

3. HEALTH EFFECTS

3.1 INTRODUCTION

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

Several different nickel compounds are discussed in this profile. These compounds can be grouped according to their solubility in water: soluble compounds include nickel chloride, nickel sulfate, and nickel nitrate, and less-soluble compounds include nickel oxide and nickel subsulfide. Both the soluble and less-soluble nickel compounds are important with regard to all relevant routes of exposure.

Generally, the soluble compounds are considered more toxic than the less-soluble compounds, although the less-soluble compounds are more likely to be carcinogenic at the site of deposition. Metallic nickel is also considered in this profile. All doses are presented as the amount or concentration of nickel to which subjects were exposed. Nickel carbonyl, a highly toxic nickel compound, is not considered in this profile. The data regarding the toxicity of nickel carbonyl are substantial; however, the likelihood of exposure at hazardous waste sites is very low. In ambient air, nickel carbonyl is relatively unstable with a half-life of ≈ 100 seconds (Stedman and Hiked 1980). Because nickel carbonyl is highly reactive, it is not likely to be found at hazardous waste sites. Also, nickel carbonyl is not very soluble in water; therefore, it will not be found in drinking water.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by end point (death, systemic, immunological, neurological, reproductive, developmental, 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).

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

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

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

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

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3.2.1 Inhalation Exposure**3.2.1.1 Death**

Death from adult respiratory distress syndrome was reported in one person who sprayed nickel with a metal arc process without wearing personal protective equipment (Rendell et al. 1994). Several days after the exposure, urinary concentrations of nickel were 700 µg/L, in comparison to levels of <0.1–13.3 µg/L in persons not occupationally exposed to nickel (Sunderman 1993). The death occurred 13 days after the 90-minute exposure to an estimated concentration of 382 mg Ni/m³ of principally metallic nickel with the majority of particle sizes of <1.4 µm. Histological examination of the lungs revealed alveolar wall damage and edema in alveolar spaces, and marked tubular necrosis was noted in the kidneys.

Human data regarding chronic inhalation exposure to nickel are limited to occupational exposure studies. The majority of these studies analyzed the toxicity of nickel, usually in the form of nickel oxide, metallic nickel, or nickel refinery dust, by calculating Standard Mortality Ratios (SMR) for all causes of death. Generally, the studies report a higher incidence of cancer deaths from lung and nasal cancers in the exposed workers (see Section 3.2.1.8). Two studies have also reported a higher incidence of deaths resulting from nonmalignant respiratory disease (Cornell and Landis 1984; Polednak 1981). However, all of the workers were exposed to other metals (arsenic, uranium, iron, lead, chromium), so it cannot be concluded that nickel was the sole causative agent. Other studies of humans occupationally exposed to nickel compounds have not reported increased mortality resulting from respiratory diseases (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh 1982; Redmond 1984; Shannon et al. 1984b, 1991).

During the first 2 days after a single 2-hour exposure, 4 of 28 rats died after exposure to nickel sulfate at 36.5 mg Ni/m³ (Hirano et al. 1994b). Severe hemorrhage of the lungs was observed in the lungs of the rats that died. During inhalation exposure of 6 hours/day, 5 days/week, for up to 12 exposures, rats and mice exposed to 12.2 or 1.4 mg Ni/m³, respectively, as nickel sulfate and mice exposed to 7.33 mg Ni/m³ as nickel subsulfide died, but those exposed to nickel oxide did not (NTP 1996a, 1996b, 1996c). Mice were more sensitive to lethality than rats; at 1.4 mg Ni/m³ as nickel sulfate, all mice and no rats died, and at 7.33 mg Ni/m³ as nickel subsulfide, all mice and 2 of 10 rats died. No rats or mice died following exposure to 23.6 mg Ni/m³ as nickel oxide. No deaths were reported in rats or mice following 13 weeks of exposure (6 hours/day, 5 days/week) to nickel at 7.9, 1.83, or 0.44 mg Ni/m³ as nickel oxide, nickel subsulfide, or nickel sulfate, respectively (NTP 1996a, 1996b, 1996c). Hamsters survived exposure to ≤48.4 mg Ni/m³ as nickel oxide for 15 or 61 days (Werner and Craig 1972).

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Significant mortality was observed during the last 26 weeks of a 78-week inhalation study of rats exposed to 0.7 mg Ni/m³ as nickel subsulfide (Ottolenghi et al. 1974). Less than 5% of the treated rats survived the study (78 weeks of exposure plus 30 weeks of observation) compared to 31% of the controls (Ottolenghi et al. 1974). All rats, guinea pigs, and mice exposed to 15 mg Ni/m³ as metallic nickel for ≤21 months died before the end of the study, with most of the guinea pigs and mice dying by 15 months (Hue per 1958). Lung lesions including edema, hyperemia, and hemorrhage were the principal effects noted. However, no controls were used in this study. A significant decrease in mean survival time was observed in rats exposed 23 hours/day for life to 0.06 mg Ni/m³ as nickel oxide (Takenaka et al. 1985). The average survival times for rats exposed to 0 or 0.06 mg Ni/m³ were 125.2 and 87.7 weeks, respectively. Survival was not affected in rats exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m³, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c). Survival of mice was also not affected by exposure to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m³, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c).

LOAEL values from each reliable study for death in each species, duration category, and nickel compound are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding ocular effects in humans or animals after inhalation exposure to nickel. Other systemic effects are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species, duration category, and nickel compound are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. A number of human studies have examined the potential of nickel and nickel compounds to induce respiratory effects. Most of these studies were cohort mortality studies in nickel-exposed workers. A significant excess of deaths from nonmalignant respiratory system disease was found among foundry workers that was associated with the duration of foundry employment, regardless of exposure to nickel (Cornell and Landis 1984). Other studies of refinery workers or workers exposed to nickel alloys have not found increases in deaths from respiratory disease (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Redmond 1984; Roberts et al. 1989b; Shannon et al. 1984b, 1991). Two studies of welders also did not find significant increases in the

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

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m³)	Serious (mg/m³)	
ACUTE EXPOSURE							
Death							
1	Human	90 min				382 M (death of one man)	Rendall et al. 1994 metal
2	Rat (Wistar)	2 hr				36.5 M (4/28 died)	Hirano et al. 1994b sulfate
3	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day				12.2 F (5/5 died)	NTP 1996c sulfate
4	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day				7.33 (10/10 died)	NTP 1996b subsulfide
5	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day				1.4 (10/10 died)	NTP 1996c sulfate
Systemic							
6	Rat (Fischer- 344)	1, 2, 4, 7, 12 d 6hr/d	Resp		0.22 (alveolitis)		Benson et al. 1995b subsulfide
7	Rat (Long- Evans)	4, 8, 12 or 16 d 6 hr/d	Resp		0.635 M (atrophy of olfactory epithelium)		Evans et al. 1995 sulfate

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

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m³)	Serious (mg/m³)	
8	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day	Resp	3.9 F	7.9 F (acute lung inflammation)		NTP 1996a oxide
			Cardio	23.6			
			Gastro	23.6			
			Musc/skel	23.6			
			Hepatic	23.6			
			Renal	23.6			
			Endocr	23.6			
			Dermal	23.6			
	Bd Wt	23.6					

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
9	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day	Resp		0.44 (chronic lung inflammation, atrophy of olfactory epithelium)	3.65 F (chronic lung inflammation with necrosis and labored breathing)	NTP 1996b subsulfide
			Cardio	7.33			
			Gastro	7.33			
			Hepatic	7.33			
			Renal	7.33			
			Endocr	7.33			
			Dermal	7.33			
			Bd Wt	1.83		3.65 (22-28% decrease in body weight gain)	

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
10	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day	Resp			0.7 (chronic lung inflammation; degeneration of bronchiolar epithelium; labored breathing; atrophy of olfactory epithelium)	NTP 1996c sulfate
			Cardio	12.2			
			Gastro	12.2			
			Musc/skel	12.2			
			Hepatic	12.2			
			Renal	12.2			
			Endocr	12.2			
			Dermal	12.2			
			Bd Wt			0.7 M (final body weights 28% lower than controls)	

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
11	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day	Resp	23.6			NTP 1996a oxide
			Cardio	23.6			
			Gastro	23.6			
			Hepatic	23.6			
			Renal	23.6			
			Endocr	23.6			
			Dermal	23.6			
			Bd Wt	23.6			
12	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day	Resp	0.44	1.83	(chronic lung inflammation)	NTP 1996b subsulfide
					0.88	(atrophy of olfactory epithelium)	
			Gastro	7.33			
			Hemato	7.33			
			Musc/skel	7.33			
			Hepatic	7.33			
			Renal	7.33			
			Endocr	7.33			
			Dermal	7.33			
			Bd Wt	1.83 M		3.65 M (emaciation)	

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
13	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day	Resp		0.7 (chronic lung inflammation)	1.4 (necrotizing lung inflammation)	NTP 1996c sulfate
			Cardio	1.4			
			Gastro	1.4			
			Musc/skel	1.4			
			Hepatic	1.4			
			Renal	1.4			
			Endocr	1.4			
			Dermal	1.4			
			Bd Wt	0.7		1.4 (animals appeared emaciated)	
Immuno/ Lymphoret							
14	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
15	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		7.33			NTP 1996b subsulfide
16	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day		0.7 F	1.4 F (hyperplasia in bronchial and mediastinal lymph nodes)		NTP 1996c sulfate

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
17	Mouse (CD-1)	2 hr			0.499 F (increased susceptibility to Streptococcal infection)		Adkins et al. 1979 chloride
				0.369 F			
18	Mouse (CD-1)	2 hr			0.657 F (decreased ability to clear bacteria from lungs)		Adkins et al. 1979 chloride
19	Mouse (CD-1)	2 hr			0.455 F (increased susceptibility to Streptococcal infection)		Adkins et al. 1979 sulfate
20	Mouse (Swiss)	2 hr		0.1 F	0.25 F (impaired humoral immunity)		Graham et al. 1978 chloride
21	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
22	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		0.44	0.88 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
23	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day		3.1			NTP 1996c sulfate
Neurological							
24	Rat (Long- Evans)	4, 8, 12, 16 d 6 hr/d			0.635 M (decrease in number of bipolar receptor cells in nasal olfactory epithelium)		Evans et al. 1995 sulfate
Reproductive							
25	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
26	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		7.33			NTP 1996b subsulfide
27	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day		12.2			NTP 1996c sulfate
28	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
29	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		3.65			NTP 1996b subsulfide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
30	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day		1.4			NTP 1996c sulfate
INTERMEDIATE EXPOSURE							
Systemic							
31	Rat (Fischer- 344)	up to 6 mo 5d/wk 6hr/d	Resp	0.49 M	1.96 M (moderate alveolitis that persisted at least 4 months after the exposure)		Benson et al. 1995a oxide
			Bd Wt	1.96 M			
32	Rat (Fischer- 344)	up to 6 mo 5d/wk 6hr/d	Resp		0.11 M (alveolitis that persisted for 4 months after exposure)		Benson et al. 1995a sulfate
33	Rat (Wistar)	> 2 wk 6 d/wk 12 hr/d	Resp		0.12 M (alveolar wall thickening)		Bingham et al. 1972 oxide
34	Rat (Wistar)	>2 wk 6 d/wk 12 hr/d	Resp		0.109 M (hyperplasia of the bronchial epithelium and peribronchial lymphocytic infiltration)		Bingham et al. 1972 chloride
35	Rat (Wistar)	1 mo 5d/wk 6hr/d	Resp		0.5 M (interstitial pneumonia)		Horie et al. 1985 oxide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
36	Rat (Fischer- 344)	13 weeks 5d/wk 6hr/d	Resp	2	3.9	(chronic active lung inflammation and granulomatous inflammation)	NTP 1996a oxide
			Cardio	7.9			
			Gastro	7.9			
			Musc/skel	7.9			
			Hepatic	7.9			
			Renal	7.9			
			Endocr	7.9			
			Dermal	7.9			
			Bd Wt	7.9			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL			Reference Chemical Form	
					Less Serious (mg/m³)		Serious (mg/m³)		
37	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day	Resp	0.11	0.22	(chronic inflammation and interstitial infiltrates)	1.83	(labored breathing during weeks 2-7)	NTP 1996b subsulfide
					0.44	(atrophy of olfactory epithelium)			
			Cardio	1.83					
			Gastro	1.83					
			Musc/skel	1.83					
			Hepatic	1.83					
			Renal	1.83					
			Endocr	1.83					
Dermal	1.83								
Bd Wt	1.83								

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
38	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day	Resp	0.06 ^b F	0.11 F (chronic lung inflammation, interstitial infiltrates)		NTP 1996c sulfate
					0.22 (atrophy of olfactory epithelium)		
			Cardio	0.44			
			Gastro	0.44			
			Musc/skel	0.44			
			Hepatic	0.44			
			Renal	0.44			
39	Rat (Wistar)	28 d 23.6 hr/d	Endocr	0.44			Weischer et al. 1980 oxide
			Dermal	0.44			
			Bd Wt	0.44			
			Hepatic	0.784 M			
			Renal	0.784 M			
			Bd Wt	0.178 M		0.385 M (30% decrease in body weight gain)	
			Metab	0.178 M	0.385 M (increased serum glucose)		

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

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
40	Rat (Wistar)	21 d 23.6 hr/d	Bd Wt			0.8 F (36% decrease in body weight gain)	Weischer et al. 1980 oxide
			Metab		0.8 F (decreased serum glucose level)		
41	Mouse (B6C3F1)	up to 6mo 5d/wk 6hr/d	Resp		0.98 M (interstitial pneumonia)		Benson et al. 1995a oxide
			Bd Wt	3.93 M			
42	Mouse (B6C3F1)	up to 6mo 5d/wk 6hr/d	Resp	0.06 M	0.22 M (interstitial pneumonia)		Benson et al. 1995a sulfate

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

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m³)	Serious (mg/m³)	
43	Mouse (B6C3F1)	13 weeks 5d/wk 6hr/d	Resp	2 F	3.9 F (perivascular lymphocytic infiltrates)		NTP 1996a oxide
			Cardio	7.9			
			Gastro	7.9			
			Musc/skel	7.9			
			Hepatic	7.9			
			Renal	7.9			
			Endocr	7.9			
			Dermal	7.9			
			Bd Wt	7.9			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m³)	Serious (mg/m³)	
44	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day	Resp	0.22 M	0.88 M (chronic lung inflammation and fibrosis)		NTP 1996b subsulfide
					0.44 M (atrophy of olfactory epithelium)		
			Cardio	1.83			
			Gastro	1.83			
			Hemato	1.83			
			Musc/skel	1.83			
			Renal	1.83			
			Endocr	1.83			
			Dermal	1.83			
			Bd Wt	1.83			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
45	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day	Resp	0.22 F	0.44 F (chronic lung inflammation and fibrosis)		NTP 1996c sulfate
			Cardio	0.44			
			Gastro	0.44			
			Musc/skel	0.44			
			Hepatic	0.44			
			Renal	0.44			
			Endocr	0.44			
			Dermal	0.44			
			Bd Wt	0.44			
46	Rabbit (NS)	1-8 mo 5d/wk 6hr/d	Resp		0.2 M (increased volume density of alveolar type II cells)		Johansson and Camner 1986 chloride or metallic
Immuno/ Lymphoret							
47	Rat (Wistar)	4wk 5d/wk 8hr/d			9.2 M (increased production of tumor necrosis factor by alveolar macrophages)		Morimoto et al. 1995 oxide
48	Rat (Fischer- 344)	13 weeks 5d/wk 6hr/d		0.9	2 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996a oxide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
49	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		0.11	0.22	(lymphoid hyperplasia in bronchial lymph nodes)	NTP 1996b subsulfide
50	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		0.11	0.22	(lymphoid hyperplasia in bronchial and mediastinal lymph nodes)	NTP 1996c sulfate
51	Rat (Wistar)	4 wk continuous		0.1	0.2	(impaired humoral immunity)	Spiegelberg et al. 1984 oxide
52	Rat (Wistar)	4 mo continuous		0.025	0.15	(impaired humoral immunity)	Spiegelberg et al. 1984 oxide
53	Mouse (B6C3F1)	65 d 5d/wk 6hr/d			0.47 F	(decreased alveolar macrophage activity)	Haley et al. 1990 oxide
54	Mouse (B6C3F1)	65 d 5d/wk 6hr/d		0.11 F	0.45 F	(decreased resistance to tumor challenge)	Haley et al. 1990 sulfate
55	Mouse (B6C3F1)	65 d 5d/wk 6hr/d		0.11 F	0.45 F	(decreased alveolar macrophage phagocytic activity)	Haley et al. 1990 subsulfide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
56	Mouse (B6C3F1)	13 weeks 5d/wk 6hr/d		0.9	2 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996a oxide
57	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		0.44 F	0.88 F (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide
58	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		0.22 F	0.44 F (hyperplasia of bronchial lymph nodes)		NTP 1996c sulfate
59	Rabbit (NS)	3 or 6 mo 5d/wk 6hr/d			1 M (inactive macrophage surfaces)		Johansson et al. 1980 metallic
60	Rabbit (NS)	4-6 wk 5d/wk 6hr/d			0.6 M (decrease lysozyme activity in alveolar macrophages)		Johansson et al. 1987 chloride
61	Rabbit (NS)	4 mo 5d/wk 6hr/d			0.6 M (decreased macrophage lysosomal activity)		Johansson et al. 1988a, 1989 chloride
Reproductive							
62	Rat (Fischer- 344)	13 weeks 5d/wk 6hr/d		3.9 M	7.9 M (decreased sperm concentration)		NTP 1996a oxide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
63	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		1.83			NTP 1996b subsulfide
64	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		0.44			NTP 1996c sulfate
65	Mouse (B6C3F1)	13 weeks 5d/wk 6hr/d		7.9			NTP 1996a oxide
66	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		1.83			NTP 1996b subsulfide
67	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		0.44			NTP 1996c sulfate
Developmental							
68	Rat (Wistar)	Gd 1-21 23.6 hr/day		0.8	1.6 (decreased fetal body weights)		Weischer et al. 1980 oxide
CHRONIC EXPOSURE							
Death							
69	Rat (Wistar)	21 mo 4-5d/wk 6hr/d				15 (100/100 deaths)	Hueper 1958 metallic
70	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d				0.7 (<11/226 survived)	Ottolenghi et al. 1974 subsulfide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
71	Rat (Wistar)	31 mo 7d/wk 23hr/d				0.06 M (decreased survival time)	Takenaka et al. 1985 oxide
72	Mouse (C57)	21 mo 4-5d/wk 6hr/d				15 F (20/20 died)	Hueper 1958 metallic
73	Gn Pig (strain 13)	21 mo 4-5d/wk 6hr/d				15 (42/42 died)	Hueper 1958 metallic
Systemic							
74	Human	occupa- tional	Renal		0.75 F (increased urinary excretion of N-acetyl-b-D- glucosamidase, total proteins, b2 -microglobulin, and retinol binding protein)		Vyskocil et al. 1994a sulfate, chloride

