2. HEALTH EFFECTS

2.1 INTRODUCTION

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

Chromium is a naturally occurring element found in animals, plants, rocks, and soil and in volcanic dust and gases. Chromium has oxidation states (or "valence states") ranging from chromium(-II) to chromium(VI). Elemental chromium (chromium(0)) does not occur naturally. Chromium compounds are stable in the trivalent state and occur in nature in this state in ores, such as ferrochromite. The hexavalent (VI) form is the second-most stable state. However, chromium(VI) rarely occurs naturally, but is usually produced from anthropogenic sources (EPA 1984a).

Trivalent chromium compounds, except for acetate, nitrate, and chromium(III) chloride-hexahydrate salts, are generally insoluble in water. Some hexavalent compounds, such as chromium trioxide (or chromic acid) and the ammonium and alkali metal (e.g., sodium, potassium) salts of chromic acid are readily soluble in water. The alkaline metal (e.g., calcium, strontium) salts of chromic acid are less soluble in water. The zinc and lead salts of chromic acid are practically insoluble in cold water. Chromium(VI) compounds are reduced to chromium(III) in the presence of oxidizable organic matter. However, in natural waters where there is a low concentration of reducing materials, chromium(VI) compounds are more stable (EPA 1984a). For more information on the physical and chemical properties of chromium, see Chapter 3.

In humans and animals, chromium(III) is an essential nutrient that plays a role in glucose, fat, and protein metabolism by potentiating the action of insulin (Anderson 1981). The biologically active form of chromium, called glucose tolerance factor (GTF), is a complex of chromium, nicotinic acid, and possibly amino acids (glycine, cysteine, and glutamic acid). Both humans and animals are capable of converting inactive inorganic chromium(III) compounds to physiologically active forms. The nutritional role of chromium is further discussed in Section 2.3.3. Although chromium(III) has been reported to be an

essential nutrient, exposure to high levels via inhalation, ingestion, or dermal contact may cause some adverse health effects. Most of the studies on health effects discussed below involve exposure to chromium(0), chromium(III), and chromium(VI) compounds. In addition, chromium(IV) was used in an inhalation study to determine permissible exposure levels for workers involved in producing magnetic tape (Lee et al. 1989).

Several factors should be considered when evaluating the toxicity of chromium compounds. The purity and grade of the reagent used in the testing is an important factor. Both industrial- and reagent-grade chromium(III) compounds can be contaminated with small amounts of chromium(VI) (Levis and Majone 1979). Thus, interpretation of occupational and animal studies that involve exposure to chromium(III) compounds is difficult when the purity of the compounds is not known. In addition, it is difficult to distinguish between the effects caused by chromium(VI) and those caused by chromium(III) since chromium(VI) is rapidly reduced to chromium(III) after penetration of biological membranes and in the gastric environment (Petrilli et al. 1986b; Samitz 1970). However, whereas chromium(VI) can readily be transported into cells, chromium(III) is much less able to cross cell membranes. The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium compounds, whereas the reduction of chromium(VI) to chromium(III) outside of cells is a major mechanism of protection.

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-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

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

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (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 chromium are indicated in Table 2-1 and Figure 2-1. Because cancer effects could occur at lower exposure levels, Figure 2-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for chromium. 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 1990a), 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

Due to the extremely high boiling point of chromium, gaseous chromium is rarely encountered. Rather, chromium in the environment occurs as particle-bound chromium or chromium dissolved in droplets. As discussed in this section, chromium(VI) trioxide (chromic acid) and soluble chromium(VI) salt aerosols may produce different health effects than insoluble particulate compounds. For example, exposure to chromium(VI) trioxide results in marked damage to the nasal mucosa and perforation of the nasal septum, whereas exposure to insoluble(VI) compounds results in damage to the lower respiratory tract.

2.2.1.1 Death

No studies were located regarding death in humans after acute inhalation of chromium or chromium compounds. An increased risk of death from noncancer respiratory disease was reported in retrospective mortality studies of workers in a chrome plating plant (Sorahan et al. 1987) and chromate production (Davies et al. 1991; Taylor 1966) (see Section 2.2.1.2, Respiratory Effects). However, a number of methodological deficiencies in these studies prevent the establishment of a definitive cause-effect relationship. Retrospective mortality studies associating chromium exposure with cancer are discussed in Section 2.2.1.8.

Acute inhalation LC_{50} values in rats for several chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) ranged from 29 to 45 mg chromium(VI)/m^3 for females and from 33 to 82 mg chromium(VI)/m^3 for males (Gad et al. 1986). Acute inhalation LC_{50} values for chromium trioxide were 87 and 137 mg chromium(VI)/m^3 for female and male rats, respectively (American Chrome and Chemicals 1989). Female rats were more sensitive than males to the lethal effects of most chromium(VI) compounds except sodium chromate, which was equally toxic

in both sexes. Signs of toxicity included respiratory distress, irritation, and body weight depression (Gad et al. 1986). The LC_{50} values are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to chromium or its compounds. Respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, and body weight effects are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. The respiratory tract in humans is a major target of inhalation exposure to chromium compounds. Chromate sensitive workers acutely exposed to chromium(VI) compounds may develop asthma and other signs of respiratory distress. Five individuals who had a history of contact dermatitis to chromium were exposed via a nebulizer to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. A 20% decrease in the forced expiratory volume of the lungs was observed and was accompanied by erythema of the face, nasopharyngeal pruritus, nasal blocking, coughing, and wheezing (Olaguibel and Basomba 1989).

Dyspnea, cough, and wheezing were reported in two cases in which the subjects inhaled "massive amounts" of chromium(VI) trioxide. Marked hyperemia of the nasal mucosa without nasal septum perforation was found in both subjects upon physical examination (Meyers 1950). In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of sneezing, rhinorrhea, labored breathing, and a choking sensation when they were working over the chromate tanks. All five of the subjects had thick nasal and postnasal discharge and nasal septum ulceration or perforation after 2–3 months of exposure (Lieberman 1941). Asthma developed in a man who had been well until one week after beginning employment as an electroplater. When challenged with an inhalation exposure to a sample of chromium(III) sulfate, he developed coughing, wheezing, and decreased forced expiratory volume. He also had a strong asthmatic reaction to nickel sulfate (Novey et al. 1983). Thus, chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low, and the number of potentially confounding variables in the chromium industry is high.

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL Less serious (mg Cr/m3)	LOAEL Serious (mg Cr/m3)	Reference/ Form
ACUTE EXPOSURE							
Death							
1	Rat (Fischer- 344)	4 hr				137 M (LC_{50}) 87 F (LC_{50})	American Chrome and Chemical 1989 CrO_3 (VI)
2	Rat (Fischer- 344)	4 hr				33 (LC_{50})	Gad et al. 1986 Na_2CrO_4 (VI)
3	Rat (Fischer- 344)	4 hr				82 M (LC_{50}) 45 F (LC_{50})	Gad et al. 1986 $(NH_4)_2Cr_2O_7$ (VI)
4	Rat (Fischer- 344)	4 hr				35 M (LC_{50}) 29 F (LC_{50})	Gad et al. 1986 $K_2Cr_2O_7$ (VI)
5	Rat (Fischer- 344)	4 hr				70 M (LC_{50}) 31 F (LC_{50})	Gad et al. 1986 $Na_2Cr_2O_7 2H_2O$ (VI)
Systemic							
6	Hamster (Syrian)	30 min	Resp		0.9 (increased acid phosphatase activity in lung tissue)		Henderson et al. 1979 $CrCl_3$ (III)

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL Less serious (mg Cr/m3)	LOAEL Serious (mg Cr/m3)	Reference/ Form
INTERMEDIATE EXPOSURE							
Systemic							
7	Human	<1 yr (occup)[b]	Resp		0.1 (epitaxis rhinorrhea, nasal ulceration and perforation)		Gomes 1972 CrO_3 (VI)
8	Human	0.5-12 mo 6 mo avg (occup)[b]	Resp		0.09 M (epitaxis, rhinorrhea ulceration of nasal septum)		Kleinfield and Rosso 1965 CrO_3 (VI)
9	Human	0.2-23.6 yr avg 2.5 yr (occup)[b]	Resp		0.002[c] (nasal mucosa atrophy, mild decreased lung function)		Lindberg and Hedenstierna 1983 CrO_3 (VI)
10	Rat (Wistar)	28 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985 $Na_2Cr_2O_7 2H_2O$ (VI)
			Gastro	0.2 M			
			Hemato	0.2 M			
			Hepatic	0.2 M			
			Renal	0.2 M			
			Bd Wt	0.2 M			

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL		Reference/ Form
					Less serious (mg Cr/m3)	Serious (mg Cr/m3)	
11	Rat (Wistar)	90 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchial alveolar lavage fluid)		Glaser et al. 1985 $Na_2Cr_2O_7 2H_2O$ (VI)
			Gastro	0.2 M			
			Hemato	0.2 M			
			Hepatic	0.1 M	0.2 M (increased levels of serum phospholipids and triglycerides)		
			Renal	0.2 M			
			Bd Wt	0.2 M			
12	Rat (Wistar)	30 - 90 d 7 d/wk 22 hr/d	Resp		0.05[d] M (increased lung weight, hyperplasia, macrophage infiltration, increased protein, albumin, lactate dehydrogenase in BAL fluid)		Glaser et al. 1990 $Na_2Cr_2O_7 2H_2O$ (VI)
			Gastro	0.4 M			
			Hemato		0.05 M (increased white blood cell count)		
			Hepatic	0.4 M			
			Renal	0.4 M			
			Bd Wt	0.1 M	0.2 M (28% decreased body weight gain)		
13	Mouse (C57BL)	12 mo 2 d/wk 120 min/d	Resp			1.81 F (emphysema, nasal septum perforation)	Adachi 1987 CrO_3 (VI)
14	Mouse (ICR)	12 mo 2 d/wk 30 min/d	Resp			3.63 F (emphysema, nasal septum perforation)	Adachi et al. 1986 CrO_3 (VI)

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL Less serious (mg Cr/m3)	LOAEL Serious (mg Cr/m3)	Reference/ Form
15	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp		0.6 M (decreased macrophage activity, impaired lung function)		Johansson et al. 1986b $Cr(NO_3)_3 9H_2O$(III)
16	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp	0.9 M			Johansson et al. 1986b Na_2CrO_4 (VI)
Immunological/Lymphoreticular							
17	Rat (Fischer- 344)	2-4 wk 5 d/wk 5 hr/d			0.36 (increased neutrophils, monocytes, and decreased macrophages in BAL fluid; decreased cytokine levels)		Cohen et al. 1998 K_2CrO_4 (VI)
18	Rat (Fischer- 344)	2-4 wk 5 d/wk 5 hr/d			0.36 (decreased tumor necrosis factor-alpha levels and production of superoxide anion and hydrogen peroxide and increased nitric oxide production)		Cohen et al. 1998 $BaCrO_4$ (VI)
19	Rat (Wistar)	28 d 7 d/wk 22 hr/d			0.025 M (increased response to sheep red blood cells, increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985 $Na_2Cr_2O_7 2H_2O$ (VI)

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL Less serious (mg Cr/m3)	LOAEL Serious (mg Cr/m3)	Reference/ Form
20	Rat (Wistar)	90 d 7 d/wk 22 hr/d			0.025 M (increased response to sheep RBC, increased % of lymphocytes in bronchoalveolar lavage fluid, increased % of macrophages in telophase, increased activity of macrophages)		Glaser et al. 1985 $Na_2Cr_2O_7 2H_2O$ (VI)
	Reproductive						
21	Rat (Wistar)	90 d 7 d/wk 22 hr/d		0.2 M			Glaser et al. 1985 $Na_2Cr_2O_7 2H_2O$ (VI)
	CHRONIC EXPOSURE						
	Systemic						
22	Human	2-12 yr (occup)[b]	Renal	0.075 M			Foa et al. 1988 Cr_2O_3 (III)
23	Human	7 yr avg (occup)[b]	Renal		0.05 M (increase in retinol binding protein and tubular antigen)		Franchini and Mutti 1988 CrO_3 (VI)
24	Human		Resp		0.414 (nasal septum perforation)		Hanslian et al. 1967 CrO_3 (VI)
			Gastro		0.414 (chronic tonsilitis, chronic pharyngitis, atrophy of larynx)		
25	Human	> 8 yr (occup)[b]	Resp	0.022			Huvinen et al. 1996 (III), (VI), chromite

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL Less serious (mg Cr/m3)	LOAEL Serious (mg Cr/m3)	Reference/ Form
26	Human		Resp	1.99			Korallus et al. 1974a Cr_2O_3 and $Cr_2(SO_4)_3$ (III)
			Hemato	1.99			
27	Human	0.2-23.6 yr avg 2.5yr (occup)[b]	Resp		0.002 (nasal mucosa atrophy, mild decreased lung function)		Lindberg and Hedenstierna 1983 CrO_3 (VI)
28	Human	0.1-26 yr 5.3 yr avg (occup)[b]	Renal		0.004 M (increased urinary beta-2-microglobulin)		Lindberg and Vesterberg 1983 CrO_3 (VI)
29	Human		Renal		0.0042 (increased prevalence of high N-acetyl-B-glucosamindase levels)		Liu et al. 1998 Cr(VI)
30	Human	7.5 yr -avg (range 3-16 yr)	Resp		0.004 M (epitaxis, rhinorrhea, nasal septum ulceration and perforation)		Lucas and Kramkowski 1975 CrO_3 (VI)
			Gastro		0.004 M (stomach pains and cramps, ulcers)		
31	Human	11-19 yr	Gastro		0.005 (gastric irritation ulcer)		Sterechova et al. 1978 Cr (VI) salts
32	Human	1-32 yr 7 yr avg (occup)[b]	Renal	0.61 M			Triebig et al. 1987 Chromium (0)

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL		Reference/ Form
					Less serious (mg Cr/m3)	Serious (mg Cr/m3)	
33	Rat (Wistar)	18 mo 7 d/wk 22 hr/d	Resp	0.1 M			Glaser et al. 1986, 1988 $Na_2Cr_2O_7 2H_2O$ (VI)
			Hemato	0.1 M			
			Hepatic	0.1 M			
			Renal	0.1 M			
			Endocr	0.1 M			
			Bd Wt	0.1 M			
34	Rat (Wistar)	18 mo 7 d/wk 22 hr/d	Resp			0.1 M (interstitial fibrosis of lung)	Glaser et al. 1986, 1988 CrO_3 and Cr_2O_3 (VI + III)
			Hemato		0.1 M (increased RBC, WBC)		
			Hepatic	0.1 M			
			Renal	0.1 M			
			Endocr	0.1 M			
			Bd Wt	0.1 M			
35	Rat (Sprague-Dawley)	2 yr 5 d/wk 6 hr/d	Resp	15.5			Lee et al. 1989 CrO_2 (IV)
			Cardio	15.5			
			Gastro	15.5			
			Hemato	15.5			
			Musc/skel	15.5			
			Hepatic	15.5			
			Renal	15.5			
			Endocr	15.5			
			Ocular	15.5			
			Bd Wt	15.5			

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL Less serious (mg Cr/m3)	LOAEL Serious (mg Cr/m3)	Reference/ Form
36	Rat (Wistar)	2 yr 4 d/wk 4-5 hr/d	Resp			1.6 (granulomata, giant cells, bronchopneumonia, abscesses)	Steffee and Baetjer 1965 Finely ground chromium roast (VI)
37	Mouse (C57BL/6)	18 mo 5 d/wk 5.5 hr/d	Resp			4.3 (epithelial necrosis, hyperplasia)	Nettesheim and Szakal 1972 $CaCrO_4$ (VI)
38	Gn pig (NS)	4.5 yr 4 d/wk 4-5 hr/d	Resp			1.6 (alveolar and interstitial inflammation; alveolar hyperplasia, interstitial fibrosis)	Steffee and Baetjer 1965 Mixed chromium roast $K_2Cr_2O_7$, Na_2CrO_4 (VI)
	Reproductive						
39	Rat (Wistar)	3 gen 130 d/gen		0.2 M			Glaser et al 1984 Sodium dichromate (VI)
40	Rat (Wistar)	18 mo 7 d/wk 22 hr/d		0.1 M			Glaser et al. 1986, 1988 Chromium (VI) trioxide, Chromium (III) oxide
	Cancer						
41	Human	90d->5yr				0.413 (CEL: lung cancer)	Hayes et al. 1979; Braver et al. 1985 mixed
42	Human	1 mo-29 yr (occup)[b]				0.5 M (CEL: lung cancer)	Hayes et al. 1989 $PbCrO_4$ and $ZnCrO_4$ (VI)

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL			Reference/ Form
					Less serious (mg Cr/m3)	Serious (mg Cr/m3)		
43	Human	4-19 yr (occup)[b]				0.5	(CEL: lung cancer)	Langard and Norseth 1975 $PbCrO_4$ and $ZnCrO_4$ (VI)
44	Human	1-49 yr (occup)[b]				0.04 M	(CEL: lung cancer)	Langard et al. 1980 Mix of (VI) and (III)
45	Human	1-7 yr (occup)[b]				0.25	(CEL: lung cancer)	Mancuso 1975 Insoluble Cr (III)
46	Human	1-7 yr (occup)[b]				0.50	(CEL: lung cancer)	Mancuso 1975 Mix of (VI) and (III)
47	Human	1-7 yr (occup)[b]				0.25	(CEL: lung cancer)	Mancuso 1975 Soluble Cr(VI)
48	Human	1-7 yr (occup)[b]				0.25	(CEL: lung cancer)	Mancuso 1997a Mix of soluble (VI) and insoluble (III) chromium
49	Human	1 mo-29 yr (occup)[b]				0.1 M	(CEL: lung cancer)	Sheffet et al. 1982 $PbCrO_4$ and $ZnCrO_4$ (VI)
50	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.1 M	(CEL: lung tumors)	Glaser et al. 1986, 1988 $Na_2Cr_2O_7 2H_2O$ (VI)

TABLE 2-1. Levels of Significant Exposure to Chromium - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg Cr/m3)	LOAEL Less serious (mg Cr/m3)	LOAEL Serious (mg Cr/m3)		Reference/ Form
51	Mouse (C57BL/6)	18 mo 5 d/wk 5 hr/d				4.3	(CEL: alveologenic adenomas and adenocarcinomas)	Nettesheim et al. 1971 $CaCrO_4$ (VI)

[a]The number corresponds to entries in Figure 2-1. Differences in levels of health effects and cancer effects between males and females are not indicated in figure 2-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Occup = occupational exposure = 5 d/wk, 8 hr/d
[c]Used to derive an intermediate inhalation minimal risk level (MRL) of 0.000005 mg chromium(VI)/m^3 for chromium (VI) trioxide and soluble chromium (VI) compounds. Exposure concentration adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for human variability and10 for extrapolating from a LOAEL).
[d]Used to derive an intermediate inhalation minimal risk level (MRL) of 0.001 mg chromium(VI)/m^3 for particulate chromium (VI) compounds. Benchmark concentration of 0.016 mg chromium (VI)/m^3 was divided by an uncertainty factor of 30 (3 for pharmacodynamic variability between species and 10 for human variability).

(0) = 0 valence; (III) = trivalent; (IV) = tetravalent; (VI) = hexavalent; avg = average; $BaCrO_4$ = barium chromate; BAL = bronchoalveolar lavage; Bd Wt = body weight; $CaCrO_4$ = calcium chromate; Cardio = cardiovascular; CEL = cancer effect level; Cr = chromium; $CrCl_3$ = chromium trichloride; $Cr(NO_3)_3 9H_2O$ = chromium nitrate; CrO_2 = chromium dioxide; CrO_3 = chromium trioxide; Cr_2O_3 = chromium oxide; $Cr_2(SO)_3$ = chromium sulfate; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); $K_2Cr_2O_7$ = potassium dichromate; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/Skel = muscular/skeletal; Na_2CrO_4 = sodium chromate; $Na_2Cr_2O_7 2H_2O$ = sodium dichromate dihydrate; $(NH_4)_2Cr_2O_7$ = ammonium dichromate; NS = not specified; NOAEL = no-observed-adverse-effect level; (occup) = occupational; $PbCrO_4$ = lead chromate; RBC = red blood cell; Resp = respiratory; WBC = white blood cell; wk = week(s); x = times; yr = year(s); $ZnCrO_4$ = zinc chromate

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

Acute (≤14 days)

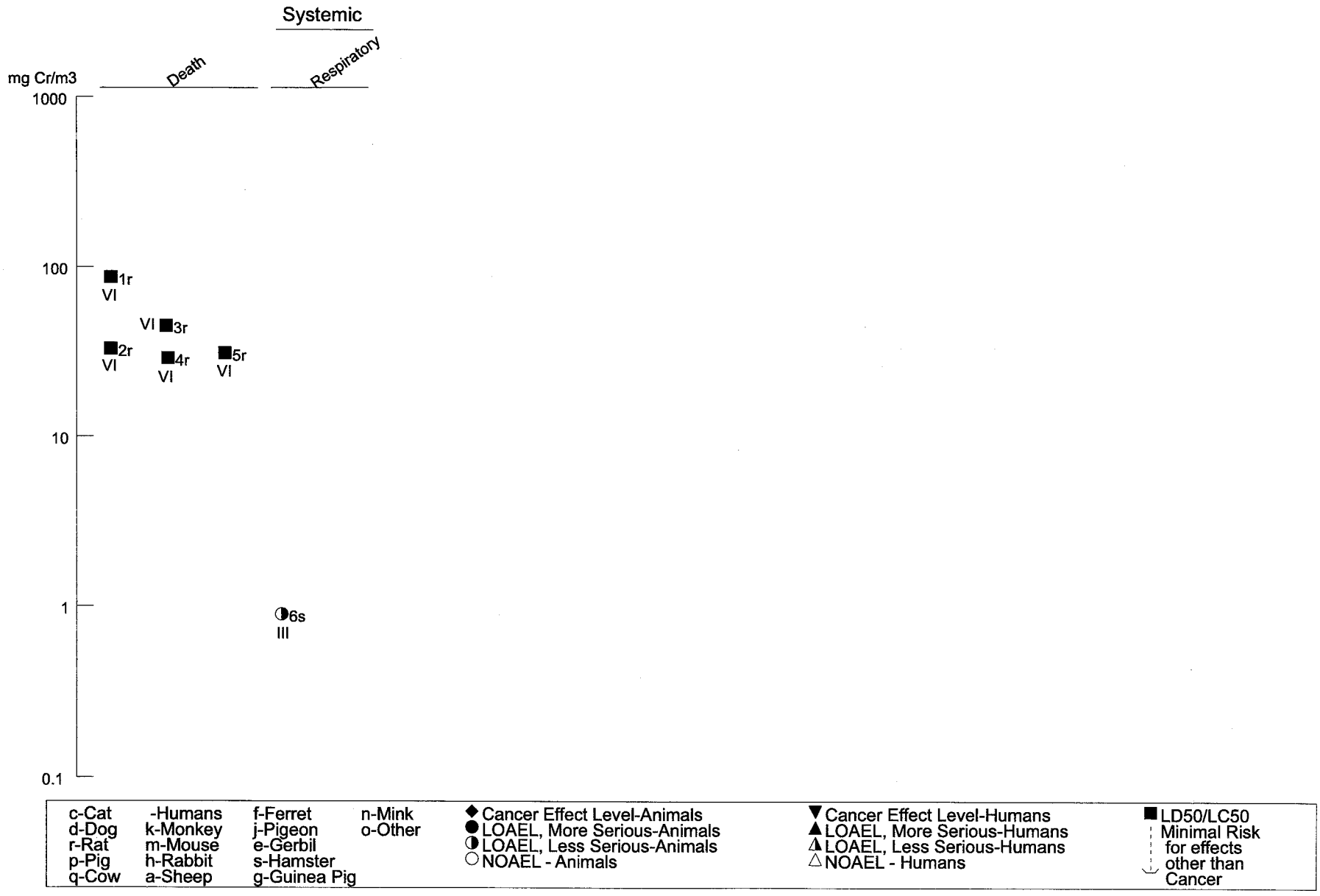


Figure 2-1. Levels of Significant Exposure to Chromium - Inhalation (*continued*)

Intermediate (15-364 days)

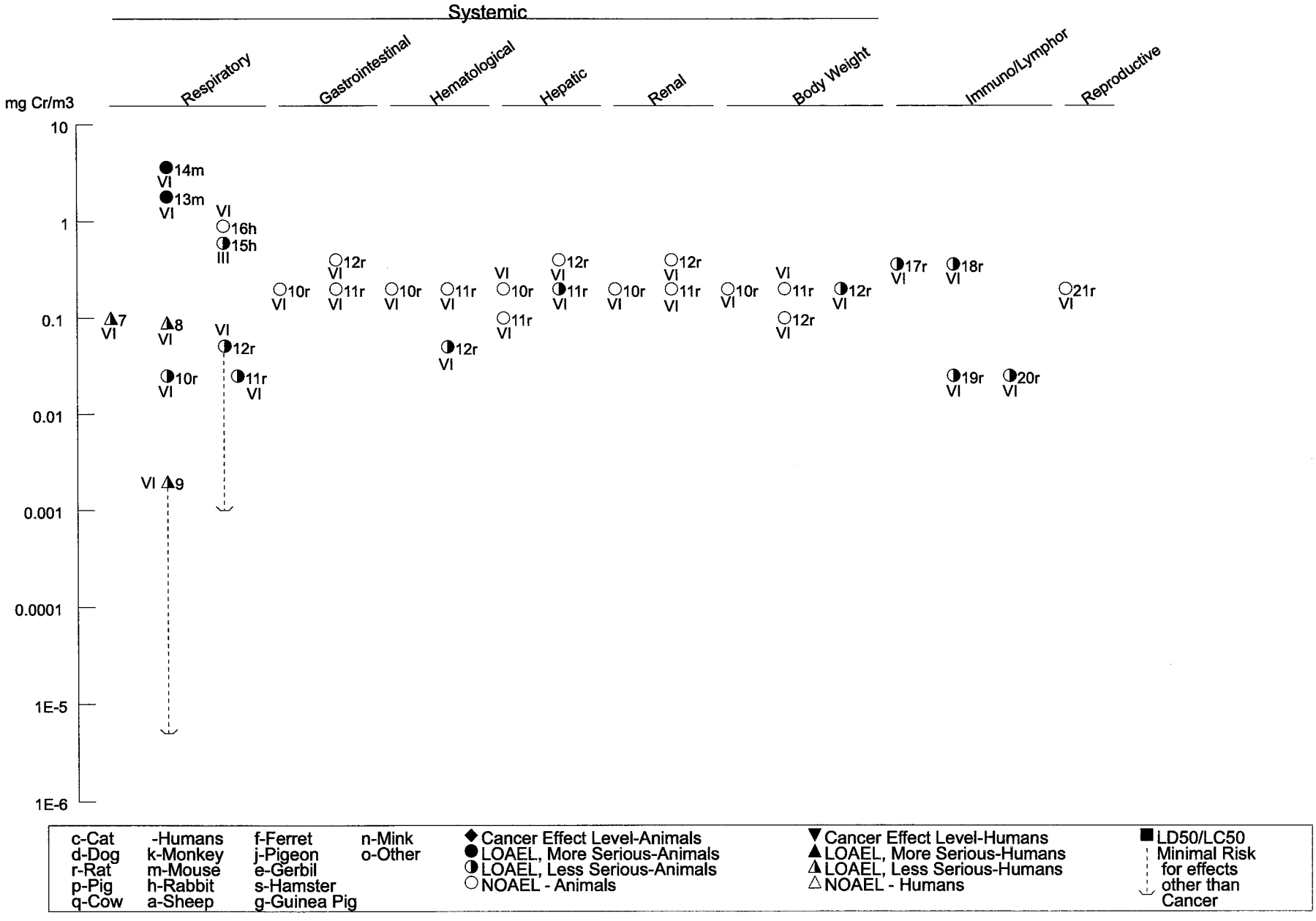


Figure 2-1. Levels of Significant Exposure to Chromium - Inhalation (*continued*)

Chronic (≥365 days)

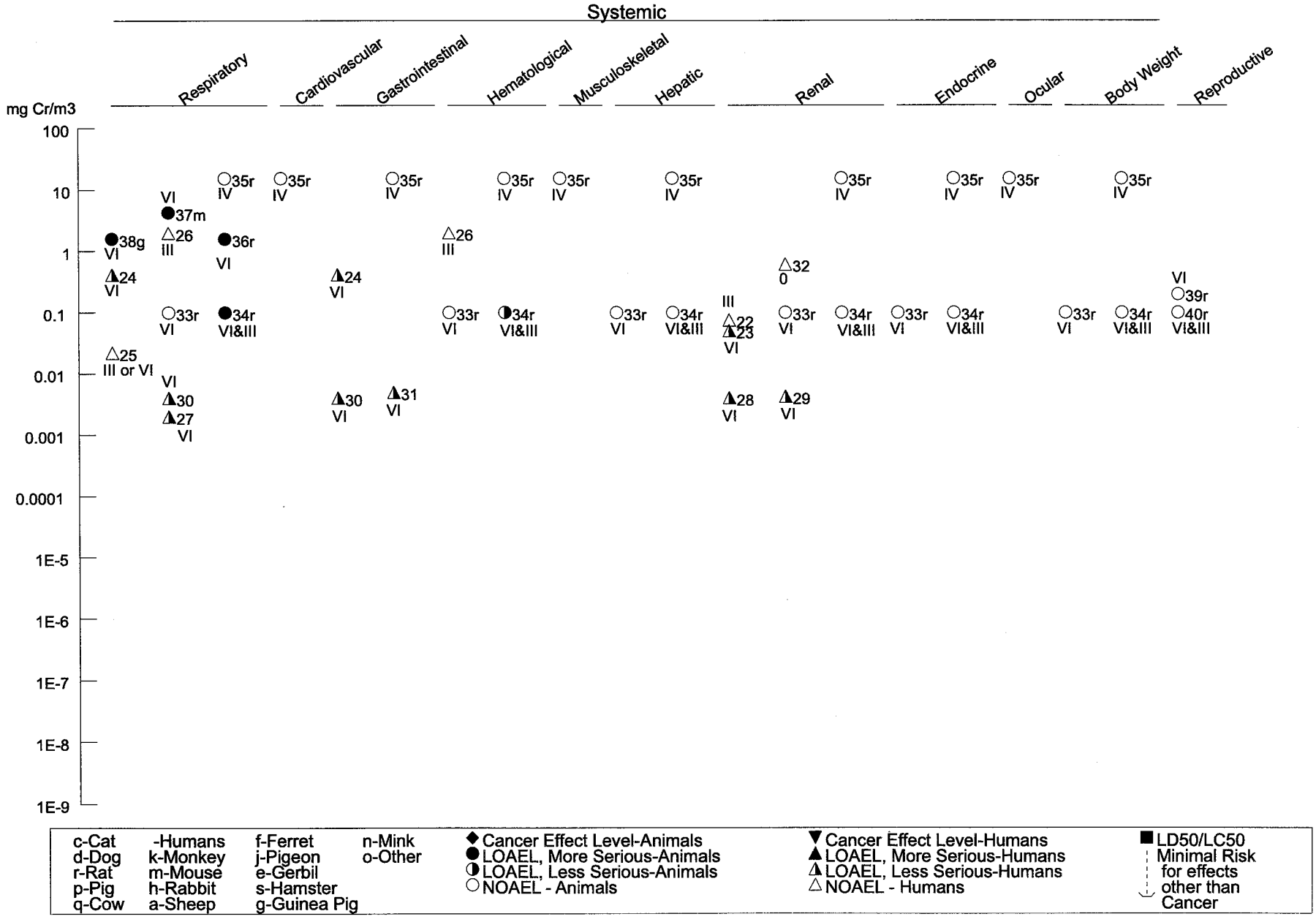
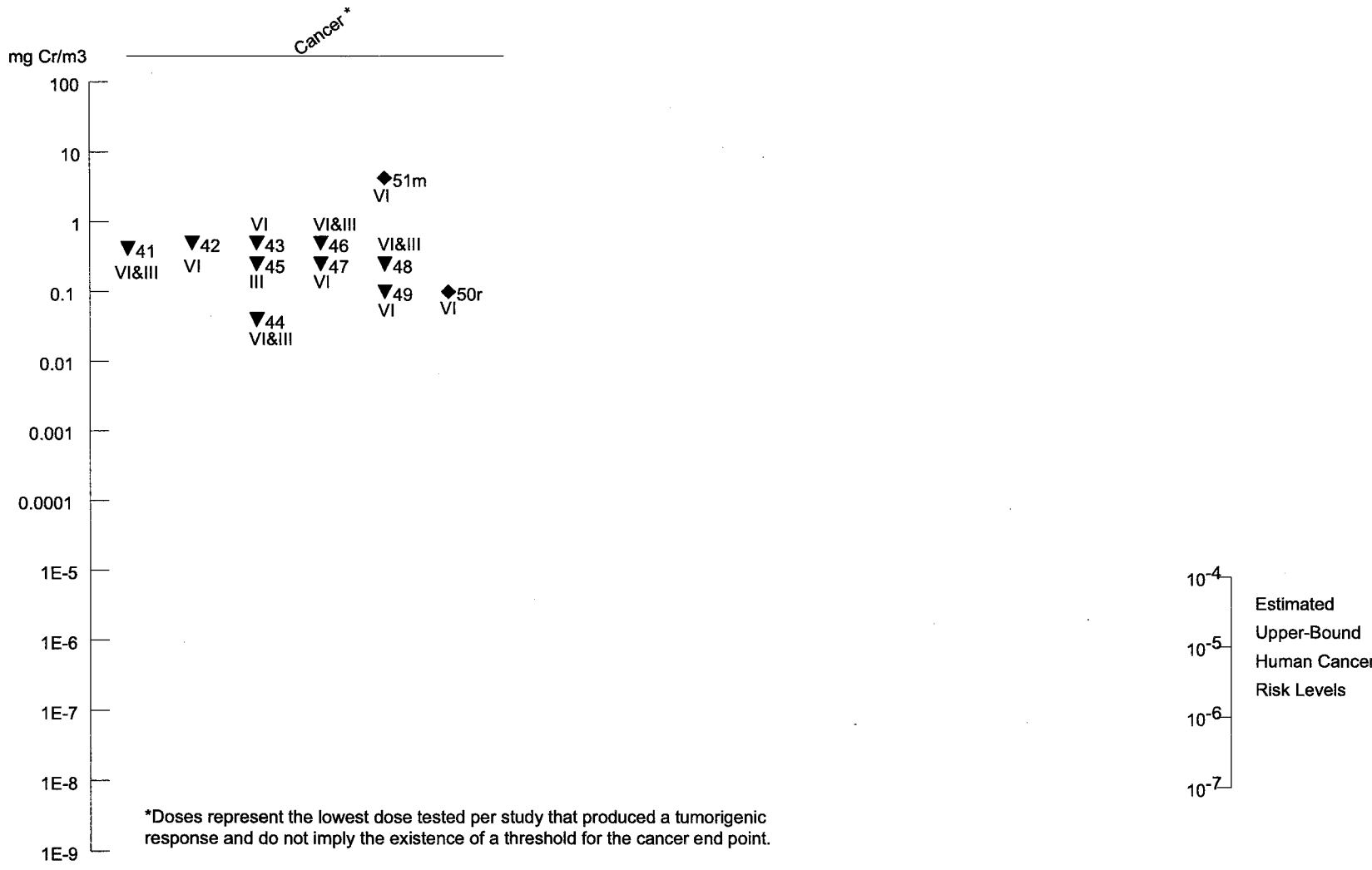


Figure 2-1. Levels of Significant Exposure to Chromium - Inhalation (*continued*)

Chronic (≥365 days)



Intermediate- to chronic-duration occupational exposure to chromium(VI) may cause an increased risk of death due to noncancer respiratory disease. In a retrospective mortality study of 1,288 male and 1,401 female workers employed for at least 6 months in a chrome plating and metal engineering plant in the United Kingdom between 1946 and 1975, a statistically significant excess of death from diseases of the respiratory system (noncancer) were obtained for men (observed/expected [O/E]=72/54.8, standard mortality ratio [SMR]=131, $p<0.05$) and men and women combined (O/E=97/76.4, SMR=127, $p<0.05$) but not for women alone. Exposure was mainly to chromium trioxide, but exposure concentrations were not precisely known. The contribution of nickel exposure to the effects was found to be unimportant, while data on smoking habits were not available (Sorahan et al. 1987). Similarly, a high SMR was found for noncancer respiratory disease among 1,212 male chromate workers who were employed for at least 3 months in 3 chromate plants in the United States during the years 1937–1940 and followed for 24 years (O/E=19/7.843, SMR=242) (Taylor 1966). The increased risk of death from respiratory effects correlated with duration of employment in chromate production, but no information on exposure levels, smoking habits, or exposure to other chemicals was provided. The nature of the respiratory diseases was not further described in either of these reports. Chromate production workers in the United Kingdom who were first employed before 1945 had a high risk of death from chronic obstructive airways disease (O/E=41/28.66, SMR=143, $p<0.05$) (Davies et al. 1991). Exposure concentrations were not known, and reliable smoking data were not available.

Occupational exposure to chromium(VI) as chromium trioxide in the electroplating industry caused upper respiratory problems. A case history of nine men in a chrome plating facility reported seven cases of nasal septum ulceration. Signs and symptoms included rhinorrhea, nasal itching and soreness, and epistaxis. The men were exposed from 0.5 to 12 months to chromium trioxide at concentrations ranging from 0.09 to 0.73 mg chromium(VI)/m^3 (Kleinfeld and Rosso 1965). Electroplating workers in Sao Paulo, Brazil, exposed to chromium trioxide vapors while working with hot chromium trioxide solutions had frequent incidences of coughing, expectoration, nasal irritation, sneezing, rhinorrhea, and nose-bleed and developed nasal septum ulceration and perforation. The workers had been employed for <1 year, and most of the workers had been exposed to concentrations >0.1 mg chromium(VI)/m^3 (Gomes 1972). Nose and throat irritation, rhinorrhea, and nose-bleed also occurred at higher incidence in chrome platers in Singapore than in controls (Lee and Goh 1988).

Numerous studies of workers chronically exposed to chromium(VI) compounds have reported nasal septum perforation and other respiratory effects. Workers at an electroplating facility exposed to 0.0001–0.0071 mg chromium(VI)/m^3 as chromium trioxide for an average of 26.9 months complained of

excessive sneezing, rhinorrhea, and epistaxis. Many of the workers had ulcerations and/or perforations of the nasal mucosa (Cohen et al. 1974). A study using only questionnaires, which were completed by 997 chrome platers and 1,117 controls, found a statistically significant increase in the incidence of chronic rhinitis, rhinitis with bronchitis, and nasal ulcers and perforations in workers exposed to chromium(VI) in the chrome plating industry in 54 plants compared to the control population (Royle 1975b). The workers had been exposed to chromium(VI) in air and in dust. The air levels were generally <0.03 mg chromium(VI)/m^3, and dust levels were generally between 0.3 and 97 mg chromium(VI)/g. The exposure levels at which effects first occurred could not be determined. A National Institute of Occupational Safety and Health (NIOSH) Health Hazard Evaluation of an electroplating facility in the United States reported nasal septum perforation in 4 of 11 workers employed for an average of 7.5 years and exposed to mean concentrations of 0.004 mg chromium(VI)/m^3. Many of the workers had epistaxis, rhinitis, and nasal ulceration (Lucas and Kramkowski 1975). Nasal mucosal changes ranging from irritation to perforation of the septum were found among 77 employees of 8 chromium electroplating facilities in Czechoslovakia where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m^3 (Hanslian et al. 1967). Increased incidences of nasal septum perforation, nasal septum ulcer, and nasal obstruction were observed in workers at chromium electroplating facilities exposed for a mean duration of 6.1 years, as compared to workers at zinc electroplating facilities (Kuo et al. 1997a). The chromium electroplating workers had 31.7 and 43.9 times greater risks of developing nasal septum ulcers or nasal perforations, respectively, than the zinc workers. A significant relationship between duration of exposure and the risk of nasal septum ulcers was also found; the chromium electroplating workers with a work duration of greater than 9 years had a 30.8 times higher risk than those with a work duration of less than 2 years. Duration did not significantly affect the risk of nasal perforation. Statistically significant decreases in vital capacity, forced vital capacity, and forced expiratory volume in one second were also observed in the chromium workers. Alterations in lung function were also reported in a study of 44 workers at 17 chromium electroplating facilities (Bovet et al. 1977). Statistically significant decreases in forced expiratory volume in 1 second and forced expiratory flow were observed; vital capacity was not altered. Lower lung function values were found among workers with high urinary chromium levels (exposure levels were not reported), and it was determined that cigarette smoking was not a confounding variable.

A study of respiratory effects, lung function, and changes in the nasal mucosa in 43 chrome plating workers in Sweden exposed to chromium(VI) as chromium trioxide for 0.2–23.6 years (median=2.5 years) reported respiratory effects at occupational exposure levels of 0.002 mg chromium(VI)/m^3. Signs and symptoms of adverse nasal effects were observed and reported at mean

exposure levels of 0.002–0.2 mg chromium(VI)/m^3. Effects noted at 0.002 mg chromium(VI)/m^3 or less included a smeary and crusty septal mucosa and atrophied mucosa. Nasal mucosal ulceration and septal perforation occurred in individuals exposed at peak levels of 0.02–0.046 mg chromium(VI)/m^3; nasal mucosal atrophy and irritation occurred in individuals exposed at peak levels of 0.0025–0.011 mg chromium(VI)/m^3; and no significant nasal effects were observed in individuals exposed at peak levels of 0.0002–0.001 mg chromium(VI)/m^3. Workers exposed to mean concentrations of 0.002–0.02 mg chromium(VI)/m^3 had slight, transient decreases in forced vital capacity (FVC), forced expired volume in 1 second (FEV_1), and forced mid-expiratory flow during the workday. Workers exposed to <0.002 mg chromium(VI)/m^3 showed no effects on lung function (Lindberg and Hedenstierna 1983). The concentrations at which minor lung function changes were observed (0.002–0.02 mg chromium(VI)/m^3) and those at which no changes were observed (<0.002 mg chromium(VI)/m^3) are similar to those for nasal effects (0.0025–0.011 mg chromium(VI)/m^3). The effects observed in this study may not have resulted from exposure levels actually measured, but may have resulted from earlier exposure under unknown conditions. Furthermore, poor personal hygiene practices resulting in transfer of chromium(VI) in chrome plating solutions from the hands to the nose could contribute to the development of nasal ulceration and perforation (Cohen et al. 1974; Lucas and Kramkowski 1975), perhaps leading to an underestimation of airborne levels of chromium(VI) necessary to cause these effects. Despite these considerations, the study by Lindberg and Hedenstierna (1983) is useful because it indicates concentration-responses of chromium(VI) compounds that cause significant nasal and respiratory effects. The LOAEL of 0.002 mg chromium(VI)/m^3 for respiratory effects in humans was used to calculate an inhalation MRL of 0.000005 mg chromium(VI)/m^3 for intermediate-duration exposure to chromium(VI) as chromium trioxide mists and other dissolved hexavalent chromium aerosols or mists as described in the footnotes in Table 2-1.

Occupational exposure to chromium(VI) and/or chromium(III) in other chromium-related industries has also been associated with respiratory effects. These industries include chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining.

In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were $0.01 mg chromium(VI)/$m^3$, high incidences of nasal septum perforation, septal atrophy and ulcerations, sinusitis, pharyngitis, and bronchitis were found among 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year (Sassi 1956). In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, evaluation for respiratory effects revealed that 63%

had perforations of the nasal septum, 86.6% had chemical rhinitis, 42.3% had chronic chemical pharyngitis, 10.35% had laryngitis, and 12.1% had sinus, nasal, or laryngeal polyps. The number of complaints and clinical signs increased as the exposure to respirable chromium(VI) and chromium(III) compounds increased, but exposure levels at which effects first occurred were not clearly defined (Mancuso 1951). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found that effects on the lungs consisted of bilateral hilar enlargement. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble hexavalent chromium compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m^3) (PHS 1953). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases (Keskinen et al. 1980). In a report of 10 cases of pneumoconiosis in underground workers in chromite mines in South Africa, radiographic analysis revealed fine nodulation and hilar shadows. Chromium in the chromite ore in South Africa was in the form of chromium(III) oxide. The cause of the pneumoconiosis was considered to be deposition of insoluble radio-opaque chromite dust in the tissues, rather than fibrosis (Sluis-Cremer and du Toit 1968). In a case report of a death of a sandblaster in a ferrochromium department of an iron works, the cause of death was silicosis, but autopsy also revealed diffuse enlargement of alveolar septae and chemical interstitial and alveolar chronic pneumonia, which were attributed to inhalation of chromium(III) oxide (Letterer 1939). In an industrial hygiene survey of 60 ferrochromium workers exposed to chromium(III) and chromium(VI) (0.02–0.19 mg total chromium/m^3) conducted in 1975, appreciably higher incidences of subjective symptoms of coughing, wheezing, and dyspnea were reported compared with controls. These workers had been employed at the plant for at least 15 years. The control group consisted of workers employed at the same plant for <5 years. Statistically significant decreased mean forced vital capacity ($p<0.01$) and forced expiratory volume in 1 second ($p<0.05$) were found in the ferrochromium workers compared with controls. Two of the ferrochromium workers had nasal septum perforations, which were attributed to previous exposure to hexavalent chromium. A major limitation of this study is that the control group was significantly younger than the study cohort. In addition, the weekly amount of tobacco smoked by the control group was slightly greater than that smoked by the study groups, and the controls began smoking 5 years earlier than the study groups. Therefore, the increase in subjective respiratory symptoms and decreased pulmonary function parameters cannot unequivocally be attributed to chromium exposure (Langård 1980). However, no increase in the prevalence of respiratory illness was found in a study of 128 workers from two factories that produced chromium(III) oxide or chromium(III)

sulfate (Korallus et al. 1974b) or in 106 workers at a factory that produced these chromium(III) compounds where workroom levels were #1.99 mg chromium(III)/m^3 (Korallus et al. 1974a). Similar results were reported in a cross sectional study that was conducted to determine whether occupational exposure to trivalent chromium or hexavalent chromium caused respiratory diseases, decreases in pulmonary function, or signs of pneumoconiosis in stainless steel production workers (Huvinen et al. 1996). The median personal exposure level for chromium(VI) was 0.0005 µg/m^3 and for chromium(III) was 0.022 µg/m^3; the 221 workers were employed for >8 years with an average potential exposure of 18 years. Spirometry measurements were taken and chest radiographic examinations were conducted. There were no significant differences in the odds ratios between the exposed workers and the 95 workers in the control group. The deficits in lung function shown in both populations could be explained by age and smoking habits.

In many of the studies attributing respiratory effects to chromium exposure, actual levels of chromium(VI) or chromium(III) to which workers were exposed over time were unknown. Furthermore, information on the contribution of cigarette smoking, exposure to other hazardous chemicals, and previous employment histories to the observed effects was often not available. A retrospective mortality and morbidity study of 398 workers who had worked in a chromate production facility in North Carolina for at least 1 year from 1971, when the facility began producing chromates, to 1989 was designed to address these limitations. Personal air monitoring results, which were available for 1974–1989, revealed 8-hour time-weighted average (TWA) concentrations of chromium(VI) ranging from below the detection limit (0.001 mg chromium(VI)/m^3 prior to 1984; 0.0006 mg/m^3 thereafter) to 0.289 mg/m^3, with >99% of the samples measuring <0.05 mg/m^3. Workroom air monitoring data were available for different areas in the plant for the years 1971–1979 and generally ranged from 0.00026 to 0.086 mg chromium(VI)/m^3. Because personal air monitoring data were not available for the years 1971–1973, workroom area levels were used to estimate the personal air levels for these years, which were included in the analysis of personal air levels. Levels of chromium(III) or total chromium were not measured. Forty-five workers also had previous occupational exposure to chromium at other chromate production facilities. Of the 45 workers with previous exposure, 42 had been employed at production facilities either in Painsville, Ohio, or Kearny, New Jersey (the number from each of these facilities and the location of the plants at which the other 3 workers had been employed were not reported). Industrial hygiene monitoring at the Painsville, Ohio plant revealed workroom air levels of 0.05–1.45 mg total chromium/m^3 for production workers and #5.67 mg total chromium/m^3 for maintenance workers (workroom air levels at the other facilities were not reported). For statistical comparisons, workers were classified as having high cumulative exposure and low cumulative exposure. Workers responded to a questionnaire to determine

medical history, smoking history, detailed work history, and exposure to known chemicals and industrial hazards. Of 289 workers who responded to the questionnaire, 40 reported at least 1 occurrence of nasal lesions and 12 of nasal perforations. Statistical analysis revealed no increased risk of the nasal effects associated with high cumulative exposure or duration of previous employment. However, those workers with longer durations of employment at the facility and those who smoked were more likely to report these effects. The authors suggested that workers in areas with higher concentrations might be more likely to apply protective cream to the nasal septum and that smokers might be less likely to wear respiratory protection and gloves. High cumulative exposure was not associated with increased risk of chronic bronchitis, emphysema, shortness of breath, or chronic cough (Pastides et al. 1991).

An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Chest x-rays and pulmonary function tests revealed no significant difference between the exposed and the control populations. The exposed population reported a higher incidence of subjective complaints of nasal irritation than the control population in the early years of the study, but in later years the difference between the two groups became progressively less (Greater Tokyo Bureau of Hygiene 1989).

The respiratory system in animals is also a primary target for inhalation exposure to chromium. Pulmonary fluid from hamsters exposed to 0.9 or 25 mg chromium(III)/m^3 as chromium trichloride for 30 minutes revealed sporadic changes in activities of acid phosphatase and alkaline phosphatase in the lavage fluid at 25 mg chromium(III)/m^3. In the lung tissue, a 75% increase in the acid phosphatase activity was found at 0.9 mg chromium(III)/m^3 and in the β-glucuronidase activity at an unspecified concentration. Histological examination revealed alterations representing mild nonspecific irritation but no morphological damage (Henderson et al. 1979).

Rats exposed to sodium dichromate for 28 or 90 days had increased lung weight but no histopathological abnormalities at concentrations #0.2 mg chromium(VI)/m^3. The percentage of lymphocytes was increased in the bronchoalveolar lavage fluid at $0.025 mg/$m^3$. A decrease in macrophage activity was observed in the 0.2 mg chromium(VI)/m^3 group exposed for 90 days. Clearance of iron oxide from the lungs decreased in rats exposed to 0.2 mg chromium(VI)/m^3 for 42 days prior to and 49 days after challenge with iron oxide particles when compared to controls. The decreased clearance of iron oxide

correlated with the decrease in macrophage activity (Glaser et al. 1985). In a similar but more extensive study, obstructive respiratory dyspnea was observed in rats exposed to sodium dichromate at $0.2 mg chromium(VI)/$m^3$ for 30 or 90 days, and mean lung weight was increased at $0.05 mg chromium(VI)/$m^3$. Slight hyperplasia was observed at high incidence in rats at $0.05 mg chromium(VI)/$m^3$. Lung fibrosis occurred at low incidence in the rats exposed to $0.1 mg chromium(VI)/$m^3$ for 30 days, but not in the 0.05 mg/m^3 or the control groups. The incidence of both these lesions declined after longer exposure, indicating repair. Accumulation of macrophages and inflammation occurred at $0.05 mg chromium(VI)/$m^3$ regardless of duration. Results of bronchoalveolar lavage analysis provided further evidence of an irritation effect that was reversible (Glaser et al. 1990). The data from the Glaser et al. (1990) study was used to develop benchmark concentrations (BMCs) (Malsch et al. 1994). The BMC of 0.016 mg chromium(VI)/m^3 for alterations in lactate dehydrogenase levels in bronchoalveolar lavage fluid was used to calculate an inhalation MRL of 0.001 mg chromium(VI)/m^3 for intermediate-duration exposure to chromium(VI) as particulate hexavalent compounds as described in the footnote of Table 2-1.

In rabbits exposed to 0.6 mg chromium(III)/m^3 as chromium nitrate or 0.9 mg chromium(VI)/m^3 as sodium chromate intermittently for 4–6 weeks, changes in the lungs were confined to the macrophage. Both chromium compounds produced nodular accumulations of macrophages in the lungs. The morphology of the macrophages of treated rabbits demonstrated black inclusions and large lysosomes. These changes represent normal physiological responses of the macrophages to the chromium particle. Phagocytosis and the reduction of nitroblue tetrazolium to formazan was impaired by chromium(III) but not chromium(VI). These effects represent a decrease in the functional and metabolic activity of the macrophage (Johansson et al. 1986a, 1986b). Mice exposed to chromium trioxide mist at concentrations of 1.81 and 3.63 mg chromium(VI)/m^3 intermittently for #12 months developed perforations in the nasal septum, hyperplastic and metaplastic changes in the larynx, trachea, and bronchus, and emphysema (Adachi 1987; Adachi et al. 1986).

Chronic exposure to chromium(VI) compounds and mixtures of chromium(VI) and chromium(III) compounds have also resulted in adverse respiratory effects in animals. Experiments in which rats were exposed to either chromium(VI) alone as sodium dichromate or a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months showed similar loading of macrophages and increases in lung weight. However, histopathology of rats exposed to 0.1 mg/m^3 of chromium(III) and chromium(VI) together revealed interstitial fibrosis and thickening of the septa of the alveolar lumens due to the large accumulation of chromium in the lungs, whereas histopathology of the lungs was normal in rats exposed only to chromium(VI) (Glaser et al. 1986, 1988). Mice exposed to 4.3 mg chromium(VI)/m^3 as calcium

chromate dust intermittently for 18 months had epithelialization of alveoli. Histopathology revealed epithelial necrosis and marked hyperplasia of the large and medium bronchi, with numerous openings in the bronchiolar walls (Nettesheim and Szakal 1972). Significantly increased incidences of pulmonary lesions (lung abscesses, bronchopneumonia, giant cells, and granulomata) were found in rats exposed chronically to a finely ground, mixed chromium roast material that resulted in airborne concentrations of 1.6–2.1 mg chromium(VI)/m^3 compared with controls. In the same study, guinea pigs exposed chronically to the chromium roast material along with mists of potassium dichromate or sodium chromate solutions that also resulted in 1.6–2.1 mg chromium(VI)/m^3 had significantly increased incidences of alveolar and interstitial inflammation, alveolar hyperplasia, and interstitial fibrosis, compared with controls. Similarly, rabbits were also exposed and also had pulmonary lesions similar to those seen in the rats and guinea pigs, but the number of rabbits was too small for meaningful statistical analysis (Steffee and Baetjer 1965).

Therefore, gross and histopathological changes to the respiratory tract resulted from inhalation of chromium(VI) compounds or a combination of chromium(VI) and chromium(III) compounds, but both chromium(VI) and chromium(III) altered the function of macrophages.

In the only study of chromium(IV) exposure, all rats treated with 0.31 or 15.5 mg chromium(IV)/m^3 as chromium dioxide dust for 2 years had discolored mediastinal lymph nodes and lungs, and dust laden macrophages. Lung weight was increased at 12 and 24 months in the 15.5 mg chromium(IV)/m^3 group (Lee et al. 1989). The increased lung weight and macrophage effects probably represent the increased lung burden of chromium dioxide dust and normal physiological responses of macrophages to dust.

Cardiovascular Effects. Information regarding cardiovascular effects in humans after inhalation exposure to chromium and its compounds is limited. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were $0.01 mg chromium(VI)/$m^3$, electrocardiograms were recorded for 22 of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year. No abnormalities were found (Sassi 1956). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found no association between heart disease or effects on blood pressure and exposure to chromates. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m^3) (PHS

1953). No excess deaths were observed from cardiovascular diseases and ischemic heart disease in a cohort of 4,227 stainless steel production workers from 1968 to 1984 when compared to expected deaths based on national rates and matched for age, sex, and calender time (Moulin et al. 1993). No measurements of exposure were provided. In a cohort of 3,408 individuals who had worked in 4 facilities that produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971, where the exposure durations of workers ranged from <1 to >20 years, and no increases in atherosclerotic heart disease were evident (Rosenman and Stanbury 1996). The proportionate mortality ratios for white and black men were 97 (confidence limits 88–107) and 90 (confidence limits 72–111), respectively.

Cardiovascular function was studied in 230 middle-aged workers involved in potassium dichromate production who had clinical manifestations of chromium poisoning (96 with respiratory effects and 134 with gastrointestinal disorders) and in a control group of 70 healthy workers of similar age. Both groups with clinical manifestations had changes in the bioelectric and mechanical activity of the myocardium as determined by electrocardiography, kinetocardiography, rheocardiography, and ballistocardiography. These changes were more pronounced in the workers with respiratory disorders due to chromium exposure than in the workers with chromium-induced gastrointestinal effects. The changes in the myocardium could be secondary to pulmonary effects and/or to a direct effect on the blood vessels and myocardium (Kleiner et al. 1970).

An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Blood pressure determinations revealed no significant difference between the exposed and the control populations (Greater Tokyo Bureau of Hygiene 1989).

No histopathological lesions were found in the hearts of rats exposed chronically to chromium dioxide at 15.5 mg chromium(IV)/m^3 (Lee et al. 1989). Additional information regarding cardiovascular effects in animals after exposure to chromium or chromium compounds was not located.

Gastrointestinal Effects. Gastrointestinal effects have been associated with occupational exposure of humans to chromium compounds. In a report of two cases of acute exposure to "massive amounts" of chromium trioxide fumes, the patients complained of abdominal or substernal pain, but further characterization was not provided (Meyers 1950).

In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, 5 of 11 workers reported symptoms of stomach pain, two of duodenal ulcer, one of gastritis, one of stomach cramps, and one of frequent indigestion. The workers were employed for an average of 7.5 years and were exposed to mean concentrations of 0.004 mg chromium(VI)/m^3 (Lucas and Kramkowski 1975). These workers were not compared to a control group. An otolaryngological examination of 77 employees of 8 chromium electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m^3, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophy of the left larynx (Hanslian et al. 1967). In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, gastrointestinal radiography revealed that 10 of the workers had ulcer formation, and of these, 6 had hypertrophic gastritis. Nearly all of the workers breathed through the mouth while at work and swallowed the chromate dust, thereby directly exposing the gastrointestinal mucosa. Only 2 cases of gastrointestinal ulcer were found in 41 control individuals, who had the same racial, social, and economic characteristics as the chromium-exposed group (Mancuso 1951). In a survey of a facility engaged in chromate production in Italy where exposure concentrations were $0.01 mg chromium(VI)/$m^3$, 15.4% of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year had duodenal ulcers and 9.2% had colitis. The ulcers were considered to be due to exposure to chromium (Sassi 1956). Gastric mucosa irritation leading to duodenal ulcer was found in 21 of 90 workers engaged in the production of chromium salts. Symptoms of gastrointestinal pathology appeared about 3–5 years after the workers' initial contact (Sterekhova et al. 1978). Most of these studies reporting gastrointestinal effects did not compare the workers with appropriate controls. Although the gastrointestinal irritation and ulceration due to exposure to chromium(VI) in air could be due to a direct action of chromium(VI) on the gastrointestinal mucosa from swallowing chromium as a result of mouth breathing (or transfer via hand-to-mouth activity), other factors, such as stress and diet, can also cause gastrointestinal effects. While occupational exposure to chromium(VI) may result in gastrointestinal effects, a lower than expected incidence of death from diseases of the digestive tract was found among a cohort of 2,101 employees who had worked for at least 90 days during the years 1945–1959 in a chromium production plant in Baltimore, Maryland, and were followed until 1977. The rate (O/E=23/36.16, SMR=64) is based on comparison with mortality rates for

Baltimore (Hayes et al. 1979). In contrast to findings with chromium(VI) compounds, no indication was found that exposure to chromium(III) resulted in stomach disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Higher incidences of subjective complaints of diarrhea and constipation were reported by the exposed population than the control population in the early years of the survey, but in later years the difference between the two groups became progressively less. Otolaryngological examinations revealed sporadic significant differences, but the investigators believed that such differences should be observed more consistently to conclude any association with exposure to chromium slag (Greater Tokyo Bureau of Hygiene 1989).

Information regarding gastrointestinal effects in animals after inhalation exposure to chromium or its compounds is limited. Histological examination of the stomachs of rats exposed to sodium dichromate dihydrate at #0.2 mg chromium(VI)/m^3 for 28 or 90 days revealed no abnormalities (Glaser et al. 1985). In mice exposed intermittently to 4.3 mg chromium(VI)/m^3 as calcium chromate for 18 months, small ulcerations in the stomach and intestinal mucosa were reported to occur occasionally, but the incidence in the treated mice, in controls, or other details regarding these lesions were not reported (Nettesheim et al. 1971). No treatment-related histopathological lesions were found in the stomach, large intestine, duodenum, jejunum, or ileum of rats chronically exposed to chromium dioxide at 15.5 mg chromium(IV)/m^3 (Lee et al. 1989).

Hematological Effects. Hematological evaluations of workers occupationally exposed to chromium compounds have yielded equivocal results. Ninety-seven workers from a chromate plant were exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble sodium chromate and dichromate. Hematological evaluations revealed leukocytosis in 14.4% or leukopenia in 19.6% of the workers. The leukocytosis appeared to be related primarily to monocytosis and eosinophilia, but controls had slight increases in monocytes and occasional increases in eosinophils without leukocytosis. Decreases in hemoglobin concentrations and slight increases in bleeding time were also observed (Mancuso 1951). Whether these hematological findings were significantly different from those seen in controls was not stated, but the effects were attributed to chromium exposure. In a survey of a facility

engaged in chromate production in Italy where exposure concentrations were $0.01 mg chromium(VI)/$m^3$, hematological evaluation of workers who worked in the production of dichromate and chromium trioxide for at least 1 year were unremarkable or inconclusive (Sassi 1956). In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, hematological evaluations revealed no effects on red blood cell counts, hemoglobin, hematocrit, or white blood cell counts. The sedimentation rate of red cells was higher than that of controls, but the difference was not statistically significant. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m^3) (PHS 1953). Likewise, no effects on red blood cell counts, white blood cell counts, hemoglobin levels, or sedimentation rate were found in a case control study of 17 male manual metal arc stainless steel welders from six industries with mean occupational durations of 20 years (Littorin et al. 1984). No hematological disorders were found among 106 workers in a chromium(III) producing plant where workroom levels were #1.99 mg chromium(III)/m^3 as chromium(III) oxide and chromium(III) sulfate (Korallus et al. 1974a).

Results from hematological evaluations in rats were also equivocal. Hematological evaluations of rats exposed to sodium dichromate at 0.025–0.2 mg chromium(VI)/m^3 for 28 or 90 days or 0.1 mg chromium(VI)/m^3 for 18 months were unremarkable (Glaser et al. 1985, 1986, 1988). However, increased white blood cell counts were found in rats exposed to $0.1 mg chromium(VI)/$m^3$ as sodium dichromate for 30 days and at $0.05 mg chromium(VI)/$m^3$ for 90 days. The white blood cell counts were not increased 30 days postexposure (Glaser et al. 1990). Rats exposed to 0.1 mg chromium/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months had increased red and white blood cell counts, hemoglobin content, and hematocrit (Glaser et al. 1986, 1988).

No changes in hematological parameters were observed in rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989).

Musculoskeletal Effects. No musculoskeletal effects have been reported in either humans or animals after inhalation exposure to chromium.

Hepatic Effects. Chromium(VI) has been reported to cause severe liver effects in four of five workers exposed to chromium trioxide in the chrome plating industry. Derangement of the cells in the liver, necrosis, lymphocytic and histiocytic infiltration, and increases in Kupffer cells were reported. Abnormalities in tests for hepatic dysfunction included increases in sulfobromophthalein retention, gamma globulin, icterus, cephalin cholesterol flocculation, and thymol turbidity (Pascale et al. 1952). In a cohort of 4,227 workers involved in production of stainless steel from 1968 to 1984, excess deaths were observed from cirrhosis of the liver compared to expected deaths (O/E=55/31.6) based on national rates and matched for age, sex, and calender time having an SMR of 174 with confidence limits of 131–226 (Moulin et al. 1993). No measurements of exposure were provided. Based on limited information, however, the production of chromium compounds does not appear to be associated with liver effects. As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds (84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of liver function tests 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981). In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were $0.01 mg chromium(VI)/$m^3$, 15 of 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year had hepatobiliary disorders. When the workers were given liver function tests, slight impairment was found in a few cases. These disorders could have been due to a variety of factors, especially heavy alcohol use (Sassi 1956). No indication was found that exposure to chromium(III) resulted in liver disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Results of clinical chemistry tests for liver function revealed no significant differences between the exposed and the control populations (Greater Tokyo Bureau of Hygiene 1989).

The hepatic effects observed in animals after inhalation exposure to chromium or its compounds were minimal and not considered to be adverse. Rats exposed to as much as 0.4 mg chromium(VI)/m^3 as sodium dichromate for #90 days did not have increased serum levels of alanine aminotransferase or alkaline phosphatase, cholesterol, creatinine, urea, or bilirubin (Glaser et al. 1990). Triglycerides and

phospholipids were increased only in the 0.2 mg chromium(VI)/m^3 group exposed for 90 days (Glaser et al. 1985). Chronic exposure of rats to 0.1 mg chromium(VI)/m^3 as sodium dichromate, to 0.1 mg total chromium/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide, or to 15.5 mg chromium(IV)/m^3 as chromium dioxide did not cause adverse hepatic effects as assessed by histological examination and liver function tests (Glaser et al. 1986, 1988; Lee et al. 1989).

Renal Effects. No increases in genital/urinary disease were evident in a cohort of 3,408 workers from 4 former facilities that produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971. The proportionate mortality ratios for white and black men were 71 (40–117) and 47 (15–111), respectively. Exposure durations ranged from less <1 year to >20 years (Rosenman and Stanbury 1996).

Renal function has been studied in workers engaged in chromate and dichromate production, in chrome platers, in stainless steel welders, in workers employed in ferrochromium production, in boilermakers, and in workers in an alloy steel plant. Workers exposed to chromium(VI) compounds in a chromate production plant were found to have higher levels of a brush border protein antigen and retinol binding protein in the urine compared with controls (Mutti et al. 1985a). A similar study was conducted in 43 male workers in the chromate and dichromate production industry, where occupational exposures were between 0.05 and 1.0 mg chromium(VI)/m^3 as chromium trioxide, and mean employment duration was 7 years. Workers with >15 µg chromium/g creatinine in the urine had increased levels of retinol binding protein and tubular antigens in the urine (Franchini and Mutti 1988). These investigators believe that the presence of low molecular weight proteins like retinol binding protein or antigens in the urine are believed to be early indicators of kidney damage. In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, analysis of the urine revealed a higher frequency of white blood cell and red blood cell casts than is usually found in an industrial population (statistical significance not reported). Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3]; water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m^3) (PHS 1953).

Some studies of renal function in chromate production workers found negative or equivocal results. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were $0.01 mg chromium(VI)/$m^3$, results of periodic urinalyses of workers who worked in the production of

dichromate and chromium trioxide for at least 1 year were generally unremarkable, with the exception of one case of occasional albuminuria and a few cases of slight urobilinuria (Sassi 1956). As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds (84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of kidney function tests (not further characterized) 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981).

Studies of renal function in chrome platers, whose exposure is mainly to chromium(VI) compounds, have also yielded equivocal results. A positive dose-response for elevated urinary levels of β_2-microglobulin was found in chrome platers who were exposed to 0.004 mg chromium(VI)/m^3, measured by personal air samplers, for a mean of 5.3 years. However, since no increase in β_2-microglobulin levels was found in ex-chrome platers who had worked for at least one year in an old chrome plating plant from 1940 to 1968, this effect may be reversible (Lindberg and Vesterberg 1983b). Liu et al. (1998) similarly found significantly higher urinary β_2-microglobulin and N-acetyl-β-glucosaminidase levels in hard-chrome electroplaters exposed to 0.0042 mg chromium/m^3 for a mean of 5.8 years, as compared to aluminum anode-oxidation workers. The prevalence of elevated levels (higher than reference values) was significantly increased for N-acetyl-β-glucosaminidase, but not for β_2-microglobulin. In another study, comparison of results of renal function tests between chrome platers and construction workers revealed that the chrome platers had significantly ($p<0.001$) increased levels of urinary chromium and increased clearance of chromium, but decreased ($p<0.05$) levels of retinol binding protein. However, no differences were found for blood urea nitrogen, serum and urinary β_2-microglobulin, serum immunoglobulin, total protein in the urine, urinary albumin, N-acetyl-β-D-glucosamidase, β-galactosidase, or lysozyme (Verschoor et al. 1988).

