found for renal damage. A NOAEL of 0.0021 mg/kg/day was derived from this value by dividing by 53 kg (average weight) and 50 years (364 days/year). The MRL is based on this NOAEL and an uncertainty factor of 10 to account for sensitive members of the population.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); endocr = endocrine; environ = environmental; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day(s); (GW) = gavage in water; GST = glutathione transferase; (IN) = ingestion; Hb = hemoglobin; Hemato = hematological; Ht = hematocrit; 5-HT = 5-hydroxytryptamine; Ld = lactational day; LD_{50} = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; metab = metabolic; MAO = monoamine oxidase; mo = month; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SDH = succinic dehydrogenase; (W) = water; wk = week(s); x = times; yr = year(s)

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

Acute (≤14 days)

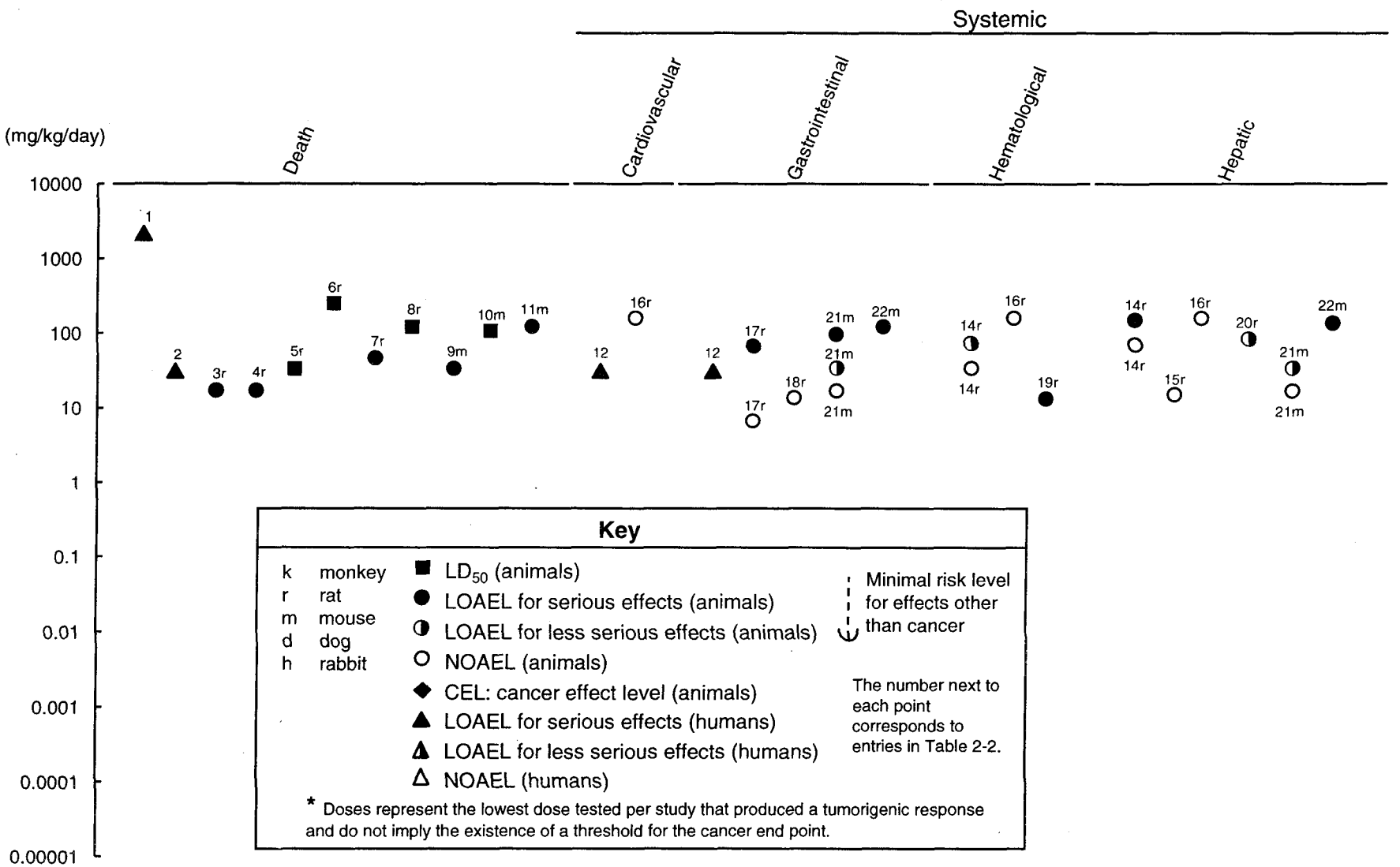


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Acute (≤14 days)

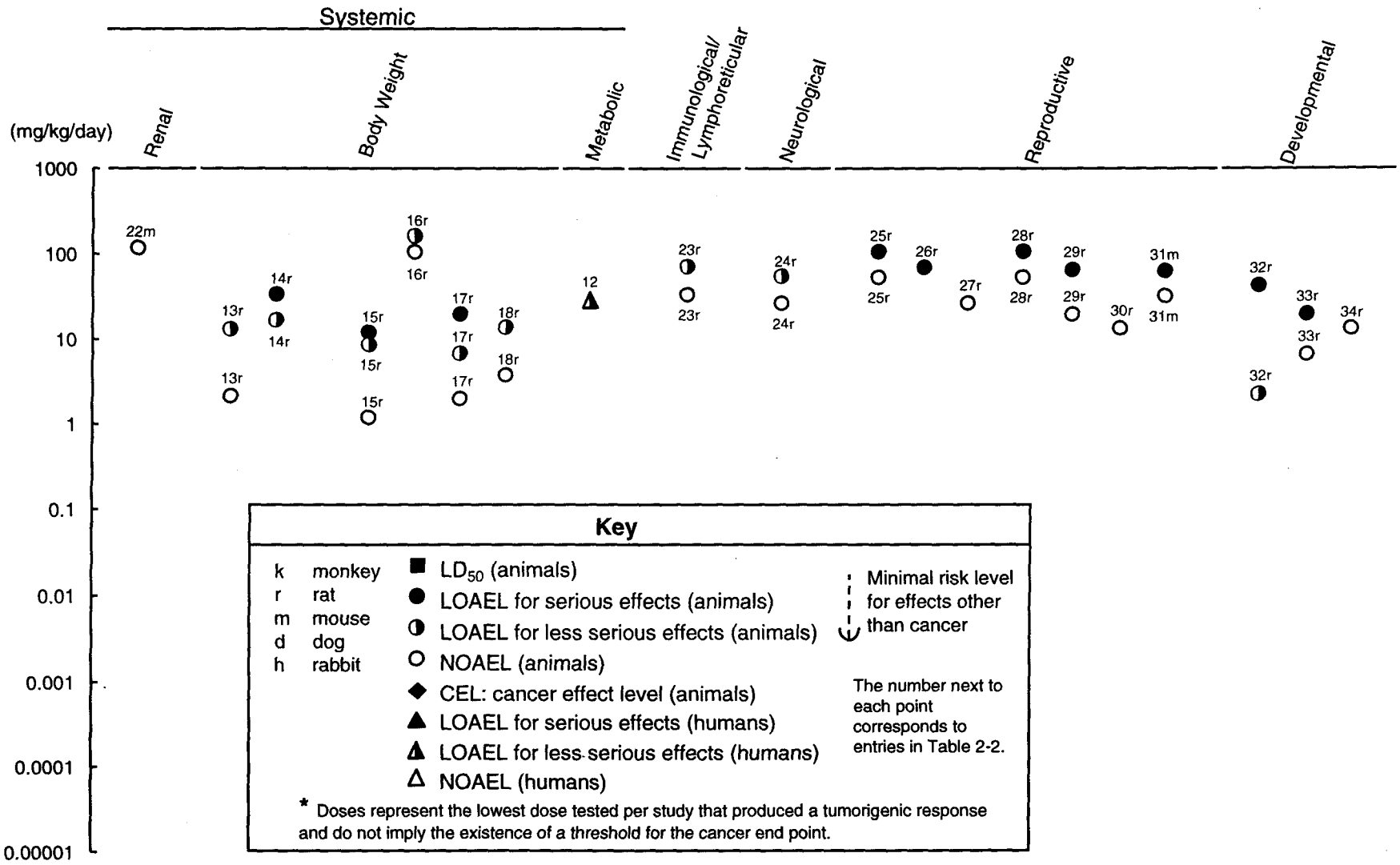


Figure 2-1. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

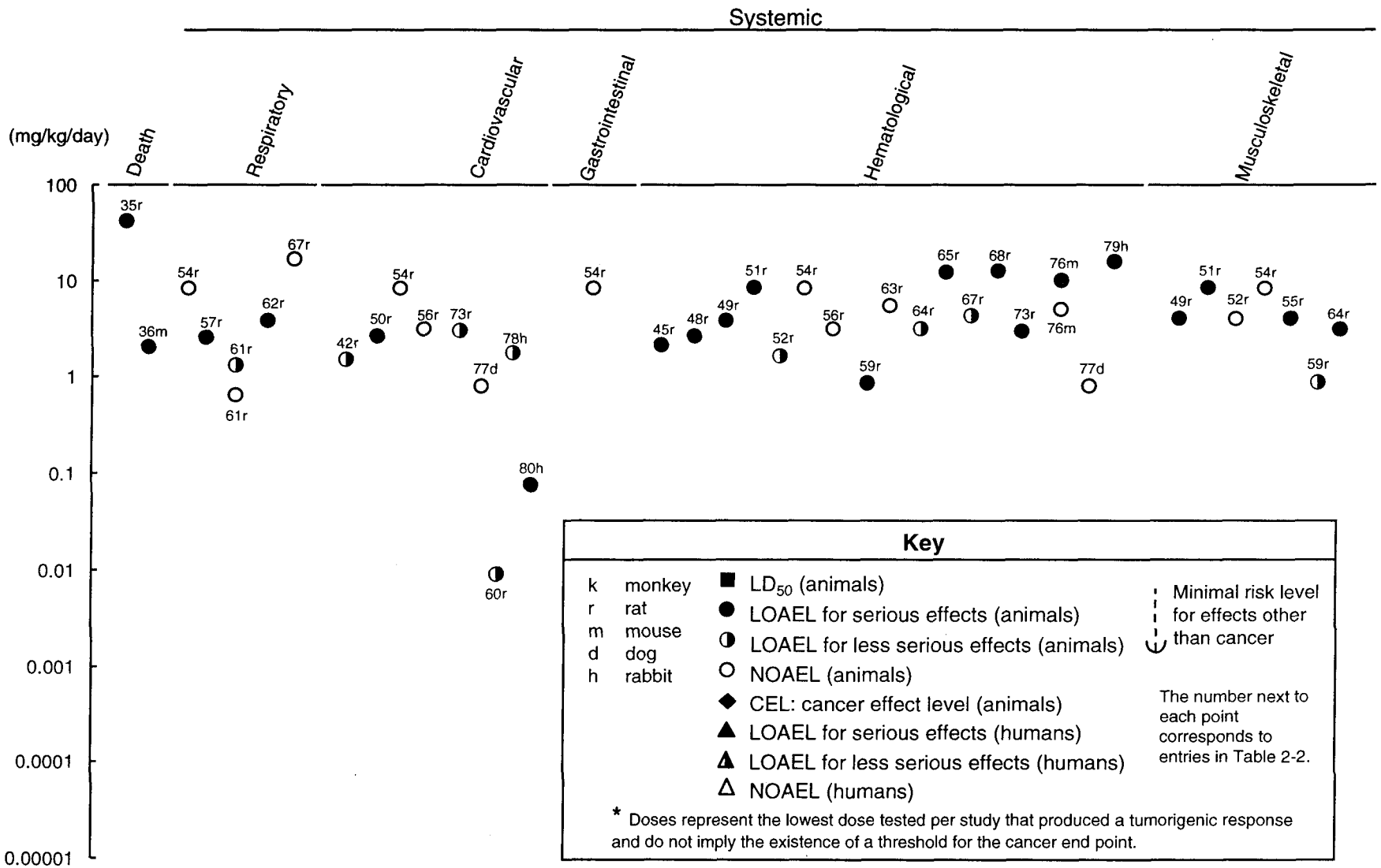


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

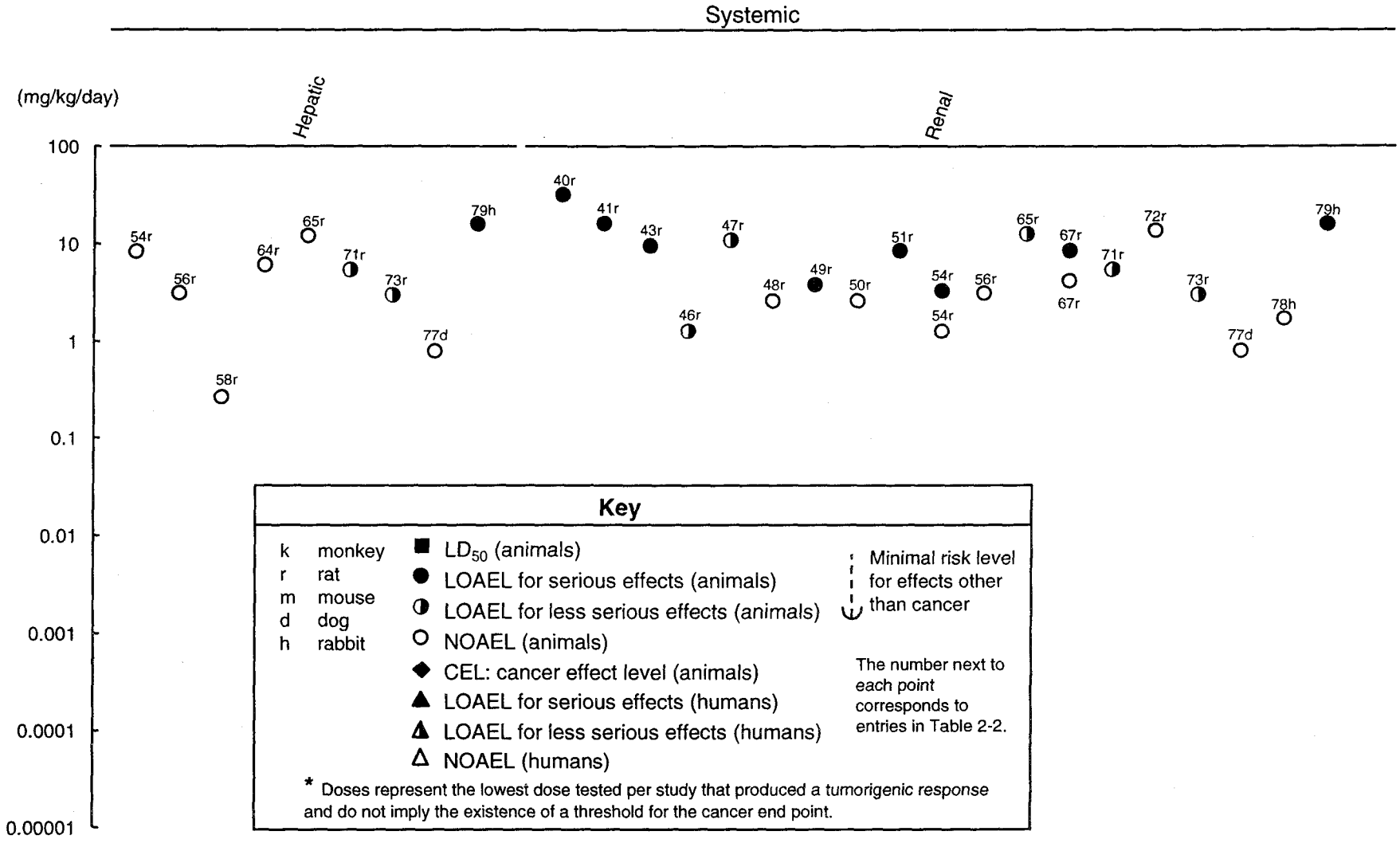


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

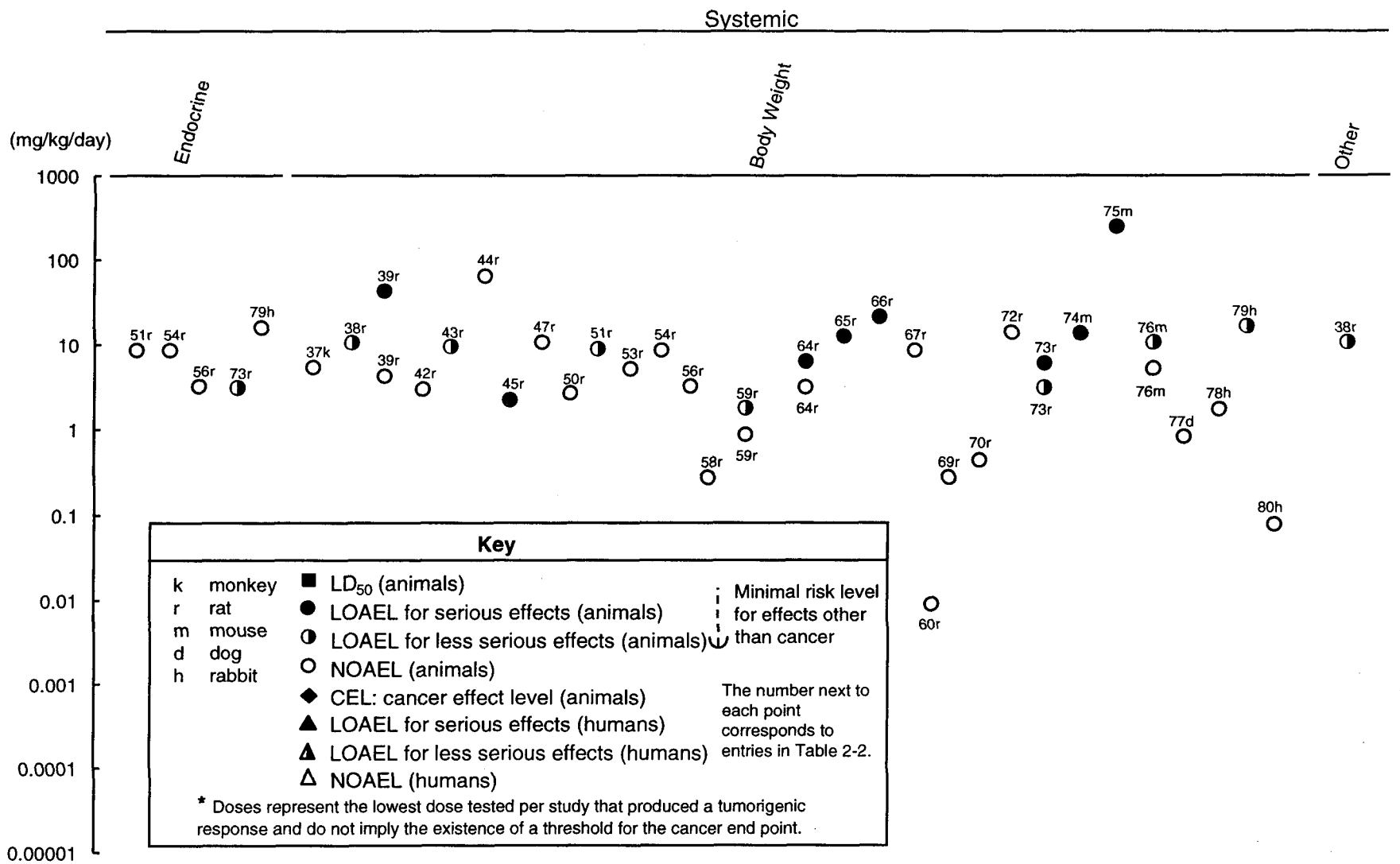


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

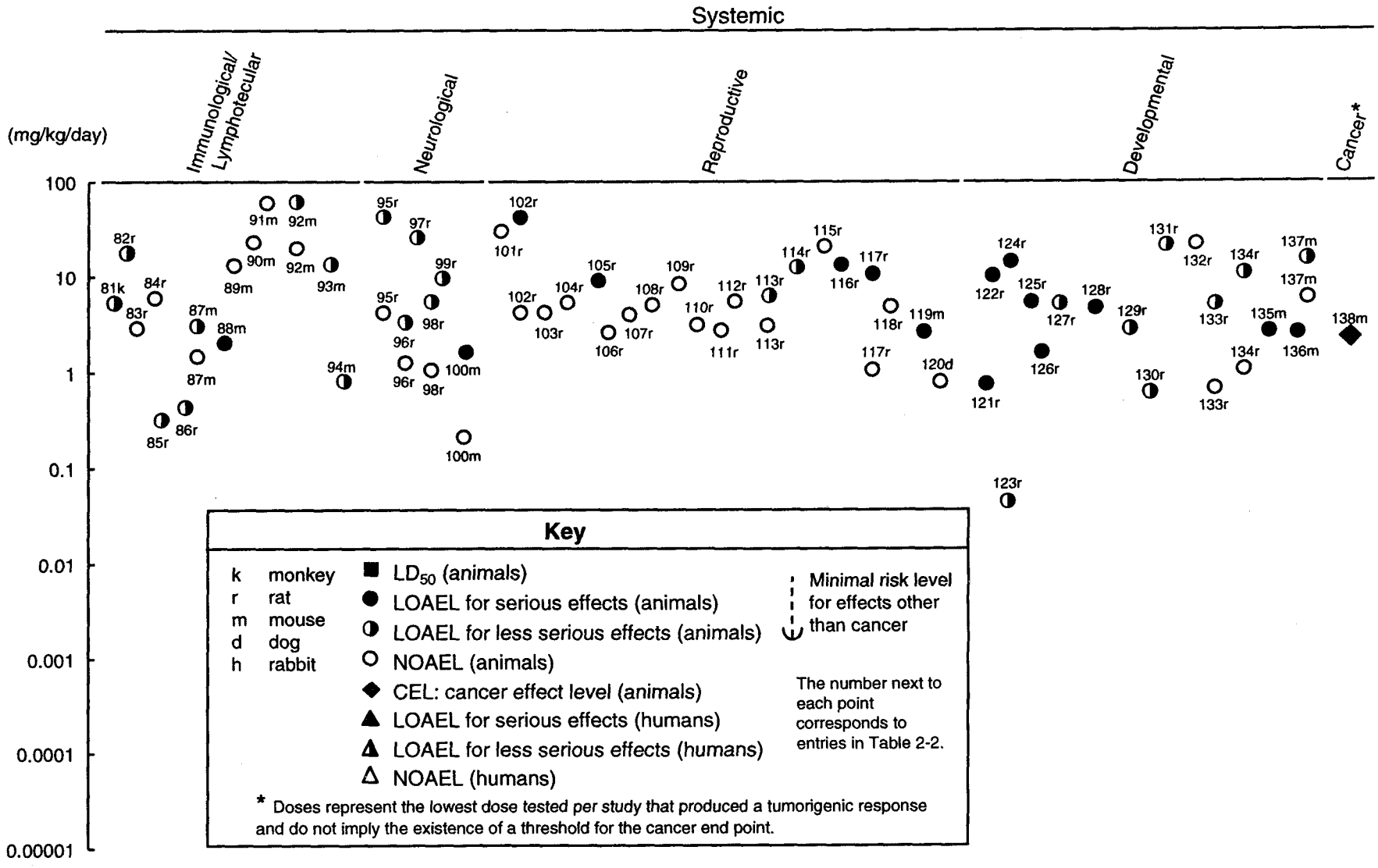
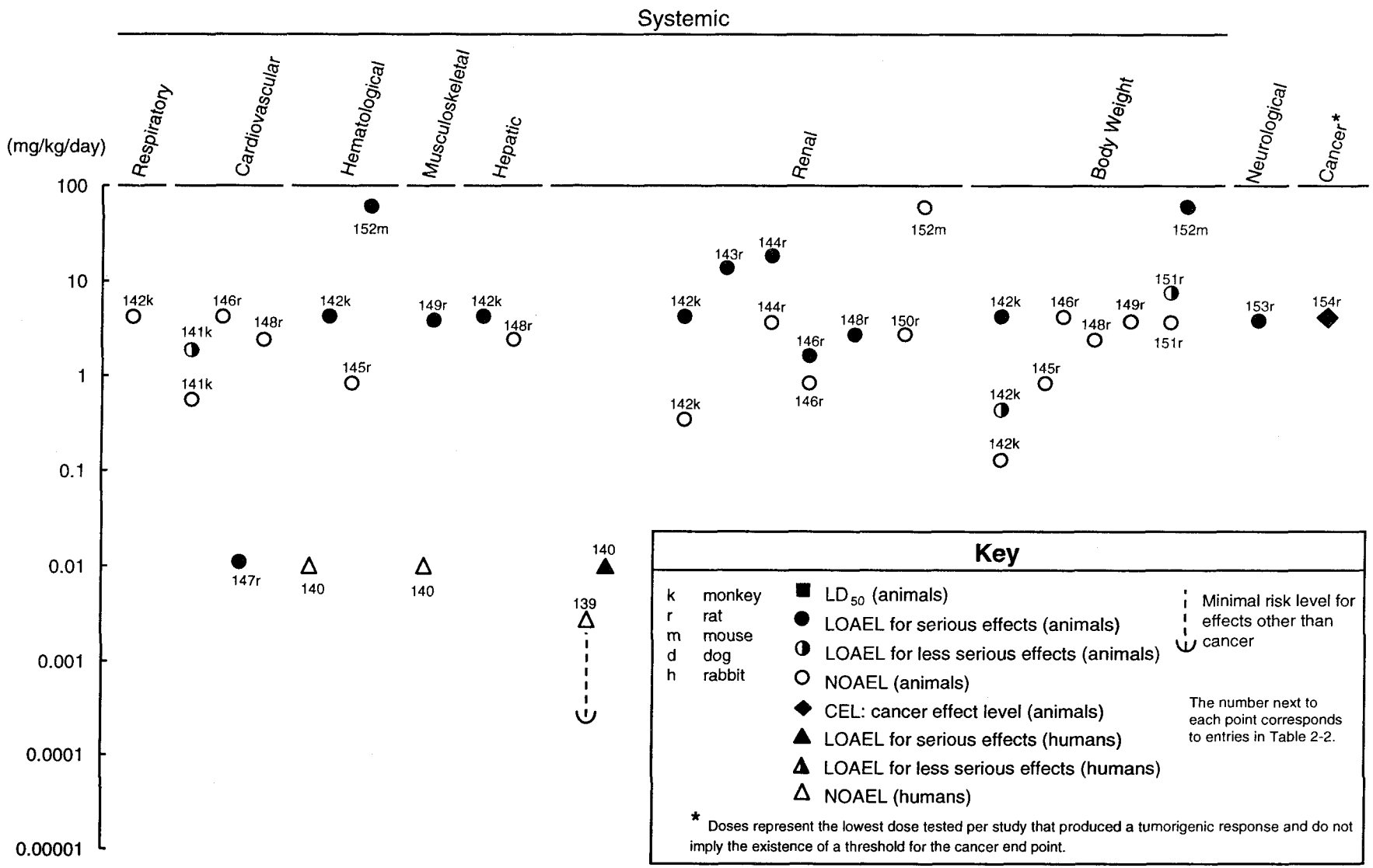


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Chronic (≥365 days)



2.2.2.2 Systemic Effects

Representative NOAEL and LOAEL values for systemic effects of oral exposure to cadmium in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to cadmium.

No respiratory effects were observed in Rhesus monkeys from 4 mg/kg/day of cadmium chloride in the food for 9 years (Masaoka et al. 1994). A dose-dependent decrease in relative lung weight was observed in male rats after gavage exposure to cadmium chloride for 10 days, but not in female rats after gavage exposure, or in male and female rats after drinking-water exposure (Borzelleca et al. 1989). Intermediate duration oral exposure caused fibrosis in lungs of rats exposed to 2.4 mg Cd/kg/day of cadmium chloride after 6 and 16 weeks (Miller et al. 1974b). Petering et al. (1979) observed a reduced static compliance and lung lesions (not specified) in male Sprague-Dawley rats exposed to 1.2 mg Cd/kg/day in water for 200 days. Zinc-deficient rats were more susceptible to lung lesions from exposure to $CdCl_2$ (Petering et al. 1979). Rats exposed to $CdCl_2$ at 3.62 mg Cd/kg/day in the drinking water for 120 days developed emphysema (Petering et al. 1979). No histopathologic lesions of the lung were found in male Sprague-Dawley rats after 24 weeks of exposure to cadmium in drinking water at a maximum dose of 8 mg/kg/day (Kotsonis and Klaassen 1978). Lung weight was unchanged in Wistar rats after 90 days of exposure in drinking water at 16 mg/kg/day (Prigge 1978a). Effects on the lung following oral exposure to cadmium may be secondary to systemic changes (Petering et al. 1979); however, the studies that found lung effects did not examine other systemic effects in the exposed rats (Miller et al. 1974b; Petering et al. 1979).

Cardiovascular Effects. Studies regarding cardiovascular effects in humans after oral exposure to cadmium have primarily investigated relationships between blood pressure and biomarkers of cadmium exposure such as cadmium levels in blood, urine, or other tissues. Smoking is an important confounding factor, because of the higher blood, urine, and tissue cadmium levels of smokers (see Section 2.3) and the known cardiovascular toxicity of cigarette smoking. Case-control and cohort epidemiologic studies that adequately control for smoking have typically found no association between body cadmium levels (primarily reflecting dietary exposure) and hypertension (Beevers et al. 1980; Cummins et al. 1980; Ewers et al. 1985; Lazebnik et al. 1989; Shiwen et al. 1990); however, some studies have found positive

correlations (Geiger et al. 1989; Tulley and Lehmann 1982) or negative correlations (Kagamimori et al. 1986; Staessen et al. 1984). Similar conflicting findings have been reported in studies analyzing death rates from cardiovascular disease among populations with dietary cadmium exposure (Inskip and Beral 1982; Shigematsu 1984). Disorders of the cardiac conduction system, lower blood pressure, and decreased frequency of cardiac ischemic changes were found among elderly women with past high dietary exposure to cadmium (Kagamimori et al. 1986). Rhythmic disturbances, including ventricular fibrillation, were seen in an individual who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

A single gavage dose of 150 mg/kg cadmium in male Sprague-Dawley rats had no effect on blood pressure (Kotsonis and Klaassen 1977). Oral exposure of rats, rabbits, and monkeys to cadmium over intermediate and chronic durations has been found to increase blood pressure in some studies (Akahori et al. 1994; Boscolo and Carmignani 1986; Carmignani and Boscolo 1984; Kopp et al. 1982; Perry et al. 1989; Tomera and Harakal 1988), but not in others (Fingerle et al. 1982; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a, 1977b; Mangler et al. 1988; Wills et al. 1981). In general, studies showing an effect on blood pressure have had control groups with lower blood pressure than studies showing no effect, and observed increases in blood pressure are generally small. At least in rats, the effect on blood pressure appears to be biphasic, reaching a maximum effect (an increase of 12-14 mm Hg in average systolic pressure) at intakes of 0.07 mg/kg/day, but decreasing to normal or even below normal at intakes 10-100 times higher (Kopp et al. 1982). Enlarged and arteriosclerotic hearts have been found in rats orally exposed to 0.35 mg Cd/kg/day for 3 years (Schroeder et al. 1965) or to 2.79 mg Cd/kg/day for 100 days (Wilson et al. 1941), but this effect is likely to be secondary to cadmium-induced anemia (Wilson et al. 1941). Histopathologic lesions of heart tissues (congestion, separation of muscle fibers) and decreased activity of antioxidant enzymes, but no increase in peroxidation, were found among rats given 2.5 mg/kg/day of cadmium in the diet for 7 weeks (Jamall et al. 1989). Overall, the evidence for cardiovascular toxicity resulting from oral exposure to cadmium is suggestive of a slight effect.

Gastrointestinal Effects. Numerous human and animal studies indicate that oral exposure to cadmium in high concentrations causes severe irritation to the gastrointestinal epithelium (Andersen et al. 1988; Frant and Kleeman 1941). Common symptoms in humans following ingestion of food or beverages containing high concentrations of cadmium include nausea, vomiting, salivation, abdominal pain, cramps, and diarrhea (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although exact doses have not been measured, gastrointestinal symptoms have been caused in children by 16 mg/L cadmium in soft drinks (Nordberg et

al. 1973) and 13 mg/L cadmium in popsicles (Frant and Kleeman 1941). Assuming an intake of 0.15 L (Nordberg et al. 1973) and a body weight of 35 kg, the emetic dose is 0.07 mg/kg. Although few studies have specifically examined gastrointestinal effects of longer-term cadmium exposure, no surveys of environmentally exposed populations have reported gastrointestinal symptoms (Morgan and Simms 1988; Roels et al. 1981a; Shigematsu 1984).

In rats and mice, histopathologic lesions (e.g., severe necrosis, hemorrhage, ulcers) in the gastrointestinal epithelium have been observed after high (>30 mg/kg/day) acute-duration oral cadmium exposure by gavage (Andersen et al. 1988; Basinger et al. 1988; Machemer and Lorke 1981), but not after lower levels (8 mg/kg/day in drinking water) for 24 weeks (Kotsonis and Klaassen 1978).

Hematological Effects. Oral cadmium exposure reduces gastrointestinal uptake of iron, which can result in anemia if dietary intake of iron is low. Anemia has been found in some instances among humans with chronic dietary exposure to cadmium (Kagamimori et al. 1986), but other studies have found no significant relationship between dietary cadmium exposure and anemia in humans (Roels et al. 1981a; Shiwen et al. 1990). Hypoproteinemia and hypoalbuminemia were reported in a male who ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

A number of studies have demonstrated that oral exposure to cadmium frequently produces anemia in laboratory animals, and that additional iron prevents anemia (Decker et al. 1958; Groten et al. 1990; Hays and Margaretten 1985; Itokowa et al. 1974; Kawamura et al. 1978; Kelman et al. 1978; Kozlowska et al. 1993; Ogoshi et al. 1989; Pleasants et al. 1992, 1993; Pond and Walker 1972; Sakata et al. 1988; Sorell and Graziano 1990; Stowe et al. 1972; Watanabe et al. 1986; Webster 1978; Wilson et al. 1941). Decreases in serum iron have also been reported (Prigge 1978a). Borzelleca et al. (1989) reported slight but statistically significant increases in hemoglobin, hematocrit, and erythrocytes in male rats at 65.6 mg/kg/day once a day for 10 days, but no change in females. Male Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium showed no signs of anemia 14 days later (Kotsonis and Klaassen 1977), but anemia was produced in male Wistar rats after 12 days of drinking-water exposure to 12 mg/kg/day (Sakata et al. 1988). Most intermediate-duration exposure studies in rats have shown evidence of anemia at doses of 2-14 mg/kg day (Decker et al. 1958; Groten et al. 1990; Itokawa et al. 1974; Kawamura et al. 1978; Pleasants et al. 1993; Pond and Walker 1972; Sakata et al. 1988; Wilson et al. 1941). However, some intermediate-duration studies have found no change in hemoglobin (Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Petering et al. 1979; Prigge 1978a) in rats treated at similar

doses. Anemia has also been seen in intermediate-duration studies in mice (Webster 1978) and rabbits (Stowe et al. 1972), but not in dogs (Loeser and Lorke 1977b). The result in dogs may be due to the relatively low dose of cadmium (0.75 mg/kg/day) used in this study. Hematological effects following chronic-duration oral exposure to cadmium are less well characterized. In monkeys maintained on 4 mg/kg/day cadmium in food, pale feces, and clinical signs of anemia occurred after 90 weeks, but the anemia was associated with a decreased food intake rather than an increase in reticulocytes (Masaoka et al. 1994). Anemia was not present in rats exposed via drinking water for 12 months to the relatively low dose of 0.79 mg/kg/day (Decker et al. 1958). The number of erythroid progenitor cells in bone marrow is decreased in mice exposed to 57 mg/kg/day of cadmium in drinking water for 12 months (Hays and Margaretten 1985), but is increased in rats exposed to 12 mg/kg/day of cadmium in drinking water for up to 100 days (Sakata et al. 1988). Thus, the question remains open whether factors in addition to reduced gastrointestinal absorption of iron such as direct cytotoxicity to marrow or inhibition of heme synthesis may contribute to anemia.

Musculoskeletal Effects. Painful bone disorders, including osteomalacia, osteoporosis, and spontaneous and painful bone fractures (an affliction called Itai-Itai or “ouch-ouch” disease), have been observed in some humans chronically exposed to cadmium in food. In the Jinzu River Basin, a cadmium contaminated area in Japan, osteomalacia and Itai-Itai disease have most often affected women with several risk factors such as poor nutrition and multiparity (Shigematsu 1984). Other Japanese populations with dietary cadmium exposure have also recently been found to have elevated osteoporosis and osteomalacia in both men and women (Kido et al. 1989b). The degree of loss of bone density is correlated with urinary excretion of β_2-microglobulin, an index of renal injury (see Section 2.5.2) (Kido et al. 1990a). Kagamimori et al. (1986) evaluated elderly Japanese women with heavy cadmium exposure from ingesting polluted drinking water, rice, and fish during World Wars I and II; and continued low-grade cadmium exposure from agricultural produce. Of 56 cases of Itai-itai disease, 26 were accompanied by osteomalacia and 26 were without osteomalacia.

Cadmium-exposed individuals exhibit a progressive disturbance in renal metabolism of vitamin D to its biologically active form (Nogawa et al. 1987, 1990) and an increased urinary excretion of calcium (Buchet et al. 1990). These results suggest that bone changes may be secondary to disruption in kidney of vitamin D metabolism and resulting imbalances in calcium absorption and excretion.