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
75	Rat (Fischer- 344)	2 yr 5d/wk 6hrs/d	Resp		0.5	(chronic lung inflammation)	NTP 1996a oxide
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Endocr	1 F	2 F	(benign pheochromocytoma and adrenal medulla hyperplasia)	
			Dermal	2			
			Bd Wt	2			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL			Reference Chemical Form	
					Less Serious (mg/m³)		Serious (mg/m³)		
76	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week	Resp		0.73	(atrophy of nasal olfactory epithelium)		0.11 (chronic inflammation, alveolar epithelium hyperplasia, fibrosis, rapid and shallow breathing)	NTP 1996b subsulfide
			Cardio	0.73					
			Gastro	0.73					
			Musc/skel	0.73					
			Renal	0.73					
			Endocr		0.11 M (pheochromocytoma)				
			Bd Wt	0.11	0.73	(11-12% decrease in body weight gain)			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
77	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d	Resp	0.03 ^c	0.11	(atrophy of olfactory epithelium)	NTP 1996c sulfate
					0.06	(chronic inflammation, bronchialization)	
			Cardio	0.11			
			Gastro	0.11			
			Hemato	0.11			
			Hepatic	0.11			
			Renal	0.11			
			Endocr	0.11			
			Dermal	0.11			
			Bd Wt	0.11			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
78	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d	Resp			0.7 (pneumonitis; bronchitis; emphysema)	Ottolenghi et al. 1974 subsulfide
			Cardio	0.7			
			Gastro	0.7			
			Hepatic	0.7			
			Renal	0.7			
			Endocr	0.7			
			Bd Wt			0.7 (body weight 20-30% less than controls)	
79	Rat (Wistar)	31 mo 7d/wk 23hr/d	Resp		0.06 M (increased lung weight; congestion; alveolar proteinosis)		Takenaka et al. 1985 oxide
			Bd Wt			0.06 M (weight loss amount not stated)	
80	Rat (Wistar)	12 mo 5d/wk 7hr/d	Resp			0.2 (pneumonia)	Tanaka et al. 1988 oxide
			Hepatic	0.9			
			Renal	0.9			
			Bd Wt	0.9			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
81	Mouse (B6C3F1)	2 yr 5d/wk 6hrs/d	Resp		1	(chronic lung inflammation, bronchialization, alveolar proteinosis)	NTP 1996a oxide
			Cardio	3.9			
			Gastro	3.9			
			Hemato	3.9			
			Musc/skel	3.9			
			Hepatic	3.9			
			Renal	3.9			
			Endocr	3.9			
			Dermal	3.9			
			Bd Wt	3.9			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
82	Mouse (B6C3F1)	2 years 6 hours/day 5 days/week	Resp		0.44	(chronic active lung inflammation, bronchialization, alveolar proteinosis, fibrosis)	NTP 1996b subsulfide
			Cardio	0.88			
			Gastro	0.88			
			Hepatic	0.88			
			Renal	0.88			
			Endocr	0.88			
			Dermal	0.88			
			Bd Wt	0.88			

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m³)	Serious (mg/m³)	
83	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d	Resp		0.11 M (atrophy of olfactory epithelium)		NTP 1996c sulfate
					0.06 ^d F (chronic active lung inflammation, alveolar proteinosis)		
			Cardio	0.22			
			Gastro	0.22			
			Hemato	0.22			
			Hepatic	0.22			
			Renal	0.22			
			Endocr	0.22			
			Dermal	0.22			
	Bd Wt	0.22					
Immuno/ Lymphoret							
84	Rat (Fischer- 344)	2 yr 5d/wk 6hrs/d			0.5 M (lymphoid hyperplasia in bronchial lymph node)		NTP 1996a oxide
85	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week			0.11 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide
86	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		0.06	0.11 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996c sulfate

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
87	Mouse (B6C3F1)	2 yr 5d/wk 6hrs/d			1	(bronchial lymph node hyperplasia)	NTP 1996a oxide
88	Mouse (B6C3F1)	2 years 6 hours/day 5 days/week			0.44	(lymphoid hyperplasia in bronchial lymph nodes)	NTP 1996b subsulfide
89	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		0.11	0.22	(bronchial lymph node hyperplasia)	NTP 1996c sulfate
Reproductive							
90	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		2			NTP 1996a oxide
91	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week		0.73			NTP 1996b subsulfide
92	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		0.11			NTP 1996c sulfate
93	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		3.9			NTP 1996a oxide
94	Mouse (B6C3F1)	2 years 6 hours/day 5 days/week		0.88			NTP 1996b subsulfide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
95	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		0.22			NTP 1996c sulfate
Cancer							
96	Human	occupa- tional				10 M (CEL: lung and nasal cancers)	Int Committee on Ni Carcinogenesis in Man 1990 soluble and less soluble forms combined
97	Human	occupa- tional				1 (CEL: lung and nasal cancers)	Int Committee on Ni Carcinogenesis in Man 1990 soluble
98	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d				1 M (CEL: alveolar/bronchiolar adenoma or carcinoma)	NTP 1996a oxide
99	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week				0.73 (CEL:alveolar/bronchiolar adenoma or carcinoma)	NTP 1996b subsulfide

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

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form
					Less Serious (mg/m ³)	Serious (mg/m ³)	
100	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d				0.7 (CEL: lung adenomas, adenocarcinomas, squamous cell carcinoma, 14% treated, 1% controls)	Ottolenghi et al. 1974 subsulfide

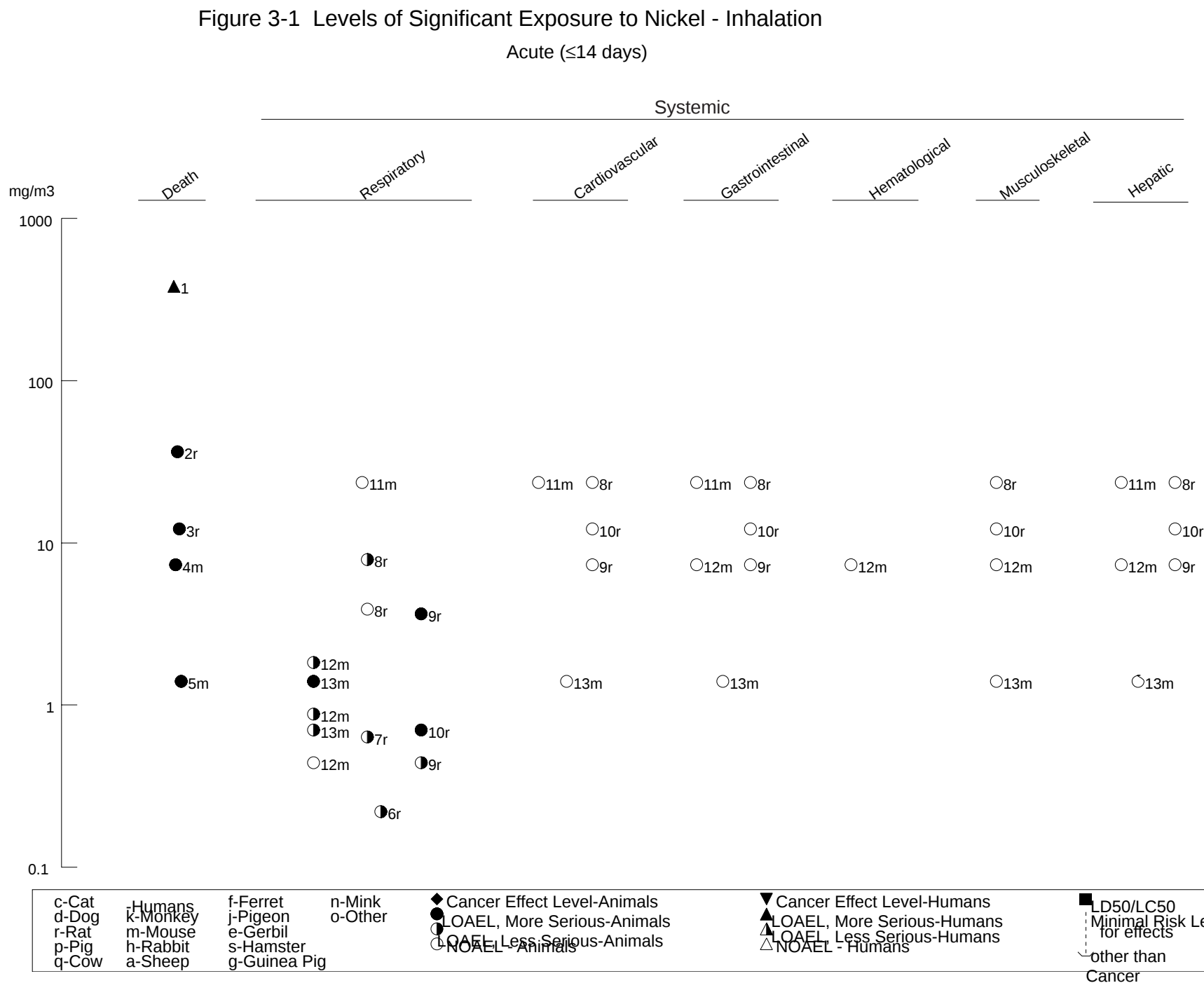
a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.0002 mg Ni/m³ ; concentration adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the Regional Deposited Dose Ratio (RDDR) of 0.474 for the pulmonary region, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to human with dosimetric adjustment, and 10 for human variability).

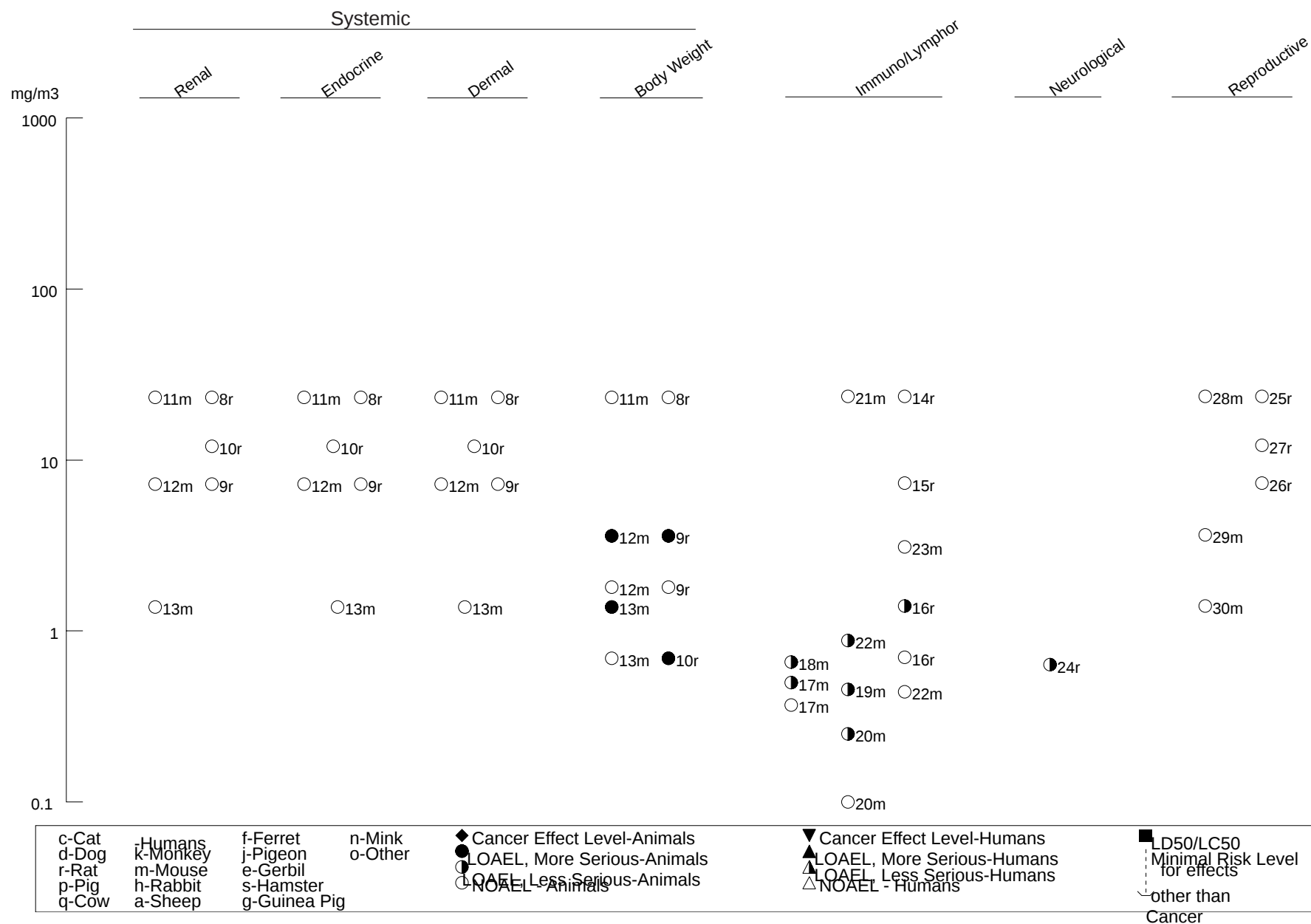
c Used to derive a chronic-duration inhalation minimal risk level (MRL) of 0.00009 mg Ni/m³ ; concentration adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the Regional Deposited Dose Ratio (RDDR) of 0.506 for the pulmonary region, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to human with dosimetric adjustment, and 10 for human variability).

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

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; Ni = nickel; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)



Acute (≤ 14 days)



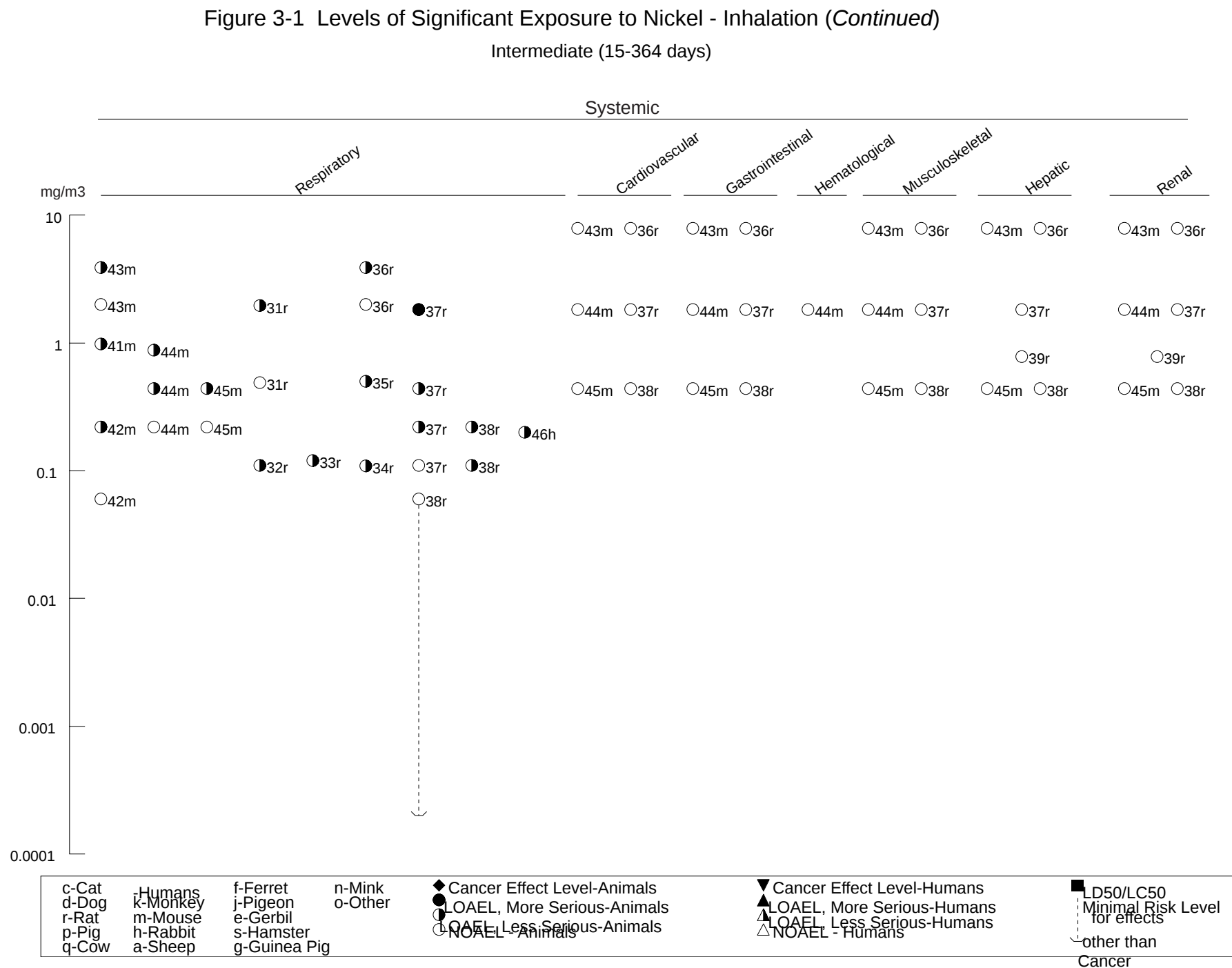
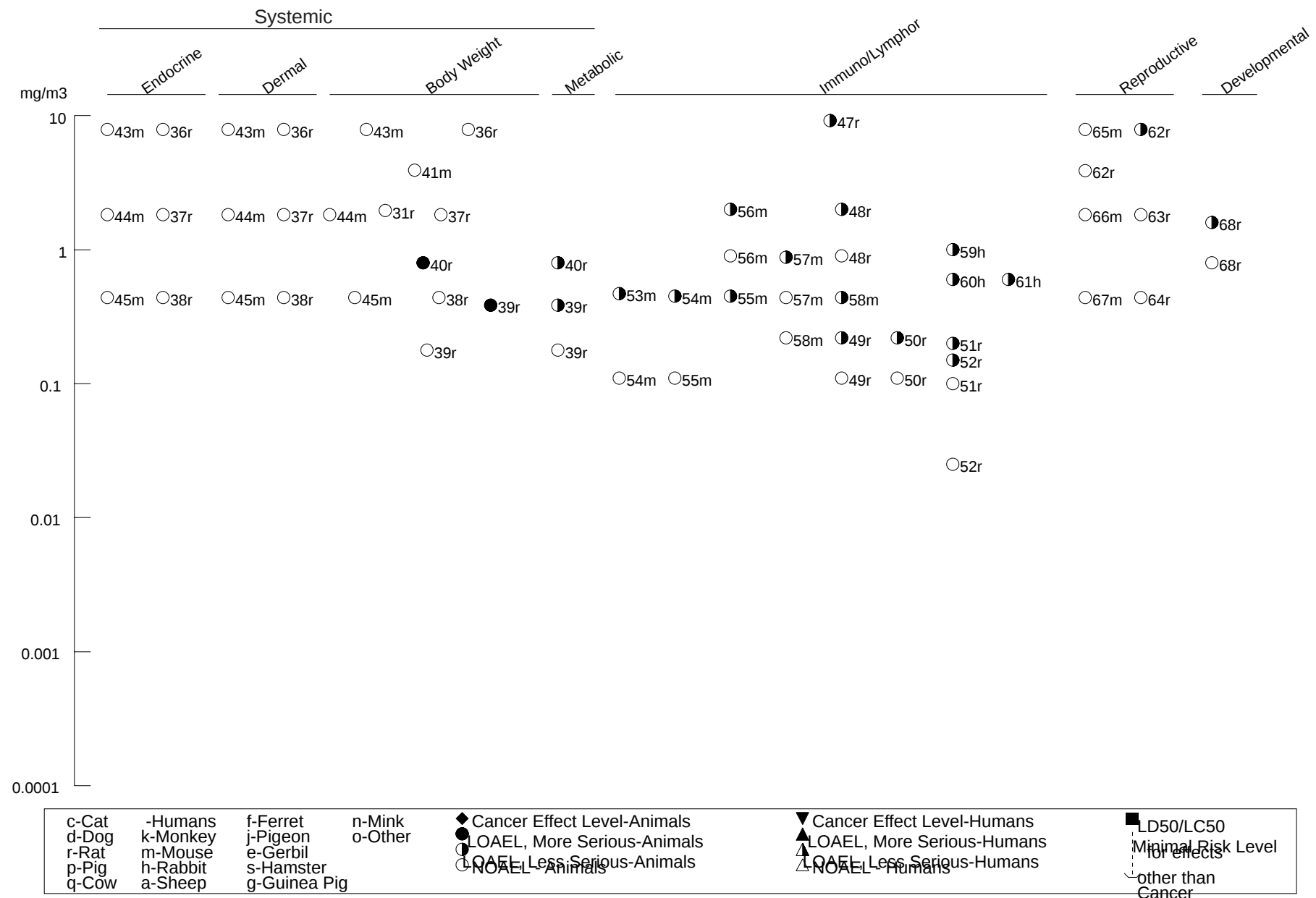