Studies of renal function in stainless steel welders, whose exposure is mainly to chromium(VI) compounds, were negative. Stainless steel welders had significantly increased ($p<0.001$) levels of urinary chromium, increased clearance of chromium, and increased serum creatinine compared with controls, but no differences were found in the levels of retinol binding protein, β_2-microglobulin or other indices of kidney damage (Verschoor et al. 1988). Similar negative results were found in another group of stainless steel welders (Littorin et al. 1984).

Occupational exposure to chromium(III) or chromium(0) does not appear to be associated with renal effects. No renal impairment based on urinary albumin, retinol binding protein, and renal tubular antigens was found in 236 workers employed in the ferrochromium production industry where

ferrochromite is reduced with coke, bauxite, and quartzite. The mean airborne concentration of chromium in various sample locations was 0.075 mg chromium(III)/m^3; chromium(VI) was below the detection limit of 0.001 mg chromium(VI)/m^3 at all locations (Foa et al. 1988). Workers employed in an alloy steel plant with a mean exposure of 7 years to metallic chromium at 0.61 mg chromium(0)/m^3 and to other metals had normal urinary levels of total protein and β_2-microglobulin, enzyme activities of alanine-aminopeptidase, N-acetyl-β-D-glucosaminidase, gammaglutamyl-transpeptidase, and β-galactosidase (Triebig et al. 1987). In boilermakers exposed to chromium(0), no increase in urinary levels of chromium, and no differences in the levels of retinol binding protein, β_2-microglobulin, or other indices of renal toxicity were found (Verschoor et al. 1988).

In a group of 30 men and 25 women who were lifetime residents of an area in northern New Jersey contaminated with chromium landfill, signs of preclinical renal damage were assessed by examining the urinary levels of four proteins, intestinal alkaline phophatase, tissue nonspecific alkaline phosphatase, N-acetyl-β-D-glucosaminidase, and microalbumin (Wedeen et al. 1996). The mean urinary chromium concentration for the women was 0.2±0.1 μg/g creatinine, and for the men was 0.3 μg/g. None of the four proteins exceeded normal urinary levels in either men or women. The authors concluded that long-term environmental exposure to chromium dust did not lead to tubular proteinurea or signs of preclinical renal damage.

An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Results of urinalysis revealed no significant differences between the exposed and the control populations (Greater Tokyo Bureau of Hygiene 1989).

Exposure of rats to sodium dichromate at #0.4 mg chromium(VI)/m^3 for #90 days did not cause abnormalities, as indicated by histopathological examination of the kidneys. Serum levels of creatinine and urea and urine levels of protein were also normal (Glaser et al. 1985, 1990). Furthermore, no renal effects were observed in rats exposed to 0.1 mg chromium/m^3 as sodium dichromate (chromium(VI)) or as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months, based on histological examination of the kidneys, urinalysis, and blood chemistry (Glaser et al. 1986, 1988). Rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years showed no histological evidence of kidney

damage or impairment of kidney function, as measured by routine urinalysis. Serum levels of blood urea nitrogen, creatinine, and bilirubin were also normal (Lee et al. 1989).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to chromium(VI) or (III) compounds. Male rats exposed 22 hours/day for 18 months to 0.1 mg chromium(VI)/m^3 as sodium dichromate or exposed to a mixture of chromium(VI) and chromium(III) (0.06 mg chromium(VI)/m^3 plus 0.04 mg chromium(III)/m^3) as chromium(VI) trioxide and chromium(III) oxide did not result in any histopathological changes in adrenal glands (Glaser et al. 1986, 1988). Rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years showed no histopathological abnormalities in adrenals, pancreas, and thyroid glands (Lee et al. 1989).

Dermal Effects. Acute systemic and dermal allergic reactions have been observed in chromium-sensitive individuals exposed to chromium via inhalation as described in Sections 2.2.3.2 and 2.2.3.3.

No studies were located regarding systemic dermal effects in animals after inhalation exposure to chromium(VI) or chromium(III) compounds.

Ocular Effects. Effects on the eyes due to direct contact of the eyes with airborne mists, dusts, or aerosols or chromium compounds are described in Section 2.2.3.2. An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Higher incidences of subjective complaints of eye irritation were reported by the exposed population than the control population in the early years of the survey, but in later years the difference between the two groups became progressively less (Greater Tokyo Bureau of Hygiene 1989).

No studies were located regarding systemic ocular effects in animals after inhalation exposure to chromium(III) compounds.

Histopathologic examination of rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years revealed normal morphology of the ocular tissue (Lee et al. 1989).

Body Weight Effects. In a report of a case of acute exposure to "massive amounts" of chromium trioxide fumes, the patient became anorexic and lost 20–25 pounds during a 3-month period following exposure (Meyers 1950).

In rats exposed to an aerosol of sodium dichromate for 30 or 90 days or for 90 days followed by an additional 30 days of nonexposure, body weight gain was significantly decreased at 0.2 and 0.4 mg chromium(VI)/m^3 for 30 days ($p<0.001$), at 0.4 mg chromium(VI)/m^3 for 90 days ($p<0.05$), and at 0.2 ($p<0.01$) and 0.4 mg chromium(VI)/m^3 ($p<0.05$) in the recovery group (Glaser et al. 1990). There was no effect on body weight gain in rats exposed for 28 days to 0.2 mg/m^3 (Glaser et al. 1985) or for #18 months to 0.1 mg chromium(VI)/m^3 as sodium dichromate (Glaser et al. 1986, 1988, 1990) or 0.1 mg chromium(III and VI)/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988). Similarly, there was no effect on body weight gain in rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989).

2.2.1.3 Immunological and Lymphoreticular Effects

Acute reactions have been observed in chromium sensitive individuals exposed to chromium via inhalation as noted in several individual case reports. A 29-year-old welder exposed to chromium vapors from chromium trioxide baths and to chromium and nickel fumes from steel welding for 10 years complained of frequent skin eruptions, dyspnea, and chest tightness. Chromium sensitivity in the individual was measured by a sequence of exposures, via nebulizer, to chromium(VI) as sodium chromate. Exposure to 0.029 mg chromium(VI)/mL as sodium chromate caused an anaphylactoid reaction, characterized by dermatitis, facial angioedema, bronchospasms accompanied by a tripling of plasma histamine levels, and urticaria (Moller et al. 1986). Similar anaphylactoid reactions were observed in five individuals who had a history of contact dermatitis to chromium, after exposure, via nebulizer, to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. Exposure resulted in decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, nasal blocking, cough, and wheezing (Olaguibel and Basomba 1989). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases produced by the welding process (Keskinen et al. 1980). A 28-year-old construction worker developed work-related symptoms of asthma which worsened during periods when he was working with (and sawing) corrugated fiber cement containing chromium. A skin patch test to chromium was negative. Asthmatic responses were elicited upon inhalation challenge with fiber cement dust or nebulized potassium chromate (Leroyer et al. 1998).

Chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low, and the number of potentially confounding variables in the chromium industry is high.

Concentrations of some lymphocyte subpopulations (CD4+ helper-inducer, CD5--CD19+ B, CD3--CD25+ activated B, and CD3--HLA-DR+ activated B and natural killer lymphocytes) were significantly reduced (about 30–50%) in a group of 15 men occupationally exposed to dust containing several compounds (including hexavalent chromium as lead chromate) in a plastics factory. Worker blood lead and urine chromium levels were significantly higher than those of 15 controls not known to be occupationally exposed to toxic agents. Serum chromium concentrations and serum immunoglobulins IgA, IgG, and IgM were not significantly different between the two groups (Boscolo et al. 1997). These results are difficult to interpret due to concomitant exposure to a number of other chemicals.

An animal study was designed to examine the immunotoxic effects of soluble and insoluble hexavalent chromium agents released during welding (Cohen et al. 1998). Rats exposed to atmospheres containing soluble potassium chromate at 0.36 mg chromium(VI)/m^3 for 5 hours/day, 5 days/week for 2 or 4 weeks had significantly increased levels of neutrophils and monocytes and decreased alveolar macrophages in bronchoalveolar lavage than air-exposed controls. Significantly increased levels of total recoverable cells were noted at 2 (but not 4) weeks of exposure. In contrast, no alterations in the types of cells recovered from the bronchoalveolar lavage fluid were observed in rats exposed to 0.36 mg chromium(VI)/m^3 as insoluble barium chromate, as compared to controls. However, the cell types recovered did differ from those recovered from rats exposed to soluble chromium. Changes seen in pulmonary macrophage functionality varied between the soluble and insoluble chromium(VI) exposure groups. The production of interleukin (IL)-1 and tumor necrosis factor (TNF)-α cytokines were reduced in the potassium chromate exposed rats; only TNF-α was decreased in the barium chromate rats. IL-6 levels were not significantly altered in either group. Barium chromate affected zymosan-inducible reactive oxygen intermediate formation and nitric oxide production to a greater degree than soluble chromium(VI). Insoluble chromium(VI) reduced the production of superoxide anion, hydrogen perodise, and nitric oxide; soluble chromium(VI) only reduced nitric oxide production.

Rats exposed to 0.025–0.2 mg chromium(VI)/m^3 as sodium dichromate for 28 or 90 days had increased spleen weights at $0.05 mg chromium(VI)/$m^3$ and increased response to sheep red blood cells at $0.025 mg chromium(VI)/$m^3$. In the 90-day study, serum immunoglobulin content was increased in the 0.05 and 0.1 mg chromium(VI)/m^3 groups but not in the 0.2 mg chromium(VI)/m^3 group. There was an

increase in mitogen-stimulated T-cell response in the group exposed for 90 days to 0.2 mg chromium(VI)/m^3. Bronchial alveolar lavage fluid had an increased percentage of lymphocytes in the groups exposed to 0.025 and 0.05 mg chromium(VI)/m^3 and an increased percentage of granulocytes in the groups exposed to 0.05 mg chromium(VI)/m^3 for 28 days. The phagocytic activity of macrophages was increased in the 0.05 mg chromium(VI)/m^3 group. A higher number of macrophages in telophase was observed in the 0.025 and 0.05 mg chromium(VI)/m^3 groups. Bronchial alveolar lavage fluid from rats exposed for 90 days had an increased percentage of lymphocytes in the 0.025, 0.05, and 0.2 mg chromium(VI)/m^3 groups and an increased percentage of granulocytes and number of macrophages in the 0.05 mg chromium(VI)/m^3 groups. The phagocytic activity of the macrophages was increased in the 0.025 mg and 0.05 mg chromium(VI)/m^3 groups and decreased in the 0.2 mg chromium(VI)/m^3 group. A greater number of macrophages in telophase and an increase in their diameter were observed in the 0.025, 0.05, and 0.2 mg chromium(VI)/m^3 groups (Glaser et al. 1985).

Low-level exposure to sodium dichromate seems to stimulate the humoral immune system (as evidenced by the significant increase in total immunoglobin levels); exposure to 0.2 mg chromium(VI)/m^3 ceases to stimulate the humoral immune system (significant decreases in total immunoglobin levels) but still may have effects on the T lymphocytes. The depression in macrophage cell count and phagocytic activities correlated with a 4-fold lower rate of lung clearance for inhaled iron oxide in the 0.2 mg chromium(VI)/m^3 group (Glaser et al. 1985). The LOAELs for immunological effects in rats are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of dizziness, headache, and weakness when they were working over the chromate tanks (Lieberman 1941). Such poor working conditions are unlikely to still occur in the United States because improvements in industrial hygiene have been made over the years.

No increases in vascular lesions in the central nervous system were evident in a cohort of 3,408 workers from 4 former facilities that produced chromium compounds from chromite ore in northern New Jersey (Rosenman and Stanbury 1996). The proportionate mortality ratios for white and black men were 78 (61–98) and 68 (44–101), respectively. The subjects were known to have worked in the four facilities sometime between 1937 and 1971 when the last facility closed. Exposure durations ranged from <1 to >20 years.

An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Higher incidences of subjective complaints of headache, tiredness, and light headedness were reported by the exposed population than the control population in the early years of the survey, but in later years the difference between the two groups became progressively less (Greater Tokyo Bureau of Hygiene 1989).

No information was located regarding neurological effects in humans or animals after inhalation exposure to chromium(III) compounds or in animals after inhalation exposure to chromium(VI) compounds. No histopathological lesions were found in the brain, spinal cord, or nerve tissues of rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989). No neurological or behavioral tests were conducted.

2.2.1.5 Reproductive Effects

Information regarding reproductive effects in humans after inhalation to chromium compounds is limited. The effect of chromium(VI) on the course of pregnancy and childbirth was studied in women employees at a dichromate manufacturing facility in Russia. Complications during pregnancy and childbirth (not further described) were reported in 20 of 26 exposed women who had high levels of chromium in blood and urine, compared with 6 of 20 women in the control group. Toxicosis (not further described) was reported in 12 exposed women and 4 controls. Postnatal hemorrhage occurred in four exposed and two control women (Shmitova 1980). Similar results were reported in a more extensive study of 407 women who worked at a factory producing chromium compounds (not otherwise specified) compared with 323 controls. The frequency of birth complications was 71.4% in a subgroup of highly exposed women, 77.4% in a subgroup of women with a lower level of exposure, and 44.2% in controls. Toxicosis in the first half of pregnancy occurred in 35.1% of the high exposure group, 33.3% of the low exposure group, and 13.6% of the controls. The frequency of post-natal hemorrhage was 19.0% for the high exposure group and 5.2% in controls (Shmitova 1978). Because these studies were generally of poor quality and results were poorly reported, no conclusions can be made regarding the potential for chromium to produce reproductive effects in humans.

The occurrence of spontaneous abortion among 2,520 pregnancies of spouses of 1,715 married Danish metal workers exposed to hexavalent chromium from 1977 through 1987 were examined (Hjollund et al. 1995). Occupational histories were collected from questionnaires and information on spontaneous abortion, live births, and induced abortion was obtained from national medical registers. The number of spontaneous abortions was not increased for pregnant women whose spouses worked in the stainless steel welding industry when compared to controls (odds ratio 0.78, 95% confidence interval 0.55–1.1). The authors believed the risk estimate was robust enough that factors such as maternal age and parity and smoking and alcohol consumptions were not confounders. There was no association found in spontaneous abortions in women whose husbands were in the cohort subpopulations who were mild steel welders and metal-arc stainless steel welders, which would lead to higher exposures to welding fumes (workplace chromium exposures not provided). This more recent study does not corroborate earlier findings (Bonde et al. 1992) which showed wives of stainless steel welders were at higher risk of spontaneous abortions. The current study was based on abortions recorded in a hospital register, while the earlier study was based on self-reporting data. The latter study probably included more early abortions and was biased because the job exposure of male metal workers is apparently modified by the outcome of their partners' first pregnancy.

Histopathological examination of the testes of rats exposed to 0.2 mg chromium(VI)/m^3 as sodium dichromate for 28 or 90 days (Glaser et al. 1985), to 0.1 mg chromium(VI)/m^3 as sodium dichromate for 18 months, or to 0.1 mg chromium/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988) revealed no abnormalities. No effects on reproduction were found in rats exposed to 0.2 mg chromium(VI)/m^3 as sodium dichromate for three generations (Glaser et al. 1984). Similarly, no histopathological lesions were observed in the prostate, seminal vesicle, testes, or epididymis of male rats or in the uterus, mammary gland, or ovaries of female rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years (Lee et al. 1989). No studies were available that examined reproductive outcome in animals after exposure to chromium(IV).

2.2.1.6 Developmental Effects

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

No developmental effects were found in rats exposed to 0.2 mg chromium(VI)/m^3 as sodium dichromate for three generations (Glaser et al. 1984).

2.2.1.7 Genotoxic Effects

Several studies were located that investigate the genotoxic effects of chromium exposure on workers in chromium contaminated atmospheres. An epidemiology study of stainless steel welders, with mean exposure levels of 0.055 mg chromium(VI)/m^3 or 0.081 mg chromium (total)/m^3, did not report increases in the number of sister chromatid exchanges in the lymphocytes of exposed workers. The welders were also exposed to nickel and molybdenum from the welding rods (Littorin et al. 1983). A similar study was conducted to detect genotoxic effects of chromium(VI) on workers in electroplating factories. Of the 24 workers examined, none showed significant differences in sister chromatid exchange frequency (Nagaya 1986). Similarly, no correlation was found between excretion of chromium in the urine and the frequency of sister chromatid exchanges in 12 male chromium platers whose mean urinary chromium level was 17.9 µg/g creatinine (Nagaya et al. 1991). No increase in chromosomal aberrations was observed in 17 tannery workers exposed primarily to chromium(III) as compared with 13 controls (Hamamy et al. 1987). However, parallel measurements in these tannery workers showed that the average chromium levels in plasma (0.115 µg/L) and in urine (0.14 µg/100 L) did not differ from the nonexposed workers. In addition, stainless steel welders occupationally exposed to chromium(VI) for a mean of 21 years did not have any increase in chromosomal aberrations or sister chromatid exchanges compared to a control group. No actual exposure levels were provided (Husgafvel-Pursiainen et al. 1982). Yet, other studies involving electroplaters and welders report a higher incidence of chromosomal aberrations or sister chromatid exchanges in lymphocytes of workers than in controls. In one study, a causal relationship between chromium exposure and the observed effects could not be established because the exposure was confounded by co-exposure to nickel and manganese (Elias et al. 1989a). In another study, although chromium workers were found to have higher rates of sister chromatid exchanges than workers exposed to nickel-chromium or controls (after adjusting for potential confounding factors), the differences were not significantly correlated to chromium concentrations in blood or urine (Lai et al. 1998). The frequency of sister chromatid exchanges in the lymphocytes of 12 workers exposed to chromium(VI) as chromic acid fumes in a chrome plating industry was significantly increased (Stella et al. 1982). Significantly increased incidences of chromosomal aberrations in peripheral lymphocytes were found in workers exposed to chromium(VI) as chromium trioxide in two of four electroplating plants. Of the two plants where the increases were significant, one was a "bright" plating plant, where exposure involved nickel as well as chromium, and one was a "hard" plating plant, where exposure involved only chromium. However, the increase in chromosomal aberrations correlated poorly with urinary chromium levels, and only the increase in the "bright" platers showed a significant correlation with duration of exposure. A significantly increased incidence of sister chromatid exchanges was found in "hard" platers compared

with controls (sister chromatid exchange was not evaluated in "bright" platers), and smoking appeared to enhance the increase (7 of 8 smokers and 7 of 11 nonsmokers had incidences significantly higher than controls). Moreover, the increased incidence of sister chromatid exchange showed a positive correlation with urinary chromium levels (Sarto et al. 1982). Repeated cytogenetic analysis of peripheral lymphocytes for 3 years revealed an increased frequency of chromosomal aberrations and sister chromatid exchanges in a group of stainless steel welders compared to controls. The workers were exposed to unreported chromium(VI) concentrations for a mean of 12.1 years, but exposure to ultraviolet rays and small amounts of manganese, nickel, iron, and magnesium could not be ruled out (Koshi et al. 1984). Compared to 39 controls, significantly elevated sister chromatid exchange values in lymphocytes and significantly higher rates of DNA single-strand breakages were found in a group of 39 welders exposed to unreported chromium(VI) and nickel concentrations (Werfel et al. 1998). Only one study was located regarding the average levels of exposure for electroplating workers: workers exposed to an average level of 0.008 mg chromium(VI)/m^3 had increases in chromosomal aberrations and sister chromatid exchanges. However, high levels of nickel as well as chromium were found in hair and stool samples when compared to controls (Deng et al. 1988). Thus, although most studies gave negative or equivocal results, chromium and its compounds, particularly chromium(VI), may cause chromosomal effects in exposed workers, indicating carcinogenic potential because interactions with DNA have been linked with the mechanism of carcinogenicity.

No elevated levels of DNA strand breaks or hydroxylation of deoxyguanosine in lymphocytes were found in 10 workers occupationally exposed in the production of bichromate when compared with 10 non-occupationally-exposed workers at the same facility Gao et al. (1994). From general background monitoring levels of chromium(VI), exposures were estimated to be between 0.001 and 0.055 mg/m^3.

Information regarding genotoxic effects in animals after inhalation exposure to chromium or its compounds is limited. Sprague-Dawley rats that inhaled chromium fumes generated from powders of chromium metal by a plasma flame thrower at 1.84 or 0.55 mg chromium(0)/m^3 (5 hours/day, 5 days/week) for 1 week or 2 months, respectively, had increased frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes, but not in bone marrow cells (Koshi et al. 1987). Some oxidation of metallic chromium may have occurred in the process of generating the chromium fumes (IARC 1990).

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Occupational exposure to chromium(VI) compounds in a number of industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, ferrochromium alloy production, and leather tanning. Studies of chromate production workers, who are exposed to a variety of chromium compounds both hexavalent and trivalent, and chromate pigment industries, where exposure is mainly to chromium(VI), have consistently demonstrated an association with respiratory system cancer. Studies in chrome platers, who are exposed to chromium(VI) and other agents, including nickel, generally support the conclusion that certain chromium(VI) compounds are carcinogenic. Studies in stainless steel welders exposed to chromium(VI) and other chemicals, and in ferrochromium alloy workers, who are exposed mainly to chromium(0) and chromium(III), but also to some chromium(VI), were inconclusive. Studies in leather tanners, who are exposed to chromium(III), were consistently negative.

Chromate Production. The first epidemiology study of chromate production workers in the United States that demonstrated an association with lung cancer was conducted with 1,445 workers in seven plants engaged in the extraction of chromates from ore from 1930 to 1947. The mortality rates and causes of deaths for 193 chromate production workers were compared with 733 deaths in industrial workers not exposed to chromates. A total of 42 deaths from cancer of the respiratory system was found in the exposed group, which represented 21.8% of all deaths and 63.6% of all deaths from cancer. In the control group, 10 deaths from cancer of the respiratory system were found representing 1.4% of all deaths and 8.7% of deaths from all cancers (Machle and Gregorius 1948). Although this study was limited by inadequate description of the cohort, relatively few deaths, and generally poor reporting, the results prompted an extensive study of workroom conditions and worker health in the same chromate producing plants. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m^3). The mortality experience of employees of the plants was compared with the expected numbers based on the average death rate for the United States for 1940–1948. The SMR for all causes of death other than cancer was 116, which was not significant. However, for all deaths from cancer of the respiratory system, exclusive of the larynx, the O/E was 26/0.9, giving an SMR of 2,889 ($p<0.001$). The cohort in this study consisted of workers with membership in a sick-benefit association and did not

include terminated employees, retirees, or individuals who died more than 1 year after the diagnosis of cancer. However, whether these exclusions would result in an overestimation or an underestimation of the risk is not known. In addition to the cases of lung cancer deaths, 10 cases of bronchogenic carcinoma were diagnosed among 897 living men who worked in the plants for an average of 22.8 years (PHS 1953). A high rate of respiratory cancer was found in a cohort of 1,212 male workers who were employed for at least 3 months in any of three chromate plants in the United States during a 4-year period from 1937 to 1940 and followed until 1960 (O/E=71/8.344, SMR=850.9). The expected death rate was determined from U.S. male rates. For the period of 1937–1960, the following values were found for respiratory cancer (Taylor 1966). The increased risk of death from respiratory cancer correlated with duration of employment in chromate production, but no information on exposure levels, smoking habits, or exposure to other chemicals was provided. A reanalysis of these data several years later found an even higher SMR for respiratory cancer (O/E=69/7.3, SMR=942.6) (Enterline 1974).

Examination of records at a hospital in Baltimore, Maryland, revealed that of 290 male lung cancer patients admitted between 1925 and 1948, 11 had been exposed to chromates and 10 had worked in a local chromate producing plant. No indication of chromate exposure was found in the referent group of 725 patients admitted for other causes (Baetjer 1950b). In a cohort of 2,101 employees who had worked for at least 90 days during the years 1945–1959 in the same chromium production plant in Baltimore, Maryland, and followed until 1977, there were 59 deaths from lung cancer compared with 29.16 expected based on the mortality rates for Baltimore. The SMR of 202 was significant ($p<0.01$). Long-term ($3 years) employees had a higher risk than short-term (90 days to 2 years) employees (Hayes et al. 1979). In a separate analysis by OSHA, concurrent exposure data for the Baltimore plant in this study were determined from monitoring records for the years of the study (1945–1959), and the usual concentration was estimated to be 0.413 mg chromium(VI)/m^3 for the years 1945–1949. Too few data were available for later years to estimate usual exposures. However, cumulative exposures were estimated to be 0.670 mg chromium(VI)/m^3-years for short-term employees and 3.647 mg chromium(VI)/m^3-years for long-term employees (Braver et al. 1985). The authors of this analysis acknowledged uncertainties in these estimates. Furthermore, reliable smoking data were not available for the cohort, but it was considered unlikely that cigarette smoking alone could account for the increased risk, or that the smoking habits of the cohort differed from that of the comparison population (Braver et al. 1985; Hayes et al. 1979). Using a statistical method called "probability window analysis," a review of all known cases of lung cancer in the chromium production plant in Baltimore, Maryland during the period of 1929–1977 revealed a decreasing trend in the incidence of lung cancer that correlated with

major process, and hence exposure, improvements made in the plant in 1951 and 1961 (Hill and Ferguson 1979).

Among 33 deaths of workers at a chromate production plant in Ohio between 1931 and 1949, 6 of the 33 deaths or 18.2% were due to respiratory cancer compared with 1.2% lung cancer deaths among residents of the county in which the plant was located. For each of the six cases of lung cancer, the concentrations of chromium(III) from insoluble chromite ore and chromium(VI) from soluble sodium chromate and dichromate were estimated to range from 0.10 to 0.58 mg chromium(III)/m^3 and from 0.01 to 0.15 mg chromium(VI)/m^3 (Mancuso and Hueper 1951). Details of cohort size and completeness of follow-up were not provided. In a follow-up at this plant, a cohort of 332 men employed for at least 1 year from 1931 to 1937 was followed to 1974. There were 173 deaths, 66 of which were due to cancer of any type. Of these, 41 cancer deaths were due to lung cancer. Although not compared to a control group, mortality from lung cancer correlated with cumulative exposure to $0.25 mg chromium(III)/$m^3$-years, <0.2 to $2.0 mg chromium(VI)/$m^3$-years, and <0.50 to $6.0 mg total chromium/$m^3$-years (Mancuso 1975).

In an update of this cohort, the 332 employees were followed to 1993 and 283 deaths were identified (Mancuso 1997a). The present study includes 66 lung cancer deaths, 25 more than in the 1975 study. The 66 lung cancer deaths constituted 23.3% of all deaths in the cohort and 64.7% of all cancer deaths. The age-adjusted lung cancer death rates per 100,000 increased with respect to increases in both insoluble chromium(III) and soluble chromium(VI) exposure gradients from 0.25 to greater than 4 mg/m^3. For insoluble chromium, the age-adjusted death rate was 187.9/100,000 and 1,045.5/100,000 at insoluble-chromium exposure levels of 0.25–0.49 mg/m^3 and greater than 6 mg/m^3, respectively. For soluble chromium the age-adjusted death rates were 503.7/100,000 and 2,848.3/100,000 at exposure levels of 0.25–0.49 mg/m^3 and greater than 4 mg/m^3, respectively. Since the lung cancer death rates appeared to be related to both insoluble and soluble forms of chromium, the study author concluded that increased lung cancer cannot be contributed solely to one form of chromium compound, but involves both chromium(III) and (VI). This conclusion has been criticized primarily because the industrial hygiene study conducted in 1949 used measured concentrations of insoluble and soluble chromium compounds as surrogates for chromium(III) and chromium(VI) compounds, respectively. The use of surrogates introduces the potential for misclassification of exposure to trivalent or hexavalent chromium (Kimbrough et al. 1999; Mundt and Dell 1997). Mancuso (1997a) assumed that chromium(III) compounds are insoluble and chromium(VI) compounds are soluble, but did not consider that there are insoluble chromium(VI) compounds. Thus, he attributed the increased cancer risk in the insoluble group to exposure to chromium(III).

A cohort of 3,408 workers from four former facilities that produced chromium compounds from chromite ore in northern New Jersey was assembled in 1990–1991 using social security records (Rosenman and Stanbury 1996). The subjects were known to have worked in the four facilities sometime between 1937 and 1971, when the last facility closed. Exposure durations ranged from less than 1 year to greater than 20 years. The overall risk of lung cancer derived from proportionate cancer mortality ratios (PCMR) was 1.51 for white males and 1.34 for black males. The risk increased with duration of employment and latency since time of first employment. The cancer mortality ratio for greater than 20 years of workplace exposure and greater than 20 years since first exposure was 194 and 308 for white and black males, respectively. This study also showed significantly increased risk for nasal cavity/sinus cancer indicated by a PCMR of 518 which has not been observed in previous studies in the United States. A cluster of bladder cancer was seen at one facility among black workers with a PCMR of 330.

The risk of lung cancer in chromate production workers has also been studied in the United Kingdom. The finding of two cases of lung cancer, diagnosed through a radiographic survey, among 786 workers employed in three chromate producing factories in 1948–1949 (Bidstrup 1951) prompted a follow-up at these factories in 1955. In this follow-up, 12 of 59 deaths that occurred from 1949–1958 were due to lung cancer. Comparison with vital statistics from the male population of England and Wales resulted in O/E=12/3.3, SMR=364 ($p<0.005$) (Bidstrup and Case 1956). Another follow-up of this study, which added new employees after 1 year of employment, followed 2,636 workers during the period 1948–1977. For deaths from all causes, O/E=602/445.3, SMR=135 ($p<0.001$). Lung cancer was the major contributory cause of the excess, with O/E=116/47.9, SMR=242 ($p<0.001$). Nasal cancer was found in two individuals (O/E=2/0.28, SMR=714, $p=0.033$). Further analysis of the cohort revealed that the risk for lung cancer had declined since modifications in the work environment were introduced in 1950 (Alderson et al. 1981). A further follow-up study of the three chromate plants in the United Kingdom updates the mortality data, paying particular attention to the workers after major industrial hygiene and process changes were introduced in 1950 and completed during 1958–1960. The analysis covered 2,298 workers in post on January 1, 1950 or who entered employment on or before June 30, 1976, and who worked for at least 1 year. Mortality was followed to December 31, 1988 (Davies et al. 1991). In contrast to the previous follow-up by Alderson et al. (1981), the analysis in the present study excluded office personnel. "Early" workers with long-term service, "prechange" workers, and "postchange" workers were defined as those workers who began employment prior to 1945, those who began employment during the years 1945–1960, and those who began employment after improvements were completed, respectively. At the two larger factories, significant excesses of death from lung cancer (O/E=175/88.97, SMR=197, $p<0.001$) and from nasal cancer (O/E=4/0.26, SMR=1,538, $p<0.001$) were

found among 1,422 "early" and "prechange" workers. No excess of lung cancer deaths was found among 677 "postchange" workers (O/E=14/13.7, SMR 102, not significant), but the possibility of an increased risk in "postchange" workers cannot be ruled out without further follow-up. In the "early" workers, the risk affected men who were employed for $2 years and was higher for those who worked for $10 years (SMR=225). Men in jobs with the highest exposure to chromate had higher risks (O/E=151/61.73, SMR=245) than workers with less exposure (O/E=21/19.57, SMR=107) (Davies et al. 1991). In these reports, reliable smoking data were not available, and exposure concentrations were not reported. However, an independent analysis of workroom levels of chromium in the three chromate production factories in the United Kingdom performed around 1950 indicated average levels for various phases in the process ranging from 0.0006 to 2.14 mg chromium(III)/m^3 and from 0.002 to 0.88 mg chromium(VI)/m^3 (Buckell and Harvey 1951). The importance of further follow-up of the cohort to confirm that the risk has declined with improvements in the working environment, of simultaneous analysis of such factors as age, duration of employment, and time since first exposure, and of examining smoking habits was emphasized (Davies et al. 1991).

The incidence of mortality due to lung cancer in two chromate production plants in the Federal Republic of Germany was examined in relation to changes in operations and industrial hygiene over the years. The cohort consisted of 1,140 workers who were employed for at least 1 year from before 1948 to 1979. For respiratory cancer, O/E=21/10.93, SMR=192 at one plant and O/E=30/13.41, SMR=224 at the other. Analysis of SMRs over 5-year periods revealed a progressive decline at both plants (Korallus et al. 1982).

Studies of chromate production workers have also been conducted in Japan and Italy. Among 544 workers at a small chromate producing factory in Japan, which had operated from 1936 to 1973, 14 cases of lung cancer were diagnosed or reported on death certificates. An excess risk of 657.9 per 100,000 was calculated and compared with a death rate from bronchial carcinoma of 13.3 per 100,000 in Japan in 1975 (Ohsaki et al. 1978). In a mortality and morbidity study of 896 men (including 120 deceased previously) engaged in the manufacture of chromium compounds in Japan for at least 1 year during 1918–1975 and followed until 1978, SMRs were significant only for lung cancer (O/E=26/2.746, SMR=950). Deaths from all respiratory cancers increased with increased length of engagement in chromium work. The overall risk for respiratory cancer for the period from 1950–1978 was O/E=31/3.358 (SMR=923). The 31 cases included 25 cases of lung cancer, 5 cases of maxillary sinus cancer, and 1 case of nasal cavity cancer. No increased risk of death due to cancer of other organs, particularly the stomach or liver, was found (Satoh et al. 1981). A survey of 85 men who worked in the production of dichromate and chromium trioxide for at least 1 year from 1938 to 1953 in a facility in Italy

revealed one case of bronchogenic carcinoma and one case of nasal cancer (Sassi 1956), but further analysis was not performed.

Among 4 cases of nasal carcinoma in men who worked for 19 and 32 years in a Japanese chromate factory, 1 patient was diagnosed with squamous cell carcinoma of the left nasal cavity 11 years after retirement (Satoh et al. 1994). The other three patients underwent lobectomy for lung cancer, and 6–15 years later, all three contracted nasal cancer, two in the nasal cavity and one in the nasopharynx. The period for the appearance of nasal cancer was about 39 years after first being exposed to chromium. No mention was made of the possibility of metastasis of lung cancer to the nasal region.

A retrospective mortality and morbidity study of 398 workers who had worked in a chromate production facility in North Carolina for at least 1 year between 1971 and 1989 was designed to address these limitations (Pastides et al. 1991, 1994). Personal air monitoring results, which were available for 1974–1989, revealed 8-hour TWA concentrations of chromium(VI) ranging from below the detection limit (0.001 mg chromium(VI)/m^3 prior to 1984; 0.0006 mg/m^3 thereafter) to 0.289 mg/m^3, with >99% of the samples measuring <0.05 mg/m^3. Workroom air monitoring data were available for different areas in the plant for the years 1971–1979 and generally ranged from 0.00026 to 0.086 mg chromium(VI)/m^3. Because personal air monitoring data were not available for the years 1971–1973, workroom area levels were used to estimate the personal air levels for these years and were included in the analysis of personal air levels. Levels of chromium(III) or total chromium were not measured. Forty-five workers also had previous occupational exposure to chromium at other chromate production facilities. Of the 45 workers with previous exposure, 42 had been employed at production facilities in Painsville, Ohio or Kearny, New Jersey (the exact number from each of these facilities and the location of the plants at which the other 3 workers had been employed were not reported). Industrial hygiene monitoring at the Painsville, Ohio plant revealed workroom air levels of 0.05–1.45 mg total chromium/m^3 for production workers and #5.67 mg total chromium/m^3 for maintenance workers (workroom air levels at the other facilities were not reported). Details of medical history, smoking history, detailed work history, and exposure to known chemicals and industrial hazards were determined from questionnaires of workers or reconstructed from personnel records and coworkers' accounts for deceased workers. There were 17 deaths, 6 of which were due to cancer (2 to lung cancer). One of the deaths from lung cancer occurred in a worker who had transferred from one of the other plants. Expected rates for cancer of any type were 4.8 using the statistics for the 8 surrounding counties in North Carolina (SMR=125, not significant) and 4.4 using the U.S. population vital statistics (SMR=137, not significant). For lung cancer, the observed/expected ratio was 2/2.1 (SMR=97, not significant) for the eight-county comparison and 2/1.6 (SMR=127, not

significant) for the U.S. population comparison. To address the apparent "healthy worker" effect, the mortality of workers with higher exposure ($0.01 mg chromium(VI)/$m^3$) or longer duration was compared with that of workers with less exposure (<0.01 mg chromium(VI)/m^3) or shorter duration. There was little difference in mortality between the groups and no evidence of an increased risk of cancer for workers with high cumulative exposure or with longer duration, controlling for age, smoking, and previous chromium exposure. A significant increased risk of cancer was found for workers who had been previously employed at the other chromate production facility before transfer to the North Carolina site. In addition to the cancer deaths, seven living workers had been diagnosed with cancer, three cases of which were lung cancer. Two of these lung cancers were diagnosed in workers with previous exposure. The risk of lung cancer was not further analyzed for these cases, but the subgroup with previous exposure accounted for three of the total five cases of lung cancer (both living and deceased). The authors noted the limited power of the study for detecting a true cancer risk because of the relatively brief 18-year history of the facility and small cohort size.

In conclusion, despite limitations of some studies, occupational exposure to chromium(VI) in the chromate production industry is associated with increased risk of respiratory cancer, but improvements in the production process and industrial hygiene appear to have reduced the risk over the past 30–40 years.

Chromate Pigments Production and Use. Studies of workers engaged in the production of chromate pigments also have consistently shown an association with increased risk of lung cancer. A study of the causes of death among 1,296 white and 650 nonwhite males who had worked at some time between 1940 to 1969 at a plant in New Jersey manufacturing lead and zinc chromate pigments showed an SMR for lung cancer of 160 (O/E=25.5/16.0, $p<0.05$) for white males compared with U.S. rates. The observed rates are not expressed as integers because they were adjusted to include the appropriate proportion of deaths from unknown causes. The cohort included workers with exposures classified as high (continuous exposure to chromate dust, >2 mg total chromium/m^3); moderate (occasional exposure to chromate dust or to dry or wet pigments, 0.5–2 mg/m^3); and low (infrequent exposure, such as, in janitors and office workers, <0.1 mg/m^3). The SMR increased to 190 (O/E=13.3/7.0, $p<0.05$) for white males employed for at least 2 years and who had "moderate" exposure to chromates (0.5–2 mg chromium(VI)/m^3). SMRs of 200 for stomach cancer (O/E=6.1/3.0, not significant), 170 for pancreatic cancer (O/E=4.8/2.8, not significant), and 290 for Hodgkins disease (O/E=2.4/0.8, not significant) were also found. Further analyses also revealed significant ($p<0.05$) risk for stomach cancer in white males (O/E=6.1/2.7, SMR=230) and lung cancer in nonwhite males (O/E=11.2/5.7, SMR=200). Air monitoring at the plant in the later years (not otherwise specified) indicated exposure concentrations from <0.1 to >2 mg

chromium(VI)/m^3 and a ratio of lead to zinc chromate of 9:1. Although nickel compounds were also present in the plant, 98.2% higher concentrations of airborne chromium were present than were concentrations of airborne nickel. Smoking histories were not available for all workers (Sheffet et al. 1982). A follow-up of this study followed the cohort through 1982. Of the 453 deaths, 41 were due to lung cancer, compared with 35.3 expected based on the U.S. population rates (SMR=116, not significant). When analyzed by duration of employment, none of the SMRs were significant, but there was a significant trend for increased risk with increasing duration of employment (p=0.04). When time since initial employment was considered in the analysis, a significantly increased risk of lung cancer was found in those employed for $10 years with $30 years since initial employment (O/E=18/9.64, SMR=190, p=0.02). Of the 41 lung cancer deaths, 24 occurred in those whose jobs involved exposure to chromate dusts (i.e., with exposures of 0.5 to >2 mg/m^3). Results of the analysis of SMRs and trends for these 24 lung cancer deaths by duration of employment and time since initial employment along with duration of employment were similar to those obtained with the 41 lung cancer deaths. For those employed for $10 years and with $30 years since initial employment, O/E=6/1.87 (SMR=321, p<0.01) (Hayes et al. 1989).

Another epidemiological study of workers at 3 chromate pigment production plants in the United States examined the causes of death in 574 male workers with known exposure to lead chromate and who had been employed for at least 6 months from the mid-1920s to December 31, 1979. At Plant 1, where lead chromate was the only chromate produced, there were 21 deaths among 246 workers. Four of the deaths were due to respiratory cancer, compared with 2.4 expected based on U.S. male population rates (SMR=164.4, not significant), and 2 of the deaths were due to digestive system cancer, compared with 1.7 expected (SMR=120.3, not significant). At least two of the deaths from lung cancer occurred in workers who smoked. Industrial hygiene monitoring at Plant 1 in 1975 revealed average workroom air concentrations of 0.05 mg total chromium/m^3 and 0.28 mg lead/m^3. At Plant 2, zinc chromate, strontium chromate, and barium chromate had also been produced at various times during the facility's operation. There were 11 deaths among 164 workers, 2 of which were due to respiratory cancer, compared with 1.0 predicted. Both of the workers with respiratory cancer had been smokers. The low number of deaths from lung cancer precluded meaningful statistical analysis. No death from digestive system cancer occurred. The industrial hygiene survey of Plant 2 in 1975 found average concentrations of 0.06 mg total chromium/m^3 and 0.26 mg lead/m^3. At Plant 3, lead chromate was one of many products, and zinc chromate had also been produced. There were 53 deaths among 164 workers, 9 of which were due to respiratory cancer, compared with 4.1 expected (SMR=218, p<0.05). For cancer of the bronchus, trachea, and lung, O/E=9/3.9 (SMR=231, p<0.05). At least five of the lung cancer patients had been moderate to

heavy smokers. An increase in deaths from stomach cancer was also observed (O/E=5/0.6; SMR=792, $p<0.01$). Average airborne levels of chromium and lead in Plant 3 in 1975 were 0.19 mg total chromium/m^3 and 0.79 mg lead/m^3. Because of the nonsignificant rate of respiratory cancer at Plant 1 and the co-exposure to other chromates at Plants two and three, no conclusions regarding the risk of lung cancer in lead chromate-exposed workers can be drawn from this study. Combining the results for lung cancer from Plants two and three yielded O/E of 11/4.8 (SMR=228, $p<0.05$), suggesting that exposure to zinc chromate (and other chromates) is associated with an increased risk of lung cancer (EEH 1976, 1983). Since Plant three was the same facility studied by Sheffet et al. (1982), whose cohort was much larger because it was not limited to men who worked with chromates, but included personnel with infrequent exposure (janitors, office workers), and where the investigators already found excess lung and stomach cancer, this study (EEH 1976, 1983) provides no additional knowledge regarding causative factors.

Three chromate pigment manufacturing plants in the United Kingdom have been studied. At Factory A, both lead and zinc chromate were produced from 1932 to 1964, after which lead chromate production ceased. The main cohort consisted of 411 men first employed between 1932 and 1967. For workers exposed to "high" and "medium" levels of chromates before 1955, when industrial hygiene improvements had been introduced, 22 cases of lung cancer death were observed compared with 9.5 expected based on rates for England and Wales (SMR=232, $p<0.01$). No excess of lung cancer was found in the group exposed after 1955 or in workers exposed to "low" levels. At Factory B, both lead and zinc chromate were produced until 1976, and strontium chromate from 1950 to 1968. The main cohort consisted of 138 men first employed between 1948 and 1967. For lung cancer deaths in workers exposed to "high" and "medium" levels of chromates before 1961, when industrial hygiene improvements were introduced, O/E=6/1.61, SMR=373 ($p<0.01$). For workers exposed to "high" and "medium" levels from 1961 to 1967, the values were O/E=5/0.89, SMR=562 ($p<0.01$) (Davies 1979, 1984). At Factory C, where only lead chromate had been produced, no excess death from lung cancer was found (Davies 1979), and meaningful analysis by subgroups was precluded (Davies 1984). The results suggested that exposure to both zinc chromate and lead chromate posed more of a risk for lung cancer than exposure to lead chromate alone. Workroom levels of chromium were not monitored at any of the factories. Although information regarding smoking habits of the workers was not available, smoking was not permitted during work, suggesting that the workers smoked no more, or perhaps less, than other members of their socioeconomic status.

In a study of 133 workers at a chromate pigment producing factories in Norway, three cases of lung cancer death compared with 0.079 expected based on national rates (SMR=3,797) were found in a subcohort of 24 workers who had worked for at least 3 years at the factories that had produced zinc and/or lead chromate from 1948 to 1972. Workroom monitoring revealed air levels ranging from 0.01 to 1.35 mg chromium(VI)/m^3 at the factories. The exposure levels of the three workers with lung cancer were estimated to be 0.5–1.5 mg chromium(VI)/m^3 for 6–9 years (Langård and Norseth 1975). A follow-up of this study on the original cohort of 133 workers to 1980 found 4 new cases of lung cancer, 3 of which were in the subcohort of 24 men (O/E=6/0.135, SMR=4,444) (Langård and Vigander 1983). At least two of the patients in the original study (Langård and Norseth 1975) and all three of the patients in the follow-up were smokers or ex-smokers, and one may have been exposed to asbestos. However, the authors did not consider smoking an important confounding factor, since smoking alone could not account for the extreme findings (Langård and Vigander 1983).

In a study of workers exposed to lead chromate and zinc chromate at five chromate pigment factories in Germany and Norway, the cohorts consisted of men employed for >6 months from 1965 to 1976 in any of the five factories. The cohorts at Factories 1, 2, 3, 4, and 5 consisted of 319, 141, 97, 174, and 247 men, respectively. Because of differences (not specified) between the factories, a pooled evaluation was precluded. Cause-specific expected numbers of death were calculated from mortality rates in each of the districts in Germany or Norway in which the factories were located. An increased risk of lung cancer was found only at Factory 2. At this factory, there were 9 deaths among 141 men compared with 9.963 expected. Of the nine deaths, two were due to lung cancer, compared with 0.789 expected (O/Ex100=386, $p<0.05$). When the cohorts at each factory were categorized by duration of exposure (i.e., 0–4 years, 5–10 years, or >10 years), a significantly increased risk of lung cancer was found only at Factory 3. At this factory, two deaths from lung cancer, compared with 0.287 expected (O/Ex100=697, $p<0.01$), occurred among 51 workers exposed for 0–4 years, but no increased-risk lung cancer was found in workers with longer durations. When subcohorts from each factory were subdivided into those with unambiguous low exposure, medium exposure, and high exposure, no significant increased risk of lung cancer was found for any of these categories at Factories 1, 4, or 5. At Factory 2, a significantly increased risk of lung cancer was found only for those categorized with medium exposure (n=36) (O/Ex100=862, $p<0.05$). At Factory 3, a significantly increased risk of lung cancer was found only for those categorized with high exposure (n=46) (O/Ex100=749, $p<0.01$). An unexplainable, significantly high risk of death from lung cancer was found in maintenance workers at Factories one and five (Frentzel-Beyme 1983). While this study suggests that working in a chromate pigment factory was associated with increased risks of lung cancer, it was unable to resolve the issue regarding the relative

carcinogenicity of lead chromate and zinc chromate because mixed exposure occurred at all of the factories. Furthermore, exposure levels were not measured, smoking histories were not available for the entire cohort or for most of the cancer cases, and the individual cohort sizes were relatively small.

Workers exposed to lead and zinc chromate in a chromate pigment manufacturing factory in France have also been studied. The cohort consisted of 251 male workers employed for $6 months prior to 1978 and who were not deceased before 1958. The reference group was the male population of the subdivision in northern France in which the factory was located. During the 20-year period, 50 deaths occurred among the workers, but causes of death were known for only 30. Of these 30 deaths, 11 were due to lung cancer compared with 2.38 expected (O/Ex100=790, $p=2x10^{-8}$). Three additional cases of lung cancer were diagnosed in 1978 and 1979. The average latency period was 17.01 years for the 14 total cases of lung cancer. All but one of the lung cancer cases were smokers or former smokers, but the authors stated that the workers probably smoked no more than the general population because deaths due to other causes associated with smoking were not increased (Haguenoer et al. 1981). No exposure data were provided, and the study could not resolve the issues regarding the relative carcinogenicity of zinc chromate and lead chromate.

A study was conducted on 977 male painters who had worked for at least 3 months within 10 years prior to 1959 at two U.S. military aircraft maintenance bases where spray painting utilized zinc chromate primer paint. They were followed through 1977. There were 21 deaths due to respiratory cancers, compared with 11.4 expected based on national rates (SMR=184, $p<0.01$). When compared with national proportionate cancer mortality rates, however, the excess (SMR=146) was not significant (Dalager et al. 1980).

Chrome Plating. Studies on the risk of cancer in chrome platers have produced both positive and negative results, but they generally support the conclusion that chromium(VI) is carcinogenic. In an analysis of the cause of death among 172 white male and 49 white female employees engaged for at least 10 years in die-casting and electroplating at an automobile hardware manufacturing plant in the United States, statistically significant SMRs were found for all cancers in men (O/E=53/39.39, SMR=135, $p<0.05$), for respiratory system cancers in men (O/E=30/15.37, SMR=195, $p<0.001$) and women (O/E=10/2.80, SMR=357, $p<0.001$), and for lung cancer specifically in men (O/E=28/14.68, SMR=191, $p<0.0.001$) and women (O/E=10/2.70, SMR=370, $p<0.001$). The SMR for lung cancer was significant in men with $15 years service, but not for men with <15 years service. When the lung cancer deaths were matched to a study population of referents of the same sex and race who died of cardiovascular disease,

an association was found between lung cancer and work in certain departments where there were mixed exposures to die-casting emissions and plating mists (Silverstein et al. 1981). A specific causative agent could not be identified from this study, and exposure concentrations were not analyzed. Although the smoking habits of the workers were not assessed, the lack of an increase in other smoking-related illnesses (emphysema, coronary heart disease, bladder cancer) was considered evidence that the increased risk of lung cancer was not due to smoking.

A study of 276 male electroplaters who were exposed to chromic acid and had worked for at least 3 months within 10 years prior to 1959 at two U.S. military aircraft maintenance bases and followed through 1977 found no excess of cancer compared with national rates (Dalager et al. 1980).

Although a significant increase in the incidence of death from all malignant diseases was found, no significant differences were found for lung cancer or stomach cancer among 1,238 past and current chrome platers in 54 facilities in Yorkshire, United Kingdom, compared with a control group of 1,099 workers in other departments (Royle 1975a). However, another mortality study of a cohort of 2,689 (1,288 men, 1,401 women) chrome platers employed for at least 6 months in a different plant in the United Kingdom between 1946 and 1975 found excess risks for several types of cancer, compared with the mortality rates for England and Wales. Statistically significant excesses among male workers were as follows: stomach cancer (O/E=21/11.3, SMR=186, $p<0.05$); primary liver cancer (O/E=4/0.6, SMR=667, $p<0.01$); nose and nasal cavity cancer (O/E=2/0.2, SMR=1,000, $p<0.05$); cancer of the lungs and bronchi (O/E=63/40.0, SMR=158, $p<0.001$), and all cancers (O/E=142/96.9, SMR=147, $p<0.001$). No excesses were found for women alone. Most of the excesses in men were attributed to working in the chrome bath works, where exposures were mainly to chromium(VI) as chromic acid. The correlation with duration of chrome bath work was positive only for cancers of the lung and bronchus. Exact exposure concentrations were not known, but the contribution of nickel exposure to the effects was found to be unimportant. While data on smoking habits were not available, the investigators did not believe that duration of chrome employment would correlate with smoking habits (Sorahan et al. 1987). In a follow-up to this study, Sorahan et al. (1998) examined mortality rates in this cohort of chrome workers for the period of 1946–1995. The job history data were further refined and workers with presumably no exposure to chromium were removed from the analyses, resulting in a cohort of 1,762 chrome workers (812 men and 950 women). As with the first study, mortality rates were compared to mortality rates for England and Wales. Significant excess risks of lung cancer were observed among males and females working in the chrome bath area for <1 year (SMR=172; 95% confidence interval [CI]=112–277; $p<0.05$) or greater than 5 years (SMR=320; 95% CI=128–658; $p<0.001$), females working in the chrome bath area for <1 year

(females: SMR=245; 95% CI=118–451; p<0.5), males starting chrome work in the period of 1951–1955 (SMR=210; 95% CI=132–317; p<0.01), and in male chrome workers 10–19 years after first chrome work (SMR=203; 95% CI=121–321; p<0.01). A significant (p<0.01) positive trend for lung cancer mortality and duration of exposure was found for the male chrome bath workers, but not for the female workers. Lung cancer mortality risks were also examined using an internal standard approach, in which mortality in chrome workers was compared to mortality in workers without chromium exposure. After adjusting for sex, age, calendar period, year of starting chrome work, period from first chrome work, and employment status, a significant positive trend (p<0.05) between duration of chrome bath work and lung cancer mortality risk was found.

No increase in lung cancer death was found in a cohort of 889 male and 63 female chrome platers in Japan compared with a control group of 2,514 men and 1,722 women (Okubo and Tsuchiya 1977, 1979) or in a follow-up cohort of 626 male chrome platers who were employed for at least 6 months in 415 plants in Japan from 1970 to 1976 (Takahashi and Okubo 1990).

However, results of a retrospective cohort study of 178 workers in nine chrome plating plants in Italy suggested an association between lung cancer and "hard" (thick) chrome plating as opposed to "bright" (thin) chrome plating. The cohort members had been employed for at least 1 year during 1951–1981. Death from any cancer was observed in 7 of the 116 hard platers compared with 2.7 expected (SMR=259, p=0.02). An excess of death from lung cancer was observed only among hard platers (O/E=3/0.7, SMR=429, p=0.03). Workroom monitoring in 1980 for hard platers, when improvements in industrial hygiene had already been made, revealed an average concentration of 0.007 mg chromium(VI)/m^3 (range 0.001–0.057 mg chromium(VI)/m^3) as chromic acid near the baths and 0.003 mg chromium(VI)/m^3 (range 0–0.012 mg chromium(VI)/m^3) in the middle of the room. Levels for bright platers in 1980 were not reported (Franchini et al. 1983). However, prior to improvements in industrial hygiene, airborne levels of total chromium near the baths have been reported to be 0.06 mg/m^3 for hard plating and 0.006 mg/m^3 for bright plating; levels in the middle of the room were 0.02 mg/m^3 for hard plating and 0.002 mg/m^3 for bright plating (Guillemin and Berode 1978). Although this study suggests that hard chrome platers may have an increased risk of lung cancer, the cohort size and the number of lung cancer deaths were small, precluding definitive conclusions.

In addition to lung, nasal, and possibly stomach cancer, exposure to chromium(VI) in the electroplating industry may also be associated with oral cavity cancer. In 77 employees of chromium electroplating factories in Czechoslovakia, 16 growths in the oral cavity were found in 14 individuals. Histological

examination of three of the growths led to the diagnosis of papilloma, which was considered to be a precancerous lesion. All of the papillomas were found to contain chromium (mean 9.25 mg %), and were believed to be due to chromium exposure via mouth breathing. Analysis of the breathing zone of the electroplaters showed that the average air level above the plating baths was 0.414 mg chromium(VI)/m^3 (Hanslian et al. 1967).

Stainless Steel Welding. Inconclusive results have been obtained in studies of stainless steel welders. A study of 1,221 stainless steel welders in the former Federal Republic of Germany found no increased risk of lung cancer or any other specific type of malignancy compared with 1,694 workers involved with mechanical processing (not exposed to airborne welding fumes) or with the general population of the former Federal Republic of Germany (Becker et al. 1985). A follow-up study (Becker 1999) which extended the observation period to 1995, found similar results for lung (includes bronchus and trachea) cancer (SMR=121.5, 95% CI=80.7–175.6). An excess risk of pleura mesothelioma was observed (SMR=1179.9; 95% CI=473.1–2430.5); however, this was attributed to asbestos exposure. A study of 234 workers from eight companies in Sweden, who had welded stainless steel for at least 5 years during the period of 1950–1965 and followed until 1984, found five deaths from pulmonary tumors, compared with two expected (SMR=249), based on the national rates for Sweden. The excess was not statistically significant. However, when the incidence of lung cancer in the stainless steel welders was compared with an internal reference group, a significant difference was found after stratification for age. The average concentration of chromium(VI) in workroom air from stainless steel welding, determined in 1975, was reported as 0.11 mg/m^3 (Sjogren et al. 1987). The cohort in this study was small, and stainless welders were also exposed to nickel fumes. Smoking was probably not a confounding factor in the comparisons with the internal reference group. Further studies of stainless steel welders were recommended.

In a study of the mortality patterns in a cohort of 4,227 workers involved in the production of stainless steel from 1968 to 1984, information was collected from individual job histories, and smoking habits were obtained from interviews with workers still active during the data collection (Moulin et al. 1993). The observed number of deaths was compared to expected deaths based on national rates and matched for age, sex, and calender time. No significant excess risk of lung cancer was noted among workers employed in melting and casting stainless steel [SMR=104]. However, there was a significant excess among stainless steel foundry workers [SMR=229]. The SMR increased for workers with length of employment over 30 years to 334 (119–705). No measurements of exposure were provided.

Ferrochromium Production. Studies of workers in the ferrochromium alloy industry are inconclusive. No significant increase in the incidence of lung cancer was found among 1,876 employees who worked in a ferrochromium plant in Sweden for at least 1 year from 1930 to 1975 compared with the expected rates for the county in which the factory was located. The workers had been exposed mainly to metallic chromium and chromium(III), but chromium(VI) was also present. The estimated levels ranged from 0 to 2.5 mg chromium(0) and chromium(III)/m^3 and 0 to 0.25 mg chromium(VI)/m^3 (Axelsson et al. 1980). An excess of lung cancer was found in a study of 325 male workers employed for >1 year in a ferrochromium producing factory in Norway between 1928 and 1977, and whose employment began before 1960. The rates of cancer deaths in the ferrochromium workers were compared with national and local rates. Seven cases of lung cancer were found in the ferrochromium workers compared with 3.1 expected using the national rate (SMR=226, p=0.08) and 1.8 expected using the local rate (SMR=389, p=0.06). When the internal reference group of ferrosilicon workers was used, the SMR was 850 (p=0.026). Because the internal reference group was recruited from the same local population as the ferrochromium group, it was considered to be the most valid basis for comparison. Workroom monitoring in 1975 indicated that the ferrochromium furnace operators worked in an atmosphere with 0.04–0.29 mg total chromium/m^3, with 11–33% of the total chromium as chromium(VI) (Langård et al. 1980). Smoking was not believed to be a confounding factor because the percentage of smokers in the cohort in 1976 was similar to that of the Norwegian population. A follow-up of this study to include workers whose employment began before 1965 expanded the cohort of ferrochromium workers to 379 and the follow-up period to 1985. Ten cases of lung cancer were found among the 379 ferrochromium workers (SMR=154, not significant), while 12 cases of prostate cancer (SMR=151) and 5 of kidney cancer (SMR=273) were found. SMRs were determined by comparison to the national rates. The statistical significance of the SMRs for prostate and kidney cancer was not reported, but the etiology was considered to be due to factors (not characterized) other than chromium exposure (Langård et al. 1990). An internal reference group of ferrosilicon workers was not used in the follow-up study.

Leather Tanning. Studies of workers in tanneries, where exposure is mainly to chromium(III), in the United States (0.002–0.054 mg total chromium/m^3) (Stern et al. 1987), the United Kingdom (no concentration specified) (Pippard et al. 1985), and in the Federal Republic of Germany (no concentration specified) (Korallus et al. 1974a) reported no association between exposure to chromium(III) and excess risk of cancer.

Environmental Exposure. In addition to the occupational studies, a retrospective environmental epidemiology study was conducted of 810 lung cancer deaths in residents of a county in Sweden where

two ferrochromium alloy industries are located. No indication was found that residence near these industries is associated with an increased risk of lung cancer (Axelsson and Rylander 1980).

A retrospective mortality study conducted on a population who resided in a polluted area near an alloy plant that smelted chromium in the People's Republic of China found increased incidences of lung and stomach cancer. The alloy plant began smelting chromium in 1961 and began regular production in 1965, at which time sewage containing chromium(VI) dramatically increased. The population was followed from 1970 to 1978. The size of the population was not reported. The adjusted mortality rates of the exposed population ranged from 71.89 to 92.66 per 100,000, compared with 65.4 per 100,000 in the general population of the district. The adjusted mortality rates for lung cancer ranged from 13.17 to 21.39 per 100,000 compared with 11.21 per 100,000 in the general population. The adjusted mortality rates for stomach cancer ranged from 27.67 to 55.17 per 100,000 and were reported to be higher than the average rate for the whole district (control rates not reported). The higher cancer rates were found for those who lived closer to the dump site (Zhang and Li 1987). Attempts to abate the pollution from chromium(VI) introduced in 1967 also resulted in additional pollution from sulfate and chloride compounds. It was not possible to estimate exposure levels based on the description of the pollution process. The exposed population was probably exposed by all environmentally relevant routes (i.e., air, drinking water, food, soil).

A follow-up study reevaluated this cohort; the adjusted total cancer death rates for the six areas analyzed were 68.8, 68.4, 64.7, 54.3, 57.5, and 45.9 (Zhang and Li 1997) . These rates were comparable to the overall provincial rate of 66.1 in which the 6 exposed regions were located. When total cancer mortality rates from five villages of the areas using the contaminated water were combined, a significant increase in cancer incidence was observed over provincial incidences. However, total cancer incidences, stomach cancer incidence, or lung cancer incidence did not correlate with the degree of exposure to chromium(VI), with the villages exposed to the lowest drinking water levels having the higher incidences. The authors commented that these more recent analyses of the data probably reflect lifestyle or environmental factors rather than exposure to chromium(VI) being responsible for cancer in these regions.

The studies in workers exposed to chromium compounds clearly indicate that occupational exposure to chromium(VI) is associated with an increased risk of respiratory cancer. Using data from the Mancuso (1975) study and a dose-response model that is linear at low doses, EPA (1984a) derived a unit risk estimate of 1.2×10^{-2} for exposure to air containing 1 µg chromium(VI)/m^3 (or potency of

$1.2x10^{-2}$ [$\mu g/m^3$]$^{-1}$) (IRIS 1998). The exposure levels associated with increased lifetime upperbound cancer risks of $1x10^{-4}$ to $1x10^{-7}$ are $8x10^{-6}$ to $8x10^{-9}$ mg/m^3 and are indicated in Figure 2-1.

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to 4.3 mg chromium(VI)/m^3 as calcium chromate had a 2.8-fold greater incidence of lung tumors, compared to controls (Nettesheim et al. 1971). Lung tumors were observed in 3/19 rats exposed to 0.1 mg chromium(VI)/m^3 as sodium dichromate for 18 months, followed by 12 months of observation. The tumors included two adenomas and one adenocarcinoma. No lung tumors were observed in 37 controls or the rats exposed to #0.05 mg chromium(VI)/m^3 (Glaser et al. 1986, 1988). The increased incidence of lung tumors in the treated rats was significant by the Fisher Exact Test (p=0.03) performed by Syracuse Research Corporation.

Several chronic animal studies reported no carcinogenic effects in rats, rabbits, or guinea pigs exposed to . 1.6 mg chromium(VI)/m^3 as potassium dichromate or chromium dust 4 hours/day, 5 days/week (Baetjer et al. 1959b; Steffee and Baetjer 1965).

Rats exposed to #15.5 mg chromium(IV)/m^3 as chromium dioxide for 2 years had no statistically significant increased incidence of tumors (Lee et al. 1989).

The Cancer Effect Levels (CELs) are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

2.2.2.1 Death

Cases of accidental or intentional ingestion of chromium that have resulted in death have been reported in the past and continue to be reported even in more recent literature. In many cases, the amount of ingested chromium was unknown, but the case reports provide information on the sequelae leading to death. For example, a 22-month-old boy died 18.5 hours after ingesting an unknown amount of a sodium dichromate solution despite gastric lavage, continual attempts to resuscitate him from cardiopulmonary arrest, and other treatments at a hospital. Autopsy revealed generalized edema, pulmonary edema, severe bronchitis, acute bronchopneumonia, early hypoxic changes in the myocardium, liver congestion, and necrosis of the liver, renal tubules, and gastrointestinal tract (Ellis et al. 1982). Another case report of a 1-year-old girl who died after ingesting an unknown amount of ammonium dichromate reported severe dehydration,

caustic burns in the mouth and pharynx, blood in the vomitus, diarrhea, irregular respiration, and labored breathing. The ultimate cause of death was shock and hemorrhage into the small intestine (Reichelderfer 1968).

Several reports were available in which the amount of ingested chromium compound could be estimated. A 17-year-old male died after ingesting 29 mg chromium(VI)/kg as potassium dichromate in a suicide. Despite attempts to save his life, he died 14 hours after ingestion from respiratory distress with severe hemorrhages. Caustic burns in the stomach and duodenum and gastrointestinal hemorrhage were also found (Clochesy 1984; Iserson et al. 1983).

A few reports have described death of humans after ingesting lower doses of chromium(VI). In one case, a 14-year-old boy died 8 days after admission to the hospital following ingestion of 7.5 mg chromium(VI)/kg as potassium dichromate from his chemistry set. Death was preceded by gastrointestinal ulceration and severe liver and kidney damage (Kaufman et al. 1970). In another case, a 44-year-old man died of severe gastrointestinal hemorrhage 1 month after ingesting 4.1 mg chromium(VI)/kg as chromic acid (Saryan and Reedy 1988).

Acute oral LD_{50} values in rats exposed to chromium(III) or chromium(VI) compounds varied with the compound and the sex of the rat. LD_{50} values for chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) range from 13 to 19 mg chromium(VI)/kg in female rats and from 21 to 28 mg chromium(VI)/kg in male rats (Gad et al. 1986). LD_{50} values of 108 (female rats) and 249 (male rats) mg chromium(VI)/kg for calcium chromate were reported by Vernot et al. (1977). The LD_{50} values for chromium trioxide were 25 and 29 mg chromium(VI)/kg for female and male rats, respectively (American Chrome and Chemicals 1989). An LD_{50} of 811 mg chromium(VI)/kg as strontium chromate was reported for male rats (Shubochkin and Pokhodzie 1980). Twenty percent mortality was observed when female Swiss Albino mice were exposed to potassium dichromate(VI) in drinking water at a dose of 169 mg chromium(VI)/kg/day (Junaid et al. 1996a). Similar exposure to a dose level of 89 mg chromium(VI)/kg/day resulted in 15% mortality among female rats of the Druckrey strain (Kanojia et al. 1998). The disparity between this dose and the LD_{50} identified in the Gad et al. (1986) study may be due to the route of administration, drinking water versus gavage. Chromium(III) compounds are less toxic than chromium(VI) compounds, with LD_{50} values in rats of 2,365 mg chromium(III)/kg as chromium acetate (Smyth et al. 1969) and 183 and 200 mg chromium(III)/kg as chromium nitrate in female and male rats, respectively (Vernot et al. 1977). The lower toxicity of chromium(III) acetate compared with chromium(III) nitrate may be related to solubility;

chromium(III) acetate is less soluble in water than is chromium(III) nitrate. Signs of toxicity included hypoactivity, lacrimation, mydriasis, diarrhea, and change in body weight. The LD_{50} values for chromium(VI) or chromium(III) compounds indicate that female rats are slightly more sensitive to the toxic effects of chromium(VI) or chromium(III) than male rats. LD_{50} values in rats are recorded in Table 2-2 and plotted in Figure 2-2. Mortality was not increased in rats fed 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975).

2.2.2.2 Systemic Effects

The systemic effects of oral exposure to chromium(III) and chromium(VI) compounds are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding musculoskeletal and ocular effects in humans or animals after oral exposure to chromium or its compounds.

Respiratory Effects. Case reports of humans who died after ingesting chromium(VI) compounds have described respiratory effects as part of the sequelae leading to death. A 22-month-old boy who ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed pleural effusion, pulmonary edema, severe bronchitis, and acute bronchopneumonia (Ellis et al. 1982). Autopsy of a 17-year-old male who committed suicide by ingesting 29 mg chromium(VI)/kg as potassium dichromate revealed congested lungs with blood-tinged bilateral pleural effusions (Clochesy 1984; Iserson et al. 1983). Respiratory effects were not reported at nonlethal doses.