Studies in rats confirm that oral cadmium exposure may affect the skeleton. Decreased calcium content of bone and increased urinary calcium excretion are common findings in intermediate- and chronic-duration studies in the 2-8 mg Cd/kg/day range (Kawamura et al. 1978; Nogawa et al. 1981b; Pleasants et al. 1992; Watanabe et al. 1986). In contrast, Kotsonis and Klaassen (1978) reported no change in bone calcification after a 24-week exposure via drinking water at 8 mg/kg/day; and Kelman et al. (1978) reported no significant change in stable or radiolabeled calcium in any maternal rat tissues from a 3.8 mg/kg/day in drinking water for 22 days during gestation. Adverse effects on bone are exacerbated by a calcium-deficient diet (Itokawa et al. 1974; Kimura et al. 1974; Larsson and Piscator 1971; Wang and Bhattacharyya 1993; Wang et al. 1994), by exposure at a young age when bones are growing (Ogoshi et al. 1989), by ovariectomy (Bhattacharyya et al. 1988c), or by multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b).

In the Ogoshi et al. (1989) study, the mechanical strength of femurs of young, adult, and elderly female rats was assessed after a 4-week exposure to $CdCl_2$ in drinking water. Young rats (21 days old; strain not specified; N=19-22F) were given $CdCl_2$ at 0, 5, or 10 ppm; adult rats (24 weeks old; strain not specified,; N=18-25NS) were given $CdCl_2$ at 0, 10, 20, 40, 80, or 160 ppm (adult rats); elderly rats (1.5 years old; strain not specified; N=25-27NS) were given $CdCl_2$ at or 0, 80, or 160 ppm. At the end of the 4-week exposure, femur compression and bending strengths, and cadmium and zinc content in bone were determined. Young rats had decreased bone strength at both doses tested, 5 and 10 ppm, while adult and elderly rats showed no effect up to doses of 160 ppm. Bone strength was correlated with cadmium content of bone but not cadmium content of liver or kidney. Young rats accumulated cadmium in the bones to a much greater extent (100 ng/g dry weight at 5 ppm, 150 ng/g at 10 ppm) then did the adult or elderly rats whose accumulation was roughly comparable and about 65 ng/g at the highest dose of 160 ppm.

In nonpregnant mice fed a calcium deficient diet, bone resorption was immediately and significantly increased by the addition of cadmium to the diet up to 25 ppm as evidenced by significant increases in fecal and serum cadmium (Wang and Bhattacharyya 1993). In pregnant mice fed a calcium deficient diet, an Itai-Itai like syndrome was produced from exposure to cadmium in the diet. Almost all of the calcium lost from the dam appeared in the pups, with 80% of that transferred via the dam’s milk during lactation and only 20% transferred during gestation (Wang et al. 1994). Some studies have detected effects in bone prior to development of proteinuria or histopathologic kidney damage in mice (Bhattacharyya et al. 1988a, 1988b; Ogoshi et al. 1989; Watanabe et al. 1986). These results raise the possibility that disturbed calcium metabolism may occur prior to proteinuria following long-term exposure to cadmium. For the

studies that establish thresholds for skeletal effects of cadmium exposure, NOAEL and LOAEL values for each species and duration category are listed in Table 2-2 and plotted in Figure 2-2.

Hepatic Effects. Liver damage is not usually associated with oral cadmium exposure, except at very high levels of exposure. In humans, a fatal dose of cadmium can cause pronounced liver damage (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). Nishino et al. (1988) reported increased serum concentrations of the urea-cycle amino acids among individuals exposed to cadmium in the diet, and that these levels reflected liver as well as kidney damage. No other studies were located regarding hepatic effects in humans after oral exposure to cadmium.

Hepatic effects have been found in rats, mice, and rabbits after oral cadmium exposure. Acute exposure via gavage at doses of 30-138 mg/kg/day causes liver necrosis in most studies (Andersen et al. 1988; Basinger et al. 1988; Borzelleca et al. 1989; Shimizu and Morita 1990), although histopathologic evidence of liver damage was not seen in one study at a gavage dose of 150 mg/kg (Kotsonis and Klaassen 1977). Exposure of rats for 10 days to drinking water containing 13.9 mg Cd/kg/day was without effect on the liver (Borzelleca et al. 1989). Depletion of liver glutathione by fasting increases the liver necrosis following acute oral exposure to cadmium in rats (Shimizu and Morita 1990).

In a 10-week study, male Rhesus monkeys exposed to 4 mg/kg/day cadmium chloride via gavage, had a significant decrease in glutathione peroxidase in liver, kidney, heart, and lung in the following order: liver>kidney>heart>lung; a significant decrease in glutathione *S*-transferase (GST) activity towards 1-chloro-2,4-dinitrobenzene in all four organs in the following order: liver>lung>kidney>heart; and a significant increase in GST activity towards ethacrynic acid in all four organs in the following order: heart>lung>kidney>liver (Sidhu et al. 1993). Intermediate-duration exposure causes histopathologic changes in the liver (e.g., necrosis of central lobules, focal hepatic fibrosis, biliary hyperplasia) at doses of 1.6-15 mg/kg/day (Cha 1987; Gill et al. 1989b; Miller et al. 1974a; Schroeder et al. 1965; Stowe et al. 1972; Wilson et al. 1941), and metabolic alterations (e.g., decreased cytochrome c oxidase activity in mitochondria, increased ALT and AST activities) at doses of 0.05-10 mg/kg/day (Groten et al. 1990; Muller and Stacey 1988; Muller et al. 1988; Sporn et al. 1970; Steibert et al. 1984; Tewari et al. 1986b). Decreased relative liver weight to body weight has also been reported in male rats fed 5.95 mg/kg/day for 6 weeks (Kozlowska et al. 1993).

Other intermediate and chronic duration studies have not found liver effects in animals following oral exposure. These studies include a daily gavage exposure of 14 mg/kg/day for 6 weeks in rats (Hopf et al. 1990), a 3-month exposure to cadmium in food at 3 mg/kg/day in rats (Loeser and Lorke 1977a), a 24-week exposure to cadmium in water at 8 mg/kg/day in rats (Kotsonis and Klaassen 1978), and a 3-month exposure in food at 0.75 mg/kg/day in dogs (Loeser and Lorke 1977b). Kopp et al. (1982) report no hepatic effects from a chronic exposure of 18 months to cadmium in water at 0.65 mg/kg/day in rats. Representative NOAEL and LOAEL values for hepatic effects for each species and duration category are listed in Table 2-2 and plotted in Figure 2-2.

Renal Effects. Numerous studies indicate that the kidney is the main target organ of cadmium toxicity following extended oral exposure, with effects similar to those seen following inhalation exposure (see Section 2.2.1.2). Elevated incidences of tubular proteinuria have been found in numerous epidemiologic studies of residents of cadmium-polluted areas in Japan (Nogawa et al. 1980, 1989), Belgium (Buchet et al. 1990; Roels et al. 1981a), and China (Shiwen et al. 1990).

A recent study of Belgians (aged 20-80 years) from polluted and nonpolluted urban and rural areas found abnormal rates of urinary excretion of β_2-microglobulin, retinol binding protein, N-acetyl-β-glucosaminidase, ammo acids, and calcium in individuals with cadmium excretion rates >2 μg/day (Buchet et al. 1990). The cadmium excretion rate of 2 μg/day was estimated to correspond to a cadmium level of 50 μg/g wet weight in the renal cortex (Buchet et al. 1990). This study suggests that the critical concentration may be lower in members of the general population than in workers (Buchet et al. 1990). However, data from Japanese residents of cadmium-polluted areas support a critical concentration of 200 μg/g wet weight, as found in occupationally exposed workers (Roels et al. 1983). Quantitative analysis of the prevalence of elevated urinary β_2-microglobulin as a function of cadmium ingestion indicates that after a total intake of approximately 2,000 mg cadmium (for a 53-kg person), renal damage will occur (Nogawa et al. 1989). This intake corresponds to a 50-year dose of approximately 0.0021 mg/kg/day. A kinetic model of cadmium metabolism predicts that this intake will produce elevated β_2-microglobulin levels in about 5% of a nonsmoking European population (body weight=70 kg) and about twice that rate in a Japanese population (body weight=53 kg), assuming a log-normal distribution in critical concentrations with 10% of the population having a critical concentration of 180 μg/g or less and 50% having a critical concentration at 250 μg/g or less (Kjellstrom 1986a). This kinetic model also assumes that kidney concentrations will be log-normally distributed in a population with a given intake (Kjellstrom

1986a); it has been suggested that the standard deviation for this distribution is 1.75 rather than 2, and that intakes to produce a given probability of renal effects are 50% higher than predicted by the model (Piscator 1985). Possible reasons for the discrepancy of the model with the Buchet et al. (1990) study, but agreement with the Nogawa et al. (1989) study, include differences in the cutoffs for elevated β_2-microglobulinuria and differences in estimation of dietary cadmium absorption.

A chronic-duration oral MRL has been derived from the NOAEL of 0.0021 mg/kg/day in the Nogawa et al. (1989) study. The MRL is 0.0002 mg/kg/day, using an uncertainty factor of 10 to account for sensitive members of the population (see the footnote to Table 2-2 and Appendix A). The chronic-duration oral MRL is shown in Figure 2-2.

Proteinuria does not decrease when oral exposure to cadmium stops. Renal tubular dysfunction and reduced glomerular filtration increase in severity after cessation of environmental exposure (Iwata et al. 1993; Kido et al. 1990b). Although kidney failure is not the primary cause of death among populations environmentally exposed to cadmium, increased rates of mortality from renal disease have been observed in populations of Belgium (Lauwerys and De Wals 198l), England (Inskip and Beral 1982) (although not significant), and Japan (Nakagawa et al. 1987) (significant for females and not significant for males). The increased calcium excretion associated with cadmium-induced renal damage may also increase the risk for osteoporosis, particularly in post-menopausal women (Buchet et al. 1990).

In two fatal cases of oral cadmium poisoning, anuria was present in one individual who ingested 25 mg/kg cadmium as cadmium iodide. Damage to the kidneys was reported at autopsy but was not further specified (Wisniewska-Knypl et al. 1971). The kidneys were reported as normal at autopsy in an individual who died 2 days after ingesting 1,840 mg/kg cadmium (Buckler et al. 1986).

Numerous studies in rats, mice, and rabbits confirm that oral exposure to cadmium causes kidney damage including proteinuria and tubular damage (Andersen et al. 1988; Bernard et al. 1980, 1988a, 1992; Bomhard et al. 1984; Borzelleca et al. 1989; Cardenas et al. 1992a, 1992b; Cha 1987; Fingerle et al. 1982; Gatta et al. 1989; Gill et al. 1989b; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Kozlowska et al. 1993; Mangler et al. 1988; Masaoka et al. 1994; Pleasants et al. 1992, 1993; Prigge 1978a; Steibert et al. 1984; Stowe et al. 1972; Wilson et al. 1941). Histopathological findings include focal necrosis of proximal tubular epithelial cells and cloudy swelling in renal tubules (Cha 1987).

Some studies have also shown no effect on renal function (Basinger et al. 1988; Borzelleca et al. 1989; Boscolo and Carmignani 1986; Groten et al. 1990; Jamall et al. 1989; Loeser and Lorke 1977a, 1977b).

In acute-duration gavage studies in rats, decreased urine flow (Kotsonis and Klaassen 1977) and histopathologic evidence of kidney damage have been reported (Borzelleca et al. 1989) at the very high doses of 150 and 138 mg/kg/day, respectively. No effect on renal function was reported in rats receiving 13.9 mg/kg/day for 10 days in drinking water (Borzelleca et al. 1989). Mice treated with a single gavage dose showed tubular necrosis at 88.8 mg/kg in one study (Andersen et al. 1988), but no effects on the, kidney in another study at a dose of 112 mg/kg (Basinger 1988). Proteinuria is a common finding in intermediate-duration oral exposure studies in rats (Bernard et al. 1988a; Cardenas et al. 1992a, 1992b; Kotsonis and Klaassen 1978; Prigge 1978a), as are histopathologic changes in the kidney (Gatta et al. 1989; Itokawa et al. 1974; Kotsonis and Klaassen 1978; Wilson et al. 1941). Renal clearance was decreased in one study (Kawamura et al. 1978). Both increases (Pleasants et al. 1992, 1993) and decreases (Kozlowska et al. 1993) in relative kidney weight have been reported. These effects occurred in rats at doses ranging from 2 to 30 mg/kg/day. No renal effects were seen in dogs receiving 0.75 mg/kg/day cadmium for 3 months (Loeser and Lorke 1977b), but interstitial renal fibrosis was observed in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972). Renal dysfunction has been reported in rhesus monkeys exposed to 1.2 mg/kg/day for 9 years, but not at 0.4 mg/kg/day (Masaoka et al. 1994). Adverse renal effects are common in rats following chronic-duration oral exposure to cadmium. Proteinuria (Bernard et al. 1992; Bomhard et al. 1984) and histopathologic damage (Fingerle et al. 1982; Mangler 1988) have been reported at doses ranging from 1.8 to 12.5 mg/kg/day cadmium.

The hypothesis that a critical concentration of approximately 200 μg/g in the renal cortex must be reached before proteinuria develops is generally supported by the animal data (Bhattacharyya et al. 1988c; Kotsonis and Klaassen 1978; Manger et al. 1988; Shaikh et al. 1989; Viau et al. 1984).

Representative NOAEL and LOAEL values for kidney effects for each species and duration category, expressed as ingested dose, are recorded in Table 2-2 and plotted in Figure 2-2.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to cadmium.

Evidence for endocrine effects in animals after oral exposure to cadmium is limited to histopathologic examination of endocrine tissues. No adverse effects were seen in parathyroid glands from female Wistar rats exposed to 8 mg Cd/kg/day via drinking water for 90 days (Kawamura et al. 1978) or in adrenal gland from male Sprague-Dawley rats exposed to 8 mg/kg/day via drinking water for 24 weeks (Kotsonis and Klaassen 1978). Pituitary, adrenals, thyroid and thymus were unaffected in Wistar rats exposed to 3 mg/kg/day cadmium via feed for 3 months (Loeser and Lorke 1977a). Wilson et al. (1941) reported pancreatic atrophy and pancreatitis in rats from cadmium at 2.79 mg/kg/day via feed for 100 days. In rabbits exposed to 14.9 mg Cd/kg body weight/day via drinking water for 200 days the pancreas had moderate concentrations of cadmium, but no interstitial fibrosis or other pathologic alterations (Stowe et al. 1972).

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

Coarse fur was reported in Long-Evans rats receiving 6.13 mg/kg/day cadmium during Gd 6-15 (Machemer and Lorke 1981). A ruffled hair coat was reported in Wistar rats receiving 40 mg/kg/day cadmium by gavage 5 days a week for 14 weeks (Baranski and Sitarek 1987). No other reports of dermal effects after oral exposure to cadmium were located.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to cadmium.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to cadmium were located.

Decreased body weight and decreased rates of growth are common findings in studies where experimental animals are orally exposed to cadmium. Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium exhibited a 12% decrease in body weight, but 100 mg/kg had no effect (Kotsonis and Klaassen 1977). Daily gavage doses of 15.3 mg/kg over a 10-day period caused a 79% decrease in body weight gain in male Sprague-Dawley rats (Borzelleca et al. 1989). Significant reductions in maternal weight gain have also been reported (Baranski 1985; Machemer and Lorke 1981).

Body weight reductions are also seen in intermediate-duration studies. For example, in a 14-week exposure via drinking water in male Long-Evans rats, 2.9 mg/kg/day had no effect on body weight gain; however, 5.8 mg/kg/day caused a 6-23% decrease and 11.6 mg/kg/day caused a 47-58% decrease (Pleasants et al. 1992, 1993). In general, intermediate-duration doses in feed or drinking water of 3 mg/kg/day or less have either no effect or only a small effect (10-20% decrease) on body weight in rats (Carmignani and Boscolo 1984; Jamall et al. 1989; Loeser and Lorke 1977a; Muller et al. 1988; Ogoshi et al. 1989; Perry et al. 1989; Wilson et al. 1941). Higher doses (4-14 mg/kg/day) had no effect in some studies (Kostial et al. 1993; Kotsonis and Klaassen 1978; Prigge 1978a; Viau et al. 1984) and small effects in others (Cha 1987; Kawamura et al. 1978; Kozlowska et al. 1993). A 29% decrease in maternal weight gain was observed in rats exposed to a high dose of 40 mg/kg/day (Baranski and Sitarek 1987). In mice, a dose of 4.8 mg/kg/day had no effect on maternal weight gain, but a dose of 9.6 mg/kg/day caused a 14% decrease (Webster et al. 1978). A high dose of 232 mg/kg/day in mice caused a 29% decrease in body weight (Waalkes et al. 1993). Beagle dogs were unaffected at 0.75 mg/kg/day (Loeser and Lorke 1977b), as were rabbits at up to 2.2 mg/kg/day (Boscolo and Carmignani 1986; Tomera and Harakai 1988). A small decrease (11%) was seen in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972).

A chronic-duration study in rhesus monkeys reported decreased growth rates at 0.4 mg/kg/day, but no effect at 0.12 mg/kg/day (Masaoka et al. 1994). No effect on body weight was seen in rats at up to 4.4 mg/kg/day (Decker et al. 1958; Fingerle et al. 1982; Mangler 1988), but a small effect was seen at 7 mg/kg/day (Waalkes and Rehm 1992). Decreased terminal body weight was observed in mice after 12 months of drinking-water exposure to a high dose of 57 mg/kg/day (Hays and Margaretten 1985).

Metabolic Effects. Hyperthermia and metabolic acidosis were reported in a human male who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

No studies were located regarding metabolic effects in animals after oral exposure to cadmium.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to cadmium.

Numerous studies in rats, mice, and monkeys have established the capability of cadmium to affect the immune system, but the clinical significance of the effects is not clear. In mice, intermediate-duration oral exposure to cadmium has been shown to increase resistance to viral infection (Exon et al. 1986), to be without effect on natural or acquired resistance to infection (Bouley et al. 1984), and to increase mortality

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2.2.2.4 Neurological Effects

A few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. These studies used hair cadmium as an index of exposure (see Section 2.7.1 for a discussion of the limitations of using hair as an indicator of exposure). End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985), and disruptive behavior in Navy recruits (Struempler et al. 1985). The usefulness of the data from these studies is limited because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and an inadequate quantification of cadmium exposure.

Although a cadmium induced neurotoxicity has not been clearly demonstrated in human studies, it has been observed in animal studies. Both a single oral exposure (Kotsonis and Klaassen 1977) and intermediate duration exposure of adult rats to cadmium resulted in significantly decreased motor activity (Kotsonis and

Klaassen 1978; Nation et al. 1990). Intermediate-duration oral exposure to cadmium has also been reported to cause weakness and muscle atrophy (Sato et al. 1978), induce aggressive behavior (Baranski and Sitarek 1987), induce anxiety as manifested by increased passive avoidance behavior (Nation et al. 1984) and by increased ethanol consumption (Nation et al. 1989), and alter brain biogenic amine content and enzyme activities (Murthy et al. 1989). Doses associated with these effects range from 5 to 40 mg/kg/day cadmium. Degenerative changes in the choroid plexus have been reported in mice exposed to 1.4 mg/kg/day cadmium in drinking water for 22 weeks (Valois and Webster 1989). Peripheral neuropathy has been reported in rats after a 31-month exposure to cadmium in drinking water (Sato et al. 1978). Neurological effects in offspring of animals orally exposed to cadmium during gestation are discussed in Section 2.2.2.5. Representative NOAEL and LOAEL values for neurological effects of oral cadmium exposure in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in men or women after oral exposure to cadmium.

A number of animal studies have shown adverse reproductive effects to male and female reproductive capacity from cadmium exposure. In male rats and mice, acute oral exposure to near-lethal (60-100 mg/kg) doses can cause testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989), and concomitant decreased fertility (Kotsonis and Klaassen 1978). Lower-dose acute exposures of 25-50 mg/kg did not result in reproductive toxicity in male animals (Andersen et al. 1988; Bon-hard et al. 1987; Dixon et al. 1976).

The following intermediate-duration dosing regimens resulted in neither testicular histopathologic lesions nor a decrease in male reproductive success: 0.25 mg Cd/kg/day via gavage for 10 weeks (Bomhard et al. 1987); 5 mg/kg/day via water for 30-90 days (Dixon et al. 1976); 2.5 mg/kg/day via food for 4 weeks (Groten et al. 1990); 8 mg/kg/day via water for 24 weeks (Kotsonis and Klaassen 1978); 3 mg/kg/day via food for 12 weeks (Loeser and Lorke 1977a, 1977b); 2.9 mg/kg/day via water for 14 weeks (Pleasants et al. 1992); and 4.64 mg/kg/day via water for 70-80 days (Zenick et al. 1982). Some dosing regimens have resulted in adverse reproductive effects. Male rats exposed to 8.58 mg Cd/kg/day in water for 10 weeks developed necrosis and atrophy of seminiferous tubule epithelium (Cha 1987). Rats exposed to 5.8 mg/kg/day via water for 14 weeks (Pleasants et al. 1992) or 11.6 mg/kg/day via water for 14 weeks (Pleasants et al. 1993) developed increased testes weight. Rats exposed to 12.9 mg/kg/day in water for 120 days developed significantly increased relative testis weight, decreased sperm count and motility,

decreased seminiferous tubular diameter, and seminiferous tubular damage (pyknotic nuclei, multinucleated giant cells, interstitial edema, and dilated blood vessels) (Saxena et al. 1989). In a protocol designed to assess the effects of vitamins on cadmium toxicity, Pleasants et al. (1992, 1993) reported that vitamins A and D_3 reduced the amount of cadmium-related increase in testis weight. Bomhard et al. (1987) reported no histopathologic lesions (other than those found in control animals as part of aging) in testes of rats receiving 10 weekly doses of 5 mg Cd/kg and followed for up to 30 months.

Higher doses of cadmium were generally needed to elicit a reproductive toxic response in females compared to the males. Although a dose of 65.6 mg Cd/kg/day via gavage for 10 days was sufficient to produce testicular atrophy and loss of spermatogenic element in male rats, no effects were seen in female rats up to 138 mg/kg/day (Borzelleca et al. 1989). Decreased percentage of fertilized females and percentage of pregnancies were reported at 61.32 mg Cd/kg/day via gavage for 10 days during gestation (Gd 6-15) (Machemer and Lorke 1981). No effect was seen at doses up to 18.39 mg/kg/day (Machemer and Lorke 1981). Baranski (1987) also reported no treatment related effects on number or percentage of females pregnant with 28.8 mg Cd/kg/day via gavage for 20 days during gestation (Gd l-20). Baranski and Sitarek (1987), however, administered 40 mg/kg by gavage 5 days a week for 14 weeks to female rats and observed a significant increased duration (twice as long) of the estrus cycle starting at 7-8 weeks and persisting to 14 weeks of exposure and the termination of the experiment. This adverse effect was not seen at 4 mg/kg (Baranski 1983; Baranski and Sitarek 1987).

Petering et al. (1979) exposed female rats to either 2.61 mg/kg/day via drinking water for 60 days prior to gestation or during gestation, or 5.23 mg/kg/day via drinking water for 111 days including 90 days prior gestation plus 21 days during gestation. These doses had no significant effects compared with controls for the number of pups stillborn. Pond and Walker (1975) also observed no effects in females from a cadmium exposure of 19.7 mg/kg/day via food for 21-25 days, including Gd 1 through lactation day (Ld) 1, on number of pups born. No effects from a cadmium exposure on number of pups born to females were observed for an exposure of 8.2 mg/kg/day via food for 15 days including Gd 6-20 (Sorell and Graziano 1990).

A dose of 10 mg Cd/kg/day once a day via gavage for 9 weeks (6 weeks prior to gestation and 3 weeks of gestation) significantly decreased the number of copulating and pregnant females, and the number of implants and live fetuses (Sutou et al. 1980). No effect was seen at 1 mg/kg/day (Sutou et al. 1980).

Reproductive effects on both male and female rats orally exposed to 2.5 mg/kg/day via drinking water for 180 days may have resulted in the observed decrease in litter size and increased interval between litters. Both males and females were treated over two generations. Three of five pairs failed to breed in the second generations (Schroeder and Mitchener 1971). No histopathologic lesions were found in testes or uteri of dogs given $CdCl_2$ at 0.75 mg/kg/day via food for 3 months (Loeser and Lorke 1977b).

Male rats were exposed to 0-14 mg Cd/kg/day via food for 77 weeks. The incidence of prostatic hyperplasias was increased above controls (1.8%) from the 3.5 mg Cd/kg/day dose. The overall incidence for prostatic lesions for all cadmium-treated groups was much lower in zinc-deficient rats, possibly because of a marked increase in prostatic atrophy that was associated with reduced zinc intake. Moreover, there was not a clear dose-response increase in prostatic proliferative lesions. Testicular tumors (exclusively benign interstitial tumors) increased significantly only at the highest-dose cadmium with diets adequate in zinc. Male Wistar rats exposed to cadmium in the drinking water at 0, 25, 50, 100, or 200 ppm developed tumors of the prostate (50 ppm), testes (200 ppm), and hematopoietic system (50 ppm), while dietary zinc deficiency has complex, apparently inhibitory effects on cadmium carcinogenesis by this route (Waalkes and Rehm 1992).

Red-white Meuse-Rhine-Yssel (MRY) dairy cows from two cohorts in Kempenland, Holland, were studied to detect reproductive effects of cadmium by using an historical data set. Data on accumulated exposure to cadmium had been recorded at slaughter over a 3-year period for cows in the 2 cohorts. Each cow was registered for fertility characteristics (decreased fertility, increased fetal death, increased complications at birth, and decreased twinning rate) and milk production; birth defects and body weights were not recorded. Cadmium content in the kidney was 2.5 times higher in the exposed cohort when compared to the unexposed. The cohort used as a control group (N=24) came from an area with cadmium ground water levels of 0.1 μg/L and cadmium soil levels of 0.4 mg/kg/dry weight. The exposed cohort (N=89) came from an area with cadmium ground water levels of 0.1-25 g/L and cadmium soil levels of 1-2.5 mg/kg/day weight. Two-sided 95% confidence intervals were calculated for all odds ratios derived from logistic regression and rate ratios resulting from the Cox proportional hazards model. A significantly increased number of inseminations were required for conception in cows from the exposed area, although the incidence of longer intervals between inseminations was not increased. Significantly fewer twins were born to cows from the exposed area and death among twins was increased (non-significantly). No increased intra-uterine death was observed in cows from the exposed area. The number of cows slaughtered for

reasons possibly related to cadmium (perinatal death and premature death) was not increased (Kreis et al. 1993).

Representative NOAEL and LOAEL values for reproductive effects in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

There are very limited data on the developmental effects of cadmium in humans. Urinary cadmium content was measured in women three days after giving birth and compared to smoking habits and birth weight of offspring. Among nonsmoking women, when cadmium content was expressed as μg/L, cadmium levels were higher in women with infants of below-normal birth weight. However, when cadmium content was expressed as μg/g creatinine, cadmium levels were lower in women with infants with below-normal birth weight. Cadmium levels in smoking women were lower in both μg/L and μg/g in women with infants with below-normal birth weight (Cresta et al. 1989).

Cadmium and lead content in hair of rural French women and their newborns related to parity, birth weight, and maternal hypertension. The cadmium content was slightly higher in the newborns' hair when compared to their mothers' hair. A positive association for cadmium content was found between newborn and mother (i.e., placental transfer). Cadmium levels in the hair of newborns of hypertensive mothers were 3 times as high as in the hypertensive mothers themselves (Hue1 et al. 1981). No other studies were located regarding developmental effects in humans after oral exposure to cadmium.

A number of studies in rats and mice indicate that cadmium can be fetotoxic from oral exposures prior to and during gestation. This fetotoxicity is most often manifested as reduced fetal or pup weights (Ali et al. 1986; Baranski 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Petering et al. 1979; Pond and Walker 1975; Sore11 and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988), but malformations, primarily of the skeleton, have been found in some studies (Baranski 1985; Machemer and Lorke 1981; Schroeder and Mitchener 1971). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the l-20 mg/kg/day range.

The most sensitive indicator of developmental toxicity of cadmium in animals appears to be neuro-behavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg/day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months (Baranski et al. 1983). Pups from dams exposed to 0.7 mg/kg/day during gestation had significant delays in cliff aversion and swimming behavior. Locomotor activity was significantly increased In post-weaning measurements, locomotor activity was significantly decreased in treated groups at 60 days of age; conditioned avoidance behavior was also significantly decreased when tested at 60 and 90 days of age (Ali et al. 1986).

Nagymajtenyi et al. (1997) also reported behavioral and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. Three consecutive generations of Wistar rats were orally treated by gavage with 3.5, 7.0, or 14.0 mg Cd/kg bw (as cadmium chloride diluted in distilled water) over the period of pregnancy, lactation, and 8 weeks after weaning. Behavioral (open field behavior) and electrophysiological (spontaneous and evoked cortical activity, etc.) parameters of male rats from each generation were investigated at the age of 12 weeks. The main behavioral outcomes were increased vertical exploration activity (rearing) and increased exploration of an open-field center. The spontaneous and evoked electrophysiological variables showed dose- and generation-dependent changes (increased frequencies in the electrocorticogram, lengthened latency and duration of evoked potentials, etc.) signaling a change in neural functions. The results indicate that low-level, multigeneration exposure of rats to inorganic cadmium can affect nervous system function.

Desi et al. (1998) continued the above studies to further evaluate cadmium associated changes in behavior and neurological function in rats following different dosage regimens during pregnancy. Female Wistar rats were given 3.5, 7.0, or 14.0 mg Cd/kg body weight (cadmium chloride dissolved in distilled water) in three different treatment regimes: days 5-15 of pregnancy; days 5-15 of pregnancy + 4 weeks of lactation; and days 5-15 of pregnancy + 4 weeks of lactation followed by the same oral treatment of male rats of the Fl generation for 8 weeks. The behavioral (open-field exploration) and electrophysiological (electrocortico gram, cortical-evoked potentials, conduction velocity and refractory periods of a peripheral nerve) parameters of Fl male rats exposed by various treatments were investigated at the age of 12 weeks. The results indicate that cadmium altered the spontaneous and evoked electrophysiological functions (e.g., increased the frequency of the electrocorticogram, lengthened the latency and duration of evoked potentials, etc.) in a dose and treatment time dependent manner. Only combining treatment during the prenatal development and the 4-week suckling period resulted in a significant dose-dependent decrease of horizontal and vertical

exploratory activity and a significantly lower exploration frequency of the open-field center. The results suggests that low-level pre- and postnatal inorganic cadmium exposure affects the electrophysiological and higher order functions of the nervous system.

A study by Gupta et al. (1993) examined the developmental profiles of DNA, RNA, proteins, DNA synthesis, thymidine kinase activity, and concentrations of zinc and cadmium in the brain of neonates from dams exposed to cadmium acetate at 5-6.3 mg/kg/day in drinking water during gestation, and 7-8 mg/kg/day during a 21-day lactation period. Pup brain and body weights were significantly decreased in the cadmium exposed pups on Ld 7-21. Cadmium brain accumulation was significantly increased in exposed pups on Ld 7 and remained at similar levels on Ld 14 and 21. DNA and thymidine kinase brain levels were significantly decreased in treated pups compared with controls on Ld 7, 14, and 21. The toxicological significance of changes in DNA incorporation and thymidine kinase activity are uncertain.

Xu et al. (1993b) determined lipid peroxide (LPO) concentrations in rat pups in various organs as an index of cadmium toxicity. Male and female Wistar mice were exposed to cadmium in drinking water at 0, 5.7, or 14.25 mg/kg/day for 2 months prior to mating. The pregnant females continued to be exposed during gestation and lactation. Litter size and pup survival rates were unaffected by cadmium. Body weights were not statistically different between the exposed and control groups. In pups, brain weights (at 5.7 and 14.25 mg/kg/day) and liver, kidney, and heart weights (at 14.25 mg/kg/day) were significantly decreased. Although the relative organ weights were lower in the high-dose group, the difference from controls was not statistically significant. LPO concentrations in all organs were significantly increased in pups on Ld 7 at 14.25 mg/kg/day except in the kidney; concentrations in the liver, heart, and brain were 131.5, 156, and 237.4%, respectively, of the concentrations in controls.

In contrast to most of the study results, Saxena et al. (1986) reported no developmental effects from an exposure to 21 mg Cd/kg/day via drinking water during gestation (Gd 0-20). This study evaluated simultaneous exposure to lindane (20 mg lindane/kg via gavage on Gd 6-14) and cadmium acetate in drinking water at doses that individually did not cause maternal or developmental effects. Maternal toxicity (significantly decreased weight gain) and developmental toxicity were only observed in the cadmium plus lindane group. Fetal body weight was significantly decreased; intrauterine death and the rate of skeletal anomalies were significantly increased. Anomalies consisted of decreased ossification, wavy ribs, and scrambled sternebrae.

Representative NOAEL and LOAEL values for developmental effects in animals from oral exposure to cadmium for acute and intermediate durations are listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

There are mixed results on the genotoxicity of oral cadmium exposure. Examination of lymphocytes from women environmentally exposed to cadmium (Itai-Itai patients) have shown statistically significant increases in chromosomal aberrations in one study (Shiraishi and Yoshida 1972), but these results were not replicated in another study (Bui et al. 1975). A recent study of inhabitants of a cadmium-polluted area of China found an increase in chromosomal aberrations that was correlated with urinary cadmium level (Tang et al. 1990).

No abnormalities of bone marrow were found in mice exposed to cadmium at 600 ppm in the diet for 1 month (Deknudt and Gerber 1979), but bone marrow abnormalities were found in mice after 1 week at 3.52 mg/kg/daily in a dosing regimen of cadmium by daily gavage for l-3 weeks with a dose range from 1.76-17.6 mg/kg (Mukherjee et al. 1988b). No evidence for germ cell mutations in male rats orally exposed to cadmium (the dominant lethal test) has been found (Sutou et al. 1980; Zenick et al. 1982). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

A few studies of cancer rates among humans orally exposed to cadmium have been performed. No significant increase in cancer rates was found among residents of a cadmium-polluted village in England (Inskip and Beral 1982) or in prostate, kidney, or urinary tract cancer among residents of a cadmium polluted area of Belgium (Lauwerys and De Wals 1981). The geographic distribution of elevated rates of prostate cancer incidence was shown to parallel the distribution of elevated cadmium concentrations in water, soil, or grain crops in Alberta, Canada (Bako et al. 1982). In none of these three studies were estimates made of cadmium exposures of populations as a whole or of individuals with cancer. A retrospective mortality study was done for three areas of Japan classified on the basis of rice Cd-content as highly polluted, slightly polluted, or non-polluted. No significant differences were found in mortality from cancer of all sites including prostate cancer (Shigematsu 1984).

One study examined cadmium, zinc, and copper in human kidney tumors and normal kidneys. Kidneys with renal cell carcinoma in cortex from 31 cases (20 men and 11 women) were compared to kidneys of patients who had died from causes other than a malignant disease from 17 controls (9 men and 8 women). No one in this study had been occupationally exposed. Smoking habits for patients were recorded. The level of cadmium in tumor tissue did not correlate with cadmium in cortex or medulla in the same kidney. No significant difference was found between cases and controls; although smoking cases had higher levels of cadmium. It was concluded that cadmium was not a risk factor for renal cell carcinoma (Hardell et al. 1994).

Inhabitants of cadmium-polluted areas of Japan with elevated urinary retinol binding protein excretion had a mortality rate from malignant neoplasms no different from expected (Nakagawa et al. 1987). Overall, there is little evidence of an association between oral exposure to cadmium and increased cancer rates in humans, but the statistical power of the available studies to detect an effect was not high.

In rats and mice, earlier studies on chronic oral exposure to cadmium have not reported an increased overall cancer incidence or the incidence of specific tumor types (Kanisawa and Schroeder 1969; Levy and Clack 1975; Levy et al. 1975; Loser 1980; Mangler et al. 1988; Schroeder et al. 1964, 1965). However, maximum daily doses tested were only 1 mg/kg/day in mice (Schroeder et al. 1964) and 3.5 mg/kg/day in rats (Loser 1980) and, in most of these studies, histopathologic examination was limited compared to contemporary standards. Loser (1980) did perform a relatively thorough histological examination. A few additional animal studies of noncancer effects of chronic-duration oral cadmium exposure have indicated that no dose-related increases in tumors were found at maximum doses of 4.01 mg/kg/day in rats (Fingerle et al. 1982) or 8 mg/kg/day in mice (Watanabe et al. 1986).

More recently, Waalkes and Rehm (1992) evaluated the effects of chronic dietary zinc deficiency on oral cadmium carcinogenesis in male Wistar rats. Rats were exposed to cadmium at 0, 25, 50, 100, or 200 ppm with adequate (60 ppm) zinc or deficient zinc (7 ppm) in the diet for 77 weeks. A complete necropsy was performed on all animals. Survival rate and food consumption were not affected in this study. The incidence of prostatic proliferative lesions, both hyperplasias and adenomas, was increased above controls (1.8%) in both zinc adequate (20%) and zinc deficient (14%) rats fed 50 ppm cadmium. The overall incidence for prostatic lesions for all cadmium-treated groups was much lower in zinc-deficient rats, possibly because of a marked increase in prostatic atrophy that was associated with reduced zinc intake. Moreover, there was not a clear dose-response increase in prostatic proliferative lesions. Cadmium

treatment resulted in an elevated leukemia incidence (large granular lymphocytes; maximum 4.8-fold over control) in both zinc-adequate and zinc-deficient groups. A significant increase in the incidence of leukemia in the zinc-adequate diet was seen at 50 and 100 ppm cadmium, but not at 200 ppm. Zinc deficiency reduced the potency of cadmium (i.e., higher doses needed for comparable incidence). There was a consistent increase in the incidence of leukemia with an increasing cadmium dose in the zinc-deficient group, but the increase was statistically significant only at 200 ppm. The highest incidence of leukemia observed from cadmium (28%), however, was seen in the 200 ppm zinc-deficient rats. Testicular tumors (exclusively benign interstitial tumors) increased significantly only at 200 ppm cadmium with diets adequate in zinc. A significant positive trend was noted for development of testicular neoplasia with increased cadmium dose. Thus, oral cadmium exposure, in this study, was associated with tumors of the prostate, testes, and hematopoietic system in rats, while dietary zinc deficiency has complex, apparently inhibitory, effects on cadmium carcinogenesis by this route.