Figure 3-1 Levels of Significant Exposure to Nickel - Inhalation (Continued)
Intermediate (15-364 days)



NICKEL

3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Nickel - Inhalation (*Continued*)

Chronic (≥ 365 days)

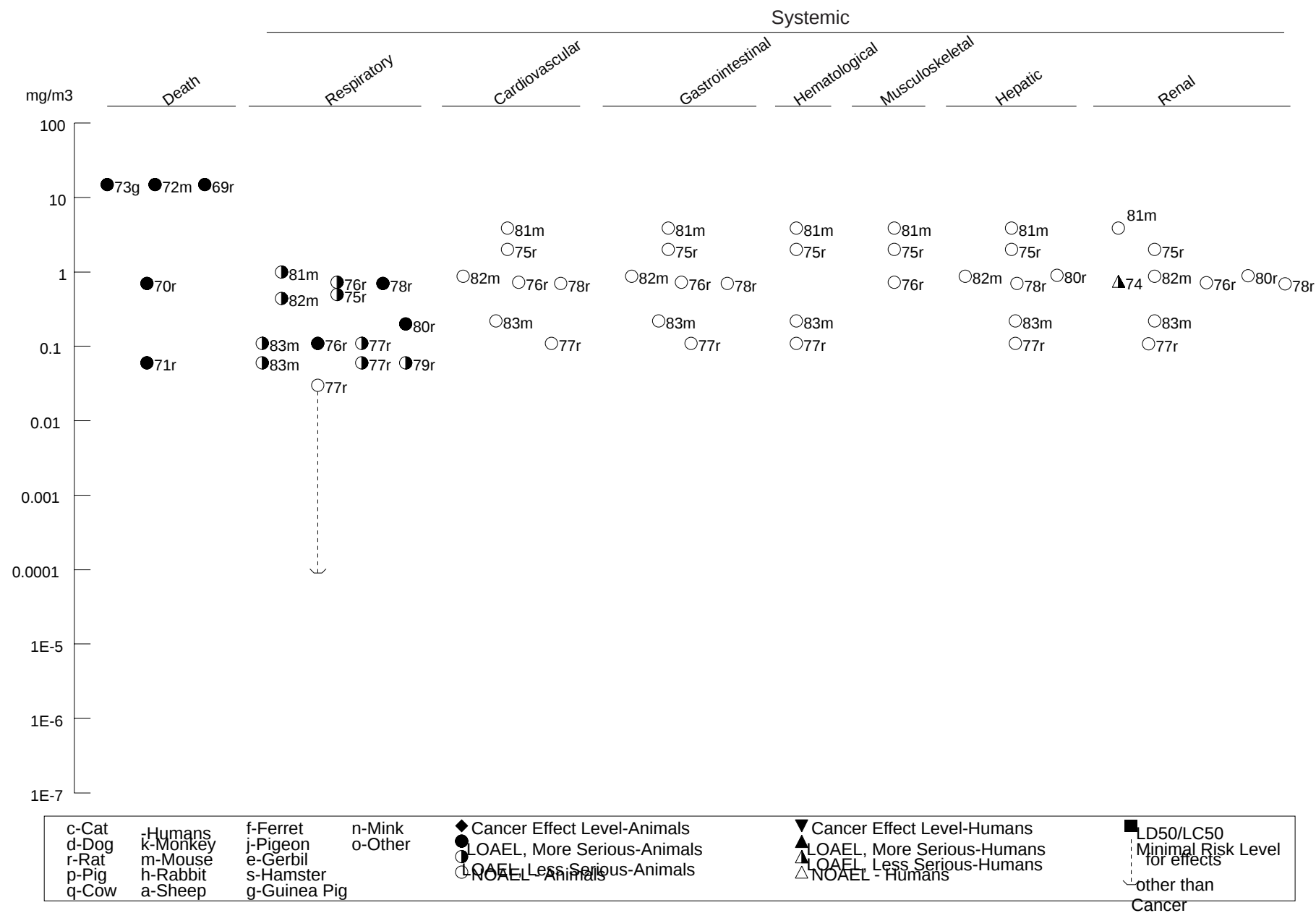
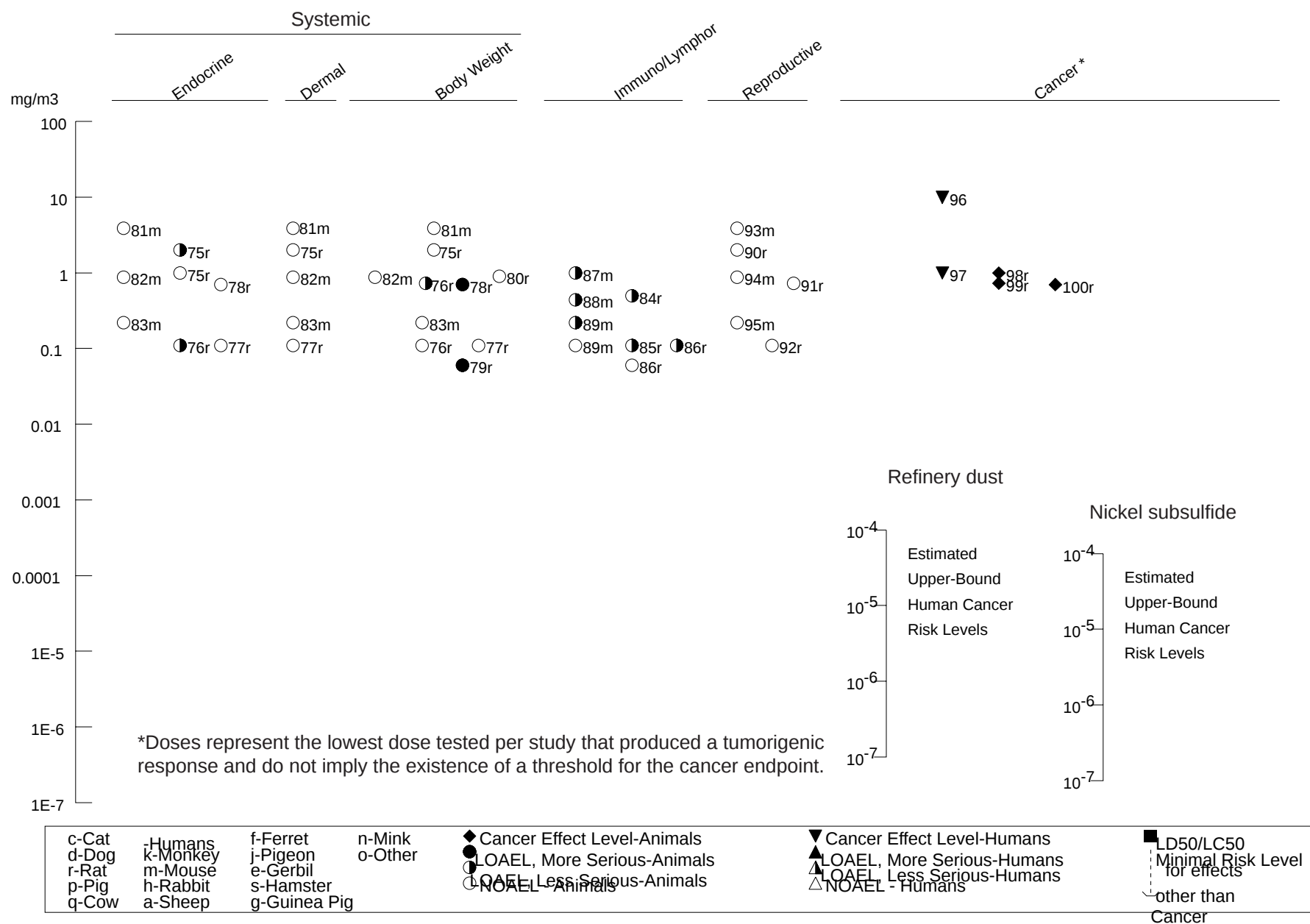


Figure 3-1 Levels of Significant Exposure to Nickel - Inhalation (Continued)

Chronic (≥ 365 days)

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risk of nonmalignant respiratory disease deaths (Moulin et al. 2000; Polednak 1981). A common limitation of the cohort mortality studies is that the number of observed deaths from all causes were lower (in many cases significantly lower) than the number expected deaths, suggesting a healthy worker effect. Additionally, the workers were exposed to other respiratory toxicants; this is particularly true for welders exposed to elevated levels of chromium. A single case of death from adult respiratory distress syndrome has been reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size ($<1.4 \text{ }\mu\text{m}$) (Rendell et al. 1994). Histological changes noted in the lungs of this case included alveolar wall damage, with fibrotic changes, and edema in the alveolar space.

A small number of studies have examined potential respiratory tract effects, not associated with lethality. Reduced vital capacity and expiratory flows were observed in stainless steel welders exposed to elevated levels of nickel and chromium (Kilburn et al. 1990). When the welders were divided into two groups based on smoking status, only the forced expiratory volume (FEV_{75-85}) was significantly different from the referent population, suggesting that current smoking status may have contributed to the observed effects. The study also found that the prevalence of chronic bronchitis was higher in both the current smoker and non-smoker groups, as compared to the referent population. Although this study provides suggestive evidence of respiratory effects in welders, establishing a causal relationship between nickel and the observed effects is limited by co-exposure to chromium and the lack of a comparison group of non-nickel-exposed welders. Examination of chest radiographs of nickel sinter plant workers exposed to nickel at concentrations as high as 100 mg/m^3 did not reveal an increase in small irregular opacities, which would be indicative of inflammatory or fibrogenic response in the lungs (Muir et al. 1993). Another study found an increased risk of moderate pulmonary fibrosis, after controlling for age and smoking, among nickel refinery workers with cumulative exposure to soluble nickel or sulfidic nickel (Berge and Skyberg 2003). A dose-response trend was also found for soluble nickel among cases in the three highest cumulative exposure categories ($0.04\text{--}\leq 0.15$, $0.15\text{--}\leq 0.6$, and $>0.6 \text{ mg/m}^3 \times \text{years}$), after adjusting for age, smoking, and exposure to asbestos. Asthma induced by occupational exposure to nickel has been documented in a small number of individuals (Dolovich et al. 1984; Novey et al. 1983; Shirakawa et al. 1990). The asthma can result from either primary irritation or an allergic response. Interpretation of these data is limited by the small number of cases, as well as by possible exposure to other sensitizing metals.

Studies in rats and mice demonstrate that chronic active inflammation in the lungs is the most prominent effect following inhalation exposure to nickel sulfate, nickel subsulfide, or nickel oxide. In acutely-exposed rats, chronic lung inflammation was observed at the lowest nickel sulfate (0.7 mg Ni/m^3) and

3. HEALTH EFFECTS

nickel subsulfide (0.44 mg Ni/m^3) concentrations tested in 12-day exposure studies (6 hours/day, 12 days in a 16-day period) (NTP 1996b, 1996c). At higher concentrations of nickel sulfate and nickel subsulfide (1.4 and 3.65 mg Ni/m^3 , respectively), the inflammation was accompanied by labored breathing. The chronic active lung inflammation was characterized by focal accumulation of alveolar macrophages and interstitial (nickel subsulfide) or inflammatory cell (nickel sulfate) infiltrates. At the higher concentrations, necrotic cellular debris was also present. Bronchiolar epithelium degeneration was also observed in rats exposed to 0.7 mg Ni/m^3 as nickel sulfate (NTP 1996c). Consistent with these findings, is the observation of alveolitis in rats exposed to 0.22 mg Ni/m^3 as nickel subsulfide 6 hours/day for 7 days (Benson et al. 1995b). Additionally, exposure to 0.95 mg Ni/m^3 as nickel subsulfide resulted in alveolitis and alveolar proteinosis after 4 days of exposure, but not after 1 or 2 days of exposure (Benson et al. 1995b). In contrast, acute lung inflammation, consisting of neutrophilic infiltrates, was first observed in rats exposed to nickel oxide at 7.9 mg Ni/m^3 (NTP 1996a); chronic lung inflammation was not observed at doses as high as 23.6 mg Ni/m^3 . Mice appear to be less sensitive than rats to the acute toxicity of nickel with LOAELs for chronic inflammation of 0.7 , 1.83 , and $>23.6 \text{ mg Ni/m}^3$ as nickel sulfate, nickel subsulfide, and nickel oxide, respectively (NTP 1996a, 1996b, 1996c).

As with acute exposure, chronic lung inflammation was typically observed at the lowest adverse effect level following intermediate-duration exposure. Thirteen-week (6 hours/day, 5 days/week) studies of rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide (NTP 1996a, 1996b, 1996c) identified LOAELs for chronic active lung inflammation of 0.11 , 0.22 , and 3.9 mg Ni/m^3 , respectively; NOAEL values of 0.06 , 0.11 , and 2 mg Ni/m^3 , respectively, were also identified for chronic inflammation. Alveolitis was reported in rats exposed to 0.11 mg Ni/m^3 as nickel sulfate and 1.96 mg Ni/m^3 as nickel oxide for 6 months (6 hours/day, 5 days/week) (Benson et al. 1995a) and interstitial pneumonia was observed at 0.5 mg Ni/m^3 as nickel oxide for 1 month (6 hours/day, 5 days/week) (Horie et al. 1985). A number of other lung effects have also been observed in rats exposed to nickel for intermediate durations. Minimal alveolar macrophage hyperplasia was observed at the lowest nickel sulfate, nickel subsulfide, and nickel oxide concentrations tested (0.03 , 0.11 , and 0.4 mg Ni/m^3 , respectively) (NTP 1996a, 1996b, 1996c). These slight changes in the number of macrophages were not considered adverse because it is considered to be part of the normal physiologic response to inhaled particles and it is not believed to compromise the lung's ability to clear foreign matter. At higher nickel concentrations, mild to moderate changes in alveolar macrophage hyperplasia were found. The effect of nickel on alveolar macrophages is also discussed in Section 3.2.1.3, Immunological and Lymphoreticular Effects. Interstitial infiltrates were observed in rats exposed to ≥ 0.11 or 0.22 mg Ni/m^3 as nickel sulfate or nickel subsulfide (NTP 1996b, 1996c) or 0.109 mg Ni/m^3 as nickel chloride (Bingham et al. 1972), granulomatous inflammation was

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observed in rats exposed to 3.9 mg Ni/m³ as nickel oxide (NTP 1996a), alveolar wall thickening was observed in rats exposed to 0.12 mg Ni/m³ as nickel oxide (Bingham et al. 1972), and hyperplasia of the bronchial epithelium was observed in rats exposed to 0.109 mg Ni/m³ as nickel chloride (Bingham et al. 1972). The highest NOAEL values for respiratory effects in rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for intermediate durations were 0.06 mg Ni/m³ (NTP 1996c), 0.11 mg Ni/m³ (NTP 1996b), and 0.49 mg Ni/m³ (Benson et al. 1995a). An intermediate-duration inhalation MRL was derived from the NOAEL (0.06 mg Ni/m³) and LOAEL (0.11 mg Ni/m³) identified from the NTP (1996c) study of nickel sulfate, as described in the footnote to Table 3-1 and Appendix A.

Similar effects have been observed in mice exposed to nickel for intermediate durations, although the LOAELs for the lung effects tend to be higher suggesting a lower sensitivity compared to rats. Chronic active lung inflammation was observed in mice exposed to ≥ 0.44 and 0.88 mg Ni/m³ as nickel sulfate or nickel subsulfide, respectively (NTP 1996b, 1996c). Lung inflammation was not found in mice exposed to nickel oxide at concentrations as high as 7.9 mg Ni/m³ (NTP 1996a); however, perivascular lymphocyte infiltrates were observed at 3.9 and 7.9 mg Ni/m³ (NTP 1996a). Interstitial pneumonia has also been observed in mice exposed to 0.22 or 0.98 mg Ni/m³ as nickel sulfate or nickel oxide (Benson et al. 1995a). Other lung effects in mice include minimal alveolar macrophage hyperplasia at 0.11, 0.22, or 0.4 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c); interstitial infiltrates at ≥ 0.44 or 0.44 mg Ni/m³ as nickel subsulfide or nickel sulfate, respectively (NTP 1996b, 1996c), and fibrosis at 0.44 and 0.88 mg Ni/m³ as nickel sulfate or nickel subsulfide, respectively (NTP 1996b, 1996c). As with the rats, minimal alveolar macrophage hyperplasia was not considered adverse. The highest NOAEL values for respiratory effects in mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide for intermediate durations were 0.22, 0.22, and 2.0 mg Ni/m³, respectively (NTP 1996a, 1996b, 1996c).

Chronic exposure to nickel (6 hours/day, 5 days/week for 2 years) resulted in chronic active lung inflammation (or pneumonia) in rats and mice at 0.06 mg Ni/m³ as nickel sulfate, in rats at 0.11 mg Ni/m³ and higher as nickel subsulfide (NTP 1996b; Ottolenghi et al. 1990), in mice at 0.44 mg Ni/m³ and higher as nickel subsulfide (NTP 1996b), in rats at 0.2 mg Ni/m³ and higher as nickel oxide (NTP 1996a; Tanaka et al. 1988), and in mice at 1 mg Ni/m³ as nickel oxide (NTP 1996a). Additional lung effects that were found at the same dose levels as inflammation included alveolar epithelium hyperplasia (or bronchialization), fibrosis in rats and mice exposed to nickel subsulfide (NTP 1996b), and bronchialization and/or alveolar proteinosis in mice exposed to nickel oxide (NTP 1996a; Takenaka et al. 1985). With the exception of the NTP (1996c) study of nickel sulfate in rats, NOAEL values for

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respiratory effects following chronic duration exposure were not identified. The NOAEL of 0.03 mg Ni/m³ and LOAEL of 0.06 mg Ni/m³ identified in rats exposed to nickel sulfate (NTP 1996c) were used to derive a chronic-duration inhalation MRL for nickel, as described in the footnote to Table 3-1 and Appendix A.

The NTP (1996a, 1996b, 1996c) studies allow for the comparison of the toxicity of nickel sulfate, nickel subsulfide, and nickel oxide in rats and mice. Following acute- or intermediate-duration exposure, the toxicity of the different nickel compounds is related to its solubility, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The difference in the toxicity across compounds is probably due to the ability of water-soluble nickel compounds to cross the cell membrane and interact with cytoplasmic proteins. In contrast, the severity of inflammatory and proliferative lesions following chronic exposure was greater in rats exposed to nickel subsulfide or nickel oxide, as compared to nickel sulfate. Additionally, parenchymal damage secondary to inflammation was evident in the rats exposed to nickel subsulfide and nickel oxide, but not nickel sulfate. For all durations and nickel compounds tested, rats appear to be more sensitive to the lung effects than mice; significant increases in the incidence of chronic lung inflammation were observed at lower concentrations in the rats than mice. Intermediate-duration studies (Benson et al. 1995a; Horie et al. 1985) that monitored animals for months after exposure termination suggest that nickel-induced lung damage is not readily reversible after exposure termination. In the Benson et al. (1995a) studies, alveolitis was observed in rats exposed to 0.11 mg Ni/m³ as nickel sulfate and 1.96 mg Ni/m³ as nickel oxide at the end of the 6-month exposure period and 4 months after exposure termination. Horie et al. (1985) reported interstitial pneumonia in rats exposed 6 hours/day, 5 days/week to 0.5 mg Ni/m³ as nickel oxide for 1 month. Twelve and 20 months after termination of exposure to 6.3 mg Ni/m³, squamous metaplasia of the bronchial epithelium, hyperplasia of the bronchial gland, and chronic bronchitis were observed.