No studies were located regarding respiratory effects in animals after oral exposure to chromium(VI) compounds. Dietary exposure of rats to 2,040 mg chromium(III)/kg/day as chromium oxide 5 days/week for 2 years did not cause abnormalities, as indicated by histopathological examination of the lungs (Ivankovic and Preussmann 1975).

Cardiovascular Effects. Case reports of humans who died after ingesting chromium(VI) compounds have described cardiovascular effects as part of the sequelae leading to death. A 22-month-old boy who ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed early hypoxic changes in the myocardium (Ellis et al. 1982). In another case, cardiac output, heart rate,

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Human	once (IN)				29[b] M (death)	Clochesy 1984; Iserson et al., 1983 $K_2Cr_2O_7$ (VI)
2	Human	once (IN)				7.5[c] M (death)	Kaufman et al. 1970 $K_2Cr_2O_7$ (VI)
3	Human	once (IN)				4.1[d] M	Saryan and Reedy 1988 CrO_3 (VI)
4	Rat (Fischer- 344)	once (G)				29 M (LD_{50}) 25 F (LD_{50})	American Chrome and Chemical 1989 CrO_3 (VI)
5	Rat (Fischer- 344)	once (GW)				21 M (LD_{50}) 14 F (LD_{50})	Gad et al. 1986 $Na_2Cr_2O_7.2H_2O$ (VI)
6	Rat (Fischer- 344)	once (GW)				28 M (LD_{50}) 13 F (LD_{50})	Gad et al. 1986 Na_2CrO_4 (VI)
7	Rat (Fischer- 344)	once (GW)				22 M (LD_{50}) 19 F (LD_{50})	Gad et al. 1986 $(NH_4)_2Cr_2O_7$ (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
8	Rat (Fischer- 344)	once (GW)				26 M (LD_{50}) 17 F (LD_{50})	Gad et al. 1986 $K_2Cr_2O_7$ (VI)
9	Rat Druckrey	2 wk (W)				89 F (15% mortality)	Kanojia et al. 1998 $K_2Cr_2O_7$ (VI)
10	Rat (NS)	once (G)				811 M (LD_{50})	Shubochkin and Pokhodzer 1980 $SrCrO_4$ (VI)
11	Rat (NS)	once (GW)				2365 (LD_{50})	Smyth et al. 1969 $Cr(CH_3COO)_3H_2O$ (III)
12	Rat (Sprague-Dawley)	once (G)				249 M (LD_{50}) 108 F (LD_{50})	Vernot et al. 1977 $CaCrO_4$ (VI)
13	Rat (Sprague-Dawley)	once (G)				200 M (LD_{50}) 183 F (LD_{50})	Vernot et al. 1977 $Cr(NO_3)_3.9H_2O$ (III)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL			Reference/ Form
					Less Serious (mg Cr/kg/day)		Serious (mg Cr/kg/day)	
	Systemic							
14	Human	once (IN)	Resp				29[b] M (congested lungs, pleural effusions)	Clochesy 1984; Iserson et al. 1983 $K_2Cr_2O_7$ (VI)
			Cardio				29[b] M (hemorrhage, cardiac arrest)	
			Gastro				29[b] M (hemorrhage)	
			Hemato				29[b] M (inhibited coagulation)	
			Renal				29[b] M (necrosis swelling of renal tubules)	
15	Human	once (IN)	Dermal		0.04 M (enhancement of dermatitis)			Goitre et al. 1982 $K_2Cr_2O_7$ (VI)
16	Human	once (C)	Dermal		0.036 (dermatitis)			Kaaber and Veien 1977 $K_2Cr_2O_7$ (VI)
17	Human	once (IN)	Gastro		7.5[c] M (abdominal pain and vomiting)			Kaufman et al. 1970 $K_2Cr_2O_7$ (VI)
			Hepatic				7.5[c] M (necrosis)	
18	Human	once (IN)	Gastro				4.1[d] M (gastrointestinal hemorrhage)	Saryan and Reedy 1988 CrO_3 (VI)
			Renal				4.1[d] M (acute tubular necrosis)	
19	Rat (NS)	once (G)	Gastro				130 (hemorrhage)	Samitz 1970 $K_2Cr_2O_7$ (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
20	Mouse (Swiss albino)	9 d Gd 6-14 (W)	Bd Wt	53.2 F	101.1 F (8.2% decrease in gestational weight gain)	152.4 F (24.3% decrease in gestational weight gain)	Junaid et al. 1996b $K_2Cr_2O_7$ (VI)
	Immunological/Lymphoreticular						
21	Human	once (IN)			0.04 M (enhancement of chromium dermatitis)		Goitre et al. 1982 $K_2Cr_2O_7$ (VI)
22	Human	once (C)			0.036 (dermatitis)		Kaaber and Veien 1977 $K_2Cr_2O_7$ (VI)
	Neurological						
23	Human	once (IN)				7.5[c] M (cerebral edema)	Kaufman et al. 1970 $K_2Cr_2O_7$ (VI)
	Developmental						
24	Mouse (Swiss albino)	9 d Gd 6-14 (W)				53.2 F (increase in resorptions)	Junaid et al. 1996b $K_2Cr_2O_7$ (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
	INTERMEDIATE EXPOSURE						
	Death						
25	Mouse (Swiss albino)	20 d (W)				169 F (3/15 died)	Junaid et al. 1996a $K_2Cr_2O_7$ (VI)
	Systemic						
26	Rat (Sprague-Dawley)	daily 20 wk (F)	Hepatic	9			Anderson et al. 1997b $CrCl_3$ (III)
			Renal	9			
			Bd Wt	9			
27	Rat (Sprague-Dawley)	daily 20 wk (F)	Hepatic	9			Anderson et al. 1997b Cr picolinate (III)
			Renal	9			
			Bd Wt	9			
28	Rat (Sprague-Dawley)	12 wk (W)	Bd Wt			40 (24% lower final body weight)	Bataineh et al. 1997 $CrCl_3$ (III)
29	Rat (Sprague-Dawley)	12 wk (W)	Bd Wt		42 M (19% lower final body weight)		Bataineh et al. 1997 $K_2Cr_2O_7$ (VI)
30	Rat Charles Foster	90 d 1x/d (G)	Bd Wt	20 M		40 M (57% decreased body weight)	Chowdhury and Mitra 1995 $Na_2Cr_2O_7$ (VI)
31	Rat (Wistar)	28 d (W)	Renal	10 M		100 M (proteinuria, oliguria)	Diaz-Mayans et al. 1986 Na_2CrO_4 (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL Less Serious (mg Cr/kg/day)	LOAEL Serious (mg Cr/kg/day)	Reference/ Form
32	Rat (BD)	90 d 5 d/wk (F)	Resp	1806			Ivankovic and Preussmann 1975 Cr_2O_3 (III)
			Cardio	1806			
			Gastro	1806			
			Hemato	1806			
			Hepatic	1806			
			Renal	1806			
33	Rat Swiss albino	20 d (W)	Bd Wt	37	70 (14% reduced maternal body weight gain)	87 (21% reduced maternal body weight gain)	Kanojia et al. 1996 $K_2Cr_2O_7$ (VI)
34	Rat Druckrey	3 mo (W)	Bd Wt	45	89 (18% reduced maternal body weight gain)	124 (24% reduced maternal body weight gain)	Kanojia et al. 1998 $K_2Cr_2O_7$
35	Rat (albino)	20 d 7 d/wk (G)	Hepatic		13.5 M (lipid accumulation)		Kumar and Rana 1982 K_2CrO_4 (VI)
			Renal		13.5 M (lipid accumulation)		
36	Rat (white)	20 d 7 d/wk (G)	Renal		13.5 M (inhibition of membrane enzymes; alkaline phosphatase, acid phosphatase, lipase)		Kumar and Rana 1984 K_2CrO_4 (VI)
37	Rat (albino)	20 d 7 d/wk (G)	Hepatic		13.5 M (changes in liver enzyme activities; inhibition of acid phosphatase; enhancement of lipase)		Kumar et al. 1985 K_2CrO_4 (VI)
38	Rat (Sprague-Dawley)	9 wk (F)	Hemato	2.1 M 2.5 F	8.4 M 9.8 F (decreased mean corpuscular volume)		NTP 1996b $K_2Cr_2O_7$ (VI)
			Hepatic	9.8			
			Renal	9.8			
			Bd Wt	9.8			

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
39	Mouse (Swiss)	12 wk (W)	Bd Wt		5 M (14% decrease in body weight gain)		Elbetieha and Al-Hamood 1997 $CrCl_3$ (III)
			Bd Wt	14 F			
40	Mouse (Swiss)	12 wk (W)	Bd Wt		6 M (10% decrease in body weight gain)		Elbetieha and Al-Hamood 1997 $K_2Cr_2O_7$ (VI)
41	Mouse (BALB/c)	9 wk (F)	Hemato	7.4 M 12 F	32.2 M (decreased mean 48 F corpuscular volume)		NTP 1996a $K_2Cr_2O_7$ (VI)
			Hepatic	1.1 M 1.8 F	3.5 M (cytoplasmic 5.6 F vacuolization of hepatocytes)		
			Renal	48			
			Bd Wt	48			
42	Mouse (BALB/c)	85 d + PND 1-74 (F1) + PND 1-21(F2) (F)	Gastro	36.7 F			NTP 1997 $K_2Cr_2O_7$ (VI)
			Hemato		7.8 F (decreased mean corpuscular volume in F1)		
			Hepatic	36.7 F			
			Renal	36.7 F			
			Bd Wt	36.7 F			
43	Mouse (albino)	19 d (W)	Bd Wt	46 F	98 F (decreased maternal weight gain)		Trivedi et al. 1989 $K_2Cr_2O_7$ (VI)
	Immunological/Lymphoreticular						
44	Rat (Fischer- 344)	3-10 wk (W)			16 (increased proliferation of T- and B-lymphocytes in response to mitogens and antigens)		Snyder and Valle 1991 K_2CrO_4 (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL			Reference/ Form
					Less Serious (mg Cr/kg/day)		Serious (mg Cr/kg/day)	
Neurological								
45	Rat (Wistar)	28 d (W)		10 M	100 M	(decreased motor activity)		Diaz-Mayans et al. 1986 Na_2CrO_4 (VI)
Reproductive								
46	Rat (Sprague-Dawley)	12 wk (W)			40	(altered sexual behavior, decreased absolute testes, seminal vesicles, and preputial gland weights)		Bataineh et al. 1997 $CrCl_3$ (III)
47	Rat (Sprague-Dawley)	12 wk (W)			42	(altered sexual behavior, decreased absolute testes, seminal vesicles, and preputial gland weights)		Bataineh et al. 1997 $K_2Cr_2O_7$ (VI)
48	Rat (Charles Foster)	90 d 1x/d (G)			20 M	(decreased testicular protein, 3 beta-hydroxy steroid dehydrogenase and serum testosterone)	40 M (28% decreased testicular wt; decreased testicular protein, DNA, RNA, seminiferous tubular diameter; decreased Leydig cells, pachytene cells, spermatocytes, spermatids, & testosterone levels)	Chowdhury and Mitra 1995 $Na_2Cr_2O_7$ (VI)
49	Rat (BD)	90 d 5 d/wk (F)		1806				Ivankovic and Preussman 1975 Cr_2O_3 (III)
50	Rat Swiss albino	20 d (W)					37 (increased resorptions)	Kanojia et al. 1996 $K_2Cr_2O_7$ (VI)
51	Rat Druckrey	3 mo (W)					45 (decreased fertility, increased pre- and post-implantation loss)	Kanojia et al. 1998 $K_2Cr_2O_7$ (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
52	Rat (Sprague-Dawley)	9 wk (F)		8.4 M 9.8 F			NTP 1996b $K_2Cr_2O_7$ (VI)
53	Mouse (Swiss)	12 wk (W)			5 M (increased testes and decreased preputial gland weights)	13 M (decreased number of pregnant females) 5 F (decreased number of implantations and viable fetuses; increased ovarian and decreased uterine weights)	Elbetieha and Al-Hamood 1997 $CrCl_3$ (III)
54	Mouse (Swiss)	12 wk (W)				6 M (decreased number of implantations and viable fetuses; increased testes weight)	Elbetieha and Al-Hamood 1997 $K_2Cr_2O_7$ (VI)
55	Mouse (Swiss)	12 wk (W)				6 F (decreased number of implantations and viable fetuses; increased number of mice with resorptions)	Elbetieha and Al-Hamood 1997 $K_2Cr_2O_7$ (VI)
56	Mouse (Swiss albino)	20 d (W)			52 F (decreased placental weight)	98 F (preimplantation loss, increased resorptions)	Junaid et al. 1996a $K_2Cr_2O_7$ (VI)
57	Mouse Swiss albino	20 d (W)			60 F (decreased number of follicles at different stages of maturation)	120 F (decreased number of ova/mouse)	Murthy et al. 1996 $K_2Cr_2O_7$ (VI)
58	Mouse (BALB/c)	9 wk (F)		32.2 M 48 F			NTP 1996a $K_2Cr_2O_7$ (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL			Reference/ Form
					Less Serious (mg Cr/kg/day)		Serious (mg Cr/kg/day)	
59	Mouse (BALB/c)	85 d + PND 1-74 (F1) + PND 1-21(F2) (F)		36.7 F				NTP 1997 $K_2Cr_2O_7$ (VI)
60	Mouse (albino)	Gd 1-19 19 d (W)					46 F (increase in fetal resorption and post implantation loss)	Trivedi et al. 1989 $K_2Cr_2O_7$ (VI)
61	Mouse (BALB/c)	7 wk 7 d/wk (F)					15.2 M (decreased spermatogenesis)	Zahid et al. 1990 $K_2Cr_2O_7$ (VI)
62	Mouse (BALB/c)	7 wk 7 d/wk (F)					9.1 M (decreased spermatogenesis)	Zahid et al. 1990 $Cr_2(SO_4)_3$ (III)
	Developmental							
63	Rat (BD)	90 d 5 d/wk (F)		1806				Ivankovic and Preussmann 1975 Cr_2O_3 (III)
64	Rat Swiss albino	20 d (W)					37 (increased post-implantation loss and decreased number of live fetuses)	Kanojia et al. 1996 $K_2Cr_2O_7$ (VI)
65	Rat Druckrey	3 mo (W)					45 (reduced fetal caudal ossification, increased post-implantation loss, reduced fetal weight, subhemorrhagic patches)	Kanojia et al. 1998 $K_2Cr_2O_7$ (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL			Reference/ Form
					Less Serious (mg Cr/kg/day)		Serious (mg Cr/kg/day)	
66	Mouse (BALB/c)	Gd12-Ld20 (W)			74	(reduced ovary and testis weights in offspring and impaired fertility in female offspring)		Al-Hamood et al. 1998 $CrCl_3$ (III)
67	Mouse (BALB/c)	Gd12-Ld20 (W)			66 F	(delayed time of vaginal opening and impaired fertility in female offspring)		Al-Hamood et al. 1998 $K_2Cr_2O_7$ (VI)
68	Mouse (Swiss albino)	20 d (W)					52 F (reduced caudal ossification in fetuses; decreased fetal weight; post-implantation loss)	Junaid et al. 1996a $K_2Cr_2O_7$ (VI)
69	Mouse (albino)	Gd 1-19 19 d (W)					46 (increased resorptions, reduced ossification, gross anomalies)	Trivedi et al. 1989 $K_2Cr_2O_7$ (VI)

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
	CHRONIC EXPOSURE						
	Systemic						
70	Human	NS (environ)	Gastro		0.57	(oral ulcer, diarrhea, abdominal pain, indigestion, vomiting)	Zhang and Li 1987 (VI)
			Hemato		0.57	(leukocytosis, immature neutrophils)	
71	Rat (BD)	2 yr 5 d/wk (F)	Resp	2040			Ivankovic and Preussmann 1975 Cr_2O_3 (III)
			Cardio	2040			
			Gastro	2040			
			Hepatic	2040			
			Renal	2040			
72	Rat (Sprague-Dawley)	1 yr (W)	Hemato	3.6			Mackenzie et al. 1958 K_2CrO_4 (VI)
			Hepatic	3.6			
			Renal	3.6			
			Bd Wt	3.6			
73	Rat (Sprague-Dawley)	1 yr (W)	Hemato	3.6			Mackenzie et al. 1958 $CrCl_3$ (III)
			Hepatic	3.6			
			Renal	3.6			
			Bd Wt	3.6			

TABLE 2-2. Levels of Significant Exposure to Chromium - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg Cr/kg/day)	LOAEL		Reference/ Form
					Less Serious (mg Cr/kg/day)	Serious (mg Cr/kg/day)	
74	Rat (Long- Evans)	2-3 yr 7 d/wk (W)	Cardio	0.46			Schroeder et al. 1965 $Cr(CH_3COO)_3$ (III)
			Hepatic	0.46			
			Renal	0.46			
			Bd Wt	0.46			

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

[b]Case study of a 17-year-old, 60 kg boy who died after ingesting 5 g potassium dichromate [1,750 mg chromium(VI)]; 1,750 mg/60 kg = 29 mg chromium(VI)/kg.

[c]Case study of 14-year-old boy who died after ingesting 1.5 g potassium dichromate [0.53 mg chromium(VI)]. Since body weight was not reported, the standard 70 kg body weight was used to calculate the dose of 7.5 mg chromium(VI)/kg.

[d]Case study of 44-year-old man who died after ingesting liquid containing ~2.8g chromium(VI) as chromium trioxide; ~4.1 mg chromium(VI)/kg body weight.

(III) = trivalent; (VI) = hexavalent; avg = average; Bd Wt = body weight; $CaCrO_4$ = calcium chromate; 1 x = one time; (C) = capsule; Cardio = cardiovascular; Cr = chromium; $Cr(CH_3COO)_3H_2O$ = chromium acetate monohydrate; $CrCl_3$ = chromium trichloride; $Cr(NO_3)_39H_2O$ = chromium nitrate nonahydrate; CrO_3 = chromium trioxide; Cr_2O_3 = chromium oxide; $Cr_2(SO_4)_3$ = chromium sulfate; d = day(s); environ = environmental; (F) = feed; F = female; F_1 = first generation; F_2 = second generation; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; (IN) = direct ingestion; $K_2Cr_2O_4$ = potassium chromate; $K_2Cr_2O_7$ = potassium dichromate; Ld = lactational day; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Na_2CrO_4 = sodium chromate; $NaCr_2O_7$ = sodium dichromate; $Na_2Cr_2O_72H_2O$ = sodium dichromate dihydrate; $(NH_4)_2Cr_2O_7$ = ammonium dichromate; NOAEL = no-observed-adverse-effect level; NS = not specified; (occup) = occupational; PND = post natal day; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; (W) = drinking water; wk = week(s); yr = year(s)

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

Acute (≤14 days)

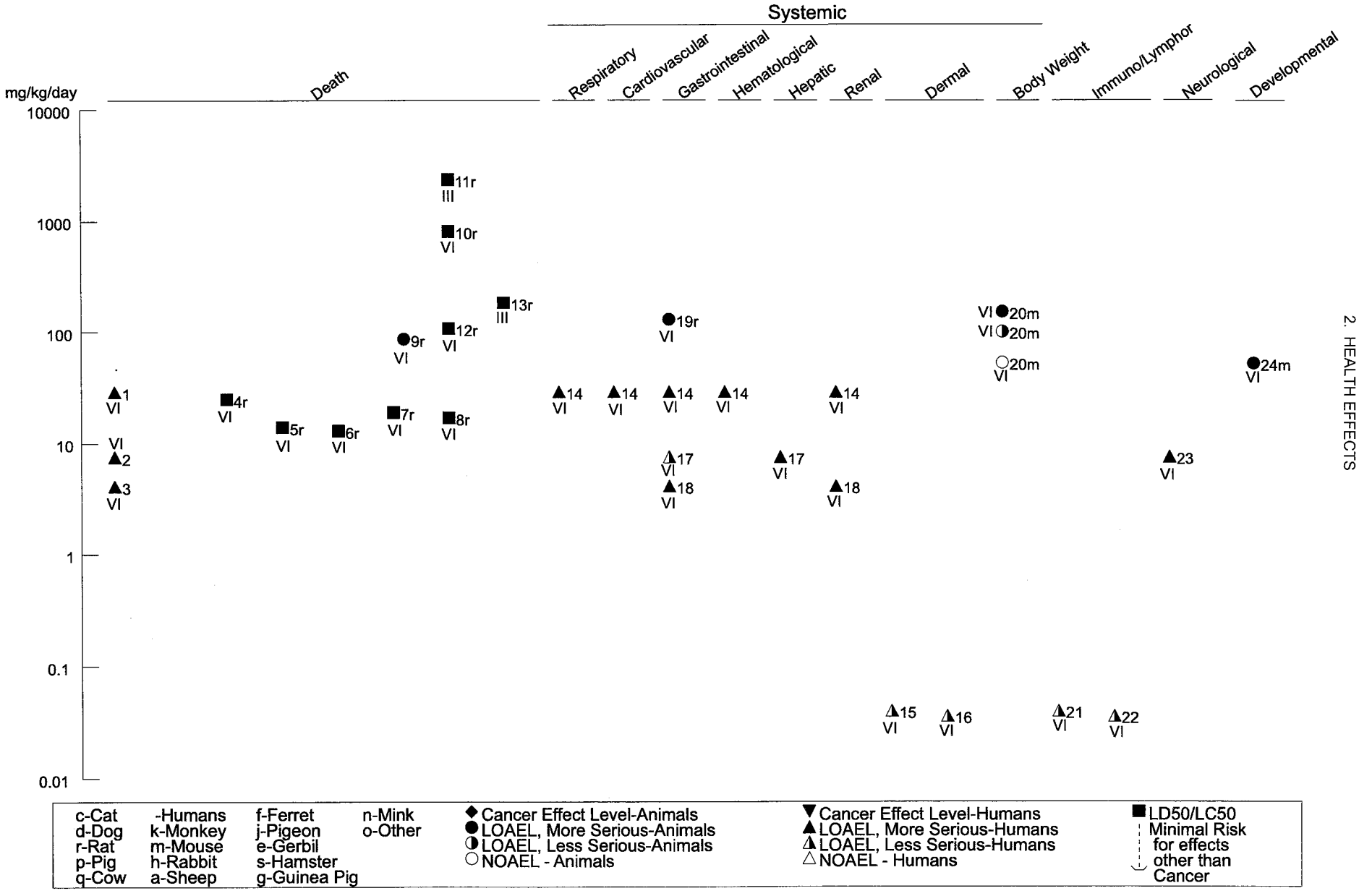


Figure 2-2. Levels of Significant Exposure to Chromium - Oral (*continued*)

Intermediate (15-364 days)

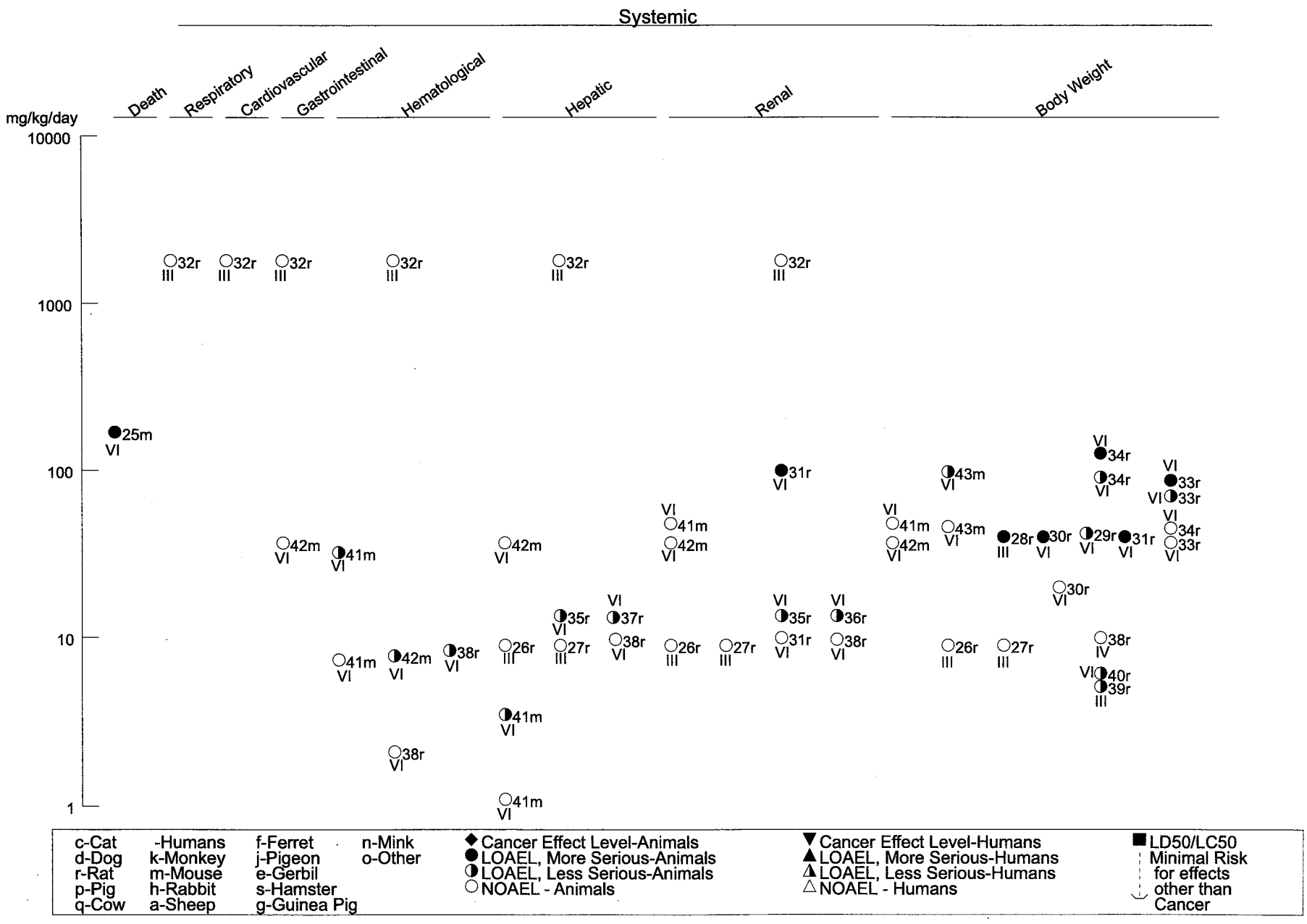


Figure 2-2. Levels of Significant Exposure to Chromium - Oral (*continued*)

Intermediate (15-364 days)

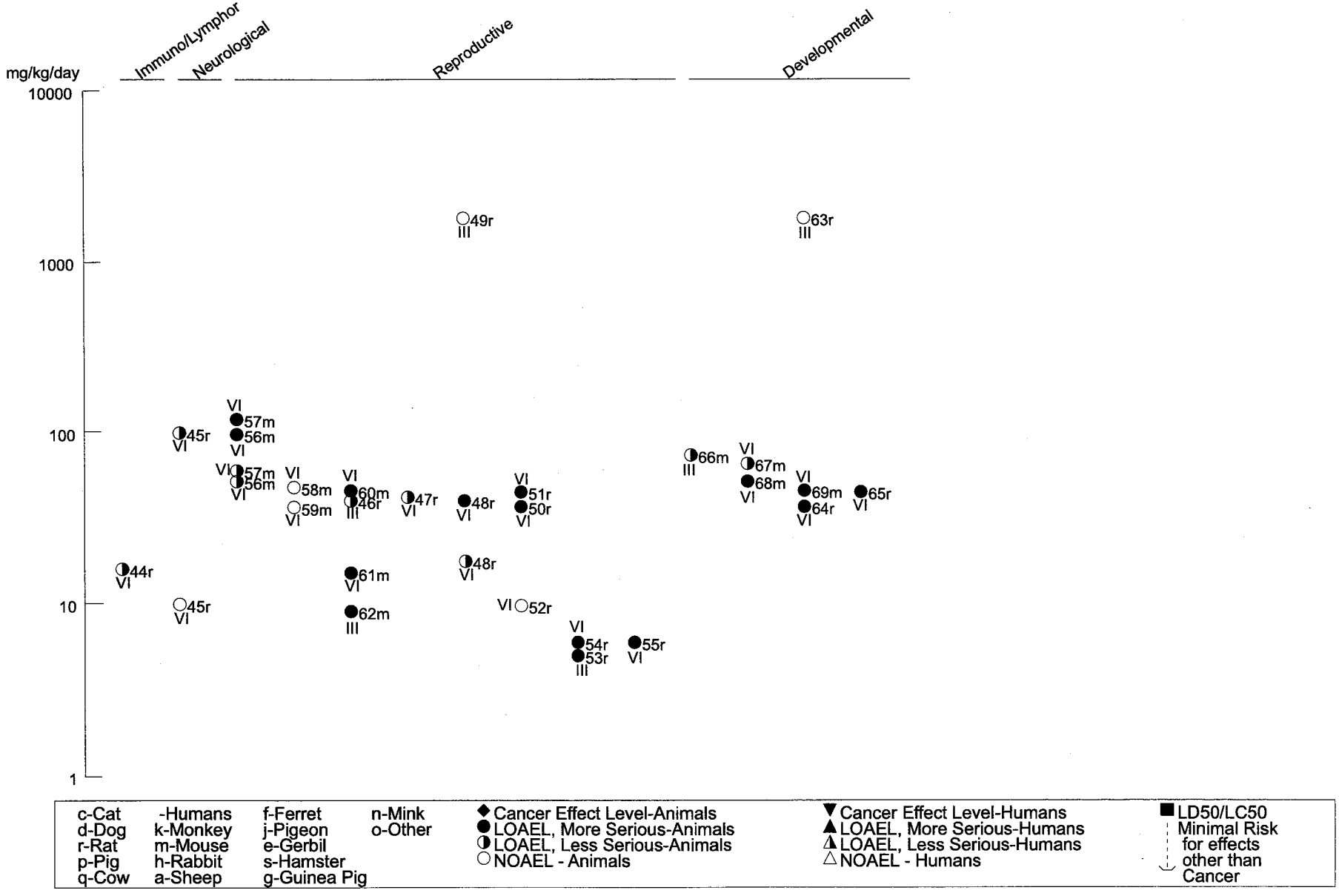
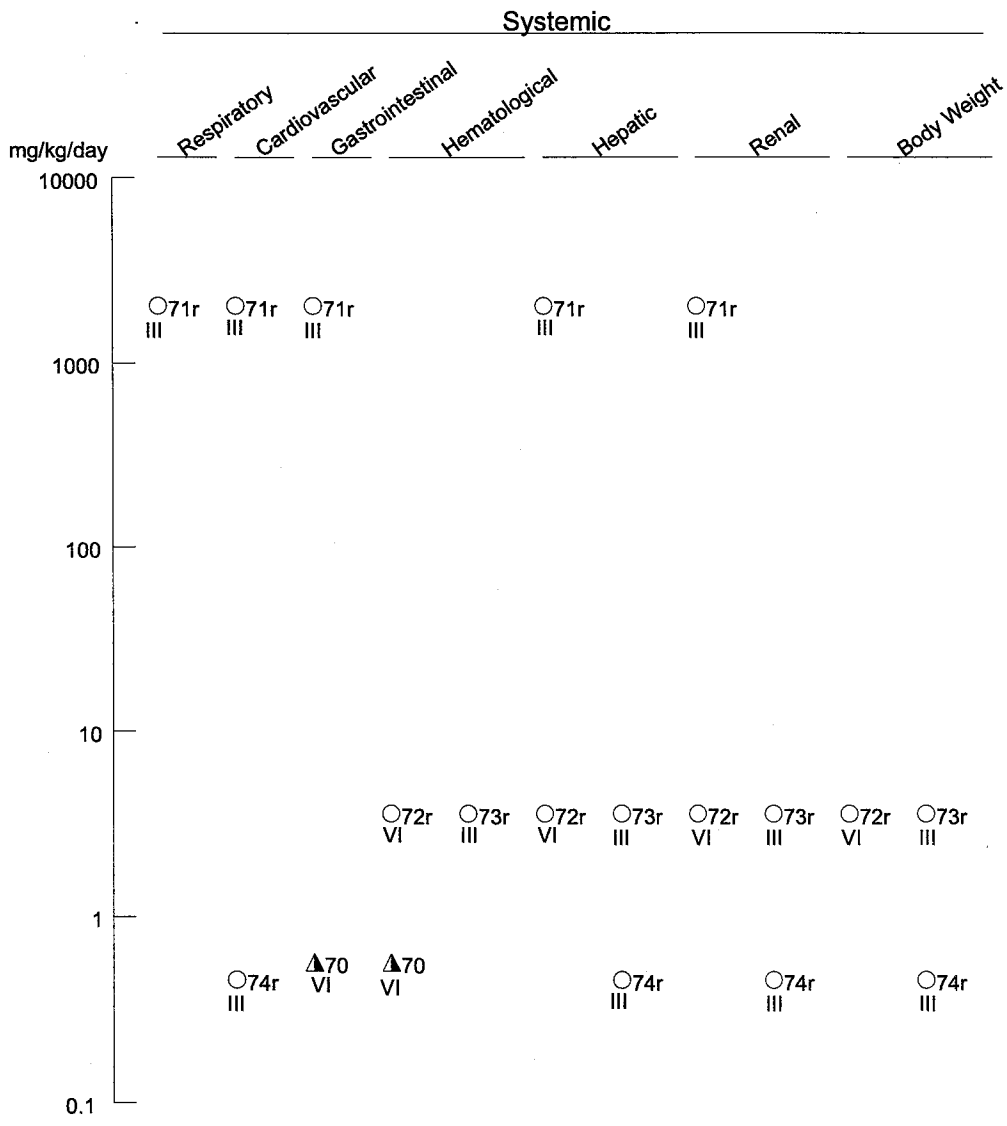


Figure 2-2. Levels of Significant Exposure to Chromium - Oral (*continued*)

Chronic (≥365)



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

and blood pressure dropped progressively during treatment in the hospital of a 17-year-old male who had ingested 29 mg chromium(VI)/kg as potassium dichromate. He died of cardiac arrest. Autopsy revealed hemorrhages in the anterior papillary muscle of the left ventricle (Clochesy 1984; Iserson et al. 1983). Cardiovascular effects have not been reported at nonlethal doses.

No reliable studies were located regarding cardiovascular effects in animals after oral exposure to chromium(VI) compounds. Histological examination revealed no lesions in the hearts of rats exposed to 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975), or in rats exposed to 0.46 mg chromium(III)/kg/day as chromium acetate in drinking water for 2–3 years (Schroeder et al. 1965). Neither of these studies assessed cardiovascular end points such as blood pressure or electrocardiograms.

Gastrointestinal Effects. Cases of gastrointestinal effects in humans after oral exposure to chromium(VI) compounds have been reported. In one study, a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate experienced abdominal pain and vomiting before death. Autopsy revealed gastrointestinal ulceration (Kaufman et al. 1970). In another study, a 44-year-old man died of gastrointestinal hemorrhage after ingesting 4.1 mg chromium(VI)/kg as chromic acid solution (Saryan and Reedy 1988). Gastrointestinal burns and hemorrhage have also been described as contributing to the cause of death of infants who ingested unknown amounts of sodium dichromate (Ellis et al. 1982) or ammonium dichromate (Reichelderfer 1968) and a 17-year-old male who ingested .29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983).

Some chromium(VI) compounds, such as potassium dichromate and chromium trioxide, are caustic and irritating to mucosal tissue. A 25-year-old woman who drank a solution containing potassium dichromate experienced abdominal pain and vomited (Goldman and Karotkin 1935). Two people who ate oatmeal contaminated with potassium dichromate became suddenly ill with severe abdominal pain and vomiting, followed by diarrhea (Partington 1950). Acute gastritis developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965).

Ingestion of chromium compounds as a result of exposure at the workplace has occasionally produced gastrointestinal effects. In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, in addition to symptoms of labored breathing, dizziness, headache, and weakness from breathing the fumes during work, workers experienced nausea and

vomiting upon eating on the premises (Lieberman 1941). Gastrointestinal effects were also reported in an epidemiology study of 97 workers in a chromate plant exposed to dust containing both chromium(III) and chromium(VI) compounds. Blocked nasal passages, as a result of working in the dust laden atmosphere, forced the individuals to breathe through their mouths, thereby probably ingesting some of the chromium dust. A 10.3% incidence of gastric ulcer formation and a 6.1% incidence of hypertrophic gastritis was reported. Epigastric and substernal pain were also reported in the chromate production workers (Mancuso 1951). Gastric mucosa irritation resulting in duodenal ulcer, possibly as a result of mouth breathing, has also been reported in other studies of chromate production workers (Sassi 1956; Sterechova et al. 1978). Subjective symptoms of stomach pain, duodenal ulcers, gastritis, stomach cramps, and indigestion were reported by workers exposed to a mean concentration of 0.004 mg chromium(VI)/m^3 in an electroplating facility where zinc, cadmium, nickel, tin, and chromium plating were carried out (Lucas and Kramkowski 1975). An otolaryngological examination of 77 employees of eight chromium electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m^3, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophic changes in the left larynx (Hanslian et al. 1967). These effects were probably also due to exposure via mouth breathing.

In a cross sectional study conducted in 1965 of 155 villagers whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The 20 mg chromium(VI)/L concentration is equivalent to a dose of 0.57 mg chromium(VI)/kg/day, using a default reference water consumption rate and body weight value of 2 L/day and 70 kg, respectively (note that these values may not be appropriate for the Chinese study population).

Gastrointestinal hemorrhage was observed in rats given a lethal gavage dose of potassium dichromate (130 mg chromium(VI)/kg) (Samitz 1970). No adverse effects were observed in rats fed 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years, as indicated by histopathology of the stomach and small intestine (Ivankovic and Preussmann 1975).

Hematological Effects. Cases of hematological effects have been reported in humans after the ingestion of lethal or sublethal doses of chromium(VI) compounds. In a case of an 18-year-old woman who ingested a few grams of potassium dichromate, decreased hemoglobin content and hematocrit, and increased total white blood cell counts, reticulocyte counts, and plasma hemoglobin were found 4 days after ingestion. These effects were indicative of intravascular hemolysis (Sharma et al. 1978). A 25-year-old woman who drank a solution containing potassium dichromate had a clinically significant increase in leukocytes due to a rise in polymorphonuclear cells (Goldman and Karotkin 1935). In another study, a 44-year-old man had decreased hemoglobin levels 9 days after ingestion of 4.1 mg chromium(VI)/kg as chromic acid solution that probably resulted from gastrointestinal hemorrhage (Saryan and Reedy 1988). Inhibition of blood coagulation was described in a case of a 17-year-old male who died after ingesting .29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). Anemia following severe hemorrhaging developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965).

In a cross sectional study conducted in 1965 of 155 villagers whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and leukocytosis and immature neutrophils. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The 20 mg chromium(VI)/L concentration is equivalent to a dose of 0.57 mg chromium(VI)/kg/day.

Minor hematological effects were observed in animals after oral exposure to chromium(VI), but no hematological effects were observed in animals after oral exposure to chromium(III) compounds. Routine hematological examination revealed no changes in rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958). In feeding studies of potassium dichromate in rats and mice, the only hematological effects consisted of slightly reduced mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values (NTP 1996a, 1996b, 1997). In rats and mice fed potassium dichromate for 9 weeks, MCV and MCH values were decreased at the highest concentration only, which was equivalent to 8.4 and 9.8 mg chromium(VI)/kg/day in male and female rats, respectively (NTP 1996b) and 32.2 and 48 mg chromium(VI)/kg/day in male and female mice respectively (NTP 1996a). These effects did not occur at lower dietary concentrations equivalent to #2.1 or #2.45 mg chromium(VI)/kg/day for male and female rats, respectively, or to #7.35 or #12 mg

chromium(VI)/day for male and female mice, respectively. In a multigeneration study of mice given potassium dichromate in the diet, F_1 males had decreased MCVs at dietary concentrations equivalent to 16 and 36.7 mg chromium(VI)/kg/day and decreased MCH values at 36.7 mg chromium(VI)/kg/day (NTP 1997). F_1 females had dose-related decreased MCVs at concentrations equivalent to $7.8 mg chromium(VI)/kg/day. Since 7.8 mg chromium(VI)/kg/day was the lowest dose in the study, a no effect level was not identified. Although the statistically significant decreases in MCVs and MCH values were small and often within normal ranges for these species, the consistent finding of these effects in the three studies led NTP to conclude that potassium dichromate exposure did result in slight hematopoietic toxicity.

No hematological abnormalities were found in rats fed diets providing 1,806 mg chromium(III)/kg/day as chromium oxide 5 days/week for 90 days (Ivankovic and Preussmann 1975), or in rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958).

Hepatic Effects. Effects on the liver have been described in case reports of humans who had ingested chromium(VI) compounds. Liver damage, evidenced by the development of jaundice, increased bilirubin, and increased serum lactic dehydrogenase, was described in a case of a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L (Fristedt et al. 1965). In a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate, high levels of the liver enzymes, glutamic-oxaloacetic transaminase (aspartate aminotransferase) and glutamic-pyruvic transaminase (alanine aminotransferase), were found in the serum 24 hours after ingestion. Upon postmortem examination, the liver had marked necrosis (Kaufman et al. 1970).

Effects on the liver of rats exposed to chromium compounds have been detected by biochemical and histochemical techniques. Rats treated by gavage with 13.5 mg chromium(VI)/kg/day as potassium chromate for 20 days had increased accumulations of lipids (Kumar and Rana 1982) and changes and relocalization of liver enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, cholinesterase, and lipase) (Kumar et al. 1985), as determined by histochemical means. No morphological changes, however, were detected in the livers of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958). In another study, no treatment-related histological changes in liver cells were observed in groups of Sprague-Dawley rats containing 24 males and 48 females that were exposed to chromium(VI) as potassium dichromate in the diet for 9 weeks followed by a recovery period of 8 weeks (NTP 1996b).

Average daily ingestion of chromium(VI) for males was 1, 3, 6, and 24 mg/kg/day and 1, 3, 7, and 28 mg/kg/day for females. Although no indication of hepatic effects was found in mice exposed to #36.7 mg/kg/day in a multigeneration feeding study (NTP 1997), some indication of liver toxicity was found in a 9-week feeding study in mice exposed to 1.1, 3.5, 7.4, and 32 mg chromium(VI)/kg/day for males and 1.8, 5.6, 12, and 48 mg chromium(VI)/kg/day for females (NTP 1996a). Hepatocyte cytoplasmic vacuolization occurred in 1/6 males at 3.5 mg/kg/day, 2/5 males at 7.4 mg/kg/day, and 2/6 males at 32 mg/kg/day, and in 1/12 control females, 0/12 females at 1.8 mg/kg/day, 3/12 females at 5.6 mg/kg/day, 2/12 females at 12 mg/kg/day, and 4/12 females at 48 mg/kg/day. The vacuoles were small, clear, and well demarcated, which is suggestive of lipid accumulation. The small number of animals and lack of a clear dose-response preclude a definitive conclusion as to whether this effect was toxicologically significant. Rats orally exposed to chromium(III) compounds had no evidence of liver damage. Histological examination revealed no morphological changes in the livers of rats exposed to 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975), of rats exposed to 2.7 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958), of rats exposed to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate in the diet for 20 weeks (Anderson et al. 1997b), or of rats exposed to 0.46 mg chromium(III)/kg/day as chromium acetate in the drinking water for 2–3 years (Schroeder et al. 1965).

Renal Effects. Case studies were located regarding renal effects in humans after oral exposure to chromium(VI) compounds. Acute renal failure, characterized by proteinuria, hematuria, followed by anuria, developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis (Fristedt et al. 1965). Necrosis of renal tubules was found upon autopsy of a 22-month-old boy who died after ingesting an unknown amount of sodium dichromate (Ellis et al. 1982) and of a 17-year-old boy who died after ingesting 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). A fatal ingestion of 4.1 mg chromium(VI)/kg as a chromic acid solution in a 44-year-old man resulted in acute tubular necrosis and renal failure (Saryan and Reedy 1988). A 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate died from renal failure 8 days after he was admitted to the hospital. Upon postmortem examination, the kidneys were pale, enlarged, and necrotic with tubular necrosis and edema (Kaufman et al. 1970). Another case study of an 18-year-old woman who ingested a few grams of potassium dichromate reported proteinuria, oliguria, and destruction of the tubular epithelium of the kidneys. She regained renal function following dialysis (Sharma et al. 1978).

Proteinuria and oliguria were also observed after ingestion of potassium dichromate by a 25-year-old woman (Goldman and Karotkin 1935).

Effects on the kidneys of rats exposed to potassium chromate have been detected by biochemical and histochemical techniques. Rats treated by gavage with 13.5 mg chromium(VI)/kg/day for 20 days had increased accumulation of lipids and accumulated triglycerides and phospholipids in different regions of the kidney than controls (Kumar and Rana 1982). Similar treatment of rats also resulted in inhibition of membrane enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, and lipase) in the kidneys (Kumar and Rana 1984). Oliguria and proteinuria were observed in rats exposed to 100 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). However, histological examination revealed no morphological changes in the kidneys of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (MacKenzie et al. 1958). Animals exposed to oral doses of chromium(III) compounds had no evidence of kidney damage. Histological examination revealed no morphological changes in the kidneys of rats exposed to 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975), of rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in drinking water for 1 year (MacKenzie et al. 1958), of rats exposed to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate in the diet for 20 weeks (Anderson et al. 1997b), or of rats exposed to 0.46 mg chromium(III)/kg/day as chromium acetate in the drinking water for 2–3 years (Schroeder et al. 1965).

Dermal Effects. Administration of 0.04 mg chromium(VI)/kg as potassium dichromate in an oral tolerance test exacerbated the dermatitis of a building worker who had a 20-year history of chromium contact dermatitis. A double dose led to dyshidrotic lesions (vesicular eruptions) on the hands (Goitre et al. 1982). Dermatitis in 11 of 31 chromium-sensitive individuals worsened after ingestion of 0.036 mg chromium(VI)/kg as potassium dichromate (Kaaber and Veien 1977). The sensitizing exposures were not discussed or quantified.

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

Body Weight Effects. Significant decreases in body weight gain have been reported in two intermediate-duration potassium dichromate drinking water studies. A 19% decrease in body weight gain was observed male rats exposed to 42 mg chromium(VI)/kg/day for 12 weeks (Bataineh et al. 1997) and a 10% decrease was reported in male mice exposed to 6 mg chromium(VI)/kg/day for 12 weeks. No

changes in body weight gain were seen in rats or mice exposed to 9.8 or 48 mg chromium(VI)/kg/day, respectively, as potassium dichromate in the diet for 9 weeks (NTP 1996a, 1996b). In contrast, gavage administration of 40 or 60 mg chromium(VI)/kg/day as sodium dichromate resulted in a 57 and 59% decrease in body weight gain, respectively (Chowdhury and Mitra 1995). No alterations in body weight gain were observed in rats chronically (1 year) exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water (Mackenzie et al. 1958).

Several studies have examined the effect of exposure to potassium dichromate in drinking water on maternal body weight gain. An acute exposure (9 days) resulted in 8 and 24% decreases in body weight gain in pregnant mice exposed to 101 or 152 mg chromium(VI)/kg/day, respectively (Junaid et al. 1996b). Similarly, a decrease in maternal body weight gain was observed in pregnant mice exposed to 98 mg chromium(VI)/kg/day as potassium dichromate for 19 days (Trivedi et al. 1989). Reduced maternal body weight gains of 8, 14, and 21% were observed in rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Similar decreases in body weight gain (18 and 24%) were observed in rats exposed to 89 or 124 mg chromium(VI)/kg/day, respectively, for 3 months prior to mating (Kanojia et al. 1998). However, no alterations in maternal body weight gain were observed in a continuous breeding study in which rats were exposed to 36.7 mg chromium(VI)/kg/day as potassium dichromate in the diet (NTP 1997).

Dietary exposure to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate for 20 weeks (Anderson et al. 1997b) or 3.6 mg chromium(III)/kg/day as chromium chloride (Mackenzie et al. 1958) did not result in significant alterations in body weight gain. However, exposure to chromium chloride in drinking water resulted in a 14 and 24% decrease in body weight gain in rats exposed to 40 mg chromium(III)/kg/day for 12 weeks (Bataineh et al. 1997) and mice exposed to 5 mg chromium(III)/kg/day for 12 weeks (Elbetieha and Al-Hamood 1997), respectively. No alterations in body weight gain were observed in rats or mice exposed to 0.46 or 0.48 mg chromium(III)/kg/day, respectively, as chromium acetate for a lifetime (Schroeder et al. 1964, 1965).

2.2.2.3 Immunological and Lymphoreticular Effects

The only reported effect of human exposure on the immune system was the exacerbation of chromium dermatitis in chromium-sensitive individuals as noted for dermal effects in Section 2.2.2.2.

Splenocytes prepared from rats given potassium chromate in their drinking water at 16 mg chromium(VI)/kg/day for 3 weeks showed an elevated proliferative response of T-and B-lymphocytes to the mitogens, concanavalin A and liposaccharide, compared with splenocytes from control rats. A 5-fold enhancement of the proliferative response to mitomycin C was also seen when splenocytes from rats exposed for 10 weeks were incubated with splenocytes from nonexposed rats and additional chromium (0.1 mg chromium(VI)/L) was added to the incubation compared to the system without added chromium. It was suggested that these increased proliferative responses represent chromium-induced sensitization (Snyder and Valle 1991). The LOAEL values are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

The only information regarding neurological effects in humans after oral exposure to chromium(VI) is the report of an enlarged brain and cerebral edema upon autopsy of a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate (Table 2-2 and Figure 2-2). These effects may be the result of accompanying renal failure (Kaufman et al. 1970).

A decrease in motor activity and balance was reported in rats given 98 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986) (Table 2-2 and Figure 2-2). Histological examination of the brain and nervous system did not reveal abnormalities in rats fed 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975); however, more sensitive neurological, neurochemical, or neurobehavioral tests were not conducted.

2.2.2.5 Reproductive Effects

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

A number of studies have reported reproductive effects in rats and mice orally exposed to chromium(VI). Sodium dichromate(VI) was administered by gastric intubation to groups of 10 mature male Charles Foster strain rats at levels of 20, 40, and 60 mg chromium(VI)/kg/day for 90 days (Chowdhury and Mitra 1995). Testis weight, population of Leydig cells, seminiferous tubular diameter, testicular protein, DNA, and RNA were all significantly reduced at 40 and 60 mg chromium(VI)/kg/day. The number of spermatogonia was not affected by treatment; however, resting spermatocytes (high dose), pachytene

spermatocytes (high dose, intermediate dose) and stage-7 spermatid (high and intermediate doses) counts were significantly reduced and were treatment related. Testicular activity of succinic dehydrogenase was significantly lowered in the two high-dose groups, testicular cholesterol concentrations were elevated in the highest-dosed group, and both serum testosterone and testicular levels of 3β-Δ^5-hydroxysteroid dehydrogenase were significantly lowered. The authors also determined that the total testicular levels of ascorbic acid in the two higher-dosing groups was about twice that of the control values whereas, in the highest-treated group the total ascorbic acid levels were about half those of controls. At the low dose (20 mg/kg/day), testicular protein, 3β-Δ^5-hydroxysteroid dehydrogenase, and serum testosterone were decreased. The authors indicated that chromium enhanced levels of the vitamin, but at the highest dose testicular levels became exhausted, thus decreasing the ability of the cells to reduce chromium(VI).

Significant alterations in sexual behavior and aggressive behavior were observed in male Sprague-Dawley rats exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in the drinking water for 12 weeks (Bataineh et al. 1997). The alterations in sexual behavior included decreased number of mounts, lower percentage of ejaculating males, and increased ejaculatory latency and post-ejaculatory interval. The adverse effects on aggressive behavior included significant decreases in the number of lateralizations, boxing bouts, and fights with the stud male and ventral presenting. No significant alterations in fertility were observed when the exposed males were mated with unexposed females.

Mice exposed for 7 weeks to 15.2 mg chromium(VI)/kg/day as potassium dichromate in the diet had reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules. Morphologically altered sperm occurred in mice given diets providing 28 mg chromium(VI)/kg/day as potassium dichromate (Zahid et al. 1990). No effect was found on testis or epididymis weight, and reproduction function was not assessed. In contrast, an increase in testes weight was observed in mice exposed to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks. At the next highest dose (14 mg chromium(VI)/kg/day), decreases in seminal vesicle and preputial gland weights were observed (Elbetieha and Al-Hamood 1997). In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 males and 48 females of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. For mice, the average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for males and 1.8, 5.7, 12.0, and 48 mg/kg/day for females. For rats, the average daily ingestions of chromium(VI) were 0.35, 1.05, 2.1, and 8.4 mg/kg/day for males and 0.35, 1.05, 2.45, and 9.8 mg/kg/day for females (NTP 1996b). Microscopic

examinations of the ovaries showed no treatment-related effects, and examination of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects.

Murthy et al. (1996) reported a number of reproductive effects in female Swiss albino mice exposed to potassium dichromate in drinking water for 20 days. The observed effects included a significant reduction in the number of follicles at different stages of maturation at $60 mg chromium(VI)/kg/day, reduction in the number of ova/mice at $120 mg chromium(VI)/kg/day, significant increase in estrus cycle duration at 180 mg chromium(VI)/kg/day, and histological alterations in the ovaries (e.g., proliferated, dilated, and congested blood vessels, pyknotic nuclei in follicular cells, and atretic follicles) at $120 mg chromium(VI)/kg/day. The severity of the reproductive effects appeared to be dose-related. In an ancillary study, electron microscopy of selected ovarian tissues revealed ultrastructural changes (disintegrated cell membranes of two-layered follicular cells and altered villiform cristae of mitochondria and decreased lipid droplets in interstitial cells) in mice exposed to 1.2 mg chromium(VI)/kg/day for 90 days; the toxicological significance of these alterations is not known. The study authors suggest that the effects observed in the interstitial cells may be due to a reduction in lipid synthesizing ability, which could lead to decreased steroid hormone production. An increase in relative ovarian weight was observed in female mice exposed for 12 weeks to 14 mg chromium(VI)/kg/day as potassium dichromate (Elbetieha and Al-Hamood 1997).

Several studies have reported increases in preimplantation losses and resorptions in rats and mice exposed to chromium(VI). Exposure of pregnant mice to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in increased preimplantation and postimplantation loss, and decreased litter size. Maternal body weight gain decreased at doses $98 mg chromium(VI)/kg/day (Trivedi et al. 1989). In female Swiss albino mice exposed for 20 days prior to mating to potassium dichromate in drinking water at concentrations that resulted in doses of 0, 52, 98, or 169 mg chromium(VI)/kg/day and then mated, the number of corpora lutea was decreased at 169 mg/kg/day, preimplantation loss and resorptions were increased at $98 mg/kg/day, and placental weights were decreased at $57 mg/kg/day (Junaid et al. 1996a). Increases in the number of resorptions were also found in female Swiss albino rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 20 days prior to mating (Kanojia et al. 1996). Additional reproductive effects observed at 70 or 87 mg chromium(VI)/kg/day include decreased number of corpora lutea, decreased number of implantations, and increased number of pre-implanation losses. A treatment-related increase in the length of estrus cycle was significantly different from controls only in the 87 mg

chromium(VI)/kg/day group. Decreased mating, decreased fertility, and increased pre- and post-implantation loss were observed in female Druckrey rats receiving doses of 45, 89, and 124 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 3 months prior to mating; the 89 and 124 mg chromium(VI)/kg/day groups exhibited increased resorptions as well (Kanojia et al. 1998). A decrease in fertility (decreased number of implantations and viable fetuses) was observed in male and female mice that were exposed to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks and then were mated with unexposed males and females (Elbetieha and Al-Hamood 1997). An increase in the number of mice with resorptions was also observed in the exposed females.

In a multigeneration reproductive assessment by continuous breeding study of BALB/c mice were fed a diet containing potassium dichromate(VI). Males and females were exposed to chromium for 7 days and then 20 pairs (F_0) in each dose group were allowed to continuously mate for 85 days (NTP 1997). The mean doses of chromium(VI) in F_0 animals were 6.8, 13.5, and 30.0 mg/kg/day. Litters produced during the 85-day mating period were examined at postnatal day 1. There were no treatment related changes in average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time. There were no dose related gross pathological organ differences observed for both F_0 males and females, nor any differences in organ to body weight ratios. At the highest dose the F_0 females had lower mean body weights than control animals by about 7%. There were no effects on sperm number or motility, nor were there any increases in abnormal sperm morphology. Histopathological examination of livers and kidneys from F_0 males and females showed no changes that were treatment related. F_1 litters produced after 85 days were reared by the dam until weaning on post-natal day 21 then separated and allowed to mature for about 74 days. At that time, 20 pairs were allowed to mate and produce F_2 progeny. Mean exposures to chromium(VI) to F_1 animals were determined to be 7.8, 16.0, and 36.7 mg/kg/day. F_2 litters were reared by the dam until weaning on post-natal day 21 before being sacrificed. There were no differences in F_2 average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time between exposed groups and controls. There were no dose-related gross pathological organ differences observed for both F_1 males and females, nor any differences in organ to body weight ratios. No histological lesions were observed in liver and kidney cells that were dose related, nor did chromium(VI) have any effects on estrous cycling.

Chromium(III) as chromium oxide did not cause reproductive effects in rats. Male and female rats fed 1,806 mg chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before gestation and throughout the gestational period were observed to have normal fertility, gestational length, and litter size (Ivankovic and Preussmann 1975). A study by Bataineh et al. (1997) found significant alterations in

sexual behavior (reductions in the number of mounts, increased post-ejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats exposed to 40 mg chromium(III)/kg/day as chromium chloride in the drinking water for 12 weeks. Male fertility indices (assessed by impregnation, number of implantations, and number of viable fetuses) did not appear to be adversely affected by exposure to chromium chloride, although the untreated females mated to treated males exhibited an increase in the total number of resorptions (Bataineh et al. 1997). In contrast, a decrease in the number of pregnant females was observed following the mating of unexposed females to male mice exposed to 13 mg chromium(III)/kg/day as chromium chloride (Elbetieha and Al-Hamood 1997). Impaired fertility (decreased number of implantations and viable fetuses) was also observed in females exposed to 5 mg chromium(III)/kg/day mated to unexposed males (Elbetieha and Al-Hamood 1997). This study also found increased testes and ovarian weights and decreased preputial gland and uterine weights at 5 mg chromium(III)/kg/day. At lower concentrations of chromium chloride (9 mg chromium(III)/kg/day in the diet for 20 weeks), no alterations in testes or epididymis weights were observed in rats (Anderson et al. 1997b). A similar exposure to chromium(III) picolinate also did not result in testes or epididymis weight alterations (Anderson et al. 1997b). This study did not assess reproductive function. Mice exposed for 7 weeks to 9.1 mg chromium(III)/kg/day as chromium sulfate in the diet had reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules. Morphologically altered sperm occurred in mice given diets providing 42.4 mg chromium(III)/kg/day as chromium sulfate (Zahid et al. 1990).

As discussed in greater detail in Section 2.2.2.6, the reproductive system is also a target in the developing organism. Delayed vaginal opening and decreased relative weights of the uterus, ovaries, testis, seminal vesicle, and preputial glands were observed in mouse offspring exposed to potassium dichromate or chromium(III) chloride on gestational day 12 through lactation day 20 (Al-Hamood et al. 1998). Impaired fertility was observed in the chromium(III) chloride-exposed female offspring when they were mated with unexposed males (Al-Hamood et al. 1998); no effect on fertility was observed in the male offspring.

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

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

Several animal studies provide evidence that chromium(VI) is a developmental toxicant in rats and mice. A series of studies (Junaid et al. 1996a; Kanojia et al. 1996, 1998) was conducted to assess whether pre-mating exposure to potassium dichromate would result in developmental effects. In the first study, groups of 15 female Swiss albino mice were exposed to 0, 52, 98, or 169 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 days (Junaid et al. 1996a) and then mated with untreated males. At 52 mg chromium(VI)/kg/day, there was a 17.5% post-implantation loss over controls and a 30% decrease in fetal weight. At 98 mg/kg/day, there were decreases in the number of implantation sites, the number of live fetuses, and the fetal weight. There were also increases in the number of resorptions and the number of pre- and post-implantation losses. At 169 mg chromium(VI)/kg/day, there was 100% pre-implantation loss. The fetuses in the 98 mg/kg/day group had higher numbers of sub-dermal hemorrhagic patches and kinky short tails and decreased fetal body weight and crown rump length. Although there were no major skeletal abnormalities in any other treated animals, there was a significant reduction in ossification at 52 mg chromium(VI)/kg/day (53% compared to 12% for controls) and significant reduction in ossification in caudal, parietal and interparietal bones of fetuses at 98 mg chromium(VI)/kg/day. There were no significant soft tissue deformities in any of the treated fetuses. Although dosing occurred prior to mating, internal chromium levels remaining in females after mating may have been toxic to the conceptus that caused adverse developmental effects.

In the second study, female Swiss albino rats were exposed to potassium dichromate concentrations in the drinking water resulting in doses of 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Lower gestational weight gain, increased post-implantation loss, and decreased number of live fetuses were observed in all treatment groups, relative to controls. Increased incidences of reduced fetal ossification in fetal caudal bones were reported at the 70 and 87 mg chromium(VI)/kg/day dose levels; additionally, the 87 mg chromium(VI)/kg/day dose group of fetuses exhibited increased incidences of reduced ossification in parietal and interparietal bones, as well as significant incidences of subdermal hemorrhagic thoracic and abdominal patches (42%), kinky tails (42%), and short tails (53%), relative to 0% in controls. No treatment-related gross visceral abnormalities were seen.

In the third study, groups of 10 female Druckrey rats were exposed to potassium dichromate in the drinking water for 3 months pre-mating at concentrations yielding dose levels of 45, 89, or 124 mg chromium(VI)/kg/day (Kanojia et al. 1998). Reduced maternal gestational weight gain, increased pre- and post-implantation loss, reduced fetal weight, fetal subdermal hemorrhagic thoracic and abdominal patches, increased chromium levels in maternal blood, placenta, and fetuses, and increased incidences of reduced ossification in fetal caudal bones were observed in all treatment groups. In addition, the 89 and 124 mg chromium(VI)/kg/day dose groups exhibited increased resorptions, reduced numbers of corpora lutea and fetuses per litter, reduced implantations, reduced placental weight, increased incidences of reduced ossification in fetal parietal and interparietal bones, and reduced fetal crown-rump length. No treatment-related gross visceral abnormalities were seen.

Exposure of pregnant mice to 57 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in embryo lethal effects (i.e., increased resorptions and increased post-implantation loss), gross abnormalities (i.e., subdermal hemorrhage, decreased cranial ossification, tail kinking), decreased crown-rump length, and decreased fetal weight. The incidence and severity of abnormalities increased at higher doses. Maternal toxicity, evidenced by decreased body weight gain, occurred at doses $120 mg chromium(VI)/kg/day. No implantations were observed in the dams given 234 mg chromium(VI)/kg/day (Trivedi et al. 1989).

Groups of 10 female Swiss albino mice received chromium(VI) as potassium dichromate in drinking water during organogenesis on days 6–14 at levels that provided 0, 53.2, 101.1, and 152.4 mg chromium(VI)/kg/day (Junaid et al. 1996b). No notable changes in behavior or clinical signs were observed in control or treated animals. Reduction of gestational weight gains of 8.2 and 30% were observed for the animals in the intermediate- and high-dose groups. The number of dead fetuses was higher in the high-dose group and fetal weight was lower in both intermediate- and high-dose groups (high dose = 1.06 g, intermediate dose = 1.14 g) as compared to the control value of 1.3 g. The number of resorption sites were 0.31 for controls, 1.00 for the low dose, 1.70 for the intermediate dose, and 2.30 for the high dose, demonstrating a dose-response relationship. The studies also showed that there was a significantly greater incidence of post-implantation loss in the two highest-dose groups of 21 and 34.60% as compared to control value of 4.32%. No significant gross structural abnormalities in any of the treated dosed groups were observed except for drooping of the wrist (carpal flexure) and subdermal hemorrhagic patches on the thoracic and abdominal regions in 16% in the offspring of the high-dose group. Significant reduced ossification in nasal frontal, parietal, interparietal, caudal, and tarsal bones were observed only in the 152.4 mg chromium(VI)/kg/day-treated animals.

Impaired development of the reproductive system was observed in the offspring of female BALB/c mice exposed to 66 mg chromium(VI)/kg/day as potassium chromate in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in vaginal opening was observed. Significant decreases in the numbers of pregnant animals, of implantations, and of viable fetuses were also observed when the female offspring were mated at age 60 days with unexposed males. No developmental effects were observed in the male offspring.

Two studies examined the developmental toxicity of chromium(III) following oral maternal exposure. In the first study, no developmental effects were observed in offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). In contrast, reproductive effects have been observed in the offspring of mice exposed to chromium(III) chloride. Significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) were observed in the offspring of BALB/c mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in timing of vaginal opening was also noted in the female offspring. At age 60 days, the male and female offspring were mated with unexposed animals. No significant alterations in fertility (number of pregnant animals, number of implantations, number of viable fetuses, and total number of resorptions) were observed in the exposed males. A significant decrease in the number of pregnant females (62.5 versus 100% in controls) was observed among the female offspring mated with untreated males. The conflicting results between the Ivankovic and Preussman (1975) study and the Al-Hamood et al. (1998) study may be a reflection on the developmental end points examined or the differences in the species tested.

The NOAEL and LOAEL values for developmental effects in each species are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

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

No increased incidence of micronuclei in polychromatic erythrocytes was observed in mice given single gavage doses of potassium chromate at #86 mg chromium(VI)/kg (Shindo et al. 1989) or in mice exposed

to potassium chromate via drinking water at 1–20 ppm for 48 hours or to bolus doses up to 4 µg/kg for 2 days (Mirsalis et al. 1996). Similarly in rats, no unscheduled DNA synthesis in hepatocytes was found. However, an increase in DNA-protein crosslinking was found in the livers of rats exposed to potassium chromate in the drinking water at $6 mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a).

The clastogenic effects of male Swiss albino mice fed chromium(VI) trioxide (20 mg/kg body weight) by gavage were studied; after 24 hours, bone marrow cells were isolated and 500 metaphase plates were scored for chromosomal aberrations (Sarkar et al. 1993). The treated cells showed a significant increase in aberrations per cell over controls by 4.4-fold. When animals were treated simultaneously with chlorophyllin (1.5 mg/kg), a sodium-copper derivative of chlorophyll and an antioxidant, numbers of aberrations were reduced to nearly background levels.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

A retrospective mortality study conducted on a population who resided in a polluted area near an alloy plant that smelted chromium in the People's Republic of China found increased incidences of lung and stomach cancer. The alloy plant began smelting chromium in 1961 and began regular production in 1965, at which time sewage containing chromium(VI) dramatically increased. The population was followed from 1970 to 1978. The size of the population was not reported. The adjusted mortality rates of the exposed population ranged from 71.89 to 92.66 per 100,000, compared with 65.4 per 100,000 in the general population of the district. The adjusted mortality rates for lung cancer ranged from 13.17 to 21.39 per 100,000 compared with 11.21 per 100,000 in the general population. The adjusted mortality rates for stomach cancer ranged from 27.67 to 55.17 per 100,000, which were reported to be higher than the average rate for the whole district (control rates not reported). The higher cancer rates were found for those who lived closer to the dump site (Zhang and Li 1987). No other information was provided, and it was not possible to estimate exposure levels based on the description of the pollution process. The exposed population was probably exposed by all environmentally relevant routes (i.e., air drinking water, food, soil).

A follow-up study reevaluated this cohort; the adjusted total cancer death rates for the six areas analyzed were 68.8, 68.4, 64.7, 54.3, 57.5, and 45.9 (Zhang and Li 1997). These rates were comparable to the overall provincial rate of 66.1 in which the six exposed regions were located. When total cancer mortality

rates from five villages of the areas using the contaminated water were combined, a significant increase in cancer incidence was observed over provincial incidences. However, total cancer incidences, stomach cancer incidence, or lung cancer incidence did not correlate with the degree of exposure to chromium(VI), with the villages exposed to the lowest drinking water levels having the higher incidences. The authors commented that these more recent analyses of the data probably reflect lifestyle or environmental factors rather than exposure to chromium(VI) being responsible for cancer in these regions.