A subsequent study by Waalkes et al. (1993) using male B6C3F$_1$ mice evaluated the effects of cadmium exposure on tumor incidence at various times after the initiation of the carcinogenic process. The possible role of metallothionein in the susceptibility of transformed cells to cadmium cytotoxicity was also evaluated. At 5 weeks of age, mice received an intraperitoneal injection of N-nitrosodiethylamine (NDEA) at 90 mg/kg. At 2, 4, 8, 16, or 32 weeks post-NDEA injection, mice received water containing 1,000 ppm cadmium *ad libitum* for up to 48 weeks of post-NDEA exposure. Cadmium exposure caused a marked “reduction” in liver tumor incidence in NDEA treated mice even when given as late as 32 weeks after the initial NDEA treatment. Cadmium alone eliminated the spontaneously occurring incidence of liver tumors (i.e., none out of 25 compared with 5 of 25 in the controls). Liver tumors produced by NDEA were typically basophilic adenomas. Cadmium resulted in a modest reduction in lung tumor incidence, statistically significant (28% reduction) only for the 16-48-week cadmium treated group pretreated with NDEA. Lung tumors were typically adenomas of alveolar cell origin. Cadmium alone eliminated spontaneously occurring lung tumors compared with the controls. Cadmium did significantly reduce the multiplicity of tumors induced by NDEA. NDEA alone typically induced 7 tumors per lung, while NDEA plus cadmium treatment reduced the number of tumors to 2.5-3.5 (data taken from a graph) with some cases showing an 80% reduction in tumor numbers. Lung tumors found in the cadmium plus NDEA treatment groups were also of a smaller overall size than those found in the NDEA-only treatment groups. Relatively little metallothionein was present in liver carcinomas,‘ liver adenomas, and lung adenomas as indicated by immunohistochemistry. This finding was confirmed biochemically for the liver tumors. The authors concluded that cadmium can effectively “impair” tumor formation in the lungs and liver of male

$B6C3F_1$ mice, and appears to be able to selectively destroy existing preneoplastic and/or tumor cells (adenomas). The mechanism may involve a reduced activity and responsiveness of the metallothionein system in transformed liver cells.

A 2-stage initiation/promotion experiment evaluated the promoting effects of cadmium chloride in the drinking water in rats. Cadmium exposure resulted in the following alterations in tumorigenic outcome: in the liver, hepatocellular carcinomas (initiated with diethyl nitrosamine) were decreased; in the stomach, tumors (initiated with N-methyl-*N*-nitro-nitrosoguanidine plus NaCl at 10% in the diet) were not affected; in the kidney, tumors (initiated with N-ethyl-*N*-hydroxyethyl nitrosamine) showed increased dysplastic foci but no increase in renal cell tumors; in the pancreas, tumors (initiated with *N*-nitroso-bis [2-oxopropyl] amine), had a nonsignificant increase in adenocarcinomas (female hamster study); and in the skin (initiated with 7,12-dimethyl benz(a)anthracene), there was no effect (female SENCAR mouse study) (Kurokawa et al. 1989).

Neither the human nor the animal studies provide sufficient evidence to determine whether or not cadmium is a carcinogen by the oral route.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to cadmium.

Some guinea pigs died 2 or 6 weeks after being exposed in a skin depot (3.1 cm^2) to 2 mL of 0.239 molar aqueous of cadmium chloride (0.14 mg/kg body weight) (Wahlberg 1965). However, it is difficult to attribute these deaths to cadmium exposure, due to the low dose compared to oral LD_{50} values and to the fact that no necropsy was done to determine whether the exposed guinea pigs might have died from pneumonia (which killed some control guinea pigs) (Wahlberg 1965).

2.2.3.2 Systemic Effects

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

Dermal Effects. Among eczema patients routinely patch-tested with 2% cadmium chloride, 25 out of 1,502 showed some reaction (Wahlberg 1977). Since no reaction was found at lower dilutions in reactive patients (Wahlberg 1977), the effect was likely direct irritation of the skin and is indicated as a LOAEL value in Table 2-3.

No studies were located regarding dermal effects in animals after dermal exposure to cadmium.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to cadmium.

Rats exposed to high concentrations of cadmium pigments or cadmium oxide in air had excessive lacrimation four hours after exposure (Rusch et al. 1986), possibly due to a direct irritation effect on the eyes.

2.2.3.3 Immunological and Lymphoreticular Effects

Dermal exposure to cadmium does not appear to affect the immune system significantly. One report of workers with extensive exposure to cadmium dust reported an increase in complaints of eczema (Friberg 1950); however, no subsequent studies have confirmed any association. Routine patch tests among dermatitis and eczema patients using up to 2% cadmium chloride solutions have found skin irritation at 2%, but no evidence of allergic reactions at a dose of 1% among people without known prior cadmium exposure (Rudzki et al. 1988; Wahlberg 1977) or among workers occupationally exposed to cadmium (Rudzki et al. 1988). Individuals with yellow tattoos containing cadmium sulfide often experience swelling of the surrounding skin on exposure to ultra violet (UV) irradiation (Bjornberg 1963); however, this may be the result of dermal damage from the photoconductivity of cadmium sulfide rather than a direct immunological reaction.

Table 2-3. Levels of Significant Exposure to Cadmium - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
ACUTE EXPOSURE								
Systemic								
Human	once	Dermal	1%	2%	(skin irritation)			Wahlberg 1977 $CdCl_2$
Rat (Sprague-Dawley)	2 hr	Ocular				112 mg/m^3	(eyes closed from exposure)	Rusch et al. 1986 CdO fume
Rat (Sprague-Dawley)	2 hr	Ocular		99 mg/m^3	(excessive lacrimation)			Rusch et al. 1986 CdS
Rat (Sprague-Dawley)	2 hr	Ocular		97 mg/m^3	(excessive lacrimation)			Rusch et al. 1986 CdSeS
Immunological/Lymphoreticular								
Human	once		1%					Rudzki et al. 1988 $CdCl_2$

hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level

Guinea pigs showed no contact sensitization following intradermal or topical exposure to cadmium chloride at concentrations up to 0.5% (Wahlberg and Boman 1979). NOAEL values for immunological effects in humans and guinea pigs after dermal cadmium exposure are shown in Table 2-3.

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

2.2.3.4 Neurological Effects
2.2.3.5 Reproductive Effects
2.2.3.6 Developmental Effects
2.2.3.7 Genotoxic Effects

Other genotdxicity studies are discussed in Section 2.5,

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to cadmium.

2.3 TOXICOKINETICS

Cadmium metal and cadmium salts have low volatility and exist in air primarily as fine suspended particulate matter. When inhaled, some fraction of this particulate matter is deposited in the airways or the lungs, and the rest is exhaled. Large particles (greater than about 10 pm in diameter) tend to be deposited in the upper airway, while small particles (approximately 0.1 pm) tend to penetrate into the alveoli. Mucociliary clearance removes cadmium particles from the upper tract. Some soluble cadmium compounds (cadmium chloride and cadmium sulfate) may undergo limited absorption from particles deposited in the respiratory tree, but the major site of absorption is the alveoli. About one-quarter of the total inhaled cadmium is absorbed. Cadmium absorption from cigarettes appears to be higher than absorption from cadmium aerosols, probably due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition. The absorption of cadmium compounds from the lung does not always correlate with solubility as defined with water as the solvent. Little is known about the solubility of cadmium compounds in the biological fluids with the levels of CO_2 present in the lung.

Inhalation exposures primarily occur in the workplace. Most people in the general population are exposed to cadmium in the food or water. Most ingested cadmium passes through the gastrointestinal tract without being absorbed. Only about 5% of the total ingested cadmium (in food or water) is absorbed. The retention of cadmium in the gut slowly decreases over a period of 1-3 weeks. Absorption from the gut appears to take place in two phases, uptake from the lumen into mucosa, then transfer into the circulation. Factors affecting cadmium absorption include metal-metal (e.g., iron, calcium, chromium, magnesium, zinc) and metal-protein interactions (glutathione, sulfhydryl containing enzymes) in the body and in the food or water. Levels of other metals and proteins can vary with age and physiological status, and affect cadmium kinetics. Cadmium absorption is known to increase with iron or calcium deficiency, and increased fat in the diet (i.e., longer residency times for absorption to occur). Cadmium is not well absorbed by the skin (about 0.5%), and there is not a significant risk from skin exposure unless contact with the skin is for long periods of time or at very high levels.

Following absorption from any route of exposure, cadmium widely distributes throughout the body, with the major portion ending up in the liver and kidney. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40-50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline. Liver cadmium concentrations also begin near zero at birth, increase to typical values of l-2 μg/g wet weight by age 20-25, then increase only slightly thereafter. Liver and kidney cadmium concentrations are comparable after short-term exposure, but the kidney concentration exceeds the liver concentration following prolonged exposure, except exposure to very high levels. Tissue distribution and retention of cadmium can differ significantly with age.

Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces and is not absorbed into the body. Of the cadmium that is absorbed into the body, most is excreted very slowly, with urinary and fecal excretion being approximately equal. Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years. In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). Half-times for the human kidney have been estimated at between 6 and 38 years, and for the human liver at between 4 and 19 years. The placenta is only a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women. Cadmium can be excreted in human milk at levels from 5-10% of the levels in blood.

Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion readily bind to anionic groups (especially sulfhydryl groups) in proteins (e.g., albumin and metallothionein) and other molecules. Of particular importance to the toxicokinetics of cadmium is its interaction with the protein metallothionein, a low-molecular-weight protein capable of binding as many as seven cadmium atoms per molecule. Metallothionein is inducible in most tissues by exposure to cadmium, zinc, and other metals, as well as organic compounds and a variety of other physiologic stresses (irradiation, food deprivation, exercise, hypothermia, and inflammation). The exact physiologic functions of metallothionein are not known. The interaction of cadmium with metallothionein may be related to the chemical similarities between cadmium and zinc. Initially cadmium in plasma circulates primarily bound to albumin. Cadmium enters the liver where it becomes bound to metallothionein and is released to the blood stream. Metallothionein-bound cadmium is readily filtered by the renal glomerulus and reabsorbed from the glomerular filtrate by the proximal tubule cells. The current hypothesis is that cadmium bound to exogenous metallothionein is degraded in tubular lysosomes releasing free cadmium that then induces synthesis of proximal tubular cell metallothionein. Renal damage is believed to occur if there is a localization of free cadmium or an excessive concentration of cadmium that remains unbound to metallothionein. Metallothionein metabolism in liver and kidney is relatively independent of the exposure route; inhalation exposure also induces metallothionein in the lung and oral exposure induces metallothionein in the intestine.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Cadmium metal and cadmium salts have low volatility and exist in air primarily as fine suspended particulate matter. When inhaled, some fraction of this particulate matter is deposited in the airways or the lungs, and the rest is exhaled. Large particles (greater than about 10 pm in diameter) tend to be deposited in the upper airway, while small particles (approximately 0.1 pm) tend to penetrate into the alveoli. While some soluble cadmium compounds (cadmium chloride and cadmium sulfate) may undergo limited absorption from particles deposited in the respiratory tree, the major site of absorption is the alveoli. Thus, particle size, which controls alveolar deposition, is a key determinant of cadmium absorption in the lung (Nordberg et al. 1985).

No direct data are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure (5-20% after 15 minutes to 2 hours) (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986) due to absorption of cadmium and lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in lung differs somewhat among chemical forms, but the pattern does not correlate with solubility (Glaser et al. 1986; Rusch et al. 1986).

Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorption of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985).

Based on the physiology of the human respiratory tree, a comprehensive model has been developed to predict the kinetics of inhaled cadmium in humans (Nordberg et al. 1985). Results of this model suggest that only about 5% of particles >10 μrn in diameter will be deposited, up to 50% of particles <0.1 μrn will be deposited, and between 50-100% of cadmium deposited in the alveoli will ultimately be absorbed (Nordberg et al. 1985).

2.3.1.2 Oral Exposure

Most ingested cadmium passes through the gastrointestinal tract without being absorbed (Kjellstrom et al. 1978). Measurement of gastrointestinal absorption is complicated by the fact that not all of a dose initially retained in the gastrointestinal system can be considered to be absorbed, because some portion may be trapped in the intestinal mucosa without crossing into the blood or lymph (Foulkes 1984). Thus, measures of whole-body cadmium retention may overestimate cadmium absorption (at least in the short-term). On the other hand, some absorbed cadmium may be excreted in urine or feces, so that retention may underestimate exposure. However, this underestimate is probably minor because excretion of absorbed cadmium is very slow (see Section 2.3.4.2).

The total retention of cadmium in the bodies of humans has been measured following ingestion of radioactive cadmium. About 25% of a dose of cadmium administered mixed with food to 5 healthy adults was retained after 3-5 days, but retention decreased to about 6% after about 20 days (Rahola et al. 1973). Similar results were obtained with 14 healthy adults, with an average of 4.6% of cadmium chloride in water taken with a meal retained in the body l-2 weeks after a simultaneously administered fecal marker (trivalent chromium) had been completely excreted (McLellan et al. 1978). The body store of iron influences cadmium absorption; subjects with low iron stores (assessed by serum ferritin levels) had an average absorption of 8.9%, while those with adequate iron stores had an average absorption of 2.3% (Flanagen et al. 1978). The influence of chemical complexation of cadmium on human absorption was evaluated in seven volunteers who ingested brown crab meat (hepatopancreas) that had been labeled with radioactive cadmium chloride by prior feeding of the crabs (Newton et al. 1984). Whole-body counting was used to evaluate uptake. Whole-body retention in the volunteers ranged from 1.2 to 7.6% with a mean of 2.7% (Newton et al. 1984), only slightly lower than the values of 4.6-6% obtained using dissolved cadmium ion (McLellan et al. 1978; Rahola et al. 1973). Comparisons of body burden of cadmium in nonsmokers with estimated daily intakes from the diet provide estimates of cadmium absorption from food of 3-5% (Ellis et al. 1979; Morgan and Sherlock 1984). These results indicated that, in general, cadmium absorption from food is not dependent on chemical complexation. However, some populations with high dietary-cadmium exposure from Bluff oysters (McKenzie-Parnell et al. 1988) or seal meat (Hansen et al. 1985) have been found not to have elevated blood-cadmium levels, perhaps due to the particular form of cadmium in these foods.

Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. In mice, 0.5-3.2% of an oral dose of cadmium chloride was retained after 5 days (Engstrom and Nordberg 1979), and in rats, 2-3% of a single oral dose of cadmium chloride was retained (Moore et al. 1973; Schafer el al. 1990). Following 30 days of oral exposure, 0.2-0.3% of an administered dose was retained in rats (Muller et al. 1986). After 4 weeks of dietary exposure to cadmium, absorption of cadmium was reduced to one-third the absorption of unexposed rats (Schafer et al. 1990). After 35 days of exposure to cadmium chloride in drinking water, whole-body retention of cadmium was about 0.2% in female mice that had undergone pregnancy and lactation, but was only 0.08% in female mice that had not been pregnant (Bhattacharyya et al. 1986). Cadmium pigments (cadmium sulfide and cadmium sulfoselenide) appear to be absorbed much less than cadmium chloride in rats (ILZRO 1977).

The absorption of cadmium from the gastrointestinal tract has been extensively studied in rats and mice, and a number of factors are recognized that influence absorption. Absorption appears to take place in two phases: uptake from lumen into mucosa, and transfer into the circulation (Foulkes 1985). Phase 1 may involve sequestering of cadmium by metallothionein (Foulkes 1980), but any protective effect is overloaded at moderate doses (Kotsonis and Klaassen 1978). Uptake behaves like a saturable process with fractional absorption decreasing at high concentrations (Foulkes 1980). There is evidence, however, to suggest that this saturation results from charge neutralization at the membrane (Foulkes 1985), so that it need not be assumed that there is a specific system for carrying cadmium into the body. At doses high enough to damage gastrointestinal mucosa, fractional absorption is increased (Andersen et al. 1988; Goon and Klaassen 1989; Lehman and Klaassen 1986). Cadmium bound to metallothionein was absorbed by rats to a lesser extent than cadmium added to the diet as cadmium chloride, but kidney cadmium content was only slightly less (Groten et al. 1990).

Maitani et al. (1984) compared the distribution of cadmium after oral administration of either cadmium ions or Cd-thionein (Cd-TH) in male CF-1 mice given 0.5 mg Cd/kg, per os (po), as $CdCl_2$ in saline, $CdCl_2$ in control rat liver homogenate, Cd-TH in saline, Cd-TH in liver homogenate, or liver homogenate from Cd-treated rats. In all cases, 85-90% of the cadmium dose was present in feces within 24 hours. However, in groups receiving $CdCl_2$, more cadmium was found in feces on days 2 and 3, compared to those receiving Cd-TH. All treatments resulted in lower levels of cadmium in liver than in kidney. In a companion study, tissue levels indicated that less cadmium was absorbed when rats received Cd-TH in saline than $CdCl_2$ in saline. Cd-TH added to liver homogenate or liver homogenate containing Cd-TH increased the absorption of cadmium, resulting in renal cadmium levels similar to those in mice receiving $CdCl_2$ in saline. The kidney/liver cadmium concentration ratio (9) was the same for Cd-TH in all 3 media. Although Cd-TH gave much higher kidney/liver cadmium ratios than $CdCl_2$ (9 versus 2), renal cadmium concentrations were the same or lower than after $CdCl_2$ treatments. The authors concluded that the high kidney/liver cadmium ratio after Cd-TH treatment versus $CdCl_2$ was due to lower concentrations of cadmium in liver rather than marked increases in renal cadmium levels. While the chemical form of cadmium administered affects the absorption and distribution, the amount of cadmium reaching the kidney after Cd-TH administration is similar to that after $CdCl_2$ administration.

At moderate doses of cadmium, the presence of divalent and trivalent cations, such as calcium, chromium, magnesium, and zinc, may decrease cadmium uptake, probably by a nonspecific effect on the charge distribution of the intestinal brush border membrane (Foulkes 1985). However, the influence of cations on

cadmium absorption is complex, because zinc can increase the amount of cadmium absorbed from the intestine (Jaeger 1990). A refined diet high in fat and protein increases cadmium absorption in mice, partially due to increased gastrointestinal passage time (Schafer et al. 1986). Iron deficiency increases cadmium absorption (Flanagan et al. 1978; Schafer et al. 1990). Zinc deficiency may result in an increased accumulation of cadmium in the intestinal wall, but does not affect transport into the blood (Foulkes and Voner 1981; Hoadley and Cousins 1985). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20-fold higher than in adult guinea pigs. Thus, for a given individual, the absorption following oral exposure to cadmium is likely to depend on physiologic status (age; body stores of iron, calcium, and zinc; pregnancy history; etc.) and, also, on the presence and levels of ions and other dietary components ingested with the cadmium.

2.3.1.3 Dermal Exposure

A few measurements of dermal absorption of cadmium in animals have been made, with only one *in vitro* study using human skin to determine the percutaneous absorption of cadmium.

A study by Wester et al. (1992) evaluated the percutaneous absorption of cadmium from water and soil into and through human skin using *in vitro* skin cells. Radioactive cadmium ($^{109}CdCl_2$) was made to a concentration of 116 ppb in water or 13 ppb in filtered soil (26% sand, 26% clay, 48% silt, 0.9% organic content). Cadmium chloride was administered either at 5 $\mu L/cm^2$ or 2 volumes of 2.5 $\mu L/cm^2$ (the same amount of cadmium apparently applied). Human cadaver skin derrnatomed at 500 pm was placed in flow through skin cells and perfused with human plasma. When an applied dose of $CdCl_2$ in water is applied to skin that is perfused for 16 hours, from 0.l- 0.6% enters the plasma perfusate over 16 hours, while 2.4-12.7% of applied dose remains in the skin. Most of the cadmium (74-93%) remained unabsorbed and was recovered from the skin surface. Total recoveries ranged from 88±20 to 103±3. No explanation was offered for the <100% recovery. When cadmium-contaminated soil (13 ppb $CdCl_2$) was applied to the skin surface, plasma levels ranged from 0.02 to 0.07% of the applied dose, while the skin contained 0.06-0.13% of applied dose. Surface wash ranged from 82 to 102% of applied dose. Total recoveries were from 83±33 to 106±2. The large differences between water and soil absorption into the plasma and retention in the skin were attributed to differences in cadmium partition coefficients, measured to be 3.61×10^1 for *stratum cormum* (powdered):water and 1.03×10^5 for soil:water. These measurements indicate that soil has

a relatively higher affinity for cadmium than does the stratum corneum. The transfer of cadmium from soil to skin depends on the soil's binding capacity and water retention and variables describing the physical contact with the skin. When cadmium levels in the soil were increased from 6.5 to 65 ppb, skin levels correspondingly increased, but plasma receptor fluid levels remained constant. This suggests that, with *in vitro* perfusion, the surface concentration of cadmium will influence skin cadmium concentration, but that absorption into plasma receptor fluid is relatively independent of the skin surface concentration. The authors offer the caveat that *in vitro* methods can influence results and so the receptor fluid accumulation must be interpreted with caution. The authors calculate that a whole body exposure to cadmium at 116 ppb in water with a 0.5% absorption will result in a daily systemic intake of about 10 μg cadmium.

A few animal studies are available that describe the percutaneous absorption of cadmium as estimated from the accumulation of cadmium in the liver and kidneys of mice and rabbits. One male rabbit (strain not specified) was dosed with $CdCl_2$ percutaneously with a 1% aqueous solution (6.1 mg Cd) or 2% ointment (12.2 mg Cd) over a 10 cm^2 shaved area. Animals were treated 5 times over 3 weeks. Only cadmium contents of liver and kidney were measured so total absorption through the skin may have been greater. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.4-0.61% 2 weeks after the end of cadmium exposure. This percentage was similar for aqueous solution or hydrocarbon ointment. Similarly, one male hairless mouse (strain not specified) was dosed with $CdCl_2$ percutaneously with a 2% ointment (containing 0.61 mg Cd). Animals were treated 5 times over 3 weeks. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.2-0.87%. Similarly, one male rabbit was dosed with $CdCl_2$ percutaneously with a 1% aqueous solution (6.1 mg Cd) or 2% ointment (12.2 mg Cd) over a 10 cm^2 shaved area. Animals were treated 5 times over 3 weeks. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.4-0.61% 2 weeks after the end of cadmium exposure (Kimura and Otaki 1972).

Cadmium was detected in liver, kidneys, and urine following dermal exposure in guinea pigs (Skog and Wahlberg 1964). The disappearance of cadmium from cadmium chloride in water applied to guinea pig skin was dependent on concentration, with a peak mean absorption of 1.8% over 5 hours at 0.239 molar cadmium (about a 2.7% solution). Less absorption occurred at both at higher and lower concentrations of a cadmium chloride solution applied to the skin (Skog and Wahlberg 1964).

The results from all of these studies suggest that dermal absorption is slow, and would be of concern only in situations where concentrated solutions would be in contact with the skin for several hours or longer.

2.3.2 Distribution

Cadmium is widely distributed in the body, with the major portion of the body burden located in the liver and kidney. Animals and humans appear to have a similar pattern of distribution that is relatively independent of route of exposure, but somewhat dependent on duration of exposure.

2.3.2.1 Inhalation Exposure

Cadmium was found in autopsy samples from nearly all organs of a worker extensively exposed to cadmium dust, with greatest concentrations in the liver, kidney, pancreas, and vertebrae (Friberg 1950). In workers dying from inhalation of cadmium, lung-cadmium concentration is somewhat lower than liver or kidney cadmium concentration (Beton et al. 1966; Lucas et al. 1980; Patwardham and Finckh 1976). The concentration of cadmium in the liver of occupationally exposed workers generally increases in proportion to intensity and duration of exposure to values up to 100 μg/g (Gompertz et al. 1983; Roels et al. 1981b). The concentration of cadmium in the kidney rises more slowly than in the liver after exposure (Gompertz et al. 1983) and begins to decline after the onset of renal damage at a critical concentration of 160-285 μg/g (Roels et al. 1981b).

In animals acutely exposed to cadmium carbonate aerosols, about 60% of the inhaled dose is found in the gastrointestinal tract, transported by mucociliary clearance (Moore et al. 1973). Following a 2-hour inhalation of approximately 100 mg/m^3 of cadmium, cadmium concentration in rat liver increased from an initial concentration of 0.8 μg/g in males and 1.9 μg/g in females immediately after exposure up to a peak of about 2 μg/g in males and 3.8 μg/g in females 1 week postexposure, then declined to 1.7 and 2.5 μg/g, respectively, by 30 days postexposure. The kidney concentrations were initially <0.5 μg/g in males and females, rising to approximately 8 μg/g in both sexes by 1 week postexposure and to 18 μg/g in males and 15 μg/g in females by 30 days postexposure (Rusch et al. 1986).

2.3.2.2 Oral Exposure

As discussed in Chapter 5, most nonoccupationally exposed people are exposed to cadmium primarily through the diet. Cadmium can be detected in virtually all tissues in adults from industrialized countries, with greatest concentrations in the liver and kidney (Chung et al. 1986; Sumino et al. 1975). Average

cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40-50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). Liver cadmium concentrations also begin near zero at birth, increase to typical values of l-2 μg/g wet weight by age 20-25, then increase only slightly thereafter (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984; Sumino et al. 1975).

Distribution of cadmium in animals after oral exposure is similar to that found in humans, with highest accumulation in the liver and kidneys, and lower levels spread throughout the rest of the body (Kotsonis and Klaassen 1978; Weigel et al. 1984). Liver and kidney cadmium concentrations are comparable after short-term exposure (Andersen et al. 1988; Jonah and Bhattacharyya 1989), but the kidney concentration exceeds the liver concentration following prolonged exposure (Kotsonis and Klaassen 1978), except at very high exposures (Bernard et al. 1980).

Maitani et al. (1984) compared the distribution of cadmium in rats after an acute oral administration of either cadmium ions or cadmium bound to metallothionein. In all cases, 85-90% of the dose was present in the feces within 24 hours postexposure. More of the cadmium-thionein was retained after 2-3 days, and less of the cadmium-thionein was distributed to the liver than was the case for the ionic cadmium. Kidney levels were comparable.

Tissue distribution and retention of cadmium differed between 4-day-old rats and 70-day-old adults. Cadmium was 3-6 times more concentrated in the newborn spleen, bone, brain, testes, and muscle than in the adult rat 2 hours after an intravenous administration of 1 mg Cd/kg body weight. Liver concentration of metallothionein was 20 times greater in the newborn than in the adult; kidney metallothionein concentrations were comparable, but liver cadmium was only 30% higher and kidney cadmium 50% higher in the newborn. Nineteen days post-cadmium exposure, the retention of cadmium in the liver, kidney, and lung was similar in both the newborn and- the adult rat. The results indicate that metallothionein does not appear to play a major role in the tissue distribution or retention of cadmium (Wong and Klaassen 1980a).

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium

concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a recent study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sorell and Graziano 1990). Thus, timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies.

Goyer et al. (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Chan and Cherian (1992) report that pregnancy in Sprague-Dawley rats previously administered cadmium chloride (1.0 mg Cd/kg body weight subcutaneously, daily for 8 days) leads to a mobilization of cadmium from the liver (40% decrease compared to nonpregnant cadmium-treated controls) and an increase in the kidneys (60% increase). A similar pattern is seen for metallothionein. Plasma cadmium and metallothionein also increased in the pregnant group. Placental cadmium increased in the cadmium-treated rats compared to the untreated controls. In this rat model, then, pregnancy resulted in a transfer of hepatic cadmium and metallothionein via the blood to the kidney and placenta.

Cadmium levels in human milk are 5-10% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to cadmium. Cadmium is found in the liver and kidneys of rats dermally exposed to cadmium, with higher accumulation in liver than kidney after 1 week and higher accumulation in kidney than liver after 3 weeks (Kimura and Otaki 1972).

2.3.3 Metabolism

Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion does bind to anionic groups (especially sulfhydryl groups) in proteins (especially albumin and metallothionein) and other molecules (Nordberg et al. 1985). Plasma cadmium circulates primarily bound to metallothionein, and also to albumin and presumably other compounds as well (Foulkes and Blanck 1990; Roberts and Clark 1988).

Of particular importance to the toxicokinetics and toxicity of cadmium is its interaction with the protein metallothionein. Metallothionein is a low-molecular-weight protein, very rich in cysteine, which is capable of binding as many as seven cadmium atoms per molecule. Metallothionein is inducible in most tissues by exposure to cadmium, zinc, and other metals, as well as organic compounds and a variety of other physiologic stresses (irradiation, food deprivation, exercise, hypothermia, and inflammation) (Waalkes and Goering 1990). The exact physiologic functions of metallothionein are not known, and the interaction of cadmium with metallothionein may be related to the chemical similarities between cadmium and zinc (Waalkes and Goering 1990). Early work indicated that metallothionein binding decreased the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appeared to be adequate to bind all the accumulated cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978).

More recently, Dorian et al. (1992a) evaluated the intra-renal distribution of ^{109}CdMT injected (intravenously) into male Swiss mice at a nonnephrotoxic dose (0.1 mg Cd/kg). Kidneys and liver were removed at 5, l 5, 30, 45, and 60 minutes; 2,4, 8, and 24 hours; and 2,4, and 7 days; and tissue concentration of cadmium determined. The radioactivity in the kidney reached a maximum level (85% of the dose) as early as 30 minutes following administration and remained essentially constant for up to 7 days after injection. Within the kidney, ^{109}Cd distributed almost entirely to the cortex. Light microscopic autoradio-graphy of the kidney showed that, within the cortex, ro9Cd distributed preferentially to the S1 and S2

segments of the proximal convoluted tubules. Within the S1 and S2 segments, the concentration of ^{109}Cd in the basal and apical parts of the cells was similar to that after the non-nephrotoxic dose of CdMT, but after a nephrotoxic dose (0.3 mg Cd/kg) the radioactivity distributed preferentially to the apical portion of the cells. In contrast, light microscopic autoradiography studies with $^{109}CdC1_2$ revealed that ^{109}Cd was more evenly distributed throughout the proximal tubules. After administration of a large dose of inorganic cadmium (3 mg Cd/kg), a similar concentration of cadmium was found in the convoluted and straight proximal tubules. The authors suggest that these date support the hypothesis that CdMT-induced nephrotoxicity might be due, at least in part, to its preferential uptake of CdMT into the S1 and S2 segments of the proximal tubules, the site of Cd-induced nephrotoxicity.

In a companion study, Dorian et al. (1992b) administered [^{35}S]CdMT intravenously to male Swiss at a nonnephrotoxic dose (0.1 mg Cd/kg), and evaluated the kidneys and liver at 5, 15, 30, 45, and 60 minutes; and 2, 4, 8, and 24 hours. The radioactivity in the kidney showed maximum level (80% of the dose) 15 minutes after the injection. This preferential renal uptake was also observed after administration of various doses of [^{35}S]CdMT. In contrast to the earlier observed persistency of ^{109}Cd in the kidney after ^{109}CdMT administration, ^{35}S disappeared rapidly (with a half-life of approximately 2 hours), and 24 hours after injection of [^{35}S]CdMT, there was very little ^{35}S left in the kidneys. These observations indicate that the protein portion of CdMT is rapidly degraded after renal uptake of CdMT and the released cadmium is retained in the kidney. Within the kidney, ^{35}S distributed mainly to the cortex. Light microscopic autoradiography showed that [^{35}S]CdMT preferentially distributed to the proximal convoluted tubule (S1 and S2), which is the site of nephrotoxicity. Within the S1 and S2 segments, a greater distribution of ^{35}S to the apical portion of the cells was observed after administration of both a non-nephrotoxic (0.1 mg Cd/kg) and a nephrotoxic (0.3 mg Cd/kg) dose. ^{109}Cd administered as ^{109}CdMT also distributed to the apical portion of the S1 and S2 cells. The results indicate that both the organic (^{35}S) and inorganic (^{109}Cd) portions of CdMT are rapidly and efficiently taken up by the S1 and S2 cells of the proximal tubules, the site of nephrotoxicity, and the protein portion is rapidly degraded to release cadmium.

The toxic effects and distribution of cadmium were compared after intravenous injection of ^{109}CdMT at 0.05 to 1 mg Cd/kg body weight and $^{109}CdC1_2$ at 0.1-3 mg/kg in male Swiss mice (Dorian et al. 1995). CdMT increased urinary excretion of glucose, and protein indicated renal injury with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by $CdCl_2$ administration, even at dosages as high as 3 mg Cd/kg. CdMT distributed almost exclusively to the kidney, whereas $CdCl_2$ preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after

$CdCl_2$ administration (i.e., the renal cadmium concentration after administration of a high but non-nephrotoxic dose of $CdCl_2$ was equal to or higher than that obtained after injection of nephrotoxic doses of CdMT). Light microscopic autoradiography studies, using 0.3 mg Cd/kg as CdMT and 3 mg Cd/kg as $CdCl_2$, indicated that cadmium from CdMT preferentially distributed to the convoluted segments (S1 and S2) of the proximal tubules, whereas cadmium from $CdCl_2$ distributed equally to the various segments (convoluted and straight) of the proximal tubules. However, the concentration of cadmium at the site of nephrotoxicity, the proximal convoluted tubules, was higher after $CdCl_2$ than after CdMT administration. A higher cadmium concentration in both apical and basal parts of the proximal cells was found after $CdCl_2$ than after CdMT administration. The authors suggest that CdMT is nephrotoxic and $CdC1_2$ is not nephrotoxic because of a higher concentration of cadmium in the target cells after CdMT.

Because ZnMT and CdMT appeared to be handled by the same renal transport mechanism, the effects of ZnMT on ^{109}CdMT renal uptake and nephrotoxicity were evaluated (Dorian and Klaassen 1995). Swiss mice received a nephrotoxic intravenous dose of ^{109}CdMT (0.51 μmol MT/kg containing 0.4 mg Cd/kg,) or an equimolar dose of unlabeled ZnMT one minute before ^{l09}CdMT administration. Marked renal toxicity was observed 24 hours after ^{109}CdMT administration. In contrast, renal function appeared normal in mice receiving ZnMT before ^{l09}CdMT, although a similar concentration of ^{109}Cd was found in kidneys of both groups. The results indicate that ZnMT is not only nontoxic to the kidney at a dose as high as 5 μmole MT/kg, but it can also protect against the nephrotoxic effect of CdMT without decreasing renal cadmium concentration.

To further test the hypothesis that nephrotoxicity produced from chronic cadmium exposure results from a CdMT complex, Liu et al. (1998) exposed MT-null mice to a wide range of $CdCl_2$ doses, 6 times per week for up to 10 weeks. Renal cadmium burden increased with dose and duration up to 140 μg Cd/g kidney in control,mice (i.e., MT normal) with a 150-fold increase in renal metallothionein levels (800 μg MT/g kidney). Renal cadmium was much lower in MT-null mice (10 μg Cd/g) and MT levels were not detectable. The maximum tolerated dose of cadmium(as indicated by routine urinalysis and histopathology measures) in control mice was approximately 8 times higher than in MT-null mice. Lesions were more sever in MT-null mice than in controls, indicating that Cd-induced renal injury is not necessarily mediated through a CdMT complex, and that metallothionein is an important intracellular protein for protection against chronic cadmium nephrotoxicity.

When metallothionein-bound cadmium is transported to the kidney, it is readily diffusible and filterable at the glomerulus and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes 1978). Exogenous metallothionein is degraded in lysosomes; this process may release cadmium, which may induce fresh metallothionein synthesis in the proximal tubule (Squibb et al. 1984). Cadmium induced renal toxicity is probably associated with cadmium not bound to metallothionein (Goyer et al. 1989; Norniyama and Nomiyama 1986); however, brush-border membranes of the renal tubule may be damaged by cadmium that is bound to metallothionein (Suzuki and Cherian 1987). Renal damage is believed to occur if the localization of cadmium or an excessive concentration of cadmium prevents it from becoming bound to metallothionein.

The route of cadmium administration does not appear to affect the metallothionein metabolism in liver and kidney, although inhalation exposure induces metallothionein in the lung (Glaser et al. 1986; Hart 1986) and oral exposure induces metallothionein in the intestine (Muller et al. 1986). Parenteral administration of cadmium can result in doses high enough to overwhelm the endogenous metallothionein content and thereby cause effects on tissues that appear to be to protected by metallothionein synthesis after inhalation or oral exposure (Sendelbach and Klaassen 1988).

2.3.4 Elimination and Excretion

Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces. However, almost all excreted cadmium represents material that was not absorbed from the gastrointestinal tract. Most absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal (Kjellstrom and Nordberg 1978). Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years (Kjellstrom and Nordberg 1985). Half-times in the slowest phase were from 20 to 50% of the maximum life span of the animal (Kjellstrom and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellstrom and Nordberg (1985) developed a range of half-times from their kinetic model for the human kidney of between 6 and 38 years, and for the human liver of between 4 and 19 years.

2.3.4.1 Inhalation Exposure

Cadmium excretion in urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion markedly increases (Roels et al. 1981b). Fecal excretion in workers occupationally exposed to cadmium reflects mainly cadmium dust swallowed from industrial air and/or incidentally ingested from contaminated hands (Adamsson et al. 1979).

In rats, following a 2-hour inhalation exposure to cadmium carbonate, cadmium was primarily eliminated in the feces, with a minor component (approximately 1% of fecal excretion) in the urine (Rusch et al. 1986). Cadmium excretion by both routes declined with time after exposure, with significantly elevated excretion found at 7 days, but not 30 days, after exposure (Rusch et al. 1986). Most of the cadmium initially excreted in the feces was probably not absorbed, but rather represented particles transported from the lung to the gastrointestinal tract (Moore et al. 1973).