In addition to the lung effects, several studies have demonstrated that exposure to nickel sulfate or nickel subsulfide can induce atrophy of the nasal olfactory epithelium (Evans et al. 1995; NTP 1996b, 1996c). The nasal lesions are typically observed at higher concentrations than the lung effects. In a study designed specifically to examine the effects of nickel on the olfactory system, rats were exposed to nickel sulfate at 0 or 0.635 mg Ni/m³ 6 hours/day for 16 days (Evans et al. 1995). Histological changes in the olfactory epithelium of exposed rats included a slight reduction in the number of bipolar sensory receptor cells, a decrease in the thickness of the olfactory epithelium resulting from a loss of sustentacular cells, a thinning of apical cytoplasm, and a reduction in the number of sensory cilia on the surface of the cells.

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After a recovery period of 22 days, fewer sensory cilia was the only change that remained, indicating that the effects of an intermediate-duration exposure to nickel were reversible.

Cardiovascular Effects. No increases in the number of deaths from cardiovascular diseases were reported in workers exposed to nickel (Cornell and Landis 1984; Cox et al. 1981; Cragle et al. 1984).

Microscopic examinations of the hearts of rats and mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 12 6-hour exposures over 16 days did not reveal any changes at concentrations as high as 12.2, 7.33, or 23.6 mg Ni/m³, respectively, in rats and 1.4, 7.33, or 23.6 mg Ni/m³, respectively, in mice (NTP 1996a, 1996b, 1996c). No cardiovascular effects were observed in rats or mice exposed to 0.44, 1.83, or 7.9 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Similarly, chronic exposure (6 hours/day, 5 days/week) of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m³, respectively, or exposure of mice to 0.22, 0.88, or 3.9 mg Ni/m³, respectively, did not result in microscopic changes in the heart (NTP 1996a, 1996b, 1996c). Intermittent exposure (6 hours/day, 5 days/week) of rats to 0.7 mg Ni/m³ as nickel subsulfide for 78 weeks also did not affect the microscopic appearance of the heart (Ottolenghi et al. 1974).

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

Microscopic examinations of the gastrointestinal tract of mice and rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 12 6-hour exposures did not reveal any changes at concentrations as high as 12.2, 7.33, or 23.6 mg Ni/m³, respectively, in rats and 1.4, 7.33, or 23.6 mg Ni/m³, respectively, in mice (NTP 1996a, 1996b, 1996c). Likewise, no histological alterations were observed in the gastrointestinal tracts of rats and mice exposed to 0.44, 1.83, or 7.9 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m³, respectively, or exposure of mice to 0.22, 0.88, or 3.9 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, did not result in microscopic changes in the gastrointestinal tract (NTP 1996a, 1996b, 1996c). Intermittent exposure (6 hours/day, 5 days/week) of rats to 0.7 mg Ni/m³ as nickel subsulfide for 78 weeks also did not affect the microscopic appearance of the intestines (Ottolenghi et al. 1974).

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Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to nickel.

A number of hematological alterations were observed in studies by Weischer et al. (1980) and NTP (1996a, 1996b, 1996c). A decrease in hematocrit level was observed in male rats continuously exposed to 0.178 or 0.385 mg Ni/m³ as nickel oxide for 28 days (Weischer et al. 1980); no significant alterations were observed at 0.785 mg Ni/m³. The biological significance of a decrease in hematocrit level in the absence of hemoglobin or erythrocyte alterations is not known. In non-pregnant females continuously exposed to nickel oxide for 21 days, increases in hematocrit and hemoglobin levels were observed at 0.8 mg Ni/m³ and higher; an increase in mean cell volume and a decrease in erythrocyte levels were observed at 1.6 mg Ni/m³ and higher (Weischer et al. 1980). Similarly, increases in hematocrit, hemoglobin, and erythrocyte levels were observed in rats exposed to nickel subsulfide at 0.73 mg Ni/m³ 6 hours/day, 5 days/week for 2 years (NTP 1996b). As noted by NTP (1996b), increases in hematocrit, hemoglobin, and erythrocytes are consistent with erythropoietin production in response to tissue hypoxia, possibly as a result of the nickel-induced lung damage. Chronic exposure of rats to nickel oxide or nickel sulfate at concentrations up to 2 or 0.11 mg Ni/m³, respectively, and chronic exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m³, respectively, did not result in significant hematological effects (NTP 1996a, 1996b, 1996c).

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

No histological alterations were observed in bone of rats and mice exposed to nickel sulfate 6 hours/day for 12 days/16 days (highest NOAEL is 12.2 mg Ni/m³), 5 days/week for 13 weeks (0.44 mg Ni/m³), or 5 days/week for 2 years (0.11 and 0.22 mg Ni/m³ for rats and mice) (NTP 1996c); the muscles were not examined histologically in these studies. No alterations were observed in bone or muscle of rats and mice exposed to nickel oxide (6 hours/day, 5 days/week) at 23.6 mg Ni/m³ for 16 days (12 days/16 days), 7.9 mg Ni/m³ for 13 weeks, or 2 (rats) or 3.9 mg Ni/m³ (mice) for 2 years (NTP 1996a). Similarly, exposure to nickel subsulfide 6 hours/day, 5 days/week did not result in alterations in bone or muscle in rats at 7.33 mg Ni/m³ for 13 weeks or 0.73 mg Ni/m³ for 2 years or mice at 7.33 mg Ni/m³ for 16 days, 1.83 mg Ni/m³ for 13 weeks, or 0.88 mg Ni/m³ (mice) for 2 years (NTP 1996b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to nickel.

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No histological alterations were observed in the livers of rats or mice exposed to nickel subsulfide, nickel sulfate, or nickel oxide at concentrations of 7.33, 12.2, or 23.6 mg Ni/m³, respectively, in rats and 1.4, 12.2, or 23.6 mg Ni/m³, respectively, in mice exposed 6 hours/day, 12 days in a 16-day period (NTP 1996a, 1996b, 1996c) or 1.83, 0.44, or 7.9 mg Ni/m³ 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Following chronic exposure, no histological changes were observed in the livers of rats exposed to nickel subsulfide at 0.7 mg Ni/m³ (Ottolenghi et al. 1974) or 0.73 mg Ni/m³ (NTP 1996b), to nickel oxide at 0.9 mg Ni/m³ (Tanaka et al. 1988) or 2 mg Ni/m³ (NTP 1996a), or to nickel sulfate at 0.11 mg Ni/m³ (NTP 1996c). Chronic exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m³, respectively, did not result in microscopic changes in the liver (NTP 1996a, 1996b, 1996c).

Renal Effects. Marked tubular necrosis was observed in the kidneys of a man who died of adult respiratory distress syndrome 13 days after a 90-minute exposure to a very high concentration (382 mg/m³) of metallic nickel of small particle size (<1.4 µm) (Rendall et al. 1994). Several days after the exposure, urinary concentrations of nickel were 700 µg/L, in comparison to levels of <0.1–13.3 µg/L in persons not occupationally exposed to nickel (Sunderman 1993).

In nickel refinery workers, a significant association was found between increased levels of nickel in urine and increased urinary β₂-microglobulin levels (Sunderman and Horak 1981). A significant increase in urinary β₂-microglobulin levels was observed in a group of workers with urinary nickel levels exceeding 100 µg/L; urinary β₂-microglobulin levels were not significantly altered in workers with urine nickel levels of less than 100 µg/L. Urinary levels of total proteins, β₂-microglobulin, retinol binding protein, and *N*-acetyl-β-D-glucosaminidase (NAG) were increased in 12 women, and urinary lysozyme and NAG were increased in 14 men occupationally exposed to soluble nickel (sulfate, chloride) compounds at an average concentration of 0.75 mg Ni/m³ (Vyskocil et al. 1994a). Although the average exposure concentration was the same for women and men, women were more highly exposed as indicated by urine concentrations of 10.3 µg Ni/g creatinine in women compared to 5 µg Ni/g creatinine in men. The markers that were changed reflected tubular dysfunction. No effects on markers of glomerular function, urinary albumin levels, or transferrin levels were noted. Sanford and Nieboer (1992) did not find significant alterations in urinary β₂-microglobulin levels in nickel refinery workers with urine nickel levels of less than 60 µg/L. Sanford and Nieboer (1992) noted that elevated urinary β₂-microglobulin levels were found in spot urine samples of three workers; however, when the levels were averaged over

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three or more voids, the average levels were within the normal range. A study of 17 electroforming workers did not find evidence of proteinuria (Wall and Calnan 1980).

No histological alterations were observed in the kidneys of rats or mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide 6 hours/day, 5 days/week, at concentrations of ≤ 12.2 , 7.33, or 23.6 mg Ni/m³, respectively, for 16 days (12 days in a 16-day period) (NTP 1996a, 1996b, 1996c), or ≤ 0.44 , 1.83, or 7.9 mg Ni/m³, respectively, for 13 weeks (NTP 1996a, 1996b, 1996c), or 0.9 mg Ni/m³ as nickel oxide for 12 months (Tanaka et al. 1988). Chronic exposure of rats to nickel oxide (NTP 1996a; Tanaka et al. 1988), nickel subsulfide (NTP 1996b), or nickel sulfate (NTP 1996c) at concentrations up to 2, 0.73, or 0.11 mg Ni/m³, respectively, did not result in histological alterations in the kidneys. Additionally, no alterations were observed in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m³, respectively (NTP 1996a, 1996b, 1996c).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to nickel.

Histological examinations did not reveal any changes in the adrenal glands, pancreas, parathyroid, pituitary, or thyroid glands in rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 6-hour exposures over 16 days or for 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). The NOAEL values for endocrine effects were 12.2, 23.6, and 7.33 mg Ni/m³ in rats and mice exposed to nickel sulfate, nickel oxide, and nickel subsulfide, respectively, for the shorter duration study and 0.44, 7.9, and 1.83 mg Ni/m³, respectively, for the 13-week study. In rats exposed intermittently to nickel subsulfide at 0.7 mg Ni/m³ for 78 weeks, no histological changes were observed in the thyroid or adrenal glands (Ottolenghi et al. 1974). Adrenal medulla hyperplasia and increased incidences of benign pheochromocytoma were observed in female rats exposed to 2 mg Ni/m³ as nickel oxide (NTP 1996a) and male and female rats exposed to 0.73 mg Ni/m³ as nickel subsulfide for 2 years (NTP 1996b); an increased incidence of benign pheochromocytoma was also observed in male rats exposed to 0.11 mg Ni/m³ as nickel subsulfide. These effects were not observed in rats exposed chronically to nickel sulfate at concentrations up to 0.11 mg Ni/m³, or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations of 3.9, 0.88, or 0.22 mg Ni/m³, respectively (NTP 1996a, 1996b, 1996c).

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure. However, contact dermatitis in persons exposed to nickel compounds is one of the most

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common effects of nickel exposure (see Section 3.2.3.2). In addition, immunological studies indicate that the dermatitis is an allergic response to nickel, and significant effects on the immune system have been noted in workers exposed to nickel (see Section 3.2.1.3).

Microscopic changes in the skin were not observed in rats or mice exposed to nickel as nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 12.2, 7.33, or 23.6 mg Ni/m³, respectively, for 6 hours/day for 12 days in a 16-day period (NTP 1996a, 1996b, 1996c) or 0.44, 1.83, or 7.9 mg Ni/m³ 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m³, respectively, or exposure of mice at concentrations up to 0.22, 0.88, or 3.9 mg Ni/m³, respectively, did not result in microscopic changes in the skin (NTP 1996a, 1996b, 1996c).

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to nickel. Significant decreases in body weight gain have been observed in rats and mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide for acute, intermediate, and chronic exposure durations. In many of the studies, the decreases in body weight gain were associated with lung inflammation, impaired lung function (as evidenced by labored breathing), and lethality. Exposure to nickel sulfate resulted in serious decreases in body weight gain (terminal body weights >25% lower than controls) in rats exposed to 0.7 mg Ni/m³ and higher and in mice exposed to 1.4 mg Ni/m³ 6 hours/day for 12 days in a 16-day period (NTP 1996c); no significant alterations in body weight gain were observed in mice exposed to 0.7 mg Ni/m³. No significant alterations in body weight gain were observed in rats or mice exposed to 0.44 mg Ni/m³ for 13 weeks (NTP 1996c), rats exposed to 0.11 mg Ni/m³ for 2 years (NTP 1996c), or mice exposed to 0.22 mg Ni/m³ for 2 years (NTP 1996c).

For nickel subsulfide, serious decreases in body weight gain (22–28%) and emaciation were observed in rats and mice, respectively, exposed to 3.65 mg Ni/m³ for 6 hours/day for 12 days in a 16-day period (NTP 1996b); a NOAEL of 1.85 mg Ni/m³ was also identified. No alterations in body weight were observed at 1.83 mg Ni/m³ 6 hours/day, 5 days/week for 13 weeks. Exposure to approximately 0.7 mg Ni/m³ for 6 hours/day, 5 days/week for a chronic-duration resulted in 11–30% decreases in body weight gains in rats (NTP 1996b; Ottolenghi et al. 1974). No alterations were observed in mice exposed to 0.88 mg Ni/m³ for 6 hours/day, 5 days/week for 2 years (NTP 1996b).

Most studies did not find significant alterations in rats and mice exposed to nickel oxide. A NOAEL of 23.6 mg Ni/m³ was identified in rats and mice exposed to 23.6 mg Ni/m³ 6 hours/day for 12 days in a

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16-day period (NTP 1996a). For intermediate exposure, NOAELs of 1.9–7.9 mg Ni/m³ were identified in rats and mice (Benson et al. 1995a; NTP 1996a). However, Weischer et al. (1980) reported 30–36% decreases in body weight gain in male and female rats exposed to 0.385 or 0.8 mg Ni/m³, respectively, continuously for 21–28 days. In pregnant rats, an 11% decrease in body weight gain was observed at 0.8 mg Ni/m³ compared to the 36% decrease observed in similarly exposed non-pregnant rats. NTP (1996a) did not find significant alterations in body weight gain in rats and mice exposed to 2 or 3.9 mg Ni/m³, respectively, 6 hours/day, 5 days/week for 2 years; a NOAEL of 0.9 mg Ni/m³ was also identified in rats exposed 7 hours/day, 5 days/week for 12 months (Tanaka et al. 1988). In contrast, Takenaka et al. (1985) reported weight loss in rats continuously exposed to 0.06 mg Ni/m³ for 31 months; the weight loss began after 13 months of exposure. These data suggest that continuous exposure is more toxic than intermittent exposure (duration adjusted NOAEL from the rat NTP study is 0.36 mg Ni/m³). Continuous exposure would result in higher lung burdens than intermittent exposure, which would lead to increased lung damage.

Metabolic Effects. No studies were located regarding metabolic effects in humans after inhalation exposure to nickel.

Significant increases in serum glucose levels were observed in male rats continuously exposed to 0.385 or 0.784 mg Ni/m³ as nickel oxide for 28 days (Weischer et al. 1980). In females rats continuously exposed to nickel oxide, decreases in serum glucose levels were observed at 0.8 and 1.6 mg Ni/m³; at 3.2 mg Ni/m³, serum glucose levels did not significantly differ from controls (Weischer et al. 1980). These data suggest that there may be a gender difference. Although no adverse pancreatic effects have been noted in inhalation studies, a single-dose intravenous injection study has reported increases in serum glucose levels and effects on pancreatic cells in rabbits at doses of 4.5–9 mg Ni/kg as nickel chloride (Kadota and Kurita 1955); Weischer et al. (1980) also found increases in serum glucose levels in male rats exposed to nickel chloride in water for 28 days. It is possible that changes in serum glucose levels reflect an effect on the pancreas or may be secondary to the marked decrease in body weight gain also observed in the Weischer et al. (1980) study.

3.2.1.3 Immunological and Lymphoreticular Effects

A number of immunological and lymphoreticular effects have been reported in humans and animals exposed to nickel. In 38 production workers exposed to nickel (compound not specified), significant increases in levels of immunoglobulin G (IgG), IgA, and IgM and a significant decrease in IgE levels

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were observed (Bencko et al. 1983, 1986). Significant increases in other serum proteins, which may be involved in cell-mediated immunity (including α_1 -antitrypsin, α_2 -macroglobulin, ceruloplasmin), were also observed. The increase in immunoglobulins and serum proteins suggests that the immune system was stimulated by nickel exposure. Similar but less-pronounced effects were observed in workers exposed to cobalt. A relationship between nickel and cobalt sensitization is further supported by the finding that nickel-reactive IgE antibodies were observed in eight patients with hard-metal asthma induced by cobalt exposure (Shirakawa et al. 1990). Exposure levels were not reported.

Alterations in innate (or non-specific) and acquired immunity have been observed in animals. Several studies examined alveolar macrophage functions. A significant reduction in macrophage phagocytic activity was observed in rats exposed to an unspecified concentration of nickel chloride for 2 hours (Adkins et al. 1979) or in mice exposed to 0.47 mg Ni/m³ as nickel oxide or 0.45 mg Ni/m³ as nickel subsulfide 6 hours/day, 5 days/week for 65 days (Haley et al. 1990). No alteration of macrophage phagocytic activity was observed in mice exposed to ≤ 0.45 mg Ni/m³ as nickel sulfate 6 hours/day, 5 days/week for 65 days (Haley et al. 1990). Other alveolar macrophage alterations include decreased lysozyme activity in rabbits exposed to 0.6 mg Ni/m³ as nickel chloride 6 hours/day, 5 days/week for 4–6 weeks (Bingham et al. 1987; Johansson et al. 1987, 1988a, 1989), alterations in macrophage production of tumor necrosis factor (Goutet et al. 2000; Morimoto et al. 1995), and morphological alterations. Morimoto et al. (1995) found increased production of tumor necrosis factor in rats exposed to 9.2 mg Ni/m³ as nickel oxide 8 hours/day, 5 days/week for 4 weeks. In contrast, Goutet et al. (2000) found a decrease in tumor necrosis factor production in rats following a single intratracheal instillation of nickel sulfate. The conflicting results may be due to exposure route, duration, or concentration differences between the studies. Alveolar macrophages from rabbits exposed to 1 mg Ni/m³ as metallic nickel 6 hours/day, 5 days/week for 3–6 months (Johansson et al. 1980) or 0.6 mg Ni/m³ as nickel chloride 6 hours/days, 5 days/week for 4–6 weeks (Johansson et al. 1987) or 4 months (Johansson et al. 1988a, 1989) had increases in membrane-bound lamellar bodies. Exposure to metallic nickel also resulted in macrophages with smooth surfaces; the frequency of occurrence was duration-related (Johansson et al. 1980).

Several studies have examined the relationship between nickel exposures and acquired immune function. An increase in susceptibility to *Streptococci* infection was observed in mice exposed to 0.499 mg Ni/m³ as nickel chloride or 0.455 mg Ni/m³ as nickel sulfate for 2 hours (Adkins et al. 1979); mice exposed to 0.657 mg Ni/m³ as nickel chloride also developed septicemia from the *Streptococci* infection and had a reduced ability to clear the inhaled bacteria (Adkins et al. 1979). Other studies have found an impaired

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response to sheep red blood cells (decrease in the number of antibody production spleen cells) in mice exposed to 0.25 mg Ni/m³ as nickel chloride for 2 hours (Graham et al. 1978) or rats continuously exposed to 0.2 mg Ni/m³ as nickel oxide for 4 weeks or 0.15 mg Ni/m³ for 4 months (Spiegelberg et al. 1984). A decreased resistance to a tumor challenge was also observed in mice exposed to 0.45 mg Ni/m³ as nickel sulfate 6 hours/day, 5 days/week for 65 days (Haley et al. 1990).