No evidence of carcinogenicity was found in mice exposed to potassium chromate in drinking water at 9 mg chromium(VI)/kg/day for three generations (880 days). In treated mice, 2 of 66 females developed forestomach carcinoma and 9 of 66 females and 1 of 35 males developed forestomach papilloma. The vehicle controls also developed forestomach papilloma (2 of 79 females, 3 of 47 males) but no carcinoma. The incidence of forestomach tumors in the treated mice was not significantly higher than controls. Co-exposure to both potassium chromate and 3,4-benzpyrene in a similar protocol showed that potassium chromate did not potentiate the carcinogenicity of 3,4-benzpyrene (Borneff et al. 1968). No evidence of carcinogenicity was observed in male or female rats fed diets containing chromium oxide at 2,040 mg chromium(III)/kg/day 5 days/week for 2 years. Moreover, no evidence of carcinogenicity was found in the offspring of these rats after 600 days of observation (Ivankovic and Preussmann 1975).

2.2.3 Dermal Exposure

Some chromium(VI) compounds, such as, chromium trioxide (chromic acid), potassium dichromate, potassium chromate, sodium dichromate, and sodium chromate, are very caustic and can cause burns upon dermal contact. These burns can facilitate the absorption of the compound and lead to systemic toxicity.

2.2.3.1 Death

A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred following the treatment with the chromium(VI) compounds. Death occurred 4 weeks after exposure (Major 1922). Twelve individuals died as a result of infection to necrotic areas of the skin that were caused by application of a salve made up with potassium chromate used to treat scabies. Renal failure was observed. Autopsies revealed fatty degeneration of the heart, hyperemia and necrosis of kidney tubules, and hyperemia of the gastric mucosa (Brieger 1920).

Single-dose dermal LD_{50} values in New Zealand rabbits exposed to chromium(VI) as sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate were determined by Gad et al. (1986). LD_{50} values ranged from 361 to 553 mg chromium(VI)/kg for females and from 336 to 763 mg chromium(VI)/kg for males. Signs of toxicity included dermal necrosis, eschar formation, dermal edema and erythema, and diarrhea and hypoactivity. The dermal LD_{50} value for chromium trioxide was 30 mg chromium(VI)/kg for combined sexes (American Chrome and Chemical 1989). The LD_{50} values are recorded in Table 2-3.

2.2.3.2 Systemic Effects

Several reports of health effects in individuals treated with potassium dichromate are discussed below (Brieger 1920; Major 1922; Smith 1931). The results of these studies should be interpreted cautiously because pre-existing conditions may have contributed to the observed effects. The highest NOAEL value and all reliable LOAEL values for dermal effects in each species and duration category are recorded in Table 2-3.

Respiratory Effects. Occupational exposure to chromium compounds results in direct contact of mucocutaneous tissue, such as nasal and pharyngeal epithelium, due to inhalation of airborne dust and mists of these compounds. Such exposures have led to nose and throat irritation and nasal septum perforation. Because exposure is to airborne chromium, studies noting these effects are described in Section 2.2.1.2.

A case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months noted that he also had breathing difficulties. However, because he also had many previous attacks of hay fever and asthma, it was not possible to distinguish whether his breathing difficulties were caused by or exacerbated by dermal exposure to ammonium dichromate (Smith 1931).

No studies were located regarding respiratory effects in animals after dermal exposure to chromium or its compounds.

TABLE 2-3. Levels of Significant Exposure to Chromium - Dermal

Species (Strain)	Exposure/[a] Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference/ Form
				Less Serious		Serious	
ACUTE EXPOSURE							
Death							
Rabbit (Fischer- 344)	24 hr					30 (LD_{50}) mg/kg	American Chrome and Chemical 1989 CrO_3 (VI)
Rabbit (New Zealand)	once					336 M (LD_{50}) 361 F (LD_{50}) mg/kg	Gad et al. 1986 $Na_2Cr_2O_7 2H_2O$ (VI)
Rabbit (New Zealand)	2 d					426 M (LD_{50}) 553 F (LD_{50}) mg/kg	Gad et al. 1986 Na_2CrO_4 (VI)
Rabbit (New Zealand)	once					403 M (LD_{50}) 490 F (LD_{50}) mg/kg	Gad et al. 1986 $K_2Cr_2O_7$ (VI)
Rabbit (New Zealand)	once					763 M (LD_{50}) 549 F (LD_{50}) mg/kg	Gad et al. 1986 $(NH_4)_2Cr_2O_7$ (VI)
Systemic							
Rat (NS)	once	Hepatic		0.175%	(altered carbohydrate metabolism)		Merkur'eva et al. 1982 $K_2Cr_2O_7$ (VI)
		Dermal		0.175%	(dermatitis)		
Gn pig (albino)	once	Dermal				1.9 M (skin corrosion) mg/kg	Samitz 1970 $K_2Cr_2O_7$ (VI)

TABLE 2-3. Levels of Significant Exposure to Chromium - Dermal (continued)

Species (Strain)	Exposure/[a] Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference/ Form
				Less Serious		Serious	
Gn pig (NS)	3 d 1x/d	Dermal	1 mg/kg				Samitz and Epstein 1962 $Cr_2(SO_4)_3$ (III)
Gn pig (NS)	3 d 1x/d	Dermal		0.35 mg/kg	(skin ulcers)		Samitz and Epstein 1962 $K_2Cr_2O_7$ (VI)
Rabbit (NS)	5 min or 24 hr	Ocular	0.1 mL M of 1000 mg/L				Fujii et al. 1976 Na_2CrO_4 and $Na_2Cr_2O_7$ (VI)
Rabbit (New Zealand)	4 hr	Dermal		47 M mg/kg	(erythema, edema, necrosis)		Gad et al. 1986 $K_2Cr_2O_7$ (VI)
Rabbit (New Zealand)	4 hr	Dermal		42 M mg/kg	(erythema, edema)		Gad et al. 1986 Na_2CrO_4 (VI)
Rabbit (New Zealand)	4 hr	Dermal		55 mg/kg	(necrosis, erythema, edema)		Gad et al. 1986 $(NH_4)_2Cr_2O_7$ (VI)
Rabbit (New Zealand)	4 hr	Dermal		47 M mg/kg	(necrosis, erythema, edema)		Gad et al. 1986 $Na_2Cr_2O_7$ (VI)
Immunological/Lymphoreticular							
Human	once			0.175%	(positive patch test)		Engelbrigsten 1952 $K_2Cr_2O_7$ (VI)
Human	48 hr			0.001%	(increased skin thickness and blood flow)		Eun and Marks 1990 $K_2Cr_2O_7$ (VI)
Human	48 hr			0.37 %	(positive patch test)		Fregert and Rorsman 1964 $CrCl_3.6H_2O$ (III)

TABLE 2-3. Levels of Significant Exposure to Chromium - Dermal (continued)

Species (Strain)	Exposure/[a] Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference/ Form
				Less Serious		Serious	
Human	48 hr			0.26% M	(erythema)		Levin et al. 1959 CrO_3 (VI)
Human	once			0.16 µg/mm^2	(positive patch test)		Mali et al. 1966 $CrCl_3$ (III)
Human	once		0.0013 µg/mm^2	0.0026 µg/mm^2	(positive patch test)		Mali et al. 1966 $K_2Cr_2O_7$ (VI)
Human	once			0.018 µg/cm^2	(positive patch test)		Nethercott et al. 1994 $K_2Cr_2O_7$ (VI)
Human	once		33 µg/cm^2				Nethercott et al. 1994 $CrCl_3$ (III)
Human	2 d			0.175%	(positive patch test)		Newhouse 1963 $K_2Cr_2O_7$ (VI)
Human	48 hr			0.175%	(chromium allergy)		Peltonen and Fraki 1983 $K_2Cr_2O_7$ (VI)
Human	once			0.09 mg	(erythema)		Samitz and Shrager 1966 $K_2Cr_2O_7$ (VI)
Human	once			0.08 mg	(erythema)		Samitz and Shrager 1966 $CrCl_3$ (III)
Human	once			0.33 mg	(erythema)		Samitz and Shrager 1966 $Cr_2(SO_4)_3$ (III)

TABLE 2-3. Levels of Significant Exposure to Chromium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference/ Form
Human	once			0.09% (positive patch test)		Wahba and Cohen 1979 $K_2Cr_2O_7$ (VI)
Human	once			0.09% (positive patch test)		Winston and Walsh 1951 $Na_2Cr_2O_7$ (VI)
Gn pig (albino)	once			0.009 mg/kg (contact sensitivity)		Gross et al. 1968 $K_2Cr_2O_7$ (VI)
Gn pig (albino)	once			0.004 mg/kg (erythematic reaction)		Gross et al. 1968 $CrCl_3$ (III)
Gn pig (NS)	once			0.04 F mg/kg (erythematic reaction)		Jansen and Berrens 1968 $K_2Cr_2O_7$ (VI)
Gn pig (NS)	once			0.03 F mg/kg (erythematic reaction)		Jansen and Berrens 1968 $Cr_2(SO_4)_3$ (III)
INTERMEDIATE EXPOSURE						
Immunological/Lymphoreticular						
Mouse (BALB/c or ICR)	18 d			0.35% (contact sensitivity)		Mor et al. 1988 $K_2Cr_2O_7$ (VI)

TABLE 2-3. Levels of Significant Exposure to Chromium - Dermal (continued)

Species (Strain)	Exposure/[a] Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference/ Form
				Less Serious	Serious	
CHRONIC EXPOSURE						
Systemic						
Human	7.5 yr -avg (range 3-16 yr) (occup)	Resp		0.004 M mg/m^3 (nasal septum ulceration and perforation)		Lucas and Kramkowski 1975 CrO_3 (VI)
		Gastro		0.004 M mg/m^3 (possible gastritis, ulcers)		
		Dermal		0.005 M mg/m^3 (chrome holes)		
Rat (Sprague-Dawley)	2 yr 5 d/wk 6 hr/d	Dermal	15.5 mg/m3			Lee et al. 1989 CrO_2 (IV)

[a]All exposures are expressed in terms of Chromium.

(III) = trivalent; (VI) = hexavalent; 1 x = one time; avg = average; (C) = capsule; $CrCl_3$ = chromium trichloride; CrO_3 = chromium trioxide; $Cr_2(SO_4)_3$ = chromium sulfate; d = day(s); F = female; Gn pig = guinea pig; hr = hour(s); $K_2Cr_2O_4$ = potassium chromate; $K_2Cr_2O_7$ = potassium dichromate; kg = kilogram; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligrams; min = minute(s); Na_2CrO_4 = sodium chromate; $Na_2Cr_2O_7$ = sodium dichromate; $Na_2Cr_2O_72H_2O$ = sodium dichromate dihydrate; $(NH_4)_2Cr_2O_7$ = ammonium dichromate; NOAEL = no-observed-adverse-effect level; NS = not specified; (Occup) = occupational; wk = week(s); yr = year(s)

Cardiovascular Effects. Information regarding cardiovascular effects in humans after dermal exposure to chromium or its compounds is limited. Weak, thready, and markedly dicrotic pulse developed . 1.5 hours after a salve made up with potassium chromate to treat scabies was applied to skin of an unspecified number of individuals. Some of the people died as a result of infection to the exposed area, and autopsy revealed degeneration of the heart (Brieger 1920).

No studies were located regarding cardiovascular effects in animals after dermal exposure to chromium or its compounds.

Gastrointestinal Effects. Vomiting occurred soon after application of a salve made up of potassium chromate to the skin of an unspecified number of individuals for the treatment of scabies. Some of these individuals died as a result of infection of the exposed area, and autopsy revealed hyperemia of the gastric mucosa (Brieger 1920).

Diarrhea was reported in New Zealand rabbits exposed to lethal concentrations of chromium(VI) compounds (Gad et al. 1986).

Hematological Effects. Severe leukocytosis, with notable increases in immature polymorphonuclear cells, myelocytes, and myeloblasts and nucleated red cells and Howell-Jolly bodies, indicative of hemolytic anemia were observed in individuals after application of a salve that contained potassium chromate to treat scabies (Brieger 1920). Leukocytosis was also described in a case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months (Smith 1931). It should be noted that the man had a history of asthma.

No studies were located regarding hematological effects in animals after dermal exposure to chromium compounds.

Musculoskeletal Effects. Information regarding musculoskeletal effects in humans after dermal exposure to chromium or its compounds is limited to a case report. A man was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months. He also had tenderness and edema of the muscles of the extremities (Smith 1931).

No studies were located regarding musculoskeletal effects in animals after dermal exposure to chromium or its compounds.

Hepatic Effects. No reliable studies were located regarding hepatic effects in humans after dermal exposure to chromium compounds.

Information regarding liver effects in animals after dermal exposure to chromium or its compounds is limited. A single application of 0.5% potassium dichromate (0.175% chromium(VI)) to the shaved skin of rats resulted in increased levels of serotonin in the liver, decreased activities of acetylcholinesterase and cholinesterase in the plasma and erythrocytes, increased levels of acetylcholine in the blood, and increased glycoprotein hexose in the serum. These effects may indicate alterations in carbohydrate metabolism (Merkur'eva et al. 1982).

Renal Effects. Acute nephritis with albuminuria and oliguria, polyuria, and nitrogen retention were observed in individuals after application of a salve that contained potassium chromate. These effects disappeared in individuals who survived. Autopsy of people who died revealed hyperemia and tubular necrosis (Brieger 1920). Acute nephritis with polyuria and proteinuria were also described in a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months (Smith 1931). A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred after treatment with the chromium(VI) compound. Urinalysis revealed marked protein in the urine. Death resulted 4 weeks after exposure. A postmortem examination of the kidneys revealed extensive destruction of the tubular epithelium (Major 1922).

No studies were located regarding renal effects in animals after dermal exposure to chromium compounds.

Dermal Effects. Occupational exposure to airborne chromium compounds has been associated with effects on the nasal septum, such as ulceration and perforation. These studies are discussed in Section 2.2.1.2 on Respiratory Effects. Dermal exposure to chromium compounds can cause contact allergic dermatitis in sensitive individuals, which is discussed in Section 2.2.3.3. Skin burns, blisters, and skin ulcers, also known as chrome holes or chrome sores, are more likely associated with direct dermal contact with solutions of chromium compounds, but exposure of the skin to airborne fumes and mists of chromium compounds may contribute to these effects.

Acute dermal exposure of humans to chromium(VI) compounds causes skin burns. Necrosis and sloughing of the skin occurred in individuals at the site of application of a salve containing potassium chromate. Twelve of 31 people died as a result of infection of these areas (Brieger 1920). In another case, a man who slipped at work and plunged his arm into a vat of chromic acid had extensive burns and necrosis on his arm (Cason 1959).

Longer-term occupational exposure to chromium compounds in most chromium-related industries can cause deep penetrating holes or ulcers on the skin. A man who had worked for a few months in a planographic printing establishment, where he handled and washed sheets of zinc that had been treated with a solution of ammonium dichromate, had skin ulceration on both hands (Smith 1931).

In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, 50% of the chromate workers had skin ulcers or scars. In addition, inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontis due to exposure of these mucocutaneous tissues to airborne chromium were observed in higher incidence in the chromate workers than in controls. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m^3 air); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m^3); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m^3 air) (PHS 1953). Among 258 electroplating workers exposed to chromium trioxide fumes at 0.1 mg chromium(VI)/m^3 for <1 year, 5% developed dental lesions, consisting of yellowing and wearing down of the teeth (Gomes 1972). In a retrospective morbidity study of employees who had worked in a chromate production facility in North Carolina for at least 1 year from 1971, when the facility began producing chromates, to 1989, 156 of 289 workers who responded to a questionnaire reported at least 1 occurrence of dermal chrome sores. Personal monitoring results, which were available for 1974–1989, revealed 8-hour TWA concentrations of airborne chromium(VI) ranging from below the detection limit (0.001 mg chromium(VI)/m^3 prior to 1984; 0.006 mg/m^3 thereafter) to 0.289 mg/m^3, with >99% of the samples measuring <0.05 mg/m^3. Forty-five workers also had previous occupational exposure to chromium at other chromate production facilities, where exposure concentrations were undoubtedly higher. Statistical analysis revealed that the chrome sores were associated with cumulative chromium exposure, duration of employment at the North Carolina facility, duration of previous employment at other chromate production facilities, and smoking. It was suggested that smokers might be less likely to wear protective gloves (Pastides et al. 1991).

Irritation and ulceration of the buccal cavity, as well as chrome holes on the skin, were also observed in workers in a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes (Lieberman 1941). Electroplaters in Czechoslovakia exposed to an average of 0.414 mg chromium(VI)/m^3 above the plating baths also had high incidences of buccal cavity changes, including chronic tonsillitis, pharyngitis, and papilloma (Hanslian et al. 1967). In a study of 303 electroplating workers in Brazil, whose jobs involve working with cold chromium trioxide solutions, >50% had ulcerous scars on the hands, arms, and feet. Air monitoring revealed that most workers were exposed to $0.1 mg chromium(VI)/$m^3$, but even those exposed to <0.1 mg chromium(VI)/m^3 developed lesions (Gomes 1972). Chrome holes were also noted at high incidence in chrome platers in Singapore, while controls had no skin ulcers (Lee and Goh 1988). The incidence of skin ulcers was significantly increased in a group of 997 chrome platers compared with 1,117 controls. The workers had been exposed to chromium(VI) in air and in dust. The air levels were generally <0.3 mg chromium(VI)/m^3, and dust levels were generally between 0.3 and 97 mg chromium(VI)/g (Royle 1975b). In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, seven workers reported past history of skin sores, and nine had scars characteristic of healed chrome sores. The workers had been employed for an average of 7.5 years and were exposed to a mean concentration of 0.004 mg chromium(VI)/m^3 in air. In addition, spot tests showed widespread contamination of almost all workroom surfaces and hands (Lucas and Kramkowski 1975).

An early report of cases of chrome ulcers in leather tanners noted that the only workmen in tanneries who suffered chrome holes were those who handled dichromate salts. In one of these cases, the penetration extended into the joint, requiring amputation of the finger (Da Costa et al. 1916). In a medical survey of a chemical plant that processed chromite ore, 198 of 285 workers had chrome ulcers or scars on the hands and arms. These workers had been exposed to one or more chromium(VI) compounds in the form of chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate (Edmundson 1951).

Similar dermal effects have been observed in animals. Dermal application of chromium(VI) compounds to the clipped, nonabraded skin of rabbits at 42–55 mg/kg resulted in skin inflammation, edema, and necrosis. Skin corrosion and eschar formation occurred at lethal doses (see Section 2.2.3.1) (Gad et al. 1986). Application of 0.01 or 0.05 mL of 0.34 molar solution of potassium dichromate (0.35 mg chromium(VI) or 1.9 mg chromium(VI)/kg) to the abraded skin of guinea pigs resulted in skin ulcers (Samitz 1970; Samitz and Epstein 1962). Similar application of 0.01 mL of a 1 molar solution of

chromium sulfate (1 mg chromium(III)/kg) however, did not cause skin ulcers in guinea pigs (Samitz and Epstein 1962).

Dermal sensitization due to hypersensitivity to chromium is discussed in Section 2.2.3.3.

Ocular Effects. An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The housewives included in the study were those who lived in the area from 1978 to 1988, and controls included housewives who lived in uncontaminated areas. Questionnaires, physical examinations, and clinical tests were conducted annually. Higher incidences of subjective complaints of eye irritation were reported by the exposed population than by the control population in the early years of the survey, but in later years the difference between the two groups became progressively less (Greater Tokyo Bureau of Hygiene 1989).

Direct contact of the eyes with chromium compounds also causes ocular effects. Corneal vesication was described in a worker who accidentally got a crystal of potassium dichromate or a drop of a potassium dichromate solution in his eye (Thomson 1903). In an extensive study of chromate workers in seven U.S. chromate production plants, eyes were examined because accidental splashes of chromium compounds into the eye had been observed in these plants. Congestion of the conjunctiva was found in 38.7% of the 897 workers, discharge in 3.2%, corneal scaring in 2.3%, any abnormal finding in 40.8%, and burning in 17.0%, compared with respective frequencies of 25.8, 1.3, 2.6, 29.0, and 22.6% in 155 nonchromate workers. Only the incidences of congestion of the conjunctiva and any abnormal findings were significantly higher in the exposed workers than in the controls (PHS 1953).

Instillation of 0.1 mL of a 1,000 mg chromium(VI)/L solution of sodium dichromate and sodium chromate (pH 7.4) was not irritating or corrosive to the eyes of rabbits (Fujii et al. 1976). Histological examination of the eyes of rats exposed to chromium dioxide (15.5 mg chromium(IV)/m^3) in air revealed no lesions (Lee et al. 1989).

2.2.3.3 Immunological and Lymphoreticular Effects

In addition to the irritating and ulcerating effects, direct skin contact with chromium compounds elicits an allergic response, characterized by eczema or dermatitis, in sensitized individuals. Numerous studies have investigated the cause of dermatitis in patients and in workers in a variety of occupations and

industries and have determined that chromium compounds are the sensitizing agents. In these studies, patch tests were conducted with chromium(VI) or chromium(III) compounds using various concentrations (see Table 2-3). In one study using 812 healthy volunteers, patch testing with a 0.5% solution of potassium dichromate chromium(VI) revealed chromium sensitivity in 14 of the volunteers (1.7% of the test population). Of the 14 positive reactions, 10 occurred in a group of 110 offset printers, lithographers, and printing plant cleaners with concurrent exposure to chromium (Peltonen and Fraki 1983). Subjects with a sensitivity to chromium and challenged with a 0.001% solution potassium dichromate had increased skin thickness and blood flow (Eun and Marks 1990). Studies conducted on chromium(VI) sensitive printers and lithographers indicate that chromium(VI) compounds elicit reactions more frequently than do chromium(III) compounds (Levin et al. 1959; Mali et al. 1966; Samitz and Schrager 1966). The authors attributed this to a greater degree of permeation of the hexavalent form than the trivalent form through the skin (see Section 2.3.1.3). Patch testing of chromium(VI)-sensitive patients with chromium(III) compounds has revealed that high concentrations of chromium(III) compounds can elicit an allergic reaction (Fregert and Rorsman 1964, 1966; Mali et al. 1966).

In a study of skin disease among workers at an automobile factory, 230 workers with skin disease and 66 controls were patch tested with potassium dichromate (0.175% chromium(VI)). Sensitivity to potassium dichromate was seen in 24% of the patients and 1% of the controls. Most of the sensitive patients were assemblers who handled nuts, bolts, screws, and washers, which were found to have chromate on the surfaces as a result of a chromate dip used in the engine assembly process. Discontinuation of use of the chromate dip resulted in a significant decrease in the prevalence of dermatitis 6 months later (Newhouse 1963). Among 300–400 men directly exposed to cement dust, 8 had clinical symptoms of cement eczema. All eight tested positive with potassium dichromate, while only four tested positive with cement (Engebrigsten 1952). Patch testing of employees of the Baltimore and Ohio Railroad system with a variety of chemicals revealed that in 32 of 98 cases of dermatitis, the antirust diesel-engine coolant compound, which contained sodium chromate, was the etiological agent (Kaplan and Zeligman 1962). Among 200 employees who worked in a diesel locomotive repair shop, 6 cases of chromate dermatitis were diagnosed by positive patch tests to samples of radiator fluid and to 0.25% sodium dichromate (0.09% chromium(VI)). The radiator fluid to which the workers were occupationally exposed contained 66% sodium dichromate (Winston and Walsh 1951). A search for the source of chromium exposure in workers who developed contact dermatitis in wet sandpapering of primer paint on automobiles revealed that the paint contained zinc chromate (Engel and Calnan 1963).

In a study of 1,752 patients considered to have occupational dermatoses, contact dermatitis was the main diagnosis in 1,496 patients (92% women, 83% men). The allergic type, as opposed to the irritant type, was more prevalent in men (73%) than in women (51%). Positive patch tests to chromium (not otherwise specified) occurred in 8% of the women and 29% of the men. Among 280 chromium-sensitized men, 50% were employed in building and concrete work, 17% in metal work, and 12% in tanneries. In the 42 chromium-sensitized women, 20% were in cement work, 19% in metal work, 28% in cleaning, and 15% in laboratory work (Fregert 1975).

Chromate sensitivity has also been reported in women who frequently used dichromate-containing detergent and bleach (Wahba and Cohen 1979).

Other industries and sources of chromium that have resulted in chromium sensitivity include welding, printing, glues, wood ash, foundry sand, match heads, machine oils, timber preservative, boiler linings, making of television screens, magnetic tapes, tire fitting, chrome plating, wood and paper industry, and milk testing (Burrows 1983).

A study was performed on 54 volunteers who were sensitive to chromium-induced allergic contact dermatitis to determine a dose-response relationship and to determine a minimum-elicitation threshold concentration (MET) that produces an allergic response in sensitive individuals (Nethercott et al. 1994). Patch testing was performed on the subjects in which the concentration of potassium chromate(VI) was varied up to 4.4 µg chromium/cm^2. Two percent (1/54) had a MET of 0.018. About 10% were sensitized at 0.089 µg/cm^2 and all were sensitized at 4.4 µg/cm^2. Comparable studies were performed with chromium(III) chloride, however, only 1 showed a positive response at 33 µg chromium/cm^2, and upon retesting was negative. Based on these findings the authors concluded that soil concentrations of chromium(VI) and chromium(III) of 450 and 165,000 ppm, respectively, should not pose a hazard of allergic contact dermatitis to 99.99% of people who might be exposed to chromium through soil-skin contact.

Animals can also be sensitized to chromium compounds. Contact sensitivity was induced in mice by rubbing a solution of 1% potassium dichromate (0.35% chromium(VI)) . 50 times on the shaved abdomens. Challenge with potassium dichromate on the ear resulted in significant induction of sensitivity, measured by ear thickness and histologically observed infiltration of nucleophilic leukocytes (Mor et al. 1988).

Guinea pigs can be sensitized to chromium(VI) and chromium(III) compounds by a series of intradermal injections of 0.009 mg chromium(VI)/kg as potassium dichromate or of 0.004 mg chromium(III)/kg as chromium trichloride. Regardless of the compound used to sensitize the guinea pigs, subsequent patch testing with chromium(VI) or chromium(III) yielded the same erythmatic reaction. The response, however, was greater when chromium(VI) was used as the sensitizer (Gross et al. 1968). Similarly, the same erythmatic response to chromium(VI) and chromium(III) compounds was noted in guinea pigs sensitized to 0.04 mg chromium(VI)/kg as potassium dichromate or 0.03 mg chromium(III)/kg as chromium sulfate (Jansen and Berrens 1968).

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

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity 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 chromium compounds.

2.3 TOXICOKINETICS

Overview.

The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. Naturally occurring chromium compounds are generally in the trivalent state (chromium(III)), while hexavalent chromium compounds (chromium(VI)) are produced industrially by the oxidation of chromium(III) compounds. Absorption of chromium(VI) compounds is higher than that of chromium(III) compounds. This is because the chromate anion $(CrO_4)^{2-}$ can enter cells via facilitated

diffusion through non-specific anion channels (similarly to phosphate and sulfate anions). Absorption of chromium(III) compounds is via passive diffusion and phagocytosis. Absorption of inhaled chromium compounds takes place in the lung via transfer across cell membranes and in the gastrointestinal tract from particles cleared from the lungs. Absorption after oral exposure in humans varies from essentially none for the highly insoluble chromium(III) compound chromic oxide, to 0.5–2.0% for chromium(III) compounds in the diet, to approximately 2–10% for chromium(VI) as potassium chromate. Dermal absorption depends on the physical and chemical properties of the compound, the vehicle, and the integrity of the skin. Concentrated solutions of chromium(VI) compounds such as potassium chromate can cause chemical burns and facilitate absorption. Once in the blood, chromium compounds are distributed to all organs of the body. Particles containing chromium can be retained in the lung for years after occupational exposure. Chromium(VI) is unstable in the body and is reduced to chromium(V), chromium(IV), and ultimately to chromium(III) by many substances including ascorbate and glutathione. It is believed that the toxicity of chromium(VI) compounds results from damage to cellular components during this process (e.g., generation of free radicals). There is also evidence in *in vitro* experiments that chromium(III) can be reduced to chromium(II) and exert toxic effects. Absorbed chromium is excreted primarily in urine, the half-time for excretion of chromium administered as potassium chromate is estimated to be 35–40 hours in humans. Hair and nails are minor pathways of excretion.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages.

The identification of chromium in urine, serum and tissues of humans occupationally exposed to soluble chromium(III) or chromium(VI) compounds in air indicates that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). In most cases, chromium(VI) compounds are more readily absorbed from the lungs than chromium(III) compounds, due in part to differences in the capacity to penetrate biological membranes. Nevertheless, workers exposed to chromium(III) lignosulfonate dust at 0.005–0.23 mg chromium(III)/m^3 had clearly detectable concentrations of chromium in the urine at the end of their shifts. Based on a one compartment kinetic

model, the biological half-life of chromium(III) from the lignosulfonate dust was 4–10 hours which is the same order of magnitude as the half-life for chromium(VI) compounds (Kiilunen et al. 1983).

Rats exposed to 2.1 mg chromium(VI)/m^3 as zinc chromate 6 hours/day achieved steady state concentrations in the blood after . 4 days of exposure (Langård et al. 1978). Rats that were exposed for a single inhalation of chromium(VI) trioxide mist from electroplating at a concentration of 3.18 mg chromium(VI)/m^3 for 30 minutes rapidly absorbed chromium from the lungs. The content of chromium in the lungs declined from 13.0 mg immediately after exposure to 1.1 mg at 4 weeks in a triphasic pattern with an overall half-life of 5 days (Adachi et al. 1981). In another study in which rats were exposed to chromium(VI) as potassium dichromate or to chromium(III) as chromium trichloride, the pulmonary clearance of both valence states was dependent on particle size, but chromium(VI) was more rapidly and extensively transported to the bloodstream than chromium(III). The rats had been exposed to 7.3–15.9 mg chromium(VI)/m^3 as potassium dichromate for 2–6 hours or to 8 or 10.7 mg chromium(III)/m^3 as chromium trichloride for 6 or 2 hours, respectively. Chromium(VI) particles of 1.5 or 1.6 µm had a two-compartment pulmonary clearance curve with half-lives of 31.5 hours for the first phase and 737 hours for the second phase. Chromium(VI) particles of 2 µm had a single component curve with a half-life between 151 and 175 hours. Following exposure to chromium(VI), the ratio of blood chromium/lung chromium was 1.44 at 0.5 hours, 0.81 at 18 hours, 0.85 at 48 hours, and 0.96 at 168 hours after exposure. Chromium(III) particles of 1.5–1.8 µm had a single component pulmonary clearance curve with a half-life of 164 hours. Following exposure to chromium(III), the ratio of blood chromium/lung chromium was 0.39 at 0.5 hours, 0.24 at 18 hours, 0.22 at 48 hours, and 0.26 at 168 hours after exposure. Therefore, the amount of chromium(VI) transferred to the blood from the lungs was always at least three times greater than the amount of chromium(III) transferred (Suzuki et al. 1984). Other studies reporting absorption from the lungs are intratracheal injection studies (Baetjer et al. 1959b; Bragt and van Dura 1983; Visek et al. 1953; Wiegand et al. 1984, 1987). These studies indicate that 53–85% of chromium(VI) compounds (particle size <5 µm) are cleared from the lungs by absorption into the bloodstream or by mucociliary clearance in the pharynx; the rest remain in the lungs. Absorption by the bloodstream and mucociliary clearance was only 5–30% for chromium(III) compounds.

The kinetics of three chromium(VI) compounds, sodium chromate, zinc chromate, and lead chromate, were compared in rats in relation to their solubility. The rats received intratracheal injections of the ^{51}chromium-labeled compounds (0.38 mg chromium(VI)/kg as sodium chromate, 0.36 mg chromium(VI)/kg as zinc chromate, or 0.21 mg chromium(VI)/kg as lead chromate). Peak blood levels of ^{51}chromium were reached after 30 minutes for sodium chromate (0.35 µg chromium/mL), and 24 hours

for zinc chromate (0.60 µg chromium/mL) and lead chromate (0.007 µg chromium/mL). At 30 minutes after administration, the lungs contained 36, 25, and 81% of the respective dose of the sodium, zinc, and lead chromate. On day 6, >80% of the dose of all three compounds had been cleared from the lungs, during which time the disappearance from lungs followed linear first-order kinetics. The residual amount left in the lungs on day 50 or 51 were 3.0, 3.9, and 13.9%, respectively. The results indicate that zinc chromate, which is . 1,000 times less soluble than sodium chromate, is more slowly absorbed from the lungs, but peak blood levels are higher than sodium chromate. Lead chromate was more poorly and slowly absorbed, as indicated by very low levels in blood and other tissues, and greater retention in the lungs (Bragt and van Dura 1983).

The fate of lead chromate(VI), chromium(VI) trioxide, chromium(III) oxide and chromium(III) sulfate were examined when solutions or suspensions of these chemicals were slowly infused into the tracheal lobe bronchus of sheep via bronchoscopic catheterization (Perrault et al. 1995). At 2, 3, 5, and 30 days the samples of bronchoalveolar lavage were taken, and on day 31 the animals were sacrificed and lung specimens were examined for chromium particulates. There was no difference in lung particle concentrations among the four different compounds. The values ranged from $1.02x10^5$ to $0.14x10^5$ particles/g dry tissue compared to control values of $0.03x10^5$. The alveolar clearance of slightly soluble chromium(III) oxide and chromium sulfate was calculated to be 11 and 80 days, respectively. The insoluble lead chromate particles appeared to break up, forming isometric particles of lead chromate as well as lead-containing particulates that may have retarded clearance. Retention of chromium particulates from exposure to soluble chromium trioxide may have resulted in the formation of a less soluble hydroxyl complex and/or chemical interaction between chromium and protein that prolongs the retention of the metal. Analyses of the particulates in lavage samples indicate that these diameters increase with time for lead chromate, decrease with time for chromium sulfate and chromium trioxide, and are unchanged for chromium(III) oxide. The authors state that their findings indicate that slightly soluble chromium(III) oxide and chromium sulfate that are chemically stable can be cleared from lungs at different rates, depending on the nature and morphology of the compound.

Amounts of total chromium were measured in lymphocytes, blood, and urine after intratracheal administration of either sodium dichromate(VI) or chromium(III) acetate hydroxide (a water-soluble chromium(III) compound) to male Wistar rats (Gao et al. 1993). The total amount of chromium administered was 0.44 mg Cr/kg body weight for each compound. The highest concentrations in tissues and urine occurred at 6 hours after treatment, the first time point examined. Mean chromium concentrations (n= 4 rats per time point) from treatment with chromium(III) were 56.3 µg/L in whole

blood, 96 µg/L in plasma, 0.44 µg/10^{10} in lymphocytes, and 4,535.6 µg/g creatinine in urine. For treatment with chromium(VI) the levels were 233.2 µg/L for whole blood, 138 µg/L for plasma, 2.87 µg/10^{10} for lymphocytes, and 2,947.9 µg/g creatinine in urine. The levels in lymphocytes in the chromium(III) treated animals were no different than in untreated animals. However, for chromium(VI) the lymphocyte levels were about 6-fold higher than control values. After 72 hours, the chromium levels were significantly reduced. These results suggest that absorbed chromium(III) compounds may be excreted more rapidly than absorbed chromium(VI) compounds because of a poorer ability to enter cells.

2.3.1.2 Oral Exposure

Chromium(III) is an essential nutrient required for normal energy metabolism. The National Research Council recommends a dietary intake of 50–200 µg/day (NRC 1989). The biologically active form is an unidentified organic complex of chromium(III) often referred to as GTF. Chromium(III) picolinate is a common form of chromium(III) nutritional supplementation.

Approximately 0.5–2.0% of dietary chromium(III) is absorbed via the gastrointestinal tract of humans (Anderson et al. 1983; Anderson 1986) as inferred from urinary excretion measurements. The absorption efficiency is dependent on the dietary intake. At low levels of dietary intake (10 µg), .2.0% of the chromium is absorbed. When intake is increased by supplementation to $40 µg, the absorption efficiency drops to .0.5% (Anderson et al. 1983; Anderson 1986). Although Mertz (1969) reported that some chromium(III) complexes are absorbed at 25%, this has not been corroborated by other studies (Anderson 1981).

The bioavailability of chromium(III) was determined in 8 healthy adults who were administered 400 µg chromium(III)/day as chromium picolinate for 3 consecutive days by Gargas et al. (1994). The mean absorption of chromium was 2.8%±1.4 % (standard deviation).

Urinary excretion data from 15 female and 27 male subjects given 200 µg chromium(III) as chromium trichloride indicated that gastrointestinal absorption was at least 0.4% (Anderson et al. 1983). Net absorption of chromium(III) by a group of 23 elderly subjects who received an average of 24.5 µg/day (0.00035 mg chromium(III)/kg/day) from their normal diets was calculated to be 0.6 µg chromium(III)/day, based on an excretion of 0.4 µg chromium/day in the urine and 23.9 µg chromium/ day in the feces, with a net retention of 0.2 µg/day. Thus about 2.4% was absorbed. The retention was considered adequate for their requirements (Bunker et al. 1984).

Studies using both chromium(VI) and chromium(III) indicated that chromium(VI) is better absorbed. The 6-day fecal and 24-hour urinary excretion patterns of radioactivity in groups of 6 volunteers given chromium(III) as chromium trichloride or chromium(VI) as sodium chromate labeled with ^{51}chromium, indicated that at least 0.5% and 2.1% of the chromium(III) and chromium(VI) compounds, respectively, were absorbed. After intraduodenal administration, absorption of the chromium(III) compound was not changed, while at least 10% of the chromium(VI) compound was absorbed. These studies further showed that chromium(VI) compounds are reduced to chromium(III) compounds in the stomach, thereby accounting for the relatively poor gastrointestinal absorption of orally administered chromium(VI) compounds (Donaldson and Barreras 1966). Gastric juices taken from the stomachs of patients effectively reduced chromium(VI) as sodium dichromate to chromium(III) *in vitro*, and the extent of reduction was directly related to the amount of gastric juice. The peak reduction occurred for gastric juice collected 3–4 hours after the patients were given meals, when gastric secretion is greatly stimulated, and amounted to tens of µg chromium(VI) reduced per mL gastric juice per hour. It was estimated that total reduction of chromium(VI) in the gastric environment is on the order of several tens of mg/day (De Flora et al. 1987a).

Comparative absorption of chromium(III) and chromium(VI) was examined under similar dosing conditions (Kuykendall et al. 1996). Four male volunteers ingested 5 mg of chromium(VI) as potassium dichromate in 0.5 L of water with the complete dose swallowed within 2 minutes. In one dosing group, the chromium(VI) was placed in orange juice to reduce the chromium(VI) to the less absorbed trivalent state. Based on body weight, the estimated dose was 0.06 mg chromium(VI)/kg in both trials. Bioavailability based on 14-day urinary excretion was 0.6% (range 0.31–0.82%) for chromium(III) and 6.9% (range 1.2–18%) for chromium(VI). Peak red blood cell levels, plasma levels, and urinary levels were increased 5.5-, 21-, and 536-fold for those treated with chromium alone but increased only 1.7-, 1.8-, and 62-fold when ingested in orange juice. Peak blood levels were observed at 15–120 minutes.

The amount of absorption of chromium(VI) and chromium(III) was measured in four male and two female volunteers (ages ranging from 25 to 39 years) treated orally with potassium chromate (chromium(VI)) or chromic oxide (chromium(III)) in capsules at doses of 0.005 mg/kg/day and 1.0 mg/kg/day, respectively (Finley et al. 1996b). Subjects were exposed to each compound for 3 days. Based on urinary excretion data, mean absorption of potassium chromate was 3.4% (range 0.69–11.9%). No statistically significant increase in urinary chromium was observed during chromic oxide dosing, indicating that little, if any, was absorbed. In a follow-up study by the same group (Finley et al. 1997), five male volunteers ingested a liter, in three volumes of 333 mL, of deionized water containing

chromium(VI) concentrations ranging from 0.1 to 10.0 mg/L (approximately 0.001–0.1 mg chromium(VI)/kg/day) for 3 days. A dose-related increase in urinary chromium was seen in all subjects and the percent of the dose excreted ranged from <2 to 8%. Dose-related increases in plasma and erythrocyte chromium levels were also observed.

The absorption of chromium, calculated from urinary excretion, was determined following ingestion of a single oral dose of 5 mg chromium as either chromium(III) chloride in 0.5 liters of distilled water, potassium dichromate(VI) in 0.5 liters of orange juice (believed to result in the reduction of the chromium(VI) to chromium(III) and the formation of chromium-organic complexes), or potassium dichromate in 0.5 liters of distilled water (Kerger et al. 1996a). Chromium chloride was absorbed in the lowest amounts (estimated 0.13% bioavailability), whereas the chromium(III)-orange juice was absorbed more efficiently (0.60% bioavailability), with the chromium(VI) absorbed most efficiently (6.9% bioavailability). Plasma concentrations generally peaked around 90 minutes following exposure for all three chromium mixtures tested. All three chromium mixtures caused transient elevations in red blood cell chromium concentrations, with a trend of chromium(IV)>chromium(III)-orange juice >chromium(III).

The absorption of a single bolus dose of chromium(VI) as potassium dichromate has been assessed in male volunteers (Kerger et al. 1997). In this study, 5 volunteers ingested either 2.5 or 5 mg chromium(VI) as a 10 mg/L solution in a 2 minute period. Based on the volunteer's weight, the estimated doses were 0.03 and 0.05 mg chromium(VI)/kg. A peak in plasma and red blood cell chromium was reached within 90 minutes after dosing for the 4 volunteers ingesting 0.05 mg chromium(VI)/kg (average plasma concentration 25 µg chromium/L; range 5.1 to 57 µg/L, average RBC concentration 17.6 µg chromium/L, range 13.5 to 24 µg/L). Peak plasma chromium concentration was 23 µg chromium/L (at 30 minutes after ingestion) for the 1 volunteer at 0.03 mg chromium(VI)/kg. No chromium(VI) was detected in any of the plasma samples from the 5 volunteers for up to 14 hours post-dosing, indicating that reduction of chromium(VI) had taken place in the gastrointestinal tract or bloodstream. Bioavailability, as assessed by urinary excretion for 4 days after dosing, averaged 5.7% but varied considerably among the volunteers (range 1.1–14.5%). The authors stated that the individual absorbing 14.5% of the dose was an "outlier" compared to other subjects in this and other absorption experiments performed by this group.

In an experiment using three of the same volunteers, chromium(VI) as potassium chromate was given in water at 5 mg chromium/day for 3 consecutive days (Kerger et al. 1997). Three divided doses were taken

at approximately 6 hour intervals over a 5–15 minute period. After at least 2 days without dosing, the 3-day exposure regimen was repeated at 10 mg chromium/day. Estimated doses based on body weight were 0.05 and 0.1 mg/kg/day, respectively. Bioavailability based on 4-day urinary excretion was 1.7% (range 0.5–2.7%) at 0.05 mg chromium(VI)/kg/day and 3.4% (range 0.8–8.0%) at 0.1 mg chromium(VI)/kg/day. Absorption of 0.05 mg chromium(VI)/kg appeared to be somewhat lower when given as three divided doses rather than when given as a single bolus dose (1.7 vs. 5.7%).

Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days. Red blood cell and plasma levels returned to background levels within a few days after exposure was stopped. The data are consistent with a bioavailability of 2% and a plasma elimination half-life of 36 hours.

Studies with ^{51}chromium in animals indicate that chromium and its compounds are also poorly absorbed from the gastrointestinal tract after oral exposure. When radioactive sodium chromate (chromium(VI)) was given orally to rats, the amount of chromium in the feces was greater than that found when sodium chromate was injected directly into the jejunum. Since chromium(III) is absorbed less readily than chromium(VI) by the gastrointestinal tract, these results are consistent with evidence that the gastric environment has a capacity to reduce chromium(VI) to chromium(III). Furthermore, the administration of radioactive chromium(III) or chromium(VI) compounds directly into the jejunum decreased the amount of chromium recovery in the feces indicating that the jejunum is the absorption site for chromium (Donaldson and Barreras 1966). Absorption of either valence state was #1.4% of the administered oral dose in rats (Sayato et al. 1980) and hamsters (Henderson et al. 1979). Based on distribution (see Section 2.3.2.2) and excretion (see Section 2.3.4.2) studies in rats administered chromium by gavage for 2–14 days from various sources, that is, from sodium chromate (chromium(VI)), from calcium chromate (chromium(VI)), or from soil contaminated with chromium (30% chromium(VI) and 70% chromium(III)), the low gastrointestinal absorption of chromium from any source was confirmed. Chromium appeared to be better absorbed from the soil than from chromate salts, but less than 50% of the administered chromium could be accounted for in these studies, partly because not all tissues were examined for chromium content and excretion was not followed to completion (Witmer et al. 1989, 1991). Adult and immature rats given chromium(III) chloride absorbed 0.1 and 1.2% of the oral dose, respectively (Sullivan et al. 1984). This suggests that immature rats may be more susceptible to potential toxic effects of chromium(III) compounds.

Although chromium or chromium compounds alone are poorly absorbed from the gastrointestinal tract, the association of chromium with chelating agents, which may be naturally present in feed, can alter the bioavailability from food. In rats that were given ^{51}chromium-chromium(III) trichloride mixed with chelating agents, either oxalate or phytate, phytate significantly ($p<0.05$) decreased the levels of radioactivity in blood, whole body, and urine achieved with chromium trichloride alone. Oxalate, however, greatly increased the levels in blood, whole body, and urine. The oxalate served as a strong ligand to protect against the tendency of chromium(III) to form insoluble macromolecular chromium oxides at physiological pH. Fasted rats absorbed significantly more ^{51}chromium than did nonfasted rats, indicating that the presence of food in the gastrointestinal tract slows the absorption of chromium. Results of an *in vitro* experiment in this study indicated that the midsection had greater uptake than the duodenum or ileum and that oxalate significantly ($p<0.05$) increased, while phytate significantly ($p<0.05$) decreased the transport of chromium(III) across all three sections, paralleling the *in vivo* results. Ethylenediamine tetraacetic acid (EDTA) and citrate were also tested in the *in vitro* system, but were found to have no effect on chromium(III) intestinal transport; therefore, these chelating agents were not tested *in vivo* (Chen et al. 1973).

Treatment of rats by gavage with a nonencapsulated lead chromate pigment or with a silica-encapsulated lead chromate pigment resulted in no measurable blood levels of chromium (detection limit=10 µg/L) after 2 or 4 weeks of treatment or after a 2-week recovery period. However, kidney levels of chromium were significantly higher in the rats that received the nonencapsulated pigment than in the rats that received the encapsulated pigment, indicating that silica encapsulation reduces the gastrointestinal bioavailability of chromium from lead chromate pigments (Clapp et al. 1991).

2.3.1.3 Dermal Exposure

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Systemic toxicity has been observed in humans following dermal exposure to chromium compounds, indicating significant cutaneous absorption (see Section 2.2.3). Fourteen days after a salve containing potassium chromate was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood, urine, feces, and stomach contents (Brieger 1920) (see Section 2.3.2.3). It should be noted that the preexisting condition of scabies or the necrosis caused by the potassium chromate (see Section 2.2.3) could have facilitated dermal absorption of potassium chromate. Potassium dichromate (chromium(VI)), but not chromium(III) sulfate, penetrated the excised intact epidermis of humans (Mali et al. 1963). Dermal absorption by humans of chromium(III) sulfate in

aqueous solution was negligible, with slightly larger amounts of chromium(III) nitrate in aqueous solution absorbed. The absorption of chromium(III) chloride was similar to potassium dichromate(VI) (Samitz and Shrager 1966). Chromium(III) from a concentrated chromium sulfate solution at pH 3 penetrated cadaverous human skin at a rate of 5×10^{-11} cm/sec, compared with a rate for chromium(VI) (source unspecified) of $5x10^{-7}$ cm/second (Spruit and van Neer 1966). In contrast, both chromium(VI) from sodium chromate and chromium(III) from chromium trichloride penetrated excised human mammary skin at similar rates, but the rate was generally slightly faster for chromium(VI). Absolute rates of absorption in nmol chromium/hour/cm^2 increased with increasing concentration of both chromium(VI) and chromium(III) (Wahlberg 1970). The average rate of systemic uptake of chromium in four volunteers submersed up to the shoulders in a tub of chlorinated water containing a 22 mg chromium(VI)/L solution of potassium dichromate for 3 hours was measured to be $1.5x10^{-4}$ µg/cm^2-hour based on urinary excretion of total chromium (Corbett et al. 1997). The study authors noted that the pattern of blood uptake and urinary excretion was consistent with chromium(III) absorption, suggesting that chromium(VI) is converted to chromium(III) prior to absorption.

The influence of solvent on the cutaneous penetration of potassium dichromate by humans has been studied. The test solutions of potassium dichromate in petrolatum or in water were applied as occluded circular patches of filter paper to the skin. Results with dichromate in water revealed that chromium(VI) penetrated beyond the dermis and penetration reached steady state with resorption by the lymph and blood vessels by 5 hours. About 10 times more chromium penetrated when potassium dichromate was applied in petrolatum than when applied in water. About 5 times more chromium penetrated when potassium dichromate was applied than when a chromium trichloride glycine complex was applied (Liden and Lundberg 1979). The rates of absorption of solutions of sodium chromate from the occluded forearm skin of volunteers increased with increasing concentration. The rates were 1.1 µg chromium(VI)/ cm^2/hour for a 0.01 molar solution, 6.4 µg chromium(VI)/cm^2/hour for a 0.1 molar solution, and 10 µg chromium(VI)/cm^2/hour for a 0.2 molar solution (Baranowska-Dutkiewicz 1981).

Chromium and its compounds are also absorbed dermally by animals. The dermal absorption of sodium chromate (chromium(VI)) by guinea pigs was somewhat higher than that of chromium(III) trichloride, but the difference was not significant. At higher concentrations (0.261–0.398 M), absorption of sodium chromate was statistically higher than that of chromium trichloride. The peak rates of absorption were 690–725 and 315–330 nmol/hour/cm^2 for sodium chromate at 0.261–0.398 M and chromium trichloride at 0.239–0.261 M, respectively. Percutaneous absorption of sodium chromate was higher at pH $6.5 compared with pH #5.6 (Wahlberg and Skog 1965).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Examination of tissues from Japanese chrome platers and chromate refining workers at autopsy revealed higher chromium levels in the hilar lymph node, lung, spleen, liver, kidney, and heart, compared to normal healthy males (Teraoka 1981). Analysis of the chromium concentrations in organs and tissues at autopsy of a man who died of lung cancer 10 years after his retirement from working in a chromate producing plant for 30 years revealed measurable levels in the brain, pharyngeal wall, lung, liver, aorta, kidney, abdominal rectal muscle, suprarenal gland, sternal bone marrow, and abdominal skin. The levels were significantly higher than in five controls with no occupational exposure to chromium. The man had been exposed mainly to chromium(VI), with lesser exposure to chromium(III) as the chromite ore (Hyodo et al. 1980). The levels of chromium were higher in the lungs, but not in the liver or kidneys, of autopsy specimens from 21 smeltery and refinery workers in North Sweden compared with that for a control group of 8 individuals. The amount of enrichment in the lungs decreased as the number of elapsed years between retirement and death increased (Brune et al. 1980). Tissues from three individuals having lung cancer who were industrially exposed to chromium were examined by Mancuso (1997b). One was employed for 15 years as a welder, a second worked for 10.2 years, and a third for 31.8 years in ore milling and preparations and boiler operations. The three cumulative chromium exposures for the three workers were 3.45, 4.59, and 11.38 mg/m^3 years, respectively. Tissues from the first worker were analyzed 3.5 years after last exposure, the second worker 18 years after, and the third worker 0.6 years after last exposure. All tissues from the three workers had elevated levels of chromium with the possible exception of neural tissues. Levels were orders of magnitude higher in lungs than other tissues. The highest lung level reported was 456 mg/10 g tissue in the first worker, 178 in the second worker, and 1,920 for the third worker. There were significant chromium levels in the tissue of the second worker even though he had not been exposed to chromium for 18 years. Chromium concentrations in lung tissues from autopsy samples were 5 times higher in subjects who originated from the Ruhr and Dortmund regions of Germany, where emissions of chromium are high, than in subjects from Munster and vicinity. The lung concentrations of chromium increased with increasing age. Men had twice as high concentrations of chromium in the lungs than did women, which may reflect the greater potential for occupational exposure by men, the higher vital capacity of men, and possibly a greater history of smoking (Kollmeier et al. 1990).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Analysis of chromium levels in women employees of a dichromate manufacturing facility in Russia during and after pregnancy revealed that the exposed women had significantly higher levels of chromium in blood and urine during pregnancy, in umbilical cord blood, placentae, and breast milk at child birth, and in fetuses aborted at 12 weeks than did nonexposed controls (Shmitova 1980). The reliability of this study is suspect because the levels of chromium reported in the blood and urine of the control women were much higher than usual background levels of chromium in these biological fluids (see Section 5.5), perhaps due to problems with analytical methods. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained <0.4 µg/L, and the mean value was 0.3 µg/L (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk.

The distribution of radioactivity in rats given ^{51}chromium as sodium dichromate intratracheally was followed for 40 days by autoradiography and scintillation counting. Three days after the administration of 0.01 mg chromium(VI)/m^3 as radioactive sodium dichromate, the tissue distribution based on the relative concentrations in the tissue was lung > kidney > gastrointestinal tract > erythrocytes > liver > serum > testis > skin. Twenty-five days after dosing, the tissue distribution was lung > kidney > erythrocytes > testis > liver > serum > skin > gastrointestinal tract. Kidney, erythrocytes, and testis maintained their chromium levels for a period of 10–15 days before decreasing (Weber 1983). The distribution of chromium(VI) compared with chromium(III) was investigated in guinea pigs after intratracheal instillation of potassium dichromate or chromium trichloride. At 24 hours after instillation, 11% of the original dose of chromium from potassium dichromate remained in the lungs, 8% in the erythrocytes, 1% in plasma, 3% in the kidney, and 4% in the liver. The muscle, skin, and adrenal glands contained only a trace. All tissue concentrations of chromium declined to low or nondetectable levels in 140 days with the exception of the lungs and spleen. After chromium trichloride instillation, 69% of the dose remained in the lungs at 20 minutes, while only 4% was found in the blood and other tissues, with the remaining 27% cleared from the lungs and swallowed. The only tissue that contained a significant amount of chromium 2 days after instillation of chromium trichloride was the spleen. After 30 and 60 days, 30 and 12%, respectively, of the chromium(III) was retained in the lungs, while only 2.6 and 1.6%, respectively, of the chromium(VI) dose was retained in the lung (Baetjer et al. 1959a).

2.3.2.2 Oral Exposure

Autopsy studies in the United States indicate that chromium concentrations in the body are highest in kidney, liver, lung, aorta, heart, pancreas, and spleen at birth and tend to decrease with age. The levels in liver and kidney declined after the second decade of life. The aorta, heart, and spleen levels declined rapidly between the first 45 days of life and 10 years, with low levels persisting throughout life. The level in the lung declined early, but increased again from mid life to old age (Schroeder et al. 1962).

The distribution of chromium in human body tissue after acute oral exposure was determined in the case of a 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate. Despite extensive treatment by dialysis and the use of the chelating agent British antilewisite, the boy died eight days after admission to the hospital. Upon autopsy, the chromium concentrations were as follows: liver, 2.94 mg/100 cc (normal, 0.016 mg/100 cc); kidneys, 0.64 and 0.82 mg/100 cc (normal, 0.06 mg/100 cc); and brain, 0.06 mg/100 cc (normal, 0.002 mg/100 cc) (Kaufman et al. 1970). Although these data were obtained after extensive treatment to rid the body of excess chromium, the levels of chromium remaining after the treatment clearly demonstrate that these tissues absorbed at least these concentrations after an acute, lethal ingestion of a chromium(VI) compound.

Chromium may be transferred to infants via breast milk as indicated by breast milk levels of chromium in women exposed occupationally (Shmitova 1980) or via normal levels in the diet (Casey and Hambidge 1984). It has been demonstrated that in healthy women, the levels of chromium measured in breast milk are independent of serum chromium levels, urinary chromium excretion, or dietary intake of chromium (Anderson et al. 1993, Mohamedshah et al. 1998), but others (Engelhardt et al. 1990) have disputed this observation.

The tissue distribution of chromium was studied in rats administered chromium from a variety of sources. In one experiment, sodium chromate in water was administered by gavage for 7 days at 0, 1.2, 2.3, or 5.8 mg chromium(VI)/kg/day. Very little chromium (generally <0.5 µg/organ) was found in the organs analyzed (liver, spleen, lung, kidney, and blood) after administration of the two lower doses. The levels were generally comparable to those in controls. After 5.8 mg/kg/day, the largest amount of chromium (expressed as µg chromium/whole organ) was found in the liver (.22 µg), followed by the kidney (.7.5 µg), lung (.4.5 µg), blood (.2 µg), and spleen (.1 µg). The total amount of chromium in these tissues represented only 1.7% of the final dose of 5.8 mg/kg/day, but not all organs were analyzed. In the next experiment, rats were exposed by gavage to 7.0 mg chromium/kg/day for 7 days from various

sources: (1) sodium chromate; (2) calcium chromate; (3) soil containing chromium (30% chromium(VI), 70% chromium(III)); or (4) a mixture of calcium chromate and the contaminated soil. The highest levels of chromium were found in liver, spleen, kidney, lung, blood, brain, and testes after dosing with sodium chromate, but the relative levels in these tissues after the other treatments followed no consistent pattern. Rats gavaged for 14 days with 13.9 mg chromium/kg/day from the four different sources had higher levels of chromium in the tissues after they were dosed with the contaminated soil or the mixture of calcium chromate and the contaminated soil than with either of the chromate salts alone. Thus, the relative organ distribution of chromium depends on the source of chromium (Witmer et al. 1989, 1991). Components in soil may affect the oxidation state and the binding of chromium to soil components, and pH of the soil may also affect the bioavailability from soil.

The chromium content in major organs of mice receiving drinking water that provided doses of 4.8, 6.1, or 12.3 mg chromium(III)/kg/day as chromium trichloride or 4.4, 5.0, or 14.2 mg chromium(VI)/kg/day as potassium dichromate was determined after 1 year of exposure. Chromium was detected only in the liver in the chromium(III)-treated mice. Mice treated with chromium(VI) compounds had accumulation in all organs, with the highest levels reported in liver and spleen. Liver accumulation of chromium was 40–90 times higher in the chromium(VI)-treated group than in the chromium(III)-treated group (Maruyama 1982). Chromium levels in tissue were 9 times higher in rats given chromium(VI) as potassium chromate in drinking water for 1 year than in rats given the same concentration of chromium(III) as chromium trichloride (MacKenzie et al. 1958). In rats exposed to potassium chromate in the drinking water for three or six weeks, a general trend of increasing chromium concentration with time of exposure was apparent in the liver and kidneys, but only the kidneys showed a difference in the concentration after exposure to 100 and 200 ppm. Blood concentrations were almost saturated by 3 weeks with little further accumulation by 6 weeks. No chromium was detected in the lungs after drinking water exposure (Coogan et al. 1991a). After acute oral dosing with radiolabeled chromium trichloride (1 μCi for immature rats, 10 μCi for adults), adult and neonatal rats accumulated higher levels of chromium in the kidneys than in the liver. At 7 days after dosing, the liver and kidney contained 0.05% and 0.12% of the dose, respectively, in the neonates and 0.002 and 0.003% of the dose, respectively, in the adult rats. The carcass contained 0.95% of the dose in the neonates and 0.07% of the dose in adult rats. The lungs contained 0.0088% of the dose in neonates and 0.0003% of the dose in adult rats. No chromium(III) was detected in the skeleton or muscle. Approximately 35 and 0.2% of the administered dose of chromium(III) at day 7 was retained in the gut of neonates and adults, respectively (Sullivan et al. 1984).

The distribution of potassium chromate(VI) was compared in male Fisher rats and C57BL/6J mice exposed either by drinking water (8 mg chromium(VI)/kg/day for 4 and 8 weeks) or by intraperitoneal injection (0.3 and 0.8 mg chromium(VI)/kg/day for 4 or 14 days) (Kargacin et al. 1993). The concentrations of chromium (µg/g wet tissue) after drinking water exposures for 8 weeks in mice were: liver 13.83, kidney 4.72, spleen 10.09, femur 12.55, lung 1.08, heart 1.02, muscle 0.60, and blood 0.42. These concentrations were not markedly different than for 4-week exposures. For rats, the concentrations were liver 3.59, kidney 9.49, spleen 4.38, femur 1.78, lung 0.67, heart 1.05, muscle 0.17, and blood 0.58. These results demonstrate that considerable species differences exist between mice and rats and need to be factored into any toxicological extrapolations across species even if the routes of administration are the same. In the drinking water experiments, blood levels in rats and mice were comparable, but in intraperitoneal injection experiments, rats' levels were about 8-fold higher than mice after 4 days of exposure. This difference appeared to be due to increased sequestering by rat red blood cells, since accumulation in white blood cells was lower in rats than mice. The higher incidence of red cell binding was also associated with greater binding of chromium to rat hemoglobin.

The feeding of five male Wistar rats at 0.49 mg chromium(III)/kg/day as chromium(III) chloride for 10 weeks resulted in increased chromium levels in liver, kidney, spleen, hair, heart, and red blood cells (Aguilar et al. 1997). Increases were highest in kidney (0.33 µg/g wet tissue in controls versus 0.83 µg/g in treated animals) and erythrocytes (1.44 µg/g wet tissue in controls versus 3.16 µg/g in treated animals).

The higher tissue levels of chromium after administration of chromium(VI) than after administration of chromium(III) (MacKenzie et al. 1958; Maruyama 1982; Witmer et al. 1989, 1991) reflect the greater tendency of chromium(VI) to traverse plasma membranes and bind to intracellular proteins in the various tissues, which may explain the greater degree of toxicity associated with chromium(VI). In an experiment to determine the distribution of chromium in red and white blood cells, rats were exposed orally to 0.0031 mg/kg of ^{51}chromium(VI) as sodium chromate. The ^{51}chromium content of the fractionated blood cells was determined either 24 hours or 7 days after exposure. After 24 hours, the white blood cells contained much more ^{51}chromium (. 250 pg chromium/billion cells) than did the red blood cells (. 30 pg chromium/billion cells). After 7 days, the ^{51}chromium content of the white blood cells was reduced only 2.5-fold, while that of the red blood cells was reduced 10-fold. Thus, white blood cells preferentially accumulated chromium(VI) and retained the chromium longer than did the red blood cells. As discussed in Section 2.3.2.4, a small amount of chromium(III) entered red blood cells of rats after intravenous injection of ^{51}chromium trichloride, but no ^{51}chromium was detectable in white blood cells (Coogan et al. 1991b).

Twelve pregnant female albino rats (Druckrey strain) and 13 Swiss albino mice were exposed to 500 ppm potassium dichromate(VI) in their drinking water during pregnancy up to one day before delivery (Saxena et al. 1990a). The chromium(VI) daily intake was calculated to be 11.9 mg chromium(VI)/day for the rats and 3.6 mg chromium(VI)/day for mice which were considered to be maximal non-toxic doses for both species. In rats, concentrations of chromium were 0.067, 0.219, and 0.142 µg/g fresh weight in maternal blood, placenta, and fetuses respectively, and 0.064, 0.304, and 0.366 µg/g fresh weight in mice, respectively. In treated rats, chromium levels were 3.2-fold higher in maternal blood, 3-fold higher in placenta, and 3.1-fold higher in fetal tissue when compared to control values. In treated mice, chromium levels were 2.5-fold higher in maternal blood, 3.2-fold higher in placenta, and 9.6-fold higher in fetuses when compared to control values. In treated mice there was a significant elevation in chromium levels in placental and fetal tissues over maternal blood levels, and a significant increase in chromium levels in fetal tissue over placental concentrations when compared to controls. These differences were not observed in rats, indicating that the distribution patterns in mice and rats are different.

A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form. Male and female rats were fed either a commercial diet that contained 500 ppb chromium or a 30% Torula yeast diet that contained <100 ppb chromium. They were also given drinking water with or without 2 ppm chromium(III) added as chromium acetate monohydrate. The rats were mated and immediately after delivery, the neonates were analyzed for chromium content. The neonates whose dams were fed the commercial diet contained almost twice as much chromium as those whose dams were fed the chromium-deficient yeast diet. Addition of chromium(III) acetate to the drinking water of the yeast-fed rats (2 ppm) did not increase the levels of chromium in the neonates. Administration of chromium(III) trichloride intravenously or by gavage before mating, during mating, or during gestation resulted in no or only a small amount of chromium in the neonates. Administration of chromium(III) in the form of GTF from Brewer's yeast by gavage during gestation resulted in chromium levels in the litters that were 20–50% of the dams' levels. The results indicate that fetal chromium is derived from specific chromium complexes in the diet (e.g., GTF) (Mertz et al. 1969).

2.3.2.3 Dermal Exposure

The findings of toxic effects in the heart, stomach, blood, muscles, and kidneys of humans who were dermally exposed to chromium compounds is suggestive of distribution to these organs (see Section 2.2.3.2). Fourteen days after a salve containing potassium chromate(VI) was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood

(2–5 mg/100 mL), urine (8 mg/L), feces (0.61 mg/100 g), and stomach contents (0.63 mg/100 mL) (Brieger 1920). The preexisting condition of scabies or the necrosis caused by the potassium chromate could have facilitated its absorption. A transient increase in the levels of total chromium in erythrocytes and plasma was observed in subjects immersed in a tank of chlorinated water containing potassium dichromate(VI) (Corbett et al. 1997).

Chromium compounds are absorbed after dermal administration by guinea pigs. Measurement of ^{51}chromium in the organs and body fluids revealed distribution, due to dermal absorption of chromium(III) and chromium(VI) compounds, to the blood, spleen, bone marrow, lymph glands, urine, and kidneys. Absorption was greater for chromium(VI) than for chromium(III) (see Section 2.3.1.3) (Wahlberg and Skog 1965).

2.3.2.4 Other Routes of Exposure

The distribution of chromium(III) in humans was analyzed using a whole-body scintillation scanner, whole-body counter, and plasma counting. Six individuals given an intravenous injection of ^{51}chromium(III) as chromium trichloride had >50% of the blood plasma chromium(III) distributed to various body organs within hours of administration. The liver and spleen contained the highest levels. After 3 months, the liver contained half of the total body burden of chromium. The study results indicated a three-compartment model for whole-body accumulation and clearance of chromium(III). The half-lives were 0.5–12 hours for the fast component, 1–14 days for the medium component, and 3–12 months for the slow component (Lim et al. 1983).

An *in vitro* study in human blood showed that chromium(VI) was rapidly cleared from the plasma (Corbett et al. 1998). The reduction capacity appears to be concentration dependent and is overwhelmed at spike concentrations between 2,000 and 10,000 µg/L. High chromium(VI) concentrations (10,000 µg/L spike concentration) resulted in an accumulation of chromium(VI) in the erythrocytes and a lower plasma:erythrocyte ratio of total chromium. This study also found that the plasma reduction capacity was enhanced by a recent meal.

Both human and rat white blood cells accumulated more ^{51}chromium per cell than red blood cells after *in vitro* exposure of whole blood to ^{51}chromium(VI). The uptake of chromium by rat blood cells was also measured after intravenous exposure to ^{51}chromium(VI) as sodium chromate. After intravenous exposure, the white blood cells contained significantly more ^{51}chromium (. 30 pg chromium/billion cells) than the

red blood cells (.4 pg chromium/billion cells), and the amount of ^{51}chromium in the cells was the same after 24 hours as it was after 1 hour. The amount of ^{51}chromium in the white blood cells, but not in the red blood cells, decreased by approximately 1.7-fold after 7 days. When rats were injected intravenously with 20 ng of radiolabeled sodium chromate (chromium(VI)) or radiolabeled chromium trichloride (chromium(III)), the amount of chromium was .2 pg/billion red blood cells but not detectable in white blood cells after injection of chromium(III) chloride. The amount of chromium was .5 pg/billion red blood cells and .60 pg/billion white blood cells after injection of sodium chromate (Coogan et al. 1991b).