2.3.4.2 Oral Exposure

Following oral exposure, the major proportion of administered cadmium is found in the feces, because absorption is so low (see Section 2.3.1.2) (Kjellstrom et al. 1978). Among 5 healthy adult volunteers, fecal excretion of a single dose of radiolabeled cadmium declined with time up to 45 days after ingestion, while urinary excretion remained at a low, near-constant level (Rahola et al. 1973). After about 20 days, fecal and urinary excretion appeared to be comparable (Rahola et al. 1973). In contrast, among 4 healthy adults ingesting cadmium in intrinsically labeled crabmeat, fecal excretion was 30 times higher than urinary excretion up to 10 weeks after ingestion of the test meal (Newton et al. 1984). In rats orally exposed to up to 0.35 mg/kg/day of cadmium in the diet for 60 days, no significant increase in urinary cadmium content was found (Weigel et al. 1984). The overall excretion of absorbed cadmium is slow, with biological halftimes of 70-270 days in rats or mice orally exposed to cadmium (Engstrom and Nordberg 1979; Moore et al. 1973).

In a comprehensive model developed for human cadmium toxicokinetics, parameters for urinary and fecal excretion were derived by adjustments to empirical data derived from human and animal studies

(Kjellstrom and Nordberg 1978, 1985). Fecal excretion constitutes unabsorbed cadmium plus "true" excretion originating from blood via the intestinal wall (a function of cadmium body burden) and from bile via the liver (a function of cadmium liver burden) (Kjellstrom and Nordberg 1985). Urinary excretion depends on blood concentration and kidney concentration, and total excretion is assumed to equal daily intake at steady state. Using these methods and assumptions, daily fecal and urinary excretion are estimated to be 0.007 and 0.009% of body burden, respectively (Kjellstrom and Nordberg 1978, 1985).

Groups of 10 female outbred albino rats were exposed to cadmium in drinking water (as $CdCl_2$) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, at 3 weeks of gestation, or 3 weeks into lactation). After weaning, exposure to cadmium was terminated. In dams, kidney concentrations exceeded liver concentrations, while in pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium concentrations considerably increased only during the second half of the lactation period (Ld 11-21). The concentrations in the dams were several orders higher than in the offspring. After discontinuation of exposure, organ concentration slightly decreased in dams (2% in liver and 12% in kidneys), while in pups the decrease was 84% in the liver and 62% in the kidneys. These values do not indicate cadmium elimination but rather dilution caused by growth (Kostial et al. 1993).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to cadmium. Cadmium was reportedly detected in urine in guinea pigs dermally exposed to aqueous cadmium chloride, but no details are available (Skog and Wahlberg 1964).

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

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

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

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

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

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

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

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

If PBPK models for cadmium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

2.3.5.1 Summary of Cadmium PBPK Models

Several models have been reported to describe the kinetics of cadmium in mammalian systems. Of these models, the Nordberg-Kjellstrom model (Kjellstrom and Nordberg 1978; Nordberg and Kjellstrom 1979) has been the most widely used for cadmium risk assessment. Three of the most relevant cadmium models will be discussed here.

2.3.5.2 Cadmium PBPK Model Comparison

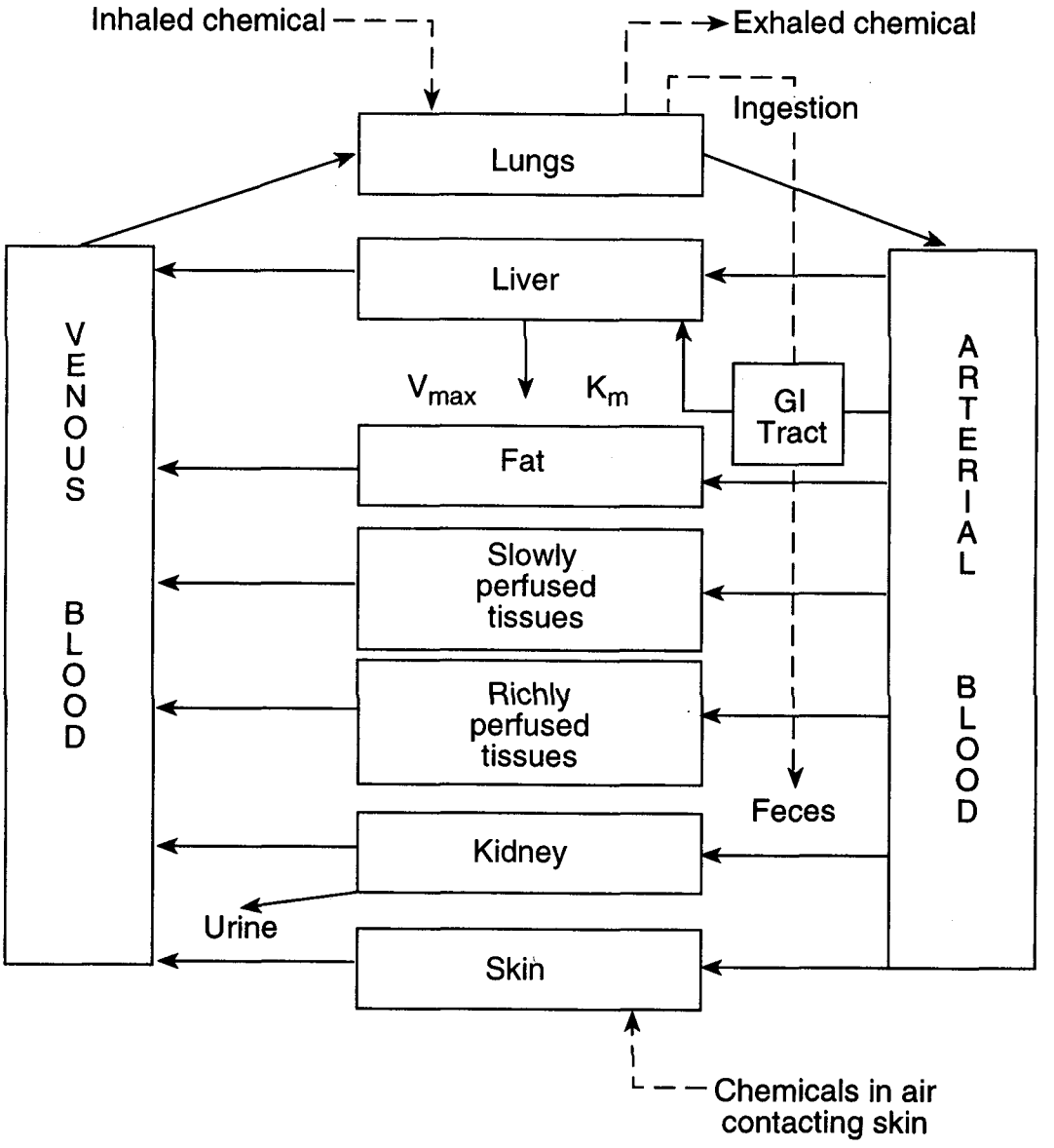
Although the Nordberg-Kjellstrom model (Kjellstrom and Nordberg 1978; Nordberg and Kjellstrom 1979) has its limitations, it provides the best overall description of cadmium toxicokinetics and is largely based on human data. The Shank (Shank et al. 1977) and Matsubara-Khan (Matsubara-Khan 1974) models are not as useful for human risk assessment applications, but they do provide useful insights into the absorption, distribution, and compartmentalization of cadmium in laboratory animals. These insights may have some future use in human risk assessment as PBPK models for cadmium continue to be refined.

2.3.5.3 Discussion of Cadmium Models

The Nordberg-Kjellstrom Model

The Nordberg-Kjellstrom model (Kjellstrom and Nordberg 1978; Nordberg and Kjellstrom 1979) is a linear multicompartment model that is the most commonly used model for cadmium risk assessment work today. The Nordberg-Kjellstrom schematic model diagram is shown in Figure 2-4.

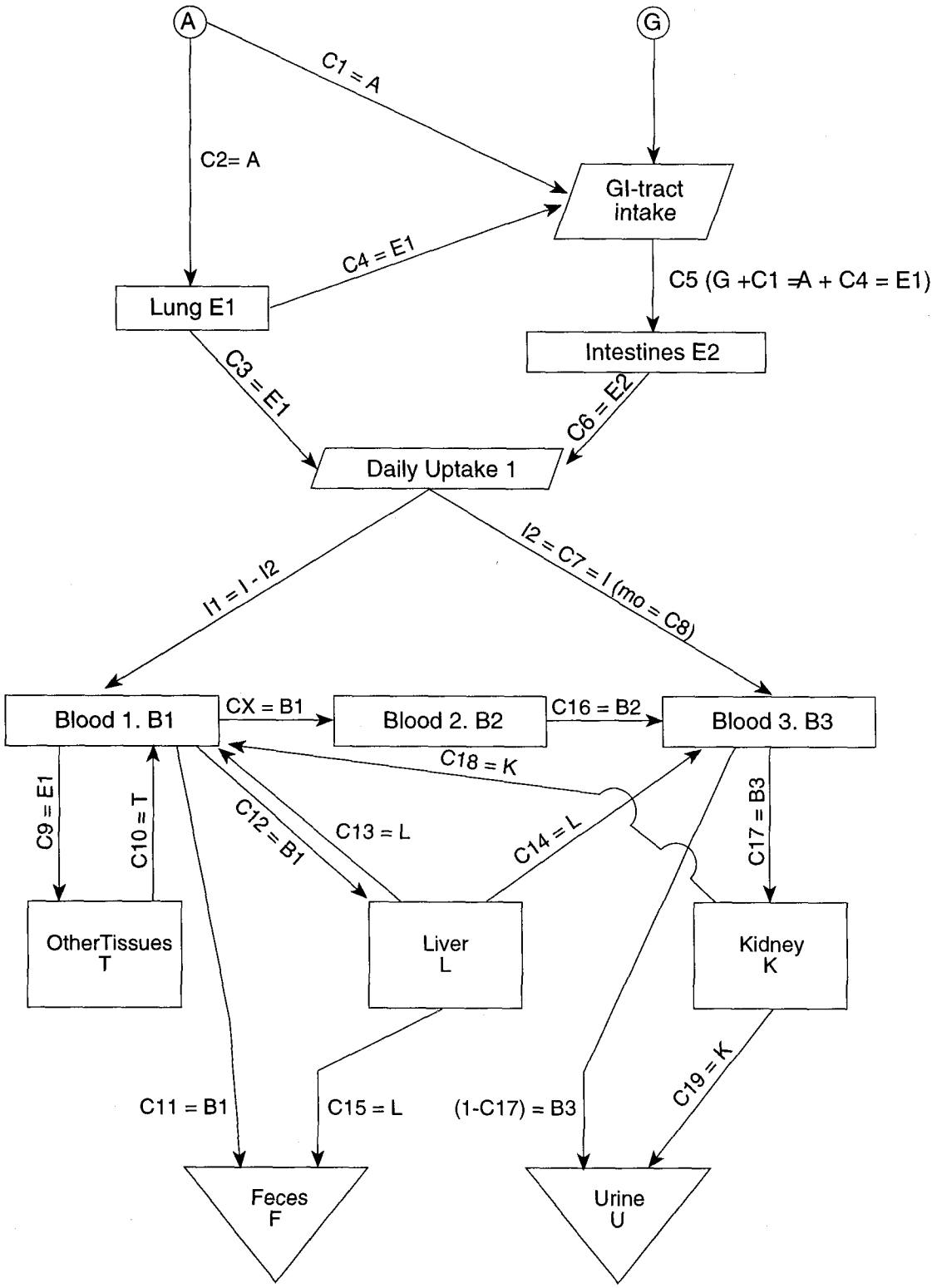
Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

Figure 2-4. A Schematic Representation of the Nordberg-Kjellström Model



Risk assessment. The Nordberg-Kjellstrom model has been demonstrated to be a useful model in human risk assessment work. Frazier (1994), however, noted that the model has two major limitations: (1) the linear nature of the model may not adequately allow a good description of known nonlinearities in biological responses to cadmium dosing, and (2) the phenomenological approach taken with this model does not provide a foundation for incorporating biological variability into the model parameters.

Description of the Model. The Nordberg-Kjellstrom model (see Figure 2-4) is a linear multicompartment model that describes the disposition of cadmium via the oral and inhalation routes of exposure only. Dermal exposure and subsequent absorption through the skin were assumed to be negligible in this model. For inhalation exposures, the model accounts for different deposition patterns for different size particles in nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract. Particles with mass median aerodynamic diameter (MMAD) of 5 pm (i.e., cadmium-laden dust) were assumed to distribute mainly to the nasopharyngeal region (75%) with lesser amounts depositing in the alveolar (20%) and tracheobronchial (5%) regions. Particles of 0.05 pm MMAD (i.e., cigarette smoke) were assumed to deposit 55% in the alveolar compartment, 10% in the tracheobronchial compartment, and none in the nasopharyngeal compartment. The remaining amounts are exhaled For all particle sizes initially deposited in the nasopharyngeal and tracheobronchial compartments, mucociliary clearance clears some particles from the respiratory tract to enter the oral compartment for absorption or out of the body and back to the environment. Assumed model coefficient values and the available physiological parameters are shown in Table 2-4.

For the oral route of exposure, cadmium may enter the gastrointestinal tract via food or water contaminated with cadmium, or as cadmium particles embedded in mucus from the respiratory tract via the mucociliary/tracheobronchial escalator. By either route of exposure, the model assumes that cadmium enters into any of three blood compartments (B) (see Figure 2-4). Bl is the plasma compartment where cadmium may bind to plasma components (i.e., albumin and other organic constituents). B2 is the redblood cell compartment which represents the accumulation of cadmium in erythrocytes, while B3 represents the binding of cadmium to metallothionein. The model does not take into account induction of metallothionein after cadmium exposure. From the blood, cadmium is calculated to distribute to either the liver, kidney, or “other tissues,” the major accumulation sites. Elimination is either via the feces or in the urine. The transport of cadmium between the compartments is assumed to follow first-order exponential functions and is driven on concentration-dependent gradients.

Table 2-4. Assumed Model Parameters and Some Physiologic Parameters for the Nordberg-Kjellström Model

Coefficient or parameter	Assumed range	Unit[a]	Values fitting to empirical data
	Model parameters		
C1	0.1–0.2 (cigarette smoke)		0.1
	0.4–0.9 (factory smoke)		0.7
C2	0.4–0.6 (cigarette smoke)		0.4
	0.1–0.3 (factory smoke)		0.13
C3	0.01–0.3	day^{-1}	0.05
C4	*0.1 x C3 = 0.001–0.03*	day^{-1}	*0.005*
C5	0.03–0.1		0.048
C6	0.05	day^{-1}	0.05
C7	0.2–0.4		0.25
C8	0.5–5.0	µg	1
C9	0.4–0.8		0.44
C10	0.00004–0.0002	day^{-1}	0.00014
C11	0.05–0.5		0.27
C12	0.1–0.4		0.25
C13	0–0.0001	day^{-1}	0.00003
C14	0.0001–0.0003	day^{-1}	0.00016
C15	0–0.0001	day^{-1}	0.00005
C16	*0.004–0.015*	day^{-1}	*0.012*
C17	0.8–0.98		0.95
C18	0–0.0001	day^{-1}	0.00001
C19	0.00005–0.0002	day^{-1}	0.00014
CX	0 01–0.05		0.04
C20	0.05–0.5		0.1
C21	0–0.000002	day^{-1}	0.0000011
	Physiologic parameters		
Average liver weight	1,500	gram	
Average blood volume	70	mL/kg	
Average blood specific gravity	1.06		
Average daily urine excretion (adult)	1.0	L	
Average daily urine excretion (aged)	0.9	L	
Average daily urine excretion (child)	0.5	L	

[a]Blanks indicate a unitless value

Validation of the model. The Nordberg-Kjellstrom model was validated using several independent sets of human data from both Sweden and Japan. The data set by Friberg et al. (1974) estimated that smoking 20 cigarettes a day would result in an inhalation of 2-4 μg/day of cadmium, assuming smoking started at 20 years of age and daily cadmium intake from food was 16 μg/day. Based on the Friberg et al. (1974) data, the model predictions of cadmium concentrations in the kidney agreed well with the observed data from a study by Elinder et al. (1978); however, the model predicted higher than expected values for liver cadmium compared to the observed data from the Elinder study. The model's urinary excretion of cadmium (0.84 μg/24 hours for a 50-year-old person) agreed well with the observed data (0.56-0.8 μg/24 hours). The model predicted blood cadmium levels for Swedish smokers to be about 2 ng/g which compared well to the actual concentration of 1.6 ng/g.

The model was also validated against a data set for an average 45year-old Japanese person living in Tokyo whose daily intake of cadmium is 40 μg via food and 2.7 μg via the inhalation route. Subjects were assumed to be smokers averaging 24 cigarettes a day starting at age 20. Based on these exposure conditions, the measured values for cadmium in the kidney, liver, and "other tissues" (in this case, muscle only) were reported to be 65, 3.4, and 0.2 μg/g, respectively, with the model predicting 48, 3.2, and 0.18 μg/g. For blood and urine, the measured values were 4.5 μg/g for blood and 1.1 μg/L for urine; the model predicted 3.4 μg/g and 1.3 μg/24 hours (assuming 1 L of urine output/day, the value would be 1.3 μg/L).

Another study of Japanese people reported cadmium concentrations in urine in relation to high cadmium concentrations in rice in their daily diet. For people who consumed rice containing 0.04 μg/g of rice (240 μg/day), the observed urinary level of cadmium was 7 μg/L; consumption of rice containing 1.1 μg cadmium/g of rice (660 μg/day), resulted in an observed value of 14 μg/L of urine. After making certain assumptions about the average daily consumption of rice containing an assumed amount of cadmium, and assuming an average urine production of 1 L/day, the model calculated urinary levels of 4.8 and 15.5 μg/L of urine, agreeing well with the observed values.

The model was also validated against a data set with high concentrations of cadmium in air (50 $\mu g/m^3$) (Piscator 1972) and blood cadmium concentrations ranging from 10 to 50 ng/g whole blood. Calculated blood, urine, liver, and kidney levels of cadmium agreed only roughly with the observed values; however, the authors concluded that the model predictions may not be accurate based on the observations that workers with long exposure histories had most likely experienced higher exposure levels in the past,

skewing the data set, resulting in poor model predictions. Another data set by Piscator (1974) involved a group of Swedish workers involved in polishing cadmium-plated objects, who were exposed to high concentrations of cadmium for 2 years or less. Cadmium levels were measured in the urine and blood. When this exposure data set was input into the model, the model could not adequately predict blood and urine levels for these workers.

Target tissues. The Nordberg-Kjellstrom model assumes that the kidney and liver are the two specific target tissues in which cadmium accumulates. The model also accounts for all other tissue accumulation in the "other tissues" compartment (i.e., muscle). The model assumes a human liver tissue half-life ($t_{1/2}$) of 4-19 years and a kidney $t_{1/2}$ of 6-38 years. For the "other tissue" compartments, $t_{1/2}$ was assumed to be 9-47 years. The Nordberg-Kjellstrbm model does account for the loss of renal tubular epithelial cells leading to a loss of tubular reabsorptive capacity. This loss of cells could conceivably result in an increase in the excretion of cadmium from the tubules and an increase in the transport of cadmium from the tubules to the blood. This loss of cells is theorized to account for the large $t_{1/2}$ range for cadmium in the kidney. The model assumed that no changes in the movement of cadmium from the kidney to blood occurred with age and that the loss of cadmium from the kidney to the urine increased linearly after the age of 30.

The Nordberg-Kjellstrom model also accounted for differences in kidney and liver weights among different age groups and between peoples of different ethnic origins. The model corrected for differences in liver, kidney, blood, and "other tissue" weights with relation to age (1 and 79 years of age) and ethnicity (Japan and Sweden).

Species extrapolation. The Nordberg-Kjellstrom model was based solely on data collected from humans and was intended for human risk assessment applications. The model did not address any potential application for this model of cadmium in laboratory animals.

High-low dose extrapolation. The Nordberg-Kjellstriim model has been shown to adequately predict fluid and tissue concentrations via the oral and inhalation routes of exposure for humans exposed to low doses of cadmium. However, the model has difficulty in adequately predicting fluid and tissue concentrations in humans exposed to high concentrations of cadmium, especially for those individuals exposed to high concentrations via the inhalation route.

Interroute extrapolation. The Nordberg-Kjellstrom model adequately predicted the fate of cadmium in target tissues after exposure via the inhalation and oral routes. The dermal route of exposure was not incorporated into the model parameters and was considered an insignificant route of exposure in humans.

The Shank Model

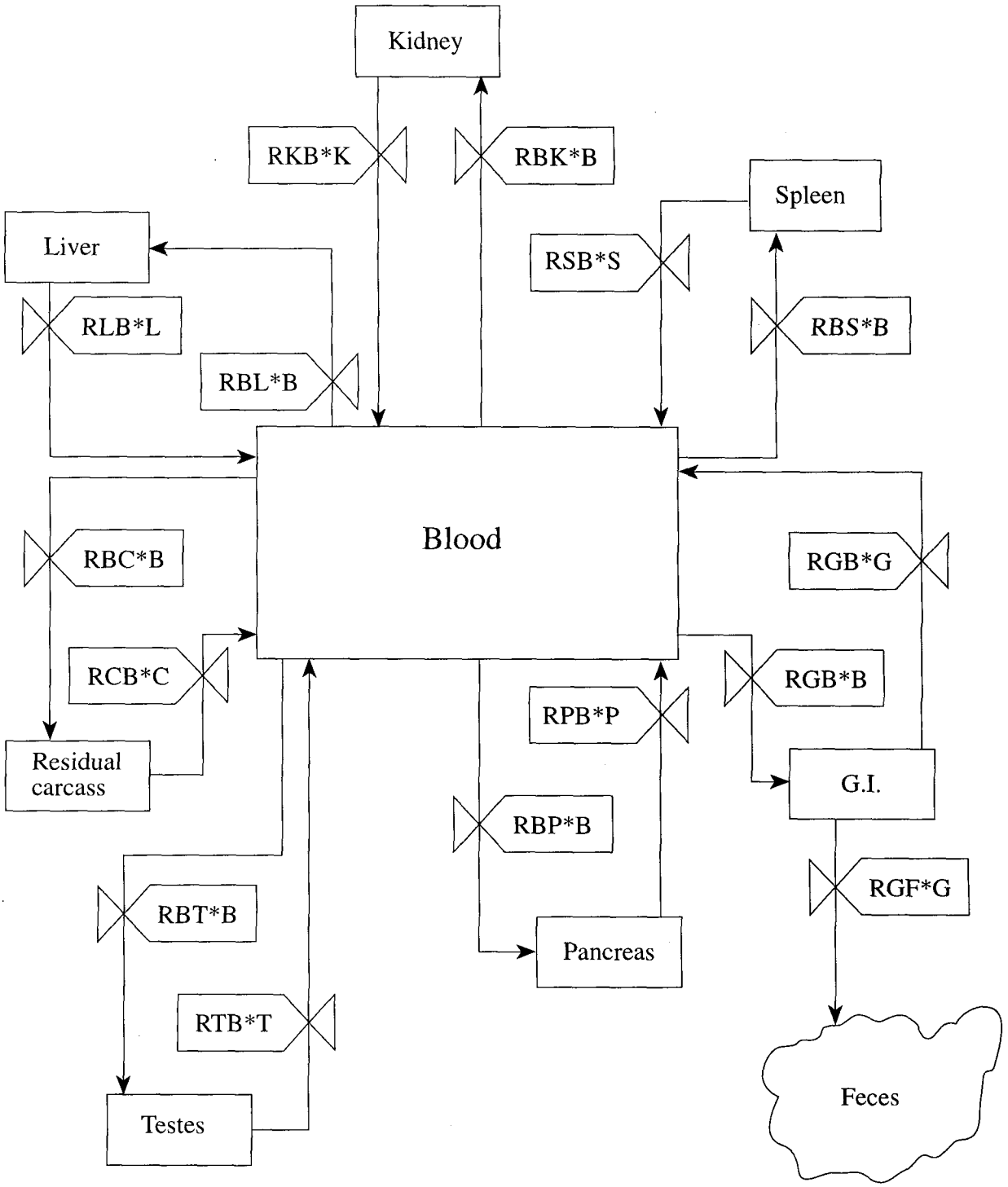
Risk assessment. The Shank model (Shank et al. 1977) may have the potential to serve as an alternative mathematical model for predicting the retention of cadmium in biological systems. Unfortunately, no human data were used to validate the Shank model for use as a risk assessment tool in cases of human exposure. In addition, the Shank model was validated only for the intravenous and subcutaneous routes of exposure; no data were presented for the oral, inhalation, or dermal routes of exposure.

Description of the model. A schematic representation of the Shank model is illustrated in Figure 2-5. The model mathematically represents the dynamic transport of cadmium between compartments in a mammalian biological system based on the male adult SW/NIH mouse as the test animal species. The intent was to predict the retention of cadmium in other species of animals (including humans) without requiring an adjustment of species-specific rate constants from within the model.

Male adult mice of the SW/NIH strain were dosed intravenously with ^{109}Cd as ^{109}Cd acetate. Mice received from 1 to 3 intravenous injections spaced 48 hours apart. Animals in each group were sacrificed at 2 minutes, 10 minutes, 1 hour, 10 hours, and 48 hours after the last dose. Tissues (liver, kidney, pancreas, spleen, gastrointestinal tract, testes, carcass, and feces) were harvested and the radioactivity recorded. A 9-compartment model was derived. Cadmium kinetics between compartments are described by first-order kinetics. The individual compartment retention values, obtained from the distribution study, were incorporated into the model equations and the rate constants derived.

Validation of the model. The Shank model was validated using three independent data sets. Mann (1973) dosed dogs, goats, and sheep with one intravenous injection of ^{109}Cd acetate (30 μCi), and the liver and kidneys were examined for cadmium content 8 weeks after administration. The Shank model's predicted values of cadmium retention in liver and kidneys at 8 weeks after a single administration were in good agreement with the observed values of the Mann (1973) study in all three species. Only data from the

Figure 2-5. A Schematic Representation of the Shank Model



Source: adapted from Forrester 1968

liver and kidneys were available for evaluation. A data set from a study by Gunn et al. (1968) was used to evaluate the ability of the Shank model to predict the retention of cadmium in liver and kidney after a single subcutaneous administration of $CdCl_2$ Animals in that study were sacrificed 2 weeks after administration, and the liver and kidneys were examined for cadmium content. The model values for the same time period were in very close agreement with observed values. Again, only data from the liver and kidneys were available for evaluation. Finally, a data set by Shanbaky (1973) was used to test the model's validity with multiple injections of cadmium acetate in rats. Five injections of cadmium acetate were administered over a 48-hour period; liver, kidneys, pancreas, spleen, and gastrointestinal tract were examined for cadmium content. The Shank model was found to be in close agreement with the arithmetic means of observed values found in the Shanbaky (1973) study.

No human data were presented to validate the model's effectiveness in predicting the cadmium retention in human target tissues after either a single or multiple dosing regime.

Target tissues. The target tissues for this model included the liver, kidney, pancreas, spleen, gastrointestinal tract, testes, and carcass of laboratory animals. No human tissue was used to derive cadmium retention in any of these tissues.

Species extrapolation. The model used goats, dogs, rats, mice, and sheep with various doses and dosing schemes of cadmium acetate and cadmium chloride and was found to serve as a good predictor of cadmium retention in the target tissues listed above. No human data were presented to determine if the model could satisfactorily predict the cadmium retention in human target tissues.

High-low dose extrapolation. High- and low-dose extrapolation was not specifically addressed by the Shank model.

Interroute extrapolation. Interroute extrapolations were addressed in a limited fashion by the Shank model. The model appeared to adequately predict the amount of cadmium retention in the target organs of laboratory animals, in particular the liver and kidney, when dosed by either the intravenous or subcutaneous routes. The inhalation and dermal routes of exposure, and other parenteral routes of exposure (intramuscular, intraperitoneal, intradermal, etc.) were not addressed by the Shank model. No human data were presented to determine if interroute extrapolations were valid.

The Matsubara-Khan Model

Risk assessment. The Matsubara-Khan model (Matsubara-Khan 1974) has not been used as a tool in risk assessment for humans. This model does demonstrate that cadmium kinetics and biological half-lives vary by tissue.

Description of the model. The Matsubara-Khan model is a simple model that attempted to fit cadmium elimination kinetic parameters into either a l- or 2-compartment model. To obtain the data for the model, male and female ICR mice (8 weeks of age) were administered a single subcutaneous injection of a known amount of $^{109}CdCl_2$. Specific groups of mice were sacrificed at 1, 2,4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents were removed and the amount of ^{109}Cd remaining in these tissues was determined.

An oral study was conducted in conjunction with the subcutaneous study described above. In the oral study, 8-week-old male mice (ddd x BALB/c; Fl) were orally administered $^{115m}CdCl_2$ by gavage. Groups of mice were sacrificed at 1, 2, 4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, liver, kidney, salivary gland, stomach wall, gonad, and spleen were removed and the amount of ^{115m}Cd remaining in these tissues was determined.

The rate of uptake, rate constants, and biological half-lives determined for the subcutaneous and orally dosed mice are summarized in Table 2-5. Matsubara-Khan found that tissue kinetics in mice dosed subcutaneously with $^{109}CdC1_2$, fit into either a l- or 2-compartment model, depending on the tissue. The data from the digestive tract organs (stomach wall, small intestine, and colon) were best fitted into *a* l-compartment model, with a strained fit of the data from the digestive tract contents (stomach, small intestine, and colon contents) to the 1-compartment model. Data from the blood, liver, kidneys, and salivary glands were best fitted to the 2-compartment model. Extremely small second-rate constants in the kidneys and salivary glands indicate that the elimination of cadmium from these tissues is very slow. For the oral study, similar findings were observed, with data from the gonads and spleen fitting the l-compartment model best. Biological half-lives were invariably longer for the subcutaneously dosed animals, while the rate constants were slightly smaller for the subcutaneously dosed animals. Sex-related

Table 2-5. Estimated Parameters, Rate of Uptake, Rate Constants and Biological Half-Lives in Selected Mouse Organs after Subcutaneous and Oral Administrations of $^{109}CdCl_2$

Organ	Rate of uptake (95% CL)		Rate constants b and c (95% CL)		Biological half-life (days)	
	SC	PO	SC	PO	SC	PO
Liver	21	8.7	0.011 0.57	0.016 0.91	631.2	430.76
Kidney	22	1.4	0.0007 0.30	0.0016 0.30	9902.3	4332.3
Salivary gland	21	0.33	0.0016 0.73	0.0047 0.78	4330.95	1500.89
Blood	0.15	NM	0.024 0.65	NM	291.1	
Stomach wall	1.7	0.36	0.0073	0.017	95	41
Stomach contents	0.68	NM	0.062	NM	11	NM
Small intestine	0.95	NM	0.01	NM	69	NM
Small intestine contents	2.5	NM	0.067	NM	10	NM
Colon	1.4	NM	0.013	NM	53	NM
Colon contents	4.1	NM	0.15	NM	4.6	NM
Gonad	NM	0.37	NM	0.012	NM	58
Spleen	NM	0.44	NM	0.0011	NM	630

CL = confidence limits; PO = oral; SC = subcutaneous; NM = Not measured

Source: adapted from Matsubara-Khan 1974

differences in rate of uptake, rate constants, and biological half-lives were not found, except in the kidney data in which females had slightly smaller rate constants.

Validation of the model. No independent data sets were used to validate the Matsubara-Khan model.

Target tissues. For the subcutaneous injection study, the Matsubara-Khan model used blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents. For the oral study, the model used liver, kidney, salivary glands, stomach wall, gonads, and spleen.

Species extrapolation. No species extrapolations were performed in the Matsubara-Khan model.

High-low dose extrapolation. No high-low dose extrapolations were performed in the Matsubara-Khan model.

Interroute extrapolation. The Matsubara-Khan model compared the oral and subcutaneous routes and reported similar rate constants for many of the tissues examined. Biological half-lives varied considerably for the kidney and salivary gland, but were not much different for liver between the two routes of exposure.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Cadmium can be absorbed by the inhalation, oral, and dermal routes of exposure regardless of its chemical form (chloride, carbonate, oxide, sulfide, sulfate, or other forms). Absorption by the dermal route of exposure, however, is relatively insignificant for cadmium, although small amounts are absorbed percutaneously over a long period of time (Wester et al. 1992). Absorption is mainly ofconcern from inhalation and oral exposures.

Gastrointestinal tract absorption of cadmium (in any chemical form) is relatively low when compared to the total amount of cadmium absorbed via the inhalation route. Gastrointestinal tract absorption of cadmium

has been determined to be l-2% in mice and rats (Decker et al. 1958; Ragan 1977), 0.5-3.0% in monkeys (Nordberg et al. 1971), 2% in goats (Miller et al. 1969), 5% in pigs and lambs (Cousins et al. 1973; Doyle et al. 1974), and nearly 16% in cattle (Miller et al. 1967). Lehman and Klaassen (1986) investigated whether the disposition of cadmium in male Sprague-Dawley rats is dependent on dose. The concentration of cadmium in tissues increased more than the increase in an oral dosage, and low dosages of cadmium (1 and 10 μg/kg) distributed preferentially to the kidney, suggesting that cadmium may be absorbed as a Cd-metallothionein complex at low dosages. The percentage of the po dosage retained 7 days after administration increased from 0.40% at the 1 μg/kg dosage to 1.65% at the 100 μg/kg and higher dosages. At a 1 μg Cd/kg po dosage, approximately 60% of cadmium in intestinal cytosol was bound to metallothionein, whereas at the 10,000 μg Cd/kg dosage, approximately 50% of the cadmium was bound to metallothionein. The results indicate that the retention of cadmium after ingestion is dosage-dependent and results from increased absorption of cadmium at higher dosages. Goon and Klaassen (1989) measured absorption of cadmium in rat intestine in situ and reported that the intestinal absorption of cadmium is dosage independent at low dosages of cadmium (<10 μg/kg) and dosage dependent at high dosages (>10μg/kg). They also evaluated the role of metallothionein and concluded that saturation of intestinal metallothionein is not a major determinant of the observed dosage-dependent absorption of cadmium.

In humans, cadmium absorption has been reported to be as much as 3-8%. Several blood and dietary factors can influence the absorption of cadmium from the gastrointestinal tract. Dietary deficiencies of calcium or iron and diets low in protein content can enhance cadmium absorption. Low blood ferritin content in women has been demonstrated to double the absorption of cadmium from the gastrointestinal tract. Zinc decreases the dietary absorption of cadmium.

In some cases, cadmium bound to metallothionein (as in food) is not absorbed or distributed from the gastrointestinal tract as readily as ionic cadmium. Mice had lower blood and liver cadmium levels from oral exposure to CdMT, compared to levels from cadmium chloride exposure for comparable doses, but the CdMT resulted in higher kidney cadmium levels. Maitani et al. (1984), however, report that less cadmium was absorbed when rats received Cd-TH in saline than $CdCl_2$ in saline. Cd-TH added to liver homogenate or liver homogenate containing Cd-TH increased the absorption of cadmium, resulting in renal cadmium levels similar to those in mice receiving $CdCl_2$ in saline. Sharma et al. (1983) reported that human exposure to very high intakes of cadmium during the consumption of oysters did not greatly elevate the whole blood and urine cadmium levels proportional to the level of intake

A higher fraction of inhaled cadmium than ingested cadmium is absorbed. The total amount of cadmium absorbed by the body via the lungs depends on the particle size. Larger particles are deposited in the nasopharyngeal and tracheobronchial airways via impaction, and are largely cleared by mucociliary processes, leading to absorption by the gastrointestinal tract. Smaller particles reach the smaller airways and alveoli, and depending on the particle's solubility, are absorbed and distributed to the rest of the body. Solubility in lung fluids plays a role in absorption from the lung into the body of cadmium salts. Theoretically, the highly soluble salts, chloride, nitrate, acetate, and sulfate would be expected to give the highest blood levels following inhalation exposure to a given air concentration. The insoluble cadmium salts, the various sulfides, should yield the lowest blood level. The lung, however, is rich in carbon dioxide that is continuously transferred from the blood. Particles of the various cadmium sulfides within the lung can react with this carbon dioxide. Lung tissue may then absorb and transfer solubilized or released cadmium ions to the blood.

No direct data, however, are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure, 5-20% after 15 minutes to 2 hours (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986), due to the absorption of cadmium and the lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in the lung differs somewhat among chemical forms, but the pattern apparently does not correlate well with solubility in water (Glaser et al. 1986; Rusch et al. 1986). Retention of cadmium has been reported to be >40% in rats (Moore et al. 1973) 40% in canines (Friberg et al. 1974), and 10-20% in mice (Potts et al. 1950).

According to Elinder et al. (1985), one cigarette may contain up to 2 μg of cadmium (10% of which is inhaled). Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorptions of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985).

Distribution and Metabolism. Once absorbed, cadmium is distributed to most tissues of the body, but tends to concentrate in the liver and kidneys of all animals, independent of the form. Cadmium enters the blood and may bind to plasma proteins (albumin, globulins, etc.), plasma metallothionein, or directly to the erythrocyte. Spleen, pancreas, and testes also have relatively high concentrations of cadmium after oral or inhalation exposures. Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion binds to anionic groups in proteins and other molecules. The sulfhydryl groups in albumin and metallothionein have a particularly high affinity for cadmium (Nordberg et al. 1985).

Shaikh et al. (1993) report that disposition of cadmium in mouse liver, kidney, and testes is different for different strains, sex, or age. Different dose levels (i.e., subcutaneous doses in the 5-30 umol/kg body weight range) also altered the disposition. Liver cadmium levels and metallothionein levels did not always correlate with hepatotoxicity. The difference in the tissue accumulation of cadmium may relate to variations in the hormonal or other intrinsic factors that affect cellular uptake of cadmium, subcellular distribution of cadmium, or metallothionein metabolism.