A significant portion of nickel that is removed from the lung enters the lymphatic system, often inducing damage to the lymph nodes. Lymphoid hyperplasia in the bronchial and mediastinal lymph nodes was observed in rats exposed to 1.4 mg Ni/m³ as nickel sulfate (NTP 1996c) or mice exposed to 0.88 mg Ni/m³ as nickel subsulfide (NTP 1996b) 6 hours/day for 12 days in a 16-day period; no effects were observed in rats exposed to 7.33 mg Ni/m³ as nickel subsulfide (NTP 1996b), rats and mice exposed to 23.5 mg Ni/m³ as nickel oxide (NTP 1996a), and mice exposed to 3.1 mg Ni/m² as nickel sulfate (NTP 1996c). In intermediate-duration studies, a 6 hour/day, 5 day/week exposure resulted in lymphoid hyperplasia in bronchial lymph nodes of rats exposed to 0.22, 0.22, or 2 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.44, 0.88, or 2 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c). Similarly, lymphoid hyperplasia was observed in the bronchial lymph nodes of rats exposed to 0.11, 0.11, or 0.5 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.22, 0.44, or 1 mg Ni/m³ as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c).

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

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to nickel.

Microscopic examinations did not reveal any changes in the whole brains of rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 6-hour exposures over 16 days (NTP 1996a, 1996b, 1996c). The maximum concentrations that did not result in deaths or changes in brain histology were 3.1, 23.6, and 7.33 mg Ni/m³ in rats for nickel sulfate, nickel oxide, and nickel subsulfide, respectively, and 0.7, 23.6, and 3.65 mg/m³ in mice for nickel sulfate, nickel oxide, and nickel subsulfide, respectively. In intermediate-duration studies, no histological alterations were observed in the whole

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brains of rats and mice exposed to 0.44, 7.9, or 1.83 mg Ni/m³ as nickel sulfate, nickel oxide, or nickel subsulfide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). In rats exposed intermittently (6 hours/day, 5 days/week) to nickel subsulfide at 0.7 mg Ni/m³ for 78 weeks, histological changes were not observed in the brain (Ottolenghi et al. 1974). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m³, respectively, or exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m³, respectively, did not result in microscopic changes in the whole brain (NTP 1996a, 1996b, 1996c).

As noted in Section 3.2.1.2, atrophy of the olfactory epithelium has been observed in rats exposed to nickel sulfate and nickel subsulfide (Evans et al. 1995; NTP 1996a, 1996b, 1996c). To determine if changes in the olfactory epithelium result in any functional changes, Evans et al. (1995) completed behavioral studies of olfactory absolute threshold and olfactory discrimination in rats exposed to nickel sulfate at 0.635 mg/m³ 6 hours/day for 16 days. Although histological changes were observed in the olfactory epithelium, including atrophy and a decrease in the number of bipolar receptor cells, no functional changes were noted. Carnosine, a neurochemical marker, was reduced in the olfactory epithelium following 12 days of exposure but was back to control levels by exposure day 16, suggesting adaptation to nickel exposure.

The LOAEL value from the Evans et al. (1995) study is recorded in Table 3-1 and plotted in Figure 3-1; the NOAELs for histological alterations in the brain were not recorded in the LSE table because this is not a sensitive indicator of functional neurotoxicity.

3.2.1.5 Reproductive Effects

An increase in the rate of spontaneous abortions (15.9%) was reported among a group of 356 women who worked in a nickel hydrometallurgy refining plant in the Arctic region of Russia as compared to the rate (8.5%) in 342 local female construction workers (Chashschin et al. 1994). Exposure concentrations were 0.08–0.196 mg Ni/m³, primarily as nickel sulfate, and nickel concentrations in the urine were 3.2–22.6 µg/L. Nickel levels in the urine of persons not occupationally exposed are generally <0.1–13.3 µg/L (Sunderman 1993). The investigators noted that the nickel-exposed women manually lifted heavy nickel anodes and that they may have experienced heat stress. These confounders, plus the lack of information on the selection of control group subjects, possible acute exposure to high concentrations of chlorine, and the lack of adequate control of possible confounding variables such as smoking habits, use of alcohol, and

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intercurrent disease, preclude establishing a causative relationship between nickel exposure and reproductive toxicity from this study.

Testicular degeneration was observed in rats and mice exposed to nickel sulfate (≥ 1.4 mg Ni/m³) and nickel subsulfide (≥ 1.83 mg Ni/m³ for rats and ≥ 3.65 mg Ni/m³ for mice) 6 hours/day for 12 days over a 16-day period (NTP 1996a, 1996b, 1996c). The study authors indicated that testicular lesions were probably the result of emaciation rather than a direct effect of nickel. In intermediate-duration studies, sperm concentration was decreased by 21% in rats exposed to nickel oxide at 7.9 mg Ni/m³, with no effects at 3.9 mg/m³ (NTP 1996a). No effects on sperm motility, morphology, or concentration were observed in rats exposed to nickel subsulfide or nickel sulfate at concentrations up to 1.83 and 0.44 mg Ni/m³, respectively, or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 7.9, 1.83, or 0.44 mg Ni/m³, respectively (NTP 1996a, 1996b, 1996c). Histological changes in the testes were not observed. No effect on the length of the estrous cycle was noted in mice or rats exposed to nickel sulfate at ≤ 0.44 mg Ni/m³, nickel oxide at ≤ 7.9 mg Ni/m³, or nickel subsulfide at ≤ 1.83 mg Ni/m³ 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m³, respectively, and exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m³, respectively, did not result in microscopic changes in the reproductive organs (NTP 1996a, 1996b, 1996c).

The highest NOAEL values from each reliable study for reproductive effects in each species, duration category, and nickel compound and the LOAEL for decreased sperm concentration in rats exposed to nickel oxide are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

In addition to the reproductive effects, Chashschin et al. (1994) also reported an increase in the incidence of structural malformations (16.9%) in the offspring of female nickel hydrometallurgy refining plant workers as compared to the incidence (5.8%) in the female construction workers. Although the specific structural malformations found were not stated, the investigators note that relative risks were 2.9 for all kinds of defects, 6.1 for cardiovascular system defects, and 1.9 for musculoskeletal defects. Exposure concentrations were 0.08–0.196 mg Ni/m³, primarily as nickel sulfate, and nickel concentrations in the urine were 3.2–22.6 µg/L. Nickel levels in the urine of persons not occupationally exposed are generally < 0.1 –13.3 µg/L (Sunderman 1993). As discussed under Reproductive Effects, a number of possible

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confounders including heavy lifting, possible heat stress, lack of information on the selection of control group subjects, possible acute exposure to high concentrations of chlorine, and the lack of adequate control of possible confounding variables such as smoking habits, use of alcohol, and intercurrent disease, preclude establishing a causative relationship between nickel exposure and developmental toxicity from this study.

A decrease in fetal body weight was observed in the offspring of rats exposed to 1.6 mg Ni/m³ as nickel oxide 23.6 hours/day on gestation days 1–21 (Weischer et al. 1980). No effect on fetal body weight was observed at 0.8 mg Ni/m³, although decreased maternal body weight gain was observed at this concentration. No effects on the number of fetuses or on the weight of placenta were observed.

The NOAEL value and the LOAEL value from the Weischer et al. (1980) study are recorded in Table 3-1 and plotted Figure 3-1.

3.2.1.7 Cancer

A large number of epidemiology studies have assessed the carcinogenic potential of nickel; it has been estimated that over 100,000 nickel workers have been examined in epidemiology studies (Seilkop and Oller 2003). These workers have been employed in nickel refinery facilities, nickel mining and smelting facilities, nickel alloy production facilities, stainless steel production facilities, nickel-cadmium battery production facilities, or as stainless steel welders. In the mid 1980s, a committee of epidemiologists was formed to investigate the human health risks associated with nickel exposure and to determine the specific forms of nickel that are associated with an increased risk of respiratory cancer (International Committee on Nickel Carcinogenesis in Man 1990). The investigators updated the existing data from 10 previously examined cohorts and estimated levels of exposure to various nickel species. Since no measurements of nickel concentrations were available for workers employed prior to 1950, the investigators estimated total nickel exposure levels using recent monitoring data and historical data on the industrial processes. Based on information on the chemistry of the industrial process, total nickel exposure levels were divided into exposure to four nickel species: soluble nickel (including nickel sulfate and nickel chloride), sulfidic nickel (including nickel subsulfide), oxidic nickel, and metallic nickel. It is noted that interpretation of the results of many of the epidemiology studies of nickel workers is confounded by poor nickel exposure characterization, exposure to relatively high concentrations of other metals, including arsenic, and in some cases, exposure to irritant gases including hydrogen sulfide, ammonia, chlorine, and sulfur dioxide (IARC 1990).

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Statistically significant increases in the risk of nasal and/or lung cancer were found among nickel refinery workers (Andersen et al. 1996; Anttila et al. 1998; Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; Grimsrud et al. 2003; International Committee on Nickel Carcinogenesis in Man 1990; Karjalainen et al. 1992; Magnus et al. 1982; Muir et al. 1994; Pedersen et al. 1973; Peto et al. 1984; Roberts et al. 1989a). In general, the nickel refinery workers were exposed to high levels of sulfidic and oxidic nickel and low levels of soluble and metallic nickel (International Committee on Nickel Carcinogenesis in Man 1990). At one nickel refinery facility (New Caledonia), the risk of respiratory tract cancers was not significantly elevated in the nickel-exposed workers (Goldberg et al. 1987, 1994; International Committee on Nickel Carcinogenesis in Man 1990). This refinery facility differs from other refineries in that the workers were primarily exposed to silicate oxide ore and oxidic nickel with very little exposure to sulfidic or soluble nickel. Sunderman and associates (Sunderman et al. 1989a) examined the histopathological diagnosis of 100 cases of sinonasal cancer and 259 cases of lung cancer among workers at three nickel refinery facilities. The primary sinonasal cancers were squamous cell carcinomas (48%), anaplastic and undifferentiated carcinomas (39%), and adenocarcinomas (6%). In an analysis of lung cancer, the cancers were primarily squamous cell carcinomas (67%), anaplastic, small cell, and oat cell carcinomas (15%), and adenocarcinomas (8%). The types of sinonasal and lung cancers were similar to those found in the general population, suggesting a lack of nickel-specific tumor types.

In contrast to the findings of nickel refinery workers, most studies in other groups of nickel workers have not found significant increases in the risk of lung cancer among workers employed in nickel mining and smelting facilities (International Committee on Nickel Carcinogenesis in Man 1990; Shannon et al. 1984b, 1991), workers employed at a hydrometallurgical refinery (Egedahl and Rice 1984, Egedahl et al. 1991, 2001), workers employed at nickel alloy and stainless steel production facilities (Cornell 1984; Cornell and Landis 1984; Cox et al. 1981; Enterline and March 1982; International Committee on Nickel Carcinogenesis in Man 1990; Jakobsson et al. 1997; Moulin et al. 1993; Sorahan 2004), workers employed as stainless steel welders (Danielsen et al. 1996; Gerin et al. 1993; Hansen et al. 1996; Simonato et al. 1991), workers involved in nickel-chromium electroplating (Pang et al. 1996), or workers employed at a barrier production facility (Cragle et al. 1984; Godbold and Tompkins 1979; International Committee on Nickel Carcinogenesis in Man 1990). Although some studies of these workers did find significant increases in respiratory tract cancers (Becker 1999; Moulin et al. 1990), the increased risk was attributed to exposure to other carcinogenic agents, such as polycyclic aromatic hydrocarbons or asbestos. Redmond (1984) and Arena et al. (1998) reported significant increases in lung cancer risks among high nickel alloy production workers as compared to the U.S. population. However, when the local population

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was used as the comparison group, the increase in lung cancer risk was no longer statistically significant (Arena et al. 1998). In general, workers employed in these industries were exposed to lower levels of sulfidic or oxidic nickel than the nickel refinery workers who were primarily exposed to metallic nickel (Cragle et al. 1984; Godbold and Tompkins 1979) or soluble nickel (Pang et al. 1996).

Because nickel workers are exposed to several nickel species, it is difficult to assess the carcinogenic potential of a particular nickel species. The International Committee on Nickel Carcinogenesis in Man (1990) investigators used cross-classification analyses to examine the dose-response to a specific nickel species independent of variations in other species. The most comprehensive cross-classification analyses were performed for cohorts of workers in different departments at the Mond/INCO (Clydach) nickel refinery and at the Falconbridge (Kristiansand) nickel refinery (only analyzed for metallic nickel). Summaries of some of these cross-characterizations showing the different risks for low and high exposure to a particular nickel species stratified by the degree of exposure to other nickel species are presented in Tables 3-2 through 3-5. The strongest evidence of carcinogenicity of a particular nickel species is for sulfidic nickel. The highest cancer risk levels were found in cohorts with the highest sulfidic nickel exposure levels, although high oxidic and soluble nickel levels were also found at these same facilities. The increased cancer risks in workers with high sulfidic nickel exposure and low oxidic and soluble nickel exposure (Table 3-2) suggests that sulfidic nickel is the causative agent. The evidence for oxidic nickel is weaker. As presented in Table 3-3, no differences in cancer risks were seen among groups of workers with low sulfidic and soluble nickel exposures when the levels of oxidic nickel were varied. However, when high soluble nickel levels are present, oxidic nickel appears to be carcinogenic. The available weight of evidence does not suggest that exposure to soluble nickel, in the absence of carcinogenic compounds, will increase the risk of cancer. At low sulfidic and oxidic nickel levels, increasing soluble nickel levels do not increase the cancer risk in the Clydach cohort (Table 3-4). However, at high oxidic nickel levels, increasing the soluble nickel levels resulted in at least a 2-fold increase in the cancer risk. There is no evidence that metallic nickel is associated with increased lung or nasal cancer risks in nickel workers based on the results of the cross-classification analyses for two cohorts of nickel refinery workers (Table 3-5) and the lack of increased cancer risk in the workers exposed to metallic nickel alone at the barrier production facility (Cragle et al. 1984; Godbold and Tompkins 1979). The International Committee on Nickel Carcinogenesis in Man (1990) concluded that lung and nasal cancers were related primarily to exposure to less soluble nickel compounds at concentrations of $\geq 10 \text{ mg Ni/m}^3$ (primarily oxidic and sulfidic compounds). Exposure to soluble nickel compounds at concentrations of $>1 \text{ mg Ni/m}^3$ appeared to enhance the carcinogenicity of insoluble nickel

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Table 3-2. Comparison of Risk of Dying of Lung Cancer at Different Levels of Cumulative Exposure to Sulfidic Nickel by Different Levels of Combined Cumulative Exposure to Oxidic and Soluble Nickel in the Mond/INCO (Clydach) Nickel Refinery^a

Degree of exposure to oxidic and soluble nickel, respectively ^b	Low exposure to sulfidic nickel ^c			High exposure to sulfidic nickel ^d			Difference in SMR value (p-value)
	O	E	SMR	O	E	SMR	
Low, low	51	26.01	196	8	1.25	638	0.004
Low, high	7	4.16	168	1	0.15	657	0.388
High, low	18	5.14	350	32	6.34	505	0.455
High, high	30	3.87	776	28	2.36	1,187	0.265

^aModified from International Committee on Nickel Carcinogenesis in Man (1990).

^bLow oxidic nickel exposure = <50 (mg Ni/m³)-years and high oxidic nickel exposure = ≥50 (mg Ni/m³)-years; low soluble nickel exposure = <10 (mg Ni/m³)-years and high soluble nickel exposure = ≥10 (mg Ni/m³)-years.

^cLow sulfidic nickel exposure = <15 (mg Ni/m³)-years.

^dHigh sulfidic nickel exposure = ≥15 (mg Ni/m³)-years.

O = observed; E = expected; SMR = standardized mortality ratio

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Table 3-3. Comparison of Risk of Dying of Lung Cancer at Different Levels of Cumulative Exposure to Oxidic Nickel by Different Levels of Combined Cumulative Exposure to Sulfidic and Soluble Nickel in the Mond/INCO (Clydach) Nickel Refinery^a

Degree of exposure to sulfidic and soluble nickel, respectively ^b	Low exposure to oxidic nickel ^c			High exposure to oxidic nickel ^d			Difference in SMR value (p-value)
	O	E	SMR	O	E	SMR	
Low, low	51	26.01	196	18	5.14	350	0.100
Low, high	7	4.16	168	30	3.87	776	<0.001
High, low	8	1.25	638	32	6.34	505	0.839
High, high	1	0.15	658	28	2.36	1,187	0.841

^aModified from International Committee on Nickel Carcinogenesis in Man (1990).

^bLow sulfidic nickel exposure = <15 (mg Ni/m³)-years and high sulfidic nickel exposure = ≥15 (mg Ni/m³)-years; low soluble nickel exposure = <10 (mg Ni/m³)-years and high soluble nickel exposure = ≥10 (mg Ni/m³)-years.

^cLow oxidic nickel exposure = <50 (mg Ni/m³)-years.

^dHigh oxidic nickel exposure = ≥50 (mg Ni/m³)-years.

O = observed; E = expected; SMR = standardized mortality ratio

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Table 3-4. Comparison of Risk of Dying of Lung Cancer at Different Levels of Cumulative Exposure to Soluble Nickel by Different Levels of Combined Cumulative Exposure to Sulfidic and Oxidic Nickel in the Mond/INCO (Clydach) Nickel Refinery^a

Degree of exposure to sulfidic and oxidic nickel, respectively ^b	Low exposure to soluble nickel ^c			High exposure to soluble nickel ^d			Difference in SMR value (p-value)
	O	E	SMR	O	E	SMR	
Low, low	51	26.01	196	7	4.16	168	0.931
Low, high	18	5.14	350	30	3.87	776	0.024
High, low	8	1.25	638	1	0.15	658	0.999
High, high	32	6.34	505	28	2.36	1,187	0.003

^aModified from International Committee on Nickel Carcinogenesis in Man (1990).

^bLow sulfidic nickel exposure = <15 (mg Ni/m³)-years and high sulfidic nickel exposure = ≥15 (mg Ni/m³)-years; low oxidic nickel exposure = <50 (mg Ni/m³)-years and high oxidic nickel exposure = ≥50 (mg Ni/m³)-years.

^cLow soluble nickel exposure = <10 (mg Ni/m³)-years.

^dHigh soluble nickel exposure = ≥10 (mg Ni/m³)-years.

O= observed; E = expected; SMR = standardized mortality ratio

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Table 3-5. Comparison of Risk of Dying of Lung Cancer at Different Levels of Cumulative Exposure to Metallic Nickel by Different Levels of Combined Cumulative Exposure to Sulfidic, Oxidic, and Soluble Nickel in the Mond/INCO (Clydach) and Falconbridge (Kristiansand) Nickel Refineries^a

Degree of exposure to sulfidic, oxidic, and soluble nickel, respectively ^b	Low exposure to metallic nickel ^c			High exposure to metallic nickel ^d			Difference in SMR value (p-value)
	O	E	SMR	O	E	SMR	
Mond/INCO (Clydach) Nickel Refinery							
None, none, none	19	11.5	166	—	—	—	—
Low, low, low	44	23.2	190 ^e	7	2.8	249 ^f	0.80
Low, low, high	5	3.8	133	2	0.4	499	0.23
Low, high, low	17	4.7	363 ^e	1	0.5	220 ^f	0.87
Low, high, high	26	3.3	783 ^e	4	0.1	732 ^g	0.99
High, low, low	2	0.3	589 ^f	5	0.9	656 ^e	0.99
High, low, high	—	—	—	1	0.2	658	—
High, high, low	2	0.9	235	30	5.5	547	0.49
High, high, high	3	0.3	865 ^g	25	2.0	1,140 ^e	0.83
Falconbridge (Kristiansand) Nickel Refinery							
None, none, none	6	3.28	186	—	—	—	—
Low, low, low	19	7.17	265 ^e	—	—	—	—
Low, low, high	10	1.75	570 ^e	—	0.18	—	—
Low, high, low	11	4.66	236 ^e	1	0.25	396	—
Low, high, high	6	0.78	770 ^e	2	0.26	1,112 ^g	—
High, low, high	1	0.13	769	—	—	—	—
High, high, low	2	0.58	344	3	0.64	471 ^f	—
High, high, high	4	0.76	524 ^g	1	0.58	171	—

^aModified from International Committee on Nickel Carcinogenesis in Man (1990).