The distribution pattern in rats treated with sodium chromite (chromium(III)) by intravenous injection revealed that most of the chromium was concentrated in the reticuloendothelial system, which, together with the liver accumulated 90% of the dose. The accumulation in the reticuloendothelial system was thought to result from colloid formation by chromite at physiological pH. Organs with detectable chromium levels 42 days postinjection were: spleen > liver > bone marrow > tibia > epiphysis > lung > kidney. Chromium trichloride given to rats by intravenous injection also concentrated in the liver, spleen, and bone marrow (Visek et al. 1953). In rats administered chromium(III) nitrate intraperitoneally for 30 or 60 days, the highest levels of chromium were found in the liver, followed by the kidneys, testes, and brain. The levels increased with increased doses but not linearly. The levels in the kidneys, but not the other organs, increased significantly with duration (Tandon et al. 1979).

Whole-body analysis of mice given a single intraperitoneal injection of 3.25 mg chromium(III)/kg as chromium trichloride showed that chromium trichloride was released very slowly over 21 days: 87% was retained 3 days after treatment, 73% after 7 days treatment, and 45% after 21 days. In contrast, mice given a single intraperitoneal injection of 3.23 chromium(VI)/kg as potassium dichromate retained only 31% of the chromium(VI) dose at 3 days, 16% at 7 days, and 7.5% at 21 days. Mice injected weekly with chromium(III) compounds at 17% of the LD_{50} retained .6 times the amount of chromium as mice injected with chromium(VI) compounds at 17% of the LD_{50}. The retention of chromium(III) was attributed to its ability to form coordination complexes with tissue components such a proteins and amino acids (Bryson and Goodall 1983).

In rats injected intraperitoneally with 2 mg chromium(VI)/kg/day as potassium chromate 6 days/week for 45 days, the mean levels of chromium (µg chromium/g wet weight) were 25.68 in the liver, 40.61 in the kidney, 7.56 in the heart, and 4.18 in the brain (Behari and Tandon 1980).

In rats injected subcutaneously with 5.25 mg chromium(VI)/kg as potassium dichromate, most of the chromium in the tissues analyzed was found in the red blood cells with a peak level (63 µg chromium/g) achieved 24 hours after dosing. White blood cells were not analyzed for chromium content. Whole plasma contained 2.7–35 µg/mL, and the plasma ultrafiltrate contained 0.15–0.79 µg/mL. Tissue distribution 48 hours after dosing was as follows: 221.2 µg/g in renal cortex, 110.0 µg/g in liver, 103.0 µg/g in spleen, 86.8 µg/g in lung, 58.9 µg/g in renal medulla, and 8.8 µg/g in bone, compared with 2.28–5.98 µg/g in any tissues in controls. When rats were given repeated subcutaneous injections of 1.05 mg chromium(VI)/kg/day, every other day for 2, 4, 8, 10, or 12 weeks, most of the chromium was again found in the red blood cells. However, while red blood cell levels rose progressively during treatment, levels as high as those seen after a single dose were never achieved, even when the total dose exceeded the dose in the single injection experiment 10-fold. The tissue levels of chromium determined 48 hours after the last dose in the rats injected for 12 weeks were of the same order of magnitude as those seen after a single injection. These results suggest little tendency of soluble chromium(VI) compounds to accumulate in tissues with repeated exposure (Mutti et al. 1979).

In an *in vitro* study, whole blood samples were spiked with water-soluble chromium(VI) or chromium(III) compounds. The results showed a greater level of chromium inside erythrocytes after treatment with chromium(VI) compounds, compared to chromium(III) compounds. The investigators reported that both chromium(VI) and chromium(III) compounds permeated the cell membrane, but only chromium(VI) compounds are taken up by erythrocytes and form complexes with intracellular proteins that could not be eliminated (Lewalter et al. 1985).

The distribution of radioactivity was compared in mouse dams and fetuses following the intravenous injection of the dams with ^{51}Chromium labelled-sodium dichromate(VI) or ^{51}chromium labelled-chromium(III) trichloride. In the maternal tissues, the highest levels of radioactivity from both treatments were achieved in the renal cortex, but the concentration of radioactivity in the tissues of dams given the hexavalent form was much higher than that of the dams given the trivalent form. The patterns of distribution of radioactivity in other tissues were identical regardless of administered valence state, with the skeleton, liver, kidneys, and ovaries accumulating the highest levels and the brain and muscle the lowest. The serum concentration of radioactivity after treatment with chromium(III) was 3 times higher than that after treatment with chromium(VI). Radioactivity after treatment with both valence forms crossed the placenta, but the radioactivity from the hexavalent form crossed more readily. For chromium(VI), . 12% of the maternal serum concentration of radioactivity was found in the fetuses when the dams were administered sodium dichromate in mid-gestation (days 12–15). When the dams were

injected in late gestation (days 16–18), .19% of the radioactivity in maternal serum was found in the fetuses. For chromium(III), the fetal concentration of radioactivity was only .0.4% of the maternal serum concentration when the dams were injected with radiolabelled chromium trichloride in mid-gestation and 0.8% of the maternal serum radioactivity concentration when injected in late gestation. Radioactivity from both treatments accumulated in fetal skeletons in calcified areas and in the yolk sac placenta (Danielsson et al. 1982). Daniellson et al. (1982) noted that the radioactivity after administration of chromium(VI) may represent chromium(III) after reduction in the tissues. Chromium(III) also crossed the placenta of mice injected intraperitoneally with chromium trichloride (Iijima et al. 1983). While the results indicate that both chromium(VI) and chromium(III) may pose developmental hazards, they cannot be used to indicate that exposure of pregnant animals to chromium(III) by inhalation or oral routes would result in significant placental transfer because chromium(III) compounds are not well absorbed by these routes (see Section 2.3.1).

Tissue distribution in rats and mice respectively after 14 days of intraperitoneal injection of 0.8 mg chromium(VI)/day as potassium chromate were: liver 6.00 μg/g wet weight in rats and 8.89 in mice, kidney 24.14 and 11.77, spleen 15.26 and 6.92, femur 6.53 and 6.30, lung 3.99 and 2.89, heart 3.13 and 1.75, muscle 1.10 and 0.51, and blood 4.52 and 1.56. (Kargacin et al. 1993). Kidney and blood chromium concentrations were 2-fold and 4-fold higher, respectively, in rats compared to mice. Red blood cell concentrations were 3-fold higher in rats than mice and hemoglobin binding of chromium was twice as high in rats. By contrast, after oral exposure levels, in blood for rats and mice were similar. The authors ascribed this to faster entry into the blood after intraperitoneal injection and thus a greater likelihood that chromium(VI) could be sequestered in rat erythrocytes by reduction.

2.3.3 Metabolism

The biologically active chromium(III) molecule often referred to as GTF appears to be a dinicotinato-chromium(III) glutathione-like complex. The molecule has not been fully characterized (Pi-Sunyer and Offenbacher 1984). This biologically active molecule functions by facilitating interaction of insulin with its receptor site, thus influencing glucose, protein, and lipid metabolism. Inorganic chromium compounds do not appear to have insulin-potentiating activity. However, humans and animals are capable of converting inactive chromium compounds to biologically active forms (Anderson 1986).

Chromium(III) compounds are essential to normal glucose, protein, and fat metabolism. In addition, chromium(III) is capable of forming complexes with nucleic acids and proteins. Chromium(VI) is

unstable inside the body and is ultimately reduced to chromium(III) *in vivo* by a variety of reducing agents. Chromium(V) and chromium(IV) are transient intermediates in this process.

In vivo and *in vitro* experiments in rats indicated that, in the lungs, chromium(VI) can be reduced to chromium(III) by ascorbate. The reduction of chromium(VI) by ascorbate results in a shorter residence time of chromium in the lungs and constitutes the first defense against oxidizing reagents in the lungs. When ascorbate is depleted from the lungs, chromium(VI) can also be reduced by glutathione. The reduction of chromium(VI) by glutathione is slower and results in greater residence time of chromium in the lungs, compared to reduction by ascorbate (Suzuki and Fukuda 1990). Other studies reported the reduction of chromium(VI) to chromium(III) by epithelial lining fluid (ELF) obtained from the lungs of 15 individuals by bronchial lavage. The average reduction accounted for 0.6 µg chromium(VI)/mg of ELF protein. In addition, cell extracts made from pulmonary alveolar macrophages derived from five healthy male volunteers were able to reduce an average of 4.8 µg chromium(VI)/10^6 cells or 14.4 µg chromium(VI)/mg protein (Petrilli et al. 1986b). Metabolism of the chromium(VI) to chromium(III) by these cell fractions significantly reduced the mutagenic potency of the chromium when tested in the Ames reversion assay. Postmitochondrial (S12) preparations of human lung cells (peripheral lung parenchyma and bronchial preparations) were also able to reduce chromium(VI) to chromium(III) (De Flora et al. 1984). Moreover, large individual differences were observed (De Flora et al. 1984, 1987b), and extracts from pulmonary alveolar macrophages of smokers reduced significantly more chromium(VI) to chromium(III) than extracts from cells of nonsmokers. Because chromium(III) does not readily enter cells, these data suggest that reduction of chromium(VI) by the ELF may constitute the first line of defense against toxicity of inhaled chromium compounds. Furthermore, uptake and reduction of chromium compounds by the pulmonary alveolar macrophages may constitute a second line of defense against pulmonary toxicity of chromium(VI) compounds. Microsomal reduction of chromium(VI) occurs in the lungs mainly as it does in the liver, as discussed below.

The first defense against chromium(VI) after oral exposure is the reduction of chromium(VI) to chromium(III) in the gastric environment where gastric juice (De Flora et al. 1987a) and ascorbate (Samitz 1970) play important roles. Studies using low-frequency electron paramagnetic resonance (EPR) spectrometry have shown that chromium(VI) is reduced to chromium(V) *in vivo* (Liu et al. 1994, 1995, 1997a, 1997b; Ueno et al. 1995b). *In vitro*, low concentrations of ascorbate favor the formation of chromium(V), whereas higher concentrations of ascorbate favor the formation of the reduced oxidation state, chromium(III) (Liu et al. 1995). EPR spectrometric monitoring also showed that chromium(VI) was rapidly reduced to chromium(V) on the skin of rats, with a 3-fold greater response when the stratum

corneum was removed (Liu et al. 1997a). Thus, dermal effects from direct skin contact with chromium(VI) compounds may be mediated by rapid reduction to chromium(V). In whole blood and plasma, increasing ascorbate levels led to an increased oxidation of chromium(VI) to chromium(III) (Capellmann and Bolt 1992).

For humans, the overall chromium(VI)-reducing/sequestering capacities were estimated to be 0.7–2.1 mg/day for saliva, 8.3–12.5 mg/day for gastric juice, 11–24 mg for intestinal bacteria eliminated daily with feces, 3,300 mg/hour for liver, 234 mg/hour for males and 187 mg/hour for females for whole blood, 128 mg/hour for males and 93 mg/hour for females for red blood cells, 0.1–1.8 mg/hour for ELF, 136 mg/hour for pulmonary alveolar macrophages, and 260 mg/hour for peripheral lung parenchyma. Although these *ex vivo* data provide important information in the conversion of chromium(VI) to reduced states, the values may over or under estimate the *in vivo* reducing capabilities (De Flora et al. 1997).

Reduction of chromium(VI) in the red blood cell occurs by the action of glutathione. Since the red blood cell membrane is permeable to chromium(VI) but not chromium(III), the chromium(III) formed by reduction of chromium(VI) by glutathione is essentially trapped within the red blood cell. Eventually the diffusion of chromium(VI), the reduction to chromium(III), and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change so that more chromium(VI) is diffused through the membrane. Thus, there is a physiological drag so that increased diffusion results in greater chromium concentrations in the cell (Aaseth et al. 1982). It appears that the rate of uptake of chromium(VI) by red blood cells may not exceed the rate at which they reduce chromium(VI) to chromium(III) (Corbett et al. 1998). *In vitro* incubation of red blood cells with an excess of sodium chromate(VI) (10 mM) decreased glutathione levels to 10% of the original amount (Wiegand et al. 1984).

The effect of glutathione-depleting agents on the amounts of cellular chromium(III) and chromium(V) was determined in Chinese hamster V-79 cells treated with sodium chromate (Sugiyama and Tsuzuki 1994). Buthionine sulfoximine at 25 μM reduced glutatione levels to about 1% of control values, and increased chromium(V) levels by about 67%. The total chromium uptake was decreased by about 20%, and chromium(III) levels were decreased by 20%. Diethylmaleate (1 mM) decreased glutathione levels less than 1%, decreased chromium(V) levels by 27%, and chromium(III) levels by 31%. However, the cellular uptake of total chromium was decreased to nearly 46%. The authors explained that the reason that the diethylmaleate inhibited the reduction of chromium(VI) to both chromium(III) and chromium(V) was not due to the decreased uptake, but involved the inhibition of the chromate-reducing enzymes in the cell.

In addition to the reduction of chromium(VI) by ascorbate or glutathione, *in vitro* studies have demonstrated reduction of chromium(VI) by microsomal enzymes. Hepatic microsomal proteins from male Sprague-Dawley rats pretreated with chromium(VI) reduced chromium(VI) to chromium(III). The rate of reduction varied both with the concentration of microsomal protein and the concentration of nicotinamide adenine dinucleotide phosphate (NADPH). In the absence of NADPH, microsomes did not reduce significant amounts of Cr(VI) over the 24-hour observation period. Therefore, the reduction of chromium(VI) in rat hepatic microsomes is NADPH-dependent (Gruber and Jennette 1978). Another study followed the kinetics of chromium(VI) reduction in hepatic microsomes from rats (Garcia and Jennette 1981). Induction of cytochrome P448 enzymes had no effect on the kinetics of the reaction, while induction of cytochrome P450 and NADPH-cytochrome P450 reductase resulted in a decrease in the apparent chromate-enzyme dissociation constant, and an increase in the apparent second-order rate constant, and no change in the apparent turnover number. Inhibition of NADPH-cytochrome P450 reductase and NADH-cytochrome b_5 reductase inhibited the rate of microsomal reduction of chromium(VI), as did the addition of specific inhibitors of cytochrome P450. The results demonstrate the involvement of cytochrome P450, NADPH-dependent-cytochrome P450 reductase, and to a lesser extent cytochrome b_5 and NADH-dependent-cytochrome b_5 reductase in the reduction of chromate by rat hepatic microsomes. The conversion of chromium(VI) to chromium(III) in rats can occur by electron transfer through cytochrome P450 and cytochrome b_5. Both oxygen and carbon monoxide were found to inhibit the *in vitro* cytochrome P450 and cytochrome b_5-dependent reduction of chromium(VI) (Mikalsen et al. 1989). The assertion that cytochrome P450 is involved in the reduction of chromium(VI) to chromium(III) has been further strengthened by Petrilli et al. (1985), who demonstrated that inducers of cytochrome P450 can increase the conversion of chromium(VI) to chromium(III) in S-9 mixtures prepared from the liver and lungs of exposed rats. Furthermore, it was observed that chromium(VI) can induce pulmonary cytochrome P450 and thus its own reduction in the lungs (Petrilli et al. 1985). Chromium(VI) apparently can alter the P450 activity in isolated rat microsomes. Witmer et al. (1994) demonstrated that hepatic microsomes from male rats treated with chromium(VI) resulted in a significant decrease in hydroxylation of testosterone at the 6β, 16α, and 2α positions, indicating a decrease in the activity of P4503A1 and 3A2. In lung microsomes, an increased hydroxylation was observed at the 16α and 16β positions, indicating an increase in P450IIB1 activity. However, hepatic microsomes from treated females showed a 4-to5-fold increase in hydroxylation activity of testosterone at the 6β position, which demonstrated that the metabolic effects of chromium differ between males and females.

Two studies have examined possible species differences in the ability of microsomes to reduce chromium(VI) (Myers and Myers 1998; Pratt and Myers 1993). Chromium(VI) reduction was enzymatic

and NADPH-dependent, and the rates were proportional to the amount of microsome added. In humans, the K_m for chromium(VI) was one to three orders of magnitude lower than K_m values in rats, although the V_{max} was similar. This suggests that the human liver has a much greater capacity to reduce chromium(VI) than the rat liver. Also contrary to the rodent data, oxygen and cytochrome P450 inhibitors (carbon monoxide, piperonyl butoxide, metyrapone, and aminopyrine) did not inhibit chromium(VI) reduction. These differences indicate that, in humans, cytochrome P450 does not play a significant role in the reduction process, but that other microsomal flavoproteins are responsible for reducing chromium(VI). Inhibition of flavoproteins by $TlCl_3$ decreased chromium(VI) reduction by 96–100%, while inhibition of cytochrome c reductase (P450 reductase) by bromo-4'-nitroacetophenone resulted in an 80–85% inhibition of chromium(VI) reduction. Combined, these observations implicate P450 reductase, working independently of cytochrome P450, as a major contributor in the reduction of chromium(VI) in human microsomes. These findings suggest that metabolism of chromium(VI) in rodent systems may not readily be extrapolated to humans.

Microsomal reduction of chromium(VI) can also result in the formation of chromium(V), which involves a one-electron transfer from the microsomal electron-transport cytochrome P450 system in rats. The chromium(V) complexes are characterized as labile and reactive. These chromium(V) intermediates persist for 1 hour *in vitro*, making them likely to interact with deoxyribonucleic acid (DNA), which may eventually lead to cancer (Jennette 1982). Because chromium(V) complexes are labile and reactive, detection of chromium(V) after *in vivo* exposure to chromium(VI) was difficult in the past. More recently, Liu et al. (1994) have demonstrated that chromium(V) is formed *in vivo* by using low-frequency electron paramagnetic resonance (EPR) spectroscopy on whole mice. In mice injected with sodium dichromate(VI) intravenously into the tail vein, maximum levels of chromium(V) were detected within 10 minutes and declined slowly with a life time of about 37 minutes. The time to reach peak *in vivo* levels of chromium(V) decreased in a linear manner as the administered dose levels of sodium dichromate decreased. The relative tissue distributions of chromium(V) indicated that most was found in the liver and much lesser amounts in blood. None was detected in kidney, spleen, heart, or lung. When the mice were pretreated with metal ion chelators, the intensity of the EPR signal decreased demonstrating that the formation of chromium(V) was inhibited. Reactions of chromium(VI) with glutathione produced two chromium(V) complexes and a glutathione thiyl radical. Reactions of chromium(VI) with DNA in the presence of glutathione produced chromium-DNA adducts. The level of chromium-DNA adduct formation correlated with chromium(V) formation. The reaction of chromium(VI) with hydrogen peroxide produced hydroxyl radicals. Reactions of chromium(VI) with DNA in the presence of high concentrations of hydrogen peroxide (millimolar compared to 10^{-7} to 10^{-9} M inside cells) produced

significant DNA strand breakage and the 8-hydroxy guanosine adduct, which correlated with hydroxyl radical production (Aiyar et al. 1989, 1991). Very little chromium(V) was generated by this pathway. It was postulated that the reaction of chromium(VI) with hydrogen peroxide produces tetraperoxo-chromium(V) species that act as a catalyst in a Fenton-type reaction producing hydroxyl radicals in which chromium(V) is continuously being recycled back to chromium(VI). The regeneration of chromium(VI) through interactions with chromium(V) and hydrogen peroxide is consistent with the findings of Molyneux and Davies (1995) (see Section 2.4.2). As discussed above, chromium(VI) is ultimately reduced to chromium(III) within the cell. Chromium(III) can form stable complexes with DNA and protein (De Flora and Wetterhahn 1989) which is discussed further in Section 2.4.2.

The mechanism for clearance of chromium(VI) once reduced inside the liver cell may involve a chromium(III)-glutathione complex. The glutathione complex would be soluble through the cell membrane and capable of entering the bile (Norseth et al. 1982). The complexing of chromium(III) to other ligands has been shown to make them more permeable to the cell membrane (Warren et al. 1981).

Although chromium(III) complexes are generally considered to be inert, Shi et al. (1993) demonstrated that free radicals could be generated from extremely high non-physiological concentrations of hydrogen peroxide and lipid hydroperoxides (t-butyl hydroperoxide and cumene hydroperoxide) *in vitro* at neutral pH in the presence of chromium(III) chloride. The reduction of peroxides may indicate that chromium(III) is capable of being reduced to chromium(II) and is consistent with other findings that have shown that cysteine and NADH are capable of reducing trivalent chromium. Later studies demonstrated that chromium(III) could enhance the formation of hydroxyl radicals from superoxide, though to a lesser extent than chromium(VI), suggesting that chromium(III) can act as a catalyst for the Haber-Weiss cycle (Shi et al. 1998). Therefore, the presence of these naturally occurring substances and cellular lipid hydroperoxides formed in lipid metabolism may contribute to the generation of free radicals that could be potentially genotoxic.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Normal urinary levels of chromium in humans have been reported to range from 0.24–1.8 µg/L (0.00024–0.0018 mg/L) with a median level of 0.4 µg/L (0.0004 mg/L) (Iyengar and Woittiez 1988). Humans exposed to 0.05–1.7 mg chromium(III)/m^3 as chromium sulfate and 0.01–0.1 mg

chromium(VI)/m^3 as potassium dichromate (8-hour time-weighted average) had urinary excretion levels from 0.0247 to 0.037 mg chromium(III)/L. Workers exposed mainly to chromium(VI) compounds had higher urinary chromium levels than workers exposed primarily to chromium(III) compounds. An analysis of the urine did not detect the hexavalent form of chromium, indicating that chromium(VI) was rapidly reduced before excretion (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Chromium(III) compounds were excreted rapidly in the urine of workers, following inhalation exposure to chromium(III) as chromium lignosulfonate. Workers exposed to 0.005–0.23 mg chromium(III)/m^3 had urine concentrations of 0.011–0.017 mg chromium(III)/L. The half-time for urinary excretion of chromium was short, 4–10 hours, based on an open, one-compartment kinetic model (Kiilunen et al. 1983). Tannery workers had higher urinary chromium(III) concentrations in postshift urine samples taken Friday afternoon and in preshift urine samples taken Monday, compared to controls. These workers also had hair concentrations of chromium that correlated with urinary levels. Analysis of workroom air revealed no detectable chromium(VI) and 0.0017 mg chromium(III)/m^3 (time-weighted average) (Randall and Gibson 1987). Elimination of chromium(III) from hair, serum, and urine has been studied in a group of 5 men who had ceased working in a leather tannery 9 months earlier (Simpson and Gibson 1992). Compared to levels recorded during employment, the mean level of chromium in hair was reduced from 28.5 to 2.9 µmol/g; serum levels were reduced from 9.4 to 3.8 nmol/L. These levels are comparable to those in the general population. Urine levels were unchanged (13.8 nmol/L while working and 14.4 nmol/L 9 months later); the authors stated that this was probably caused by consumption of beer (a source of chromium) the night before sampling.

Peak urinary chromium concentrations were observed at 6 hours (the first time point examined) in rats exposed intratracheally to 0.44 mg/kg chromium(III) as chromium acetate hydroxide or chromium(VI) as sodium dichromate (Gao et al. 1993). Chromium urinary concentrations decreased rapidly, falling from 4,535 µg chromium/g creatinine at 6 hours to 148 µg chromium/g at 72 hours for the chromium acetate hydroxide and from 2,947 µg chromium/g creatinine at 6 hours to 339 µg chromium/g at 72 hours for sodium dichromate.

Elimination of chromium was very slow in rats exposed to 2.1 mg chromium(VI)/m^3 as zinc chromate 6 hours/day for 4 days. Urinary levels of chromium remained almost constant for 4 days after exposure and then decreased, indicating that chromium bound inside the erythrocyte is released slowly (Langård et al. 1978).

2.3.4.2 Oral Exposure

Given the low absorption of chromium compounds by the oral route, the major pathway of excretion after oral exposure is through the feces.

An acute, oral dose of radioactive chromium(III) as chromium chloride or chromium(VI) as sodium chromate was administered to humans after which feces and urine were collected for 24 hours and 6 days, respectively, and analyzed for chromium. The amount of chromium in the 6-day fecal collection was 99.6 and 89.4% of the dose for chromium(III) and chromium(VI) compounds, respectively. The amount of chromium in the 24-hour urine collection was 0.5 and 2.1% of the dose for chromium(III) and chromium(VI) compounds, respectively (Donaldson and Barreras 1966). In subjects drinking 0.001–0.1 mg chromium(VI)/kg/day as potassium chromate in water for 3 days, <2–8% of the dose was excreted in the urine (Finley et al. 1997). The percentage of the dose excreted appeared to increase with increasing dose.

Urinary excretion rates have been measured in humans after oral exposure to several chromium compounds (Finley et al. 1996b). A group of four male and two female volunteers ingested capsules containing chromium(III) picolinate at a dose of 200 µg/day for 7 days, to ensure that chromium deficiency was not a confounding factor. They then ingested 0.005 mg/kg/day chromium(VI) as potassium chromate (3 days), and 1.0 mg/kg/day chromium(III) as chromic oxide (3 days), with 3 days without dosing between the potassium chromate and chromic oxide doses. Urinary excretion rates of chromium were significantly elevated compared to post-dosing control levels after seven daily doses of chromium(III) picolinate (2.4±0.8 µg/day vs 0.75±0.53 µg/day). The excretion rate increased sharply on the first of 3 days of potassium chromate dosing (11±17 µg/day) and remained steady over the next 2 days (13–14 µg/day). Excretion rates fell to 2.5±0.72 during 2 days without dosing and continued to fall during the three days of chromic oxide dosing, reaching rates similar to those seen post-dosing. Mean pooled urinary concentrations during the dosing periods were 2.4 µg chromium/g creatinine from exposure to chromium(VI) and 0.4 µg chromium/g creatinine from exposure to chromium(III) as compared to 0.23 µg chromium/g creatinine during the post-dosing time periods. The lower urinary excretion of chromium(III) after exposure to chromic oxide reflects the poorer absorption of inorganic chromium(III) compounds compared to inorganic chromium(VI) compounds.

The half-life for chromium urinary excretion after administration in drinking water as potassium dichromate has been estimated in humans (Kerger et al. 1997). Ingestion of 0.05 mg chromium(VI)/kg

resulted in an extended time course of excretion. Approximately 76–82% of the 14-day total amount of chromium in the urine was excreted within the first 4 days (mean peak concentration 209 µg chromium/g creatinine; range 29–585 µg chromium/g creatinine). The average urinary excretion half-life for four of the volunteers was 39 hours at this dose. All subjects had returned to background concentrations (0.5–2.0 µg chromium/g creatinine) by 14 days post-dosing. About 87% of the total amount of chromium in the urine measured over 8 days was excreted during the first 4 days for one volunteer ingesting 0.03 mg chromium(VI)/kg (peak 97 µg chromium/g creatinine on day of ingestion). Urinary chromium concentrations had returned to an average of 2.5 µg chromium/g creatinine within 7 days post-dosing, the last time point measured. Urinary excretion half-life in this volunteer was 37 hours. Similar time courses of excretion were observed when volunteers took the same doses as daily doses over 3-day periods. An earlier study by this group (Kerger et al. 1996a) examined urinary excretion half-lives following a bolus dose of 10 ppm (approximately 0.06 mg chromium/kg) chromium(III) chloride, potassium dichromate reduced with orange juice (presumably, the juice reduced the potassium dichromate to chromium(III)-organic complexes and chromium(III) ions), or potassium dichromate. The calculated urinary excretion half-lives for the three chromium solutions were 10.3, 15, and 39.3 hours, respectively. The potassium dichromate half-life is consistent with the results from the Kerger et al. (1997) study.

The urinary excretion kinetics of chromium have also been examined in eight adults that were administered chromium(III) at 400 µg/day as chromium(III) picolinate for 3 consecutive days (Gargas et al. 1994). The mean time to peak urinary concentration was 7.18±2.11 hours (range 2.9–13.0 hours), the mean peak concentration being 7.92±4.24 µg chromium/g creatinine (range 3.58–19.13 µg/g creatinine). Excretion diminished rapidly after the peak but did not appear to return to background in most of the volunteers before the next daily dose.

Pharmacokinetic models were used to predict the retention and excretion of ingested chromium(III) picolinate (Stearns et al. 1995a). A single dose of 5.01 mg (assuming 2.8% or 140 µg of the chromium(III) picolinate is absorbed) resulted in 11 µg (7.9%) retained after 1 year. The model predicted that about 1.4 µg would still be present in body tissues 10 years after dosing, and continuous dosing over a 1-year period would result in 6.2 mg of chromium(III) picolinate being retained, requiring about 20 years to reduce the retained level to 0.046 mg. These projected retention estimates may be two- to four-fold lower than results obtained from actual clinical findings. The authors caution that accumulative daily intake of chromium(III) may result in tissue concentrations that could be genotoxic.

Daily urinary excretion levels of chromium were nearly identical in men and women (averages of 0.17 and 0.20 µg/L, respectively; 0.18 µg/L combined) who ate normal dietary levels of chromium (. 60 µg chromium(III)/day). When the subjects' normal diets were supplemented with 200 µg chromium(III)/day as chromium trichloride to provide intakes of . 260 µg chromium(III)/day, urinary excretion of chromium rose proportionately to an average of 0.98 µg/L combined. Thus a five-fold increase in oral intake resulted in about a five-fold increase in excretion, indicating absorption was proportional to the dose regardless of whether the source was food or supplement (Anderson et al. 1983). A group of 23 elderly subjects who received an average of 24.5 µg/day (0.00035 mg chromium(III)/kg/day) from their normal diets excreted 0.4 µg chromium/day in the urine (1.6%) and 23.9 µg chromium/day in the feces (97.6%), with a net retention of 0.2 µg/day (0.8%). Based on the 1980 daily requirement for absorbable chromium of 1 µg/day by the National Academy of Science Food and Nutrition Board, the retention was considered adequate for their requirements (Bunker et al. 1984).

An estimate of the half-life of elimination from plasma has been reported in humans. Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days and a plasma elimination half-life of 36 hours was estimated.

Measurement of the chromium content in 255 milk samples from 45 lactating American women revealed that most samples contained <0.4 µg/L with a mean value of 0.3 µg/L (Casey and Hambidge 1984). Another study (Anderson et al. 1993) measured chromium levels in the breast milk of 17 women 60 days postpartum, and reported mean levels of ~0.2 µg/L. Lactation, therefore, represents a route of excretion of chromium and a potential route of exposure to the nursing infant. However, the precise relationship between maternal chromium levels and levels in breast milk is unclear, if such a relationship exists at all (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Chromium can be excreted in hair and fingernails. Mean trace levels of chromium detected in the hair of individuals from the general population of several countries were as follows: United States, 0.23 ppm; Canada, 0.35 ppm; Poland, 0.27 ppm; Japan, 0.23 ppm; and India, 1.02 ppm (Takagi et al. 1986). Mean levels of chromium in the fingernails of these populations were: United States, 0.52 ppm; Canada, 0.82 ppm; Poland, 0.52 ppm; Japan, 1.4 ppm; and India, 1.3 ppm (Takagi et al. 1988).

Rats given 18 mg chromium(VI)/kg as potassium dichromate by gavage excreted about 25 µg chromium in the first 24 hours after dosing and . 10 µg chromium in each of the next 24-hour periods (Banner et al. 1986).

In rats and hamsters fed chromium compounds, fecal excretion of chromium varied slightly from 97 to 99% of the administered dose. Urinary excretion of chromium varied from 0.6 to 1.4% of the dose administered as either chromium(III) or chromium(VI) compounds (Donaldson and Barreras 1966; Henderson et al. 1979; Sayato et al. 1980). The urinary and fecal excretion over 2-day periods in rats treated for 8 days by gavage with 13.92 mg chromium/kg/day in corn oil was higher when soil containing 70% chromium(III) and 30% chromium(VI) was the source of chromium than when chromium(VI) as calcium chromate was the source (see Section 2.3.2.2). Total urinary and fecal excretion of chromium on days 1 and 2 of dosing were 1.8 and 19%, respectively, of the dose from soil and <0.5 and 1.8%, respectively, of the dose from calcium chromate. Total urinary and fecal excretion of chromium on days seven and eight of dosing were higher than on days one and two. For contaminated soil, urinary excretion was 1.12% and fecal excretion was 40.6% of the dose. For calcium chromate, urinary excretion was 0.21% and fecal excretion was 12.35% of the dose (Witmer et al. 1991). Whether the higher excretion of chromium after dosing with soil than with the chromate salt represents greater bioavailability from soil could not be determined because about 50% of the administered dose could not be accounted for from the excretion and distribution data (see Section 2.3.2.2). Excretion of chromium(III) in dogs was approximately equal to the clearance of creatinine, indicating little tubular absorption or reabsorption of chromium in the kidneys (Donaldson et al. 1984).

2.3.4.3 Dermal Exposure

Information regarding the excretion of chromium in humans after dermal exposure to chromium or its compounds is limited. Fourteen days after application of a salve containing potassium chromate(VI), which resulted in skin necrosis and sloughing at the application site, chromium was found at 8 mg/L in the urine and 0.61 mg/100 g in the feces of one individual (Brieger 1920). A slight increase (over background levels) in urinary chromium levels was observed in four subjects submersed in a tub of chlorinated water containing 22 mg chromium(VI)/L as potassium dichromate(VI) for 3 hours (Corbett et al. 1997). For three of the four subjects, the increase in urinary chromium excretion was less than 1 µg/day over the 5-day collection period.

^{51}Chromium was detected in the urine of guinea pigs after radiolabeled sodium chromate(VI) or chromium(III) trichloride solutions were placed over skin depots that were monitored by scintillation counting to determine the dermal absorption (Wahlberg and Skog 1965).

2.3.4.4 Other Routes of Exposure

Elevated levels of chromium in blood, serum, urine, and other tissues and organs have been observed in patients with cobalt-chromium knee and hip arthroplasts (Michel et al. 1987; Sunderman et al. 1989). Whether corrosion or wear of the implant can release chromium (or other metal components) into the systemic circulation depends on the nature of the device. In one study, the mean postoperative blood and urine levels of chromium of nine patients with total hip replacements made from a cast cobalt-chromium-molybdenum alloy were 3.9 and 6.2 µg/L, respectively, compared with preoperative blood and urine levels of 1.4 and 0.4 µg/L, respectively. High blood and urinary levels of chromium persisted when measured at intervals over a year or more after surgery. These data suggest significant wear or corrosion of the metal components. No significant difference was found for patients with hip replacements made from the alloy and articulated with polyethylene (Coleman et al. 1973). Similarly, serum and urinary levels of chromium in patients with implants made from a porous coated cobalt chromium alloy with polyethylene components (to prevent metal-to-metal contact) were not significantly different from patients with implants made without chromium (Sunderman et al. 1989).

A number of factors have been shown to alter the rate of excretion of chromium in humans. Intravenous injection of calcium EDTA resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Both acute and chronic exercises have been shown to increase chromium excretion in the urine, though the increased excretion did not appear to be accompanied with decreased levels of total native chromium (Rubin et al. 1998). An increased rate of chromium excretion has been reported in women in the first 26 weeks of pregnancy (Morris et al. 1995b). Chromium supplementation did not appear to alter the rate of excretion into breast milk in postpartum women (Mohamedshah et al. 1998).

The urinary excretion of chromium after a single or during repeated subcutaneous injections of potassium dichromate was followed in rats. Following a single dose of 5.35 mg chromium(VI)/kg, chromium was excreted rapidly in two phases and was essentially complete at 48 hours. The filtered chromium load rose considerably during the first few hours after dosing and exceeded the tubular reabsorption rate. This increase was followed by a decrease that paralleled the urinary excretion of chromium. During repeated

injections with 1.05 mg chromium(VI)/kg/day, every other day for 12 weeks, urinary excretion and diffusible chromium renal clearance rose at relatively high parallel rates, and reached plateaus at 10 ng/min for urinary excretion and 550 µL/min for renal clearance. The filtered load increased slightly. Since high levels of chromium were found in the renal cortex (see Section 2.3.2.4), the tubular reabsorption appeared to be limited by the accumulation of chromium in the tubular epithelium (Mutti et al. 1979).

Rats given a subcutaneous injection of potassium dichromate (chromium(VI)) and chromium nitrate (chromium(III)) excreted 36% of the chromium(VI) dose in urine and 13.9% in the feces within 7 days; 8% and 24.2% of the chromium(III) was excreted in the urine and feces within the same time period, respectively (Yamaguchi et al. 1983). Within 4 days after an intravenous dose of ^{51}chromium as chromium(III) chloride at 3 mg/kg chromium, rats excreted 5.23% of the dose in the feces and 16.3% in the urine (Gregus and Klaassen 1986).

In rats treated by intravenous injection with ^{51}chromium-labeled sodium chromate (chromium(VI)) or chromium(III) trichloride at 0.0003 or 0.345 mg chromium/kg, the bile contained 2–2.5% of the dose following chromium(VI) exposure; however, after chromium(III) exposure the concentration in the bile was .50 times lower (Manzo et al. 1983). Similarly, 3.5–8.4% of chromium(VI) compounds was excreted in the bile as chromium(III), compared to 0.1–0.5% of chromium(III) compounds, after intravenous injection in rats (Cirkt and Bencko 1979; Norseth et al. 1982). Administration of diethylmaleate, which depletes glutathione, resulted in only chromium(VI) in the bile after injection of sodium chromate.

Two hours after dosing rats intravenously with potassium dichromate at 0.45–4.5 mg chromium(VI)/kg, 1.4–2.2% of the chromium was recovered in the bile. Less than 1% of the total measurable chromium in the bile was identified as chromium(VI) compounds (Cavalleri et al. 1985).

Male Swiss mice exposed to 52 mg chromium(III)/kg as chromium chloride by single intraperitoneal injection or subcutaneous injection had plasma clearance half-times of 41.2 and 30.6 hours, respectively. In each case, blood levels reached control levels by 6–10 days (Sipowicz et al. 1997).

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) is adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

If PBPK models for chromium 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.

PBPK models for chromium are discussed below.

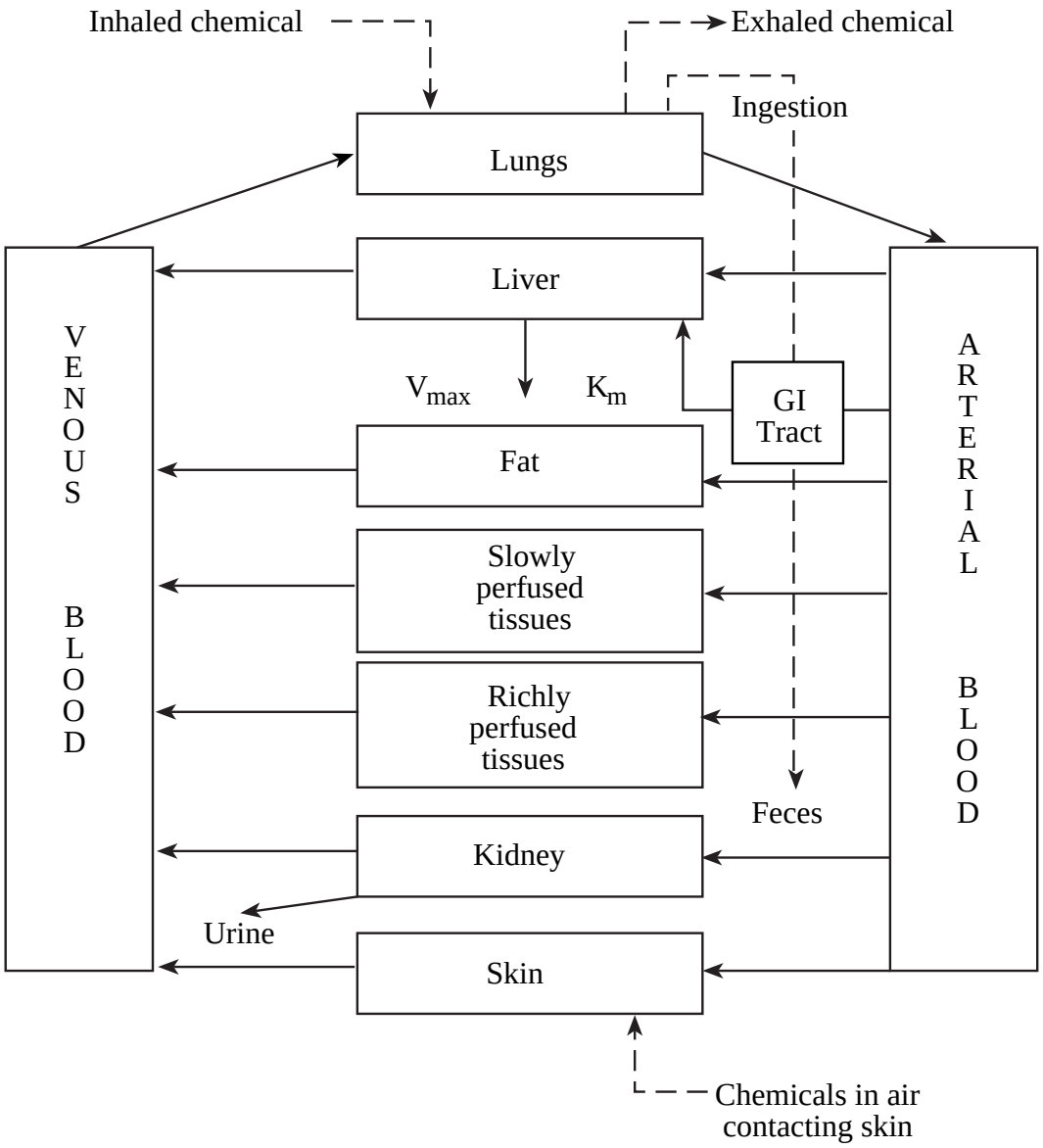
2.3.5.1 Summary of PBPK Models.

One PBPK model for chromium has been published. The O'Flaherty model (O'Flaherty 1993a, 1996) simulates the absorption, distribution, metabolism, elimination, and excretion of chromium(III) and chromium(VI) compounds in the rat. Two kinetic models describing the distribution and clearance of chromium(III) compounds in humans are described at the end of this section.

2.3.5.2 Chromium PBPK Model Comparison.

The O'Flaherty model is the only PBPK model available for chromium.

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.

2.3.5.3 Discussion of Models.

The O'Flaherty Model.

Risk assessment. The model accounts for most of the major features of chromium(VI) and chromium(III) absorption and kinetics in the rat, and reduction from the chromium(VI) to the chromium(III) valence state, but the bioavailability/absorbability of chromium from environmental sources is mostly unknown, except for bioavailability/absorbability of a few chemically defined salts. Furthermore, the mechanisms by which chromium reserves from bone tissue are released into plasma as well as age, physiological conditions and species variations are important considerations in the refinement of any PBPK model for risk assessment purposes.

Description of the model. The original model (O'Flaherty 1993a) was based on a PBPK model for lead and contained 10 compartments, alveolar space, well-perfused tissues, poorly-perfused tissues, kidney, liver, intestine, blood, and intestinal tract contents. The blood compartment was divided into plasma and red blood cells. Reduction of chromium(VI) to chromium(III) was considered to occur in every compartment except bone. The refined model (O'Flaherty 1996) replaced the alveolar space compartment with a two pool lung compartment, Pool A representing bioavailable chromium for entering either blood or the gastrointestinal tract, and Pool B containing non-bioavailable chromium that only moves into the gastrointestinal tract. The intestinal tract compartment was modified so that absorbed chromium entered the liver. A urinary retention compartment was added to better fit the data. The parameters of the model are given in Table 2-4 and the structure of the model is shown in Figure 2-4.

The model was developed from several data sets in which rats were dosed with chromium(VI) or chromium(III) intravenously, orally, or by intratracheal instillation, because depending on route of administration, different distribution and excretion patterns occur. In cases where parameters were not available (absorption rates, tissue affinity, biotransformation), estimates were obtained by fitting. This was done by duplicating the initial conditions of published experiments in the model, varying the unknown parameters and comparing the results of the simulation to the reported results. Tissue affinity constants were estimated using reported chromium levels in tissues at various times after exposure. Metabolic rate constants and absorption rate constants were estimated using data for excretion of chromium in urine and feces. The model includes exchanges of chromium between plasma and bone, and

Table 2-4. Parameters of the O'Flaherty PBPK Model

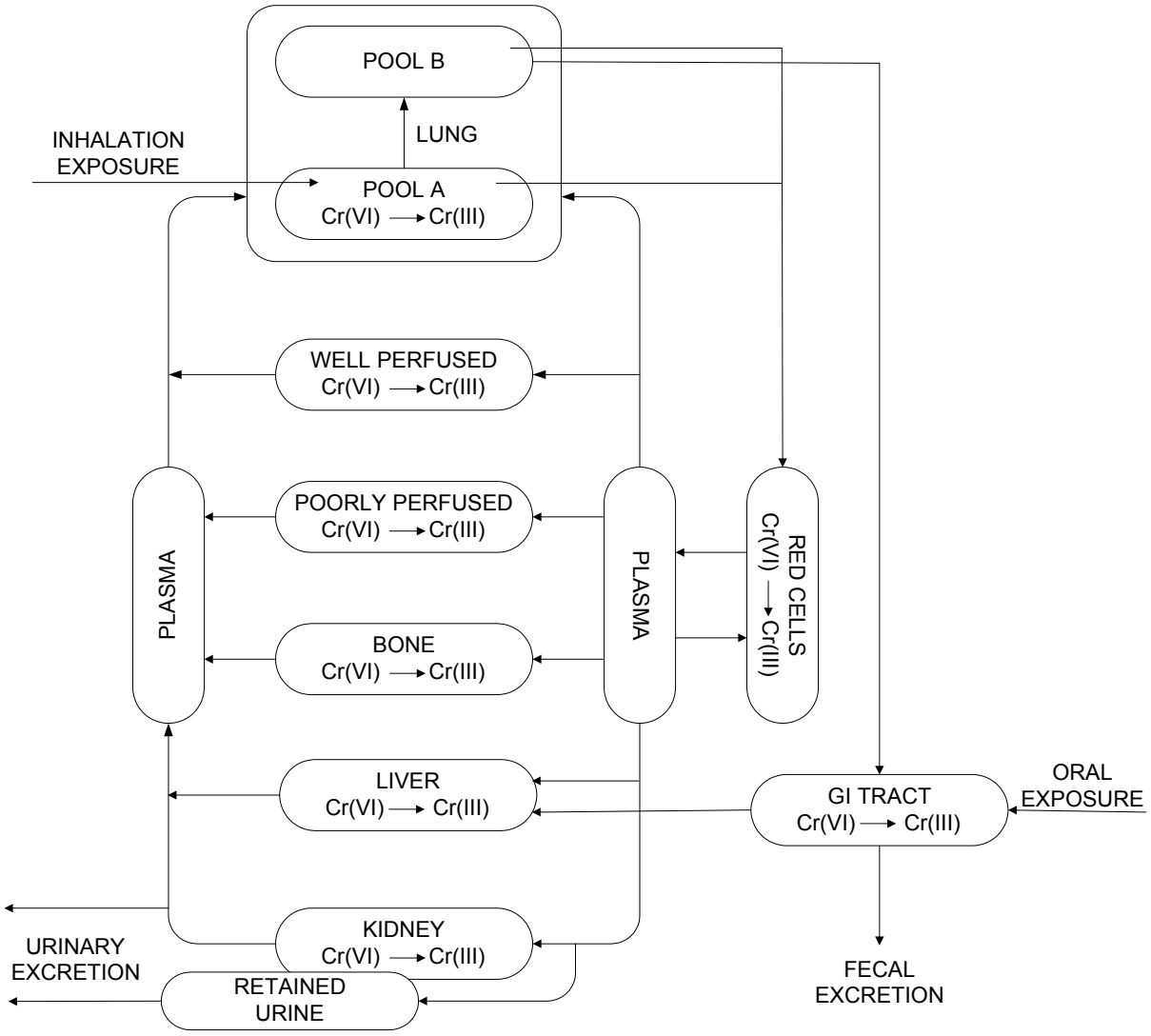
Value[a]	Definition
Absorption	
0.01, 0.4	First-order rate constant for absorption from the gastrointestinal tract (day^{-1})
0.2, 2.0	First-order rate constant for absorption from the bioavailable lung pool (pool A) (day^{-1})
0.8	First-order rate constant for mucociliary clearance from pool A to the gastrointestinal tract (day^{-1})
0.025	First-order rate constant for mucociliary clearance from nonbioavailable lung (pool B) to the gastrointestinal tract (day^{-1})
1.2	First-order rate constant for transfer from pool A to pool B (day^{-1})
Distribution	
5.0, 15.0	Relative clearance of chromium into mineralizing bone (liters of blood plasma cleared per liter of new bone formed)
0.0003, 1.5	Clearance from plasma to red cell (liters/day)
0.007, 1.5	Clearance from plasma to kidney (liters/day)
0.0001, 1.5	Clearance from plasma to liver (liters/day)
0.0001, 1.5	Clearance from plasma to other well-perfused tissues (liters/day)
0.0001, 0.1	Clearance from plasma to poorly-perfused tissues (liters/day)
0.0001, 0.1	Clearance from plasma to bone (liters/day)
0.0003, 10.0	Clearance from red cell to plasma (liters/day)
0.001, 10.0	Clearance from kidney to plasma (liters/day)
0.0003, 10.0	Clearance from liver to plasma (liters/day)
0.001, 10.0	Clearance from other well-perfused tissues to plasma (liters/day)
0.003, 10.0	Clearance from poorly perfused tissues to plasma (liters/day)
0.003, 10.0	Clearance from bone to plasma (liters/day)
Excretion	
1.5	First-order rate constant for loss of chromium from intestinal tract contents to the feces (day^{-1})
0.065, 0.065	Excretion clearance from the plasma (urinary clearance) (liters/kg/day)
0.0, 0.0	Fraction of body burden secreted in the bile
0.0, 0.0	Fraction of body burden excreted via the gastrointestinal tract

Table 2-4. Parameters of the O'Flaherty PBPK Model (*continued*)

Value[a]	Definition
Reduction	
0.7	First-order rate constant for reduction of Chromium(VI) to Chromium(III) in the red cell (day^{-1})
0.5	First-order rate constant for reduction of Cr(VI) to Cr(III) in all other tissues and in lung contents (day^{-1})
10.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in gastrointestinal tract contents (day^{-1})
Lag time for excretion of urine	
0.7	Fraction of urinary chromium not excreted immediately; that is, temporarily held in pool
0.05	First-order rate constant for excretion from the retained urine pool (day^{-1})
0.10	Fraction of chromium in retained urine that is associated with the kidney

[a]First value listed represents Cr(III), second value represents Cr(VI)

Figure 2-4. A Physiologically Based Model of Chromium Kinetics in the Rat*



*O'Flaherty 1996

incorporation of chromium into actively mineralizing bone. It also includes the reductive process for conversion of chromium(VI) to chromium(III) and takes into account differences in their absorption through tissues of the body as well as in the lung and gastrointestinal tract. The chromium model needed to be modified to include two lung compartments. Chromium via inhalation or intratracheal routes enters the lung in compartment A where it can be systemically absorbed, transferred to the second lung compartment B, or cleared by mucociliary action and enter the digestive tract. Chromium entering compartment B can only be cleared by mucociliary action, and no chromium re-enters compartment A from B. In order to account for the urinary excretion delay observed in the experimental data, a urinary retention compartment was added. Because the absorption of chromium compounds into the body and various tissues depends on the type and solubility of the complexes formed with ligands, adjustments to the model must be made based on physicochemical characteristics of individual chromium compounds.

Validation of the model. The model was run with the exposure regimen of an inhalation study of chromium(VI) as zinc chromate dust in Wistar rats (Langård et al. 1978). This study was chosen for validation because none of the studies used to develop the model were inhalation studies. Rats were exposed to 2.1 mg chromium(VI)/m^3 for 6 hours/day for 4 days, blood chromium was measured before and after each exposure and 4 times over the next 37 days post-exposure. The model tended to overpredict chromium blood levels during the 4-day exposure period, but agreement during the post-exposure period was good. The exposure conditions of a drinking water exposure to potassium chromate(VI) for 1 year at concentrations of 045, 2.2, 4.5, 7.7, 11.2, and 25 ppm in Sprague-Dawley rats were also simulated (MacKenzie et al. 1958).

The model overestimated final liver chromium concentrations, but bone and kidney concentrations were well-predicted. This was not a completely independent test of the model's validity since data from this study were used to set parameters for fractional uptake of chromium into bone.

Target tissues. Tissue levels of chromium(III) and chromium(VI) in the rat lung, erythrocyte, liver, and kidney can be predicted by this model.

Species extrapolation. No species extrapolation was attempted in this model. The model is based entirely on data from rat kinetic studies.

Interroute extrapolation. The model was developed initially using kinetic data from intravenous studies and then refined using data from oral and intratracheal routes. The final model was able to reasonably predict the results from an inhalation exposure experiment.

Two kinetic models describing distribution and clearance in humans have been developed based on studies in volunteers. A model for distribution and clearance of chromium(III) as chromium(III) trichloride was developed by Lim et al. (1983) that has fast, medium, and slow exchange compartments. The model's parameters were based on distribution measurements obtained from whole body scintillation scanning after intravenous injections of radiolabeled chromium into volunteers. Total chromium remaining in the body as a function of time was determined with a whole-body scanner, plasma clearance was determined by measurement of radiolabel in the blood. Measurements taken immediately after injection showed that 96% of the label was bound to plasma proteins while 4% was free, after 24 hours the label was too low to measure. Whole-body scanning showed labeled chromium primarily in the liver, spleen, body soft tissues, and bone with highest concentrations in the liver and spleen. Examination of the scanning images over time revealed three major accumulation and clearance components in each organ, half-lives were 0.5–12 hours, 1–14 days, and 3–12 months. Each organ exhibited this pattern, i.e., each organ has varying proportions of fast, medium, and slow components for chromium clearance. A model was constructed based on a central compartment of plasma chromium in equilibrium with three pools defined by clearance rate and elimination from the body taking place at the kidney through filtration of unbound chromium and loss of bound chromium by shedding of epithelial cells. The model indicates that in a normal individual in chromium balance, absorbed chromium distributes into three pools, a fast pool containing approximately 0.13 µg, and a clearance half-time of 5.2 minutes, a medium pool containing 0.8 µg and a half-time of 2.2 days, and a slow pool containing 24.7 µg and a half-time of 315 days.

Gargas et al. (1994) employed a three compartment model describing the urinary excretion of chromium (Aitio et al. 1988) to estimate the bioavailability of chromium(III) from chromium(III) picolinate in volunteers ingesting capsules containing 400 µg. The model contained 3 compartments, a fast-exchange compartment receiving 40% of absorbed chromium with a half-life of 7 hours, a medium-exchange compartment receiving 50% of absorbed chromium with a half-life of 15 days, and a slow-exchange compartment receiving 10% of absorbed calcium with a half-life of 3 years. Estimates of absorbed chromium were used as inputs to the model and predicted urinary excretion was compared to that observed. Adjustments to the estimate of absorbed chromium were made until the predictions agreed

with the observed data. Bioavailability of chromium(III) as chromium(III) picolinate was estimated as 2.80±1.14% (standard deviation).

Using these models for estimating bioavailability, distribution, and excretion, Stearns et al. (1995a) predicted that chromium(III) may accumulate in the body of humans ingesting large doses of chromium picolinate dietary supplements.

2.4 MECHANISMS OF ACTION

Chromium(III) is an essential nutrient required for normal energy metabolism. The biologically active form is an unidentified organic complex of chromium(III) often referred to as GTF. Chromium is poorly taken up by cells in any valence state, but chromium(III) is absorbed less efficiently than chromium(VI). This is believed to be due to the tetrahedral configuration of the chromate anion, which allows it to enter the cells via facilitated diffusion and through non-specific anion channels. In contrast, chromium(III) is absorbed via passive diffusion and phagocytosis, resulting in much lower total uptake into cells. Once absorbed, chromium(VI) is reduced to chromium(III), with chromium(V) and chromium(IV) as intermediates in the process. Chromium(V) and chromium(IV) are believed to be able to react with intracellular constituents, resulting in either the formation of free radicals or direct binding to macromolecules. Most of the effects of chromium(III) are mediated by direct binding to macromolecules, although there is a slight possibility that it may also contribute to free radical formation. The radical intermediates and the direct binding to macromolecules, can then result in DNA-protein crosslinks, DNA-DNA crosslinks, DNA strand breaks, lipid peroxidation, and alterations in cellular signaling pathways. All of these may contribute to toxicity and carcinogenicity of chromium compounds.

2.4.1 Pharmacokinetic Mechanisms

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages. Chromium has been identified in the tissues of occupationally-exposed humans, suggesting that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). Animal studies have also demonstrated increased amounts of chromium in the blood following inhalation or intratracheal instillation exposures (Baetjer et al. 1959b; Bragt and van Dura 1983; Langård et al. 1978; Visek et al. 1953; Wiegand et al. 1984, 1987). Chromium(VI) is more rapidly absorbed into

the bloodstream than is chromium(III) (Gao et al. 1993; Suzuki et al. 1984). Chromium that is not absorbed in the lungs may be cleared via mucociliary clearance and enter the gastrointestinal tract.

Chromium is poorly absorbed from the gastrointestinal tract; the primary site of chromium absorption appears to be the jejunum (Donaldson and Barreras 1966). The bioavailability of chromium compounds seems to be most dependant on the oxidation state of the chromium atom. However, other factors, including dose level and formulation of the chromium, can influence the extent of absorption. Chromium(III) is very poorly absorbed, with only 0.5–2.8% of dietary chromium absorbed via the gastrointestinal tract of humans (Anderson 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Gargas et al. 1994; Kerger et al. 1996a; Kuykendall et al. 1996). Chromium(III) absorption efficiency appears to be related to dietary intake; the efficiency decreases with increasing dose (Anderson 1986; Anderson et al. 1983). Human studies demonstrate that chromium(VI) is effectively reduced to chromium(III) by gastric juices (De Flora et al. 1987a) and in general, chromium(VI) is better absorbed than chromium(III) following oral exposure in humans (Donaldson and Barreras 1966; Finley et al. 1996b; Kerger et al. 1996a; Kuykendall et al. 1996). Absorption efficiencies ranging from 1.7 to 6.9% have been estimated in humans (Finley et al. 1996a; Kerger et al. 1996a, 1997; Kuykendall et al. 1996). Unlike chromium(III), absorption efficiency appears to increase with dose; Kerger et al. (1997) estimated an efficiency of 1.7% at 0.05 mg chromium(VI)/kg/day and 3.4% at 0.1 mg chromium(VI)/kg/day. Ingestion of chromium with a meal appears to increase the absorption efficiency (Chen et al. 1973).

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Following dermal exposure, chromium has been detected in the blood, feces, and urine of exposed humans (Brieger 1920), though in this study, the skin was damaged, which likely facilitated absorption. An average rate of systemic uptake of chromium(VI) in humans submersed in chlorinated water containing potassium dichromate(VI) for 3 hours was 1.5×10^{-4} µg/cm^2-hour (Corbett et al. 1997). Chromium(VI) appears to penetrate the skin faster than chromium(III) (Mali et al. 1963; Spruit and van Neer 1966; Wahlberg 1970), though many other factors may be involved, including solvent (Liden and Lundberg 1979) and concentration (Baranowska-Dutkiewicz 1981).

Absorbed chromium is carried throughout the body in the blood, eventually being distributed to all tissues. Greatest concentrations of chromium are found in the blood, liver, lung, spleen, kidney, and heart (Kaufman et al. 1970; Schroeder et al. 1962; Teraoka 1981). Because insoluble chromium is not completely cleared or absorbed following inhalation exposure, greater levels of chromium are often found in lung tissues following inhalation of chromium compounds than following other methods of exposure.

Tissue levels appeared to be higher after exposure to chromium(VI) than to chromium(III). This may be due to the greater ability of chromium(VI) to cross cell membranes and may also be a function of administration of doses high enough to overwhelm the chromium(VI) reduction mechanisms. De Flora et al. (1997) have demonstrated that liver, erythrocytes, whole blood, lung epithelial fluid, alveolar macrophages, and peripheral parenchyma cells all have the ability to reduce chromium(VI) to chromium(III). Chromium has been detected in breast milk (Casey and Hambidge 1984; Schmitova 1980), but the relationship between chromium exposure, dietary or otherwise, and breast milk chromium levels is inconclusive (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Systemic chromium does not appear to be stored for extended periods of time within the tissues of the body. Single- and multiple-exposure studies in humans have shown a one-compartment clearance half-time in humans on the order of 36 hours (Kerger et al. 1997; Paustenbach et al. 1996) following oral exposure. However, this half-time is sufficiently long to allow for accumulation of chromium following regular repeated exposure. Following inhalation exposure, insoluble chromium that is not cleared from the lungs may remain for a considerable time. Chromium may also persist within erythrocytes, bound to intracellular constituents.

Inhaled chromium can be eliminated from the lungs by absorption into the bloodstream, by mucociliary clearance, and by lymphatic system clearance (Bragt and van Dura 1983; Perrault et al. 1995; Visek et al. 1953; Weigand et al. 1984, 1987). The primary routes of elimination of absorbed chromium is urine and feces. It can also be eliminated in hair and fingernails (Randall et al. 1992; Stearns et al. 1995a; Takagi et al. 1986). Chromium, once reduced to chromium(III) in the liver, is then conjugated with glutathione and enters bile where it is excreted in the feces (Norseth et al. 1982). Because chromium is poorly absorbed following oral exposure, a large percentage of the amount ingested is excreted in the feces. The half-time of urinary excretion of chromium is short, 4–10 hours for inhalation exposure (Kiilunen et al. 1983), 10 hours for oral exposure to chromium(III) (Kerger et al. 1996a), and 40 hours for oral exposure to chromium(VI) (Kerger et al. 1996a, 1997). Following dermal exposure, chromium that is not absorbed into the bloodstream will remain on the skin until it is eliminated, usually by washing or other physical processes. Absorbed chromium is primarily eliminated in the urine.

2.4.2 Mechanisms of Toxicity

Following inhalation exposure, the majority of chromium-induced effects are seen in the respiratory tract, with some systemic effects reported at extremely high concentrations, but generally being lesser in

prevalence. Following oral exposure, hepatic and renal effects are most prevalent, with effects being generally lesser in other tissues. Studies of systemic effects following dermal exposure are limited, but the primary target organ following such exposures seems to be the skin.

The toxicity of chromium is dependent on the oxidation state of the chromium atom, with chromium(VI) being significantly more toxic than chromium(III). One of the factors believed to contribute to this increased toxicity is the greater ability of chromium(VI) to enter cells, compared to chromium(III). Chromium(VI) exists as the tetrahedral chromate anion at physiological pH, and resembles the forms of other natural anions, such as sulfate and phosphate, which are permeable across nonselective membrane channels. Chromium(III), however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity to chromium(III) may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of chromium(VI) to chromium(III) may result in a decreased penetration of chromium into cells, and therefore, a decreased toxicity.

Once it is taken into cells, chromium(VI) has been shown to undergo a reduction to chromium(III), with chromium(V) and chromium(IV) as intermediates. These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Hojo and Satomi 1991; Kim and Yurkow 1996; Lin et al. 1992; Liu et al. 1997b; Mao et al. 1995; Wiegand et al. 1984; Zhitkovich et al. 1996). Chromium(VI), chromium(V), and chromium(IV) have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species (Aiyar et al. 1991; Chen et al. 1997; Liu et al. 1997b; Luo et al. 1996; Mao et al. 1995; Molyneux and Davies 1995; Tsou et al. 1996). Although unlikely to occur under physiological conditions, chromium(III) may be able to undergo radical-generating cycling, though at lesser levels than chromium(IV) or chromium(V) (Shi et al. 1993, 1998; Tsou et al. 1996). It is believed that the formation of these radicals may be responsible for many of the deleterious effects of chromium on cells, including the formation of DNA strand breaks (Aiyar et al. 1991; Kuykendall et al. 1996b; Manning et al. 1992; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996b; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; Zhitkovich et al. 1996), and alterations in cellular communication and signaling pathways (Chen et al. 1997; Kim and Yurkow 1996; Mikalsen 1990; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Cellular damage from exposure to many chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity (Luo et al. 1996; Tsou et al. 1996; Ueno et al. 1995a).

The products of metabolic reduction of chromium(VI) (free radicals and chromium(IV) and (V)) and the newly generated chromium(III) are thought to be primarily responsible for the carcinogenic effects seen in human and animal studies. The interaction of free radicals, chromium(V), chromium(IV), and chromium(III) with DNA can result in structural DNA damage, functional damage, and cellular effects (Singh et al. 1998a). The types of structural damage include DNA strand breaks (Aiyar et al. 1991; Manning et al. 1992; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986; Umeda and Nishmura 1979; Wise et al. 1993). Functional damage includes DNA polymerase arrest (Bridgewater et al. 1994a, 1994b, 1998), RNA polymerase arrest, mutagenesis, and altered gene expression. Chromium can also interact with DNA to form adducts/complexes and DNA-protein crosslinks that interfere with DNA replication and transcription, and can promote the expression of regulatory genes such as nuclear factor-κβ, or may inhibit regulatory genes such as GRP78 (Chen et al. 1997; Kim and Yurkow 1996; Manning et al. 1992; Mikalsen 1990; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Disruption of these pathways by other compounds has been implicated in carcinogenesis. The structural and functional damage can lead to growth arrest (Xu et al. 1996) and apoptosis (Carlisle et al. 2000; Singh et al. 1999). As discussed by Singh et al. (1998a), the mechanism by which chromium induces apoptosis is not fully understood, but is believed to involve oxidative stress and DNA-DNA crosslinks and transcriptional inhibition.

2.4.3 Animal-to-Human Extrapolations

Species-related differences in chromium pharmacokinetics have been demonstrated, both between rodent species and between rodents and humans. However, studies directly examining species differences have been limited. Human microsomal chromium(VI) reduction is different from the P450-mediated microsomal reduction in rodents; specifically, the human system is much less oxygen-sensitive, has a much greater affinity for chromate, and is apparently mediated by flavoproteins (Myers and Myers 1998; Pratt and Myers 1993). Tissue distributions of chromium were found to be different between rats and mice after administration of bolus amounts of chromium(VI). Rat erythrocytes had a greater capacity to sequester chromium(VI) and reduce it to chromium(III) than mouse erythrocytes (Coogan et al. 1991b; Kargacin et al. 1993), thus demonstrating that both physiologic and metabolic differences can exist among species.

2.5 RELEVANCE TO PUBLIC HEALTH

Issues relevant to children are explicitly discussed in Sections 2.7, Children's Susceptibility, and 5.6, Exposures of Children.

Overview.

Chromium(III) is an essential nutrient required for normal energy metabolism. The National Research Council (NRC) recommends a dietary intake of 50–200 µg/day (NRC 1989). The biologically active form of an organic chromium(III) complex, often referred to as GTF, is believed to function by facilitating the interaction of insulin with its cellular receptor sites. The exact mechanism of this interaction is not known (Anderson 1981; Evans 1989). Studies have shown that chromium supplementation in deficient and marginally deficient subjects can result in improved glucose, protein, and lipid metabolism.

Evidence of overt signs of chromium deficiency in humans is limited to a few case reports. In one such case report, a woman receiving total parenteral nutrition for 3 years exhibited peripheral neuropathy, weight loss, and impaired glucose metabolism. Administration of insulin did not improve glucose tolerance. Administration of 250 µg/day chromium without exogenous insulin resulted in normal glucose tolerance of an oral load of glucose and the absence of peripheral neuropathy (Jeejeebhuoy et al. 1977).

In animals, severe chromium deficiency has resulted in hyperglycemia, decreased weight gain, elevated serum cholesterol levels, aortic plaques, corneal opacities, impaired fertility and lethality. Administration of inorganic trivalent chromium compounds or extracts of brewers' yeast resulted in decreased blood glucose levels and cholesterol levels and regression of atherosclerotic plaques (Pi-Sunyer and Offenbacher 1984). Improved insulin sensitivity also resulted in an increased incorporation of amino acids into proteins and cell transport of amino acid in rats receiving supplemental chromium (Roginski and Mertz 1969).