In 10-day-old rats, high levels of metallothionein (young rats innately have high levels of metallothionein compared to adults) have been reported to play an important role in their resistance to liver damage, presumably by binding and retaining cadmium (Goering and Klaassen 1984). There was a 67% increase in liver cadmium levels in the young compared to the adult, but this is not as dramatic as the 10-fold increase in liver metallothionein. Wong and Klaassen (1980a) reported only a 30% increase in liver cadmium in 4-day-old rats compared to the adults, but a 10-fold difference in liver metallothionein compared to the adults. These and other tissue distribution data led Wong and Klaassen to propose that metallothionein does not play a major role in the tissue distribution and retention of cadmium in the young.

More recent studies support this hypothesis. Liu and Klaassen (1996) evaluated the use metallothionein-I transgenic (MT-TG) mice to determine whether increased concentrations of metallothionein affected cadmium absorption and distribution. A single dose of ^{109}Cd was given to control and MT-TG mice orally (0.3-300 μmol/kg [200 μCi/kg]) or intravenously (0.03-10 μmol/kg [20 μCi/kg]). Cadmium concentrations in 15 tissues were quantified 7 days later. Higher metallothionein concentrations in tissues of MT-TG mice had no appreciable effects on the concentration of cadmium in tissues compared to controls. An exception to this was the MT-TG mice given the highest dose of cadmium (300 μmol Cd/kg, PO), which had twice the tissue cadmium concentration of controls. Approximately 60% of the cadmium

administered intravenously was retained in the tissues and retention of cadmium in MT-TG mice was similar to that in controls. In both control and MT-TG mice only 0.l-0.3% of cadmium administered po was retained, except for l-3% at the higher doses (100 and 300 μmol/kg). The higher concentrations of metallothionein in MT-TG mice did not appear to inhibit the gastrointestinal absorption of cadmium nor alter the organ distribution of cadmium.

In a companion study on MT-null mice, Liu et al. (1996) report that metallothionein does not play a role in the initial distribution of cadmium to tissues, but does play a major role in the elimination of cadmium, especially from liver, kidney, and pancreas. They conclude that the persistence of cadmium in the body is at least partially due to cadmium binding to metallothionein in tissues. The study investigated the role of metallothionein in the tissue distribution and retention of cadmium using MT-I and -11 null (MT-null) mice. Mice were given $^{109}CdCl_2$ (15 μmol/kg [25 μCi/kg] intraperitoneally), and radioactivity was quantified in 14 major organs at 2 hours, and 1, 2, 3, 7, and 15 days thereafter. The lack of metallothionein in MT-null mice 2 hours after cadmium administration (74% versus 72% of the dose, respectively) did not affect distribution. However, the elimination of cadmium was much faster in MT-null mice than in control mice. In control mice, approximately 40% of cadmium administered was found in the liver 24 hours after administration, and the majority was bound to metallothionein. In contrast, only 20% of cadmium was found in the liver of MT-null mice, which was not bound to metallothionein. Cadmium concentrations in kidney, pancreas, and spleen were also lower in MT- null than in control mice 1 week after administration. No apparent difference in cadmium retention in other organs was noted between control and MT-null mice over the 15-day period. Cadmium concentration in kidney continued to increase with time in control but not in MT-null mice, indicating that an important source of cadmium in the kidney is the uptake of CdMT.

Excretion. Since little of the cadmium presented to the gastrointestinal tract is absorbed, most of the oral dose is excreted via the feces. After inhalation exposure to cadmium, the initial lung burden of cadmium-laden particles depositing in the nasopharyngeal or central airways will be cleared via the mucociliary mechanisms, possibly undergoing a small amount of absorption by the oral route. The remaining cadmium particles will be absorbed in the lung. Once absorbed cadmium has distributed throughout the body (primarily to the liver and kidney), the amounts of fecal and urinary excretion of cadmium are approximately equal. The amount of cadmium in the urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion increases markedly (Roels et al. 1981b).

Klaassen and Kotsonis (1977) evaluated biliary excretion of an intravenous bolus of cadmium chloride in the rat, rabbit, and dog. Marked species variation in biliary excretion was observed with rabbits at about 1/6th the rate of the rats, and dogs about 1/300th the rate of the rats. The bile/plasma concentration ratio of cadmium was highly dose dependent, increasing with higher dose. The bile/liver concentration ratio of cadmium was equal to or much lower than 1 decreasing to <1% for the low dose regimen. Biliary excretion increased approximately 4-fold in rats as the temperatures increased from 30 to 40 ^{o}C. Following the administration of different microsomal enzyme inducers (phenobarbital, spironolactone, pregnenolone-16-α-carbonitrile, or 3-methylcholanthrene), only phenobarbital significantly increased biliary excretion.

2.4.2 Mechanisms of Toxicity

Cadmium is toxic to a wide range of organs and tissues; however, the primary target organs of cadmium toxicity are the kidneys and liver. Organs such as the testis, pancreas, thyroid, adrenal glands, bone, central nervous system, and lung have also been studied for toxic effects.

Changes in the kidney due to cadmium toxicosis have been well established. Chronic exposure to cadmium by the oral or inhalation routes has produced proximal tubule cell damage, proteinuria (mainly lowmolecular weight proteins, such as β_2-microglobulin), glycosuria, amino aciduria, polyuria, decreased absorption of phosphate, and enzymuria in humans and in a number of laboratory animal species. The clinical symptoms result from the degeneration and atrophy of the proximal tubules, or (in worse cases) interstitial fibrosis of the kidney (Stowe et al. 1972). Cadmium has been shown to perturb lipid composition and enhance lipid peroxidation (Gill et al. 1989). Depletion of antioxidant enzymes, specifically glutathione peroxidase and superoxide dismutase, has been proposed as the mechanism of cadmium's cardiotoxic effects (Jamall and Smith 1985a), but subsequent studies showed that cardiotoxic mechanisms other than peroxidation are also present (Jamall et al. 1989). Cadmium has been shown to alter zinc, iron and copper metabolism (Petering et al. 1979) as well as selenium (Jamall and Smith 1985b). Xu et al. (1995) propose that an initiating step in cadmium-induced toxicity to the testes is cadmium interference with zinc-protein complexes that control DNA transcription which subsequently leads to apoptosis. Cadmium sequestration by metallothionein (or a chelator in the case of the Xu et al. [19951 study) prevents cadmium from disrupting zinc-dependent transcriptional controls.

Cardenas et al. (1992) investigated a cadmium-induced depletion of glomerular membrane polyanions and the resulting increased excretion of high-molecular-weight proteins. Interference with glomerular

membrane polyanionic charge may precede the tubular damage as a more sensitive and early response to cadmium (Roels et al. 1993). Acute or chronic doses of cadmium, have also been reported to reduce hepatic glycogen stores and to increase blood glucose levels. Intralobular fibrosis, cirrhosis, focal mononuclear infiltrates, and proliferation of the smooth endoplasmic reticulum are among the non-specific histopathological indicators of cadmium toxicity.

Cadmium complexed with metallothionein from the liver can redistribute to the kidney (Dudley et al. 1985). When metallothionein-bound cadmium is transported to the kidney, it readily diffuses and is filtered at the glomerulus, and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes 1978). Exogenous metallothionein is thought to be degraded in lysosomes and released. This non-metallothionein-bound cadmium can then induce new metallothionein synthesis in the proximal tubule (Squibb et al. 1984).

Early work indicated that metallothionein binding decreased the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appeared to be adequate to bind all the accumulated cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). The rate of metallothionein synthesis in the kidney is lower than in the liver (Sendelbach and Klaassen 1988), and is thought to be insufficient, at some point, to bind the intrarenal cadmium (Kotsonis and Klaassen 1978). Renal damage is believed to occur when the localization of cadmium, or an excessive concentration of cadmium, is unbound to metallothionein. Acute exposure to low levels of cadmium bound to metallothionein produced an intracellular renal damage as described above (Squibb et al. 1984), but damage to brush-border membranes of the renal tubule has also been reported from metallothionein-bound cadmium (Suzuki and Cherian 1987) suggesting other toxic mechanisms may be present.

More recently, Dorian et al. (1992a) evaluated the intra-renal distribution of ^{109}CdMT injected (intravenously) into male Swiss mice at a nonnephrotoxic dose (0.1 mg Cd/kg) and concluded that CdMT-induced nephrotoxicity might be due, at least in part, to its preferential uptake of CdMT into the S1 and S2 segments of the proximal tubules, the site of Cd-induced nephrotoxicity. In a companion study, Dorian et al. (1992b) reported that this preferential renal uptake was also observed after administration of various doses of [^{35}S]CdM. In contrast to the earlier observed persistency of ^{109}Cd in the kidney after ^{109}CdMT administration, however, ^{35}S disappeared rapidly (with a half-life of approximately 2 hours); 24 hours after injection of [^{35}S]CdMT, there was very little ^{35}S left in the kidneys. These observations

indicate that the protein portion of CdMT is rapidly degraded after renal uptake of CdMT and that the released cadmium is retained in the kidney.

The toxic effects and distribution of cadmium were compared after intravenous injection of ^{109}CdMT at 0.05-l mg Cd/kg body w eight and $^{109}CdC1_2$ at 0.1-3 mg/kg in male Swiss mice (Dorian et al. 1995). CdMT increased urinary excretion of glucose, and protein indicated renal injury, with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by $CdCl_2$ administration, even at dosages as high as 3 mg Cd/kg. CdMT distributed almost exclusively to the kidney, whereas $CdCl_2$ preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after $CdCl_2$ administration (i.e., the renal cadmium concentration after administration of a high but nonnephrotoxic dose of $CdCl_2$ was equal to or higher than that obtained after injection of nephrotoxic doses of CdMT). Light microscopic autoradiography studies indicated that cadmium from CdMT preferentially distributed to the convoluted segments (S1 and S2) of the proximal tubules, whereas cadmium from $CdCl_2$ distributed equally to the various segments (convoluted and straight) of the proximal tubules. However, the concentration of cadmium at the site of nephrotoxicity, the proximal convoluted tubules, was higher after $CdCl_2$ than after CdMT administration. A higher cadmium concentration in both apical and basal parts of the proximal cells was found after $CdCl_2$ than after CdMT administration. The authors suggest that CdMT is nephrotoxic, and $CdCl_2$ is not nephrotoxic because of a higher concentration of cadmium in the target cells after CdMT. Dorian and Klaassen (1995) evaluated the effects of ZnMT on ^{109}CdMT renal uptake and nephrotoxicity and concluded that ZnMT is not only nontoxic to the kidney at a dose as high as 5 μmole MT/kg, but it can also protect against the nephrotoxic effect of CdMT without decreasing renal cadmium concentration.

To further test the hypothesis that nephrotoxicity produced from chronic cadmium exposure results from a Cd-metallothionein complex, Liu et al. (1998) exposed MT-null mice to a wide range of $CdCl_2$ doses, 6 times per week for up to 10 weeks. Renal cadmium burden increased with dose and duration up to 140 μg Cd/g kidney in control mice (i.e., MT normal) with a 150-fold increase in renal metallothionein levels (800 μg MT/g kidney). Renal cadmium was much lower in MT-null mice (10 μg Cd/g), and metallothionein levels were not detectable. The maximum tolerated dose of cadmium (as indicated by routine urinalysis and histopathology measures) was approximately 8 times higher in control mice than in MT-null mice. Lesions were more severe in MT-null mice than in controls, indicating that Cd-induced renal injury is not necessarily mediated through a CdMT complex and that metallothionein is an important intracellular protein for protection against chronic cadmium nephrotoxicity.

The critical concentration of cadmium in the renal cortex that is likely to produce renal dysfunction also remains a topic of intense investigation. Whether the critical concentration of urinary cadmium is closer to 5 μg Cd/g creatinine or to 10 μg Cd/g creatinine, corresponding to about 100 and 200 μg cadmium/g kidney, respectively, is the current focus of the debate. In one analysis, the critical concentration producing dysfunction in 10% of a susceptible population has been estimated to be approximately 200 μg cadmium/g kidney; 50% of the susceptible population would experience dysfunction with a kidney concentration of 300 μg/g (Ellis et al. 1984, 1985; Roels et al. 1983).

2.4.3 Animal-to-Human Extrapolations

The effects of cadmium toxicosis have been studied in humans and in many laboratory animal species. The target organs are similar among species, with the liver and kidneys being the primary organs for cadmium induced toxicosis. Absorption, distribution, and excretion of cadmium after oral and inhalation exposures are roughly similar among species; however, there are some notable differences and caveats. Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. Differences in the breathing patterns between rats (obligatory nose breathers) and humans (mouth and nose breathers) may also result in radically different lung burden patterns (and hence, different absorption profiles) of cadmium particles in the lungs. Many of the common laboratory animals (in particular the mouse and rat) provide useful information on the toxic effects of cadmium; due to their relatively short lifespan, however, they may not be as useful from a risk assessment point of view in determining the human lifetime effects from inhaling cadmium in air, or ingesting it in food and water. Rates of synthesis and inducibility of metallothionein also differ among species, sex, and target organ.

Even within species there can be significant differences in metallothionein synthesis, and these differences correlate to the degree of cadmium toxicity observed (e.g., the mouse) (Shaikh et al. 1993). The Shaikh et al. (1993) study employed acute exposures. Strain differences in carcinogenic effects have also been reported for chronic exposures of subcutaneously administered cadmium chloride in male DBA and NFS mice. DBA mice developed lymphomas, while NFS mice developed hepatocellular adenomas and carcinomas, and sarcomas at the injection site. Both strains developed nonneoplastic testicular lesions (fibrosis and mineralization) (Waalkes and Rhem 1994).

Metal-metal interactions are also an important factor in cadmium kinetics and toxicity, and organ specific metal concentrations and metabolism can differ among species. It is thought that further development of PBPK/PD models will assist in addressing these differences and in extrapolating the animal data to support risk assessments in humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview. Since the early 1950s, when the hazards of occupational cadmium exposure were recognized (Friberg 1950), a large amount of information has been generated concerning the toxic effects of cadmium exposure. The toxicological properties of cadmium are similar in humans and animals and, as a consequence, rats, mice, rabbits, and monkeys may all provide suitable models for experimental investigation of cadmium toxicity. Toxicological properties are also similar for the several different salts and oxides of cadmium that have been investigated, although differences in absorption and distribution lead to different effect levels. For inhalation exposure, particle size and solubility in biological fluids (in contrast to solubility in water) appear to be the more important determinants of the toxicokinetics (Hirano et al. 1989a, 1989b; Oldiges and Glaser 1986; Rusch et al. 1986). For oral exposure, most experimental studies have used soluble cadmium, which exists as the Cd^{+2} ion regardless of the initial salt. Absorption appears to be similar for cadmium ion and cadmium complexed with proteins in food, except for a few specific types of foods such as Bluff oysters and seal meat (see Section 2.3.1.2). Also, poorly soluble cadmium pigments may be absorbed to a lesser extent than soluble cadmium ion (ILZRO 1977; Oldiges and Glaser 1986).

Cadmium is a cumulative toxicant, and the human exposure conditions of most concern are long-term exposure to elevated levels in the diet. For populations surrounding hazardous waste sites, increased dietary consumption could occur from cadmium-contaminated dust on food or hands, from garden vegetables or fruit grown in cadmium-contaminated soil, and from cadmium-contaminated water used for drinking or garden irrigation. Fugitive dust emissions from cadmium-contaminated soil would expose such populations by the inhalation route. Measurement of cadmium in air, soil, drinking water, and groundwater at these sites is necessary to predict whether adverse health effects may occur. There presently is not enough information to judge the potential absorption or toxicity of cadmium from a dermal exposure. The remainder of this section discusses the toxicity of cadmium exposure for important health effects end

points. Issues relevant to children are explicitly discussed in Sections 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels for Cadmium.

A minimal risk level (MRL) is defined as "an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of noncancer adverse health effects over a specified duration of exposure." No MRLs have been derived for inhalation exposure to cadmium. An MRL for cadmium has been derived for a chronic oral exposure.

Inhalation MRLs.

No MRLs have been derived for inhalation exposure to cadmium.

Oral MRLs.

- An MRL of 0.0002 mg/kg/day has been derived for a chronic-duration oral exposure (365 days or more) to cadmium.

The oral MRL is based on a lifetime accumulated threshold of 2,000 mg of cadmium from dietary sources. This threshold is associated with an increased incidence of proteinuria identified in residents of cadmium polluted areas of Japan (Nogawa et al. 1989). Using an uncertainty factor of 10 for variability in the human population, an MRL of 0.0002 mg/kg/day is derived based on a NOAEL of 0.0021 mg/kg/day. The current average dietary intake of adult Americans is approximately 0.0004 mg/kg/day (Gartrell et al. 1986); and smokers receive about an equal amount from cigarettes (Nordberg et al. 1985). This indicates that Americans currently do not have a large margin of safety with respect to cadmium intake, This interpretation is consistent with studies showing peak kidney cadmium concentrations in North American adults of 20 μg/g wet tissue weight (wet weight) in nonsmokers and 40 μg/g wet weight in smokers (Chung et al. 1986). The level in smokers is only a factor of 5 less than the critical concentration of 200 μg/g wet weight for renal damage in occupationally exposed workers (Roels et al. 1983). A recent large-scale epidemiologic study in Belgium (Buchet et al. 1990) suggests that the critical concentration may be lower (approximately 50 μg/g wet weight in members of the general population, and that 10% of the population of Belgium may exhibit early signs of cadmium-induced renal changes (proteinuria and increased calcium excretion). Taken together, these results suggest that current cadmium exposures, primarily from the diet

and smoking, would have to be lowered significantly before protection from renal damage could be assured for all members of the population.

Alternative methods of deriving an MRL based on the benchmark dose approach and pharmacokinetic modeling for cadmium (Clewell et al. 1997; Crump 1995) have been investigated by the K.S. Crump Group and the results presented in a special report prepared for ATSDR (Crump 1998). Crump (1998) used the Nogawa et al. (1989) end point of kidney dysfunction based upon abnormal urinary β_2-microglobulin and creatinine levels, and the percent response data was converted to quanta1 response rates. The quanta1 end points were then modeled using Weibull or polynomial models. Benchmark dose levels ($BMDL_{10}$s) were derived for the 95% lower bound on the estimated benchmark dose (BMD_{10}) that corresponded to a 10% extra risk. Separate BMDs were estimated for males and females using the two models (Weibull and polynomial). Cumulative exposure levels in mg/kg were converted to mg/kg/day by dividing by 70 years of environmental exposure and 365 days/year resulting in BMDLlos of 0.00075-0.0013 mg/kg/day. Dividing by an uncertainty factor of 10 for human variability, the resulting MRLs would be 0.000075-0.00013 mg/kg/day, a factor of 1.5-3 times lower than the current MRL of 0.0002 mg/kg/day (Crump 1998).

A BMD could not be derived from the data of Buchet et al. (1990) because only very broadly grouped data were reported (Crump 1998). However, a modification of a pharmacokinetic model developed by Oberdorster (1990) was used to calculate the lifetime daily oral intake of cadmium that would result in a urinary excretion of 2.7 μg Cd/day. Based upon this pharmacokinetic modeling approach, and assuming a half-life of 20 years for cadmium excretion from the body, a urinary cadmium level of 2.7 μg Cd/day corresponding to a daily oral intake of 0.84 μg/kg body weight/day was derived. This estimate assumes that all cadmium intake is via the oral route. The 0.84 μg/kg/day estimate, based upon the Buchet et al. (1990) data, represents a LOAEL (i.e., the Buchet et al. analysis is a best estimate of the critical cadmium concentration in the kidney). An uncertainty factor for interindividual variability was not considered necessary because of the large size of the population in the Buchet et al. (1990) study. Using an uncertainty factor of 3 for a minimal LOAEL an MRL of 0.0003 mg/kg/day was derived, which is a factor of 1.5 times greater than the current MRL based on the Nogawa et al. (1989) study.

Death. High levels of exposure to cadmium by the inhalation or oral routes can cause death in humans or animals (Andersen et al. 1988; Barrett et al. 1947; Beton et al. 1966; Buckler et al. 1986; Lucas et al. 1980; Patwardhan and Finckh 1976; Seidal et al. 1993). Inhalation of a lethal dose of cadmium can occur without signs of acute distress during exposure (Beton et al. 1966). The cause of death following inhalation exposure is pulmonary failure due to excessive pulmonary edema, in conjunction with other signs of pulmonary distress and chemical pneumonitis. High oral doses of cadmium induce vomiting; massive fluid imbalance; and widespread gastrointestinal, liver, and other organ damage (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). No accidental oral exposures in humans are known to have caused death (Frant and Kleeman 1941; Shipman 1986). These effects are mainly due to the destruction of cell membranes at the point of entry (the lung for inhalation exposure and the gastrointestinal tract for oral exposure). Parenteral administration of cadmium can also cause death, usually as the result of liver destruction (Goering and Klaassen 1984a, 1984b, 1984c). Environmental levels of cadmium are unlikely to be high enough to cause acute lethality by the inhalation or oral routes, and no studies were found that report such an event.

Systemic Effects.

Respiratory Effects. Acute inhalation exposure to cadmium at concentrations above about 5 mg/m^3 may cause destruction of lung epithelial cells, resulting in pulmonary edema, tracheobronchitis, and pneumonitis in both humans and animals (Beton et al. 1966; Greenspan et al. 1988; Grose et al. 1987; Snider et al. 1973). A single, high-level cadmium exposure can result in long-term impairment of lung function (Beton et al. 1966; Dervan and Hayes 1979; Townshend 1982). At the cellular level, catalase, superoxide dismutase, non-protein sulfhydryl, glucose-6-phosphate dehydrogenase, and glutathione peroxidase are decreased in response to cadmium lung insults. The respiratory response to cadmium is similar to the response seen with other agents that produce oxidative damage (Boudreau et al. 1989). There typically is an alveolar pneumocyte type 2 cell hyperplasia in response to type 1 cell damage and necrosis. The type 2 cell hyperplasia is typically measured with biochemical and cytological assays of bronchoalveolar lavage fluid (Boudreau et al. 1989). Alveolar macrophages are also mobilized in the lung (Driscoll et al. 1992). Longer-term inhalation exposure at lower levels also leads to decreased lung function and emphysema (Cortona et al. 1992; Davison et al. 1988; Glaser et al. 1986; Leduc et al. 1993). Some tolerance to cadmium-induced lung irritation develops in exposed humans (Barnhart and Rosenstock 1984) and animals (Hart et al. 1989a), and respiratory function may recover after cessation of cadmium exposure (Chan et al.

1988). Another effect of long-term inhalation cadmium exposure is damage to the olfactory function (Rose et al. 1992). Lung damage has also been seen in a few studies of oral cadmium exposure in rats (Borzelleca et al. 1989; Miller et al. 1974b; Petering et al. 1979) but the lung effects are likely to be related to liver or kidney damage and subsequent changes in cellular metabolism. Nonoccupational exposure to cadmium is unlikely to be high enough to cause significant respiratory effects.

Cardiovascular Effects. Conflicting evidence has been obtained in both human and animal studies for the effect of cadmium exposure on the cardiovascular system. In some studies on rats, rabbits, and monkeys, cadmium exposure was shown to increase blood pressure (Akahori et al. 1994; Boscolo and Carmignani 1986; Kopp et al. 1982), or to cause cardiac lesions (Jamall et al. 1989). However, studies of exposed humans have found positive (Geiger et al. 1989) negative (Kagamimori et al. 1986) and no (Cummins et al. 1980) association between cadmium exposure and hypertension. This suggests that if cadmium does affect blood pressure, the magnitude of the effect is small compared to other determinants of hypertension. Death rates for cardiovascular disease do not appear to be elevated in populations exposed to cadmium by inhalation or in the diet (Kazantzis et al. 1988; Shigematsu 1984). Overall, the weight of evidence suggests that cardiovascular effects are not a sensitive end point indicator for cadmium toxicity.

Gastrointestinal Effects. The gastrointestinal tract is the target organ for high-level, acute, oral exposure to cadmium in both humans and animals (Andersen et al. 1988; Borzelleca et al. 1989; Frant and Kleeman 1941; Shipman 1986), due to direct irritation of the gastric epithelium. The main symptoms following ingestion of cadmium at doses above about 0.07 mg/kg in humans are nausea, vomiting, and abdominal pain (Nordberg et al. 1973). Gastrointestinal toxicity is not observed in humans or animals after lower levels of oral exposure or after inhalation exposure to cadmium, indicating that gastrointestinal effects are not likely to occur from environmental exposures to cadmium.

Hemtological Effects. Both oral and inhalation exposure to cadmium can cause anemia in humans and animals (Bernard et al. 1979; Friberg 1950; Groten et al. 1990; Kagamimori et al. 1986; Kozlowska et al. 1993; Pleasants et al. 1992, 1993). Oral exposure to cadmium has been shown to reduce uptake of iron from the diet in animals (Hays and Margaretten 198.5; Kelman et al. 1978; Sakata et al. 1988). It is likely that cadmium transported to the gastrointestinal system from the lung following inhalation exposure would also reduce iron absorption. Therefore, anemia induced by inhalation exposure to cadmium is likely to be caused by reduced iron absorption. Those studies of humans exposed to cadmium by inhalation or in the diet that have not found anemia (Chan et al. 1988; Davison et al. 1988; Roels et al. 1981a; Shiwen et al.

1990) may have examined populations with dietary iron intakes adequate to compensate for reduced absorption. Cadmium-induced anemia is unlikely to be of concern for general population exposure.

Musculoskeletal Effects. Prolonged inhalation or ingestion exposure of humans to cadmium at levels causing renal dysfunction can lead to painful and debilitating bone disease in individuals with risk factors such as poor nutrition (Kazantzis 1979; Shigematsu 1984). Evidence from both human and animal studies suggests that lower-level chronic exposure to cadmium causes alternations in renal metabolism of vitamin D, which then may cause milder bone effects (osteoporosis) (Blainey et al. 1980; Kido et al. 1990a; Nogawa et al. 1987, 1990). These effects may be compounded by loss of calcium and phosphate with more severe renal damage, leading to osteomalacia (Kazantzis 1979; Shigematsu 1984). Some studies in mice have found measurable effects in bone prior to development of proteinuria or histologic kidney lesions (Bhattacharyya et al. 1988c; Ogoshi et al. 1989; Watanabe et al. 1986). A recent large-scale cohort study in Belgium found that increased urinary calcium excretion was significantly associated with urinary cadmium levels, an index of kidney cadmium burden (Buchet et al. 1990). This evidence suggests that either cadmium may have a direct effect on bone at levels lower than those causing kidney damage, or that interference with vitamin D metabolism in the proximal tubule may be a more sensitive indicator of cadmium-induced renal damage than proteinuria.

Hepatic Effects. Cadmium accumulates in the liver following inhalation or oral exposure in humans (Lauwerys et al. 1984; Roels et al. 198lb), but there is little evidence for liver damage in humans exposed to cadmium (Nishino et al. 1988). Exposure to cadmium can cause liver damage in animals (necrosis of hepatocytes, metabolic changes, membrane peroxidation), but generally only after high levels of exposure (Andersen et al. 1988; Groten et al. 1990; Kotsonis and Klaassen 1977, 1978). Decreased relative liver weight to body weight ratios have also been reported in male rats, in addition to slightly lower plasma cholesterol and triglyceride levels in monkeys (Akahori et al. 1994; Kozlowska et al. 1993). The resistance of the liver to oral and inhalation cadmium toxicity is apparently due to its ability to synthesize sufficient quantities of metallothionein to sequester all accumulated cadmium (Kotsonis and Klaassen 1978). When cadmium exposure is by injection, a high concentration of cadmium ion that is not bound to albumin or metallothionein reaches the liver, causing hepatic necrosis and even death (Goering and Klaassen 1984a, 1984b, 1984c).

Renal Effects. The kidney is the main target organ for cadmium toxicity following intermediate- or chronic-duration exposure by the inhalation or oral routes, as has been shown by numerous studies in

humans and animals. The first manifestation of kidney damage is decreased reabsorption of filtered lowmolecular- weight proteins, indicating damage to the renal tubules. Production of tubular proteinuria is a relatively specific effect of cadmium on the kidneys and has been observed even following acute parenteral exposure in animals (Wang and Foulkes 1984). This damage has been associated with increased urinary levels of β_2-microglobulin, retinol-binding protein, or other low-molecular-weight proteins (Bernard and Lauwerys 1989). At higher levels or durations of exposure, increased excretion of high-molecular-weight proteins occurs, indicating either glomerular damage (Roels et al. 1989) or severe tubular damage (Mason et al. 1988). Kidney damage, progressing from mild tubular lesions to widespread necrosis, depending on dose, can be demonstrated in animals following parenteral or subcutaneous administration of cadmium salts or cadmium bound to metallothionein (Kjellstrom 1986c).

The sensitivity of the kidney to cadmium is related to the metabolism of cadmium in the body (see Section 2.3.3). Except for extremely high-dose exposure, cadmium exists in the body primarily bound to metallothionein. The CdMT complex is readily filtered at the glomerulus and reabsorbed in the proximal tubule (Foulkes 1978). Within the tubular cells, the metallothionein is degraded in lysosomes and free cadmium is released (Squibb et al. 1984). The synthesis of endogenous metallothionein by the tubular cells is then stimulated, but when the total cadmium content in the renal cortex exceeds approximately 200 μg/g wet weight, the amount of cadmium not bound to metallothionein becomes sufficiently high to cause tubular damage (Roels et al. 1983). Free cadmium ion may inactivate metal-dependent enzymes, activate calmodulin, and/or damage cell membranes through activation of oxygen species (Waalkes and Goering 1990).

Acute exposure to low levels of cadmium bound to metallothionein produced an intracellular renal damage (Squibb et al. 1984), but damage to brush-border membranes of the renal tubule has also been reported from metallothionein-bound cadmium (Suzuki and Cherian 1987) suggesting other toxic mechanisms may be present. Recent studies indicate that the protein portion of CdMT is rapidly degraded after renal uptake of CdMT and that the released Cd is retained in the kidney (Dorian et al. 1992a, 1992b). CdMT has been shown to be more toxic than $CdCl_2$ (Dorian et al. 1995). CdMT renal injury occurred with dosages as low as 0.2 mg Cd/kg, while renal function was unaltered by $CdCl_2$ even at dosages as high as 3 mg Cd/kg. CdMT distributed almost exclusively to the kidney, whereas $CdCl_2$ preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after $CdCl_2$ administration (i.e., the renal cadmium concentration after administration of a high but nonnephrotoxic dose of $CdCl_2$ was equal to or higher than that obtained after injection of nephrotoxic doses of CdMT). The higher nephrotoxicity of

CdMT appears to result from a higher concentration of cadmium in the target cells compared to a comparable exposure to $CdCl_2$. ZnMT is not only nontoxic to the kidney at a dose as high as 5 μmole MT/kg, but it can also protect against the nephrotoxic effect of CdMT without decreasing renal cadmium concentration (Dorian and Klaassen 1995).

Studies in MT-null mice (Liu et al. 1998) indicate that Cd-induced renal injury is not necessarily mediated through a CdMT complex, but that metallothionein is an important intracellular protein for protection against chronic cadmium nephrotoxicity. Studies in MT-transgenic mice also have demonstrated that higher metallothionein concentrations in tissues of MT-TG mice had no appreciable effects on the concentration of cadmium in tissues compared to controls, except for an exception for MT-TG mice given the highest dose of cadmium (300 μmol Cd/kg, po). The high dose MT-TG mice had twice the tissue cadmium concentration of controls (Liu and Klaassen 1996).

The health significance of the early kidney damage is difficult to assess. The decreased resorption of low molecular-weight proteins is not adverse in and of itself, but may be indicative of increased excretion of other solutes. Deaths from renal failure due to cadmium exposure are rare, but even after cadmium exposure ceases, the renal damage continues to progress (Kido et al. 1990b; Roels et al. 1989). Evidence that cadmium exposure may affect kidney vitamin D metabolism with subsequent disturbances in calcium balance and bone density (Buchet et al. 1990; Kido et al. 1989b; Nogawa et al. 1990) suggests that decreased bone density, particularly in elderly women, may be a significant adverse effect of kidney cadmium accumulation.

Dermal Effects. Based on the lack of reported effects among workers occupationally exposed to fairly high concentrations of cadmium dust, cadmium appears to have relatively low dermal toxicity. However, few studies have specifically examined the dermal toxicity of cadmium exposure. Scant information is available on the *in vivo* percutaneous absorption of the different forms of cadmium, although it is believed that very little of any chemical form of cadmium is absorbed through the skin to pose serious health risks. Cadmium binding to soil components and differences in partition coefficients significantly reduces the overall availability and percutaneous absorption of cadmium.

Ocular Effects. Based on the lack of reported effects among workers occupationally exposed to fairly high concentrations of cadmium dust, cadmium appears to have relatively low ocular toxicity. However, few studies have specifically examined the ocular toxicity of cadmium exposure.

Body Weight Effects. Inhaling cadmium has not been shown to affect body weight in humans, but high exposures in animals have significantly reduced body weights. Acute exposures to cadmium in the 4-7 mg Cd/m^3 range have caused significant reductions of body weight in male rats (Buckley and Bassett 1978b; Bus et al. 1978; Grose et al. 1987). No effect levels for acute exposures have been reported at <0.5 mg Cd/m^3 (Grose et al. 1987; Klimisch 1993), except for the less soluble pigments like cadmium sulfide and cadmium selenium sulfide where much higher levels of 99 mg Cd/m^3 for 2 hours and 97 mg Cd/m^3 for 2 hours, respectively, did not result in a decreased body weight (Rusch et al. 1986). Levels of cadmium that significantly reduce rat body weights when administered for an intermediate-duration exposure have been reported for cadmium chloride at around 1 mg Cd/m^3 for female and male rats (Baranski and Sitarek 1987; Kutzman et al. 1986), for cadmium chloride at around 0.394 mg Cd/m^3 for pregnant females (Prigge 1978a), and for cadmium dusts at 0.1 mg Cd/m^3 for female rats (Prigge 1978a). NOAELs have been reported for intermediate exposures to cadmium chloride at 0.394 mg Cd/m^3 for nonpregnant female rats (Prigge 1978a), 0.33 mg Cd/m^3 for rats (Kutzman et al. 1986), and 0.0508 mg Cd/m^3 for male rats (Takenaka et al. 1983). NOAELs have been reported for intermediate exposures to cadmium oxide dust at 0.16 mg Cd/m^3 for female rats (Baranski and Sitarek 1987) and 0.45 mg Cd/m^3 for male rabbits (Grose et al. 1987); and for cadmium sulfide at 1.034 mg Cd/m^3 for male rats (Glaser et al. 1986). A NOAEL for chronic exposure in rats to cadmium sulfate has been reported as 0.95 mg Cd/m^3 (Oldiges and Glaser 1986).

Decreased body weight and decreased rates of growth are common findings in studies where experimental animals are orally exposed to cadmium. Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium exhibited a 12% decrease in body weight, but 100 mg/kg had no effect (Kotsonis and Klaassen 1977). Daily gavage doses of 15.3 mg/kg over a I0-day period caused a 79% decrease in body weight gain in male Sprague-Dawley rats (Borzelleca et al. 1989). Significant reductions in maternal weight gain have also been reported (Baranski 1985; Machemer and Lorke 1981).

Body weight reductions are also seen in intermediate-duration studies. In general, intermediate-duration doses in feed or drinking water of 3 mg/kg/day or less have either no effect or only a small effect (10-20% decrease) on body weight in rats (Carmignani and Boscolo 1984; Jamall et al. 1989; Loeser and Lorke 1977a; Muller et al. 1988; Ogoshi et al. 1989; Perry et al. 1989; Wilson et al. 1941). Higher doses(4-14 mg/kg/day) had no effect in some studies (Kostial et al. 1993; Kotsonis and Klaassen 1987; Prigge 1978a; Viau et al. 1984) and small effects in others (Cha 1987; Kawamura et al. 1978; Kozlowska et al. 1993). A 29% decrease in maternal weight gain was observed in rats exposed to a high dose of

40 mg/kg/day (Baranski and Sitarek 1987). In mice, a dose of 4.8 mg/kg/day had no effect on maternal weight gain, but a dose of 9.6 mg/kg/day caused a 14% decrease (Webster et al. 1978). A high dose of 232 mg/kg/day in mice caused a 29% decrease in body weight (Waalkes et al. 1993). Beagle dogs were unaffected intraperitoneally mg/kg/day (Loeser and Lorke 1977b), as were rabbits at up to 2.2 mg/kg/day (Boscolo and Carmignani 1986; Tomera and Harakai 1988). A small decrease (11%) was seen in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972).

A chronic-duration study in rhesus monkeys reported decreased growth rates at 0.4 mg/kg/day, but no effect at 0.12 mg/kg/day (Masaoka et al. 1994). No effect on body weight was seen in rats at up to 4.4 mg/kg/day (Decker et al. 1958; Fingerle et al. 1982; Mangler 1988), but a small effect was seen at 7 mg/kg/day (Waalkes and Rehm 1992). Decreased terminal body weight was observed in mice at a high dose of 57 mg/kg/day (Hays and Margaretten 1985).

No studies were located that reported on changes in body weight after dermal exposure to cadmium.

Metabolic Effects. Hyperthermia and metabolic acidosis were reported in a human male who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

No studies were located regarding metabolic effects in animals after oral or inhalation exposure to cadmium.