^bClydach: low sulfidic nickel exposure = <15 (mg Ni/m³)·years and high sulfidic nickel exposure = ≥15 (mg Ni/m³)·years; low oxidic nickel exposure = <50 (mg Ni/m³)·years and high oxidic nickel exposure = ≥50 (mg Ni/m³)·years; low soluble nickel exposure = <10 (mg Ni/m³)·years and high soluble nickel exposure = ≥10 (mg Ni/m³)·years.

Kristiansand: low sulfidic nickel exposure = <5 (mg Ni/m³)·years and high sulfidic nickel exposure = ≥5 (mg Ni/m³)·years; low oxidic nickel exposure = <15 (mg Ni/m³)·years and high oxidic nickel exposure = ≥15 (mg Ni/m³)·years; low soluble nickel exposure = <5 (mg Ni/m³)·years and high soluble nickel exposure = ≥5 (mg Ni/m³)·years.

^cClydach: low exposure = <15 (mg Ni/m³)·years; Kristiansand: low exposure = <5 (mg Ni/m³)·years.

^dClydach: high exposure = ≥15 (mg Ni/m³)·years; Kristiansand: high exposure = ≥5 (mg Ni/m³)·years.

^ep<0.001

^fp<0.05

^gp<0.01

O = observed; E = expected; SMR = standardized mortality ratio

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compounds. These concentrations are presented as human cancer effect levels for lung and nasal cancers in Table 3-1 and Figure 3-1.

Significant increases in cancer risks at sites other than the respiratory tract have been found in some cohorts of nickel workers. The International Committee on Nickel Carcinogenesis in Man (1990) noted that if nickel exposure was associated with nonrespiratory tract cancer, increased risks would be seen among the workers with the highest nickel exposures (cohorts that also had increased levels of respiratory tract cancer). Among the three cohorts with the highest nickel exposures (Clydach, INCO Ontario sinter plants, and Kristiansand), no consistent patterns of increased nonrespiratory tract cancer risks were found. When the three cohorts were combined, significant increases in pharynx (SMR 201; 95% confidence interval 117–322) and bone (SMR 206; 95% confidence interval 111–353) cancers were found. The investigators noted that cancers of the ethmoid and maxillary sinuses are sometimes classified as bone cancer and that bone cancer is sometimes listed on death certificates if the primary lung cancers are occasionally unrecognized and death is attributed to the site of metastasis. Among workers with low-level nickel exposures without significant increases in respiratory tract cancer, no significant increases in cancer risks were found. Thus, the investigators concluded that there was insufficient evidence that nickel exposure results in tumors outside of the respiratory tract (International Committee on Nickel Carcinogenesis in Man 1990). Two studies published after this analysis found significant increases in the incidence of stomach cancer among nickel refinery workers (Antilla et al. 1998) and nickel platers (Pang et al. 1996). These data are insufficient to conclude whether the increases in stomach cancer risks are due to exposure to nickel, other agents, or chance. A meta-analysis of occupational exposure studies on pancreatic cancer (Ojajärvi et al. 2000) found a significant association between exposure to nickel and pancreatic cancer risk. However, the Ojajärvi et al. (2000) meta-analysis has been criticized (Sielkop 2001) for excluding a study of nickel mining and smelting workers (Shannon et al. 1991) and a study of nickel alloy production workers (Arena et al. 1998). The addition of these studies lowered the meta-analysis ratio from 1.9 (95% confidence interval 1.2–3.2) to 1.3 (95% confidence interval 0.9–1.9); Ojajärvi accepted Sielkop's comments. Overall, there does not appear to be sufficient evidence that exposure to airborne nickel is associated with increased cancer risks outside of the respiratory tract.

A number of animal studies have examined the carcinogenic potential of nickel subsulfide, nickel oxide, and nickel sulfate. Chronic exposure to nickel subsulfide resulted in significant increases in lung tumors in two rat studies. Adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcoma were observed in rats exposed to 0.7 mg Ni/m³ as nickel subsulfide 6 hours/day, 5 days/week, for 78 weeks

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(Ottolenghi et al. 1974). Similarly, significant increases in the combined incidences of alveolar/bronchiolar adenoma or carcinoma were observed in male and female rats exposed to 0.11 or 0.73 mg Ni/m³ as nickel subsulfide, 6 hours/day, 5 days/week for 2 years (NTP 1996b); incidence data for this study are presented in Table 3-6. Significant increases in the incidence of benign or malignant pheochromocytoma in the adrenal medulla were also observed in males at 0.11 or 0.73 mg Ni/m³ and females at 0.73 mg Ni/m³. In contrast to the findings in rats, no significant alterations in tumor incidences were observed in mice exposed to 0.44 or 0.88 mg Ni/m³ as nickel subsulfide 6 hours/day, 5 days/week for 2 years (NTP 1996b) (see Table 3-7 for incidence data) or in mice following weekly intratracheal injections of ≤ 0.8 mg Ni/m³ as nickel subsulfide for ≤ 15 weeks, followed by observation for ≤ 27 months (Fisher et al. 1986; McNeill et al. 1990). Acute (6 hours/day, 5 days/week, for 1 month) inhalation exposure to ≤ 6.3 mg Ni/m³ as nickel oxide resulted in no significant increase in lung cancer in rats ≤ 20 months after exposure (Horie et al. 1985). However, significant increases in the incidence of alveolar/bronchiolar adenoma or carcinoma were observed in male and female rats exposed to 1 or 2 mg Ni/m³ as nickel oxide 6 hours/day, 5 days/week for 2 years (NTP 1996c) (see Table 3-6 for incidence data), but not in rats exposed to 0.5 mg Ni/m³ or in mice exposed to 1, 2, or 3.9 mg Ni/m³. Significant increases in the incidence of benign or malignant pheochromocytoma in the adrenal medulla were also observed in rats exposed to 3.9 mg Ni/m³ (NTP 1996c). In contrast to the less soluble nickel compounds, chronic (6 hours/day, 5 days/week for 2 years) exposure to nickel sulfate did not result in significant increases in neoplasms in rats or mice (NTP 1996a); the highest concentrations tested were 0.11 and 0.22 mg Ni/m³, respectively; incidence data reported in Tables 3-6 and 3-7. The nickel concentrations as nickel subsulfide and nickel oxide resulting in cancer in rats are presented as Cancer Effect Levels in Table 3-1 and Figure 3-1.

The Department of Health and Human Services (NTP 2002) has determined that metallic nickel may reasonably be anticipated to be a human carcinogen and that nickel compounds are known to be human carcinogens. Similarly, IARC (1990) classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). EPA has classified nickel refinery dust and nickel subsulfide in Group A (human carcinogen) (IRIS 2005). Other nickel compounds have not been classified by the EPA. Based on the occupational data, inhalation unit risk levels of $2.4 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ and $4.8 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ were derived for nickel refinery dust and nickel subsulfide, respectively (IRIS 2003). The risk levels for these compounds are presented in Figure 3-1. The risk levels range from 4×10^{-1} to $4 \times 10^{-4} \mu\text{g}/\text{m}^3$ for a risk ranging from 1×10^{-4} to 1×10^{-7} , respectively, for nickel refinery dust (IRIS 2005) and from 2×10^{-1} to $2 \times 10^{-4} \mu\text{g}/\text{m}^3$ for a risk ranging from 1×10^{-4} to 1×10^{-7} , respectively, for nickel subsulfide (IRIS 2005). These risk levels are presented in Figure 3-1.

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Table 3-6. Alveolar/Bronchiolar Neoplasms and Adrenal Medulla Proliferative Lesions in Rats^a

Effect	Number of rats with neoplasms or proliferative lesions/number of rats examined										
	Exposure to nickel sulfate hexahydrate (mg nickel/m ³)				Exposure to nickel subsulfide (mg nickel/m ³)			Exposure to nickel oxide (mg nickel/m ³)			
	0	0.03	0.06	0.11	0	0.11	0.73	0	0.5	1	2
Male											
Alveolar/bronchiolar adenoma/carcinoma	2/54	0/53	1/53	3/53	0/53	6/53 ^b	11/53 ^c	1/54	1/53	6/53 ^b	4/52 ^b
Adrenal medulla benign, malignant, or complex pheochromocytoma	16/54	19/53	13/53	12/53	14/53	30/52 ^c	42/53 ^c	27/54	24/53	27/53	35/54 ^c
Female											
Alveolar/bronchiolar adenoma/carcinoma	0/52	0/53	0/53	1/54	2/53	6/53 ^d	9/53 ^b	1/53	0/53	6/53 ^d	5/54 ^d
Adrenal medulla benign, malignant, or complex pheochromocytoma	2/51	4/53	3/53	3/54	3/53	7/53	36/53 ^c	4/53	7/53	6/53	18/54 ^c

^aAdapted from NTP 1996a, 1996b, 1996c^bp≤0.05^cp≤0.01^dp≤0.05 versus historical data (1.4%, 3/210 males; 1.4%, 4/208 females) (Dunnick et al. 1995)

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Table 3-7. Alveolar/Bronchiolar Neoplasms in Mice^a

	Number of mice with tumors/number of mice examined											
	Exposure to nickel sulfate hexahydrate (mg nickel/m ³)				Exposure to nickel subsulfide (mg nickel/m ³)			Exposure to nickel oxide (mg nickel/m ³)				
	0	0.06	0.11	0.22	0	0.44	0.88	0	1	2	3.9	
Male	13/61	18/61	7/62	8/61	13/61	5/59	6/58	9/57	14/67	15/66	14/69	
Female	7/61	6/60	10/60	2/60	9/58	2/59	3/60	6/64	15/66 ^b	12/63	8/64	

^aAdapted from NTP 1996a, 1996b, 1996c^bp≤0.05

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3.2.2 Oral Exposure**3.2.2.1 Death**

One human death following oral exposure to nickel was reported (Daldrup et al. 1983). Nickel sulfate crystals (rough estimate of 570 mg Ni/kg) were accidentally ingested by a 2-year-old child. Four hours after ingestion, cardiac arrest occurred, and the child died 8 hours after exposure.

Single-dose oral lethality studies indicate that soluble nickel compounds are more toxic than less-soluble nickel compounds. Oral LD₅₀ values of 46 or 39 mg Ni/kg as nickel sulfate in male and female rats (Mastromatteo 1986) and 116 and 136 mg Ni/kg as nickel acetate in female rats and male mice, respectively (Haro et al. 1968) have been reported for soluble nickel compounds. In contrast, the oral LD₅₀ values in rats for less-soluble nickel oxide and subsulfide were >3,930 and >3,665 mg Ni/kg, respectively (Mastromatteo 1986).

Increases in mortality (6/52, 60/60) were observed in rats administered via gavage 8.6 or 25 mg Ni/kg/day as nickel chloride hexahydrate for 91 days (American Biogenics Corporation 1988). Clinical signs observed included lethargy, ataxia, irregular breathing, hypothermia, salivation, squinting, and loose stools. As part of a longer-term study, rats were provided with drinking water containing 1,000 ppm nickel as nickel chloride (approximately 140 mg/kg/day) (RTI 1988a). Within 2 weeks, 7/62 died and the dose was eliminated from the study. In other studies, no deaths were observed in rats given doses up to 92 mg Ni/kg as nickel chloride in drinking water for 15 days (RTI 1985), 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999), or 22 mg Ni/kg/day (males) or 33 mg Ni/kg/day (females) as nickel sulfide administered via gavage for 90 days (Springborn Laboratories 2002); no deaths were observed in mice provided with nickel sulfate in the drinking water at doses up to 150 mg Ni/kg/day for 180 days (Dieter et al. 1988).

In a multigeneration study (RTI 1988a, 1988b) in which rats were treated with nickel chloride in the drinking water, the death of female rats from pregnancy complications at the time of delivery suggests that females are more susceptible to nickel toxicity during parturition. Although the number of deaths was not significantly above controls and not clearly dose related (P₀: 0/31 in controls, 1/31 at 7 mg/kg/day, 3/30 at 30 mg/kg/day, and 3/31 at 55 mg/kg/day; F₁: 0/30 at 0 and 7 mg/kg/day, 3/30 at 30 mg/kg/day, and 1/30 at 55 mg/kg/day), death in dams during delivery is a relatively rare event. The results of this study (RTI 1988a, 1988b) are confounded by a decrease in food and water intake observed

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in the exposed animals. Deaths in offspring before weaning have also been reported in multigeneration, multilitter studies (RTI 1988a, 1988b; Schroeder and Mitchener 1971; Smith et al. 1993). Because cross-fostering studies have not been completed, it is not possible to know if the pre-weaning deaths are a result of an inherent defect in the pups, nickel exposure through the milk, or a change in the quality or quantity of the milk produced by the dam (Smith et al. 1993).

An increase in mortality was not observed in chronic studies in rats or dogs fed nickel sulfate in the diet at doses up to 188 mg/kg/day for rats and 62.5 mg/kg/day for dogs (Ambrose et al. 1976). In mice provided with 0.95 mg/Ni/kg as nickel acetate in drinking water until death (last death at 991 days for males and 904 days for females), an increase in life expectancy was observed (Schroeder and Mitchener 1975).

Oral LD₅₀ values and all LOAEL values from each reliable study for death in each species and duration category are recorded in Table 3-8 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects for each species, duration category, and nickel compound are recorded in Table 3-8 and plotted in Figure 3-2.

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

Pneumonitis was observed in 6/19 male rats and 9/17 female rats treated for 91 days by gavage with 8.6 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988). Significant increases in absolute and relative lung weights were observed in rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999). This study also found alterations in enzyme activity in bronchoalveolar lavage (BAL) fluid and lung tissues, including increases in protein levels in BAL fluid at 14.4 mg Ni/kg/day and higher, decreases in alkaline phosphatase activity in BAL fluid at 5.75 mg Ni/kg/day and higher, and decrease in alkaline phosphatase activity in lung tissue at 28.8 mg Ni/kg/day. No histological alterations were observed in the lungs. The study authors suggested that the decrease in alkaline phosphatase activity was indicative of decreased activity of type II alveolar cells and the increased total protein was indicative of increased air-blood barrier permeability. In a multigeneration study (RTI 1988a, 1988b), increased lung weights were observed in rats provided with nickel chloride in

Table 3-8 Levels of Significant Exposure to Nickel - Oral

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (Fischer- 344)	once (G)				120 M (LD50) 116 F (LD50)	Haro et al. 1968 acetate
2	Rat (Sprague- Dawley)	once (G)				46 M (LD50) 39 F (LD50)	Mastromatteo 1986 sulfate
3	Rat (CD)	14d (W)				140 (7/64 died)	RTI 1988a, 1988b chloride
4	Mouse (Swiss- Webster)	once (G)				136 M (LD50) 139 F (LD50)	Haro et al. 1968 acetate
Systemic							
5	Human	2 d 2x/d (C)	Dermal	0.03			Burrows et al. 1981 sulfate
6	Human	once or 1 dose for 2 d (C)	Dermal	0.043 F	0.097 F (allergic dermatitis in sensitized individuals)		Gawkrodger et al. 1986 sulfate
7	Human	once (C)	Dermal	0.014 F	0.057 F (dermatitis in nickel sensitive subjects)		Hindsen et al. 2001 sulfate

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Human	once (C)	Dermal	0.014 F	0.057 F (dermatitis in nickel sensitive subjects)		Jensen et al. 2003 sulfate
9	Human	1 d (W)	Gastro		7.1 M (vomiting, cramps, diarrhea)		Sunderman et al. 1988 sulfide/chloride
10	Dog (Beagle)	3 days (F)	Gastro	25	62.5 (vomiting)		Ambrose et al. 1976 sulfate
Neurological							
11	Human	1 d (W)			7.1 M (giddiness, headache, weariness)		Sunderman et al. 1988 sulfate/chloride
Reproductive							
12	Mouse (Iacca)	once (GW)			23 M (3.7-fold increase in sperm head abnormalities)		Sobti and Gill 1989 nitrate
Developmental							
13	Mouse (CD-1)	Gd 8-12 1x/day (G)		45.3			Gray et al. 1986 chloride
14	Mouse	Gd 8-12 (GW)		90.6			Seidenberg et al. 1986 chloride
INTERMEDIATE EXPOSURE							
Death							
15	Rat (Sprague- Dawley)	91 d daily (GW)			8.6 (6/52 died)		American Biogenics Corp 1988 chloride

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic							
16	Human	91-178 d (W)	Dermal	0.02 F			Santucci et al. 1994 sulfate
17	Rat (Sprague- Dawley)	91 d daily (GW)	Resp		8.6	(pneumonitis)	American Biogenics Corp 1988 chloride
			Cardio	8.6			
			Gastro	8.6		25 (ulcerative gastritis and enteritis)	
			Hemato	1.2 F	8.6 F	(increased platelet count)	
			Hepatic	8.6			
			Renal	8.6			
			Dermal	8.6			
			Ocular	8.6			
			Bd Wt	1.2 F	8.6 F	(12% decrease in body weight gain)	
			Metab	1.2 F	8.6 F	(decreased blood glucose level)	

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
18	Rat (Sprague- Dawley)	daily 13 weeks (W)	Resp		5.75 M (decreased alkaline phosphatase activity in bronchioalveolar lavage fluid)		Obone et al. 1999 sulfate
			Cardio	28.8 M			
			Gastro	28.8 M			
			Hepatic	28.8 M			
			Renal	5.75 M	14.4 M (increased realtive kidney weight, decreased urine volume and urine glucose)		
			Bd Wt	28.8 M			
19	Rat (CD)	F: 27-30 wk M:21-24 wk (W)	Resp	4 M	20 M (histiocytic cellular infiltration in lungs in F1 generation)		RTI 1988a, 1988b chloride
20	Rat (Long- Evans)	11 wk breeding- lactation 2 litters (W)	Endocr	6.8 F	31.6 F (21% decreased prolactin)		Smith et al. 1993 chloride
			Bd Wt	31.6 F			

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
21	Rat (Sprague- Dawley)	daily 18 weeks (GW)	Cardio	2.2			Springborn Laboratories 2000a sulfate
			Gastro	2.2			
			Hepatic	2.2			
			Renal	2.2			
			Bd Wt	2.2			
22	Rat (Fischer- 344)	Daily 90 days (GW)	Resp	22 M			Springborn Laboratories 2002 sulfate
			Cardio	22 M			
			Gastro	22 M			
			Hepatic	22 M			
			Renal	22 M			
			Endocr	22 M			
			Bd Wt	11 M	17 M (12.2% decrease in final body weight)		
23	Rat (Wistar)	3 or 6 mo (W)	Renal		7.6 F (increased urinary albumin)		Vyskocil et al. 1994b sulfate
			Bd Wt	7.6 F			

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
24	Rat (OSU brown)	6 wk (F)	Hemato	5 M	25 M (10% decreased hemoglobin)		Whanger 1973 acetate
			Bd Wt	5 M	25 M (88% decrease in body weight gain)		
25	Mouse (B6C3F1)	180 d daily (W)	Hepatic	150 F			Dieter et al. 1988 sulfate
			Renal	44 F	108 F (hyaline casts, loss of tubular epithelial cells)		
			Bd Wt	44 F	108 F (body weight 10% lower than controls)	150 F (body weight 26% lower than controls)	
Immuno/ Lymphoret							
26	Rat (Sprague-Dawley)	daily 13 weeks (W)		5.75 M	14.4 M (alterations in spleen and thymus lymphocyte T-cell and B-cell subpopulations)		Obone et al. 1999 sulfate
27	Mouse (B6C3F1)	180 d daily (W)			44 F (mild thymic atrophy, impaired B-cell immune function, decreased granulocyte macrophage progenitor cell levels)		Dieter et al. 1988 sulfate