Although the incidence of severe chromium deficiency is low, the occurrence of marginal chromium deficiency may be common. Studies have shown that the daily dietary intake of chromium in the United States is 25–224 µg/day, with an average of 75 µg/day (Kumpulainen et al. 1979). An average daily intake of 60 µg has been reported by Bennett (1986). Numerous studies have been designed to determine the effect of chromium supplementation in individuals exhibiting abnormal glucose tolerance and/or

elevated lipid levels. Serum chromium levels before and after supplementation were often not measured because of limitations in analytical techniques available. Brewer's yeast, extracts of brewer's yeast, synthetic chromium compounds with biological activity, chromium(III) picolinate, and inorganic trivalent chromium have been used as chromium supplements (Pi-Sunyer and Offenbacher 1984). In general, these studies have demonstrated improved glucose tolerance to an oral glucose load in Type II diabetics (adult onset) and nondiabetic elderly subjects receiving a 4–200 µg/day chromium supplement (Evans 1989; Levine et al. 1968; Liu and Morris 1978; Offenbacher and Pi-Sunyer 1980). The subjects receiving the daily chromium supplements had significantly lower blood glucose levels than the controls and no difference in serum insulin levels between the groups. This reduction in blood glucose without a change in insulin levels provides support that chromium enhances insulin sensitivity. Decreases in total cholesterol, LDL-cholesterol, and serum lipids and increases in HDL-cholesterol have also been observed in Type II diabetics and nondiabetics administered chromium supplements (Anderson et al. 1997c; Evans 1989; Lee and Reasner 1994; Offenbacher and Pi-Sunyer 1980; Press et al. 1990). This improvement in serum lipids and cholesterol levels may be secondary to the decreased serum glucose levels.

In recent years, the use of chromium picolinate as a dietary supplement to aid in weight loss and increase lean body mass has gained in popularity. As discussed by (Anderson 1998b), the role of chromium in the regulation of lean body mass, percentage body fat, and weight reduction is highly controversial with negative and positive results being reported in the literature. Initial studies (Evans 1989; Hasten et al. 1992) on chromium picolinate supplementation during resistance training served as the basis for the marketing of chromium picolinate to promote muscle growth and fat loss. Evans (1989) found that administration of 200 µg chromium(III)/day as chromium picolinate for 6 weeks to healthy males performing daily weight training exercises resulted in an increase in body weight that was mostly due to an increase in lean body mass. Control subjects undergoing the same exercise regimen but given a placebo of calcium phosphate gained significantly less lean body mass and lost significantly less body fat than the subjects receiving the chromium supplement; the weight gain in the controls was mostly due to increased fat tissue. Hasten et al. (1992) reported an increase in lean body mass in women receiving 200 µg chromium(III)/day as chromium picolinate during 12 weeks of resistance training. Although some other studies have found increases in lean body mass (Bulbulian et al. 1996; Kaats et al. 1996) in adults taking 200 or 400 µg chromium(III) as chromium picolinate along with an exercise program, many studies did not find any alterations in lean body mass (Campbell et al. 1999; Clancy et al. 1994; Hallmark et al. 1996; Lukaski et al. 1996; Trent and Thieding-Cancel 1995).

Several studies have also looked at the relationship between weight loss or increases in lean body mass in sedentary adults and chromium picolinate supplementation. Kaats et al. (1992) reported an improvement in body composition (loss of body fat without a loss of lean body mass) in obese subjects consuming 400 µg chromium(III)/day as chromium picolinate for 72 days. In contrast to these studies, Grant et al. (1997) found a significant increase in body weight gain with no change in percent body fat or fat free mass in sedentary, young, obese women consuming 400 µg chromium(III)/day as chromium picolinate for 9 weeks. If the women participated in a exercise program, then no significant alterations in body weight, percent body fat, fat mass, or fat free mass were observed. Proponents of chromium picolinate supplementation have made numerous claims as to the benefits of chromium picolinate for weight loss and increasing lean body mass. However, for the most part, clinical studies have not supported these claims (Campbell et al. 1999; Clancy et al. 1994; Grant et al. 1997; Hallmark et al. 1996; Lukaski et al. 1996; Trent and Thielding-Cancel 1995). The potential toxicity of chromium picolinate has not been thoroughly investigated. An intermediate-duration rat study did not find any adverse effects in rats ingesting #9 mg chromium(III)/kg/day as chromium picolinate in the diet (Anderson et al. 1997b). Wasser et al. (1997) reported a case of an individual with chronic renal failure following ingestion of 0.6 mg/day (approximately 0.085 mg/kg/day) of chromium picolinate supplements for 6 weeks. This dose is 3 times the recommended doses for dietary supplements and 12–45 times the usual intake. Thus, individuals using these supplements are cautioned to avoid taking more than recommended doses.

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products or soils that contain chromium. As discussed in Section 5.4, ambient air in U.S. urban and nonurban areas typically contains mean total chromium concentrations ranging from 0.01 to 0.03 µg/m^3. The levels of chromium in U.S. river waters typically range from <1 to 30 µg/L, with a median value of 10 µg/L. Typical U.S. drinking water supplies contain total chromium levels mainly as chromium(III) ranging from 0.4 to 8.0 µg/L, with a mean of 1.8 µg/L. U.S. soil levels of total chromium range from 1.0 to 2,000 mg/kg, with a mean level of 37 mg/kg. Chromium content in foods varies greatly and depends on the processing and preparation. In general, most fresh foods typically contain <50 µg total chromium/kg. Although workers in chromium-related industries in the past were exposed to much higher levels of chromium than present day workers, present day workers in chromium-related industries can be exposed to chromium concentrations two orders of magnitude higher than the general population. Current OSHA TWA standards for an 8-hour workday, 40-hour workweek are 0.5 mg chromium/m^3 for water soluble chromic (chromium(III)) or chromous (chromium(II)) salts and

1 mg chromium/m^3 for chromium(0) and insoluble salts. For chromic acid and chromates, a ceiling limit has been set at 0.1 mg/m^3 (0.052 mg chromium(VI)/m^3] (OSHA 1999a).

Chromium(VI) is better absorbed from the lung, gastrointestinal tract, and skin than is chromium(III). Chromium(VI) is reduced to chromium(III) within the stomach, limiting the bioavailability of chromium after ingestion and accounting for the relatively low oral toxicity of chromium(VI). Although chromium(III) occurs naturally in the environment, chromium(VI) in the environment is almost always related to anthropogenic activity. The presence of chromium compounds at hazardous waste sites can contribute to the exposure of populations residing or working nearby through exposure to air containing particulates or mists of chromium(VI) compounds, through drinking water if soluble forms of chromium(VI) leach into groundwater, or through skin contact with soil at hazardous waste sites. The potential for exposure to chromium(VI) at hazardous waste sites must be determined on a case-by-case basis.

Effects in humans exposed occupationally to high levels of chromium or its compounds, primarily chromium(VI), by inhalation may include nasal septum ulceration and perforation, and other irritating respiratory effects, possible cardiovascular effects, gastrointestinal and hematological effects, liver and kidney effects, and increased risks of death from lung cancer. In addition to the respiratory effects, exposure to chromium(VI) and (III) compounds can be associated with allergic responses (e.g., asthma and dermatitis) in sensitized individuals. Chromosome aberrations have been observed in some humans occupationally exposed to chromium(VI) compounds and other substances. Accidental or intentional ingestion of extremely high doses of chromium(VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects as part of the sequelae leading to death or in patients who survived because of medical treatment. Dermal exposure to chromium(VI) compounds has lead to death of humans that had pre-existing medical conditions. Severe renal and hematological effects, and effects on the cardiovascular system and gastric mucosa were observed in people with pre-existing medical conditions who died as a result of dermal exposure. Occupational exposure by dermal contact can result in deeply penetrating ulcers (known as chrome sores, chrome holes, or chrome ulcers) on the skin if left untreated. Dermal contact in chromium sensitized individuals can also lead to an allergic type dermatitis.

Inhalation studies in animals with chromium(VI) and chromium(III) compounds generally support the respiratory and immunological findings in humans. Inhalation and intratracheal studies with certain chromium(VI) compounds in animals also support the carcinogenic findings in humans. Oral exposure of

animals to very high doses of chromium(VI) and chromium(III) compounds has resulted in gastrointestinal, hepatic, renal, immunological, neurological, developmental, and reproductive effects. Dermal exposure of animals to chromium(VI) and chromium(III) compounds has resulted in skin ulcers and allergic response.

In general, chromium(VI) compounds are more toxic than chromium(III) compounds. The toxicity of hexavalent chromium is in part due to the generation of free radicals formed during reduction to chromium(III) in biological systems.

Chromium(IV) dioxide is a tetravalent chromium compound with limited industrial application. It is used to make magnetic tape, as a catalyst in chemical reactions, and in ceramics (Hartford 1979). Because of its limited industrial uses, the potential for human exposure is less for chromium dioxide than for the more industrially important chromium(VI) and chromium(III) compounds. A single chronic inhalation study in rats exposed to 15.5 mg chromium(IV)/m^3 as chromium dioxide reported no respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, or dermal/ocular effects (Lee et al. 1989).

Minimal Risk Levels for Chromium.

Inhalation MRLs.

- An MRL of 0.000005 mg chromium(VI) /m^3 has been derived for intermediate (15–364 days) exposure as chromic acid (chromium trioxide mist) and other dissolved hexavalent chromium aerosols and mists.

[Note: An MRL of 0.0001 mg chromium(VI)/m^3 for intermediate and chronic exposure to chromic acid was previously derived in the Draft for Public Comment. Refer to Chapter 7 for detailed information.]

The MRL is derived from the study by Lindberg and Hedenstierna (1983) and is based on nasal irritation, mucosal atrophy, and ulceration, and decreases in spirometric parameters observed in workers occupationally exposed to $0.002 mg chromium (VI) /$m^3$ as chromic acid with a median exposure period of 2.5 years. The MRL was obtained by adjusting the LOAEL (0.002 mg chromium(VI)/m^3) to 0.0005 mg chromium(VI)/m^3 for continuous exposure and dividing by an uncertainty factor of 10 for human variability and 10 for extrapolating from a LOAEL. The MRL of 0.000005 mg/m^3 is set for intermediate- duration because the effects began to occur in workers exposed for less than 1 year. An MRL of 0.000005 mg/m^3 based on chromic acid will also be health-protective against exposures to less irritating soluble chromium(VI) compounds.

The respiratory tract is the major target of inhalation exposures to chromium compounds. Respiratory effects due to inhalation exposures are likely due to direct action of chromium at the site of contact. Workers exposed to chromium(VI) compounds for intermediate- and chronic-durations were found to exhibit epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulcerations of the nasal septum, bronchitis, pneumonoconiosis, decreased pulmonary function, and pneumonia (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gomes 1972; Greater Tokyo Bureau of Hygiene 1989; Hanslian et al. 1967; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Lee and Goh 1988; Letterer 1939; Liebermann 1941; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Pastides et al. 1991; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al.1987; Taylor 1966).

The intermediate inhalation MRL derived from the Lindberg and Hedenstierna (1983) study is primarily based on effects in the nose due to direct contact with irritating properties of soluble chromates. Furthermore, the likelihood for environmental exposure to chromium trioxide and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds. Therefore, it is also appropriate to derive an inhalation MRL for particulate chromium(VI) compounds.

- An MRL of 0.001 mg chromium(VI)/m^3 was derived for intermediate exposures to particulate chromium(VI) compounds.

[Note: An MRL of 0.0005 mg chromium(VI)/m^3 for intermediate exposures to particulate chromium(VI) compounds was previously derived in the Draft for Public Comment. Refer to Chapter 7 for detailed information.]

The MRL was based on a benchmark concentration (BMC) of 0.016 mg/m^3 determined by Malsch et al. (1994) for alterations in the level of lactate dehydrogenase in bronchoalveolar lavage fluid (Glaser et al. 1990). Glaser et al. (1990) exposed rats to 0.05–0.4 mg chromium (VI)/m^3 as sodium dichromate particulate aerosols for 22 hours/day, 7 days/week for 90 days. The BMC was converted to a BMC_{ADJ} and divided by an uncertainty factor of 30 (3 to account for pharmacodynamic differences not addressed by the dose conversion and 10 for human variability). The MRL is supported by a similar study by Glaser et al. (1985) in which an increase in the number of bronchoalveolar lavage macrophages in telephase was observed in rats exposed to 0.025 mg chromium(VI)/m^3 as sodium dichromate. Because the deposition of chromium in the respiratory tract will be dependent on particle size, this MRL may be not be applicable to particle sizes that differ appreciatively from those used in the Glaser et al. (1990) study (MMAD 2.8 μm, σ_g 1.63).

Oral MRLs

No MRLs were derived for oral exposure to chromium(VI) or chromium(III). The available data on reproductive and developmental effects are insufficient or too contradictory to establish acute-, intermediate-, or chronic-duration oral NOAELs or LOAELs which are both used in the uncertainty factor approach to derive MRL values. However, the upper range of the estimated safe and adequate daily dietary intake (ESADDI) of 200 µg chromium/day (0.003 mg/kg/day for a 70 kg individual) (NRC 1989) has been adopted as provisional guidance for oral exposure to chromium(VI) and chromium(III). This guidance is necessary because of the prevalence of chromium at hazardous waste sites, the fairly complete database, and the fact that chromium is an essential nutrient.

Death. Human deaths have occurred after accidental or intentional ingestion (Clochesy 1984; Ellis et al. 1982; Iserson et al. 1983; Kaufman et al. 1970; Reichelderfer 1968; Saryan and Reedy 1988) or dermal (Brieger 1920; Major 1922) exposure to chromium(VI) compounds. Although no studies were located regarding death in humans after acute inhalation exposure to chromium compounds, occupational exposure to chromium via inhalation has been associated with increased mortality due to lung cancer and possibly noncancer respiratory disease; however, methodological deficiencies in the studies reporting increased risk from noncancer respiratory disease prevent establishing a causal relationship. Acute inhalation LC_{50} values of chromium(VI) compounds ranged from 29 to 87 mg chromium(VI)/m^3 for female rats and from 33 to 137 mg chromium(VI)/m^3 for male rats (American Chrome and Chemicals 1989; Gad et al. 1986). Acute, oral LD_{50} values for chromium(VI) compounds ranged from 13 to 108 mg chromium(VI)/kg for female rats and from 21 to 811 mg chromium(VI)/kg for male rats (American Chrome and Chemicals 1989; Gad et al. 1986; Shubochkin and Pokhodzei 1980; Vernot et al. 1977). Dermal LD_{50} values for potassium dichromate, sodium chromate and dichromate, and ammonium dichromate ranged from 361 to 553 mg chromium(VI)/kg for female rabbits and from 336 to 763 mg chromium(VI)/kg for male rabbits (Gad et al. 1986). A dermal LD_{50} value of 30 mg chromium(VI)/kg as chromium trioxide in rabbits was also reported (American Chrome and Chemicals 1989). No inhalation LC_{50} values or dermal LD_{50} values for chromium(III) compounds were located. Oral LD_{50} values for chromium(III) compounds in rats were 2,365 mg chromium(III)/kg as chromium acetate (Smyth et al. 1969) and 183 and 200 mg chromium(III)/kg as chromium nitrate for females and males, respectively (Vernot et al. 1977). Female animals are generally more susceptible to the lethal effects of chromium compounds, and chromium(VI) compounds are more toxic than chromium(III) compounds. The environmental or workroom concentrations of chromium(III) or chromium(VI) compounds are not likely to be high enough to cause death in humans.

Systemic Effects

Respiratory Effects. The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. Intermediate- and chronic-duration exposure of workers to chromium(VI) compounds has resulted in epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumonoconiosis, decreased pulmonary function, and pneumonia (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gomes 1972; Greater Tokyo Bureau of Hygiene 1989; Hanslian et al. 1967; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Kuo et al. 1997a; Lee and Goh 1988; Letterer 1939; Lieberman 1941; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Pastides et al. 1991; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966). In some chromium-sensitive patients, inhalation of airborne chromium(VI) compounds in the workplace may result in asthma (Keskinen et al. 1980; Novey et al. 1983; Olaguibel and Basomba 1989). The chromium-related industries associated with these effects include chrome plating, chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining. Nasal irritation and mucosal atrophy and decreases in pulmonary function have occurred at occupational exposure levels $0.002 mg chromium(VI)/$m^3$ as chromium trioxide mist (Lindberg and Hedenstierna 1983). The LOAEL value of 0.002 mg chromium(VI)/m^3 for respiratory effects in workers exposed 8 hours/day, 5 days/week for <1 to >1 year was used as a basis for an inhalation MRL of 0.000005 mg chromium(VI)/m^3 for intermediate-duration exposure to chromium(VI) as chromium trioxide mist and other dissolved hexavalent chromium aerosols and mists. Autopsies of humans who died from cardiopulmonary arrest after ingesting chromium(VI) compounds have revealed pleural effusion, pulmonary edema, bronchitis, and acute bronchopneumonia (Clochesy 1984; Ellis et al. 1982; Iserson et al. 1983). Respiratory effects due to ingestion of nonlethal doses are not likely to occur. It is not certain whether skin contact with chromium compounds could result in respiratory effects.

Adverse effects on the respiratory system following inhalation exposure to chromium(III) and chromium(VI) have also been observed in animals. Acute- and intermediate-duration exposure to moderate levels of chromium(III) and/or chromium(VI) compounds generally caused mild irritation, accumulation of macrophages, hyperplasia, inflammation, and impaired lung function (Glaser et al. 1985; Henderson et al. 1979; Johansson et al. 1986a, 1986b). A LOAEL of 0.025 mg chromium(VI)/m^3 as potassium dichromate particles for increased percentage of lymphocytes in bronchoalveolar lavage fluid in rats exposes for 28 or 90 days was identified (Glaser et al. 1985). Obstructive respiratory dyspnea at $0.2 mg chromium(VI)/$m^3$,

fibrosis at $0.1 mg chromium(VI)/$m^3$, and hyperplasia at $0.05 mg chromium(VI)/$m^3$ were found in the lungs of rats exposed to sodium dichromate for 30 or 90 days. The fibrosis and hyperplasia were reversible (Glaser et al. 1990). Increases in the levels of total protein, albumin, and activity of lactate dehydrogenase and β-glucuronidase were observed in the bronchoalveolar lavage fluid. A benchmark concentration of 0.016 mg chromium(VI)/m^3 was developed from the lactate dehydrogenase data. This benchmark concentration was used to derive an intermediate-duration inhalation MRL of 0.001 mg chromium(VI)/m^3 for exposure to chromium(VI) particulates. Nasal septum perforation, hyperplasia and metaplasia of the larynx, trachea, and bronchus, and emphysema developed in mice exposed to chromium trioxide mists for one year (Adachi 1987; Adachi et al. 1986). Mice exposed chronically to 4.3 mg chromium(VI)/m^3 as calcium chromate also had epithelial necrosis and hyperplasia of the bronchiolar walls (Nettesheim and Szakal 1972). Rats, guinea pigs, and rabbits exposed chronically to a dust of mixed chromium roast material (1.6–2.1 mg chromium(VI)/m^3) developed pulmonary lesions, such as granulomata, abscesses, bronchopneumonia, inflammation, or alveolar infiltration and hyperplasia (Steffee and Baetjer 1965). Chronic exposure of rats to a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide at 0.1 mg total chromium/m^3 caused interstitial fibrosis and thickening of the septa of the alveolar lumens, while exposure to chromium(VI) alone at 0.1 mg chromium(VI)/m^3 as sodium dichromate resulted only in increased lung weight and loading of macrophages. The reason for the differential response to sodium dichromate and the mixture of chromium(VI) trioxide and chromium(III) oxide is probably related to solubility differences, with the less soluble oxides having a longer residence time in the lungs than the more soluble sodium dichromate (Glaser et al. 1986, 1988). Cytochrome-P450 activity in lungs of rats was significantly increased after intraperitoneal injections of potassium dichromate(VI) (Witmer et al. 1994). Cytochrome P450 activity was determined by hydroxylation of testosterone.

Occupational exposure to chromium(VI) primarily as mist/aerosol can result in respiratory effects. Animal studies have reported respiratory effects following exposure to chromium(VI) or chromium(III) mists and particulates. Exposure to chromium in ambient air is mainly to chromium(III) adhered to dust particles (see Section 5.4.1). The possibility that inhalation exposure to chromium in the environment, from industrial sources, or at hazardous waste sites could result in respiratory effects cannot be ruled out.

Cardiovascular Effects. Cardiovascular effects, such as changes in the bioelectric and mechanical activity of the myocardium, were reported in potassium dichromate production workers in Russia (Kleiner et al. 1970), but studies of chromate workers in Italy (Sassi 1956) and the United States (PHS 1953) found no electrocardiogram abnormalities or association with heart disease or blood pressure. Likewise, the examination of mortality records of large cohorts that worked in the production of stainless steel and

chromium mining industries revealed no increases in cardiovascular disease or ischemic heart disease compared to overall national incidences (Moulin et al. 1993; Rosenman and Stanbury 1996). Case reports of humans who died after ingesting sodium or potassium dichromate have described such effects as cardiopulmonary arrest, hypoxic changes in the myocardium, progressive drops in cardiac output, heart rate, and blood pressure, and hemorrhages in the left ventricle muscle as sequelae leading to death (Ellis et al. 1982; Iserson et al. 1983). Weak pulse was observed in some people after dermal application of a salve containing potassium chromate to treat scabies, and degeneration of the heart was seen in others who died after such an exposure (Brieger 1920).

Based on the limited information in humans, cardiovascular effects due to inhalation, oral, and dermal exposure to chromium compounds in the workplace, in the environment, or at hazardous waste sites does not seem likely.

No histopathological cardiac lesions were observed in rats exposed chronically to diets containing chromium oxide at 2,040 mg chromium(III)/kg/day (Ivankovic and Preussmann 1975) or drinking water containing chromium acetate at 0.46 mg chromium(III)/kg/day (Schroeder et al. 1965). However, degenerative changes in the myocardium were found in rabbits injected intraperitoneally with 2 mg chromium(VI)/kg as potassium dichromate or 2 mg chromium(III)/kg as chromium nitrate daily for 6 weeks (Mathur et al. 1977). Intraperitoneal injection studies may not be predictive of effects or doses by environmentally relevant routes.

Gastrointestinal Effects. Workers in chromate plants or electroplating facilities exposed to high levels of atmospheric chromium(III) and chromium(VI) have developed stomach pains and cramps, duodenal ulcers, gastric ulcers, and gastritis (Lucas and Kramkowski 1975; Mancuso 1951; Sassi 1956; Sterekhova et al. 1978). The gastrointestinal irritation and ulceration could be due to direct action of chromium on gastric mucosa as a result of mouth breathing or transfer via hand to mouth activity. It should be noted that these gastrointestinal effects could be caused by other factors, such as stress and diet, and most of the studies did not include a control group. Higher incidences of complaints of diarrhea and constipation were reported in housewives who lived in an area contaminated with chromium slag in Japan than in housewives who lived in an uncontaminated area (Greater Tokyo Bureau of Hygiene 1989). Cases of tonsillitis, chronic pharyngitis, and atrophy of the larynx have been reported in chromium electroplaters, probably due to mouth breathing of high levels of chromium(VI) above the plating baths (Hanslian et al. 1967). Abdominal pain, vomiting, and gastrointestinal burns and hemorrhage have occurred in humans after ingesting lethal doses of chromium(VI) as potassium dichromate, chromium trioxide, sodium dichromate, or ammonium dichromate (Clochesy 1984; Ellis et al. 1982; Iserson et al. 1983; Kaufman et al. 1970; Reichelderfer 1968; Saryan and Reedy 1988).

Nausea and vomiting occurred in some workers upon eating on the premises of a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide (Lieberman 1941), and acute gastritis occurred in a worker who accidentally swallowed plating fluid containing chromium trioxide (Fristedt et al. 1965). Ingestion of oatmeal contaminated with potassium dichromate led to abdominal pain, vomiting, and diarrhea in two people (Partington 1950). Oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting were found to be associated with drinking well water contaminated with 20 mg chromium(VI)/L from an alloy plant in China (Zhang and Li 1987). Dermal application of a salve containing potassium chromate resulted in vomiting of some people, and autopsy of some people who died after such exposure revealed hyperemia of the gastric mucosa (Brieger 1920).

Rats exposed by inhalation to #0.2 mg chromium(VI)/m^3 as sodium dichromate for #90 days did not have histopathological lesions in the gastrointestinal tract (Glaser et al. 1985). Mice exposed chronically to 4.3 mg chromium(VI)/m^3 were reported to have occasional small ulcerations in the stomach and intestinal mucosa (Nettesheim et al. 1971). A lethal gavage dose of 130 mg chromium(VI)/kg as potassium dichromate to rats resulted in gastrointestinal hemorrhage (Samitz 1970), but chronic dietary exposure of rats to 2,040 mg chromium(III)/kg/day as chromium oxide did not result in gastrointestinal lesions (Ivankovic and Preussmann 1975). Diarrhea also occurred in rabbits exposed dermally to lethal concentrations of chromium(VI) compounds (Gad et al. 1986). The findings of gastrointestinal effects in humans and animals after inhalation, oral, and dermal exposure to chromium compounds, especially chromium(VI) compounds, provide strong evidence for the irritating effects on the gastrointestinal mucosa at high doses.

Hematological Effects. Hematological evaluations of workers occupationally exposed to chromium compounds have yielded equivocal results. Leukocytosis or leukopenia has been observed in workers exposed to chromium(III) and chromium(VI) in a chromate production plant. The leukocytosis was expressed as either monocytosis or eosinophilia. Decreased hemoglobin and increased bleeding time were also observed (Mancuso 1951). Other studies examined hematological parameters of chromate and dichromate production workers (PHS 1953; Sassi 1956) and stainless steel welders (Littorin et al. 1984); however, no significant hematological effects were observed. In cases of ingestion of potassium dichromate or chromium trioxide, such hematological effects as anemia following severe hemorrhaging, intravascular hemolysis, inhibition of coagulation, leukocytosis, and decreased hemoglobin, have been observed in humans (Clochesy 1984; Fristedt et al. 1965; Goldman and Karotkin 1935; Iserson et al. 1983; Sarayan and Reedy 1988; Sharma et al. 1978). Leukocytosis and immature neutrophils were associated with drinking well water contaminated with 20 mg chromium(VI)/L by villagers near an alloy plant in China (Zhang and Li 1987). Hematological effects in humans after dermal exposure to chromium compounds included severe

leukocytosis and hemolytic anemia in individuals after application of a salve containing potassium dichromate (Brieger 1920).

Generally, inhalation exposure of intermediate duration to sodium dichromate did not cause hematological effects in animals, except for an increased spleen weight and reversible increases in white blood cells in rats (Glaser et al. 1985, 1990). Chronic exposure of rats to 0.1 mg chromium/m^3 as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide, however, resulted in increased red and white blood cell counts, hemoglobin content, and hematocrit (Glaser et al. 1986, 1988). No hematological effects were observed in rats exposed orally to chromium(VI) or chromium(III) compounds (Ivankovic and Preussmann 1975; MacKenzie et al. 1958). It is possible that occupational exposure to chromium compounds could change the hematological profiles of humans, but hematological effects due to exposure in the environment or at hazardous waste sites seems less likely.

Musculoskeletal Effects. The only information regarding musculoskeletal effects after exposure to chromium or its compounds *in vivo* is that a man who was admitted to the hospital with skin ulcers due to exposure to ammonium dichromate in a planographic printing establishment also had tenderness and edema of the muscles of the extremities (Smith 1931). Other musculoskeletal effects have not been reported in humans or animals in any other *in vivo* studies. Nasu et al. (1993) examined the effects of potassium dichromate(VI) on the contraction of ileal longitudinal smooth muscle isolated from male Hartley guinea pigs. They reported that tonic tensions induced by high-K^+ levels were not affected by exposing the tissue to 0.01–1 mM chromium(VI) for 5 minutes, but at a longer exposure of 30 minutes, there was a dose-dependent inhibition to the contraction response. Chromium(VI) also inhibited the Ca^{2+} concentration in depolarized muscle in a dose-dependent manner. The low affinity binding sites of calcium and decreased tissue concentrations of ATP during K^+-induced contractions were observed after 5 minutes and more so after 30 minutes exposure to chromium(VI). The authors suggested that these effects on smooth muscle contraction were probably caused by interference with calcium influx at the cell membrane resulting from the chromium-reducing mitochondrial oxidative phosphorylation.

Hepatic Effects. Histological examination of liver samples and analysis of blood chemistry of five workers exposed to chromium trioxide in the chrome plating industry revealed liver damage in four of the workers (Pascale et al. 1952). Also, examination of mortality patterns in stainless steel workers revealed excess incidences of cirrhosis based on national rates (Moulin et al. 1993). Some workers in a chromate production plant had hepatobiliary disorders, and slight impairment was found in liver function testing in a few cases. These disorders may not have been due solely to chromate exposure (Sassi 1956). However,

the production of chromium compounds does not appear to be associated with long-term liver effects. Liver function parameters of Japanese workers engaged in the production of chromium compounds were within normal limits when tested 3 years after exposure (Satoh et al. 1981). Testing of workers employed in factories that produced chromium(III) compounds found no signs of liver disorders (Korallus et al. 1974b), and testing of housewives who lived near a chromium slag construction site revealed no clinical evidence of liver dysfunction (Greater Tokyo Bureau of Hygiene 1989). However, liver effects, such as jaundice, increased bilirubin, increased levels of serum lactic dehydrogenase, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase, and necrosis have been reported in humans after ingestion of lethal doses of potassium dichromate or chromium trioxide (Fristedt et al. 1965; Kaufman et al. 1970).

Only mild liver effects (increase in triglycerides and phospholipids) were observed in rats exposed to 0.2 mg chromium(VI)/m^3 as sodium dichromate for 90 days (Glaser et al. 1985). These effects on the liver are minimal and were not observed in chronic exposure studies (Glaser et al. 1986, 1988). Effects on the liver of rats exposed orally to chromium(VI) compounds have been detected by biochemical and histochemical techniques. These consisted of increased accumulations of lipids (Kumar and Rana 1982) and changes in levels and localization of enzymes (Kumar et al. 1985) in rats treated by gavage with potassium chromate. Intermediate or chronic oral exposure of rats to chromium(III) compounds in the drinking water (MacKenzie et al. 1958; Schroeder et al. 1965) or the diet (Anderson et al. 1997b; Ivankovic and Preussmann 1975) did not cause liver effects. Changes in liver enzymes indicative of altered carbohydrate metabolism were reported in rats after a single dermal application of 0.175% potassium dichromate (Merkur'eva et al. 1982). Although liver effects in animals exposed to chromium compounds by inhalation, oral, and dermal routes appear to be mild, studies in which animals were exposed by other routes indicate more serious effects. Necrosis with regeneration occurred in rats injected subcutaneously with 3.5 mg chromium(VI)/kg as potassium dichromate (Baines 1965), lipid peroxidation occurred in rats injected intraperitoneally with 10 mg chromium/kg as chromium(III) nitrate or potassium dichromate (Ueno et al. 1988), and vacuolization of hepatocytes occurred in hamsters after intravenous injection of 5.2 mg chromium(VI)/kg as chromium trioxide (Gale 1978). Rats injected intraperitoneally with 2 mg chromium/kg/day, 3 days/week for 15–60 days developed liver necrosis with sodium chromate and vacuolization of hepatocytes with chromium(III) trichloride (Laborda et al. 1986). Cytochrome P450 activity in liver of rats was significantly increased after intraperitoneal injections of potassium dichromate(VI) (Witmer et al. 1994). P450 activity was measured by hydroxylation of testosterone. Rabbits injected for 6 weeks intraperitoneally with 2 mg chromium/kg/day developed marked congestion, large areas of focal necrosis, extensive hemorrhage, bile duct proliferation, and

hyperplasia in the liver with either potassium dichromate or chromium(III) nitrate (Tandon et al. 1978). While these studies indicate that the liver is a target organ of chromium toxicity in animals, the methods of administration may not be predictive of effects or doses by environmentally relevant routes. While occupational exposure to chromium(VI) in the past may have caused adverse liver effects, they are not expected to occur in humans currently exposed to chromium or its compounds occupationally or in people living near hazardous waste sites. It is unlikely that oral exposure to the low levels of chromium(III) or chromium(VI) compounds detected in drinking water or in the ambient environment would cause hepatic effects in humans.

Renal Effects. Renal function has been studied in workers occupationally exposed to chromium compounds. Some studies of workers exposed to chromium(VI) and chromium(III) in the chromate production industry have found increased urinary levels of low molecular weight proteins indicative of renal damage, such as retinol binding protein and antigens, and white blood cell and red blood cell casts, in the urine (Franchini and Mutti 1988; Mutti et al. 1985a; PHS 1953). Other studies of renal function in workers engaged in chromate production and manufacturing of chromium compounds found negative or inconclusive results (Sassi 1956; Satoh et al. 1981). Two studies of renal function in chrome platers, whose exposure is mainly to chromium(VI), reported elevated levels of β_2-microglobulin in the urine of current platers (Lindberg and Vesterberg 1983b; Liu et al. 1998); an increase in N-acetyl-β-glucosaminadase levels was also found (Liu et al. 1998). When the prevalence of elevated levels (defined as higher than reference values) of these markers of potential kidney damage was compared to aluminum-anode-oxidation workers, only N-acetyl-β-glucosaminadase was significantly altered (Liu et al. 1998). No differences in levels of blood urea nitrogen, serum and urinary β_2-microglobulin, and other proteins were found between chrome platers and controls in another study (Verschoor et al. 1988). Studies in stainless steel welders, whose exposure is mainly to chromium(VI) showed no indication of kidney damage (Littorin et al. 1984; Verschoor et al. 1988). Occupational exposure to chromium(III) in the ferrochromium production industry (Foa et al. 1988) and to chromium(0) in an alloy steel plant (Triebig et al. 1987) and in boilermakers (Verschoor et al. 1988) does not appear to be associated with renal effects. Death records from a large cohort who worked in industries that produced chromium products from chromite ore did not show signs of increases in urinary disease when compared to matched control populations (Rosenman and Stanbury 1996). Examination of the urine of people who were lifetime residents of a contaminated area near chromium landfills where environmental exposures to chromium dust occurred did not reveal evidence of tubular proteinurea or signs of preclinical kidney disease (Wedeen et al. 1996). Results of urinalysis revealed no difference between housewives who lived near a chromium slag construction site and the control population (Greater Tokyo Bureau of Hygiene 1989).

Severe renal impairment, renal failure, and necrosis of renal tubules have been reported in cases of fatal or near fatal ingestion of chromium(VI) compounds by humans (Clochesy 1984; Ellis et al. 1982; Fristedt et al. 1965; Goldman and Karotkin 1935; Iserson et al. 1983; Kaufman et al. 1970; Saryan and Reedy 1988; Sharma et al. 1978). Acute nephritis has also been reported in cases of dermal exposure of chromium(VI) compounds (Brieger 1920; Major 1922; Smith 1931).

Intermediate- and chronic-duration inhalation studies using #0.4 mg chromium(VI)/m^3 as sodium dichromate or 0.1 mg total chromium as a mixture of chromium(VI) trioxide and chromium(III) oxide (Glaser et al. 1985, 1986, 1988, 1990) reported no clinical or histological evidence of adverse effects on the kidneys of rats. Effects on the kidneys of rats exposed orally to chromium(VI) compounds have been detected by biochemical and histochemical techniques. These consisted of increased accumulation of lipids, altered distribution of the lipids, and inhibition of membrane enzymes in the kidneys in rats treated by gavage with 13.5 mg chromium(VI)/kg/day as potassium chromate (Kumar and Rana 1982, 1984). Urinalysis of rats given 98 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days showed an increase in protein and a decrease in urine volume (Diaz-Mayans et al. 1986). Histological examination revealed no morphological changes in the kidneys of rats exposed to drinking water providing 2.7 mg chromium(VI)/kg/day as potassium chromate for 1 year (MacKenzie et al. 1958). No histological evidence of kidney damage in animals was reported in oral studies of chromium(III) compounds (Anderson et al. 1997b; Ivankovic and Preussmann 1975; MacKenzie et al. 1958; Schroeder et al. 1965).

Numerous studies in animals using other routes of administration of chromium compounds have reported renal effects. In acute experiments, necrosis of the proximal tubules and alterations of kidney enzymes (Franchini et al. 1978; Gumbleton and Nicholls 1988; Siegel et al. 1984; Sparrow et al. 1988) and altered kidney function (Appenroth and Braunlich 1988; Siegel et al. 1984) were observed in rats injected subcutaneously with 1.8–6.4 mg chromium(VI)/kg as potassium chromate, potassium dichromate, sodium chromate, or sodium dichromate; lipid peroxidation (Ueno et al. 1988), proteinuria (Diaz-Mayans et al. 1986), and degeneration of proximal tubules (Evan and Dail 1974) occurred in rats injected intraperitoneally with 2–10 mg chromium(VI)/kg as sodium chromate or potassium chromate. Mice injected with 0.6 mmole chromium(VI)/kg or 1 mmole chromium(VI)/kg had increases in serum urea nitrogen and a decrease in kidney glutathione reductase activity, whereas treatment with 0.6 mmole chromium(III)/kg resulted in no marked changes (Hojo and Satomi 1991). Proteinuria was also seen in rabbits (Nomiyama et al. 1982) and renal tubule necrosis was seen in monkeys (Hunter and Roberts 1932) after acute subcutaneous injection of 1.8 and 8.8 mg chromium(VI)/kg, respectively, as potassium dichromate.

Necrosis of proximal tubules also occurred in hamsters after an acute intravenous dose of chromium trioxide (Gale 1978). Rats repeatedly injected intraperitoneally with potassium dichromate and chromium trioxide developed proximal tubular necrosis and enlargement of tubules, respectively (Laborda et al. 1986). Rabbits injected intraperitoneally at 2 mg chromium/kg/day for 6 weeks developed marked tubular necrosis, derangement of the glomeruli, and infiltration of lymphocytes with either potassium dichromate or chromium(III) nitrate (Mathur et al. 1977). Subcutaneous injection of monkeys with 2.8 mg chromium(VI)/kg/day as potassium dichromate for 162 days resulted in massive proximal tubular necrosis (Hunter and Roberts 1932). While these studies provide strong evidence that the kidney is a target organ of chromium toxicity in animals, the methods of administration may not be predictive of effects or doses by environmentally relevant routes. Nevertheless, occupational exposure or exposure to high levels of chromium(VI) compounds by any route may result in kidney effects in humans, but it seems less likely that exposure levels in the ambient environment or at hazardous waste sites would cause renal effects in humans.

Dermal Effects. Chromium compounds can produce effects on the skin and mucous membranes. These include irritation, burns, ulcers, an allergic type of dermatitis. Irritation of the nasal mucosa and other mucosal tissues of the respiratory system, and nasal septum ulcers, and perforation were considered under Respiratory Effects discussed above. Dermatitis is considered under Immunological Effects discussed below.

Acute dermal exposure to chromium(VI) compounds can cause skin burns. Application of a salve containing potassium chromate to the skin of some individuals to treat scabies resulted in necrosis and sloughing of the skin, and some individuals even died as a result of infections of these areas (Brieger 1920). A worker whose skin came into direct contact with the chromic acid as a result of an industrial accident developed extensive skin burns (Cason 1959).

Although skin contact with chromate salts may cause rashes, untreated ulcers or sores (also called chrome holes) on the skin can be a major problem because they can deeply penetrate the skin with prolonged exposure. For example, in an early case of a tannery worker, the penetration extended into the joint, necessitating amputation of the finger (Da Costa et al. 1916). However, chrome sores heal if exposure is discontinued, leaving a scar. Chrome sores are more often associated with occupational exposure to chromium(VI) compounds. Although chrome sores are more likely associated with direct dermal contact with solutions of chromates, exposure of the skin to airborne fumes and mists of chromium(VI) compounds may contribute to the development. Industries that have been associated with the

development of chrome sores in workers include chromate and dichromate production (Pastides et al. 1991; PHS 1953), chrome plating (Gomes 1972; Lee and Goh 1988; Lieberman 1941; Lucas and Kramkowski 1975; Royle 1975b), leather tanning (Da Costa et al. 1916), planographic printing (Smith 1931), and chromite ore processing (Edmundson 1951). Among the chromium(VI) compounds that workers in these industries are exposed to are chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate.

In addition, tonsillitis, pharyngitis, atrophy of the larynx, and irritation and ulceration of mouth structures and buccal mucosa can occur from exposure to high levels of chromium(VI) compounds. These effects were seen in workers in chrome plating plants, where excessively high concentrations of chromium trioxide fumes were present (Hanslian et al. 1967; Lieberman 1941). High incidences of inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontis were also observed in chromate production workers (PHS 1953). Oral doses of potassium dichromate exacerbated the dermatitis of chromium sensitized individuals (Goitre et al. 1982; Kaaber and Veien 1977).

Dermal effects observed in animals after direct application of potassium dichromate to their skin include inflammation, necrosis, corrosion, eschar formation, and edema in rabbits (Gad et al. 1986) and skin ulcers in guinea pigs (Samitz 1970; Samitz and Epstein 1962).

Most dermal effects reported were either due to occupational intermediate-chronic exposure or acute exposure to high levels of chromium compounds. Environmental exposure to chromium compounds is not likely to result in dermal effects. However, hypersensitive individuals may develop rashes and erythema from contact with contaminated soil or consumer products containing chromium.

Ocular Effects. Ocular effects can occur as a result of direct contact of eyes with chromium compounds. These include corneal vesication in a man who got a drop or a crystal of potassium dichromate in his eye (Thomson 1903) and congestion of the conjunctiva, discharge, corneal scar, and burns in chromate production workers as a result of accidental splashes (PHS 1953). Higher incidences of subjective complaints of eye irritation were reported by housewives who lived near a chromium slag construction site than by controls (Greater Tokyo Bureau of Hygiene 1989).

Body Weight Effects. The only other systemic effects that have been reported regard body weight changes, for which information is limited. Information in humans consists of a case of acute exposure to "massive amounts" of chromium trioxide fumes. The patient became anorexic and lost 20–25 pounds

during a 3-month period after exposure (Meyers 1950). Decreased body weight gain was observed in rats exposed by inhalation to sodium dichromate for intermediate durations (Glaser et al. 1990), in female rats orally exposed to potassium chromate for 20 days or 3 months (Kanojia et al. 1996, 1998), in male rats orally exposed to potassium dichromate or chromium chloride for 12 weeks (Bataineh et al. 1997; Elbetieha and Al-Hamood 1997) in pregnant mice orally exposed to potassium dichromate during gestation (Junaid et al. 1996b; Trivedi et al. 1989), and in male rats treated with sodium dichromate by gavage for 90 days (Chowdhury and Mitra 1995).

Immunological and Lymphoreticular Effects. Chromium and its compounds cause sensitization that can result in asthma and dermatitis. Based on numerous reports in the literature, the prevalence of the chromium sensitivity in the general U.S. population has been conservatively estimated at 1.6% (Paustenbach et al. 1992). A more recent estimate of 0.08% was reported for chromium(VI) sensitivity (Proctor et al. 1998). The sensitivity to chromium(VI) compounds is greater than the sensitivity to chromium(III) compounds (Levin et al. 1959; Peltonen and Fraki 1983; Samitz and Schrager 1966). However, chromium(III) compounds are also allergens if the exposure concentration is high enough (Fregert and Rorsman 1964, 1966; Mali et al. 1966). The greater sensitivity to chromium(VI) may be due to the greater ability of chromium(VI) compounds to be absorbed. Asthmatic attacks have occurred in chromium-sensitive individuals exposed by inhalation in occupational settings to chromium trioxide vapors and chromium fumes from stainless steel welding (Keskinen et al. 1980; Moller et al. 1986). When challenged with sodium chromate or potassium dichromate via nebulizer, chromium-sensitive patients displayed anaphylactoid reactions, characterized by dermatitis, facial angioedema and erythema, nasopharyngeal pruritus, cough, wheezing, bronchospasms, increased plasma histamine levels, urticaria, and decreased forced expiratory volume (Moller et al. 1986; Olguibel and Basomba 1989). While chromium-induced asthma might occur in some sensitized individuals exposed to elevated concentrations of chromium in air, the number of sensitized individuals is low, and the number of potentially confounding variables in the chromium industry is high. Oral doses of potassium dichromate exacerbated the dermatitis of sensitive individuals (Goitre et al. 1982; Kaaber and Veien 1977).

Direct skin contact with chromium compounds may elicit an allergic response, characterized by eczema and dermatitis, in sensitized individuals. Exposure to chromium compounds in chromium-related occupations appears to be the major cause of chromium contact dermatitis. Patch testing has identified chromium sensitized workers in the printing and lithography industry (Levin et al. 1959; Samitz and Schrager 1966), in automobile factories where assemblers handled nuts, bolts, and screws (Newhouse 1963) in wet sandpapering of primer paint were exposed to zinc chromate (Engel and Calnan 1963), in

the cement industry (Engebrigsten 1952), in railroad systems and diesel locomotive repair shops where antirust diesel-engine coolants and radiator fluids contained sodium chromate (Kaplan and Zeligman 1962; Winston and Walsh 1951), in tanneries (Fregert 1975), and in the welding, plating, wood and paper industries (Burrows 1983). Other sources of chromium that have resulted in chromium sensitivity include dichromate-containing detergents and bleach (Wahba and Cohen 1979), glues, machine oils, foundry sand, match heads, boiler linings, and magnetic tapes (Burrows 1983).

Several studies have estimated the exposure level necessary to elicit a 10% response in chromium-sensitized individuals. Nethercott et al. (1994) examined 54 individuals known to be sensitive to chromium-induced allergic contact dermatitis. For chromium(VI), about 10% elicited a response at 0.09 µg chromium(VI)/cm^2, whereas similar studies with chromium(III) were essentially negative. Stern et al. (1993) examined the data from seven studies conducted mostly in the 1960s on chromium(VI) patch tests and developed an aggregate dose-response curve using the Probit model. Although there were considerable differences in methodologies and in the chromium(VI) compounds used (potassium chromate, potassium dichromate, chromic acid, and lead acetate) with some administered in basic water solutions, the aggregate data described a regular and consistent dose-response relationship which had a strong linear correlation (r=0.85). From this line, a 10% response of allergic dermatitis would occur in the sensitized population at 10 ppm chromium(VI) and 5% at 7.6 ppm chromium(VI). Similarly, Paustenbach et al. (1992) used computer data fitting techniques to estimate the 10% threshold level. The data from eight historical chromium sensitization threshold studies involving patch testing with potassium dichromate were used to estimate a weighted mean 10% threshold of 54 ppm chromium(VI) (150 ppm potassium dichromate). As noted by Paustenbach et al. (1992), there are a number of methodical limitations to the older patch test studies, including failure to disclose information on the diagnostic criteria used to determine allergy, duration of application, and analytical method used to verify chromium concentration and valence. Thus, the 54 ppm threshold level may be somewhat conservative. Scott and Proctor (1997) re-analyzed the data from three older chromium sensitization threshold elicitation studies with information on the surface area of the patches and the more recent study by Nethercott et al. (1994). The 10% minium elicitation threshold ranged from 0.55 to 12.5 µg/cm^2 for the historical studies, as compared to 0.09 µg/cm^2 for the Nethercott et al. (1994) study. Scott and Proctor (1997) note that the difference between the 10% elicitation thresholds may be due to the use of 0.5% potassium dichromate diagnostic patches in the historical studies compared to 0.25% potassium dichromate in the more recent study. Using the lower concentration probably eliminated individuals who were less sensitive and those who had an irritant rather than allergic response to the higher concentration.

The threshold concentration of extractable chromium(VI) in solid material was considered by Stern et al. (1993) to be as low as 10 ppm. The lowest observed effect level for elicitation of allergic contact dermatitis from ingestion of chromium(VI) was considered to be 0.26 ppm. In regard to the threshold concentration of chromium(VI) in soil for elicitation of contact dermatitis, the extractability of chromium(VI) from soil matrix was considered to be a factor. The effective concentration at the surface of the skin is determined by the concentration of chromium(VI) in solution following extraction from soil matrix. A study by Horowitz and Finley (1993) suggests that dermal contact with soil contaminated with chromite ore processing residue would probably not elicit allergic contact dermatitis in sensitized individuals. This study estimated that 0.1% or less of the chromium(VI) in chromite ore processing residue would leach out in the presence of human sweat. Thus, the chromium(VI) concentration in the soil would have to be 10,000–54,000 ppm (estimation based on 10–54 ppm sensitization elicitation threshold).

An inhalation immunological study in rats indicated that sodium dichromate stimulated the humoral immune system, affected the T-lymphocytes, and increased the phagocytic activity of macrophages (Glaser et al. 1985). Pulmonary inflammation was indicated in rats repeatedly exposed to atmospheres containing soluble potassium chromate, as evidenced by increases in total recoverable cells, neutrophils, and monocytes in bronchoalveolar lavage, and reduced percentages of pulmonary macrophages (Cohen et al. 1998); this was not seen in rats similarly exposed to insoluble barium chromate. Splenocytes from rats that were exposed to potassium chromate in the drinking water showed increased proliferative responses to T- and B-cell mitogens and to the antigen mitomycin C. The response to mitomycin C was enhanced 5-fold when potassium chromate was added to splenocytes from chromium(VI)-exposed rats, indicating a sensitization phenomenon (Snyder and Valle 1991). Contact dermatitis has been elicited in guinea pigs and mice by both chromium(VI) and chromium(III) compounds (Gross et al. 1968; Jansen and Berrens 1968; Mor et al. 1988).

Since exposure to low levels of chromium as found in consumer products can result in sensitization, hypersensitive individuals may develop rashes and erythema from contact with soil contaminated with high concentrations or consumer products containing chromium.

Neurological Effects. Information regarding neurological effects after exposure to chromium or its compounds is limited. Dizziness, headache, and weakness were experienced by workers in a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide (Lieberman 1941). Such poor working conditions are unlikely to still exist in the United States due to

improved industrial hygiene. Higher incidences of complaints of headache, tiredness, and light headedness were reported in housewives who lived in an area contaminated with chromium slag in Japan than in housewives who lived in an uncontaminated area (Greater Tokyo Bureau of Hygiene 1989). Brain enlargement and cerebral edema were observed upon autopsy of a boy who died after ingesting potassium dichromate (Kaufman et al. 1970). However, more chronic lower exposures to chromium(III) did not result in any somatopsychic changes in patients on total parenteral nutrition (TPN) solutions (Lovrincevic et al. 1996). In this study, the TPN patients were examined for somatopsychic responses. A steady increase in serum chromium was found with length of time on TPN. In some patients, the serum chromium levels were near the upper normal value of 0.2 mg/L and others were up to 8- to 25-fold greater then normal values. No significant correlations were observed with respect to sleep disturbances, daytime mental changes, colorful dreams, frightening dreams, or nightmares.

In animals, motor activity and ponderal balance decreased in rats dosed orally with 98 mg chromium(VI)/kg/day as sodium chromate for 28 days (Diaz-Mayans et al. 1986).

It is unlikely that members of the general population would be exposed to concentrations of chromium(VI) in air or drinking water high enough to cause neurological effects.

Reproductive Effects. Female employees at dichromate manufacturing factories in Russia had greater incidences of complications during pregnancy and childbirth, toxicosis during pregnancy, and postnatal hemorrhage than did controls (Shmitova 1978, 1980). The nature of the complications and toxicosis was not specified. The poor quality and reporting of these studies preclude their use for drawing conclusions regarding potential reproductive effects of chromium in humans. However, in a study of spontaneous abortion among 2,520 women whose spouses worked in the chromium stainless steel welding industry, the rate of spontaneous abortions was not different from populations not exposed to chromium (Hjollund et al. 1995). The authors felt that their study was robust enough that confounders such as cigarette smoking and alcohol consumption did not influence their findings.

In animals, oral exposure to chromium(VI) appears to adversely affect the reproductive system in males and females. Testicular effects and alterations in sexual behavior have been observed following oral or parenteral exposure. In male mice fed potassium dichromate for 7 weeks, reduced sperm counts and degeneration of the outer layer of the seminiferous tubules were seen at 15.1 mg chromium(VI)/kg/day, and morphologically altered sperm were seen at 28 mg chromium(VI)/kg/day (Zahid et al. 1990). Similarly, decreases in testicular weight, in testicular testosterone, Leydig cells, pachytene spermatocytes,

and stage-7 spermatids were found in male rats administered sodium dichromate(VI) by gavage for 90 days at 20 mg chromium(VI)/kg/day (Chowdhury and Mitra 1995). These effects were not replicated in potassium dichromate feeding studies conducted by NTP in which rats were exposed to 8.4 mg chromium(VI)/kg/day (NTP 1996b) and mice were exposed to 32.2 mg chromium(VI)/kg/day (NTP 1996a). Alterations in sexual behavior, aggressive behavior, and decreases in absolute testes, seminal vesicles, and preputial glands weights were observed in male rats exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in drinking water (Bataineh et al. 1997). An increase in testes weight was observed in mice exposed to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks; at 14 mg chromium(VI)/kg/day, decreases in seminal vesicle and preputial gland weights were also observed (Elbetieha and Al-Hamood 1997). Intraperitoneal injection studies provide supporting evidence that the male reproductive system is a target of chromium(VI) toxicity. Intraperitoneal injections of rabbits with 0.7 mg chromium(VI)/kg as potassium dichromate for 6 weeks resulted in morphological changes in the testes consisting of marked edema of interstitial tissues, congestion of blood vessels, and complete absence of spermatocytes in the seminiferous tubules (Behari et al. 1978). In rats receiving intraperitoneal injections of 2 or 3 mg chromium(VI)/kg as potassium dichromate for 69 days, a number of dose-related testicular effects were observed including decreased sperm counts and motility, testicular tubules with disturbed spermatogenesis, decreased late stage spermatids and germ cell numbers at stage VII, and altered testicular enzyme levels (Saxena et al. 1990b). The pathological alterations were not seen after 34 days of exposure. In another study by this group, intraperitoneal injections of 2 mg chromium(VI)/kg/day as potassium dichromate resulted in ultrastructural changes in the testes (leakage of Sertoli cell tight junctions in seminiferous tubules, cytoplasmic vacuolization and degeneration of mitochondira in the seminferous epithelium, and disruption of mitochondrial sheaths of tail midpieces of spermatids) (Murthy et al. 1991).

In females, a reduction in the number of medium- and large-sized follicles was noted in rats exposed to $60 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 days (Murthy et al. 1996). At higher concentrations, histological alterations in the ovaries, a decrease in the number of ova/mouse, and an increase in estrus cycle duration were observed. Additionally, delayed vaginal opening and impaired fertility were observed in female mouse offspring exposed to 66 mg chromium(VI)/kg/day as potassium dichromate in drinking water on gestational day 12 through lactation day 20 (Al-Hamood et al. 1998).

Mixed results have been found in studies designed to assess the impact of chromium(VI) exposure on fertility. Two multigeneration studies in which rats were exposed to 0.2 mg chromium(VI)/m^3 as sodium

chromate in air (Glaser et al. 1984) or mice were exposed to #37 mg chromium(VI)/kg/day as potassium dichromate in the diet (NTP 1997) did not find any effects on fertility. Decreased mating and fertility, increased preimplantation losses, and increased resorptions have been observed in rats and mice exposed to $37 mg chromium(VI)/kg/day or 52 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 or 90 days prior to mating (Junaid et al. 1996a; Kanojia et al. 1996, 1998). Pre- and post-implantation loss and decreased litter size was also observed in mice exposed to $46 mg chromium(VI)/kg/day as potassium dichromate in drinking water throughout gestation (Trivedi et al. 1989). Significant decreases in the number of implantations and viable fetuses were observed when male mice exposed to 6 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks were mated with unexposed female mice (Elbetieha and Al-Hamood 1997). However, a similarly designed study did not find any alterations in the number of implantations or viable fetuses in unexposed female rats mated with males exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks (Bataineh et al. 1997). It is not known if the species difference contributed to these conflicting results. Decreases in the number of implantations and viable fetuses and an increase in the number of animals with resorptions were also seen in females exposed for 12 weeks to 6 mg chromium(VI)/kg/day as potassium dichromate mated with unexposed males (Elbetieha and Al-Hamood 1997).

In contrast to chromium(VI), chromium(III) oxide fed to males and female rats at 1,806 mg chromium(III)/kg/day before mating and during gestation had no effects on fertility, gestational length, or litter size (Ivankovic and Preussmann 1975). However, male mice fed chromium sulfate for 7 weeks were reported to have reduced sperm counts and degeneration of the outer layer of the seminiferous tubules at 9.1 mg chromium(III)/kg/day and morphologically altered sperm at 42.4 mg chromium(III)/kg/day (Zahid et al. 1990). Altered sexual behavior, decreased aggressive behavior toward other males, and lower absolute weight of testes, seminal vesicles, and preputial glands were observed in male Sprague-Dawley rats exposed to 40 mg chromium(III)/kg/day as chromium chloride in the drinking water for 12 weeks (Bataineh et al. 1997). In mice exposed to potassium dichromate in drinking water for 12 weeks, an increase in testes weight and decreases in preputial gland weights were observed at 5 mg chromium(VI)/kg/day (Elbetieha and Al-Hamood 1997). When the males exposed to 13 mg chromium(VI)/kg/day were mated with unexposed females, a significant decrease in the number of pregnant females was observed. Furthermore, decreased spermatogenesis was observed in rabbits injected intraperitoneally with 0.26 mg chromium(III)/kg as chromium nitrate (Behari et al. 1978). Delayed vaginal opening and impaired fertility (when mated to unexposed males) were observed in the female offspring of mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in drinking

water (Al-Hamood et al. 1998). Several reproductive effects have been observed in female mice exposed to 5 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks, including a decrease in the number of implantations and viable fetuses, an increase in relative ovarian weight, and a decrease in uterine weight (Elbetieha and Al-Hamood 1997).

The results of animal studies therefore indicate that chromium(VI) and chromium(III) compounds are reproductive toxicants at high doses. Levels of chromium found in drinking water and food, however, are probably not high enough to elicit reproductive effects.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to chromium compounds.

A number of oral exposure animal studies have shown that chromium(VI) is a developmental toxicant following premating and/or *in utero* exposure. Exposure of female rats to $37 mg chromium(VI)/kg/day and mice to $52 mg chromium(VI)/kg/day to potassium dichromate(VI) in drinking water for 20 or 90 days followed by mating to unexposed males resulted in fetal mortality (post-implantation losses, resorptions, and decreased number of live fetuses), decreased growth (decreased fetal body weights and crown-rump length), reduced ossification, subdermal hemorrhagic patches, and kinky tails (Junaid et al. 1996a; Kanojia et al. 1996, 1998). Similar effects (increased resorptions, increased post-implantation losses, subdermal hemorrhages, decreased cranial ossification, tail kinking, decreased fetal body weight and decreased crown-rump length) were observed in the offspring of mice exposed to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation (Trivedi et al. 1989). In mice exposed to 53 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestational days 6–14, fetal mortality, subdermal hemorrhagic patches, and reduced ossification were observed in the offspring (Junaid et al. 1996b). Impaired development of the reproductive system (delayed vaginal opening) was observed in the offspring of mice exposed to 66 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). No developmental effects were seen in a multigeneration study involving inhalation exposure of rats to sodium dichromate at 0.2 mg chromium(VI)/m^3 (Glaser et al. 1984).

In addition, intravenous injection of pregnant hamsters with 3.9 or 4.2 mg chromium(VI)/kg as chromium trioxide on various days during gestation resulted in developmental effects. Treatment on gestation day eight resulted in cleft palate, poor ossification of the skull, vertebrae, sternum, fore-, and hind-limb, and hyoid bone, tail bud abnormalities, hydrocephalus, and encephalocoele in the fetuses (Gale 1978, 1982).

In another experiment, treatment of dams on gestation days 7, 8, and 9 resulted in fetal malformations, whereas no developmental effects were noted in the fetuses of dams treated on days 10 or 11. The malformations consisted of cleft palate from treatment on day 9, and small or absent kidneys after treatment on days 7 or 8 (Gale and Bunch 1979). Furthermore, the intravenous administration of 0.005 mg chromium(VI)/kg as sodium dichromate to pregnant mice from days 8–18 of gestation resulted in the accumulation of . 19% of the dose in the calcified areas of fetal skeleton and yolk sac (Danielsson et al. 1982).

In contrast to chromium(VI), conflicting results have been found for chromium(III). No developmental effects were observed in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period (Ivankovic and Preussmann 1975). Alterations in the development of the reproductive system (decreases in relative weights of reproductive tissues and decreased number of pregnancies among female offspring) were observed in the male and female offspring of mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). Intravenous administration of 0.005 mg chromium(III)/kg as chromium trichloride to pregnant mice from days 8 to 18 of gestation resulted in the accumulation of only . 0.8% of the dose in the calcified areas of fetal skeleton and yolk sac (Danielsson et al. 1982). However, intraperitoneal injection of mice with $14 mg chromium(III)/kg as chromium trichloride during gestation resulted in cleft palate, exencephaly, neural tube defects, and bone fusions (Iijima et al. 1983; Matsumoto et al. 1976).

The results of animal studies therefore indicate that chromium(VI) compounds are development toxicants. Chromium(III) oxide was not a developmental toxicant in mice by the oral route but chromium(III) chloride was a developmental toxicant.

Genotoxic Effects. *In vivo* studies of chromium compounds are summarized in Table 2-5. *In vitro* studies on the genotoxicity of chromium(VI) and chromium(III) compounds are summarized in Tables 2-6 and 2-7, respectively. Chromium(VI) compounds are capable of penetrating cell membranes while chromium(III) compounds, in general, are not; therefore, chromium(VI) compounds are of greater concern with regard to health effects. Studies involving workers exposed to chromium(VI) in stainless steel welding and electroplating (Husgafvel-Pursianen et al. 1982; Littorin et al. 1983; Nagaya 1986; Nagaya et al. 1991), and to chromium(III) in tanneries (Hamamy et al. 1987) did not report increases in the number of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes of these workers. No elevations in DNA strand breaks or hydroxylation of deoxyguanosine were detected in

lymphocytes of workers exposed to chromium(VI) involved in the production of bichromate (Gao et al. 1994). In contrast, other studies involving electroplaters and stainless steel welders reported higher levels of chromosomal aberrations or sister chromatid exchanges in workers exposed to chromium(VI) compared to controls (Deng et al. 1988; Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982; Werfel et al. 1998). The studies in humans were limited in several aspects. Generally, the levels of exposure to chromium(VI) were not known and co-exposure to other potentially active compounds (namely ultraviolet rays and other potentially genotoxic metals) occurred in several studies. Some negative results (Hamamy et al. 1987) were probably due to low exposure, because the chromium levels in plasma and urine of exposed and unexposed workers did not differ. Furthermore, some of the studies (Deng et al. 1988; Hamamy et al. 1987; Stella et al. 1988) used groups that were too small (<20 individuals) to have the statistical power to reliably assess the cytogenetic changes in workers.

Urine samples from six workers working in chromium plating factories were tested for the induction of unscheduled DNA synthesis (UDS) in pleural mesothelial cells (Pilliere et al. 1992). The mean chromium concentration in the urine samples was 11.7±8.8 µg/L. The urine from five of the workers showed a significant elevated in UDS over control subjects who were nonsmokers, with a trend toward increasing amounts of urine being tested. However, there was no correlation between UDS and chromium concentrations in urine.