Immunological and Lymphoreticular Effects. There is little evidence for immunological effects in people following inhalation exposure to cadmium (Guillard and Lauwerys 1989; Karakaya et al. 1994) and no studies were found regarding immunological effects after oral exposure. Cadmium does not appear to cause contact sensitization after dermal exposure in humans or animals (Rudzki et al. 1988; Wahlberg 1977; Wahlberg and Boman 1979). A wide variety of immunologic alterations have been associated with inhalation or oral cadmium exposure in animals (Blakley 1985, 1986, 1988; Bouley et al. 1982, 1984; Cifone et al. 1989a). Inhalation exposures have been shown to suppress the primary humoral immune response (Graham et al. 1978), to be cytotoxic to spleen lymphocytes (Krzytyniak et al. 1987), to increase spleen weight (Kutzman et al. 1986; Prigge 1978b), to enlarge the thoracic lymph nodes (Oldiges and Glaser 1986), to have no effect on natural killer cell activity or viral induction of interferon in mice (Daniels et al. 1987), and to decrease resistance to bacterial infection while increasing resistance to viral infection (Bouley et al. 1982). Numerous oral exposure studies in rats, mice, and monkeys have established the capability of cadmium to affect the immune system including increasing resistance to viral

infection (Exon et al. 1986), to increase mortality from virally-induced leukemia (Blakley 1986; Malave and de Ruffino 1984), to depress the humoral immune response of 6 week old mice (Blakley 1985), but not of 12-month-old mice (Blakley 1988) to increase the cell-mediated immune response of monkeys (Chopra et al. 1984), to induce anti-nuclear antibodies in mice (Ohsawa et al. 1988) to increase circulating leukocytes in female rats (Borzelleca et al. 1989), to exhibit time-dependent inhibitory and stimulative effects (Cifone et al. 1988b), or to have no effect (Bouley et al. 1984; Stacey et al. 1988a) on natural killer cell activity in rats.

The results are, therefore, conflicting, indicating that cadmium exposure can either stimulate or suppress the immune system, and some observed effects may not be clinically significant. Few studies have directly examined immune function of cadmium-exposed humans and the relevance of the immunologic effects observed in animals to public health is difficult to assess.

Neurological Effects. Neurotoxicity is not generally associated with inhalation exposure to cadmium, although a few studies have specifically looked for neurological effects. Hart et al. (1989b) reported a modest correlation between cadmium exposure and decreased performance on neuropsychologic tests for attention, psychomotor speed, and memory in a small cohort of men exposed to cadmium in the workplace air (average exposure=14.5 years). The small number of men studied makes it difficult to evaluate the significance of this effect. Ijomah et al. (1993) studied an increased prevalence of dementia in elderly people living near an aluminum smelter, but observed no significant difference in the prevalence of dementia between the smelter group and the reference group even though there were significant elevations of plasma and red blood cell aluminum and cadmium concentrations. Rose et al. (1992) reported that the workers chronically exposed to cadmium fumes generated during a brazing operation at sufficient levels to cause renal damage also had impairment in olfactory function.

A few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. These studies used hair cadmium as an index of exposure which has limitations. End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985), and disruptive behavior in Navy recruits (Struempler et al. 1985). The usefulness of the data from these studies is limited because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and an inadequate

quantification of cadmium exposure. No other human neurological studies on inhaled on ingested cadmium were found.

Acute inhalation exposures to cadmium results in neurotoxicity (i.e., tremors or reduced activity) only at high levels (Rusch et al. 1986). Continuous exposure at lower levels were not neurotoxic (Glaser et al. 1986) although a mid-level dose (1 mg/kg/m^3) did lead to significantly increased relative brain weight (Kutzman et al. 1986). The evidence for neurotoxicity is fairly strong from animal studies with oral exposures. Both a single oral exposure (Kotsonis and Klaassen 1977) and intermediate-duration exposure of adult rats to cadmium have been observed to decrease motor activity significantly (Kotsonis and Klaassen 1978; Nation et al. 1990). Intermediate-duration oral exposure to cadmium has also been reported to cause weakness and muscle atrophy (Sato et al. 1978), to induce aggressive behavior (Baranski and Sitarek 1987), to induce anxiety as manifested by increased passive avoidance behavior (Nation et al. 1984) and by increased ethanol consumption (Nation et al. 1989), and to alter brain biogenic amine content and enzyme activities (Murthy et al. 1989). Doses associated with these effects range from 5 to 40 mg/kg/day cadmium. Degenerative changes in the choroid plexus have been reported in mice exposed to 1.4 mg/kg/day cadmium in drinking water for 22 weeks (Valois and Webster 1989). Peripheral neuropathy has been reported in rats after a 31-month exposure to cadmium in drinking water (Sato et al. 1978). Nerve cell or brain damage following parenteral exposure have also been reported (Arivison 1980; Wong and Klaassen 1982). Four-day-old rats were more susceptible to lesions in the corpus callosum, caudateputamen, and cerebellum than were 8-week old adults following a single subcutaneous injection of cadmium chloride. Postexposure brain lesions and hyperactivity were also evident in newborns at dose levels that produced no such effects in adults (Wong and Klaassen 1982).

In general, however, there is little available human evidence to indicate that cadmium adversely affects the human nervous system at exposures even up to levels that result in renal toxicity.

Reproductive Effects. Evidence is insufficient to determine an association between inhalation exposure to cadmium and reproductive effects in humans. Study results are conflicting, with some showing no effect on male fertility (Gennart et al. 1992), male hormone levels (Mason 1990), sperm density (Noack-Fuller et al. 1992), or semen quality (Saaranen et al. 1989); others found a reduction in sperm number or viability (Xu et al. 1993a). Animal studies with inhalation exposures have reported increased duration of the estrous cycle (Baranski and Sitarek 1987; Tsvetkova 1970), and increased relative testes weight, but no loss in reproductive success (Kutzman et al. 1986).

No studies were located regarding reproductive effects in men or women after oral exposure to cadmium. A number of animal studies have shown adverse reproductive effects to male and female reproductive capacity from oral cadmium exposure. In male rats and mice, acute oral-exposure near-lethal doses (60-100 mg/kg) can cause testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al, 1989), and concomitant decreased fertility (Kotsonis and Klaassen 1978). Lower-dose acute exposures of 25-50 mg!kg did not result in reproductive toxicity in male animals (Andersen et al. 1988; Bomhard et al. 1987; Dixon et al. 1976). A number of intermediate-dosing regimens in the 0.25-5 mg/kg/day range resulted in neither testicular histopathologic lesions nor a decrease in male reproductive success (Bomhard et al. 1987; Dixon et al. 1976; Groten et al. 1990; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a, 1977b; Pleasants et al. 1992; Zenick et al. 1982). Some dosing regimens in the 5-14 mg/kg/day range resulted in necrosis and atrophy of seminiferous tubule epithelium (Cha 1987); increased testes weight (Pleasants et al. 1992, 1993); increased prostatic hyperplasias (Waalkes and Rehm 1992); or significantly increased relative testes weight, decreased sperm count and motility, decreased seminiferous tubular diameter, and seminiferous tubular damage (Saxena et al. 1989). Vitamins A and D_3 have been reported to reduce cadmium-related increase in testes weight (Pleasants et al. 1992, 1993).

Higher doses of cadmium are needed to elicit a reproductive toxic response in females than in the males, at least for the effects reported in the literature (Borzelleca et al. 1989). Effects include decreased percentage of fertilized females and percentage of pregnancies (Machemer and Lorke 1981; Sutou et al. 1980) and increased duration of the estrus cycle (Baranski and Sitarek 1987). Reduction in the number of pups born has generally not been seen from female exposures (Petering et al. 1979; Pond and Walker 1975; Sorell and Graziano 1990), but have been observed when both males and females were exposed (Schroeder and Mitchener 1971).

In pregnant albino rats, kidney concentrations of cadmium in the dam exceeded those concentrations found in the liver, while in the pups, renal and liver concentrations were very similar. Body concentrations of cadmium were several orders higher in dams than in the pups (Kostial et al. 1993). Environmental exposures may not be likely to cause reproductive toxicity in exposed humans.

Developmental Effects. There is very little human data on developmental effects from exposure to cadmium, and the studies that do indicate that maternal cadmium exposure may cause decreased birth weight in humans (Hue1 et al. 1984; Tsvetkova 1970) are of limited use because of weaknesses in the study design and lack of control for confounding factors.

In animals, cadmium has been shown to be a developmental toxin by the inhalation, oral, and parenteral routes (Baranski 1985, 1987; Prigge 1978b). Decreased fetal weight and skeletal malformations are produced by relatively high maternal doses due to placental toxicity, interference with fetal metabolism, and damage to the maternal liver (Holt and Webb 1987). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the 1-20 mg/kg/day range. The most sensitive indicator of developmental toxicity appears to be impaired neurological development. This observation is supported by later studies that noted brain weights of mice dosed orally with cadmium had significantly decreased brain weights, with high levels of cadmium deposits in the brain (Kostial et al. 1993; Xu et al. 1993b). The lowest exposures shown to cause these effects in animals are 0.02 mg/m^3, 5 hours a day, 5 days a week, by inhalation (Baranski 1985) and 0.04 mg/kg/day, 5 days a week orally (Baranski et al. 1983). These exposures are above the chronic NOAELs calculated for renal effects in humans. However, insufficient information is available on developmental toxicity in humans to determine whether developmental effects of cadmium are of concern at levels of environmental exposure.

Genotoxic Effects. Tables 2-6 and 2-7 summarize some of the genotoxicity studies that have been performed for cadmium. Evidence concerning chromosomal aberrations in humans following inhalation (Bauchinger et al. 1976; Deknudt and Leonard 1975; O'Riorden et al. 1978) or oral (Bui et al. 1975; Tang et al. 1990) exposure to cadmium is conflicting. Cadmium does not appear to cause germ cell mutations or chromosomal damage following oral (Sutou et al. 1980; Zenic et al. 1982) or-intraperitoneal (Epstein et al. 1972; Mailhes et al. 1988; Suter 1975) exposure in animals, but does so following subcutaneous exposure (Watanabe and Endo 1982; Watanabe et al. 1979). Positive mutagenicity results have been found in some studies using bacterial cells (Bruce and Heddle 1979; Kanematsu et al. 1980; Mandel and Ryser 1984; Wong 1988), and in most studies using yeast or mammalian cell cultures (Denizeau and Marion 1989; Oberly et al. 1982; Schiestl et al. 1989). Chromosomal aberrations have been found in most studies using

Table 2-6. Genotoxicity of Cadmium *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberrations	+	Deknudt et al. 1973
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Deknudt and Leonard 1975
Human lymphocytes	Chromosomal aberrations	+	Bauchinger et al. 1976
Human lymphocytes	Chromosomal aberrations	–	O'Riordan et al. 1978
Human lymphocytes	Chromosomal aberrations	+	Alessio et al. 1993
Oral exposure:			
Mouse bone marrow	Chromosomal aberrations	–	Deknudt and Gerber 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988b
Rat spermatogenesis	Dominant lethal mutations	–	Sutou et al. 1980
Rat spermatogenesis	Dominant lethal mutations	–	Zenick et al. 1982
Human leukocytes	Chromosomal aberrations	+	Shiraishi and Yoshida 1972
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Tang et al. 1990
Intraperitoneal exposure:			
Syrian hamster embryo cells	Transformation	+	DiPaulo and Casto 1979
Mouse bone marrow	Chromosomal aberrations	–	Bruce and Heddle 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988a
Mouse bone marrow	Sister chromatid exchanges	+	Mukherjee et al. 1988a
Mouse bone marrow	Micronuclei	(+)	Mukherjee et al. 1988a
Mouse spermatocytes	Chromosomal translocations	–	Gilliavod and Leonard 1975
Mouse spermatozoa	Sperm morphology	–	Bruce and Heddle 1979
Mouse spermatozoa	Sperm morphology	+	Mukherjee et al. 1988a
Mouse spermatogenesis	Dominant lethal mutations	–	Epstein et al. 1972
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberations	+	Deknudt et al. 1973

Table 2-6. Genotoxicity of Cadmium *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberrations	+	Deknudt et al. 1973
Mouses spermatocytes	Chromosomal aberations	+	Selypes et al. 1992
Mouse spermatogenesis	Dominant lethal mutations	–	Gilliavod and Leonard 1975
Mouse oocytes	Dominant lethal mutations	–	Suter 1975
Mouse oocytes	Aneuploidy	–	Mailhes et al. 1988
Subcutaneous exposure:			
Syrian hamster oocytes	Chromosomal aberrations	+	Watanabe et al. 1979
Mouse blastocysts	Aneuploidy	+	*Watanabe and Endo 1982*
Mouse bone marrow	Sister chromatid exchanges	–	Nayak et al. 1989
Mouse fetal liver and lung cells	Sister chromatid exchanges	–	Nayak et al. 1989

+ = positive result; – = negative result; (+) = weakly positive result

Table 2-7. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Bacillus subtilis	DNA repair	No data	(+)	Nishioka 1975
B. subtilis	DNA repair	No data	(+)	Kanematsu et al. 1980
Salmonella typhimurium (plate incorporation)	Gene mutation	–	–	Bruce and Heddle 1979
S. typhimurium (liquid suspension)	Gene mutation	–	–	Milvy and Kay 1978
S. typhimurium (liquid suspension)	Gene mutation	No data	(+)	Mandel and Ryser 1984
S. typhimurium (plate incorporation)	Gene mutation	–	+	Wong 1988
Eukaryotic organisms:				
Yeast:				
Saccharomyces cerevisiae	Gene mutation	No data	+	Putrament et al. 1977
S. cerevisiae	Intrachromosomal recombination	No data	+	Schiestl et al. 1989
Insects:				
Drosophila melanogaster	Sex-linked recessive lethal mutations	No data	–	Inoue and Watanabe 1978
D. melanogaster	Dominant lethal mutations	No data	+	Vasudev and Krishnamurthy 1979
D. melanogaster	Nondisjunction	No data	–	Ramel and Magnusson 1979
Mammalian cells:				
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	(+)	Amacher and Paillet 1980

Table 2-7. Genotoxicity of Cadmium *In Vitro* (continued)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	+	Oberly et al. 1982
Chinese hamster ovary Hy cells	Chromosomal aberration	No data	+	Rohr and Bauchinger 1976
Chinese hamster ovary CHO cells	Chromosomal aberration	No data	+	Deaven and Campbell 1980
Syrian hamster embryo cells	Transformation	No data	+	Casto et al. 1979
Rat ventral prostate cells	Transformation	No data	+	Terracio and Nachtigal 1988
Rat hepatocytes	Unscheduled DNA synthesis	No data	+	Denizeau and Marion 1989
Human blood lymphocytes	Chromosomal aberration	No data	–	Paton and Allison 1972
Human blood lymphocytes	Chromosomal aberration	No data	+	Shiraishi et al. 1972
Human blood lymphocytes	Chromosomal aberration	No data	–	Deknudt and Deminatti 1978
Human blood lymphocytes	Chromosomal aberration	No data	(+)	Gasiorek and Bauchinger 1981
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Bassendowska-Karska and Zawadzka-Kos 1987
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Avitabile et al. 1993
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Avitabile et al. 1993
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Avitabile et al. 1993

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

cadmium treatment of mammalian cells (Deaven and Campbell 1980; Rohr and Bauchinger 1976) and in some studies using human lymphocytes in culture (Gasiorek and Bauchinger 1981; Shirashi and Yoshida 1972), and in bone marrow cells following intraperitoneal (Mukherjee et al. 1988a) and oral (Mukherjee et al. 1988b) exposure in mice. Overall, cadmium appears to have the capability of altering genetic material, particularly chromosomes in mammalian cells, but germ cells appear to be protected except at high acute parenteral doses.

Cancer. The relationship between occupational exposure to cadmium and increased risk of cancer (specifically lung and prostate cancer) has been explored in a number of epidemiologic studies. For inhalation exposures, the results of epidemiology studies that evaluated cadmium's effects on increased lung cancer are conflicting. Many of the studies had inadequate controls for confounding factors such as co-exposure with other metal carcinogens and smoking, and there is only a small number of lung cancer mortality cases in the only U.S. cohort studied. Overall, however, the results provide little evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium. For prostate cancer, the initial studies in European worker populations exposed to cadmium indicated an elevation in prostate cancer (Kipling and Waterhouse 1967; Kjellstrom et al. 1979; Lemen et al. 1976), but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant (Elinder et al. 1985; Kazantzis et al. 1988; Sorahan 1987; Thun et al. 1985). Based on an analysis of the mortality data from a 5-year update of the cohort from 17 plants in England, and a review of the other epidemiological evidence, Kazantzis et al. (1992) concluded that cadmium does not appear to act as a prostatic carcinogen.

Studies of occupationally exposed cohorts in countries other than the United States have found some increases in lung cancer, but no clear relationship between level and duration of cadmium exposure and increased risk of lung cancer. Cigarette smoking was also a confounding factor. These cohorts included workers from an English zinc-lead-cadmium smelter (Ades and Kazantzis 1988), from 17 different manufacturing or processing facilities involving cadmium in England (Kazantzis et al. 1988), from a nickel-cadmium battery plant in Sweden (Elinder et al. 1985c), and from a nickel-cadmium battery plant in England (Sorahan 1987). The most recent report comes from Sorahan et al. (1995) who studied mortality rates (lung cancer and nonmalignant respiratory diseases) in 347 copper cadmium alloy workers in the United Kingdom. The authors present results that are consistent with the hypothesis that exposure to cadmium oxide fume increases risk of mortality from chronic non-malignant diseases of the respiratory

system, but that do not support the hypothesis that exposure increases the risks of mortality for lung cancer.

An increased risk of lung cancer from cadmium exposure was reported in studies on the only U.S. cohort (workers in a cadmium recovery plant in Globe, Colorado) (Thun et al. 1985, Stayner et al. 1992), but subsequent studies have attributed the increase to either arsenic exposure and/or smoking (Lamm et al. 1992, 1994; Sorahan et al. 1997). These studies and the conflicting results are discussed in more detail below.

A statistically significant, 2-8-fold excess risk of lung cancer was reported in the highest exposure group (cumulative exposures >8 years x mg/m^3), and the dose-response trend over the three exposure groups was highly significant (Thun et al. 1985). Confounding factors included possible exposure to the heavy metals, arsenic (Thun et al. 1989; Kazantzis et al. 1992) and nickel (Sorahan 1987), which are known human lung carcinogens. The data for the U.S. cohort supported an analysis that controlled for the effects of smoking.

Stayner et al. (1992) used data from a retrospective study on lung cancer mortality in the U.S. to further analyze the lung cancer risk associated with cadmium exposure in the U.S. cohort. The analysis controlled for smoking and for ethnicity (i.e., Hispanic and non-Hispanic workers). Lung cancer mortality rates are lower for Hispanics compared to non-Hispanics. Lung cancer mortality was significantly elevated among non-Hispanics and less than expected among Hispanics (as would be predicted from the use of the white male referent rate). The lung cancer SMR increased with cumulative cadmium exposure and was nearly significant for the entire cohort (SMR=149, 95% CI=95, 222; p=0.076, two-tails). The SMR was significantly elevated in the highest exposure group (>2,921 mg-days/m^3) for the combined cohort (SMR=272, 95% CI=123, 513), and for the three highest exposure groups for the non-Hispanic groups. A significant excess of lung cancer mortality was also observed among workers in the longest time-since-firstexposure category (>20 years) for the combined cohort (SMR=161, 95% CI=l00, 248) and for non-Hispanics (SMR=233, 95% CI=141, 365). A statistically significant dose-response relationship was evident in nearly all of the regression models evaluated. Based on this analysis, the lifetime excess of lung cancer at the previous OSHA standard for cadmium fume of 100 μg/m^3 would be approximately 50-111 lung cancer deaths per 1,000 workers exposed to cadmium for a working lifetime (45 years). At the current OSHA standard of 5 μg/m^3 (OSHA 1992) the lifetime risk of lung cancer was predicted to be approximately 2.6-6 lung cancer deaths per 1,000 workers exposed to cadmium for 45 years (Stayner et al. 1992).

Stayner et al. (1992) also performed an indirect assessment of confounding effects of exposure to arsenic. The analysis indicated that there was no significant effect on lung cancer mortality from cumulative cadmium exposure because of year of hire; in fact, the authors report that their dose-response analysis demonstrated a greater dose-response relationship for workers hired after 1939.

Lamm et al. (1992, 1994) used nearly the same data set for the U.S. cohort as Stayner et al. (1992) in a nested case-control analysis that used the period of hire as a surrogate for arsenic exposure. Based on this analysis, Lamm et al. (1992, 1994) reported no residual association of lung cancer with cadmium in the Globe, Colorado, cohort; they reported that cases were more than eight times more likely to have been cigarette smokers than were their controls. They concluded that arsenic exposure and cigarette smoking were the major determinants of lung cancer risk, not cadmium exposure.

The reasons for these conflicting conclusions based on the same cohort data are unclear. Doll (1992) suggested some possible reasons including: (1) that the total number of cases was small (n=25) and that only 21 of these cases were included in both studies (i.e., each study included some cases that were not included in the other study); (2) that Stayner et al. (1992) used national rather than regional mortality rates; (3) that the Lamm et al. (1992, 1994) control series was overmatched, although the matching by date of hire was necessary to control for arsenic exposure; and (4) that there are some concerns about the validity (i.e., biological relevance) of the dose-response-models used by Stayner et al. (1992). In a response to Doll (1992), Stayner et al. (1993) reported that use of regional mortality rates would increase rather than decrease support for their conclusion, and that the nested case-control analysis of Lamm et al. (1992) used overmatched controls. Stayner et al. (1993) provide additional analyses including the use of the Armitage-Doll multistage model to support the conclusion of an increased risk of cancer from cadmium exposure.

Sorahan and Lancashire (1994) subsequently raised concerns about inconsistencies and inaccuracies in the NIOSH job history data used in these studies on the U.S. cohort. Sorahan and Lancashire (1997) then conducted further analyses, based on detailed job histories extracted from time sheet records, to better resolve the potential confounding affects of arsenic. After adjustment for age attained, year of hire, and Hispanic ethnicity; Sorahan and Lancashire (1997) report a significant positive trend ($p<0.05$) between cumulative exposure to cadmium and risks of mortality from lung cancer. However, when the exposure to cadmium was evaluated with or without concurrent exposure to arsenic, a significant trend for lung cancer was only found for exposure to cadmium received in the presence of arsenic trioxide. Since there were only 21 deaths from lung cancer, Sorahan and Lancashire (1997) state that it is impossible to determine which

of the following three hypotheses is the correct one: (1) cadmium oxide in the presence of arsenic trioxide is a human lung carcinogen, (2) cadmium oxide and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulphide are not (i.e., cadmium sulphate and cadmium sulphide were the main cadmium compounds of exposure when arsenic was not present), or (3) arsenic trioxide is a human carcinogen and the three cadmium compounds are not carcinogenic.

There were no human studies found (occupational or environmental exposures) that associated an increase in cancer with oral exposure in humans. Available epidemiologic studies, however, had no reliable estimates of individual doses (Bako et al. 1982; Inskip and Beral 1982; Lauwerys and De Wals 1981; Nakagawa et al. 1987), and so had limited sensitivity to detect a carcinogenic effect.

The controversy about the adequacy of the human cancer data for cadmium is reflected in the cancer classifications from different agencies. The Environmental Protection Agency EPA has classified cadmium as a probable human carcinogen by inhalation (Group Bl), based on its assessment of limited evidence of an increase in lung cancer in humans (Thun et al. 1985) and sufficient evidence of lung cancer in rats (IRIS 1996; Takenaka et al. 1983). EPA has calculated an inhalation unit risk (the risk corresponding to lifetime exposure to 1 $\mu g/m^3$) of $1.8x10^{-3}$ (IRIS 1996). The National Toxicology Program (NTP) has classified cadmium and certain cadmium compounds as substances that are reasonably anticipated to be carcinogens, based on an assessment of limited evidence for carcinogenicity from studies in humans and sufficient evidence for carcinogenicity in humans (NTP 1994). In contrast, the International Agency for Research for Research on Cancer (IARC) has classified cadmium as carcinogenic to humans (Group 1) based on an assessment of sufficient evidence for carcinogenicity in both human and animal studies (IARC 1993).

Strong evidence from animal studies exists that cadmium inhalation can cause lung cancer, but only in rats. Inhalation exposure of rats to various chemical forms of cadmium for 18 months caused lung tumors during the subsequent 13-month follow-up period (Oldiges et al. 1989; Takenaka et al. 1983). No other type of tumor showed any significant dose-response trend (Takenaka et al. 1983). Mice similarly exposed had only marginally significant elevations in lung cancer rate, but the rate of lung cancers in control mice was high and variable (Heinrich et al. 1989). No evidence for lung carcinogenicity in hamsters was found, possibly due to lung damage and subsequent decreased survival at high doses (Heinrich et al. 1989). Intratracheal instillation of up to three doses of cadmium oxide caused no increase in lung tumors in male rats, but did increase the incidence of mammary fibroadenomas (Sanders and Mahaffey 1984). The increase was significant when all dose groups were pooled (Sanders and Mahaffey 1984).

All but one of the animal studies show no cadmium-related increase in cancer from oral exposure. The early animal carcinogenicity experiments had limited sensitivity because the maximum doses used were 1 mg/kg/day in mice (Schroeder et al. 1964) and 2.5 mg/kg/day in rats (Loser 1980). Doses up to 6.5 mg/kg/day in mice (Bhattacharyya et al. 1988b) and 12.5 mg/kg/day in rats (Bornhard et al. 1984) have been used in noncancer chronic-duration animal studies, so the doses used in the oral carcinogenicity studies were clearly below the maximum tolerated dose. More recently, Waalkes and Rehm (1992) reported that cadmium in a zinc controlled diet increased prostatic proliferative lesions (both hyperplasias and adenomas), leukemia, and testicular tumors in rats. The overall incidence for tumors of the prostate, testes, and hematopoietic system decreased in zinc-deficient rats. These results indicate that dietary zinc deficiency has complex, apparently inhibitory, effects on cadmium carcinogenesis by the oral route.

Waalkes et al. (1993) also report that cadmium can effectively “impair” tumor formation in the lungs and liver of male $B6C3F_1$ mice given a tumor promotor (n-nitrosodiethylamine) and exposed to a relatively high level of cadmium (232 mg/kg/day) via the drinking water for up to 48 weeks. Cadmium appeared to be able to destroy existing preneoplastic and/or tumor cells (adenomas) selectively. The mechanism may involve a reduced activity and responsiveness of the metallothionein system in transformed liver cells.

Injection of cadmium into the skin or muscle causes tumors in rats, primarily at the site of injection and in the testes (Bornhard et al. 1987; Poirer et al. 1983; Waalkes et al. 1989). The induction of testicular tumors following cadmium injection appears to be directly related to the testicular degeneration (Bomhard et al. 1987). When rat testes do not experience degeneration following cadmium injection, either because the cadmium injection is intramuscular or because the testes are protected by subcutaneous injection of zinc, no testicular tumors occur (Waalkes et al. 1989). A consequence of testicular degeneration caused by subcutaneous cadmium injection is atrophy of prostatic tissue, but when testicular degeneration does not occur, the prostate does not atrophy and prostatic tumors develop (Waalkes et al. 1989). This latter finding indicates that systemic exposure to cadmium may induce prostate tumors, but further suggests that these tumors can only be detected when cadmium-induced testicular degeneration is prevented.

The relevance of carcinogenicity experiments using parental exposure is uncertain because of the substantial differences in the toxicity and toxicokinetics of cadmium after oral or inhalation exposure compared to the toxicity and toxicokinetics of injected cadmium ion (Goering and Klaassen 1984a, 1984b, 1984; Kotsonis and Klaassen 1977, 1978). Strain differences in carcinogenic effects have also been reported for chronic exposures of subcutaneously administered cadmium chloride in male DBA and NFS

mice. DBA mice developed lymphomas, while NFS mice developed hepatocellular adenomas and carcinomas, and sarcomas at the injection site. Both strains developed nonneoplastic testicular lesions (fibrosis and mineralization) (Waalkes and Rehm 1994a). Waalkes and Rehm (1994b) also report a cadmium associated increase in hematopoietic tumors, primarily follicular center-cell lymphomas, in BALB/c mice following subcutaneous injection; however, not only was there an effect on the incidence of lung tumors, cadmium suppressed the multiplicity of pulmonary tumors (i.e., the mean number of lung tumors per animal).

Maximilien et al. (1992) raises concerns about the appropriateness of the rat model for cadmium induced lung tumors in humans. This is a serious concern because the strength of the animal data in support of a cadmium dose-response increase in lung tumors from inhalation exposure primarily rests on the rat model. These authors argue that cadmium is a contact carcinogen and that differences in the morphology of the rat respiratory tract result in a deposition pattern and target cell population that are quite different from the deposition pattern and target cell population that would result from human inhalation exposure. Differences between the rat and human clearance rates, speciation at the level of the target cell, and protein transporters (as they relate to solubility and susceptibility) are not well characterized. Data are also presented in support of the hypothesis that cadmium is not an initiator in rats, and that cadmium carcinogenicity in this model may be phenomenon limited to older rats. These concerns merit further investigation.

2.6 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults, They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

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

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

The health effects seen in children from exposure to toxic levels of cadmium are expected to be similar to the effects seen in adults (i.e., kidney, lung, and intestinal damage depending on the route of exposure).

Because cadmium is a cumulative toxin and has a very long half-time in the body, exposures to children in even low amounts may have long-term adverse consequences. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40-50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). Liver cadmium concentrations also begin near zero at birth, increase to typical values of l-2 μg/g wet weight by age 20-25, then increase only slightly thereafter (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984; Sumino et al. 1975).

A potential for cadmium to have adverse neurological effects is an important consideration. However, only a few studies have reported an association between environmental cadmium exposure and neuro-psychological functioning. End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), and acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985). The usefulness of the data from these studies is limited, however, because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and because of an inadequate quantification of cadmium exposure (i.e., the studies used hair cadmium as an index of exposure which has some limitations because of potential confounding from exogenous sources).

The human information for developmental effects following exposure to cadmium is very limited. Russian women occupationally exposed to cadmium at concentrations ranging from 0.02 to 35 mg/m^3 had offspring with decreased birth weights but without congenital malformations, compared to unexposed controls (Tsvetkova 1970). However, no association was found between birth weights of offspring and length of maternal cadmium exposure, and no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight. A nonsignificant decrease in birth weight was found in offspring of women with some occupational exposure to cadmium in France; however, no adverse effects were documented in these newborns (Hue1 et al. 1984). Hue1 et al. (1984) used hair samples to estimate exposure but the usefulness of this data is limited because there were no controls to distinguish between exogenous and endogenous sources. No other human studies were located regarding developmental effects in humans after inhalation exposure to cadmium.

Developmental toxicity from exposure to cadmium is most often reported in animal studies from an oral exposure. Baranski (1985), however, reported developmental toxicity in offspring of female rats exposed to cadmium oxide at 0.02 mg Cd/m^3 for 5 hours a day, 5 days a week, for 4-5 months prior to mating and

during the first 20 days of gestation. The effects reported included delayed ossification, decreased locomotor activity, and impaired reflexes in offspring. Decreases in weight gain, osteogenesis, and viability were also noted at concentrations of 0.16 mg/m^3 (Baranski 1985).

Many studies in rats and mice indicate that cadmium can be fetotoxic from oral exposures prior to and during gestation. This fetotoxicity is most often manifested as reduced fetal or pup weights (Ali et al. 1986; Baranski 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Petering et al. 1979; Pond and Walker 1975; Sore11 and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988), but malformations, primarily of the skeleton, have been found in some studies (Baranski 1985; Machemer and Lorke 1981; Schroeder and Mitchener 1971). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the l-20 mg/kg/day range.

The most sensitive indicator of developmental toxicity of cadmium in animals appears to be neurobehavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg/day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months (Baranski et al. 1983). Pups from dams exposed to 0.7 mg/kg/day during gestation had significant delays in cliff aversion and swimming behavior. Locomotor activity was significantly increased. In post-weaning measurements, locomotor activity was significantly decreased in treated groups at 60 days of age; conditioned avoidance behavior was also significantly decreased when tested at 60 and 90 days of age (Ali et al. 1986).

Nagymajtenyi et al. (1997) also reported behavioral and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. Three consecutive generations of Wistar rats were orally treated by gavage with 3.5, 7.0, or 14.0 mg Cd/kg body weight (as cadmium chloride diluted in distilled water) over the period of pregnancy, lactation, and 8 weeks after weaning. Behavioral (open-field behavior) and electrophysiological (spontaneous and evoked cortical activity, etc.) parameters of male rats from each generation were investigated at the age of 12 weeks. The main behavioral outcomes were increased vertical exploration activity (rearing) and increased exploration of an open-field center. The spontaneous and evoked electrophysiological variables showed dose- and generation-dependent changes (increased frequencies in the electrocorticogram, lengthened latency and duration of evoked potentials, etc.)

signaling a change in neural functions. The results indicate that low-level, multigeneration exposure of rats to inorganic cadmium can affect nervous system function.

Desi et al. (1998) continued the above studies to further evaluate cadmium-associated changes in behavior and neurological function in rats following different dosage regimens during pregnancy. Female Wistar rats were given 3.5, 7.0, or 14.0 mg Cd/kg body weight (cadmium chloride dissolved in distilled water) in three different treatment regimes: days 5-15 of pregnancy; days 5-15 of pregnancy + 4 weeks of lactation; days 5-15 of pregnancy + 4 weeks of lactation followed by the same oral treatment of male rats of the Fl generation for 8 weeks. The behavioral (open-field exploration) and electrophysiological (electrocorticogram, cortical evoked potentials, conduction velocity and refractory periods of a peripheral nerve) parameters of Fl male rats exposed by various treatments were investigated at age 12 weeks. The results indicate that cadmium altered the spontaneous and evoked electrophysiological functions (e.g., increased the frequency of the electrocorticogram, lengthened the latency and duration of evoked potentials, etc.) in a dose- and treatment-time-dependent manner. Only the combination of treatment during prenatal development and the 4-week suckling period resulted in a significant dose-dependent decrease of horizontal and vertical exploratory activity and a significantly lower exploration frequency of the open-field center. The results suggests that low-level pre- and postnatal inorganic cadmium exposure affects the electrophysiological functions and higher order functions of the nervous system.

Gupta et al. (1993) examined the developmental profiles of DNA, RNA, proteins, DNA synthesis, thymidine kinase activity, and concentrations of zinc and cadmium in the brain of neonates from dams exposed to cadmium acetate at 5-6.3 mg/kg/day in drinking water during gestation, and 7-8 mg/kg/day during a 21-day lactation period. Pup brain and body weights were significantly decreased in the cadmium exposed pups on lactation days (Ld) 7-21. Cadmium brain accumulation was significantly increased in exposed pups on Ld 7 and remained at similar levels on Ld 14 and 21. DNA and thymidine kinase brain levels were significantly decreased in treated pups compared with controls on Ld 7, 14, and 21. The toxicological significance of changes in DNA levels and thymidine kinase activity are uncertain.

Xu et al. (1993b) determined lipid peroxide (LPO) concentrations in rat pups in various organs as an index of cadmium toxicity. Male and female Wistar mice were exposed to cadmium in drinking water at 0, 5.7, or 14.25 mg/kg/day for 2 months prior to mating. The pregnant females continued to be exposed during gestation and lactation. Litter size and pup survival rates were unaffected by cadmium. Body weights were not statistically different between the exposed and control groups. In pups, brain weights (at 5.7 and

14.25 mg/kg/day) and liver, kidney, and heart weights (at 14.25 mg/kg/day) were significantly decreased. Although the relative organ weights were lower in the high-dose group, the difference from controls was not statistically significant. LPO concentrations in all organs were significantly increased in pups on Ld 7 at 14.25 mg/kg/day except in the kidney; concentrations in the liver, heart, and brain were 131.5, 156, and 237.4%, respectively, of the concentrations in controls.

In contrast to most of the study results, Saxena et al. (1986) reported no developmental effects from an exposure to 21 mg Cd/kg/day via drinking water during gestation (Gd 0-20). This study evaluated simultaneous exposure to lindane (20 mg lindane/kg via gavage on Gd 6-14) and cadmium acetate in drinking water at doses that individually did not cause maternal or developmental effects. Maternal toxicity (significantly decreased weight gain) and developmental toxicity were only observed in the cadmium plus lindane group. Fetal body weight was significantly decreased; intrauterine death and the rate of skeletal anomalies were significantly increased. Anomalies consisted of decreased ossification, wavy ribs, and scrambled sternebrae.

Cadmium is known to dramatically increase resorption of bone calcium in animals fed calcium deficient diets, resulting in painful bone disorders, including osteomalacia, osteoporosis, and spontaneous and painful bone fractures (an affliction called Itai-Itai or “ouch-ouch” disease). Long-term exposures of cadmium to infants and children would result in the accumulation of cadmium in the bone.

Ogoshi et al. (1989) studied the mechanical strength of femurs of young, adult, and elderly female rats after a 4-week exposure to $CdCl_2$ in drinking water. Young rats (21 days old; strain not specified; N=19-22F) were given $CdCl_2$ at 0, 5, or 10 ppm; adult rats (24 weeks old; strain not specified; N=18-25NS) were given $CdCl_2$ at 0, 10, 20, 40, 80, or 160 ppm (adult rats); elderly rats (1.5 years old; strain not specified; N=25-27NS) were given $CdCl_2$ at or 0, 80, or 160 ppm. At the end of the 4 week exposure, femur compression and bending were evaluated. Young rats had decreased bone strength at both doses tested (5 and 10 ppm), while adult and elderly rats showed no effect up to doses of 160 ppm. Bone strength was correlated with cadmium content of bone but not cadmium content of liver or kidney. Young rats accumulated cadmium in the bones to a much greater extent (100 ng/g dry weight at 5 ppm, 150 ng/g at 10 ppm) then did the adult or elderly rats whose accumulation was roughly comparable and about 65 ng/g at the highest dose of 160 ppm.