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
28	Mouse (BALB/c)	10-11wk (W)			20.3 F (enhanced inflammatory response in the hearts of mice challenged with coxsackie virus B3)		Ilback et al. 1994 chloride
Neurological							
29	Rat (Sprague- Dawley)	91 d daily (GW)		1.2		8.6 (ataxia, prostation, hypothermia)	American Biogenics Corp 1988 chloride
Reproductive							
30	Rat (Wistar)	about 24 wk (F)		90			Ambrose et al. 1976 sulfate
31	Rat (Wistar)	daily 62 days (W)		13 F			Kakela et al. 1999 chloride
32	Rat (Wistar)	daily 28 or 42 days (W)				3.6 M (decreased fertility)	Kakela et al. 1999 chloride
33	Rat (Wistar)	daily 28--76 days (W)				3.6 (decreased fertility)	Kakela et al. 1999 chloride
34	Rat (Sprague- Dawley)	daily 13 weeks (W)		28.8 M			Obone et al. 1999 sulfate

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
35	Rat (CD)	F: 27-30 wk M:21-24 wk (W)		7 F	30 F (increased gestation length in first P0 pregnancy)		RTI 1988a, 1988b chloride
36	Rat (Long- Evans)	11 wk breeding- lactation 2 litters (W)		31.6			Smith et al. 1993 chloride
37	Rat (Sprague- Dawley)	daily 18 weeks (GW)		2.2			Springborn Laboratories 2000a sulfate
38	Rat (Sprague- Dawley)	daily 35-56 days (GW)		16.7			Springborn Laboratories 2000b sulfate
39	Mouse (NS)	5 days/week 35 days (GW)		1.1 M	2.2 M (decreased sperm motility; increased sperm abnormalities)		Pandey and Srivastava 2000 sulfate
40	Mouse (NS)	5 days/week 35 days (GW)		1.2 M	2.5 M (decreased sperm motility and count; increased sperm abnormalities)		Pandey and Srivastava 2000 chloride

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg)	Serious (mg/kg)	
41	Mouse (Swiss)	5 days/week 35 days (GW)			1.1 M (increased total number of sperm abnormalities)		Pandey et al. 1999 sulfate
42	Mouse (Swiss)	5 days/week 35 days (GW)				2.2 M (decreased fertility)	Pandey et al. 1999 sulfate
Developmental							
43	Rat (Wistar)	about 24 wk (F)				22.5 (increased number of stillborns)	Ambrose et al. 1976 sulfate
44	Rat (Wistar)	daily 62 days (W)		4 F		13 F (decreased litter size and pup survival)	Kakela et al. 1999 chloride
45	Rat (Wistar)	daily 28 or 42 days (W)				3.6 M (decreased pup viability and survival)	Kakela et al. 1999 chloride
46	Rat (Wistar)	daily 28--76 days (W)				3.6 (increased fetal mortality and decreased pup survival)	Kakela et al. 1999 chloride

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
47	Rat (CD)	F: 27-30 wk M: 21-24 wk (W)		7 M		30 M (increased mortality in F1b rats on pnd 22-42; decreased pup body weight in F1b rats)	RTI 1988a, 1988b chloride
48	Rat (Long- Evans)	11 wk breeding- lactation 2 litters (W)				1.3 (decreased pup survival)	Smith et al. 1993 chloride
49	Rat (Sprague- Dawley)	daily 18 weeks (GW)		2.2			Springborn Laboratories 2000a sulfate
50	Rat (Sprague- Dawley)	daily 49-70 days (GW)		4.5 F		6.7 F (increased post-implantation loss)	Springborn Laboratories 2000b sulfate
51	Mouse (CD-1)	Gd 2-17 (W)		80		160 (increased spontaneous abortions)	Berman and Rehnberg 1983 chloride

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Systemic							
52	Rat (Wistar)	2 yrs (F)	Resp	187.5			Ambrose et al. 1976 sulfate
			Cardio	187.5			
			Gastro	187.5			
			Hemato	187.5			
			Musc/skel	187.5			
			Hepatic	187.5			
			Renal	187.5			
			Endocr	187.5			
			Dermal	187.5			
			Bd Wt	7.5	75	(10-18% decreases in body weight gain)	

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
53	Dog (Beagle)	2 yrs (F)	Resp	25		62.5	(cholesterol granulomas, emphysema, bronchiolectasis)	Ambrose et al. 1976 sulfate
			Cardio	62.5				
			Gastro	62.5				
			Hemato	25	62.5	(decreased hematocrit and hemoglobin levels)		
			Musc/skel	62.5				
			Hepatic	62.5				
			Renal	25	62.5	(polyuria in 2/6 dogs, increased kidney weight)		
			Endocr	62.5				
			Dermal	62.5				
			Bd Wt	25	62.5	(10% decrease in body weight gain)		
Immuno/ Lymphoret								
54	Rat (Wistar)	2 yrs (F)		187.5			Ambrose et al. 1976 sulfate	
55	Dog (Beagle)	2 yrs (F)		62.5			Ambrose et al. 1976 sulfate	
Neurological								
56	Rat (Wistar)	2 yrs (F)		187.5			Ambrose et al. 1976 sulfate	

Table 3-8 Levels of Significant Exposure to Nickel - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
57	Dog (Beagle)	2 yrs (F)		62.5			Ambrose et al. 1976 sulfate

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

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; (GW) = gavage in water; hemato = hematological; Immuno = immunological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; Ni = nickel; NOAEL = no-observed-adverse-effect level; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

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

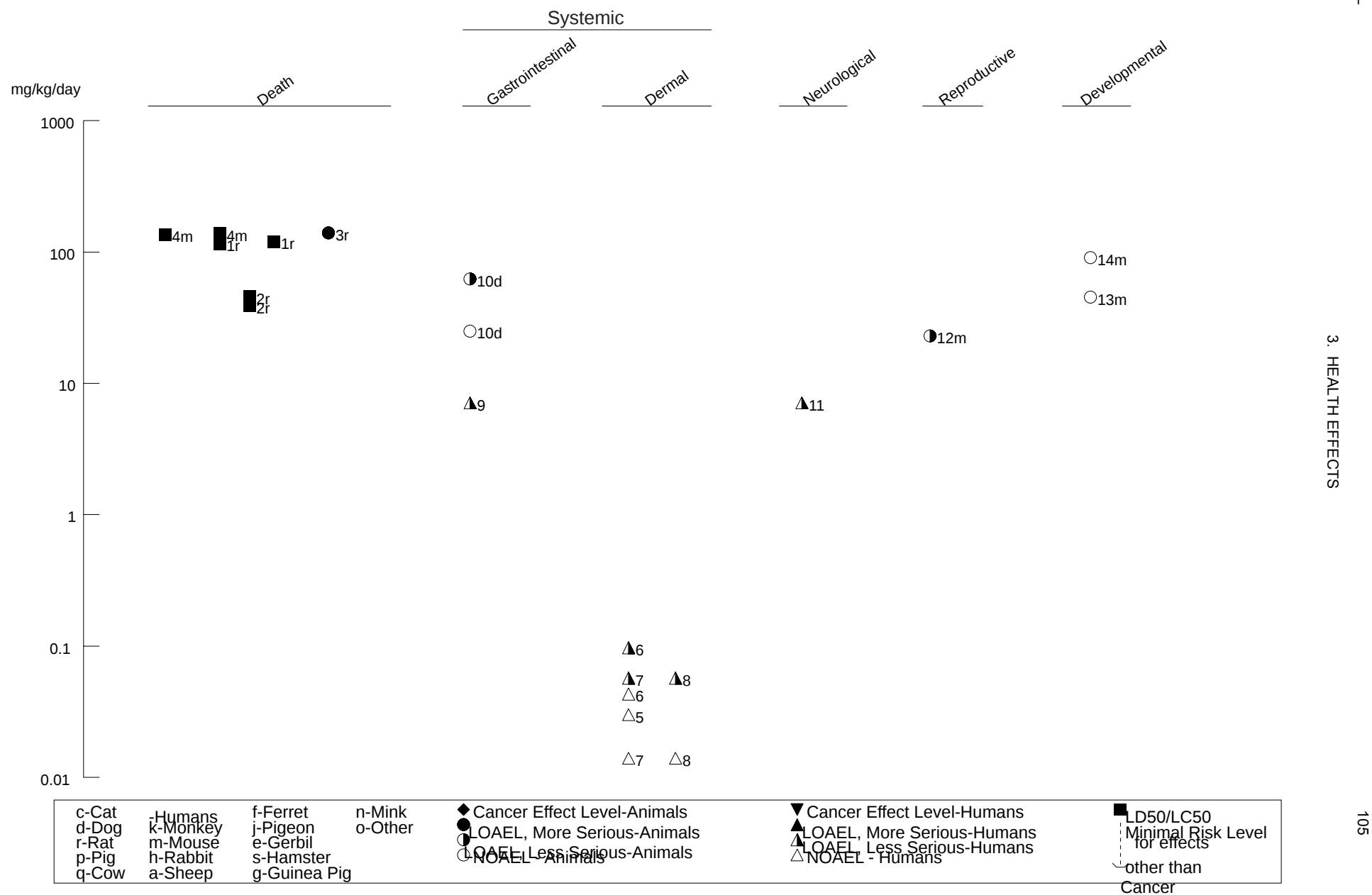
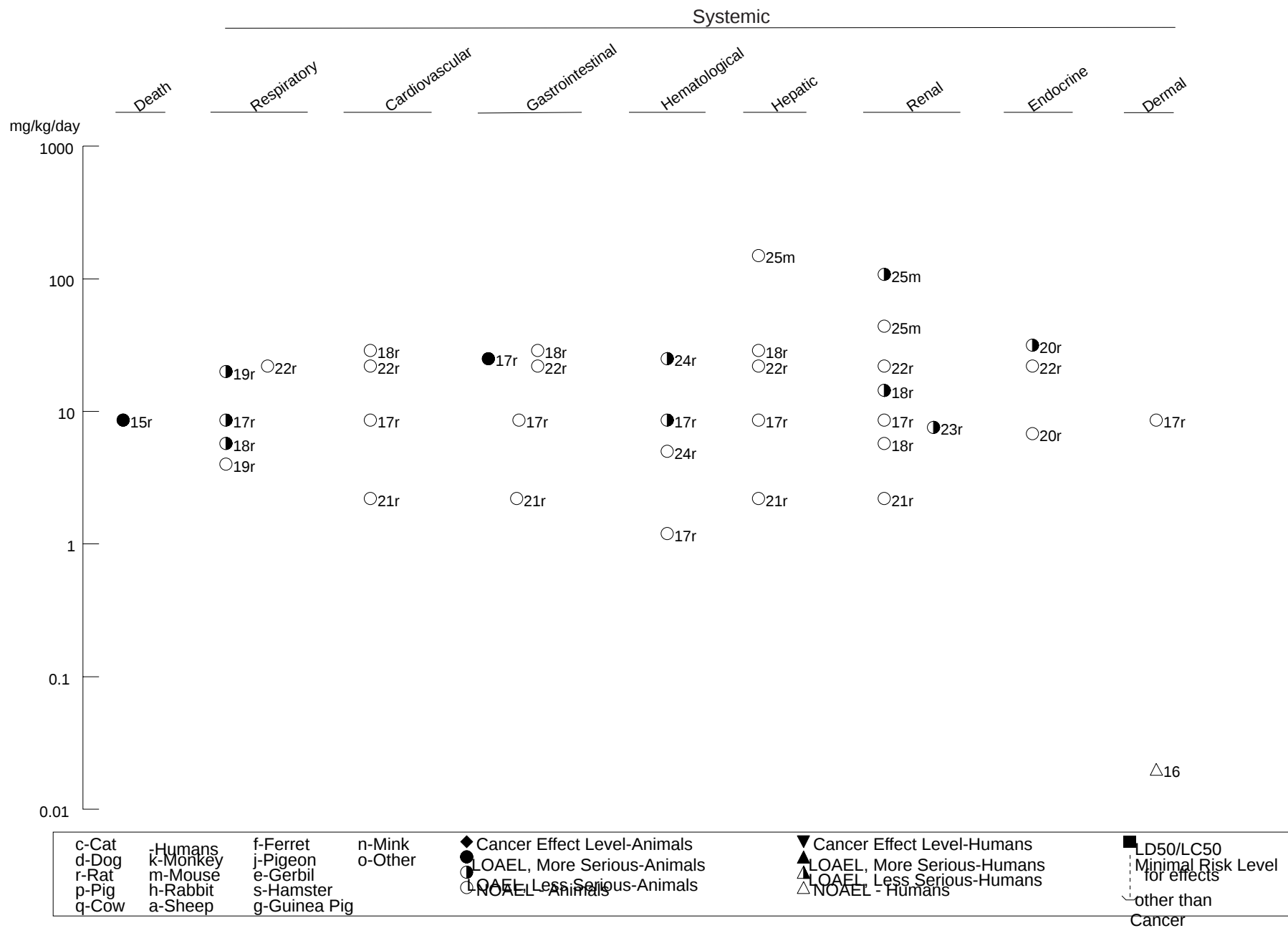


Figure 3-2 Levels of Significant Exposure to Nickel - Oral
Intermediate (15-364 days)



NICKEL

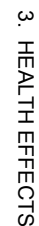
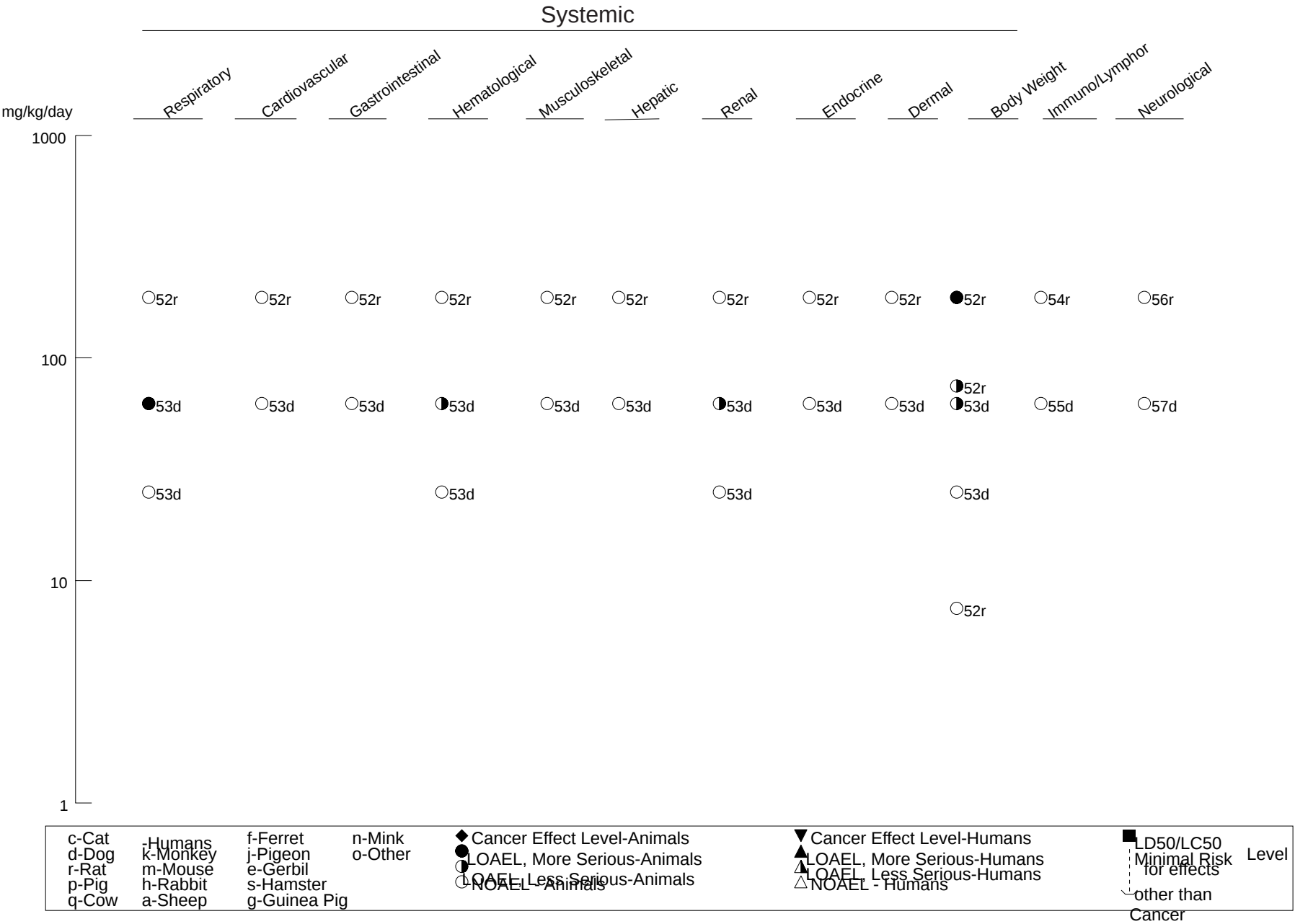


Figure 3-2 Levels of Significant Exposure to Nickel - Oral

Chronic (≥ 365 days)



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the drinking water at 55 mg Ni/kg/day, and an increase in cellular infiltration of the lungs was observed at 20 mg Ni/kg/day. This study is confounded by decreased food and water intake observed in exposed animals. Emphysema, bronchiolectasis, and cholesterol granulomas were also observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years, but not in rats exposed at up to 187.5 mg/kg/day for 2 years (Ambrose et al. 1976).

Cardiovascular Effects. Nickel sulfate crystals (rough estimate of 570 mg Ni/kg) were accidentally ingested by a 2-year-old child (Daldrup et al. 1983). Four hours after ingestion, cardiac arrest occurred, and the child died 8 hours after exposure.

Rats exposed to 8.6 mg Ni/kg/day as nickel chloride for 91 days had decreased heart weight (American Biogenics Corporation 1988), whereas rats exposed to 75 mg Ni/kg/day as nickel sulfate for 2 years had increased heart weight (Ambrose et al. 1976). Because the changes in heart weight were not accompanied by histological changes and decreases in body weight gain were also observed, the significance of these changes is not known. Histological changes in the heart were not observed in rats treated with nickel chloride in the drinking water at 40 mg/kg/day for up to 30 weeks (RTI 1988a), rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water (Obone et al. 1999), rats exposed to 187.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976), rats administered via gavage 22 mg Ni/kg/day (males) or 33 mg Ni/kg/day (females) as nickel sulfate for 90 days (Springborn Laboratories 2002), or dogs provided with nickel sulfate in the diet at a dose of 62.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976).

Gastrointestinal Effects. Symptoms of gastrointestinal distress were reported by workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The symptoms included nausea (15 workers), abdominal cramps (14 workers), diarrhea (4 workers), and vomiting (3 workers). Although the actual contribution of boric acid to these effects is not known, the investigators (Sunderman et al. 1988) indicate that the intake of 20–200 mg boric acid probably did not contribute to the observed effects because the effects of boric acid are generally observed only following ingestion of ≥ 4 g by adults.

Gastrointestinal effects were observed in rats that died following treatment by gavage with 25 mg Ni/kg/day as nickel chloride hexahydrate for up to 91 days (American Biogenics Corporation 1988). The

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effects included discolored gastrointestinal contents, ulcerative gastritis, and enteritis. Discolored (green) gastrointestinal contents were also observed at 1.2 and 8.6 mg/kg/day. The discoloration may have been due to the presence of nickel chloride in the gastrointestinal tract and is not considered an adverse effect. Adverse gastrointestinal effects were not observed in rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999), rats treated with nickel sulfate in the diet at 187.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976), or rats receiving gavage doses of 22 (males) or 33 (females) mg Ni/kg/day as nickel sulfate (Springborn Laboratories 2002). During the first 3 days of a 2-year study, dogs vomited following treatment with nickel sulfate in the diet at 62.5 mg Ni/kg/day (Ambrose et al. 1976). The dose was lowered to 37.5 mg Ni/kg/day for 2 weeks, and then incrementally raised at 2-week intervals back to 62.5 mg/kg/day, at which time, no further gastrointestinal distress was noted. These studies indicate that high doses of nickel can be irritating to the gastrointestinal tract, although acclimation to high levels of dietary nickel can occur. The toxicological significance of the results of the American Biogenics Corporation (1988) is not known, particularly since studies in rats (Ambrose et al. 1976; Obone et al. 1999; Springborn Laboratories 2002) have not reported gastrointestinal effects.