Inhalation exposure of rats to fumes of chromium(0) (1.84 or 0.55 mg chromium(0)/m^3) for 1 week or 2 months induced increased chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes, but not in bone marrow cells (Koshi et al. 1987). An increase in DNA-protein crosslinking

Table 2-5. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Drosophila melanogaster	Gene mutation	+	Gava et al. 1989b; Rasmuson 1985; Rodriquez-Arnaiz and Martinez 1986; Zimmering et al. 1985	(VI)	Potassium dichromate, sodium dichromate, chromium trioxide, calcium chromate
D. melanogaster	Gene mutation	+	Olvera et al. 1993	(VI)	Chromium trioxide
Human lymphocytes	Chromosomal aberrations	+	Koshi et al. 1984; Sarto et al. 1982	(VI)	Stainless steel, welding fumes, chromium trioxide
Human lymphocytes	Chromosomal aberrations	–	Hamamy et al. 1987	(III)	Chrome alum (primarily chromium sulfate)
Human lymphocytes	Chromosomal aberrations	–	Husgafvel-Pursiainen et al. 1982	(VI)	Stainless steel, welding fumes
Human lymphocytes	Sister chromatid exchanges	+	Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982	(VI)	Chromium plating, stainless steel, welding fumes, chromium trioxide
Human lymphocytes	DNA strand breaks, hydroxylation of deoxyquanosine	–	Gao et al. 1994	(VI)	Production of bichromate
Human lymphocytes	Sister chromatid exchanges	–	Nagaya et al. 1991	(VI)	Chromium plating
Human lymphocytes	Sister chromatid exchanges, DNA strand breaks	+	Werfel et al. 1998	(VI)	Welding fumes

Table 2-5. Genotoxicity of Chromium *In Vivo (continued)*

Species (test system)	End point	Results	Reference	Valence	Compound
Human lymphocytes	Sister chromatid exchanges	–	Nagaya 1986	(VI)	Chromium plating
New polychromatic erythrocytes	Micronuclei	+	LeCurieux et al. 1992	(VI)	Potassium chromate
Rat peripheral lymphocytes (inhalation exposure)	Chromosomal aberrations, sister chromatid exchanges	+	Koshi et al. 1987	(0)	Chromium fumes
Rat bone marrow cells (inhalation exposure)	Chromosomal aberrations	–	Koshi et al. 1987	(0)	Chromium fumes
Rat lung (intratracheal exposure)	DNA alterations	+	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (intratracheal exposure)	DNA alterations	–	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (oral exposure)	DNA-protein crosslinks	+	Coogan et al. 1991a	(VI)	Potassium chromate
Rat liver and kidney nuclei (intraperitoneal exposure)	DNA crosslinks, DNA-protein crosslinks, DNA strain breaks	–	Cupo and Wetterhahn 1985	(III)	Chromium oxide
Rat liver, kidney, and lung nuclei (intraperitoneal exposure)	DNA-protein crosslinks	+	Tsapalos et al. 1983b	(VI)	Sodium dichromate
Rat hepatocytes (oral exposure)	Unscheduled DNA synthesis	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Mouse erythrocytes (oral exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate

Table 2-5. Genotoxicity of Chromium *In Vivo (continued)*

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1997; Wild 1978	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Itoh and Shimada 1996	(III)	Chromium chloride
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1996	(VI)	Potassium chromate
Mouse bone marrow cells (oral exposure)	Micronuclei	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Mouse bone marrow cells (gavage)	Chromosomal aberrations	+	Sarkar et al. 1993	(VI)	Chromium trioxide
Mouse bone marrow (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1998	(VI)	Potassium dichromate
Mouse hepatocytes (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1997, 1998	(VI)	Potassium dichromate
Mouse bone marrow (intraperitoneal exposed)	Micronuclei	+	Chorvatovi…ová et al. 1993; Wroûska-Nofer et al. 1999	(VI)	Potassium dichromate
Mouse (intraperitoneal exposure)	Dominant lethality	+	Paschin et al. 1982	(VI)	Potassium dichromate

– = negative results; + = positive results; (0) = 0 valence; (III) = trivalent; (VI) = hexavalent; DNA = deoxyribonucleic acid;

Table 2-6. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Subcellular targets:					
Escherichia coli DNA	DNA-protein crosslinks	No data	–	Fornance et al. 1981	Potassium chromate
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	–	Fornance et al. 1981	Potassium chromate
Double-standed M13mp2 bacteriophage DNA transferred to *E. coli*	Forward mutations	No data	+	Snow and Xu 1989	Potassium chromate
Puc 19 plasmid DNA	Gene mutation	No data	+	Kortenkamp et al. 1996b	Potassium chromate
Papilloma virus	Gene mutation	No data	+	Kowalski et al. 1996	Potassium chromate
PSV2neo-based plasmid DNA	DNA polymerase arrest	+	–	Bridgewater et al. 1994b, 1998	Sodium dichromate
Prokaryotic organisms:					
Bacillus subtilis	Recombinations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1975	Potassium chromate, potassium dichromate
E. coli PQ37, PQ35	Induction of SOS response	–	+	Olivier and Marzin 1987	Potassium chromate, potassium dichromate
E. coli AB1157, GC2375, UA4202, PQ30	Induction of SOS response	No data	+	Llagostera et al. 1986	Chromium chromate, potassium dichromate, chromium trioxide
E. coli Wp2, Hs30R, B/rWP2	Reverse mutations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1978; Nestmann et al. 1979; Venitt and Levy 1974	Potassium dichromate, potassium chromate, sodium chromate

Table 2-6. Genotoxicity of Chromium(VI) *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Prokaryotic organisms (*cont.):*					
E. coli K–12/343/113	Forward mutations	No data	–	Nestmann et al. 1979	Lead chromate
E. coli, WP2/pKM101, WP2 *uvrA*/pKM101	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
Salmonella typhimurium TA100	Base pair substitutions	No data	+	DeFlora 1978	Sodium dichromate
S. typhimurium TA100	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA102	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA92	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA1535	Base pair substitutions	No data	–	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA97	Frame shift mutations	No data	+	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA1537, TA1538	Frame shift mutations	No data	–	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA1978	Frame shift mutations	No data	(+)	Bennicelli et al. 1983	Sodium dichromate
S. typhimurium TA100	Base pair substitutions	–	+	Nestmann et al. 1979	Lead chromate
S. typhimurium TA1535	Base pair substitutions	–	–	Nestmann et al. 1979	Lead chromate
S. typhimurium TA1537, TA1538	Frame shift mutations	–	+	Nestmann et al. 1979	Lead chromate

Table 2-6. Genotoxicity of Chromium(VI) *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Prokaryotic organisms (*cont.):*					
S. typhimurium TA98	Frame shift mutations	+	+	Nestmann et al. 1979	Lead chromate
S. typhimurium TA1535	Base pair substitutions	–	(+)	Nakamura et al. 1987	Potassium dichromate
S. typhimurium TA100	Base pair substitutions	+	+	Venier et al. 1982	Potassium dichromate
S. typhimurium TA1538	Frame shift mutations	–	–	Venier et al. 1982	Potassium dichromate
S. typhimurium TA98	Frame shift mutations	–	(+)	Venier et al. 1982	Potassium dichromate
S. typhimurium TA100	Base pair substitutions	–	+	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
S. typhimurium TA1535	Base pair substitutions	–	–	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
S. typhimurium TA100, TA1535	Base pair substitutions	No data	+	Haworth et al. 1983	Calcium chromate
S. typhimurium TA98, TA1537	Frame shift mutations	No data	+	Haworth et al. 1983	Calcium chromate
Prokaryotic organisms (*cont.):*					

Table 2-6. Genotoxicity of Chromium(VI) *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
S. typhimurium TA100, TA1535	Base pair substitutions	No data	–	Kanematsu et al. 1980	Potassium dichromate
S. typhimurium TA100, TA1537, TA1538	Frame shift mutations	No data	–	Kanematsu et al. 1980	Potassium dichromate
S. typhimurium TA102, TA2638	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
Eukaryotic organisms:					
Yeasts: *Saccharomyces cerevisiae* D7	Mitotic gene conversions	No data	+	Fukunaga et al. 1982; Singh 1983	Chromium trioxide
S. cerrevisiae D7	Reverse mutations	No data	+	Singh 1983	Potassium dichromate
S. cerrevisiae D7	Reverse mutations	–	+	Nestmann et al. 1979	Lead chromate
S. cerrevisiae D7	Mitotic cross-over	No data	+	Fukunaga et al. 1982	Chromium trioxide
Schizosacharomyces pombe	Mitotic gene conversion	No data	+	Bonatti et al. 1976	Potassium dichromate
S. pombe	Forward mutations	No data	+	Bonatti et al. 1976	Potassium dichromate
Chickens: Chick embryos	DNA damage cross links, strand breaks, DNA-protein cross-links	No data	+	Tsapakos et al. 1983a	Sodium chromate

Table 2-6. Genotoxicity of Chromium(VI) *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Mammalian cells:					
Human embryonic lung fibroblasts (IMR-90)	DNA-protein crosslinks, DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human bronchial epithelial cells	DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human lung fibroblasts	DNA polymerase arrest, DNA-DNA crosslinks	No data	+	Xu et al. 1996	Sodium chromate
Chinese hamster lung DON cells	Sister chromatid exchange, chromosomal aberrations	No data	+	Koshi 1979, Koshi and Iwaski 1983	Lead chromate, chromium trioxide, zinc bromate, calcium chromate, potassium chromate
Chinese hamster ovary cells	Chromosomal damage	No data	+	Wise et al. 1993	Lead chromate
Chinese hamster ovary cells	Chromosomal aberrations, DNA fragmentation	No data	+	Blankenship et al. 1997	Lead chromate, sodium chromate
Mouse L1210 leukemia cells	DNA fragmentation, DNA-protein crosslink	No data	+	Fornace et al. 1981	Potassium chromate
Mouse embryo fibroblast cells	Chromosomal aberrations	No data	+	Sugiyama et al. 1986	Calcium chromate
Mammalian cells (*cont.*):					

Table 2-6. Genotoxicity of Chromium(VI) *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	+	Raffetto et al. 1977	Potassium dichromate
Mouse primary fetal cells	Transformations, chromosomal aberrations	No data	+	Raffetto et al. 1977	Potassium dichromate
Mouse mammary FM3A carcinoma cells	Chromosomal aberrations	No data	+	Umeda and Nishmura 1979	Potassium dichromate, potassium chromate, chromium trioxide
Rat liver epithelial cells	Transformations	No data	+	Briggs and Briggs 1988	Potassium chromate

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

Table 2-7. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Subcellular targets:					
Escherichia coli DNA	DNA-protein crosslinks	No data	+	Fornance et al. 1981	Chromium trichloride
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	+	Fornance et al. 1981	Chromium trichloride
Single-stranded M13mp2 bacteriophange DNA	Replication assay: increased nucleotide incorporation	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
Double-stranded M13mp2 bacteriophage DNA transferred to *E. coli*	Forward mutations	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
pSV2neoTS DNA	DNA polymerase arrest	No data	+	Bridgewater et al. 1994b	Chromium trichloride
Prokaryotic organisms:					
Bacillus subtilis	Recombinations	No data	–	Kanematsu et al. 1980	Chromium sulfate, chromium potassium sulfate
B. subtilis	Recombinations	No data	–	Matsui 1980; Nakamuro et al. 1978; Nishioka 1975	Chromium trichloride
B. subtilis	Recombinations	No data	(+)	Nakamuro et al. 1978	Chromium nitrate
B. subtilis	Recombinations	No data	(+)	Nakamuro et al. 1978	Chromium acetate

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

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Prokaryotic organisms *(cont.)*:					
E. coli	Gene mutations	No data	+	Sugden et al. 1990	cis-Dichlorobis (2,2'-bipyridyl) chromium(III)
E. coli AB1157, GC275, VA4202, PQ30	Induction of SOS response	No data	–	Llagostera et al. 1986	Chromium trichloride, chromium nitrate, chromium acetate
E. coli PQ37, PQ35	Induction of SOS response	–	–	Olivier and Marzin 1987	Chromium trichloride hexahydrate
E. coli PQ37	Induction of SOS response	–	–	Venier et al. 1989	Chromium trichloride, chromium nitrate
E. coli PQ37	Induction of SOS response	–	(+)	Venier et al. 1989	Chromium acetate
Salmonella typhimurium	Reverse mutations				
TA100, TA1535	Base pair substitutions	–	–	De Flora 1981; Petrilli and De Flora 1978b	Chromium trichloride hexahydrate, chromium nitrite, monohydrate, chromium potassium sulfate, chromium acetate, neochromium, chromium alum, chromite
TA98, TA1537, TA1538	Frame shift mutations	–	–		
S. typhimurium TA102	Base pair substitutions	–	–	Bennicelli et al. 1983	Chromium nitrate
S. typhimurium					
TA100, TA1535	Base pair substitutions	–	–	Venier et al. 1982	Chromium chloride hexahydrate, chromium nitrate monohydrate
TA98, TA1538	Frame shift mutations	–	–		

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

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Eukaryotic organisms:					
Yeasts:					
Saccharomyces cerevisiae	Reverse mutations, mitotic gene conversions	No data	+	Bronzetti et al. 1986	Chromium trichloride
Chickens:					
Chick embryos	DNA damage (crosslinks, strand breaks)	No data	–	Tsapakos et al. 1983a	Chromium nitrate
Mammalian cells:					
Human skin fibroblasts	Unscheduled DNA synthesis	No data	–	Whiting et al. 1979	Chromium trichloride
Human skin fibroblasts	DNA fragmentation	No data	–	Whiting et al. 1979	Chromium trichloride
Human leukocytes	Chromosomal aberrations	No data	(+)	Nakamuro et al. 1978	Chromium trichloride, chromium nitrate, chromium acetate
Human lymphocytes	Chromosomal aberrations	No data	(+)	Stella et al. 1982	Chromium trichloride hexahydrate
Human lymphocytes	Chromosomal aberrations	No data	–	Sarto et al. 1980	Chromium trichloride
Human lymphocytes	Sister chromatid exchange	No data	–	Stella et al. 1982	Chromium trichloride hexahydrate
Chinese hamster V79 cells	Chromosomal aberrations	No data	–	Newbold et al. 1979	Chromium acetate

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

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Compound
Syrian hamster embryonal cells	Chromosomal aberrations	No data	–	Tsuda and Kato 1977	Chromium trichloride hexachloride, chromium sulfate tetrahydrate
Chinese hamster lung DON cells	Chromosomal aberrations	No data	–	Ohno et al. 1982	Chromium trichloride hexahydrate, chromium sulfate tetrahydrate
Chinese hamster ovary cells	Chromosomal aberrations	No data	(+)	Levis and Majone 1979	Chromium trichloride hexachloride, chromium nitrate monohydrate, chromium potassium sulfate, chromium acetate
Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Levis and Majone 1979; MacRae et al. 1979; Venier et al. 1982	Chromium trichloride hexachloride, chromium nitrate, monohydrate, chromium potassium sulfate, chromium acetate
Mammalian cells *(cont.)*:					
Mouse leukemia cells	Chromosomal aberrations	No data	–	Fornace et al. 1981	Chromium trichloride
Mouse mammary carcinoma Fm3A cells	Chromosomal aberrations	No data	–	Umeda and Nishimura 1979	Chromium sulfate
Mouse fetal cells	Chromosomal aberrations	No data	(+)	Raffetto et al. 1977	Chromium trichloride
Mouse fetal cells	Morphological transformations	No data	+	Raffetto et al. 1977	Chromium trichloride
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	–	Raffetto et al. 1977	Chromium trichloride

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

was found in the livers of rats that had been exposed to potassium chromate in the drinking water at $6 mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a). Bone marrow cells from male mice fed chromium(VI) trioxide at 20 mg chromium(VI)/kg by gavage had a 4.4 fold increase in chromosomal berration over controls (Sarkar et al. 1993). Significant DNA alterations were seen in the lung, but not the liver, of rats exposed to chromium (VI) by intratrachael instillation of sodium dichromate (Izzotti et al. 1998). Micronucleated polychromatic erythrocytes were found in mice following intraperitoneal, but not oral, exposure to chromium(VI) as potassium chromate (Chorvatovi…ová et al. 1993; Itoh and Shimada 1996, 1997; Mirsalis et al. 1996; Shindo et al. 1989; Wild 1978; Wroûska-Nofer et al. 1999). No unscheduled DNA synthesis was found in rat hepatocytes after the rats were exposed to potassium chromate in drinking water (Mirsalis et al. 1996). The contrasting results may relate to route-specific differences in absorption or metabolic fate of chromate *in vivo*. Furthermore, intraperitoneal exposure to chromium(VI) as potassium dichromate induced dominant lethality in mice (Paschin et al. 1982) and a significant increase in mutant frequency within mouse hepatocytes (Itoh and Shimada 1997, 1998) and bone marrow cells (Itoh and Shimada 1998). Intraperitoneal injection in rats with sodium dichromate (chromium(VI)) resulted in DNA cross-links in liver, kidney, and lung nuclei (Tsapakos et al. 1983b), while similar injection in rats with chromium(III) trichloride did not cause DNA interstrand cross-links, DNA-protein cross-links, or DNA strand breaks in liver and kidney nuclei (Cupo and Wetterhahn 1985). Chromium caused slight but significant elevation in micronucleic over controls in newts (9.55% versus 9.00%) (Le Curieux et al. 1992). In addition, studies in *Drosophila melanogaster* showed an induction of gene mutations after exposure to chromium(VI) (Gava et al. 1989a; Rasmuson 1985; Rodriquez-Arnaiz and Martinez 1986; Olvera et al. 1993; Zimmering et al. 1985).

In vitro studies indicated that soluble chromium(VI) compounds are mutagenic in *Salmonella typhimurium* reverse mutation assays (Bennicelli et al. 1983; De Flora 1978, 1981; Haworth et al. 1983; Nakamura et al. 1987; Venier et al. 1982; Watanabe et al. 1998a). In addition, lead chromate, a water insoluble compound, was mutagenic in bacteria when dissolved in sodium hydroxide or sulfuric acid (Nestmann et al. 1979). Only one study reported negative results with chromium(VI) in all tested strains (Kanematsu et al. 1980). In contrast, studies with chromium(III) did not report the induction of reverse mutations in *S. typhimurium* (Bennicelli et al. 1983; De Flora 1981; Petrilli and De Flora 1978b; Venier et al. 1982). After preincubation with mammalian microsomes, the mutagenicity of chromium(VI) compounds was reduced or abolished due to concentrations of the reductant glutathione, cysteine, or NADPH capable of converting chromium(VI) to chromium(III) compounds (Bennicelli et al. 1983; De Flora 1978,1981; Nestmann et al. 1979). Chromium(VI) compounds caused gene mutations in *Bacillus subtilis* (Kanematsu et al. 1980; Nakamuro et al. 1978; Nishioka 1975) and *Escherichia coli* (Llagostera

et al. 1986; Kanematsu et al. 1980; Kortenkamp et al. 1996b; Nakamuro et al. 1978; Nestmann et al. 1979; Olivier and Marzin 1987; Venitt and Levy 1974; Watanabe et al. 1998a). Forward mutations were not induced in *E. coli* in one study (Nestmann et al. 1979). Negative or weakly positive results were reported in *B. subtilis* with chromium(III) (Kanematsu et al. 1980; Matsui 1980; Nakamuro et al. 1978; Nishioka 1975) and mostly negative results in *E. coli* (Llagostera et al. 1986; Olivier and Marzin 1987; Venier et al. 1989).

A chromium(IV) ester was synthesized with 2,4-dimethyl-pentane-2,4-diol to examined its ability to cause DNA double strand breaks (Luo et al. 1996). Calf thymus DNA was reacted with the chromium(IV) complex (1.3 mg/mL) in the presence of 2 mM hydrogen peroxide for 6 days at pH 6.8. The results showed that the complex in the presence of hydrogen peroxide significantly damaged DNA by causing double strand breaks. Neither chromium(IV) or hydrogen peroxide alone damaged DNA. The kinetics of the reaction of chromium(IV) with hydrogen peroxide, showed the formation of proportional amounts of hydroxyl radical with chromium(V). Use of a free radical scavenger prevented DNA strand breaks. Other studies have shown that chromium(IV) is a better Fenton reagent than chromium(V) for reducing hydrogen peroxide and thus chromium(IV)-type damage by generating hydroxyl radicals may also be a contributor of *in vivo* genotoxicity.

Studies in eukaryotic organisms indicated that chromium(VI) was genotoxic in *Saccharomyces cerevisiae* (Fukunaga et al. 1982; Nestmann et al. 1979; Singh 1983) and in *Schizosaccharomyces pombe* (Bonatti et al. 1976). One study demonstrated the genotoxicity of chromium(III) in *S. cerevisiae* (Bronzetti et al. 1986). Sodium chromate induced DNA damage (DNA interstrand crosslinks, DNA strand breaks, DNA-protein crosslinks) in cultured chick embryo hepatocytes (Tsapakos et al. 1983a). The vast majority of studies reported genotoxic effects of chromium(VI) in mammalian cells *in vitro* (Briggs and Briggs 1988; DiPaolo and Casto 1979; Douglas et al. 1980; Elias et al. 1989b; Fornace et al. 1981; Gomez-Arroyo et al. 1981; Koshi 1979; Koshi and Iwasaki 1983; Kowalski et al. 1996; Levis and Majone 1979; MacRae et al. 1979; Majone and Levis 1979; Montaldi et al. 1987; Nakamuro et al. 1978; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Stella et al. 1982; Sugiyama et al. 1986; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979; Yang et al. 1992). Although no increase in DNA damage was observed in Chinese hamster ovary cells exposed to lead chromate, probably due to the limited solubility of the tested compound (Douglas et al. 1980), an increase in chromosome aberrations was found in Chinese hamster ovary cells treated with lead chromate in another study (Wise et al. 1993).

In contrast, mostly negative results were reported for chromium(III) in mammalian cells (Fornace et al. 1981; Levis and Majone 1979; MacRae et al. 1979; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Stella et al. 1982; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979) and chick embryo hepatocytes (Tsapakos et al. 1983a). The only positive results were obtained in Chinese hamster ovary cells (Levis and Majone 1979), mouse fetal cells (Raffetto et al. 1977), and weakly positive responses were observed in human cell lines (Nakamuro et al. 1978; Stella et al. 1982). However, it should be noted that in positive studies, the genotoxic potency of chromium(III) compounds was several orders lower than that of chromium(VI) compounds tested in the same systems. Positive results of chromium(III) in intact cells could be due to contamination of the test compounds with traces of chromium(VI) (De Flora et al. 1990; IARC 1990), nonspecific effects at very high doses, experimental conditions that would increase the penetration of chromium(III) into cells (e.g., detergents), or a technical artifact formed during the extraction procedures (De Flora et al. 1990). In one case, chromium(III) compounds showed genotoxicity that was linked to redox cycling of a chromium-DNA complex (Sugden et al. 1990). Although chromium(III) compounds are less toxic than chromium(VI) compounds because of their relative inability to cross cell membranes, chromium(III) is more genotoxic than chromium(VI) when tested *in vitro* in subcellular targets (Bridgewater et al. 1994a, 1994b, 1998; Fornace et al. 1981; Snow 1991; Snow and Xu 1989).

In conclusion, chromium(VI) compounds were positive in the majority of tests reported, and their genotoxicity was related to the solubility and, therefore, to the bioavailability to the targets. Chromium(III) was more genotoxic in subcellular targets, but lost this ability in cellular systems. The reduction of chromium(VI) in the cells to chromium(III) and its subsequent genotoxicity may be greatly responsible for the final genotoxic effects (Beyersmann and Koster 1987). Reduction of chromium(VI) can also result in the formation of chromium(V), which is highly reactive and capable of interaction with DNA (Jennette 1982; Norseth 1986).

Cancer. Epidemiology studies discussed in Section 2.2.1.8 clearly indicate an increased respiratory cancer risk in workers engaged in chromate production and chromate pigment production and use. Studies in chrome platers, who are exposed to chromium(VI) and other agents, including nickel, generally support the conclusion that chromium(VI) is carcinogenic. Many of the studies in stainless steel workers exposed to chromium(VI) and other chemicals, and in ferrochromium alloy workers, who are exposed mainly to chromium(0) and chromium(III), but also to some chromium(VI), were inconclusive. However, in a recent update by (Mancuso 1997a) of his 1975 study of lung cancer in workers employed in chromate manufacturing that were first employed between 1931 and 1937, the author concluded that the lung

cancer death rates appear to be related to both insoluble chromium(III) and soluble chromium(IV). This conclusion has been criticized primarily because the industrial hygiene study conducted in 1949 used measured concentrations of insoluble and soluble chromium compounds as surrogates for chromium(III) and chromium(VI) compounds, respectively. The use of surrogates introduces the potential for misclassification of exposure to trivalent or hexavalent chromium; Kimbrough et al. (1999) and Mundt and Dell (1997) note that the increased cancer deaths in the insoluble chromium compound group may have been due to exposure to insoluble chromium(VI) compounds. Moulin et al. (1993) also reported a significant excess of lung cancer in stainless steel foundry workers which was correlated with length of employment; however, there was no significant excess in lung cancer among workers in the manufacturing of ferroalloys, or in melting or casting stainless steel. In addition to lung cancer, Rosenman and Stanbury (1996) found that workers employed in industries producing chromium compounds had significantly increased nasal and sinus cavity cancers. Likewise, Satoh et al. (1994) reported four cases of nasal carcinoma in workers employed for greater than 19 years in a chromate factory in Japan. Studies in leather tanners, who are exposed to chromium(III), were consistently negative. The epidemiology studies do not clearly implicate specific compounds, but do implicate chromium(VI) compounds. Animal studies tend to implicate chromium(VI) compounds as carcinogens; the data are more limited for chromium(III) compounds. Calcium chromate and sodium dichromate caused a weak increased incidence of lung tumors in animals exposed via inhalation (Glaser et al. 1986, 1988; Nettesheim et al. 1971); chromium(III) compounds have not been tested by inhalation. No evidence of carcinogenicity was found in mice exposed to potassium chromate in drinking water (Borneff et al. 1968) or in male or female rats fed chromium(III) oxide or in their offspring (Ivankovic and Preussmann 1975). No studies were located regarding cancer in humans or animals after dermal exposure to chromium or its compounds.

Increases in tumor incidence have also been found in a number of studies involving intratracheal, intrapleural, intramuscular, intraperitoneal, intravenous, and subcutaneous injections (Dvizhkov and Federova 1967; Furst et al. 1976; Hueper 1955, 1958; Hueper and Payne 1959, 1962; Laskin et al. 1970; Payne 1960; Roe and Carter 1969; Steinhoff et al. 1986). In addition, a study to determine the carcinogenic potential of 20 different chromium(VI)-containing compounds and pigments intrabronchially implanted into rats found three groups that produced a statistically significant number of bronchial carcinomas. These were different samples of strontium chromate, zinc chromate, and calcium chromate (Levy et al. 1986). It should be noted that the chromate particles were suspended and implanted in a cholesterol pellet and that this does not model the direct interaction of the particles with lung cells during inhalation. While some of these routes of administration have little relevance to the occupational

or environmental exposures experienced by humans, they have been useful in identifying the carcinogenic potential of specific compounds. No significant alterations in the number of malignant tumor-bearing rats or in the incidence of lung tumors were observed in rats administered soil suspensions containing calcium chromate(VI) via intratracheal instillation (Snyder et al. 1997).

NTP (1998) lists certain chromium compounds as substances that are known to be human carcinogens. This classification is based on sufficient evidence for a number of chromium(VI) compounds (calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate). IARC (1990) classifies chromium(VI) in Group 1, carcinogenic to humans, based on sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate production, chromate pigment production, and chromium plating industries; sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate, and lead chromates; limited evidence in experimental animals for the carcinogenicity of chromium trioxide and sodium dichromate; and data that support the concept that chromium(VI) ions generated at critical sites in the target cells are responsible for the carcinogenic action observed. EPA has classified chromium(VI) as Group A, a known human carcinogen by the inhalation route of exposure. For the oral route, chromium(VI) is classified as Group D, not classified as to human carcinogenicity (IRIS 2000b).

There is inadequate evidence for the carcinogenicity of elemental chromium and trivalent chromium compounds in experimental animals (IARC 1990; NTP 1998). IARC (1990) classifies chromium(0) and chromium(III) in Group C, that is, not classifiable as to carcinogenic potential. EPA has classified chromium(III) in Group D, not classifiable as to its human carcinogenicity (IRIS 2000a).

The genotoxic action of chromium(VI) compounds in cells depends on the reduction of chromium(VI) compounds inside the cell to generate a highly reactive chromium species as well as the formation of highly reactive free radical species that forms complexes with DNA. The highly reactive intermediate may be chromium(V) (Norseth 1986). It is possible that all chromium(VI) compounds have carcinogenic potential depending upon their bioavailability. However, there are some forms of chromium(III) that are essential nutrients. There are also mechanisms that limit the bioavailability and attenuate the potential effects of chromium(VI) compounds *in vivo*; hence, it may not be practical to consider all chromium compounds equally carcinogenic (Petrilli and De Flora 1987).

2.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to chromium.

2.7 CHILDREN'S SUSCEPTIBILITY

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

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

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

Chromium(III) is an essential nutrient required for maintaining normal glucose metabolism. The NRC established estimated safe and adequate daily dietary intakes (ESADDIs) of 10–80 µg/day for children aged 1–3 years; 30–120 µg/day for children aged 4–6 years, and 50–200 µg/day for children aged 7 years or older (NRC 1989). These recommendations were derived by extrapolating the adult ESADDI value of 50–200 µg/day on the basis of expected food intake.

There is a limited amount of information available on the toxicity of chromium in children. Most of the available data comes from several case reports of children ingesting lethal concentrations of chromium(VI). A variety of systemic effects were observed in a 22-month-old who accidentally ingested an unknown amount of sodium dichromate (Ellis et al. 1982), a 1-year-old who ingested an unknown amount of ammonium dichromate (Reichelderfer 1968), a 17-year-old who intentionally ingested 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983), and a 14-year-old who ingested 7.5 mg chromium(VI)/kg as potassium dichromate (Kaufman et al. 1970). The effects included pleural effusion, bronchopneumonia, hypoxic changes in the myocardium, decreased blood pressure and cardiac output, abdominal pain and vomiting, gastrointestinal burns and hemorrhage, and liver and kidney necrosis. An enlarged brain and cerebral edema were also observed in the 14-year-old (Kaufman et al. 1970). These effects are similar to effects observed in adults who have ingested lethal doses and are part of the sequelae leading to death.

A number of additional health effects have been observed in adults exposed to chromium (primarily chromium(VI)) at work. The primary targets appear to be the respiratory tract, gastrointestinal tract, hematological system, liver, and kidneys; an increased cancer risk has also been observed. Dermal contact in chromium sensitized individuals can lead to an allergic type dermatitis. In the absence of data to the contrary, it is likely that these organs/systems will also be sensitive targets in children. There is insufficient information to determine whether the susceptibility of children would differ from that of adults.

Although there are no human studies that examined developmental end points, animal studies have consistently shown that chromium, particularly chromium(VI), is a developmental toxicant. The only inhalation developmental toxicity study available is a 3-generation study that did not find developmental effects following maternal exposure to 0.2 mg chromium(VI)/m^3 as sodium dichromate (Glaser et al. 1984). A number of developmental effects have been reported in oral studies involving maternal exposure to $46 mg chromium(VI)/kg/day as potassium dichromate (Al-Hamood et al. 1998; Junaid et al. 1996b; Trivedi et al. 1989). The observed effects included increases in post-implantation losses, gross

abnormalities (e.g., subdermal hemorrhage, decreased ossification, kinky tail), and impaired development of the reproductive system (e.g., impaired fertility in female offspring). Similar developmental effects (e.g., post implantation losses, subdermal hemorrhage, decreased ossification) have also been observed in the offspring of rats and mice exposed to $37 mg chromium(VI)/kg/day for 20 or 90 days prior to mating (Junaid et al. 1996a; Kanojia 1996, 1998). Conflicting results have been found for chromium(III). No developmental effects were reported in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). However, impaired development of the reproductive system (decreased reproductive tissue weight and impaired fertility) were observed in the offspring of mice exposed to 74 mg chromium(III)/kg/day as chromium chloride (Al-Hamood et al. 1998). Developmental effects have also been observed following intraperitoneal administration of chromium(III) chloride (Iijima et al. 1983; Matsumoto et al. 1976).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Elevated levels of chromium have been reported in umbilical cord blood, placentae, and breast milk of women working in a dichromate(VI) manufacturing facility (Shmitova 1980). As noted elsewhere in the profile, the reliability of this study is suspect because the levels of chromium in the blood and urine of the control women were much higher than background levels. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained <0.4 µg/L, and the mean value was 0.3 µg/L (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk. These findings in humans are supported by animal data. Studies in rats and mice have shown that chromium(VI) and chromium(III) crosses the placenta and enters into fetal tissue. Elevated levels of chromium have been observed in the placenta and fetal tissue of rats and mice exposed to potassium dichromate(VI) in drinking water during pregnancy (Saxena et al. 1990a). The levels of chromium in the placenta were 3-and 3.2-fold higher in the exposed rats and mice, respectively, than in controls and fetal tissue chromium levels were 3.1-and 9.6-fold higher, respectively; the difference over control was only statistically significant in the mice. Another study (Daniellson et al. 1982) also found elevated fetal tissue levels of chromium. The chromium levels in the fetal tissues were 12–19% of maternal blood levels following maternal intravenous injections of sodium dichromate(VI) on gestational days 12–15 or 16–18 and 0.4–0.8% following maternal intravenous injections of chromium(III) trichloride on gestational days 12–15 or 16–18. A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form (Mertz et al. 1969). Higher levels of chromium were found in the neonates of rats fed chromium in a commercial diet as compared to neonates of rats fed a chromium-deficient diet and given drinking water containing

chromium acetate monohydrate. Similarly chromium levels were significantly elevated in the offspring of rats administered chromium in the form of GTF from Brewer's yeast by gavage than in the offspring of rats administered chromium trichloride intravenously or by gavage.

There is very little information available in which to assess whether the pharmacokinetic properties of chromium would be different in children. Sullivan et al. (1984) found that gastrointestinal absorption of radiolabelled chromium chloride, administered by gavage, was 10 times higher in 2-day-old rats as compared to levels absorbed in adult rats. A similar pattern of distribution in the body was found in the immature and mature rats.

2.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself 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 chromium are discussed in Section 2.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial

cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by chromium are discussed in Section 2.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.10, "Populations That Are Unusually Susceptible".

2.8.1 Biomarkers Used to Identify or Quantify Exposure to Chromium

Normal chromium levels in human fluid and tissues should be interpreted with caution. The low sensitivity of the most commonly used detection methods and the ubiquitous presence of chromium in laboratories make detection of low levels of chromium in blood and urine difficult. Everyone is exposed to chromium in the diet, estimated to range from 25 to 224 µg/day with an average of 76 µg/day (Kumpulainen et al. 1979). Only a small amount of dietary chromium is absorbed (#3%). Normal endogenous chromium levels for the general population (exposed only via the diet) have been reported as 0.01–0.17 µg/L (median 0.06 µg/L) in serum (Sunderman et al. 1989), 0.24–1.8 µg/L (median 0.4 µg/L) in urine (Iyengar and Woittiez 1988), and 0.234 mg/kg in hair (Takagi et al. 1986).

A group of elderly subjects, who received an average of 24.5 µg chromium(III)/day (0.00035 mg/kg/day) from their normal diets over a 5-day period, excreted an average of 0.4 µg chromium/day in the urine and 23.9 µg chromium/day in the feces. The individual intake of chromium correlated linearly with the total amount excreted (urine plus feces) (Bunker et al. 1984).

There is a strong correlation between occupational exposure to chromium compounds and chromium levels in blood, urine, hair, and erythrocytes (Gylseth et al. 1977; Kilburn et al. 1990; Lewalter et al. 1985; Lindberg and Vesterberg 1983a; McAughey et al. 1988; Minoia and Cavalleri 1988; Mutti et al. 1985b; Randall and Gibson 1987, 1989; Saner et al. 1984; Simpson and Gibson 1992; Sjogren et al. 1983; Takagi et al. 1986; Tola et al. 1977; Wiegand et al. 1988).

Biological monitoring has been used to relate serum and urine chromium levels to occupational exposure levels. A statistically significant ($r=0.95$, $p<0.001$) relationship between total chromium exposure and urinary chromium concentrations at the end of the workday were observed in five welders exposed to chromium(VI) compounds. The urinary chromium concentrations of 40–50 µg/L immediately after work correlated with exposure levels corresponding to the American Conference of Governmental Industrial Hygienists (ACGIH 1998) Threshold Limit Value (TLV) of 0.05 mg chromium(VI)/m^3 for soluble chromium(VI) compounds. Individual variations in habits make it difficult to state an exact biological threshold, but urinary concentrations of $40 µg/L could be used to indicate the need for air monitoring in the workplace (Gylseth et al. 1977). Post-work-shift urinary levels of chromium were measured in 22 workers exposed mainly to chromium(VI) as chromium trioxide and potassium dichromate, but also to chromium(III) (0.008–0.212 mg chromium(VI)/m^3, 0.010–0.10 mg chromium(III)/m^3) and in 15 workers exposed mainly to chromium(III) as chromium sulfate, but also to chromium(VI) (0.046–1.689 mg chromium(III)/m^3, 0.002–0.023 mg chromium(VI)/m^3) in a dichromate producing facility. Post-work-shift urinary levels of chromium averaged 31.5 µg total chromium/L in the workers exposed mainly to chromium(VI) and 24.7 µg total chromium/L in workers exposed mainly to chromium(III). As chromium(VI) was not detected in the urine samples (detection limit = 0.05 µg chromium(VI)/L), the urinary chromium was primarily chromium(III), due to *in vivo* reduction of chromium(VI) to chromium(III). Total chromium was also measured in post workshift samples of whole blood, serum, and erythrocytes of workers exposed mainly to chromium(VI) (0.039 mg chromium(VI)/m^3, 0.008 mg chromium(III)/m^3) or mainly to chromium(III) (0.789 mg chromium(III)/m^3, 0.004 mg chromium(VI)/m^3). In the workers exposed mainly to chromium(VI), the mean levels of total chromium were 2.2 µg/L in serum, 8.9 µg/L in erythrocytes, and 6.9 µg/L in whole blood, compared with control levels of 1.1 µg/L in serum, 1.0 µg/L in erythrocytes, and 1.4 µg/L in whole blood. In the workers exposed mainly to chromium(III), the mean levels of total chromium were 3.1 µg/L in serum, 1.4 µg/L in erythrocytes, and 1.8 µg/L in whole blood. The level of chromium in serum of the workers exposed mainly to chromium(III) was significantly ($p<0.001$) higher than that measured in workers exposed mainly to chromium(VI) or in controls. The level of chromium in erythrocytes of the workers exposed mainly to chromium(III) was significantly ($p<0.001$) less than that in workers exposed mainly to chromium(VI). The finding of higher levels of chromium in serum and lower levels of chromium in erythrocytes of workers exposed mainly to chromium(III) than in workers exposed mainly to chromium(VI) reflects the relative inability of chromium(III) to enter erythrocytes (Minoia and Cavalleri 1988).

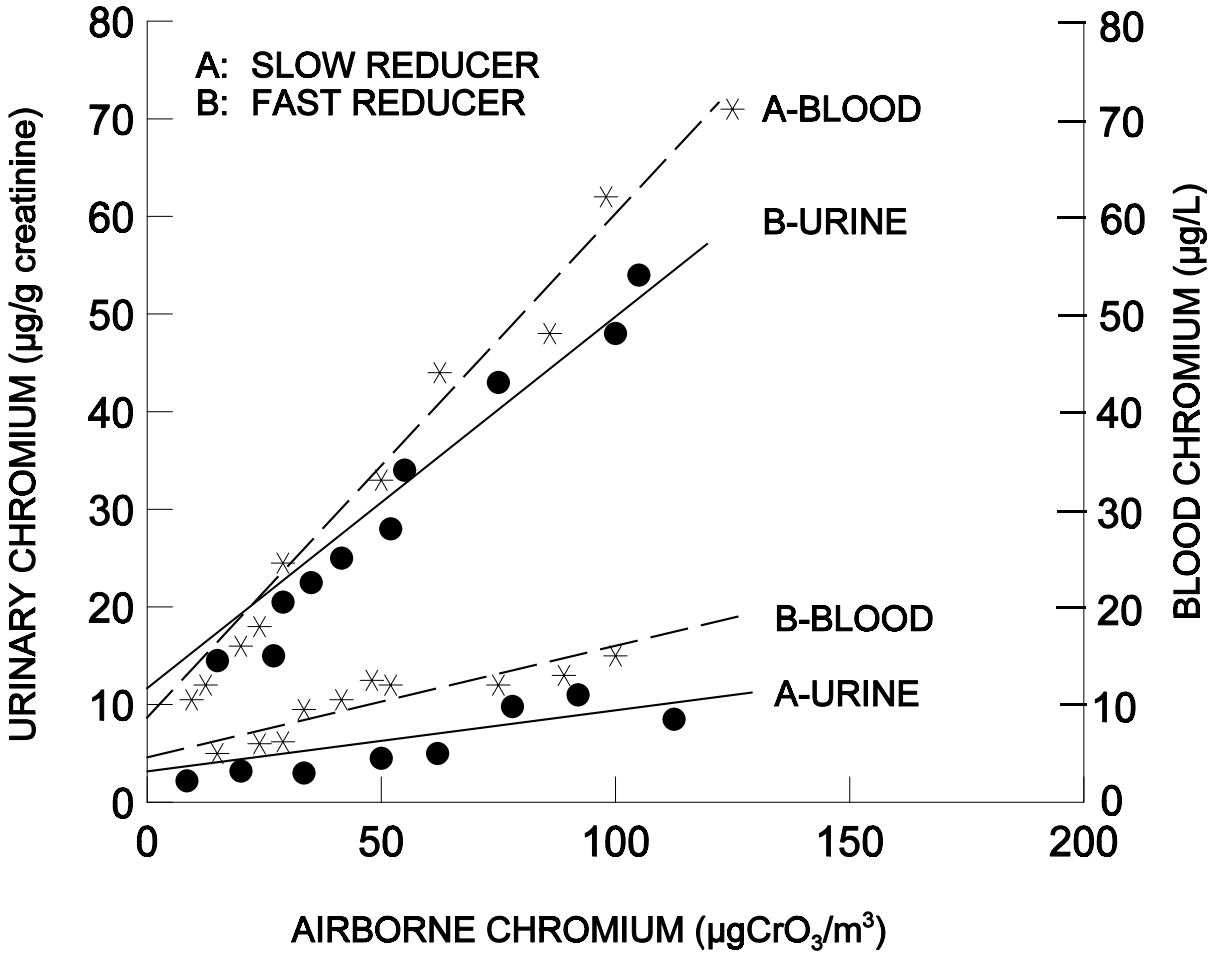
Human variability in plasma reduction capacity can influence the ratio between blood and urinary chromium levels (Korallus 1986a, 1986b). *In vitro* experiments indicate that when chromium(VI) plasma levels exceed the plasma reduction capacity (PRC), chromium(VI) enters erythrocytes, is reduced, and binds to hemoglobin. The bond persists for the lifetime of the erythrocytes (120 days); therefore, a single determination allows a longitudinal evaluation of exposure for an extended period in the past. Low chromium concentrations in erythrocytes indicate that the amount of chromium(VI) uptake did not exceed the PRC. The capacity of human plasma to reduce chromium(VI) compounds to chromium(III) compounds varies, with slow and fast reducers recognized (Korallus 1986a, 1986b). It is not clear what is responsible for individual differences in the PRC, although difference in magnitude of PRC appears to correlate with the levels of ascorbic acid in plasma. The relationship between blood and urine chromium levels and air chromium trioxide concentrations in slow and fast reducers at the end of a 5-day shift at a dichromate plant is shown in Figure 2-5. This figure indicates that individuals who reduce chromium(VI) compounds slowly have much higher blood chromium levels, while fast reducers have higher urinary chromium levels.

A significant correlation (r=0.71) was found between exposure levels and postshift, urinary chromium in workers exposed to chromium(VI) as chromium trioxide in the chrome plating industry. The urinary chromium level of 5.2 µg/L reflects a time-weighted average exposure of 0.002 mg chromium(VI)/m^3. This correlation was obtained by excluding workers with obvious skin contamination (Lindberg and Vesterberg 1983a).

Examination of end-of-shift chromium levels indicated a correlation between urinary chromium levels and exposure to soluble chromium(VI) compounds, but not to insoluble chromates or chromium(III) compounds (Minoia and Cavalleri 1988; Mutti et al. 1985b). The relationship between workroom air concentrations of water soluble chromium(VI) compounds and daily increases in urinary chromium (pre-exposure values subtracted from end-of-shift values) are shown in Figure 2-6. An increase in urinary chromium of 12.2 µg/g creatinine above pre-exposure values or a total concentration of 29.8 µg/g creatinine (end-of-shift values) corresponded to an air concentration of 50 µg chromium(VI)/m^3 from welding fumes (Mutti et al. 1985b).

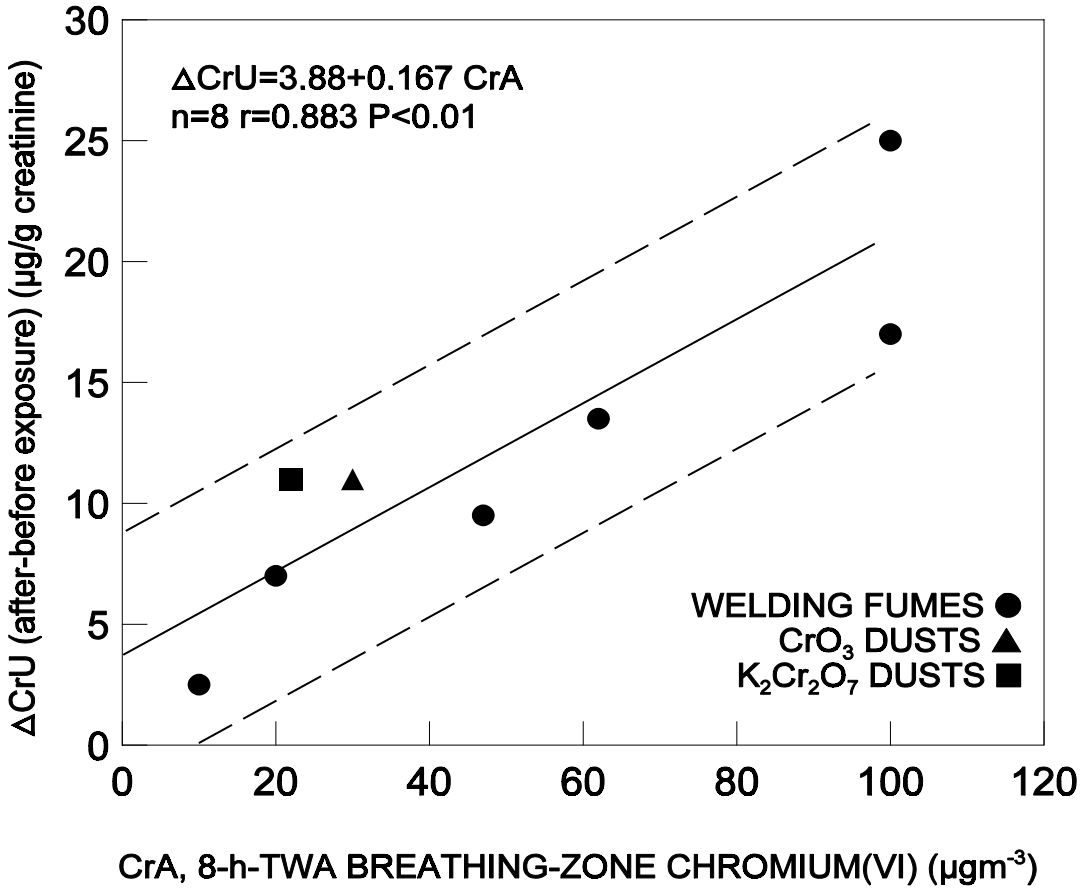
Serum and urine concentrations of chromium were significantly elevated in a group of 73 tannery workers, compared to a group of 52 control subjects, at the end of the workweek on Friday and before exposure began on Monday. Serum and urine chromium levels did not correlate with length of

Figure 2-5. Linear Relationship Between Water Soluble Chromium Concentrations in Workroom Air and the Chromium Concentrations in Blood and Urine at the End of a 5-Day Shift in Workers of a Dichromate Plant*



*Adapted from Korallus 1986a

Figure 2-6. Relationship Between Water-Soluble Chromium(VI) Concentration in Workroom Air (CrA) and Daily Increase in Urinary Chromium Levels (CrU) (Pre-exposure Values were Subtracted from End-of-Shift Values)*



*Adapted from Mutti et al. 1985b

employment in the tanning industry, but did correlate with work area of the tannery. Workers who handled wet hides in the chrome tanning and wringing departments had the highest chromium levels in blood and urine. The tanning compounds contained chromium primarily as chromium(III) compounds. The time-weighted average level of total chromium in tannery air was 1.7 μg/m^3 and did not vary significantly among the various tanneries involved in the study or among the various work areas of each tannery. Chromium(VI) levels in tannery air were below the detection limit of -0.1 μg/m^3. Since the tannery workers appeared to be exposed almost exclusively to chromium(III), serum and urine levels of chromium may be useful indices of chromium(III) exposure in this industry (Randall and Gibson 1987). In the same population of tannery workers, the median concentration of chromium in hair (0.55 mg/kg) was significantly higher than for the controls (0.12 mg/kg). Hair concentrations of chromium in the tannery workers were also significantly correlated with the serum level ($r=0.52$, $p<0.01$) and with the preshift and postshift urinary chromium to creatinine ratios ($r=0.43$, $p<0.01$ for preshift; $r=0.64$, $p<0.01$ for the postshift). The hair concentrations represented absorbed chromium(III) compounds rather than deposited chromium on the hair, since the hair samples had been washed before analysis. Thus, hair concentrations of chromium resulting from absorption of chromium(III) compounds in the tanning industry may be used to monitor industrial exposure to chromium(III) (Randall and Gibson 1989). Use of hair for assessment of past exposure appears to be limited to a timespan of months (Simpson and Gibson 1992). Compared to levels recorded during employment, the mean level of chromium in hair was reduced from 28.5 to 2.9 μmol/g in a group of five men who had ceased working in a leather tannery nine months earlier. These levels are comparable to those in the general population.

Results of biological monitoring for exposure to chromium in 17 people who worked in a park near a known chromium-contaminated area in Hudson County, New Jersey, showed no significant difference in the urinary and blood levels of chromium compared with 36 subjects who worked at state parks outside Hudson County (Bukowski et al. 1991). The two groups of subjects were pooled for analysis of possible confounding variables in biological monitoring for environmental chromium exposure. Chromium was detectable in the urine and blood of all but two urine samples (detection limit=0.09 μg/L). Median levels generally ranged from 0.38 to 0.74 μg/L in urine and from 0.0016 to 0.0021 μg/g hemoglobin in red blood cells. Results of the analysis for confounding variables revealed no significant influence of cigarette smoking (either current or past), gender, supplementation of diet with brewer's yeast, ingestion of recent meals, participation in hobbies that involve use of chromium-containing materials, and regular aerobic exercise on urinary or red blood cell levels of chromium. However, a significant difference was found for median urinary chromium levels between beer drinkers (0.67 μg/L) and nondrinkers (0.49 μg/L) ($p=0.04$). Higher but not statistically significant urinary levels were found for exercisers who

had not exercised in the previous 24 hours (0.67 µg/L) than for those who had (0.56 µg /L) (p=0.08), for diabetics (1.38 µg/L) than for nondiabetics (0.58 µg/L) (p=0.09), and for those with past working experience in chromium industries (0.74 µg/L) than for those with no previous occupational exposure (0.6 µg/L) (p=0.14). While the results of this study indicate that monitoring urine and red blood cells for chromium may not be useful in environmentally exposed individuals, the number of individuals studied was small. However, any biological monitoring for low-level environmental exposure to chromium should consider confounding variables, including chromium dietary supplements.

The chromium content in spot urine samples of 1,740 persons living or working in Hudson County, New Jersey and vicinity where there are over 160 chromium waste sites was examined by Fagliano et al. (1997). This group was recruited among people living within one or two blocks of a known waste site. The comparison group was composed of 315 people from 7 surrounding counties. The screening was performed in 1992 and 1993, and exposure may have resulted from inhalation, ingestion, or skin contact with contaminated soils. Approximately half of the individuals in both groups had urinary chromium concentrations below the limit of quantitation (0.2 µg/L). For analysis, values below the quantitation limit were assigned a value of 0.1 µg/L, one-half the quantitation limit. The average urine chromium levels of both residents and workers were slightly higher than those from the comparison group (0.20 versus 0.22 µg/L), but the median of both groups was 0.2 µg/L. The 90^{th} percentile was 0.53 µg/L in the comparison group and 0.72 µg/L in the screening group. Higher chromium levels were seen among those with exposure to dust in the prior 48 hours (house cleaning, sweeping at work, dusty work environment). The largest difference among age groups was among children ages 1–5 with a mean of 0.19 µg/L in the comparison group (N=18) and 0.35 µg/L in the screening group (N=52). Of the 1,740 individuals screened, 158 had urine levels above 0.5 µg/L and were referred for further medical evaluation. Of this group, three had medical conditions (persistent respiratory allergies and dermatologic conditions) where chromium exposure could not be ruled out as a cause.

The usefulness of biomarkers of exposure depends largely on the form of chromium in the environment. A series of experiments in volunteers (Finley et al. 1996b; Gargas et al. 1994; Kerger et al. 1997) have demonstrated bioavailabilty ranging from <1% (chromic oxide) to as high as 18% for potassium chromate in a single individual. Intraindividual variation in urinary chromium levels has also been demonstrated in an experiment where 8 individuals ingested 400 µg/day of chromium(III) picolinate, a chromium dietary supplement (Gargas et al. 1994). For five of the eight subjects, the background concentrations on days one and two prior to dosing fluctuated by as much as an order of magnitude. Variations were not explained by diet; food diaries kept by the subjects gave a possible explanation for only a few of the

unexpected rises in urine chromium excretion (e.g., after eating certain seafoods known to contain high levels of chromium, drinking beer). Sequential urine sampling was much more accurate than 24-hour and spot urine collection for detecting excretion of chromium subsequent to chromium(III) picolinate exposure. The 24-hour sampling was marginally better than spot urine collection. An estimate was made that about 74 µg of organic chromium(III) would result in a peak urinary concentration of about 2 µg/L. If an adult ingested soil containing chromium at a rate of 10 mg of soil/day and assuming that the bioavailabilty of chromium from the soil was the same as chromium(III)-picolinate (2.8%), then the soil would need to contain 7,400 µg chromium(III)/kg of soil in order to detect an elevation in urinary levels of the metal. The authors felt that this value is most-likely an overestimate, since it is unlikely that the bioavailabilty from soil would be as high as for the soluble chromium-picolinate complex.

Paustenbach et al. (1997) discuss some of the limitations of using urinary chromium as a biomarker of environmental exposure. The limitations include that significant exposure must occur immediately prior to sampling, that urinary concentrations must be higher than the range of background concentrations and analytical limit of detection, and high inter- and intrapersonal variability. The short half-lives of chromium compounds make it difficult to assess exposure incidents; at least 90% of absorbed chromium is eliminated within 24 hours. Thus, low-level, intermittent exposure, such as would occur with environmental exposures to soil, dust, and residential drinking water, may not be detected with urinary monitoring. This is not likely to occur following continuous or daily inhalation exposure to chromium(VI). The analytical limit of detection is 0.2 µg/L, and typical background urinary chromium levels range from 0.24 to 1.8 µg/L. Paustenbach et al. (1997) note that chromium intakes would have to exceed 2 µg/day in order to distinguish the exposure from background. Large interpersonal variability (as high as a factor of 10) and interpersonal variability (as high as a factor of 3) can result in highly variable erroneous conclusions regarding significant differences among populations.

In vitro studies with human and rat blood cells and *in vivo* studies with rats showed that white blood cells accumulated much more chromium than did red blood cells after exposure to (^{51}chromium)-labeled potassium chromate (chromium(VI)). Exposure of rat blood cells to (^{51}chromium)-labeled chromium(III) trichloride *in vitro* resulted in very little accumulation of label in red blood cells and no detectable accumulation in white blood cells (Coogan et al. 1991b). Lymphocytes are of interest as potential biomarkers because they have a considerably longer residence time in the blood than erythrocytes (months to years vs. 90 days) and are nucleated, thus allowing assessment of effects (e.g., DNA-protein crosslinking). A comparison of chromium concentrations in lymphocytes, erythrocytes, and urine was made between 14 male chrome-plater workers with 18 control individuals consisting of 13 males and

5 females (Lukanova et al. 1996). The ambient total chromium worker exposures ranged from 0.009 to 0.327 mg/m^3 (median 0.041 mg/m^3), chromium(VI) ranged from 0.0005 to 0.13 mg/m^3 (median 0.003 mg/m^3). No exposure measurements were provided for the control group. The results showed that mean chromium concentrations in lymphocytes of workers were 115 µg/10^{12} cells as compared to control values of 64 µg/10^{12} cells, and for erythrocytes were 2.1 µg/10^{12} cells for workers and 0.19 µg/10^{12} cells in controls. Preshift and postshift mean urine chromium levels were 4.2 µg/g creatinine and 8.9 µg/g creatinine, respectively. The control group urine levels were 0.99 µg/g creatinine. Chromium concentrations in the lymphocytes were correlated with workplace chromium(VI) air levels ($r=0.59$, $p<0.05$). Comparison with the control groups, however, indicated that erythrocyte chromium is a more sensitive measure (9-fold higher in exposed) of chromium exposure than chromium in lymphocytes (2-fold higher in exposed).

Exposure to chromium(VI) can result in DNA-protein complexes, the identification of which may be useful as biomarkers of exposure to chromates (Costa 1991). Gel electrophoresis and immunochemical techniques were used to identify actin as the protein in a DNA-protein complex induced by potassium chromate in cultured Chinese hamster ovary cells. While the DNA-protein complexes induced by formaldehyde and ultraviolet light were different from those induced by chromate, actin was also identified as the protein in the complex induced by cis-platinum, indicating that the DNA-actin complex is not specific for chromium. However, an experiment in a group of four volunteers did not demonstrate an increase in DNA-protein crosslinks in leukocytes over a 240 minute period following the ingestion of 5 mg chromium(VI) as potassium dichromate in a 10 mg chromium/L solution or the same amount added to 300 mL of orange juice (presumably reducing chromium(VI) to chromium(III)) and diluted to 500 mL with deionized water (Kuykendall et al. 1996). Chromium levels in red cells, plasma and urine were increased. In a separate experiment in this study, a threshold dose of 52 µg chromium(VI)/L was determined for crosslink formation in cultured lymphoma cells.

2.8.2 Biomarkers Used to Characterize Effects Caused by Chromium

Occupational exposure to chromium and its compounds has caused respiratory effects, such as pneumonitis, impaired pulmonary function, nasal septum perforations, irritation of the mucosa, inflammation, and cancer. In addition, chromium can be irritating and corrosive to the skin. Chromium exposure may cause asthma attacks and dermatitis in sensitive individuals. Workers with urinary levels of chromium >15 µg/g creatinine had increased retinol binding protein and tubular antigens in the urine. The workroom levels ranged from 0.05 to 1.0 mg chromium(VI)/m^3 as chromium trioxide (Franchini and

Mutti 1988). The urine of chromium(VI) exposed workers in a chromate production plant contained higher levels of a brush border protein and of retinol-binding protein in the urine than did nonexposed controls (Mutti et al. 1985a). In a study of currently exposed chrome platers, ex-chrome platers, and referent groups of nonexposed workers, the urinary levels of β_2-microglobulin were significantly higher ($p=0.045$), and elevated levels occurred more often in the presently exposed groups compared with its age-matched control group. The levels of β_2-microglobulin in the urine of the ex-chrome platers, however, were not different than those of its age-matched control group (Lindberg and Vesterberg 1983b). Another study of hard chrome electroplaters found a higher prevalence of workers with elevated N-acetyl-β-glucosamindase levels (Liu et al. 1998). Although this study also found higher levels of β_2-microglobulins in the chrome plater, the prevalence of elevated values was not significantly increased. The presence of low molecular weight proteins, such as retinol binding protein, antigens, or $ß_2$-microglobulin in the urine is believed to be an early indication of kidney dysfunction. The lack of a significant difference in the ex-chrome platers compared with the control group suggests that the chromium-induced kidney damage may be reversible. Cell culture and cell free studies discussed in Section 2.4.2 demonstrated that chromium forms protein-DNA crosslinks and adducts with DNA, and that these end points may be potentially useful biological markers indicating the possibility of genotoxic effects or cancer in humans exposed to chromium. However, no increases in protein-DNA crosslinks were observed in white cells from volunteers that were exposed to chromium(VI) in drinking water (Kuykendall et al. 1996).

The possibility of using an immune-function assay as a potential biomarker for humans exposed to chromium has been examined (Snyder et al. 1996). Isolated mononuclear cells from 46 individuals who lived and/or worked in areas in northern New Jersey at sites contaminated by chromium processing were stimulated by pokeweed mitogen. Rates of stimulated cell growth and production of interleukin 6 (IL-6) were measured and compared to a control population which lived/worked in uncontaminated areas. There was no significant increase in mitogen stimulation between people from contaminated areas and controls, but there was a significant (36%) decrease in the levels of IL-6 in monocytes in the chromium exposed group. IL-6 is an important cytokine that is involved in the T-cell helper pathway of antibody production. The significance of the lower levels may lead to decreased levels of antibody production.

The effects of chromium(III) chloride, sodium chromate(VI) and potassium chromate(VI) on proliferation of mononuclear leukocytes obtained from chromium sensitive individuals (confirmed with positive patch tests) was compared to nonsensitive controls (confirmed by negative patch tests) (Räsänen et al. 1991). Isolated cells were exposed to 25–50 μg/mL culture medium of chromium(III) chloride and to 0.025 to

0.1 µg/mL culture medium chromium(VI) salts which gave optimum responses and cell growth ratios of treated/nontreated cells from eight sensitive individuals ranging from 1.56 to 13.22, average=5.8 (chromium(III)), from 2.24 to11.43, average 5.4 sodium chromate and from 1.82 to 9.48, average 5.4potassiium dichromate. The nonsensitive individuals' ratios were consistently lower with ranges from 0.90 to 2.28 and average ratios of 1.14, 1.30, and 1.56. The authors felt that this *in vitro* methodology could be used diagnostically to assess chromium sensitive individuals.

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

2.9 INTERACTIONS WITH OTHER CHEMICALS

Potassium dichromate (10 mg/kg) administered by subcutaneous injection potentiated the effects of the nephrotoxins, mercuric chloride, citrinin, and hexachloro-1,3-butadiene, in rats. Effects on renal function included changes in urine volume, osmolality, electrolyte and glucose excretion, and a reduction in renal cortical slice organic ion transport. Chromium(VI) compounds potentiated the effect of mercuric chloride on organic acid uptake but not organic base uptake by renal cortical slices (Baggett 1986; Haberman et al. 1987). A similar experiment with another nephrotoxin, maleic acid, demonstrated the potentiating effect of potassium dichromate (10 mg/kg administered subcutaneously) (Christenson et al. 1989). Christenson et al. (1989) suggested that the combination of potassium dichromate with maleic acid might enhance damage to the brush border of the renal proximal tubules or that damage to the luminal cells by potassium dichromate might allow maleic acid to more easily enter the cells.

Interactions between selenium in the diet and ammonium dichromate in the drinking water were investigated in a study using rats. During the experiment, one rat died and the other rats had atrophy of the central liver lobe when given selenium alone. Dietary selenium and ammonium chromate in combination caused hepatic necrosis, resulting in the death of four rats (Moxon and DuBois 1939). Although the rats were not fed chromium alone, other studies indicate that the liver is a target for chromium exposure (see Section 2.2). The mechanism for the interaction was not discussed.

A number of studies indicate an increase in the mutagenic effects of chromium(VI) compounds in combination with other chemicals. Synergism has been observed between chromium(VI) and 9-aminoacridine, nitrilotriacetic acid, and azide (Bronzetti and Galli 1989; Gava et al. 1989a; LaVelle

1986a, 1986b; Montaldi et al. 1987), but the mechanisms are not clearly understood. Potassium dichromate potentiated mutations produced by sodium azide in *S. typhimurium* or by 9-aminoacridine in *S. typhimurium* and *E. coli*. Although the data were insufficient for speculation on the specific biochemical mechanism, it was suggested that the potentiation involved a specific effect of potassium dichromate on the interaction of 9-aminoacridine or sodium azide with DNA or on subsequent DNA replication and/or repair (LaVelle 1986a, 1986b). Nitrilotriacetic acid, which appears to have no genotoxic potential itself, increased the frequencies of sister chromatid exchanges in Chinese hamster ovary cells and of micronuclei and chromosomal aberrations in cultured human lymphocytes that were seen with lead chromate alone. However, nitrilotriacetic acid had no effect on the dose-related induction of sister chromatid exchanges in Chinese hamster ovary cells that was seen with potassium chromate alone. It was suggested that nitrilotriacetic acid increased the solubility of the originally insoluble lead chromate, leading to increased uptake of the metal cation by the cells and subsequent increased genotoxicity (Montaldi et al. 1987). Nitrilotriacetic acid increased the frequency of point mutations in *S. cerevisiae* observed with a low concentration of sodium chromate, but decreased the frequency with a five-fold higher concentration of sodium chromate. It was suggested that at the low concentration of sodium chromate, nitrilotriacetic acid affected the uptake of chromium(VI), favoring reduction to chromium(III) ions, which formed a complex with nitrilotriacetic acid that can cross the membrane and interact with DNA. At the high dose of sodium chromate, nitrilotriacetic acid may have affected the mechanism of recombination repair of DNA breaks induced by chromate oxidizing activity (Bronzetti and Galli 1989). Nitrilotriacetic acid also increased the mutagenicity of potassium dichromate in *S. typhimurium* and *D. melanogaster* presumably by favoring the reduction of chromium(VI) to chromium(III) (Gava et al.1989a). Thus, it is possible that other hazardous substances at hazardous waste sites may be more dangerous due to the presence of chromium(VI).

Ascorbic acid has been shown to have a protective effect in rats administered lethal dermal doses of potassium dichromate (25 mg chromium(VI)/rat), and in preventing ulcerations of the skin (Samitz 1970). The nephrotoxicity due to subcutaneous injections of potassium chromate in rats was prevented by intramuscular administration of ascorbic acid (Powers et al. 1986). This occurred mainly through the reduction of chromium(VI) to the less toxic chromium(III) state. Vitamin E protected against, while vitamin B_2 enhanced, the cytotoxicity and DNA strand breaks induced by sodium chromate in Chinese hamster cells *in vitro*. Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991) (see Section 2.11.3). N-Acetylcysteine, the glutathione precursor, was reported to be effective in increasing the urinary excretion of chromium in rats (Nadig 1994).

Recent studies have examined the effects of interactions between chromium and arsenic on blood cholesterol and glucose levels and changes in organ weight in rats (Aguilar et al. 1997). Groups of five male Wistar rats were given food containing 5 μg/g of either arsenic(V) oxide, chromium(III) chloride, or a combination of both chemicals for 10 weeks. Organ weight to body weight ratios of liver, spleen, lung, kidney, and heart were similar to control values for the three exposed groups. Arsenic alone increased the cholesterol blood level from 47.27(±6.85 SD) mg/dL in the control group to 96.83(±6.11). The combination of arsenic and chromium reduced the blood cholesterol level to 46.69(±6.11 SD) mg/dL. Neither chemical alone or in combination effected blood glucose levels. In most tissues the combination of chemicals reduced the chromium level appreciably below control values. Supplemental chromium increased arsenic levels in liver, kidney, spleen, heart, and red blood cells, and reduced levels of arsenic in lung and hair tissues. Chromium did not appear to alter concentrations of arsenic in the liver.

A study examining the chromium(VI) reduction in microsomes noted that the level of iron in the test system markedly influenced the V_{max} of chromium(VI) reduction, suggesting that coexposure to chromium(VI) and agents that increase intracellular iron might lead to increased risk for chromium(VI) toxicity (Myers and Myers 1998).

The effects of chromium(III) chloride and sodium chromate(VI) on the hepatotoxicity of carbon tetrachloride exposure to mouse hepatocytes were examined by Tezuka et al. (1995). Primary cultures of mouse hepatocytes were pretreated with 10 or 100 μM chromium for 24 hours followed by exposure to 1–5 mM carbon tetrachloride for up to 1 hour. Chromium(VI) pretreatment significantly reduced the cell toxicity as well as lipid peroxidation caused by carbon tetrachloride. Chromium(III) pretreatment did not have any effect on cell toxicity. About 50% of chromium(VI) was taken up and reduced in the cells by 90% to chromium(III) within 10 minutes. The initial uptake rate of chromium(III) into cells was greater than 500-fold less than chromium(VI), and only about 5% was absorbed. The protection against carbon tetrachloride damage by chromium(VI) was attributed to its rapid uptake and conversion to chromium(III), and it was determined that chromium(III) acts as a radical scavenger for the free radicals generated by carbon tetrachloride within the cell. Furthermore, chromium(VI) pretreatment reduced the activity of NADPH cytochrome c reductase which metabolizes carbon tetrachloride to reactive species. In a previous study (Tezuka et al. 1991), the same group found that pretreating mice and rats with chromium(III) also protected against hepatic toxicity.

In order to examine the speciation of chromium in lemonade, Kool Aid, tea, dripped coffee, percolated coffee, and orange juice, potassium chromate(VI) was added to each of the beverages at a chromium

concentration of 10 mg/L (Kerger et al. 1996b). After 15 minutes, the concentrations of chromium(VI) were determined to be <0.4 mg/L for orange juice, <0.3 mg/L for coffee and tea, 2 mg/L for Kool Aid, and 0.3 mg/L for lemonade. After 3–5 hours, essentially no residual chromium(VI) remained. At higher concentrations (50 mg/L chromium(VI)) more than 99% of the chromium(VI) was reduced after 3–5 hours, 100% in tea, 40% in lemonade, and 84% in coffee. The reducing capacities were not correlated with total organic carbon or pH. The reducing capacities of the beverages were attributed in part to ascorbic acid in lemonade and orange juice and to tannins in tea and coffee.

2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chromium than will most persons exposed to the same level of chromium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of chromium, or compromised function of organs affected by chromium. Populations who are at greater risk due to their unusually high exposure to chromium are discussed in Section 5.7, Populations With Potentially High Exposures.

Acute inhalation LC_{50} and oral and dermal LD_{50} studies suggest that female animals are more sensitive to the lethal effects of chromium(VI) compounds (see Sections 2.2.1.1, 2.2.2.1, and 2.2.3.1). Whether human females are more sensitive than males to toxic effects of chromium or its compounds is not known. Other information identifying possible susceptible populations was not located. Some individuals who are sensitive to chromium may develop asthma as an anaphylactic response to inhaled chromium. Also, some individuals have less ability than others to reduce chromium(VI) in the bloodstream and are more likely to be affected by the adverse effects of chromium exposure (Korallus 1986a, 1986b). The ability to reduce chromium(VI) in the bloodstream may be related to the ascorbic levels in the plasma.

Since chronic inhalation of cigarette smoke may result in squamous metaplasia in the respiratory mucosa, the risk of lung cancer due to inhalation of carcinogenic chromium compounds may be exacerbated in individuals who smoke cigarettes or are excessively exposed to passive smoke (Albert 1991).

2.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chromium. 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 chromium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following text provides specific information about treatment following exposures to chromium:

Nadig RJ. 1994. Cadmium and other metals and metalloids. In: Goldfrank LR, Weisman RS, Flomenbaum NE, et al, eds. Goldfrank's toxicologic emergencies. 5th ed. Norwalk, CT: Appleton and Lange,1063-1069.