Oral cadmium exposure has also been reported to suppress the T-lymphocyte and macrophage dependent humoral immune response of 6-week-old mice against sheep red blood cells (Blakley 1985), but not of 12-month-old mice (Blakley 1988). In 6-week-old mice, Blakley (1985) studied the effect of cadmium chloride on the immune response in female BDF_1 mice (N=22) administered $CdCl_2$ in drinking water for 3 weeks at doses of 0, 5, 10, or 50 μg/mL. Parameters monitored included body weight gain, response of splenic lymphocytes to specific mitogens in the presence or absence of cadmium, humoral response of spleen cells against sheep red blood cells (SRBC) as measured by plaque counts, and kidney cadmium levels. No overt clinical signs, weight gain, or gross pathology were observed following cadmium exposure at these levels. A-dose-response increase in kidney cadmium was observed with concentrations in 0, 5, 10 and 50 ppm groups of 0.17,0.33, 1.02 and 5.98 μg/g wet weight, respectively. A dose-dependent suppression of the immune response of spleen cells to SRBC antigen was observed with a reduction in plaque count of 28.2% in the high dose group. The B-lymphocyte response to SRBC antigen is T lymphocyte dependent and requires the presence of macrophages. Cadmium-induced dysfunction to any or all 3 cell types could lead to the observed suppressed humoral response. To evaluate a potential suppression of the proliferation of T- and B-lymphocytes by cadmium, splenic lymphocytes were exposed to 0, 0, 5, 10, or 50 μg cadmium/ml in conjunction with the known mitogens, concanavalin A for T-lymphocytes, or *Escherichia coli* lipopolysaccharide for B-lymphocytes. Proliferative response from exposure to mitogen was measured as an increase in DNA synthesis. Rather than lessen the proliferative response, T-lymphocyte proliferative response to concanavalin A was not affected by cadmium exposure. Further, the proliferative response of B-lymphocytes to *Escherichia coli* lipopolysaccharide was signif-icantly enhanced by cadmium in a dose-responsive manner. Cadmium alone was, itself, mildly mitogenic, thus cadmium suppression of the primary humoral immune response to SRBC antigen does not appear to result from an impaired lymphocyte proliferative response. Further evaluation is needed, but the author notes that the suppressed humoral response in young mice occurred at relatively low kidney cadmium levels, indicating that the immune system of the young mouse is relatively sensitive to the effects of cadmium.

In contrast to the suppressed humoral response to SRBC antigen observed in 6-week-old mice, Blakley (1988) did not observe a similar response under similar test conditions for 12-month-old mice. The author suggests that “natural” age-related immune system dysfunction masked any cadmium suppressive effect.

Children are most likely to be exposed to cadmium in food or water. Most ingested cadmium passes through the gastrointestinal tract without being absorbed. In adults, only about one-twentieth of the total ingested cadmium (in food or water) is absorbed (McLellan et al. 1978, Rahola et al. 1973). The retention

of cadmium in the gut slowly decreases over a period of l-3 weeks after ingestion in adults (Rahola et al. 1973). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20 fold higher than in adult guinea pigs.

Absorption from the gut appears to take place in two phases, uptake from the lumen into mucosa, then transfer into the circulation. Factors affecting cadmium absorption include metal-metal (e.g., iron, calcium, chromium, magnesium, zinc) and the form of cadmium (i.e., protein or sulfhydryl bound, or ionic) in the food or water. Levels of other metals and proteins can vary with age and physiological status, and affect cadmium kinetics. Animal studies have shown that low levels of iron, calcium, or protein in the diet can increase the amount of cadmium absorbed into the body (Friberg et al. 1974). Increased fat in the diet can also increase cadmium absorption (i.e., probably from the longer residency times for absorption to occur). Cadmium is not well absorbed by the skin (about 0.5%), and there is not a significant risk from skin exposure unless contact with the skin is for long periods of time or at very high levels.

Differences in individual sensitivity to cadmium have not been systematically studied, but based on what is known about cadmium toxicity, inferences can be made. The body store of iron influences cadmium absorption; subjects with low iron stores (assessed by serum ferritin levels) had an average absorption of 8.9%, while those with adequate iron stores had an average absorption of 2.3% (Flanagen et al. 1978). Women with depleted stores of calcium, iron, or other dietary components due to multiple pregnancies and/or dietary deficiencies can be expected to have increased cadmium absorption from the gastrointestinal tract, while oral zinc supplementation has been shown to decrease the oral absorption of cadmium. Children with depleted stores of iron, calcium, or protein may also have increased absorption of cadmium.

Tissue distribution and retention of cadmium differed between 4-day-old rats and 70-day-old adult rats. Cadmium was 3-6 times more concentrated in the newborn spleen, bone, brain, testes, and muscle than in the adult rat 2 hours after an intravenous administration of 1 mg Cd/kg body weight. Liver concentration of metallothionein was 20 times greater in the newborn than in the adult; kidney metallothionein concentrations were comparable, but liver cadmium was only 30% higher and kidney cadmium was 50% higher in the newborn. Nineteen days post-cadmium exposure, the retention of cadmium in the liver, kidney, and lung was similar in both the newborn and the adult rat (Wong and Klaassen 1980a). Goering and Klaassen (1984) report that high levels of metallothionein in 10-day-old rats play an important role in their resistance

to liver damage, presumably by binding and retaining cadmium. However, the tissue distribution data led Wong and Klaassen (1990a) to propose that metallothionein does not play a major role in the tissue distribution and retention of cadmium in the young.

Cadmium can be transferred to offspring in breast milk. Cadmium levels in human milk are 5-l 0% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987). In female outbred albino rats exposed to cadmium in drinking water (as $CdCl_2$) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, at 3 weeks of gestation, or 3 weeks into lactation), kidney concentrations exceeded liver concentrations, while in their pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium concentrations considerably increased only during the second half of the lactation period (Ld 11-21). The cadmium tissue concentrations in dams were several orders higher than in offspring.

Although studies on elimination of cadmium from the tissues of children are not available, the results of studies in animals provide some insight. Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces. Of the cadmium that is absorbed into the body, most is excreted very slowly, with urinary and fecal excretion being approximately equal (Kjellstrom and Nordberg 1978). Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years (Kjellstrom and Nordberg 1985). Half-times in the slowest phase were from 20 to 50% of the maximum life span of the animal (Kjellstrom and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellstrom and Nordberg (1985) developed a range of half-times from their kinetic model for the human kidney of between 6 and 38 years, and for the human liver of between 4 and 19 years. These high values indicate the persistence of cadmium in the body and the importance of minimizing exposures in children to prevent long-term accumulation and toxicity.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a recent study in Czechoslovakia, the concentration of cadmium in the

placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sore11 and Graziano 1990). Thus, timing and level of cadmium exposure may influence the utake of cadmium by the placenta, perhaps explaining the conflicting human studies.

Of particular importance to the toxicokinetics and toxicity of cadmium is its interaction with the protein metallothionein. Metallothionein is a low-molecular-weight protein, very rich in cysteine, which is capable of binding as many as seven cadmium atoms per molecule and is inducible in most tissues by exposure to cadmium, zinc, and other metals (Waalkes and Goering 1990). Metallothionein binding decreases the toxicity of cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). Goyer et al. (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Chan and Cherian (1992) report that pregnancy in Sprague-Dawley rats previously administered cadmium chloride (1.0 mg Cd/kg body weight subcutaneously, daily for 8 days) leads to a mobilization of cadmium from the liver (40% decrease compared to nonpregnant cadmium treated controls) and an increase in the kidneys (60% increase). A similar pattern is seen for metallothionein. Plasma cadmium and metallothionein also increased in the pregnant group. Placental cadmium increased in the cadmium-treated rats ompared to the untreated controls. In this rat model, then, pregnancy resulted in a transfer of hepatic admium and metallothionein via the blood to the kidney and placenta.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cadmium are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cadmium are discussed in Section 2.7.2.

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 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Cadmium

Cadmium levels in blood, urine, feces, liver, kidney, hair, and other tissues have been used as biological indicators of exposure to cadmium. A discussion of the utility and limitations of each for human biomonitoring is provided below.

Blood cadmium levels are principally indicative of recent exposure(s) to cadmium rather than whole body burdens (see Section 2.3) (Ghezzi et al. 1985; Jarup et al. 1988; Lauwerys et al. 1994; Roels et al. 1989). Concentrations of cadmium in blood in normal populations range from about 0.4 to 1.0 μg/L for non-smokers and 1.4-4 μg/L for smokers (Elinder 1985b; Sharma et al. 1982). Environmental exposure can elevate blood cadmium concentration to above 10 μg/L (Kido et al. 1990a, 1990b; Shiwen et al. 1990). Workers occupationally exposed to cadmium by inhalation may have blood cadmium levels ranging up to 50 μg/L (Roels et al. 1981b). Blood concentrations <10 μg/L are considered acceptable in occupational exposures (WHO 1980). In one estimate, workers with cumulative cadmium exposure equivalent to a blood concentration of 10 μg/L for 20 years would be expected to have a 14% incidence of renal dysfunction (Jarup et al. 1988).

Urine cadmium levels primarily reflect total body burden of cadmium, although urine levels do respond somewhat to recent exposure (Bernard and Lauwerys 1986). When the critical level for renal damage has been reached, urinary cadmium levels rise sharply because of the release of intrarenal cadmium along with decreased renal reabsorption of cadmium (see Section 2.3) (Lauwerys et al. 1994; Roels et al. 1981b). In the general population, the average urinary cadmium level is about 0.35 μg/g creatinine in nonsmokers and values above 2 μg/g creatinine are rare (Lauwerys and Malcolm 1985; Mueller et al. 1989). In populations with substantial environmental or occupational exposure, values can range up to 50 μg/g creatinine, even among individuals with no signs of renal dysfunction except high cadmium excretion levels (Falck et al. 1983; Roels et al. 1981b; Tohyama et al. 1988). In environmentally exposed individuals, Buchet et al. (1990) report that abnormal values of various biomarkers are found in 5% of the population with urinary excretion of cadmium above the 2-4 μg Cd/24 hour level (approximately l-3 μg/g creatinine). Based on a review of several cross-sectional epidemiological studies, Lauwerys et al. (1994) proposed a biological limit value of 5 nmol Cd/mmol creatinine (= 5 μg/g) and 2 nmol/mmol (≈ 2 μg/g) for adult male workers and the general population, respectively.

Fecal cadmium may be used as a direct indicator of daily dietary intake of cadmium because dietary cadmium is poorly absorbed in the gastrointestinal tract (see Section 2.3) (Kjellstrom et al. 1978). In workers exposed by inhalation, fecal cadmium has been used to estimate the amount of inhaled cadmium

transported to the gastrointestinal tract and the amount of dust ingested incidentally at work (Adamsson et al. 1979). Fecal cadmium primarily reflects recently ingested cadmium and, therefore, is not a good indicator of past cadmium exposure (Shaikh and Smith 1984).

Liver and kidney tissues preferentially accumulate cadmium, and concentrations of cadmium in liver and kidney may be measured *in vivo* by neutron activation analysis or in the kidney by X-ray fluorescence analysis (Christoffersson et al. 1987; Scott and Chettle 1986). Levels in both tissues increase with age and level of cadmium exposure, but kidney cadmium concentration tends to peak around age 50-60, while liver cadmium concentration continues to rise (see Section 2.3). Typical values for a 60-year-old North American with average environmental cadmium exposure are 25-40 μg/g wet weight in kidney cortex and l-3 μg/g wet weight in liver (Elinder 1985b). In workers exposed to cadmium by inhalation, values up to 300 μg/g wet weight in kidney and 100 μg/g wet weight in liver can be found (Christoffersson et al. 1987; Roels et al. 1981b). Because kidney cadmium content begins to decline after the onset of cadmium-induced renal dysfunction, liver cadmium may be a better indicator of cadmium exposure than kidney cadmium, and it has been suggested that kidney dysfunction is likely to appear at liver cadmium concentrations between 30 and 60 μg/g wet weight (Roels et al. 1981 b). *In vivo* liver and kidney cadmium measurements involving neutron activation analysis or X-ray fluorescence require complex and costly equipment and may pose a radiation hazard (Shaikh and Smith 1984), and those involving biopsy specimens (Lindqvist et al. 1989) require a painful and invasive procedure. Therefore, these methods for *in vivo* analysis are better suited for monitoring of occupationally exposed workers than environmentally exposed populations (Scott and Chettle 1986).

Hair levels of cadmium have been used as a measure of cadmium exposure, although the possibility of exogenous contamination has led to substantial controversy concerning the reliability of hair levels as a measure of absorbed dose (Frery et al. 1993; Hue1 et al. 1984; Lauwerys et al. 1994, Shaikh and Smith 1984; Wilhelm et al. 1990). Recent evidence has shown a correlation between cadmium levels in the hair of newborn infants and their mothers (Hue1 et al. 1984) and between cadmium levels in scalp and pubic hair (Wilhelm et al. 1990), indicating that among environmentally exposed populations, external contamination may not be significant for hair samples taken close to the scalp. Under occupational conditions, external contamination may be a more substantial problem (Shaikh and Smith 1984).

On the other hand, Frery et al. (1993) evaluated hair levels in a male population with a high expected exposure to tobacco smoke and in a population of pregnant woman and their newborns; they concluded that cadmium hair analysis was a reliable indicator for the subjects with the highest exposure, but was not sensitive enough to resolve differences for low level exposures, Newborn cadmium hair levels were a more

sensitive indicator than mother's hair, but the research was not able to determine if this was attributable to physiological changes or the lower reliability of the mother's head hair. Exogenous contamination is not considered a problem for newborn hair. The authors state that the variability introduced by exogenous contamination can be minimized by using the first 8 cm of hair from the scalp and by using careful washing techniques. There was also no significant difference between hair levels for passive or non-smokers indicating that either the above mentioned precautions worked or that the passive smoke source of exposure was not significant.

Cadmium measurements have been made on a variety of other biological materials, including milk (Schulte-Lobbert and Bohn 1977; Sikorski et al. 1989) placenta (Kuhnert et al. 1982; Roels et al. 1978; Saarenen et al. 1989), nails (Takagi et al. 1988), teeth (Sharon 1988), and cataractous lenses (Racz and Erdohelyi 1988). Although in some cases it could be established that levels in these tissues were higher among smokers than nonsmokers, the significance of cadmium levels as a marker of recent or total cadmium exposure has not been established for any of these tissues.

2.7.2 Biomarkers Used to Characterize Effects Caused by Cadmium

Acute inhalation exposure to high levels of cadmium causes respiratory damage and may lead to death. No information was located on biomarkers of respiratory effects in humans, but based on animal experiments, activity of alkaline phosphatase in the surfactant fraction of BALF has been suggested as a sensitive marker of pulmonary damage following acute cadmium inhalation (Boudrea et al. 1989). Such a biomarker of effect is not specific to cadmium exposure and would be most relevant to occupational exposures.

Renal dysfunction, usually first manifested as impaired tubular reabsorption of filtered solutes, is generally considered the primary toxic effect of chronic cadmium exposure (see Section 2.2). Impaired kidney function has been measured by increased levels of solutes (proteins, amino acids, uric acid, calcium, copper, phosphorous, etc.) in urine and/or serum. Excess urinary excretion of low-molecular-weight proteins and solutes is associated with decreased tubular reabsorption. Increased excretion of high molecular-weight proteins or decreased serum clearance of creatinine reflect glomerular dysfunction, which is generally associated with progressive renal damage (Roels et al. 1989). A brief discussion of the utility and limitations of several measures of tubular damage as biomarkers of effects of cadmium exposure is provided below.

Urinary β_2-microglobulin, a low molecular weight protein, has been widely used as an indicator of tubular renal dysfunction (Piscator 1984; Roels et al. 1981a; Smith et al. 1980). However, tubular renal dysfunction can be caused by exposures and diseases other than cadmium, so β_2-microglobulin is not a specific marker of cadmium-induced effects (Shaikh and Smith 1984). Practical considerations in using urinary β_2-microglobulin as a marker of tubular renal dysfunction include the need to control the pH of samples to prevent the rapid degradation that occurs at pH values below 5.5 (Shaikh and Smith 1984), and the fact that urinary β_2-microglobulin excretion normally rises with age (Roels et al. 1989).

Urinary retinol-binding protein is also considered to be a sensitive indicator of decreased tubular reabsorption, but it also is not specific for cadmium-induced damage in the kidney (Shaikh and Smith 1984; Topping et al. 1986). Retinol-binding protein is more stable in urine than β_2-microglobulin (Bernard and Lauwerys 1981) and appears to be of approximately equal sensitivity and specificity for detecting tubular proteinuria in cadmium-exposed populations (Topping et al. 1986). Levels of both proteins fluctuate over time, so regular, repeated sampling may be necessary to establish abnormal levels (Ormos et al. 1985).

Urinary metallothionein correlates with cadmium concentrations in liver, kidney, and urine (Shaikh and Smith 1984). Relatively strong correlations have been found between urinary metallothionein and urinary cadmium levels in exposed humans (Kawada et al. 1990), and a dose-related increase in urinary metallothionein was found in rats exposed to cadmium in drinking water for up to 2 years (Shaikh et al. 1989). However, the specificity of metallothionein for cadmium exposure may be questioned, because many other exposures are known to induce metallothionein (Waalkes and Goering 1990). Also, once renal damage becomes pronounced, urinary metallothionein levels increase sharply (Shaikh and Smith 1984).

Urinary N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme present in high concentrations in the proximal tubule, has a better correlation with urinary cadmium levels than does β_2-microglobulin at low cadmium exposure levels (urinary cadmium <10 ug/g creatinine) (Chia et al. 1989; Kawada et al. 1990; Mueller et al. 1989). However, increased urinary NAG activity can result from effects other than nephrotoxicity (Bernard and Lauwerys 1989).

Other enzymes, proteins, and amino acids in urine have been suggested as biological markers of incipient renal or liver damage resulting from cadmium exposure. Markers found to be sensitive indicators in exposed humans include β_2-microglobulin (Tohyama et al. 1986), trehalase (Iwata et al. 1988), alanine aminopeptidase (Mueller et al. 1989), and calcium (Buchet et al. 1990). Changes in urinary alkaline phosphatase, y-glutamyl transferase, urate, and phosphate tend to be significant only after other markers of

renal damage are clearly elevated (Mason et al. 1988). Several other enzymatic markers of cadmium induced renal damage have been suggested based on animal studies (Bomhard et al. 1984; Gatta et al. 1989; Girolami et al. 1989). Aminoaciduria has been found to be more sensitive than proteinuria for renal damage in animal studies (Nomiyama et al. 1975), but less sensitive in humans (Axelsson and Piscator 1966). At present, not enough information is available to determine which, if any, of these parameters provide sensitive and specific indicators of cadmium-induced renal damage.

At the present time, there is no single biological indicator for cadmium toxicity that is entirely adequate when considered alone. Measurement of cadmium levels in various biological materials can provide an indication of recent or total cadmium exposure, but the probability of adverse effects cannot be reliably predicted except at high exposure levels. Measurement of a variety of markers of renal dysfunction can provide a sensitive measure of early kidney toxicity, but cannot establish whether cadmium exposure was the cause.

There is also considerable controversy as to whether the critical concentration of urinary cadmium is closer to 5 μg Cd/g creatinine or to 10 μg Cd/g creatinine, corresponding to about 100 and 200 ppm in the kidney, respectively. Roels et al. (1993) correlated a number of markers with cadmium in blood and urine in a study population of workers occupationally exposed to cadmium from cadmium smelting operations. Three main groupings of thresholds were identified corresponding with different markers of effects: one around 2 μg Cd/g creatinine mainly associated with biochemical alterations (increased urinary 6-ketoprostaglandin F_{1x} and urinary sialic acid), a second around 4 μg Cd/g creatinine associated with increased excretion of high molecular weight proteins (possibly due to disruption of the glomerular membrane polyanionic charge) and tubular antigens or enzymes (BBA, NAG), and a third around 10 μg Cd/g creatinine associated with increased excretion of low molecular weight proteins and other indicators. The 10 μg Cd/g creatinine level had previously been proposed as the biological threshold for Cd-induced nephropathy. Whether the earlier changes are indicative of irreversible adverse renal effects remains an area of continued nvestigation.

To further evaluate the reversibility of proteinuria, Roels et al. (1997) studied the progression of Cd-induced renal tubular dysfunction in cadmium workers according to the severity of the microproteinuria at the time the exposure was substantially decreased. A total of 32 cadmium male workers was divided into two groups on the basis of historical records of urinary cadmium concentration (CdU) covering the period until 1984. The workers with CdU values of >10 μg Cd/g creatinine were subdivided further on the basis of the urinary concentration of β_2-microglobulin (β_2-MG-U) measured during the first observation period (1980-1984). In each group, the tubular microproteinuria as reflected by β_2-MG-U and the

concentration of retinol-binding protein in urine as well as the internal cadmium dose as reflected by the concentration of cadmium in blood and urine were compared between the first and second (1990-1992) observation periods. Increased microproteinuria was often diagnosed in cases with CdU values of >10 μg Cd/g creatinine. The progression of tubular renal function was found to depend on the extent of the body burden of cadmium (as reflected by CdU) and the severity of the initial microproteinuria at the time high cadmium exposure was reduced or ceased. When cadmium exposure was reduced and β_2-MG-U did not exceed the upper reference limit of 300 μg/g creatinine, the risk of developing tubular dysfunction at a later stage was likely to be low, even in cases with historical CdU values occasionally >10 but always <20 μg Cd/g creatinine. When the microproteinuria was mild β_2-MG-U >300 and < 1,500 μg/g creatinine) at the time exposure was reduced, and the historical CdU values had never exceeded 20 μg Cd/g creatinine, there was indication of a reversible tubulotoxic effect of cadmium. When severe microproteinuria (β_2MC-U >1,500 μg/g creatinine) was diagnosed in combination with historical CdU values exceeding 20 μg Cd/g creatinine, Cd-induced tubular dysfunction was progressive in spite of reduction or cessation of cadmium exposure.

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

2.8 INTERACTIONS WITH OTHER SUBSTANCES

Cadmium toxicity can be influenced by a wide variety of other chemicals. In humans, dietary deficiencies of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects following cadmium exposure (Kjellstrom 1986). Iron deficiency has been shown to increase gastro-intestinal absorption of cadmium in humans (Flanagan et al. 1978), while oral zinc supplementation has been demonstrated to decrease the oral absorption of cadmium. No other information was located concerning interaction of cadmium with other chemicals in humans.

In animals, a few interactions following inhalation exposure have been evaluated. In rats exposed to cadmium chloride by inhalation, simultaneous exposure to zinc oxide prevents fatalities (Oldiges and Glaser 1986) and lung cancer (Oldiges et al. 1989). Exposure to an atmosphere containing 80% oxygen aggravated pulmonary damage from cadmium chloride inhalation in mice (Martin and Witschi 1985).

The toxicity of oral exposure to cadmium in animals has been shown to be influenced by several factors. In Japanese quail, cadmium toxicity was intensified by single or combined deficiencies of zinc, copper, iron,

calcium, and protein (Fox et al. 1979). A calcium-deficient diet in animals has been shown to aggravate cadmium immunotoxicity (Chopra et al. 1984) and fetotoxicity (Pond and Walker 1975). Simultaneous exposure to lindane increased the developmental toxicity of cadmium in rats (Saxena et al. 1986). Rats have an increased susceptibility to cadmium-induced bone loss due to multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b) or ovariectomy (Bhattacharyya et al. 1988c), possibly related to associated effects on trace element status. Hopf et al. (1990) report that exposure to ethanol and cadmium in a liquid diet produced liver damage in rats at doses that were not separately hepatotoxic. In contrast, Kershaw et al. (1990) reported that ethanol pretreatment in male Sprague-Dawley rats substantially reduced the lethal and hepatotoxic properties of cadmium, possibly due to a reduced interaction between cadmium and target sites in liver organelles and cytosolic high-molecular-weight (HMW) proteins. Ethanol pretreatment in this study decreased (approximately 60%) the content of cadmium in nuclei, mitochondria, and endoplasmic reticulum, and nearly eliminated the association of cadmium with cytosolic HMW proteins. Reduction in the concentration of cadmium in potential target sites of intoxication was caused by a metallothionein-promoted sequestration of cadmium to the cytosol.

When cadmium is co-administered with ethanol in rats, there is a pronounced increase in cadmium accumulation in various regions of the brain (e.g., the corpus striatum and cerebral cortex). The cadmium is not bound to metallothionein, and there is a marked increase in lipid peroxidation and inhibition of membrane bound enzymes. Cadmium or ethanol alone did result in any effects on lipid peroxidation (Pal et al. 1993a, 1993b). Rats pretreated with acetaminophen are more sensitive to the renal toxicity of cadmium in water (Bernard et al. 1988a). Co-administration of lead and cadmium in the diet of rats had additive effects in reducing body weights, but neurologic toxicity was antagonized (Nation et al. 1990).

Numerous interactions have been demonstrated in animals using parenteral exposure, generally indicating that induction of metallothionein by pretreatment with zinc, selenium, or other metals, reduces toxicity of parenteral cadmium exposure (Gunn et al. 1968a, 1968b; Naruse and Hayashi 1989; Yamane et al. 1990). Zinc, calcium, or magnesium can prevent injection site, testicular, and prostatic cancers induced by subcutaneous or intramuscular injection of cadmium, but these interactions have been shown to be a complex phenomenon, dependent on dose, route, and target organ (Poirer et al. 1983; Waalkes et al. 1989). Mn(I1) pretreatment reduces Cd(II)-induced lethality (Goering and Klaassen 1985). Cadmium has been noted to have an inhibitory effect on manganese uptake (Gruden and Matausic 1989). In addition, manganese appears to be capable of increasing the synthesis of the metal-binding protein metallothionein. (Waalkes and Klaassen 1985). Data from a study by Goering and Klaasen (1985) suggest that manganese pretreatment increases the amount of Cd^{+2} bound to metallothionein, thereby decreasing hepatotoxicity due

to unbound Cd^{+2}. The significance of these observations to humans exposed to cadmium and manganese by the oral or inhalation routes is not clear.

Induction of hepatic metallothionein by cold stress reduced the acute toxicity of cadmium given by gavage to mice (Baer and Benson 1987). In addition to effects on metallothionein induction, substances may interact with cadmium by altering the competition among metal ions for enzyme or regulatory protein binding sites. For example, simultaneous administration of garlic (which is high in reduced sulfhydryl groups) decreases oral cadmium renal toxicity in rats (Cha 1987).

Coexposure to selenium reduced the clastogenic effect of cadmium on mouse bone marrow (Mukherjee et al. 1988b). Selenium deficiency enhances cadmium-induced cardiotoxicity possibly mediated via lipid peroxidation indicated by a significant reduction in the activities of the selenoenzyme, glutathione peroxidase. Selenium supplements in the diet prevented cadmium's cardiotoxic effect (Jamall and Smith 1985a). Selenium has also been shown to prevent testicular damage in rats (Kar et al. 1960; Omaye and Tappel 1975). In testes, selenium as selenite given before or during cadmium administration was shown to divert the binding of cadmium from low molecular proteins to higher molecular weight proteins (Chen et al. 1975; Whanger 1992). In contrast, Jamall and Smith (198%) report a shift in cadmium binding from metallothionein to lower weight proteins in kidney and liver from a diet supplemented with selenium compared to a selenium deficient diet. The selenium-cadmium interaction thus appears to be dependent on the duration and sequence of coexposure and possibly the organ-specific levels of selenoenzymes or other essential metals.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cadmium than will most persons exposed to the same level of cadmium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of cadmium, or compromised function of target organs affected by cadmium. Populations who are at greater risk due to their unusually high exposure to cadmium are discussed in Section 5.6, Populations With Potentially High Exposure.

Differences in individual sensitivity to cadmium have not been systematically studied, but based on what is known about cadmium toxicity, some inferences can be made. Populations with depleted stores of calcium, iron, or other dietary components due to multiple pregnancies and/or dietary deficiencies could be expected to have increased cadmium absorption from the gastrointestinal tract. Cadmium also is known to

dramatically increase resorption of bone calcium in animals fed calcium deficient diets, producing an Itai-Itai like syndrome. Animal studies have shown that young animals absorb more cadmium than adults (Sasser and Jarboe 1977, 1980) and that the bones of young animals are more susceptible to damage to cadmium than in older animals (Ogoshi et al. 1989). Infants and children may also have a higher rate of gastrointestinal absorption of cadmium, and their bones may be more susceptible to damage. Populations with kidney damage from causes unrelated to cadmium exposure, including diabetes, some drugs and chemicals, and the natural age-related decline in kidney function, could be expected to exhibit nephrotoxicity at lower cadmium exposures than those of normal healthy adults (Buchet et al. 1990).

Animal studies report conflicting results on the increased resistance or susceptibility of newborns and young for a variety of organ specific toxicities compared to adults, and the role of the relatively increased levels of metallothionein in the young on tissue distribution. There is some evidence to support the theory that high levels of metallothionein in young animals play an important role in their resistance to liver damage (Goering and Klaassen 1984), even though the increase in liver cadmium levels in the young compared to the adult (67% increase) is not as dramatic as the 10-fold increase in liver metallothionein. Wong and Klaassen (1980a) reported only a 30% increase in liver cadmium in 4-day-old rats and a 20-fold increase in liver metallothionein compared to the adults.

Further discussion of the susceptibility of children is found in Section 2.6, Children’s Susceptibility.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

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

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 1994. *Goldfrank’s Toxicologic Emergencies.* Fifth edition. Norwalk. CT: Appleton & Lange, 1063-1067.

Angle, CR. *Organ Specific Therapeutic Intervention.* 1995. Metal Toxicology Goyer RS, Klaassen CD, and Waalkes MP, eds. Academic Press, 78,82-83.

ATSDR. 1990. Agency for Toxic Substances and Disease Registry. Case *Studies in Environmental Medicine: Cadmiwn Toxicity,* Atlanta, GA.

2.10.1 Reducing Peak Absorption Following Exposure

Inhalation exposure to high concentrations of cadmium can be particularly dangerous because initial symptoms are often as mild as those associated with low-level exposure, and exposed individuals who are unaware either of the presence of cadmium or of the dangers of inhaling cadmium may allow exposure to continue until a harmful or even fatal dose is received (Beton et al. 1966; Lucas et al. 1980). Severe respiratory symptoms that may develop within a few hours of high-dose inhalation exposure include tracheobronchitis, pneumonitis, and pulmonary edema, accompanied by additional nonspecific flu-like symptoms (sweating, shivering, malaise) (Beton et al. 1966). Aside from removing a victim to fresh air and providing supportive medical care, no effective means have been reported for reducing absorption following inhalation exposure to cadmium (Bronstein and Currance 1988; EPA 1989d). Supportive medical care of individuals with inhalation exposure to high levels of cadmium includes monitoring for respiratory distress, assisting ventilation as needed, and administering humidified oxygen (Bronstein and Currance 1988; EPA 1989d). If pulmonary edema develops, individuals may be treated with supplemental oxygen, positive-pressure mechanical ventilation, administration of diuretics, intravenous fluids, and steroid medications. Antibiotic therapy and monitoring fluid balance (due to kidney function impairment) may also be required (Beton et al. 1966; Bronstein and Currance 1988; EPA 1989d; Haddad and Winchester 1990).

Oral exposure to cadmium is not an immediate threat because high doses are irritating enough to induce vomiting. In fact, the only known acute fatalities from oral exposure to cadmium followed intentional ingestion of high doses (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although inducing vomiting is sometimes recommended following ingestion of cadmium (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988), concentrated cadmium solutions may be caustic, and esophageal damage could result from spontaneous or induced vomiting. Administration of water or milk may be indicated for patients able to swallow (Bronstein and Currance 1988; EPA 1989d). Administration of cathartics such as sorbitol or magnesium sulfate to enhance elimination from the gastrointestinal tract has been recommended (EPA 1989d; Stutz and Janusz 1988); however, the administration of activated charcoal to bind unabsorbed cadmium does not appear to be effective (ATSDR 1990; Ellenhorn and Barceloux 1988).

The intestinal absorption of cadmium at levels below those leading to gastrointestinal damage is relatively low (5-10% of the administered dose) (Flanagen et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973). Other polyvalent cations including calcium, magnesium, and zinc can interfere with cadmium uptake (Foulkes 1985), but administration of competing cations can in some cases increase rather than decrease cadmium absorption (Jaeger 1990), and is, therefore, not recommended for the treatment of cadmium ingestion. Oral administration of some compounds that chelate cadmium such as meso-2,3-dimercaptosuccinic acid has been found in rodent studies to reduce absorption following acute oral exposure to cadmium, but other chelators such as dithiocarbamates can increase toxicity (see Section 2.3.1.2). At present, no recommendations for chelation treatment to reduce absorption can be made (Jones and Cherian 1990). Administration of garlic (which is high in reduced sulfhydryl groups) has been shown to decrease oral cadmium toxicity in rats (Cha 1987). Thus, use of garlic could be an area of future research.

Dermal or ocular exposure to high levels of cadmium may cause irritation (Wahlberg 1977) and should be treated by removing contaminated clothing, washing the skin, and thoroughly flushing the eyes (EPA 1989d; Stutz and Janusz 1988). These measures will also reduce the relatively small potential for dermal absorption of cadmium (see Section 2.3.1.3).

2.10.2 Reducing Body Burden

No effective means have been found to reduce the body burden of cadmium (ATSDR 1990; Goldfrank et al. 1994), although a variety of new chelating agents are actively being developed and tested (Cantilena and Klaassen 1981; Jones et al. 1992, 1994; Kostial et al. 1996; Singh and Jones 1995). Some of the more familiar chelators that are beneficial for other toxic metals actually increase cadmium toxicity by mobilizing the cadmium and substantially increasing the renal concentrations and toxicity (ATSDR 1990; Goldfrank et al. 1990; Jones and Cherian 1990). One such agent is the chelating agent dimercaprol (also known as BAL, British Anti-Lewisite), commonly used for treating cases of lewisite toxicosis. BAL is widely recognized as harmful in treating cadmium exposures. Some sources recommend using ethylenediamine tetraacetic acid (EDTA) salts (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988) or use of EDTA with caution about potential nephrotoxicity (EPA 1989d; Haddad and Winchester 1990). Other promising chelators include diethylenetriaminepentaacetic acid (DTPA), 2,3-dimercaptosuccinic acid (DMSA), and various bis(carbodithioates).

Cantilena and Klaassen (1982) demonstrated the importance of rapid administration of DTPA, EDTA, or DMSA following acute cadmium exposure if they are to be effective. Waalkes et al. (1983) evaluated the role of metallothionein in the acute drop in chelator efficacy following cadmium poisoning in male Sprague- Dawley rats. Although the chelator, diethylenetriaminepentaacetic acid (DTPA), reduced cadmium content in the various organs when given immediately after cadmium, DTPA was ineffective at all later times. Increases in hepatic and renal metallothionein did not occur until 2 hours after cadmium, and did not coincide with the earlier drop in chelator efficacy. Blockade of metallothionein synthesis by actinomycin D treatment (1.25 mg/kg, 1 hour before Cd) failed to prolong the chelators effectiveness. Furthermore, newborn rats have high levels of hepatic metallothionein which had no effect on the time course of chelator effectiveness since DTPA still decreased cadmium organ contents, if given immediately following cadmium but had no effect if given 2 hours after cadmium. The authors concluded that metallothionein does not have an important role in the acute decrease in efficacy of chelation therapy for cadmium poisoning. The quick onset of chelator ineffectiveness may be due to the rapid uptake of cadmium into tissues, which makes it relatively unavailable of chelation.

Jones et al. (1992) reports on the development of a new series of monoalkyl esters of meso-2,3-dimercaptosuccinic acid, one of which, monoisoamyl meso-2,3-dimercaptosuccinate (Mi-ADMS), was an effective chelating agent for reduction of kidney and liver cadmium when administered either parenterally or orally. Jones et al. (1994) continue to evaluate monoaralkyl- and monoalkyl esters of DMS to develop chelators that can successfully remove “aged” cadmium deposits and that can be administered via a variety of routes. Eybl et al. (1994) demonstrated that Mi-ADMS, administered orally every 48 hours for 12 days after acute cadmium exposure, was effective at reducing cadmium in the kidney and liver, but not in the testes and brain.

Another area of chelation therapy research is in the use of multiple chelators. Blaha et al. (1995) evaluated the ability of two carbodithioate chelators, sodium N-(4-methylbenzyl)-4-O-(β-D-galactopyranosyl)-Dglucamine- N-carbodithioate (MeBLDTC) and sodium 4-carboxyamidopiperidine-N-carbothioate (INADTC), singly or in combination to reduce cadmium burden from chronically exposed rats. The combination therapy resulted in a synergistic effect on increased biliary excretion and reduced renal cadmium that, in the case of biliary excretion, was more than doubled that expected for a simple additive interaction.

Since cadmium is a cumulative toxin, individuals with known past high exposure to cadmium by either the oral or inhalation route should attempt to minimize further exposure (ATSDR 1990). Sources such as contaminated vegetable gardens and metal-working hobbies should be identified and controlled (ATSDR 1990). Cigarettes constitute a major source of cadmium exposure (Nordberg et al. 1983, and smokers would substantially reduce their further cadmium exposure by ceasing to smoke. Food is another major source of cadmium exposure (see Section 5.5). However, grains, cereal products, and potatoes, which are the major dietary sources of cadmium (Gartrell et al. 1986), are essential to a healthy diet. Therefore, no specific recommendations can be made at this time for a low-cadmium diet. Anemia enhances dietary cadmium absorption (Flanagen et al. 1978), so if anemia is present, successful treatment might reduce subsequent cadmium accumulation.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The toxic effects of cadmium are generally thought to be caused by “free” cadmium ions; that is, cadmium not bound to metallothionein or other proteins (Goyer et al. 1989). However; cadmium bound to metallothionein may have the capacity to directly damage renal tubular membranes during uptake (Suzuki and Cherian 1987). Free cadmium ions may have a number of adverse effects, including inactivation of metal-dependent enzymes, activation of calmodulin, and initiation of the production of active oxygen species (Palmer et al. 1986; Waalkes and Goering 1990).

Respiratory damage caused by acute, high-level inhalation exposure to cadmium can cause impaired lung function that can last many years after exposure (Barnhart and Rosenstock 1984; Townshend 1982). No treatments other than supportive care and avoidance of additional risk factors for lung injury are presently known.

The kidneys appear to be the tissue most vulnerable to chronic cadmium exposure by either the oral or inhalation routes. The basis for the preferential sensitivity of the kidney is related to the filtering and reabsorption of circulating CdMT complex, which is then thought to be degraded in the tubular cell lysosomes and released as free intracellular cadmium. The toxic effect results from the limited ability of the kidney to synthesize new cytosolic metallothionein in response to an increasing cadmium load (Goyer et al. 1989). Cadmium bound to metallothionein, however, may also have nephrotoxic activity (Suzuki and Cherian 1987).

No treatments are currently available that specifically target free cadmium ions in the renal cortex, but zinc and calcium can stimulate metallothionein synthesis and may also compete with cadmium for enzyme binding sites (see Section 2.6). Thus, zinc, and/or calcium supplementation might help reduce renal cadmium toxicity, at least in zinc- or calcium-deficient individuals. It is not known whether administration of these compounds would be beneficial in individuals with adequate zinc and calcium intakes, and their clinical use is not currently recommended. Since one of the postulated mechanisms of cadmium toxicity is the stimulation and production of active oxygen species, it is possible that increasing the cellular levels of antioxidants such as superoxide dismutase, reduced sulfur compounds (particularly glutathione), vitamin C, vitamin E, or p-carotene could reduce renal cadmium toxicity by scavenging active oxygen species prior to reaction with cellular components. Adequate levels of selenium may also provide some protection against cadmium nephrotoxicity or cardiotoxicity. However, no data exist to indicate whether antioxidant treatment is actually beneficial in cases of cadmium toxicity, and antioxidants are not currently recommended for the treatment of cadmium-exposed humans.

Research in chelation therapy is promising for agents that can interfere or possibly reverse the toxic effec of cadmium. Xu et al. (1995, 1996) recently demonstrated that one of the more promising of DMSA derivatives, monoisoamyl meso-2,3-dimercaptosuccinate, when administered within 1 hour after acute exposure prevents the formation of cadmium-induced apoptotic DNA fragmentation and associated histopathological injury the testes of rats. Perry and Erlanger (1989) report a reversal of the cadmium induced hypertension in rats with the chelator d-myo-inositol-1,2,6-triphosphate.

Diabetes appears to make individuals more vulnerable to the renal effects of cadmium, and is itself a common causes of kidney damage (Buchet et al. 1990). Diabetics could reduce their risks of cadmium induced kidney toxicity by practicing good glycemic control and other measures to prevent diabetes-induced kidney damage. Cadmium exposure may increase calcium excretion and calcium loss from the bone especially in calcium deficient diets. This can be a substantial risk factor for pregnant women and for postmenopausal women who are prone to osteoporosis (Buchet et al. 1990). It might be prudent for women with elevated cadmium exposure to take steps to reduce their osteoporosis risk (e.g., hormone replacement therapy, dietary calcium and vitamin D supplementation, exercise). These measures, however, are based on limited data and should not be considered preventive of or therapeutic for cadmium toxicity until confirmed or refuted by future studies.

2.11 ADEQUACY OF THE DATABASE

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

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

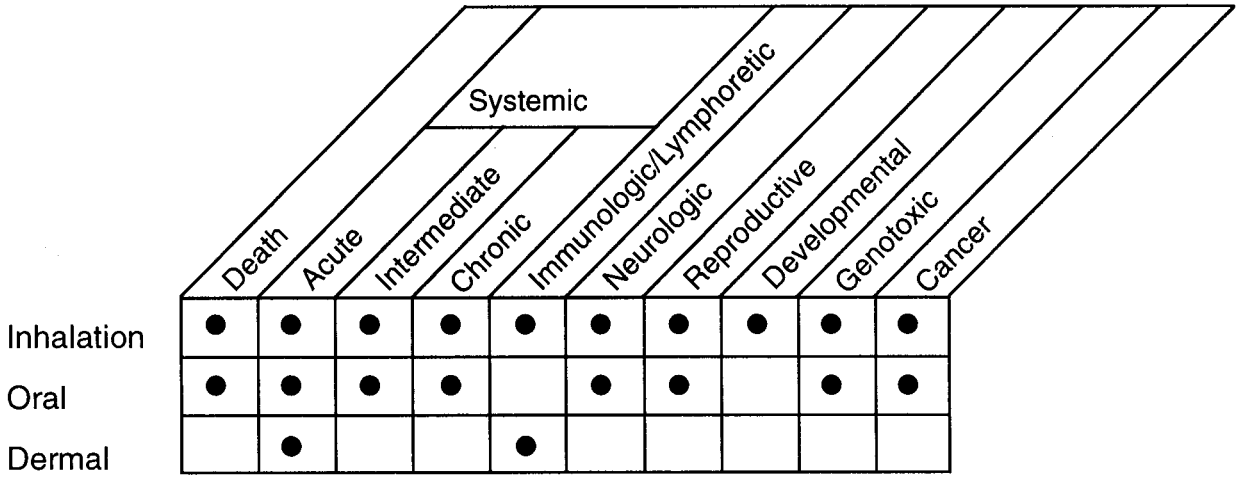
2.11.l Existing Information on Health Effects of Cadmium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cadmium are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of cadmium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need.”

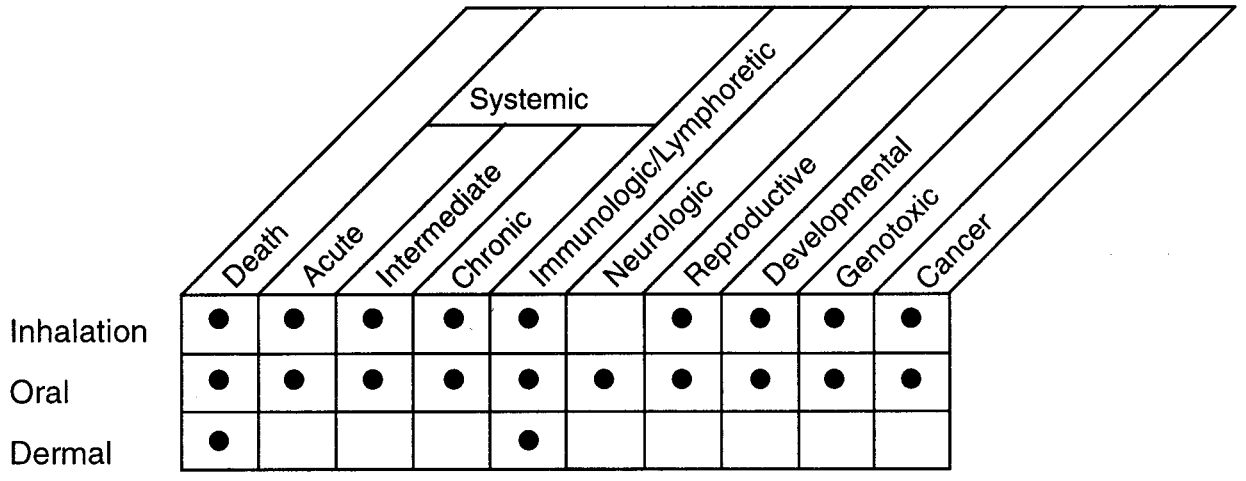
A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There is a massive database regarding the health effects of cadmium. In humans, the majority of studies have involved workers exposed by inhalation or residents of cadmium-polluted areas exposed primarily in the diet. Quantitative estimates of exposure levels are not available for many of these studies. Lethality, systemic toxicity, genotoxicity, and cancer have been studied in humans more extensively than

Figure 2-6. Existing Information on Health Effects of Cadmium



Human



Animal

● Existing Studies

immunotoxicity or neurotoxicity, with less being known about reproductive or developmental toxicity of cadmium in humans following inhalation or oral exposure. In animals, effects following oral exposures have generally been more thoroughly investigated than those following inhalation exposure, and few studies of cadmium toxicity following dermal exposure in humans were located.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Based on observations in both humans and animaIs, the target organ for inhalation exposure following acute exposure to cadmium is the lung; and the gastrointestinal tract is the target organ for oral exposure. Human respiratory or gastrointestinal toxicity has occurred after accidental exposures (Beton et al. 1966; Frant and Kleeman 1941; Lucas et al. 1980); Nordberg et al. 1973), but quantitative estimates of levels causing the effects are not reliable enough for comparison to animal data. Graham et al. (1978) reported the lowest no effect level for immunological effects from acute inhalation exposure to mice, but a human equivalent dose could not be derived to support an MRL. There is also no evidence for immunological effects in humans from acute inhalation exposure to cadmium. Additional information on immunological or other adverse effects and the associated no effect level from acute exposure to cadmium are needed to evaluate potential health effects and minimum risk levels in humans.

No reliable information was located regarding toxicity following dermal exposure to cadmium, but based on the lack of reported effects in the workers handling cadmium compounds, it seems unlikely that dermal exposure could deliver a significant dose of cadmium. It is apparent that acute toxicity occurs following inhalation or oral exposures at levels that are much higher than those likely to be received from environmental media, and establishing exposures at which respiratory or gastrointestinal effects occur in humans following acute exposure may not be essential for evaluating hazards to populations surrounding hazardous waste sites.

Intermediate-Duration Exposure. The kidney is likely to be the target organ following intermediate duration exposure to cadmium by the inhalation and oral routes, because of the preferential accumulation of cadmium in the kidney (Waalkes and Goering 1990). A variety of other systemic effects are known to occur following intermediate-duration cadmium exposure, particularly impaired lung function following inhalation exposure (Barnhart and Rosenstock 1984; Townshend 1982) and osteoporosis following oral exposure (Watanabe et al. 1986). However, the dose which led to these effects would most likely also lead

to kidney damage, even though some of the experiments did not allow sufficient follow-up time to demonstrate renal effects. Sufficient information from human or animal studies is not available to derive intermediate oral or inhalation MRLs, because estimates of levels of exposure for intermediate-durations causing renal effects in humans are not available. Investigation of long-term kidney toxicity expected from intermediate-duration exposure to cadmium is needed to evaluate risks to populations surrounding hazardous waste sites that may be exposed for limited periods. Studies of possible toxicity in animals following intermediate-duration dermal exposure to cadmium are needed to evaluate potential health effects in humans exposed to cadmium primarily by the dermal route.

Chronic-Duration Exposure and Cancer. The kidney is the main target organ following chronicduration exposure to cadmium by the inhalation and oral routes in both humans and animals. Loss of calcium from the bone and increased urinary excretion of calcium are associated with chronic cadmium exposure. The adverse effects on bone and calcium metabolism may be the result of a direct effect of cadmium or may be secondary to the renal damage and subsequent disruption of calcium metabolism and kinetics. Some studies indicate that disruption of calcium metabolism may be an earlier indicator of cadmium toxicity than the development of proteinuria. Additional studies are needed on the prevalence and mechanism of the cadmium-induced bone loss and wasting of calcium in humans.

Sufficient information from human studies is available to derive a chronic oral MRL (Nogawa et al. 1989). Additional investigation into the NOAEL in humans is needed to evaluate the minimum risk level from long-term inhalation exposure to cadmium. Better determinations of the critical concentration in the general population or in sensitive subpopulations and of the most sensitive indicator of kidney damage are also needed to evaluate risks of long-term cadmium exposure. No information was located regarding dermal toxicity of chronic cadmium exposure in humans or animals, and studies of dermal toxicity are needed to evaluate risks to populations exposed to cadmium primarily by dermal contact.

Evidence for the carcinogenicity of cadmium by the inhalation route is available from studies in rats (Takenaka et al. 1983). The evidence of carcinogenicity from human studies is limited, due to uncertainties in cadmium exposure estimates and confounding factors including exposure to arsenic, a known human lung carcinogen, and smoking (Kazantzis et al. 1992). Additional studies controlling for these exposures and providing more precise cadmium dose estimates are needed to provide more definitive evidence of the carcinogenic potential in humans of inhaled cadmium. Additional studies in animals are needed to evaluate the lack of an observed increase in lung cancer in mice and hamsters exposed to cadmium by inhalation

(Heinrich et al. 1989). Cadmium has not been shown to be carcinogenic following oral exposure in humans. In rats, however, cadmium increased tumors of the prostate, testes, and hematopoietic system (Waalkes et al. 1992). Additional lifetime-exposure studies in rats, mice, and hamsters orally exposed to cadmium at sufficiently high doses are needed to further define the carcinogenic potential of cadmium.

Zinc was reported to have an inhibitory effect on cadmium tumor formation in lungs and liver when mice are first dosed with the tumor promotor NDEA followed by a relatively high level of cadmium. Additional investigation of the zinc-related reduction of cadmium-induced tumors and zinc's effects on the mechanism of cadmium carcinogenesis is needed to evaluate the importance of the nutritional status of zinc in susceptible populations. Additional studies on the nutritional status and interactions of other essential metals (including selenium and copper) on cadmium carcinogenicity or cadmium's potential to induce a proliferative response are also needed.

Genotoxicity. The evidence for the genotoxicity of cadmium is mixed (see Tables 2-6 and 2-7). In vitro studies have provided both positive and negative results (Bruce and Heddle 1979; Oberly et al. 1982; Shirashi et al. 1972). Studies of chromosomdl aberrations in humans exposed to cadmium have also found both positive and negative results (Bui et al. 1975; Deknudt and Leonard 1975; O'Riordan et al. 1978; Tang et al. 1990). In animals, parenteral, but not oral, cadmium exposure has been found to cause germ cell mutations (Sutou et al. 1980; Watanabe and Endo 1982). Additional studies investigating effects in exposed humans using larger populations with quantitative estimates of exposure are needed to evaluate the human genotoxicity of cadmium.

Reproductive Toxicity. Only limited or conflicting evidence is available to evaluate the pptential for cadmium exposure to cause reproductive toxicity in humans. Some studies report no effect on male fertility (Gennart et al. 1992), male hormone levels (Mason 1990), sperm density (Noack-Fuller et al. 1992), or semen quality (Saaranen et al. 1989), while others report a reduction in sperm number or viability (Xu et al. 1993a). In one study, men occupationally exposed to cadmium at levels resulting in renal damage had no change in testicular function (Mason 1990). Adverse effects in animals from inhalation exposure have been reported including increased duration of the estrous cycle (Baranski and Sitarek 1987; Tsvetkova 1970), and increased relative testes weight but no loss in reproductive success (Kutzman et al. 1986). Adverse reproductive effects in animals from high-dose, acute, oral cadmium exposure have been reported including testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et

al. 1987; Borzelleca et al. 1989) and decreased fertility (Kotsonis and Klaassen 1978; Machemer and Lorke 1981). At lower doses and intermediate exposures, adverse effects have included necrosis and atrophy of seminiferous tubule epithelium (Cha 1987); increased testes weight (Pleasants et al. 1992, 1993); increased prostatic hyperplasias (Waalkes and Rehm 1992); significantly increased relative testes weight, decreased sperm count and motility, decreased seminiferous tubular diameter, seminiferous tubular damage (Saxena et al. 1989); and decreased fertility (Sutou et al. 1980). Other animal studies for lower dose intermediate-exposures, however, report no adverse effects (Baranski et al. 1983; Bomhard et al. 1987; Groten et al. 1990; Kostial et al. 1993; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Pleasants et al. 1992; Pond and Walker 1975; Zenick et al. 1982). Additional studies in animals, as well as retrospective, case-matched studies of reproductive success of populations for which occupational or environmental exposure to cadmium has been estimated, are needed to further evaluate the potential reproductive toxicity of cadmium in humans. Additional studies are needed (preferably with larger sample sizes) to evaluate the robustness of the association between cadmium and adverse effects on sperm.

Developmental Toxicity. The potential for cadmium exposure to cause developmental toxicity from pre- or postnatal exposures in humans is not known. One study in occupationally exposed women reported children with lowered birth weights, but with no increase in malformations (Tsetkova 1970). However, no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight. Many animal studies demonstrate that developmental toxicity may occur following cadmium exposure by oral routes with a relatively few studies reporting developmental effects following inhalation exposure (Ali et al. 1986; Baranski 1985, 1987; Baranski et al. 1983; Gupta et al. 1993; Machemer and Lorke 1981; Schroeder and Mitchener 1971; Webster 1978). Malformations of the skeleton effects, such as fused lower limbs, absence of one or more limbs, and delayed ossification of the sternum and ribs, have been reported. In addition, neurobehavioral end points such as locomotor activity and conditioned avoidance behavior were decreased. Retrospective, case-matched studies of developmental toxicity among children of women with known occupational or environmental exposure to cadmium are needed to evaluate the potential for cadmium exposure to cause human developmental toxicity such as skeletal malformations and neurobehavioral effects (as suggested in animal studies). Studies are also needed to follow-up on the results of increased susceptibility of young to bone damage (Ogoshi et al. 1989) or suppression of the immune response (Blakley 1985) reported in animals. The difference in the immune response (using the same protocol) between young mice (Blakley 1985) and older mice (Blakley 1988) should also be further evaluated. Studies of postnatal cadmium exposure to children, especially for children with diets deficient in calcium, protein, or iron, are needed to evaluate whether increased cadmium absorption from the diet leads to developmental effects.

Immunotoxicity. A variety of immunologic effects have been found in animals exposed to cadmium by the oral or inhalation routes (Blakley 1988; Bouley et al. 1984; Cifone et al. 1989a). However, the biological significance of these effects is not clear, and there is little information available on immunotoxicity in humans. Investigations of immunologic function of populations occupationally or environmentally exposed to cadmium, and follow-up mechanistic studies in animals are needed to evaluate the potential immunotoxicity of cadmium exposure in humans.

Neurotoxicity. A few studies have suggested an association between cadmium exposure in humans and impaired neuropsychologic functioning at levels below those causing nephrotoxicity (Hart et al. 1989b; Marlowe et al. 1985; Thatcher et al. 1982). Neurotoxicity has also been found in animal studies (Nation et al. 1984; Wong and Klaassen 1982). Additional studies to investigate neurologic effects in populations with known cadmium exposure, and studies of possible mechanisms of neurotoxicity in animals are needed to evaluate the potential neurotoxicity of cadmium exposure to humans. In addition, studies examining neurobehavioral end points in children would be useful.

Epidemiological and Human Dosimetry Studies. Cause/effect relationships for renal toxicity of cadmium have been derived from studies of workers occupationally exposed to cadmium by inhalation and of populations environmentally exposed to cadmium in the diet (Jarup et al. 198.5; Nogawa et al. 1989). Measurement of additional toxicity end points (musculoskeletal, reproductive, developmental, immunological, and neurological) in these well characterized populations are needed to evaluate whether any of these effects may occur at exposure levels below those leading to kidney damage. Additional development of physiologically based pharmacokinetic and pharmacodynamic models (PBPWPD models) is needed to evaluate human exposure scenarios.

Biomarkers of Exposure and Effect.

Exposure. Cadmium levels can be measured in a variety of tissues and fluids, including blood, urine, milk, liver, kidney, hair, and nails (Elinder and Lind 1985; Roels et al. 1981b; Sharma et al. 1982). Blood cadmium is a useful indicator of recent cadmium exposure, and urinary cadmium is a useful indicator of total body burden (Shaikh and Smith 1984). The most important indicator of the potential for toxicological injury is generally considered to be the cadmium concentration in the renal cortex, but individuals vary in the concentration causing renal effects (the “critical concentration”) (Roels et al. 1981b). Methods for in

vivo measurement of cadmium content in the kidney exist, but they are complex and expensive, and involve some exposure to ionizing radiation (Scott and Chettle 1986). Efforts to develop easier, safer, and less costly methods for *in vivo* analysis are needed, as well as studies to determine factors influencing individual variation in critical concentrations.

Effect. A number of sensitive tests are available to detect early stages of renal dysfunction that are known to be caused by cadmium exposure. These include analysis of urinary excretion of β_2-microglobulin, retinol-binding protein, or enzymes (Shaikh and Smith 1984). However, renal damage detected by these tests is not necessarily associated with cadmium exposure. Additional studies are needed to evaluate current or potentially new urinary or serum biomarkers in cadmium-exposed populations and their association with incipient injury to the kidney caused by cadmium.

Absorption, Distribution, Metabolism, and Excretion. Good information exists on cadmium toxicokinetics in humans and animals. PBPK/PD models have been developed to predict the critical organ dose as a function of route, duration, and level of exposure by the inhalation and oral routes (Kjellstrom and Nordberg 1978, 1985). Although general factors influencing absorption, distribution, metabolism, and excretion are known, additional studies are needed to provide information on metal metabolism and interactions that support quantitative evaluation of individual variations and resulting differences in renal cadmium accumulation. Very limited information exists on the dermal absorption of cadmium (Skog and Wahlberg 1964; Wester et al. 1992). Additional studies on the dermal absorption of cadmium are needed.

Comparative Toxicokinetics. Animal and human studies have generally reported comparable toxicokinetics of cadmium (Kjellstrom and Nordberg 1985; Nordberg 1985), suggesting that rats, mice, and rabbits are suitable models for cadmium toxicity in humans. However, some concerns have been raised about the appropriateness of the rat model for cadmium-induced lung tumors in humans because of differences in the morphology of the rat respiratory tract and resulting differences in cadmium particle deposition patterns and target cell populations. This is especially of concern because cadmium appears to be a contact carcinogen for lung cancer. Additional studies on the differences between the rat and human clearance rates, speciation at the level of the target cell, and protein transporters (as they relate to solubility and susceptibility) are needed to evaluate.the appropriateness of the rat model for predicting cadmium induced human lung cancers. Additional studies on differences in species, strain, sex, age, and other factors on cadmium kinetics and carcinogenic or other systemic effects are also needed to extrapolate the

animal data to potential human toxicity. Additional studies establishing the toxicokinetics of cadmium in pregnant animals are needed to assess the relevance of the developmental effects observed in animals.

Methods for Reducing Toxic Effects. The mechanisms of cadmium absorption across epithelial layers is likely to be via nonspecific mechanisms (Foulkes 1989). No methods are known for influencing absorption across the lung, but absorption across the gastrointestinal tract may be influenced by dietary status (Flanagan et al. 1978). Studies to determine whether dietary adjustments might help decrease cadmium uptake from food or water are needed. Studies to determine the effects of dietary deficiencies in calcium are needed to further evaluate the risk of cadmium exposure to susceptible populations. Uptake across the skin is probably sufficiently slow that simple washing of exposed areas is adequate to prevent excessive absorption (Skog and Wahlberg 1964).

Once cadmium is absorbed, it tends to accumulate in the kidney, which is the main target tissue for chronic low-dose exposure. The cellular and molecular basis for the preferential accumulation in the kidney is only partially understood (Waalkes and Goering 1990), and additional studies to define the rate-limiting steps in renal uptake and renal clearance of cadmium are needed to design strategies for reducing the rate of cadmium accumulation in this tissue. Additional studies on existing and new chelating agents and different treatment regimens are needed to improve the clinical therapies for acute and chronic exposures to cadmium.

The mechanism of cadmium toxicity in renal cells and other tissues probably involves binding of free cadmium ions to key cellular enzymes and proteins (Waalkes and Goering 1990). Thus, any agent that prevents cadmium from binding might help prevent toxicity. The endogenous cadmium-binding protein can serve this function; however, metallothionein-cadmium complexes may have renal toxicity (Suzuki and Cherian 1987). Additional studies on the role of metallothionein in cadmium toxicity are needed. Additional studies are needed on alternative substrate molecules or drugs that could interact with free cadmium and prevent binding to key cellular enzymes, as well as the ability of antioxidants to reduce damage from active-oxygen species produced by cadmium in tissues.

The impaired renal function that is the typical adverse effect of excessive cadmium exposure is neither clinically treatable nor reversible (ATSDR 1990; Roels et al. 1989). Studies on potential supportive treatment or remedies for cadmium-induced mild renal impairment would be valuable.

Children's Susceptibility. There is very little good information on the human health effects of cadmium, and virtually none for exposures to children. In part, this may be due to cadmium toxicity being primarily associated with either long-term low-level exposures, or to occupational inhalation. Moreover, critical toxic end points for children (developmental and neurological effects) have not been observed in human case histories even at doses that produce severe renal or musculoskeletal effects. Data needs relating to developmental effects are discussed in detail under the heading of developmental toxicity above. The data needs listed below address the health effects of cadmium for children from both acute and longer term exposures. Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures of Children.

Additional research is needed on the toxicokinetics of cadmium during long-term low-level exposures *to* determine the potential long-term tissue burdens that are likely to result especially for the susceptible tissues of liver, kidney, and bone. Additional information is needed on cadmium transport across the blood-brain barrier in the developing fetus, and the role of metallothionein in the placenta.

Neurological and behavioral studies are needed that use the more sophisticated measures available today to evaluate children for *in utero,* acute, and longer term exposures. These studies should have the appropriate controls for confounding factors such as lead, parental use of ethanol, and Iiving conditions.

Additional studies are needed to evaluate whether or not biomarkers of cadmium exposure and effects that have been developed for adults are also applicable to children. If not, new biomarkers of exposure and effect need to be developed.

The effects of nutritional status (iron, zinc, and calcium levels) on cadmium absorption and accumulation in children need further evaluation. Improved regimens and choices for chelation therapy are also needed.

2.11.3 Ongoing Studies

A number of research projects are in progress investigating the health effects of cadmium. These projects are summarized in Table 2-8.

Table 2-8. Ongoing Studies on the Health Effects of Cadmium

Investigator	Affiliation	Research description	Sponsor
Tuan, RS	Thomas Jefferson University	Placental calcium-binding protein and calcium transport	NICHHD
Gairola, CG	University of Kentucky	Cigarette smoke--mechanisms of reproductive toxicity	NICHHD
Goldstein, SA	Yale University	Structure and function of the tok1 potassium channel	NIGMD
Hajdu, J	California State University Northridge	Structure and reactions of coordinated quinones	NIGMD
Williams, JC	University of Memphis	Microanalysis of physiological fluids and heart tissue	NIGMD
Penner-Hahn, JE	University of Michigan Ann Arbor	Structural character of metalloprotein metal site	NIGMD
Ellis, PD	Battelle Pacific Northwest Laboratories	Cadmium-113 nmr of systems of biological interest	NIGMD
Mason, AZ	California State University Long Beach	Processes of metal selection by metal accumulating cells	NIGMD
Weaver, A	Florida Agricultural and Mechanical Univ	Zinc dietary alterations of cadmium induced hepatic toxicity in rats	NIGMD
Latinwo, LM	Florida Agricultural And Mechanical Univ	Molecular basis of chromate and cadmium toxicity in mammalian systems	NIGMD
Marly, JI	Florida Agricultural And Mechanical Univ	Selenium compounds and cadmium induced toxicity in lung	NIGMD
Mrotek, JJ	Meharry Medical College	Characterizing cadmium effects at extracellular/intracellular adrenal cell sites	NIGMD
Gardea-Torresda, JL	University of Texas El Paso	Recovery of toxic heavy metals from contaminated water supplies using plants	NIGMD
Miller, DS	NIEHS	Intracellular receptors and metabolic control	NIEHS
Chapin, RE	NIEHS	Short-term comprehensive reproductive and developmental toxicity screen	NIEHS
Morgan, DL	NIEHS	Toxicity of chemicals used in the semiconductor industry	NIEHS
Helzlsouer, KJ	Johns Hopkins University	Molecular epidemiology of prostate cancer	NIEHS
Sens, DA	West Virginia University	Metallothionein isoforms and human nephrotoxicity	NIEHS
Hoorn, CM	Western Michigan University	Environmental toxicants and endothelial function	NIEHS
Bhattacharyya, MH	University of Chicago	Metallothionein in cadmium and radiation toxicity	NIEHS
Simpson, HJ	Mount Sinai School of Medicine	Urban heavy metal exposure--elemental and isotopic composition of samples	NIEHS
Callard, GV	Boston University	Neural and endocrine effects of environmental exposure to chemicals	NIEHS

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Belitz, K	Dartmouth College	Subsurface transport and fate of cadmium, arsenic and lead	NIEHS
Friedland, AJ	Dartmouth College	Sources and mobility of lead and cadmium in soil, groundwater, and vegetation	NIEHS
Hamilton, JW	Dartmouth College	Molecular basis for effects of carcinogenic metals on inducible gene expression	NIEHS
Mirkes, PE	University of Washington	BCl 2, ROS, and cell death in developmental toxicity	NIEHS
Bieberich, CJ	American National Red Cross	Environmental toxicants effect on hox gene expression	NIEHS
Thiele, DJ	University of Michigan Ann Arbor	Metal detoxification in eukaryotic cells	NIEHS
Prozialeck, WC	Midwestern University	Mechanisms of cadmium toxicity in epithelial cells	NIEHS
Mills, John W	Clarkson University	Effect of heavy metals on the actin cytoskeleton	NIEHS
Mason, AZ	California State University Long Beach	Cadmium-induced alterations in copper metabolism	NIEHS
Welsh, MJ	University of Michigan at Ann Arbor	Mechanisms of toxicity in testes	NIEHS
Ruegg, CHE	University of Maryland Balt Prof School	Mechanisms underlying segment-specific nephrotoxicity	NIEHS
Liu, J	University of Kansas Medical Center	Protection against hepatotoxicity by oleanolic acid	NIEHS
Long, GJ	Olivet Nazarene University	Cadmium effects on calcium homeostasis and modulation	NIEHS
Lion, LC	Cornell University Ithaca	Enhanced pollutant desorption kinetics by bacterial extracellular polymers	NIEHS
Clements, WH	Colorado State University	The influence of previous exposure to a mixture of heavy metals on tolerance	NIEHS
Korrish, S	Harvard University	*In utero* PCB and metal exposure and infant development	NIEHS
Ford, TE	Harvard University	Assessment of metal contamination and ecological implications	NIEHS
Friedman, PA	Dartmouth College	Cellular cadmium transport in cultured kidney cells	NIEHS
Hinkle, PM	University of Rochester	Transport and actions of metal ions	NIEHS
Andrews, GK	University of Kansas Medical Center	Environmental toxicology using transgenic mouse models	NIEHS
Sunderman, FW, Jr	University of Connecticut Health Center	Zinc finger proteins as targets of metal embryotoxicity	NIEHS
Noelle, RJ	Dartmouth College	Mercury, cadmium, and B-lymphocyte function	NIEHS
Gandolfi, AJ	University of Arizona	Metal-metal interactions in the kidney	NIEHS
Fernando, Q	University of Arizona	Determination of toxic metal species with high energy ion beams	NIEHS

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Conklin, MH	University of Arizona	Transport of trace metals in a polluted aquifer	NIEHS
Thomann, RV	New York University	Modeling transfer and bioaccumulation of metals in aquatic food webs	NIEHS
Ditoro, DM	New York University	Development of a sediment flux model for cadmium and chromium	NIEHS
Young, LY	New York University	Microbial mediated transformations of chromium and cadmium in the environment	NIEHS
Evans, HL	New York University	Behavioral and biochemical markers of neurotoxicity	NIEHS
Christie, NT	New York University	Assessment of oxidative DNA damage	NIEHS
Garte, S J	New York University	Molecular assays for toxicant exposure	NIEHS
Snyder, CA	New York University	Immune function assays as biomarkers of metal exposure	NIEHS
Costa, M	New York University	Methods to detect and predict exposure to toxic chemicals	NIEHS
Hammock, BD	University of California Davis	Immunochemical methods to monitor toxic substances in humans and other species	NIEHS
Hemond, HF	Massachusetts Institute of Technology	Chemical transport and human exposure on the aberjona watershed	NIEHS
Maines, MD	University of Rochester	Multiple forms of heme oxygenase--regulation by toxins	NIEHS
Petering, DH	University of Wisconsin Milwaukee	Cadmium, zinc, metallothionein and kidney toxicity	NIEHS
Ausiello, D	Mount Desert Island Biological Lab	Expression of atp channels in shark rectal gland in response to cadmium exposure	NIEHS
Kinne, R	Mount Desert Island Biological Lab	Effects of cadmium and mercury on Na-K-Cl cotransporter in shark rectal gland	NIEHS
Forrest, JN	Mount Desert Island Biological Lab	Cadmium, cobalt, nickel effect on signal transduction in shark rectal gland	NIEHS
Winge, DR	University of Utah	Metal chelation in proteins with polymetallic clusters	NIEHS
Shaikh, ZA	University of Rhode Island	Metallothionein and cadmium nephrotoxicity	NIEHS
Hart, BA	University of Vermont & State Agricultural College	Synthesis and role of metallothionein in the lung	NIEHS
Jones, MM	Vanderbilt University	Chelate antidotes for cadmium intoxication	NIEHS
Oberdoerster, G	University of Rochester	Mechanisms of particle and cadmium-induced lung injury	NIEHS
Klaassen, CD	University of Kansas Medical Center	Cadmium toxicology	NIEHS

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Sauer, GR	University of South Carolina Columbia	Metal metabolism in calcifying cells	NIDR
Nation, JR	Texas A&M University Health Science Center	Heavy metals and cocaine--interactions	NIDR
Martin, Mary B	Georgetown University	Cadmium and breast cancer etiology	NCI
Ho, Shuk-Mei	Tufts University Medford	Metallothionein and cadmium carcinogenesis in rat prostate	NCI
Rubin, CS	Yeshiva University	Regulation and function of metallothionein genes	NCI
Walter, CA	University of Texas Health Sciences Center San Antonio	Carcinogenesis in metallothionein-deficient mice	NCI
Jacob, ST	Finch Univ of Health Sciences Chicago Med Sch	Role of metallothionein in cancer and drug resistance	NCI
Rossman, TG	New York University	Metallothionein--effects on mutagenesis	NCI
Lazo, JS	University of Pittsburgh Pittsburgh	Metallothioneins and electrophiles	NCI
Andrews, GK	University of Kansas Medical Center	Metallothionein in reproduction and development	NCI
Shuman, LM	University of Georgia	Equilibrium of metals in soils and effects on water quality	USDA
Parker, DR; Crowley, De	University of California Riverside	Potentially toxic metals as influenced by complexation in the rhizosphere	USDA
Kochian, LV	Agricultural Research Services Ithaca, NY	Phytoremediation of metal-polluted soils: mechanisms of heavy metal transport and accumulation	USDA
Grunes, DI; Norvell, WA	Agricultural Research Services Ithaca, NY	Factors limiting the availability to plants of essential and toxic elements in soils	USDA
Ow, DW	Agricultural Research Services Albany, CA	Defining the molecular cellular mechanisms of heavy metal chelation and sequestration in plants	USDA
Kochian, LV	Agricultural Research Services Ithaca, NY	Investigation of heavy metal bioaccumulation in plants grown on metal-polluted soils	USDA
Welch, RM; Norvell, WA; Grunes, DI	Agricultural Research Services Ithaca, NY	Uptake, transport and interaction of essential and toxic mineral elements in food crops	USDA
Kochian, LV; Norvell, WA; Grunes, DI	Agricultural Research Services Ithaca, NY	Cellular basis of essential and toxic mineral ion and absorption and translocation on food crops	USDA
Reeves, PG; Vanderpool, RA	Agricultural Research Services Grand Forks, ND	Health effects and bioavailability of cadmium from sunflower seed kernels: a human study	USDA

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Chaney, RI; Wright, RJ	Agricultural Research Services Beltsville, MD	Soil and plant factors affecting concentration and bioavailability of cadmium in US. crops	USDA
Jones, RI	University of Illinois	Trace minerals in Illinois surface soils	USDA
Smith, DE	North Carolina State University	Effects of metal ions on *in vitro* estrogen action in rat uterus	USDA
Brams, EA	Prairie View A & M University	Toxic trace metals in an agricultural food chain: a quality assessment	USDA
Wagner, GJ	University of Kentucky	Characterization and modification of heavy metal accumulation in plants with emphasis on tobacco	USDA
Chang, AC; Page, AI; Amrhein, C	University of California Riverside	Chemistry and bioavailability of waste constituents in soils	USDA
Helmke, PA	University of Wisconsin	Ion exchange and complex ion formation affecting the solubility and plant uptake of trace elements	USDA
Blumenthal; SS	Department of Veteran Affairs - Medical Center Milwaukee, WI	Cadmium, zinc, metallothionein and kidney cytotoxicity	DVA-R&D
Bhattacharyya, MH	Argonne National Laboratory - Biological And Medical Research Division	Biochemical mechanisms of chemically induced health effects	DOE
Peterson, L	Francis Marion University	Synthesis and characterization of cadmium and zinc model compounds of biological relevance	NSF
Not specified	Grand Forks Human Nutrition Center	Health effects of cadmium from sunflower kernels: a human study	ILZRO
Not specified	McMaster University	Relationships of blood and urine cadmium levels to quantities of the element stored in the liver and kidney	ILZRO
Not specified	Universite Catholique de Louvain	Early biomarkers of health risks related to environmental exposure to toxic metals: validation in a prospective study	ILZRO
Lamm, SH	Consultants in Epidemiology and Occupational Health, Inc.	Further analysis of the globe, Colorado cohort for the relationship between lung cancer mortality rates and exposure to cadmium	Not specified

NICHHD = National Institute of Child Health And Human Development; NCI = National Cancer Institute; NIGMD = National Institute of General Medical Sciences; NIEHS = National Institute of Environmental Health Sciences; NIDR = National Institute of Dental Research; USDA = United States Department of Agriculture; DVA-R&D = Department of Veteran Affairs - Research and Development; DOE = US Department of Energy; NSF = National Science Foundation; ILZRO = International Lead Zinc Research Organization, Inc.

Source: FEDRIP 1998