2.11.1 Reducing Peak Absorption Following Exposure

General recommendations for reducing absorption of chromium following acute inhalation exposure have included moving the patient to fresh air, monitoring for respiratory distress, and administering humidified supplemental oxygen with assisted ventilation if required (HSDB 1998). The absorption of inhaled chromium compounds depends on such factors as oxidation state, particle size, and solubility. Chromium(VI) passes through the alveolar lining of the lungs to the bloodstream more readily than does chromium(III) (see Section 2.3.1.1), and more soluble compounds are absorbed more readily than those that are less soluble (Bragt and van Dura 1983). Although chromium(VI) is more readily absorbed from the lungs than chromium(III), various components of the respiratory system can reduce chromium(VI) to chromium(III), which is far less capable of crossing cell membranes than chromium(VI), thereby reducing the bioavailability of chromium to target cells (De Flora and Wetterhahn 1989). Epithelial lining fluid (ELF) is capable of reducing chromium(VI) (Petrilli et al. 1986b) and may represent the first line of defense against inhaled chromium(VI). Ascorbic acid (vitamin C) and glutathione, both of which were found to reduce chromium(VI) to chromium(III) in cell-free bronchoalveolar lavage fluid or soluble fractions of rat lungs *in vitro*, appear to be involved in this activity of ELF (Suzuki and Fukuda 1990). Uptake and reduction of chromium(VI) by pulmonary alveolar macrophages, catalyzed by NADH- or NADPH-dependent cytosolic enzyme activities, may lead to virtually irreversible sequestration and efficient removal by mucociliary action (De Flora and Wetterhahn 1989; De Flora et al. 1984, 1987b). Reduction of chromium(VI) within pulmonary alveolar macrophage homogenates was stimulated in rats by the administration of the glutathione precursor, N-acetylcysteine (De Flora and Wetterhahn 1989). As

mentioned above, the reduction of chromium(VI) to chromium(III) by these various processes within the lungs serves as a natural defense mechanism by decreasing the amount of chromium absorbed and enhancing mucociliary clearance of chromium(III). Theoretically, further clearance from the lungs might be achieved by the administration of expectorants, but the efficacy of such a procedure has not been tested.

Chromium(III) is also poorly absorbed by the gastrointestinal tract, and chromium(VI) is reduced to chromium(III) in the gastric environment, limiting the bioavailability of chromium(VI) (De Flora et al. 1987a; Donaldson and Barreras 1966). Thus the oral toxicity of chromium metal is low. However, chromium(VI) compounds are highly corrosive to the gastrointestinal tract and can lead to hepatic, renal, hematological, and neurological effects (Clochesy 1984; Coogan et al. 1991a; Diaz-Mayans et al. 1986; Iserson et al. 1983; Kaufman et al. 1970; Kumar and Rana 1982, 1984; Samitz 1970; Saryan and Reedy 1988). The reduction of chromium(VI) to chromium(III) in the stomach is greatly enhanced at low pH and shortly after meals due to increased gastric juice secretion (De Flora et al. 1987a). Therefore, administration of food might help decrease the gastrointestinal absorption of chromium. The enhanced reduction of chromium(VI) at low pH suggests that, theoretically, oral administration of bicarbonates and antacids should be avoided. Oral administration of ascorbic acid to further reduce chromium(VI) to chromium(III) might further decrease bioavailability (HSDB 1998), although this has not been proven (MEDITEXT® 1997). Other recommendations for reducing gastrointestinal absorption of chromium include diluting with water or milk followed by gastric lavage. Inducing emesis with syrup of ipecac is not recommended because of the possibility of irritation or burns to the esophagus (Nadig 1994; MEDITEXT® 1997). Activated charcoal has not been evaluated in chromate poisoning, but activated charcoal adsorbs metals poorly, so it would probably be of little use (MEDITEXT® 1997).

In cases of dermal exposure, the skin should be thoroughly washed to prevent chromium absorption by the skin (HSDB 1998). As chromium(VI), but not chromium(III), is readily absorbed by the skin, ascorbic acid in the washing solution could reduce chromium(VI) to chromium(III), thus decreasing absorption. Application of the calcium disodium salt of ethylenediamine tetraacetic acid (EDTA), which acts as a chelating agent, has also been recommended after washing with water and application of ascorbic acid (Nadig 1994), especially in cases where the skin has been cut or abraded (Burrows 1983). Ascorbic acid was found to protect chromium-sensitive workers who handled chromates in the lithographing and printing industries from dermatitis. The ascorbic acid (10% solution) was kept near the work areas, and the workers soaked their hands and forearms as soon as possible after handling the chromate mixtures. In addition, ascorbic acid prevented ulcerations of the skin in rats treated with

potassium dichromate dermally (Samitz 1970). An antichrome powder consisting of a mixture of 40% sodium metabisulfite, 20% ammonium chloride, 20% tartaric acid, and 20% sucrose as a 10% aqueous solution was effective in reducing the healing time of chrome sores on the skin of guinea pigs to which potassium dichromate had been applied (Samitz and Epstein 1962). In cases of severe dermal exposure, excision of the skin has been recommended to prevent chrome sores (HSDB 1998). Thorough irrigation with water has been recommended if the eyes have been exposed (HSDB 1998).

Both the cytotoxic effects of chromium(III) chloride, chromium(III) nitrate, sodium chromate, sodium dichromate, potassium dichromate(VI), and chromium(V) potassium sulfate dodecahydrate and the ability of ascorbic acid, glutathione 4-acetamido-4'-isothiocyanato-2,2-stibenedisolphonic acid (SITS) to prevent chromium toxicity in transformed human keratinocytes were examined (Little et al. 1996). This cell line was used because histopathological studies have shown that dichromate compounds have caused keratinocyte necrosis. Cells were exposed to the chromium salts for 24 hours, and the viability of the cultures was examined for their ability to take up neutral red dye and release lactate dehydrogenase into the media. None of the chromium(III) or chromium(V) salts seemed toxic to the cells at concentrations up to about 100 μM. The chromium(VI) salts showed toxicity at about 8 μM and there was little cell survival at 100 μM. The dose-response curves were similar for all chromium(VI) salts tested. Similar experiments were conducted with normal human keratinocytes obtained from abdominoplasties or breast reductions from six donors and treated with sodium dichromate. The toxicity to normal cells overall seemed to be less than in the transformed line. Ascorbic acid at 500 μM completely inhibited the cell toxicity caused by chromium(VI), whereas glutathione and SITS were less effective. Ascorbate probably protected cells by reducing chromium(VI) and chelation to the reduced complex. Glutathione may have formed complexes with the chromium(VI) which eventually led to chromium(III), whereas SITS may have inhibited the cellular uptake of the chromate by altering the non-specific membrane anion carrier. The authors conclude that these available drugs provide protection against cytotoxicity to keratinocytes involved in dermatitis and may be useful to prevent toxic reactions to metals contacting the skin.

The effect of decreasing the concentration of water-soluble chromium in cement from about 10 to below 2 ppm on the incidences of chromium-induced dermatitis was examined among construction workers in Finland (Roto et al. 1996). After 1987, when the decrease occurred, allergic dermatitis caused by chromium in the industry was reduced by 33% from previous levels, whereas irritant contact dermatitis remained unchanged.

2.11.2 Reducing Body Burden

Once chromium has been absorbed, it can be widely distributed throughout the body (see Section 2.3.2). Forced diuresis with careful monitoring of fluid and electrolyte status has been suggested, but not proven to increase the elimination of chromates. If hemolysis occurs in chromate poisoning, alkalinizing the urine with intravenous sodium bicarbonate and ensuring a brisk urine flow, while not increasing the urinary elimination of chromium, may help protect the kidney from the harmful effects of erythrocyte breakdown products. Serum electrolyte status, including calcium, should be carefully monitored during this procedure (MEDITEXT® 1997). In a case report of a fatality after ingestion of potassium chromate, hemodialysis and charcoal hemoperfusion did not significantly remove chromium from whole blood and had little effect on the management of chromium toxicity (Iserson et al. 1983). However, hemodialysis was effective in saving the life of an electroplater who accidentally swallowed plating fluid containing chromium trioxide (Fristedt et al. 1965). Because chromium may be sequestered in erythrocytes, exchange transfusion has been used as a way to decrease the body burden in serious acute poisoning (Kelly et al. 1982).

Both chromium(VI) and chromium(III) can be transported in the blood. Chromium(III) tends to bind to plasma proteins and is excreted in the urine. Chromium(VI) may be poorly reduced to chromium(III) in plasma, but this reduction can be enhanced by the intravenous administration of ascorbic acid (Korallus et al. 1984). N-acetylcysteine, the glutathione precursor, was reported to be more effective than EDTA or dimercaptosuccinic acid in increasing the urinary excretion of chromium in rats (Banner et al. 1986; Nadig 1994). Furthermore, chelation with agents available in human clinical medicine, such as British Anti Lewisite (dimercaprol) and EDTA, has been shown to be generally ineffective in increasing the elimination of chromium (Ellis et al. 1982; MEDITEXT® 1997). However, calcium EDTA, administered intravenously, resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Other polyaminocarboxylic acid chelating agents may be effective in removing chromium from organs. In rats injected with potassium chromate, subsequent treatment with various polyaminocarboxylic acid chelating agents resulted in significant removal of chromium from the liver, kidney, heart, or brain, depending on the agent. Ethylenediamine N,N'-diacetic acid (EDDA) removed significant amounts of chromium from the liver and heart. Ethylenediamine N,N'-di(O-hydroxyphenyl acetic acid (EDDHA) removed significant amounts of chromium from the kidney, heart, and brain. N-(2-hydroxyethyl)ethylenediamine triacetic acid (HEDTA) removed significant amounts of chromium from the liver and kidney. Hexamethylene 1,6-diamino N,N,N',N'-tetraacetic acid (HDTA) removed significant amounts of chromium from the liver, kidney, and brain. Triethylene tetramine

N,N,N',N',N",N"-hexaacetic acid (TTHA) removed significant amounts of chromium from the liver. Ethyleneglycol-bis-(2-aminoethyl) tetraacetic acid (EGATA) did not remove significant amounts of chromium from any of the organs. The relative ability of the polyaminocarboxylic acids to remove chromium from organs may be related to the number of amino or carboxyl groups as complexing centers or by the presence of hydroxyl groups (Behari and Tandon 1980). The use of these agents in humans has not been tested. Chromium(VI), but not chromium(III), can readily cross cell membranes. Chromium(VI) readily enters erythrocytes, where it is reduced to chromium(III) by glutathione, and chromium(III) is essentially trapped within erythrocytes, where it binds to proteins, primarily hemoglobin. This may explain the fact that chromium shows little toxicity at sites distant from administration sites (De Flora and Wetterhahn 1989). The chromium(III) trapped within the erythrocytes would be released upon natural destruction of the erythrocyte and excreted in the urine.

2.11.3 Interfering with the Mechanism of Action for Toxic Effects

The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium, whereas, reduction of chromium(VI) outside of cells may be a major mechanism of protection. After entering target cells, chromium(VI) itself and/or the metabolically reduced valence states exert toxic effects (De Flora and Wetterhahn 1989). Thus, one way to interfere with the mechanism of toxicity would be to prevent chromium(VI) from penetrating target cells in the nasal tissue, lungs, liver, kidneys, skin, etc. Administration of ascorbate or other reducing agents early enough after exposure to reduce chromium(VI) to chromium(III) before penetration of cells might avert toxicity, but this has not been proven in humans. However, ascorbic acid had a protective effect in rats administered lethal dermal doses of potassium dichromate (25 mg chromium(VI)/kg) (Samitz 1970). Furthermore, the nephrotoxicity due to subcutaneous injections of potassium chromate in rats was prevented by intramuscular administration of ascorbic acid (Powers et al. 1986). Once in the cell, however, ligand displacement and/or redox reactions of chromium(VI) with enzymes, proteins, and other molecules leads to reduction to chromium(V), chromium(IV), and chromium(III), with the generation of active oxygen species and radicals. The resulting toxicity depends on the nature of the cellular component that reacts with chromium(VI) and on the nature of the reactive species formed from the reaction. Chromium(III) can form stable complexes with DNA and proteins (Manning et al. 1992; Xu et al. 1996). Chromium(VI) can be reduced metabolically by a number of cellular components under physiological conditions. Reduction by glutathione or cysteine can lead to generation of all valence states (particularly chromium(V)) and radicals. For example, *in vitro* reaction of chromium(VI) with glutathione led to the formation of glutathione thiyl radicals and chromium(V) complexes (Aiyar et al. 1991). Chromium(V)-

glutathione complexes have been shown to form DNA adducts. Reduction by ascorbate leads to chromium(III), but chromium(V) has been generated by the reaction of chromium(VI) with riboflavin (vitamin B_2) and ribose derivatives (De Flora and Wetterhahn 1989). Reaction of chromium(VI) with hydrogen peroxide has led to the formation of chromium(V) complexes and hydroxyl radicals (Aiyar et al. 1991). Other important intracellular reduction reactions of chromium(VI) involve enzyme-catalyzed and NADPH-dependent mechanisms. Microsomal reduction of chromium(VI) by cytochrome P450 to chromium(III) may involve the transient formation of chromium(V) (De Flora and Wetterhahn 1989).

Hojo and Satomi (1991) examined the toxicity of potassium dichromate(VI) (0.6 mmol chromium/kg), potassium tetraperoxochromate(V) (1.0 mmol/kg), green chromium(V)-glutathione complex (1.0 mmol/kg), and chromium nitrate (III) (0.6 mmol/kg) on kidneys of male ddY mice (6 animals per dose group). Twenty-four hours after injections, mice were sacrificed and changes in kidney weight and function were assessed. Chromium(VI) resulted in a 10.7%±2.7 decrease in body weight, a 2-fold increase in serum urea nitrogen, a decrease in kidney nonprotein sulfhydryl contents (3.3±0.1 versus control values of 3.7±0.1) and a decrease of kidney-glutathione reductase activity from a control value of 17.4±1.5 to 14.1±1.3 U/g. Potassium tetraperoxochromate(V) treatment resulted in 50% of the animals dying. Body weights and kidney-glutathione reductase activity were much lower than for animals treated with chromium(VI), and serum urea levels were 102.9±17.7 mg/dL, which is about twice that observed in animals treated with chromium(VI). The chromium(V) glutathione complex was much less toxic and showed values that were similar or close to control values. Pretreatment with 10 mmol/kg glutathione methyl ester in the chromium(VI)-treated animals appeared to reduce the body weight loss and caused the serum urea levels to be normal. Butathione sulfoximine (an inhibitor of glutathione synthesis) greatly enhanced the levels of serum urea, loss of glutathione reductase activity and decrease in kidney nonprotein sulfhydryl groups. Butathione sulfoximine pretreatment resulted in one of the six animals dying. Animals treated with chromium(III) experienced weight loss, but other parameters were not markedly changed from control values. Pretreatment with butathione sulfoximine in animals treated with chromium(III) only caused a decrease in kidney nonprotein sulfhydryl groups. The authors indicated that with excess levels of glutathione, chromium(VI) is more readily reduced to chromium(III), whereas at lower levels of glutathione the reduction process is slower, resulting in slower reduction of the more toxic intermediate chromium(V). Also, at higher concentrations of glutathione, chromium(V)-glutathione complexes may form which may prevent chromium(V) from reacting at target sites that elicit toxic responses.

Differences in the intracellular metabolic pathways that result in the reduction of chromium(VI) will affect the nature of the reactive intermediates. For example, chelating ligands, such as glutathione and sugars, stabilize chromium(V) as an oxidation state, increasing its lifetime in the cell and ability to reach DNA in the nucleus. Cytochrome P450-dependent reduction of chromium(VI) to chromium(V) and chromium(IV), with generation of reactive radicals, which takes place in the endoplastic reticulum, could occur in close enough proximity to the nuclear membrane and nonenzymatic reduction within the nucleus could occur in close enough proximity to chromatin for the transient intermediates to exert their effects, such as DNA strand breaks and radical-DNA adducts. Chromium(III), the final stable product, can form chromium-DNA adducts and mediate cross-linking of DNA strands and DNA protein (De Flora and Wetterhahn 1989).

Thus the metabolic reduction of chromium(VI) may represent bioactivation and/or detoxification. If a bioactivation process, intracellular reduction of chromium(VI) would lead to the ultimate toxic species. Conversely, if chromium(VI) is the toxic agent, effects would be elicited only if the amount of chromium(VI) entering target cells saturates the reducing mechanisms.

In vitro studies indicated that vitamin E protected against, while vitamin B_2 enhanced, the cytotoxicity and DNA single-strand breaks induced by sodium chromate in Chinese hamster cells. The vitamins had no effects on sodium chromate-induced DNA-protein crosslinks. Formation of DNA-protein crosslinks by chromium(VI) in cell culture was prevented by addition of ascorbic acid (Capellmann et al. 1995), and ascorbic acid protected cells against chromosomal breakage and apoptosis. Vitamin E also protected cells against chromosomal breaks (Blankenship et al. 1997). Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991). Other vitamins might also be effective in mitigating the effects of chromium by modulating the metabolic processes. The use of vitamins for reducing the toxicity of chromium has not been studied in humans.

Thyroxine was found to ameliorate acute renal failure induced in rats by potassium dichromate, possibly by stimulating gluconeogenesis and Na-K ATPase activity in the renal cortex, influencing protein synthesis, and promoting glucose and amino acid uptake by epithelial cells. These events would be expected to aid the repair and regeneration of the damaged tubular epithelial cells (Siegel et al. 1984). The use of thyroxine has not been tested in humans.

Todralazine, an antihypertensive drug, was found to reduce markedly the mutagenic activity of potassium dichromate (VI) in the bacterial tester strain TA100 and in the *B. subtilis* rec assay (Gasiorowski et al.

1997). Spectroanalysis indicated that chromium(VI) was reduced to chromium(III) by todralazine and that todralazine formed a complex with the chromium(III) ions. The reduction and complexing of chromium may have prevented chromium from crossing the membrane and may have prevented harmful interactions with DNA. Another study by this group found that complexing copper(II) chromate(VI) to organic ligands (e.g., 2-(2'-pyridyl)imidazole, 2,2'-bipyridyl, 1,10-phenanthroline) resulted in a decrease in the mutagenicity of chromium(VI) as assessed by the Ames and *B. subtilis* rec assays (Gasiorowski et al. 1998).

2.12 ADEQUACY OF THE DATABASE

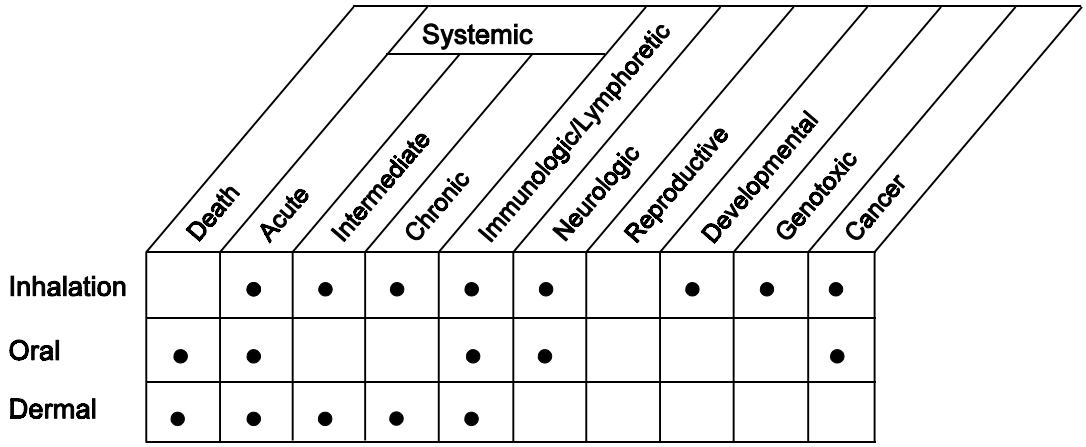
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chromium is available. Where adequate information is not available, 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 chromium.

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.

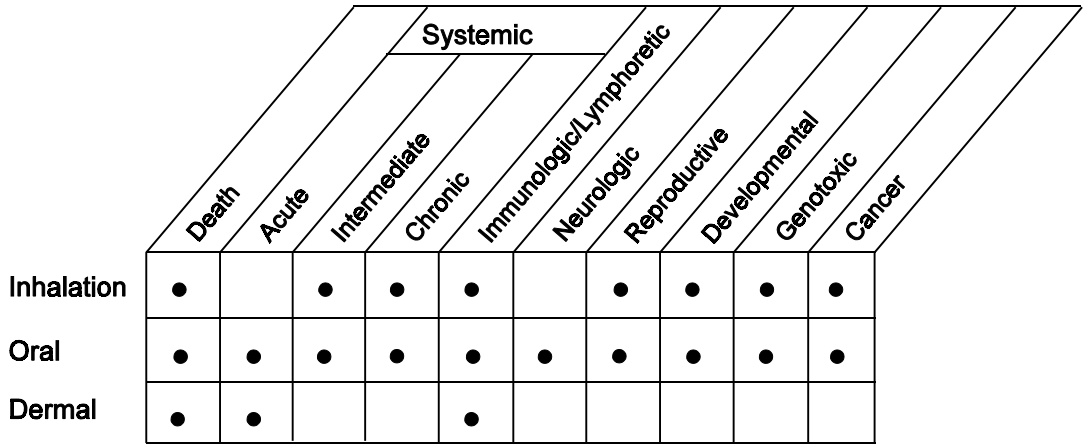
2.12.1 Existing Information on Health Effects of Chromium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chromium are summarized in Figures 2-7 and 2-8. The purpose of this figure is to illustrate the existing information concerning the health effects of chromium. 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.

Figure 2-7. Existing Information on Health Effects of Chromium(VI)



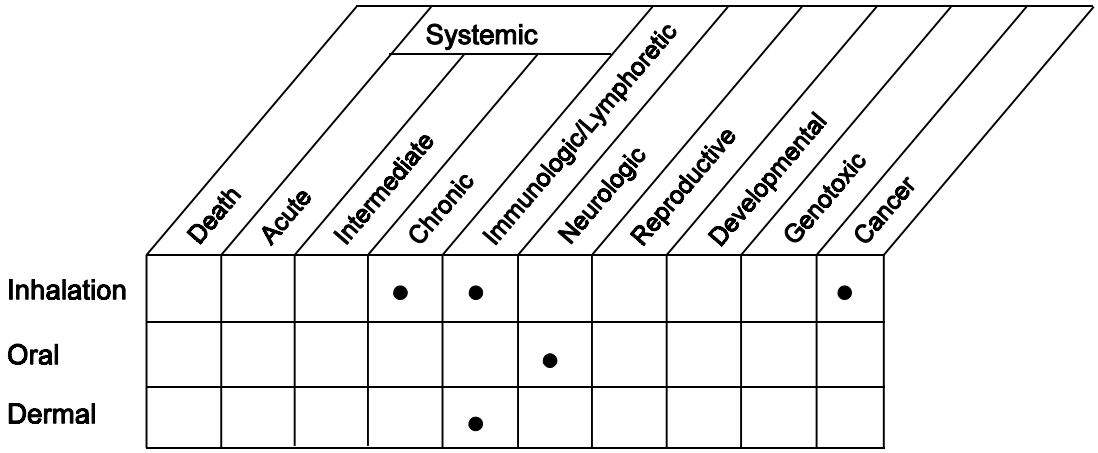
Human



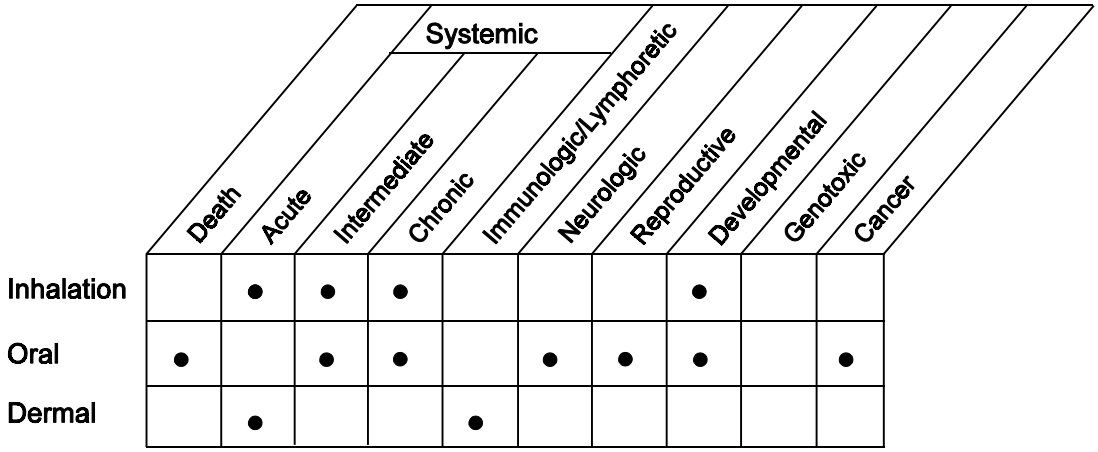
Animal

● Existing Studies

Figure 2-8. Existing Information on Health Effects of Chromium(III)



Human



Animal

● Existing Studies

A major source of oral exposure of humans to chromium is via the diet including chromium-rich diet supplements. Chromium(III) at low levels is essential to nutrition, and studies of chromium deficiency have been conducted. Information regarding health effects of exposure to chromium(VI) or chromium(III) in humans (see Figures 2-7 and 2-8) comes mainly from case reports of acute accidental or intentional ingestion, acute accidental dermal exposure, and from occupational case reports and epidemiology studies, which primarily involve inhalation and dermal exposure. In occupational studies, it is often difficult to separate exposure to chromium(VI) from chromium(III). Case reports have shown that ingestion and dermal contact with chromium(VI) can cause death. These reports have also described the serious systemic and neurological sequelae of exposure leading to death. Occupational exposures to chromium(VI) and/or chromium(III) are associated with respiratory and nasal, cardiovascular, gastrointestinal, hematological, hepatic, renal, and dermal effects. Immunological effects in humans exposed by inhalation and dermal contact consist of sensitization resulting in asthma and contact dermatitis, which can be exacerbated by oral exposure. Limited information was available regarding reproductive effects of occupational exposure to chromium(VI). Limited information was found on neurological behavioral effects. Information is also available regarding genotoxic effects in workers exposed to chromium(VI) and cancer in workers exposed to chromium(VI) and/or chromium(III).

Information regarding the levels of exposure to chromium(VI) compounds that cause death in animals is available for the inhalation, oral, and dermal routes (Figure 2-7). Information regarding respiratory effects of acute inhalation exposure of animals to chromium(VI) was available. The only information regarding systemic effects in animals after oral exposure to chromium(VI) is that lethal doses caused gastrointestinal effects. Acute dermal exposure of animals to chromium(VI) can cause irritation, edema, necrosis, and chrome sores. Information on systemic effects of chromium(VI) in animals is available for intermediate- and chronic-duration exposure by the inhalation route. Information regarding effects of oral exposure is available for the intermediate duration. The immunological effects of chromium(VI) in animals have been studied after inhalation and dermal exposure. An inhalation study reported no developmental or reproductive effects of chromium(VI). Oral studies of chromium(VI) in animals indicate that both developmental and reproductive effects can occur after exposure. Information regarding the genotoxicity and carcinogenicity of chromium(VI) is available for both the inhalation and oral routes. One report of chronic renal failure after ingestion of over-the-counter chromium picolinate at 0.6 mg/day was found in literature (Wasser et al. 1997).

Information regarding levels of chromium(III) compounds that result in death is available only for the oral route. Systemic effects of acute- and intermediate-duration inhalation exposure to chromium(III) are

limited to the respiratory system. Information on systemic effects of chronic inhalation exposure to chromium(III) is limited to a study that used a mixture of chromium(VI) and chromium(III). Studies of intermediate- and chronic duration oral exposure to chromium(III) failed to find any systemic, neurological, developmental, reproductive, or carcinogenic effects. The immunological and genotoxic effects of chromium(III) in animals have not been tested by the oral route. Information regarding effects of dermal exposure of animals to chromium(III) is limited to a study of skin ulceration after acute exposure and dermal sensitization tests.

In addition to the information on chromium(VI) and chromium(III), limited information is available regarding health effects of chromium(0) and chromium(IV) (not included in Figures 2-7 and 2-8). Briefly, the available information on chromium(0) consists of studies that examined workers at an alloy steel plant (Triebig et al. 1987) and boilermakers (Verschoor et al. 1988) for possible renal effects, with negative results, and a genotoxicity study in rats exposed by inhalation to chromium(0) dust, which found increased incidences of chromosomal aberrations and sister chromatid exchanges in lymphocytes (Koshi et al. 1987). Information on chromium(IV) consists of a 2-year inhalation study of chromium dioxide in rats that found no effects upon hematological, clinical chemistry, and urinalysis parameters and no histopathological effects on respiratory, cardiovascular, gastrointestinal, hepatic, renal, dermal/ocular, neurological, and reproductive organs (Lee et al. 1989).

2.12.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure of humans to chromium(VI) as occurs in occupational settings can result in respiratory irritation (dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation), dizziness, and headache at high concentrations, and trigger asthmatic attacks in sensitized individuals (Lieberman 1941; Meyers 1950; Novey et al. 1983; Olaguibel and Bosamba 1987). High airborne levels of chromium(VI) can also cause gastrointestinal irritation (Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950). Information on toxic effects in humans after oral exposure to chromium(VI) is limited to case reports of humans who ingested lethal or near lethal doses. Serious respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects have been described as sequelae leading to death (Clochesy 1984; Iserson et al. 1983; Kaufman et al. 1970; Saryan and Reedy 1988). Acute dermal exposure can cause skin burns and can also have similar sequelae that lead to death (Brieger 1920; Major 1922). No information regarding systemic effects of acute inhalation exposure of animals to chromium(VI) was located. Information regarding effects of acute oral exposure of animals to chromium(VI) is limited to a report of gastrointestinal hemorrhage in rats given a

lethal dose of potassium dichromate (Samitz 1970) and increased resorptions in mice given potassium dichromate during gestation (Junaid et al.1996b). Information regarding effects of acute dermal exposure of animals to chromium(VI) is limited to studies of dermal irritation and sensitization (Gad et al. 1986; Merkur'eva et al. 1982; Samitz 1970; Samitz and Epstein 1962). The information in humans indicates that many organs can be targets of acute exposure to chromium(VI) if exposure levels are high enough, but the target organs of low level exposure have not been sufficiently identified from animal studies. Therefore, data are insufficient for the derivation of acute inhalation or oral MRLs for chromium(VI). However, any MRL derived for the oral route would have to take into consideration the essentiality of chromium. No information was located regarding systemic effects in humans after acute exposure to chromium(III) compounds by any route. An acute inhalation study of chromium trichloride in hamsters indicated that the respiratory system is also a target of chromium(III) exposure (Henderson et al. 1979), and acute dermal studies show that chromium(III) can be a sensitizer, although not as effectively as chromium(VI) (Samitz and Epstein 1962). LD_{50} values for chromium(VI) and chromium(III) compounds indicate that chromium(III) is less toxic than chromium(VI) (Shubochkin and Pokhodzei 1980; Smyth et al. 1969; Vernot et al. 1977).

Additional studies involving acute exposure to both chromium(VI) and chromium(III) compounds by all routes would be helpful, especially if they consider target organs and exposure-response relationships. Studies defining the possible synergistic effects of chromium with other nephrotoxins, such as mercury and cadmium, which may be stored together at toxic waste sites, would also be useful. There are populations surrounding hazardous waste sites that might be exposed to the substance for short periods; therefore, this information is important.

Intermediate-Duration Exposure. There are no studies regarding systemic effects in humans after oral exposure of intermediate duration to either chromium(VI) or chromium(III). Intermediate-duration exposure to primarily chromium(VI) in occupational studies caused nasal and respiratory effects (Bovet et al. 1977; Davies et al. 1991; Gomes 1972; Kleinfeld and Rosso 1965; Lee and Goh 1988; Sorahan et al. 1987; Taylor 1966). Intermediate-duration exposure in occupational settings involving dermal exposure also can cause chrome ulcers or holes in the skin (Gomes 1972; Lee and Goh 1988; Lieberman 1941; PHS 1953; Smith 1931). A MRL of 0.000005 mg chromium(VI)/m^3 has been determined for upper respiratory effects in humans after intermediate-duration inhalation exposure to chromium(VI) as chromium(VI) trioxide mist and other hexavalent chromium mists and dissolved aerosols, based on the study by Lindberg and Hedenstierna (1983).

The respiratory tract and the immune system are targets in animals exposed to chromium(VI) and chromium(III) via inhalation for intermediate durations (Adachi 1987; Adachi et al. 1986; Glaser et al. 1985, 1990; Johansson et al. 1986a, 1986b). Pharmacokinetic studies indicate that chromium is distributed to the spleen of rats exposed to chromium(VI) via inhalation, oral, or dermal routes (Baetjer et al. 1959a; Wahlberg and Skog 1965; Witmer et al. 1989, 1991), but chromium(III) and chromium(VI) are not readily absorbed from the gut (Anderson 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Sullivan et al. 1984; Witmer et al. 1987, 1991). LOAEL values have been identified for respiratory and immune effects after inhalation (Glaser et al. 1985, 1990). A MRL of 0.001 mg chromium(VI)/m^3 has been determined for lower respiratory effects in humans after intermediate-duration inhalation exposure to chromium(VI) as particulate hexavalent compounds based on the study in rats by Glaser et al. (1990). An oral study of intermediate duration in rats reported no effects of chromium(III) in any system (Ivankovic and Preussmann 1975). One oral study in rats, however, found proteinuria and decreased motor activity at relatively high drinking water concentrations of chromium(VI) (Diaz-Mayans et al. 1986). In addition, intermediate-duration oral exposure of rats resulted in biochemical and histochemical changes in the liver and kidney (Kumar and Rana 1982, 1984; Kumar et al. 1985). In addition, developmental and reproductive studies identify chromium(VI) as a reproductive and developmental toxicant in mice and rats after oral exposure (Al-Hamood et al. 1998; Bateineh et al. 1997; Chowdhury and Mitra 1995; Junaid et al. 1996b; Kanojia et al. 1996, 1998; Trivedi et al. 1989; Zahid et al. 1990). No oral MRL has been derived for chromium(VI) or chromium(III) because a NOAEL for reproductive effects has not been adequately characterized. Additional studies are needed to identify a threshold for toxicity and establish dose-response relationships. However, any MRL derived for the oral route would have to take into consideration the essentiality of chromium. No dermal studies of intermediate duration in animals were located. The toxicity of intermediate-duration exposure to chromium compounds is relatively well characterized for the oral and inhalation routes. Dermal studies would be useful to determine possible target organs other than the skin. There are populations surrounding hazardous waste sites that might be exposed to the substance for similar durations.

Chronic-Duration Exposure and Cancer. The respiratory system (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Kuo et al. 1997a; Letterer 1939; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989; Pastides et al. 1991; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966) and the skin (Gomes 1972; Hanslian et al. 1967; Lee and Goh 1988; Leiberman 1941; PHS 1953; Royle 1985b) are the primary target organs for occupational exposure to chromium and its compounds. There are more data regarding the effects of chronic inhalation exposure in humans and

animals than there are regarding the effects of oral exposure. Studies of populations residing in areas contaminated with chromium(VI) in Japan and China have found such effects as oral ulcer, diarrhea, abdominal pain, indigestion, vomiting, constipation, nose and eye irritation, headache, fatigue, dizziness, and leukocytosis (Greater Tokyo Bureau of Hygiene 1989; Zhang and Li 1987). Chronic inhalation studies with rats, mice, guinea pigs, and rabbits also identify the respiratory system as the main target of chromium(VI) and chromium(III) exposure (Glaser et al. 1986, 1988; Nettesheim and Szakal 1972; Steffee and Baetjer 1965). Chronic oral exposure to chromium(III) and chromium(VI) compounds did not result in any target organ toxicity in animals (Ivankovic and Preussmann 1975; MacKenzie et al. 1958; Schroeder et al. 1965), probably due to the poor absorption of chromium through the gastrointestinal tract. No MRLs for systemic effects after chronic oral exposure have been derived because the target organs have not been identified and no NOAEL for reproductive effects of oral exposures has been adequately characterized. However, the upper range of the estimated safe and adequate daily dietary intake of 200 µg/day (0.003 mg/kg/day for a 70 kg individual) (NRC 1989) has been adapted as provisional guidance for oral exposure to chromium(VI) and chromium(III). This guidance is necessary because of the prevalence of chromium at hazardous waste sites and the fact that chromium is an essential nutrient. As noted above, the skin is a sensitive target of toxicity in workers exposed to airborne chromium (the effects resulted from direct dermal contact with chromium). No chronic dermal studies in animals were located. Because water and soil sources can be contaminated near hazardous waste sites, more information regarding chronic oral or dermal exposure would be useful.

Occupational and environmental epidemiological studies indicate a correlation between long-term exposure to chromium(VI) compounds and lung cancer (Alderson et al. 1981; Baetjer 1950b; Bidstrup 1951; Bidstrup and Case 1956; Braver et al. 1985; Dalager et al. 1980; Davies 1979, 1984; Davies et al. 1991; EEH 1976, 1983; Enterline 1974; Franchini et al. 1983; Frentzel-Beyme 1983; Haguenoer et al. 1981; Hayes et al. 1979, 1989; Korallus et al. 1982; Langård and Norseth 1975; Langård and Vigander 1983; Langård et al. 1980; Machle and Gregorius 1948; Mancuso 1975, 1997a; Mancuso and Hueper 1951; Ohsaki et al. 1978; Pastides et al. 1991, 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1981; Sheffet et al. 1982; Silverstein et al. 1981; Sjogren et al. 1987; Sorahan et al. 1987; Taylor 1966; Zhang and Li 1987). Occupational studies generally consider inhalation exposures, while environmental studies involve exposure by inhalation, ingestion, and dermal contact. Additional studies on populations exposed to chromium in drinking water would be useful to determine if a causal relationship with cancer exists. A unit risk for cancer from inhalation exposure to chromium(VI) compounds has been derived (IRIS 1998) from an occupational study (Mancuso 1975). Chronic inhalation of chromium(VI) compounds was carcinogenic in rats (Glaser et al. 1986) and mice

(Nettesheim et al. 1971). Cancer studies by parenteral route support the conclusions that chromium(VI) is carcinogenic (Furst et al. 1976; Hueper 1955, 1958; Hueper and Payne 1959, 1962; Laskin et al. 1970; Levy et al. 1986; Roe and Carter 1969; Steinhoff et al. 1986). Conversely, chronic oral exposure to chromium did not have significant carcinogenic effects (Borneff et al. 1968; Ivankovic and Preussmann 1975). The available human and animal data are sufficient for determining that chromium is carcinogenic following inhalation exposure. However, additional animal studies are needed to adequately assess the carcinogenic potential following oral exposure.

Genotoxicity. Several studies evaluating chromosomal aberrations and sister chromatid exchange in workers exposed to chromium(VI) have been conducted, some reporting positive results (Deng et al. 1988; Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982; Werfel et al. 1998) and some reporting negative results (Gao et al. 1994; Hamamy et al. 1987; Husgafvel-Pursianen et al. 1982; Littorin et al. 1983; Nagaya 1986; Nagaya et al. 1991). However, most of these studies are limited by factors such as lack of exposure data, co-exposure to other potentially genotoxic agents, and too few workers for meaningful statistical analysis. Mostly positive results have been found in rodents and *D. melanogaster* exposed to chromium(VI) compounds *in vivo* (Gava et al. 1989a; Itoh and Shimada 1993; Mirsalis et al. 1996; Olvera et al. 1993; Paschin et al. 1982; Rasmuson 1985; Rodriquez-Arnaiz and Martinez 1986; Sarkar et al. 1993; Shindo et al. 1989; Tsapakos et al. 1983b; Wild 1978; Zimmering et al. 1985). Numerous *in vitro* genotoxicity studies have been conducted in bacteria (Bennicelli et al. 1983; De Flora 1978, 1981; Haworth et al. 1983; Kanematsu et al. 1980; Kortenkamp et al. 1996b; Llagostera et al. 1986; Nakamuro et al. 1978; Nestmann et al. 1979; Nishioka 1975; Olivier and Marzin 1987; Venier et al. 1982; Venitt and Levy 1974; Watanabe et al. 1998a), yeast (Bonatti et al. 1976; Fukanaga et al. 1982; Singh 1983), and cultured animal cell systems (Briggs and Briggs 1988; DiPaolo and Casto 1979; Douglas et al. 1980; Elias et al. 1989b; Fornace et al. 1981; Kowalski et al. 1996; Levis and Majone et al. 1979; MacRae et al. 1979; Montaldi et al. 1987; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sugiyama et al. 1986; Tsuda and Kato 1977; Ueno et al. 1995a; Umeda and Nishimura 1979; Venier et al. 1982; Wise et al. 1993; Yang et al. 1992) and human cell systems (Douglas et al. 1980; Fornace et al. 1981; Gomez-Arroyo et al.1981; MacRae et al. 1979; Montaldi et al. 1987; Nakamuro et al. 1978; Sarto et al. 1980; Stella et al. 1982; Sugiyama et al. 1986; Whiting et al. 1979), mostly with positive results. The vast majority of studies, therefore, clearly indicated that chromium(VI) compounds are genotoxic.

Genotoxicity data are also available for chromium(III) compounds. A study in tannery workers, who were exposed mainly to chromium(III), reported negative results for chromosomal aberrations and sister

chromatid exchange (Hamamy et al. 1987). Chromium trichloride also did not cause DNA damage in rats exposed *in vivo* (Cupo and Wetterhahn 1985), however, rats inhaling powders of chromium metal had increased frequencies of both chromosomal aberrations and sister chromatid exchanges in circulating lymphocytes (Kaski et al. 1987). Mostly negative results have been found in *in vitro* genotoxicity studies of chromium(III) compounds in bacteria (Bennicelli et al. 1983; De Flora 1981; Kanematsu et al. 1980; Llagostera et al. 1986; Matsui 1980; Nishioka 1975; Olivier and Marzin 1987; Petrilli and De Flora 1978b; Venier et al. 1982, 1989) and mammalian cell systems (Fornace et al. 1981; Itoh and Shimada 1996; Le Curieux et al. 1992; Levis and Majone 1979; MacRae et al. 1979; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarkar et al. 1993; Sarto et al. 1980; Stella et al. 1982; Tsuda and Kato 1977; Ueno et al. 1995a; Umeda and Nishimura 1979; Whiting et al. 1979; Wise et al. 1993; Yang et al. 1992). Chromium(III) did not increase the number of micronuclei in polychromatic erythrocytes in mice (Itoh and Shimada 1996). A few studies have found weakly positive results in Chinese hamster ovary cells (Levis and Majone 1979), mouse fetal cells (Raffetto et al. 1977), and human cell lines (Nakamuro et al. 1979; Stella et al. 1982).

Chromium(III) compounds are less genotoxic than chromium(VI) compounds in intact cell systems because of the relative inability of chromium(III) to cross cell membranes; however, chromium(III) is more genotoxic than chromium(VI) when tested *in vitro* in subcellular targets (Kolwalski et al. 1996; Snow 1991; Snow and Xu 1989). The reduction of chromium(VI) to chromium(III) as the ultimate genotoxicant within cells may account for the genotoxicity of chromium(VI) (Beyersmann and Koster 1987).

Additional studies in workers with known levels of chromium exposure that control for confounding factors would be useful for defining levels at which chromosomal aberrations occur in humans exposed to chromium(VI) in the workplace. Also, better dose-response relationships would be useful for the various genotoxic and regulatory effects observed with chromium to better determine which end points are the most sensitive and dominant at exposures near environmental levels.

Reproductive Toxicity. No reliable information was located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to chromium or its compounds. Studies in women exposed occupationally also show that chromium can be transferred to fetuses through the placenta (Shmitova 1980). A three-generation inhalation study in rats found no reproductive effects (Glaser et al. 1984). Additional inhalation studies would be useful for determining the reproductive toxicity of inhaled chromium and compounds and for establishing exposure-response relationships. Effects on

spermatogenesis were reported in male rats given chromium(VI) by gavage for 90 days (Chowdhury and Mitra 1995). In male mice, oral exposure of intermediate duration to chromium(VI) or chromium(III) was reported to result in decreased spermatogenesis and cellular degeneration of the outer layer of seminiferous tubules (Zahid et al. 1990); alterations in testicular, seminal vesicle, and preputial gland weights and decreased fertility were observed in mice following intermediate-duration exposure to chromium(III) or chromium(VI) (Elbetieha and Al-Hamood 1997). But other studies found no reproductive effects in male or female mice (NTP 1996a, 1997) or rats (NTP 1996b) exposed to chromium(VI). Alterations in sexual behavior and aggressive behavior toward other males were observed in male rats exposed to chromium(VI) or chromium(III) (Bataineh et al. 1997). Female mice or rats exposed orally to chromium(VI) compounds prior to mating (Junaid et al. 1996a; Kanojia et al. 1996, 1998) or female mice exposed during gestation (Junaid et al. 1996b; Trivedi et al. 1989) had increased fetal resorptions and decreased litter size. Alterations in ovarian and uterine weights and impaired fertility were observed in female mice that were exposed to chromium(III) or chromium(VI) and then were mated with unexposed mice (Elbetieha and Al-Hamood 1997). Reductions in numbers of follicles and ova/mouse were seen following oral chromium(III) exposure (Murthy et al. 1996). Impaired development of the reproductive system was observed in the female offspring of mice exposed to potassium dichromate(VI) or chromium(III) chloride (Al-Hamood et al. 1998). Distribution studies in pregnant rats given chromium(VI) or chromium(III) orally (Mertz et al. 1969) or intravenously (Danielsson et al. 1982) and in pregnant mice given chromium(III) intraperitoneally (Iijima et al. 1983) indicated that chromium can cross the placenta after administration of either valence state. The available data on reproductive effects of chromium and its compounds are inadequate for establishing dose relationships; further studies to establish the LOAEL and NOAEL values would be valuable for considering the derivation of oral MRLs. No dermal toxicity studies examining reproductive end points were identified; dermal studies would be useful for assessing the reproductive toxicity of chromium and compounds following dermal contact and for establishing exposure-response relationships.

Developmental Toxicity. No reliable information was located regarding developmental toxicity in humans after inhalation, oral, or dermal exposure or in animals after dermal exposure to chromium or its compounds. A study in women exposed occupationally reported that chromium can be transferred to fetuses through the placenta (Shmitova 1980), but the poor quality and reporting of this study preclude its use for drawing conclusions regarding potential developmental effects of chromium in humans. No developmental effects were observed in a three-generation inhalation study in rats (Glaser et al. 1984). In female rats and mice, oral exposure of acute or intermediate duration to chromium(VI) compounds

resulted in fetal toxicity (Junaid et al. 1996a, 1996b; Kanojia et al. 1996, 1998; Trivedi et al. 1989), but a NOAEL for these effects was not identified. Impaired development of the reproductive system was observed in the female offspring of mice exposed to potassium dichromate(VI) or chromium(III) chloride (Al-Hamood et al. 1998). Distribution studies in rat dams given chromium(VI) or chromium(III) intravenously (Daniellson et al. 1982) or orally (Mertz et al. 1969) and in mouse dams given chromium(III) intraperitoneally (Iijima et al. 1983) indicated that chromium can cross the placenta after administration of either valence state. No studies regarding developmental effects from chromium(III) exposure were located. No pharmacokinetic studies have been conducted regarding the distribution of chromium or its compounds to the fetus after inhalation or dermal exposure of the dams. Further oral developmental studies of chromium(VI) and chromium(III) in mice and other species would be useful to determine a NOAEL. These studies should include examination of developmental/ neural end points. Developmental studies using inhalation exposure would be useful to determine if developmental effects are route specific. Data from oral and inhalation studies would be useful for determining dose-response relationships.

Immunotoxicity. In humans, hypersensitivity, characterized by asthma attacks and dermatitis, has been reported after occupational inhalation or occupational dermal exposure (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989) or dermal exposure (Burrows 1983; Engel and Calnan 1963; Engebrigsten 1952; Eun and Marks 1990; Fregert 1975; Kaplan and Zeligman 1962; Levin et al. 1959; Newhouse 1963; Peltonin and Fraki 1983; Samitz and Shrager 1966; Wahba and Cohen 1979; Winston and Walsh 1951) to chromium or its compounds. Two occupational studies suggest that chromium exposure affects the leukocyte populations in the blood of workers (Boscolo et al. 1997; Mancuso 1951). Delayed anaphylactoid reaction was observed in one case (Moller et al. 1986). Dermatitis was exacerbated in sensitized individuals by oral exposure to chromium(VI) (Goitre et al. 1982; Kaaber and Veien 1977).

In rats, nonspecific disease resistance mechanisms of the lung are inhibited by inhalation exposure to chromium and its compounds (Glaser et al. 1985). Inhalation exposure of intermediate duration alters immunoglobulin levels, lymphocyte responses to antigen and lectin, and spleen weight in rats (Glaser et al. 1985), as well as altered numbers of total recoverable cells, neutrophils, and monocytes, and percentages of pulmonary macrophages in bronchopulmonary lavage (Cohen et al. 1998). Intermediate-duration oral exposure of rats to chromium(VI) increased the proliferative response of T- and B-lymphocytes to mitogens and antigens (Snyder and Valle 1991).

There are sufficient data to determine that chromium or its compounds affect the immune system. More sensitive tests of the immune function after inhalation, oral, or dermal exposure to chromium or its compounds would be useful to determine the threshold levels for effects in humans. Additional studies that explore changes in cytokine levels (Snyder et al. 1996) caused by chromium exposure should prove helpful since they may provide mechanistic information as to how chromium may affect immune function.

Neurotoxicity. Exposure of humans to high levels of airborne chromium(VI) in occupational and environmental settings produced symptoms of dizziness, headache, and weakness (Greater Tokyo Bureau of Hygiene 1989; Lieberman 1941). Cerebral edema was found in a case of fatal poisoning by ingestion (Kaufman et al. 1970). No studies were located describing neurotoxic effects in animals after inhalation and dermal exposure to chromium or its compounds. A 28-day drinking water study in rats reported decreased motor activity and ponderal balance (Diaz-Mayans et al. 1986). Some distribution studies have detected chromium in the brain (Behari and Tandon 1980; Danielsson et al. 1982; Kaufman et al. 1970; Tandon et al. 1979). More recently, patients with 8 to 25-fold higher chromium blood levels that resulted from parenteral feeding, did not have increased signs of somatopsychic responses (Lovrinceic et al. 1996). However, the number of patients studied was small and they were suffering from serious clinical diseases.

Since the central nervous system may be a target organ for exposure to chromium or its compounds, additional inhalation, oral, and dermal studies would be useful to corroborate the limited data and would provide useful information for populations near hazardous waste sites. More information on people (adults, children) environmentally exposed to chromium would be useful to assess its potential to effect neuro/behavioral end points.

Epidemiological and Human Dosimetry Studies. Most epidemiology studies use cohorts of occupationally exposed individuals and provide consistent data indicating that inhaled chromium can be carcinogenic (Alderson et al. 1981; Baetjer 1950b; Bisdtrup 1951; Bidstrup and Case 1956; Braver et al. 1985; Dalager et al. 1980; Davies 1979, 1984; Davies et al. 1991; EEH 1976, 1983; Enterline 1974; Franchini et al. 1983; Frentzel-Beyme 1983; Haguenoer et al. 1981; Hayes et al. 1979, 1989; Korallus et al. 1982; Langård and Norseth 1975; Langård and Vigander 1983; Langård et al. 1980; Machle and Gregorius 1948; Mancuso 1975, 1997a; Mancuso and Hueper 1951; Ohsaki et al. 1978; Pastides et al. 1991, 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1981; Sheffet et al. 1982; Silverstein et al. 1981; Sjogren et al. 1987; Sorahan et al. 1987; Taylor 1966) and can cause other toxic

effects such as respiratory irritation, nasal septum perforation, and chrome sores on the skin (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gomes 1972; Hanslian et al. 1967; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Lee and Goh 1988; Leiberman 1941; Letterer 1939; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989; Pastides et al. 1991; PHS 1953; Royle 1985b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966). Epidemiology studies in the chromate production industry and in chrome pigment manufacture and chrome plating have consistently shown an association with increased risk of lung cancer, but studies in other industries, such as stainless steel welding, electroplating, and ferrochromium production have yielded inconclusive results. Exposure to chromium(VI) in these industries is associated with these effects, but the case for chromium(III) is less clear. Further studies in these industries may lead to more conclusive results. Measurements of chromium in urine and blood are useful for monitoring occupational exposure to chromium compounds. However, chromium(III) is an essential nutrient, and levels in biological fluids might be enough to mask low level exposures. One environmental epidemiology study suggested that residence near a ferrochromium plant did not pose a risk of cancer (Axelsson and Rylander 1980), but an environmental study in China found that residence near an alloy plant that smelted chromium was associated with increased incidences of lung and stomach cancer (Zhang and Li 1987), but a more recent analysis by Zhang and Li (1997) concluded that increased incidences were more likely due to lifestyle factors or other environmental factors. The populations residing near other chromium-related industries or near hazardous waste sites containing chromium or its compounds might be the subject for additional epidemiology studies to determine if chromium levels are elevated in body fluids and if there is an increased incidence of cancer or respiratory diseases.

Biomarkers of Exposure and Effect.

Exposure. There are studies correlating chromium in urine (Gylseth et al. 1977; Kilburn et al. 1990; Lindberg and Vesterberg 1983a; Lukanova et al. 1996; McAughey et al. 1988; Minoia and Cavalleri 1988; Mutti et al. 1985b; Sjogren et al. 1983; Tola et al. 1977), blood (Kilburn et al. 1990; McAughey et al. 1988; Minoia and Cavalleri 1988; Randall and Gibson 1987), hair (Randall and Gibson 1989; Saner et al. 1984; Takagi et al. 1986), and erythrocytes (Lukanova et al. 1996; Minoia and Cavalleri 1988) to occupational exposure levels. All current methods of biological monitoring are useful primarily for occupational exposure scenarios. Since chromium is an essential element, levels of chromium compounds have to be relatively high in humans before they signify an increase due to exposure. Hair has been useful in determining chronic occupational exposure to chromium in high concentrations (Randall and Gibson 1989); the usefulness of this method for detecting prior exposures is limited to a

timespan of months (Simpson and Gibson 1992). Erythrocytes (with a half-life of 120 days) can be used to monitor intermediate exposures, and blood or urine can be used to determine acute exposures (Korallus 1986a, 1986b). Occupational exposure to chromium can cause chromosomal aberrations (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Therefore, chromosomal abnormalities may be useful for monitoring chromium exposure, however, other chemicals are capable of causing these effects. Chromium(VI) compounds are able to bind to macromolecules in the body and can form DNA-protein crosslinks (Coogan et al. 1991b). However, no increase in these crosslinks was observed in leukocytes from volunteers over a 240 minute time period after ingestion of chromium(VI) as potassium chromate (Kuykendall et al. 1996). The identification of chromium-protein/peptide complexes specific for chromium(VI) exposure and small enough to be excreted in the urine may be useful for biomonitoring in detecting low level exposure to populations near hazardous waste sites. As discussed in Section 2.8.1, there are a number of limitations (e.g., significant exposure must occur immediately prior to sampling, high inter- and intraperson variability) to using urinary monitoring to assess environmental exposure to chromium (Paustenbach et al. 1997). However, urinary monitoring has the advantage of easy sample collection and is noninvasive. Mathematical models have been used to identify "excess" urinary chromium in a population exposed to low levels of chromium (Fagliano et al. 1997). Further refinement of these models as more data is collected from unexposed and exposed populations will also be useful in detecting low level exposures.

Effect. Chromosomal aberrations have been observed in workers exposed by inhalation to chromium compounds (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Moreover, chromium(VI) compounds can bind to macromolecules that are excreted in the urine (Coogan et al. 1991b). The use of these techniques to detect chromosomal aberrations and chromium-macromolecular complexes would be useful in identifying populations near hazardous waste sites who would be at higher risk. In addition, the finding of increased retinol binding protein, $ß_2$-microglobulin, and brush border proteins in the urine of workers exposed to chromium may serve as an early indication of kidney damage (Franchini and Mutti 1988; Lindberg and Vesterberg 1983b; Liu et al. 1998; Mutti et al. 1985b). Additional screening for low molecular weight proteins in occupationally exposed individuals will help to determine if these proteins can be used as reliable indicators of renal damage due to chromium exposure. Snyder et al. (1996) found no difference in mitogenic stimulation of mononuclear cells isolated from people environmentally/ occupationally exposed to chromium as compared to nonexposed individuals. However, monocytes in the exposed population had a 36% lower level of the cytokine IL-6 that is involved in antibody production. As discussed in Section 2.4.2 chromium induces many types of DNA lesions such as chromium-DNA complexes, DNA adducts, and DNA-protein crosslinks that are potential markers of

genotoxic or cancer effects due to chromium exposure. However, only one study has attempted to utilize such end points and reported that human volunteers exposed to chromium in drinking water showed no increase in protein-DNA crosslinking in blood cells (Kuykendall et al. 1996). However, further studies may show that other types of lesions induced by chromium may be more sensitive. Räsänen et al. (1991) developed an *in vitro* method to assess chromium sensitivity by measuring mononuclear leukocyte proliferation in response to chromium(III) chloride, sodium chromate(VI), and potassium chromate(VI). Additional studies would be useful to validate this method.

Absorption, Distribution, Metabolism, and Excretion. The pharmacokinetics database is substantial for human and animal exposure to chromium compounds. Chromium and its compounds can be absorbed after oral (Anderson 1981, 1986; Anderson et al. 1983; Bunker et al. 1984; Donaldson and Barreras 1966; Finley et al. 1996b; Gargas et al. 1994; Kerger et al. 1997; Kuykendall et al. 1996; Paustenbach et al. 1996), inhalation (Adachi et al. 1981; Cavalleri and Minoia 1985; Glyseth et al. 1977; Langård et al. 1978; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Suzuki et al. 1984; Tossavainen et al. 1980), and dermal (Baranowski-Dutkiewicz 1981; Brieger 1920; Liden and Lundberg 1979; Mali et al. 1963; Samitz and Shrager 1866; Spruit and van Neer 1966; Wahlberg 1970; Wahlberg and Skog 1965) exposure. For the general population, oral exposure via the diet to chromium(III) is the most significant route. Occupational exposure usually involves inhalation and dermal routes. Pharmacokinetic data are generally consistent with regard to absorption, distribution, and excretion among species. Chromium(VI) compounds are absorbed more readily through cell membranes than are chromium(III) compounds (MacKenzie et al. 1958; Maruyama 1982; Witmer et al. 1989, 1991). Absorption is greater through the lungs than through the gastrointestinal tract (Baetjer et al. 1959b; Bragt and van Dura 1983; Kuykendall et al. 1996; Visek et al. 1953; Wiegand et al. 1984, 1987).

Examination of tissues taken at autopsy from occupationally and environmentally exposed people indicate widespread distribution of chromium (Brune et al. 1980; Hyodo et al. 1980; Kollmeier et al. 1990; Mancuso 1997b; Schroeder et al. 1962; Teraoka 1981). Widespread distribution of chromium has also been found in animals after oral exposure (Kargacin et al. 1993; Witmer et al. 1989, 1991). The distribution of chromium in animals after intratracheal, parenteral, or dermal exposure is greatest in the lungs, liver, kidneys, blood, spleen, testes, and brain (Baetjer et al. 1959a; Behari and Tandon 1980; Bryson and Goodal 1983; Coogan et al. 1991b; Lim et al. 1983; Mutti et al. 1979; Tandon et al. 1979; Visek et al. 1953; Wahlberg and Skog 1965; Weber 1983). Oral exposure studies indicate that higher levels of chromium(VI) compounds are absorbed than are levels of chromium(III) compounds. Studies in humans occupationally and environmentally exposed to chromium(VI) (Casey and Hambidge 1984;

Shmitova 1980) and in animals exposed to chromium(VI) or chromium(III) demonstrate the ability for chromium to cross the placenta (Mertz et al. 1969; Saxena et al. 1990a). Chromium(VI) crosses more readily than chromium(III).

There are no data to indicate that the route of exposure influences the metabolism of chromium. Regardless of the route of exposure, chromium(VI) inside the body is reduced to chromium(III) by ascorbic acid, glutathione, or by the NADPH-dependent cytochrome P450 system (Aaseth et al. 1982; De Flora et al. 1984, 1997; Garcia and Jennette 1981; Gruber and Jennette 1979; Liu et al. 1995; Mikalsen et al. 1989; Petrilli et al. 1985, 1986a; Samitz 1970; Suzuki and Fukuda 1990; Wiegand et al. 1984).

Analysis of the urine of workers occupationally exposed to chromium(VI) indicate that chromium is excreted in the trivalent form, which is consistent with *in vivo* reduction of chromium(VI) to chromium(III) (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Oral studies in humans and animals indicate that most of the chromium(VI) or chromium(III) ingested is excreted in the feces (Bunker et al. 1984; Donaldson and Barreras 1986; Donaldson et al. 1984; Henderson et al. 1979; Sayoto et al. 1980), consistent with the poor gastrointestinal absorption of chromium. After dermal exposure of humans and animals, chromium can be found in the urine and feces (Brieger 1920; Wahlberg and Skog 1965). Chromium has been detected in hair and fingernails of the general population of several countries (Takagi et al. 1986, 1988) and in the breast milk of nursing mothers (Casey and Hambidge 1984), indicating these media as routes of excretion. Data regarding excretion after exposure of animals to chromium(VI) or chromium(III) by other routes indicated that excretion occurs rapidly, and primarily via the kidneys, once chromium(VI) is reduced (Gregus and Klaassen 1986; Yamaguchi et al. 1983). Thus, absorption, distribution, and excretion of chromium have been studied extensively. Additional studies examining the enzymatic reduction of chromium(VI) compounds in rodents and humans would be of value in determining the potential biological impact of the reported differences in those pathways.

Comparative Toxicokinetics. Human and animal data indicate that targets of chromium exposure are similar among species (e.g., the respiratory and immune systems). Toxicokinetic data in humans, dogs, rats, mice, rabbits, and hamsters generally correlate well among species (see references above). However exposures to chromium(VI) resulted in different organ distribution patterns between rats and mice(Kargacin et al. 1993), and the chromium levels in mouse fetal tissues were elevated over maternal blood levels, whereas in rats these differences were not found (Saxena et al. 1990a). In addition, comparisons of human and rat hepatic microsomal ability to reduce chromium(VI) indicated differences in microsomal complexes involved (Myers and Myers 1998; Pratt and Myers 1993). Therefore,

additional comparison studies among species would be useful to determine variations in the absorption, distribution, metabolism, and excretion of chromium. A PBPK model (O'Flaherty 1996) that has been partially validated has been developed based on rats. As described previously, the model is quite sophisticated, but additional physiological and kinetic parameters from both humans and other animal species are needed in order for the model to be employed for extrapolation across species and for use in risk assessment. Furthermore, additional metabolic data are needed with regard to insoluble chromium and its elimination and solubilization, particularly in lung tissue.

Methods for Reducing Toxic Effects. Methods for reducing the absorption of chromium from the lungs consist primarily of administering ascorbic acid or N-acetylcysteine, which enhance the reduction of chromium(VI) to chromium(III) (De Flora and Wetterhahn 1989; Suzuki and Fukuda 1990). Chromium(III) passes the alveolar lining into the bloodstream less readily than chromium(VI) and is cleared by mucociliary clearance. A study might be conducted to determine whether administration of expectorants would enhance clearance from the lungs. After ingestion, ascorbic acid therapy also appears to be effective in reducing absorption by the gastrointestinal tract (HSDB 1998; Kuykendall et al. 1996). After dermal exposure, thorough washing and ascorbic acid therapy to enhance the reduction of chromium(VI) to chromium(III) (HSDB 1998), followed by chelation with EDTA (Nadia 1994), would greatly reduce dermal absorption. Administration of ascorbic acid has also been used to enhance the reduction of chromium(VI) to chromium(III) in plasma (Korallus et al. 1984), which would reduce the body burden of chromium because chromium(III) would bind to plasma protein and be excreted in the urine. Studies could be conducted to determine if other reducing agents would be more effective than ascorbic acid. Once inside the cell, chromium(VI) can enter many reactions resulting in reduction to various oxidation states with the generation of reactive oxygen species and radicals, all of which may be more or less toxic than chromium(III) (De Flora and Wetterhahn 1989). Gasiorowski et al. (1997, 1998) showed that stabilizing chromium in the hexavalent oxidation state, via complexing to a ligand, decreased the mutagenicity of chromium(VI). Methods could be developed to interfere with these various reactions, but such methods may be counterproductive because they might shift one reaction to another with undesirable consequences. *In vitro* studies have indicated that vitamin E, ascorbic acid, and glutatione protected against chromosomal breakage, DNA-protein crosslinks, and apoptosis (cell death) (Blankenship et al. 1997), while vitamin B_2 enhanced the cytotoxicity and DNA single-strand breaks induced by chromium(VI) (Sugiyama 1991). Vitamin E may have scavenged radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991). Other vitamins might also be effective in mitigating chromium's effects. Although the administration of thyroxine has been shown to ameliorate potassium dichromate-induced acute renal failure in rats (Siegel et al. 1984), it's use in humans

has not been tested. Further studies are needed to assess the safety of administering thyroxine to mitigate chromium toxicity.

Children's Susceptibility. A limited amount of information is available on the toxicity of chromium in children; most of the available data comes from children ingesting lethal doses of chromium(VI) (Clochesy 1984; Ellis et al. 1982; Iserson et al. 1983; Kaufman et al. 1970; Reichelderfer 1968). Studies that examine sensitive end points such as respiratory effects following inhalation exposure, or gastrointestinal, hematological, liver and kidney effects in young animals would be useful for assessing whether children will be unusually susceptible to chromium toxicity. The available animal data suggest that chromium is a developmental toxicant. As discussed in Section 2.2.2.6, the observed developmental effects include postimplantation losses, gross abnormalities, and impaired reproductive development in the offspring (Al-Hamood et al. 1998; Junaid et al. 1996a, 1996b; Kanojia 1996, 1998; Trivedi et al. 1989). Data needs relating to development are discussed in detail in the Developmental Toxicity subsection above. There are some data in humans and animals which provide evidence that chromium can cross the placenta and be transferred to an infant via breast milk (Casey and Hambidge 1984; Daniellson et al. 1982; Mertz et al. 1969; Saxena et al. 1990; Shmitova 1980). There are no data on whether chromium is stored in maternal tissues and whether these stores can be mobilized during pregnancy or lactation.

An age-related difference in the extent of gastrointestinal absorption of chromium(III) was reported in one study (Sullivan et al. 1984); it is not known if a similar relationship would exist for chromium(VI). No other information is available which evaluated potential differences between adults and children. Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of chromium, particularly chromium(VI) would be useful in assessing children's susceptibility to chromium toxicity. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. There is very little available information on methods for reducing chromium toxic effects or body burdens; it is likely that research in adults would also be applicable to children.

Child health data needs relating to exposure are discussed in Section 5.8.1 Identification of Data Needs: Exposures of Children.

2.12.3 Ongoing Studies

Ongoing studies pertaining to chromium have been identified and are shown in Table 2-8.

Table 2-8. Ongoing Studies on Chromium[a]

Investigator	Affiliation	Research description	Sponsor
Anderson RA	Agricultural Research Service	Chromium absorption and transport	USDA
Billings RE	Colorado State University	Interaction among chromium, lead, arsenic, benzene, and phenol	NIEHS
Dixon K	University of Cincinnati	Molecular mechanism of chromium mutagenesis	NIEHS
Gandolfi AJ	University of Arizona	Interactions of chromium and mercury, cadmium, and arsenic in the kidney	NIEHS
Hermann J	Oklahoma State University	Interaction of chromium and copper in humans	USDA
Kasprzak KS	NCI	Mechanisms of chromium-induced carcinogenesis	NCI
Liu J	Dartmouth College	Reduction of chromium(VI) on skin	NCRR
Longnecker MP	NIEHS, NIH	Use of toenail chromium levels as a biomarker of exposure	NIEHS
Myers C	Medical College of Wisconsin	Reduction of chromium(VI) to chromium(III)	NCRR
Patierno SR	George Washington University	DNA crosslinking in chromium toxicity and carcinogenesis	NIEHS
Patierno SR	George Washington University	Particulate chromium toxicity and carcinogenesis	NIEHS
Schlesinger RB	New York University	Interaction of ozone and chromium in the lung	NIOSH
Singh J	George Washington University	Cellular and molecular mechanisms of chromium-induced genotoxicity and apoptosis in the lung	NIEHS
Stearns DM	Northern Arizona University	Chromium(III) mechanisms of carcinogenesis	NCI
Zhitkovich A	Brown University	Genotoxicity of chromium compounds	NIEHS
		Epidemiology study of chromium(VI) workers	IHF[b]

[a]Unless otherwise noted, information on ongoing studies was taken from FEDRIP 1999
[b]Source: OSHA (1998b)

IHF = Industrial Health Foundation; NCI = National Cancer Institute; NCRR = National Center for Research Resources; NIEHS = National Institute of Environmental Health and Science, NIOSH = National Institute for Occupational Health and Safety; USDA = U.S. Department of Agriculture