Hematological Effects. A transient increase in blood reticulocytes was observed in workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Rat studies have indicated that intermediate-duration exposure to ≥ 0.7 mg Ni/kg/day as various nickel salts produce hematological effects. Effects included a decrease in hemoglobin level in rats exposed to 25 mg Ni/kg/day as nickel acetate in the diet for 6 weeks (Whanger 1973), an increase in leukocyte levels in rats exposed to 0.49 mg Ni/kg/day as nickel chloride in drinking water for 28 days, but not at 0.97 mg Ni/kg/day (Weischer et al. 1980), and an increase in platelet counts in rats administered via gavage 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988). No hematological effects were observed in rats treated with nickel sulfate in the diet at a dose of 187.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976). Low hematocrit levels were observed in dogs after chronic dietary exposure to 62.5 mg Ni/kg/day as nickel sulfate (Ambrose et al. 1976).

Musculoskeletal Effects. Muscular pain was reported by one worker who drank water contaminated with nickel sulfate, nickel chloride, and boric acid during one work shift (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported

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symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Microscopic changes in skeletal muscle were not observed in rats or dogs fed nickel sulfate in the diet at doses up to 187.5 mg Ni/kg/day for rats (Ambrose et al. 1976; Springborn Laboratories 2002) and 62.5 mg Ni/kg/day for dogs (Ambrose et al. 1976).

Hepatic Effects. A transient increase in serum bilirubin levels was observed in 3 of 10 workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). The workers who reported symptoms (20 of 35) or were hospitalized (10 of 35) were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Decreased liver weight was observed in rats exposed to 0.97–75 mg Ni/kg/day as nickel chloride or nickel sulfate for 28 days to 2 years (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Weischer et al. 1980) and mice exposed to 150 mg Ni/kg/day as nickel sulfate in drinking water for 180 days (Dieter et al. 1988). No alterations in absolute liver weights were observed in male and female rats administered via gavage 22 or 33 mg Ni/kg/day as nickel sulfate, respectively, for 90 days (Springborn Laboratories 2002); no histological alterations were reported in this study. A significant increase in relative liver weight, however, was observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate for 2 years (Ambrose et al. 1976). Because histological changes in the liver were not observed in these studies and decreases in body weight gain were often observed at the same dose levels, the significance of the liver weight changes is unclear.

Renal Effects. A transient increase in urine albumin levels was observed in 3 of 10 workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Renal tubular damage at the corticomedullary junction described as minor was observed in mice exposed to ≥ 108 mg Ni/kg/day as nickel sulfate in the drinking water for 180 days (Dieter et al. 1988). The renal effects included the loss of renal tubular epithelial cells and the presence of hyaline casts in the tubule (suggesting protein loss). No changes in markers of renal tubular function (urinary lactate dehydrogenase

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and NAG levels and β_2 -microglobulin levels) were observed in rats exposed to nickel sulfate in the drinking water for 6 months at a concentration that supplied doses of 6.9 mg/kg/day for males and 7.6 mg/kg/day for females (Vyskocil et al. 1994b). Urinary albumin levels, a marker of glomerular barrier dysfunction, was significantly increased in nickel-exposed female rats. Albumin excretion also tended to be higher in male rats, but did not reach statistical significance because of two control rats with very high values. The investigators noted that male rats develop a spontaneous nephrosis as they age and that this may have obscured the effect of nickel. Significant decreases in urine volume and urine glucose levels and increases in relative kidney weight at 14.4 or 28.8 mg Ni/kg/day and increases in blood urea nitrogen (BUN) at 28.8 mg Ni/kg/day were observed in rats exposed to nickel sulfate in drinking water for 13 weeks (Obone et al. 1999); no changes in γ -glutamyl transpeptidase activity, NAG activities, or histological alterations were observed.

In dogs, polyuria and increased kidney weight were observed after exposure to 62.5 mg Ni/kg/day as nickel sulfate for 2 years; however, renal effects were not observed in similarly treated rats (Ambrose et al. 1976). Several studies in rats have reported significant changes in kidney weights following exposure to 0.97–55 mg Ni/kg/day as nickel salts for 28 days to 9 months (American Biogenics Corporation 1988; RTI 1988b; Weischer et al. 1980). However, there was no consistency in direction of the change; some studies reported increases in kidney weights while others reported decreases. The toxicological significance of these data is not known. Additionally, no histological alterations were observed in the kidneys of male and female rats exposed to 22 or 33 mg Ni/kg/day, respectively, as nickel sulfate administered via gavage for 90 days (Springborn Laboratories 2002).

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

Although histological changes were not observed, increases in pituitary weights were observed in male rats, but not female rats, treated with nickel chloride at doses ≥ 20 mg Ni/kg/day for up to 30 weeks (RTI 1986, 1988a, 1988b). The multigeneration study (RTI 1988a, 1988b) is confounded by a decrease in both food and water intake. Decreased prolactin levels were observed in female rats treated with 31 mg Ni/kg/day as nickel chloride in the drinking water throughout the breeding and lactation of two litters (11 weeks before breeding, 2-week rest period after weaning of the first litter, followed by a second breeding), but not at a 6.8-mg/kg/day dose (Smith et al. 1993). Histological examinations did not reveal any adverse effects in the pituitary, thyroid, and adrenal glands or in the pancreas of rats and dogs treated

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with nickel sulfate in the diet for 2 years at 187.5 mg Ni/kg/day for rats and 62.5 mg Ni/kg/day for dogs (Ambrose et al. 1976).

Dermal Effects. Contact dermatitis, which results from dermal exposure to nickel, is the most prevalent effect of nickel in the general population (see Section 3.2.3.2). Several studies indicate that a single oral dose of nickel given as nickel sulfate can result in a flare-up in the dermatitis in nickel-sensitive individuals (Burrows et al. 1981; Christensen and Moller 1975; Cronin et al. 1980; Gawkrödger et al. 1986; Hindsén et al. 2001; Jensen et al. 2003; Kaaber et al. 1978; Veien et al. 1987). Observed effects included erythema on the body, worsening of hand eczema, and a flare-up at the patch test site. Although some of the older studies reported fairly low LOAEL values (e.g., 0.009 mg Ni/kg), these studies have several design limitations including small sample size, the observation of placebo effects, and non-double-blind study designs (possibly introducing investigator bias). Two more recent studies have addressed a number of these concerns by using a large number of test subjects and a double-blind study design. One month after patch testing, an oral challenge dose of 1.0 mg nickel as nickel sulfate (0.014 mg/kg) resulted in dermatitis in two of nine nickel-sensitive subjects (not significantly different than placebo incidence of 0/9); exposure to 4.0 mg nickel (0.057 mg/kg) resulted in dermatitis in nine of nine subjects (Hindsén et al. 2001). Similarly, an oral challenge of 0, 0.3, 1.0, or 4.0 mg nickel as nickel sulfate (0, 0.0043, 0.014, or 0.057 mg/kg) administered 1 month after patch testing resulted in dermatitis in 1/10, 4/10, 4/10, and 7/10 nickel-sensitized individuals, respectively; no cutaneous reactions were observed in healthy controls receiving an oral challenge dose of 0 or 4.0 mg nickel (Jensen et al. 2003). Although some sensitive individuals may react to very low oral doses of nickel, the threshold for dermatitis in nickel-sensitized individuals appears to be around 0.01 mg Ni/kg; a dose of approximately 0.06 mg Ni/kg will result in a response in the most sensitized individuals.

Nielsen et al. (1990) fed 12 women with hand eczema and known allergy to nickel a diet (oatmeal, soy beans, cocoa) with 5 times the normal level of nickel (about 0.007 mg/kg/day) for 4 days. An aggravation of hand eczema was found in 6/12 by day 4 after the start of the challenge, and although excess nickel was excreted by 2 days after the last treatment, further exacerbation of hand eczema was observed in 10/12 by day 11. It is not clear how well the diets were controlled after the challenge period, and the subjects may have eaten foods that contained vasoactive substances that could exacerbate an allergic reaction. This study also suggests that withdrawal of nickel rather than the peak nickel levels may contribute to the dermatitis observed in some sensitive individuals.

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Intermediate-duration studies suggest that longer-term oral exposure can be tolerated by some nickel-sensitive individuals and may even serve to desensitize some individuals. Jordan and King (1979) found flaring of dermatitis in only 1/10 nickel-sensitive women given nickel sulfate at 0.007 mg/kg/day for 2 weeks. Patch test responses to nickel were reduced in nickel-sensitive women given one weekly dose of 0.05 or 0.07 (but not 0.007) mg Ni/kg as nickel sulfate for 6 weeks (Sjovall et al. 1987). Santucci et al. (1994) gave increasing daily doses of nickel (0.01–0.03 mg/kg/day) as nickel sulfate to eight nickel-sensitive women for up to 178 days. A significant clinical improvement in hand eczema was observed in all subjects after 1 month of treatment, and continued treatment resulted in healing of all dermal lesions except for those on the hands. Measurement of urine and serum nickel suggested a decrease in the absorption of nickel and an increase in the excretion of nickel with longer exposure. The Santucci et al. (1994) study indicates that a daily dose of 0.01–0.03 mg Ni/kg can be tolerated by some nickel-sensitive people and may also serve to reduce their sensitivity. Among 44 sensitive subjects treated with a regimen of 1–2 ng nickel sulfate every other day, or daily for up to 2–3 years, 7 stopped the treatment for unspecified reasons, 7 had reactivation of symptoms, and complete (29) or partial (1) disappearance of symptoms for 2–4 years was observed in 30 subjects. In guinea pigs sensitized before oral treatment with nickel, only a transient desensitization was observed (van Hoogstraten et al. 1991).

Oral exposure before the sensitizing exposure may also help prevent nickel sensitization in some individuals. A study of 2,159 subjects examining the relationship between ear piercing and orthodontic treatment found that nickel sensitivity was reduced significantly when orthodontic treatment preceded ear piercing (23.3 versus 38.1%) (van Hoogstraten et al. 1991). The investigators hypothesized that the oral nickel exposure that occurred during orthodontic treatment helped prevent the sensitization that occurred following ear piercing with earrings containing nickel. Orthodontic treatment after ear piercing did not affect the risk of nickel sensitization. Further evidence that oral exposure to nickel before a sensitizing exposure can prevent hypersensitivity is provided by the observation that nickel sensitivity in mice could be consistently produced only when metal frames to cover the cages and metal water nipples that released nickel were replaced with glass covers and nipples free of nickel (van Hoogstraten et al. 1991). Oral treatment of guinea pigs with nickel sulfate (30 mg/week for 6 weeks) has also been shown to prevent dermal sensitization (van Hoogstraten et al. 1991). Skin exposure of guinea pigs to nickel (non-sensitizing contacts) before oral exposure was also shown to interfere with oral tolerance induction.

Histological changes in the skin have not been observed in rats treated by gavage with nickel chloride at a dose of 8.6 mg Ni/kg/day for 91 days (American Biogenics Corporation 1988), or in rats and dogs exposed to nickel sulfate in the diet for 2 years at doses of 187.5 and 62.5 mg Ni/kg/day, respectively

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(Ambrose et al. 1976). These studies suggest that the skin is not affected by orally administered nickel in animals that have not been previously sensitized to nickel.

Ocular Effects. In a pharmacokinetic study in humans, transient left homonymous hemianopsia (loss of sight in the corresponding lateral half of the eyes) occurred in one male subject following ingestion of 0.05 mg Ni/kg as nickel sulfate in the drinking water (Sunderman et al. 1989b). No adverse effects were found in other subjects (n=9) when lower doses of 0.018 and 0.012 mg Ni/kg were used.

No treatment-related ophthalmological changes were observed in rats treated by gavage with 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988).

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

Decreased body weight gain of 10% or more, associated with reduced food and/or water intake, has been observed in rats treated by gavage with nickel chloride at 8.6 mg Ni/kg/day for 91 days (American Biogenics Corporation 1988) or 55 mg Ni/kg/day for 30 weeks (RTI 1988a), in rats exposed to 0.23-0.97 mg Ni/kg/day as nickel chloride in the drinking water for 28 days (Weischer et al. 1980), and in rats treated with nickel sulfate in the diet at 75 mg Ni/kg/day for 2 years (Ambrose et al. 1976). The concomitant decreases in food and/or water consumption limit the interpretation of these results. Decreases in body weight gain were also observed in male and female rats administered via gavage 17 or 28 mg Ni/kg/day, respectively, as nickel sulfate (Springborn Laboratories 2002); however, the 10–13% decreases in body weight gain were not associated with consistent alterations in food intake (water consumption data were not reported). Decreased body weight gain has also been reported in mice treated with nickel sulfate in drinking water at a dose of 108 mg Ni/kg/day for 180 days (Dieter et al. 1988), and in dogs treated with nickel sulfate in the diet at a dose of 62.4 mg/kg/day for 2 years (Ambrose et al. 1976). Decreases in body weight gain of 10% or more were not observed in rats treated with nickel chloride in the drinking water at 31.6 mg Ni/kg/day for 11 weeks (Smith et al. 1993), with nickel sulfate in drinking water at 28.8 mg Ni/kg/day for 13 weeks (Obone et al. 1999), or with nickel chloride at a dose of 7.6 mg Ni/kg/day for 3 or 6 months (Vyskocil et al. 1994b).

Metabolic Effects. No studies were located regarding metabolic effects in humans after oral exposure to nickel.

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Two studies reported significant alterations in serum glucose levels in rats exposed to nickel chloride. A significant decrease in blood glucose levels was observed in rats administered 8.6 mg Ni/kg/day via gavage for 91 days (American Biogenics Corporation 1988). In contrast, Weischer et al. (1980) reported a significant increase in blood glucose levels in rats administered 0.23 mg Ni/kg/day via drinking water for 28 days. In both studies, significant decreases in body weight gain (20% and higher) were also observed at the same dose effect levels. Thus, it is difficult to assess whether this is a direct effect of nickel or secondary to the effect on body weight.

3.2.2.3 Immunological and Lymphoreticular Effects

Dermatitis resulting from nickel allergy is well reported in the literature (see Section 3.2.2.2 for further discussion of allergic dermatitis following oral exposure).

Effects on the immunological system following exposure to 44 mg Ni/kg/day and higher as nickel sulfate in the drinking water for 180 days were assessed in mice (Dieter et al. 1988). Mild thymic atrophy was observed at 44 mg Ni/kg/day and higher and mild splenic atrophy was observed at 108 mg Ni/kg/day and higher. Although several tests of immune function were performed, only two alterations were found—decreased spleen cellularity at 150 mg Ni/kg/day and impaired lymphoproliferative response to the B-cell mitogen, *Escherichia coli* lipopolysaccharide (LPS), at 44 mg Ni/kg/day and higher; a marginal response to sheep red blood cells was also observed at 150 mg Ni/kg/day. No response to concanavalin A (con A), natural killer cell activity, or resistance to *Listeria monocytogenes* challenge were observed. In addition to the immune function responses, exposure to nickel sulfate resulted in alterations in bone marrow: decreases in bone marrow cellularity at 108 mg Ni/kg/day and higher, decreases in granulocyte-macrophage progenitor cells (CFU-GM) at 44 mg Ni/kg/day and higher, and multipotential stem cells (CFU-S) at 108 mg Ni/kg/day and higher. The stem cell alterations were associated with alterations in glucose-6-phosphate dehydrogenase activity—increased at 44 mg Ni/kg/day and decreased at 108 and 150 mg Ni/kg/day. Obone et al. (1999) reported alterations in T-cell and B-cell subpopulations in the thymus and splenic lymphocytes in rats exposed to nickel sulfate in drinking water for 13 weeks. In the spleen, the changes consisted of an increase in the total number of cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; an increase in CD⁴⁺ T cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; increases in CD⁸⁺ T cells at 14.4 and 28.8 mg Ni/kg/day; an increase in the number of B cells at 14.4 mg Ni/kg/day; and a decrease in the ratio of B cells to total cells at 14.4 mg Ni/kg/day. In the thymus, the changes consisted of an increase in the total number of cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; an increase in CD⁴⁺ T cells at 14.4 mg Ni/kg/day and a decrease at

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28.8 mg Ni/kg/day; a decrease in the ratio of CD⁴⁺ T cells to total cells at 28.8 mg Ni/kg/day; increases in CD⁸⁺ T cells at 5.75 and 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; increases in the ratio of CD⁸⁺ T cells to total cells at 5.75 mg Ni/kg/day and higher; and an increase in the number of B cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day. When challenged with Coxsackie virus B3, an enhanced inflammatory response was observed in the hearts of mice treated with nickel chloride in drinking water at 20.3 mg Ni/kg/day for 10–11 weeks (Ilback et al. 1994). Nickel treatment had no adverse effect on virus-induced lethality, spleen or thymus weights, or the number of cells in the spleen or thymus. Gross and microscopic examinations of the spleen did not reveal any adverse effects in rats or dogs fed nickel sulfate in the diet for 2 years at doses of 187.5 mg/kg/day for rats and 62.5 mg/kg/day for dogs (Ambrose et al. 1976).

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species, duration category, and nickel compound are recorded in Table 3-8 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Neurological effects were observed in workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The dose to which the workers with symptoms were exposed was estimated to be 7.1–35.7 mg Ni/kg. The neurological effects included giddiness (seven workers), weariness (six workers), and headache (five workers). The contribution of boric acid to these effects is not known.

In a study designed to determine the absorption and elimination of nickel in humans, one male who ingested a single dose of 0.05 mg Ni/kg as nickel sulfate in drinking water developed left homonymous hemianopsia (loss of sight in the corresponding lateral half of the eyes) 7 hours later; the condition lasted for 2 hours (Sunderman et al. 1989b). The loss of sight occurred soon after the peak serum concentration of nickel was reached, leading the investigators to suspect a causal relationship between nickel exposure and the loss of sight. The doses given to other subjects were lowered to 0.018 and 0.012 mg Ni/kg with no adverse effects.

In a 90-day study, lethargy, ataxia, prostration, irregular breathing, and cool body temperature were observed in rats treated by gavage with nickel chloride (American Biogenics Corporation 1988). These effects were observed frequently at 25 mg Ni/kg/day, a dose at which all rats died, and at lower

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incidences at 8.6 mg Ni/kg/day, a dose at which 6/52 rats died. At the lower dose, it is not clear if the adverse neurological effects were observed only in the animals that died. No signs of neurological dysfunction were observed at 1.2 mg/kg/day. Microscopic examinations of whole brains did not reveal any changes in the brains of rats or dogs treated with nickel salts at doses of 8.6 mg Ni/kg/day for up to 2 years (Ambrose et al. 1976; American Biogenics Corporation 1988).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species, duration category, and nickel compound are recorded in Table 3-8 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

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

A number of studies have examined the reproductive toxicity of nickel following oral exposure to rats, mice, or dogs. The studies have found conflicting results, with some studies identifying LOAELs for serious health effects and others identifying NOAELs at very similar dose levels. Pandey et al. (1999) reported an accumulation of nickel (in descending order of concentration) in the epididymis, testes, seminal vesicles, and prostate gland in mice orally exposed to nickel sulfate for 35 days. The accumulation of nickel in male reproductive tissues resulted in histological damage in the epididymis and seminal vesicles and sperm damage. Regressed epithelium and vacuolated cells were observed in the epididymis of mice administered 1.1 mg Ni/kg as nickel sulfate via gavage 5 days/week for 35 days (Pandey et al. 1999). In the seminiferous tubules, the damage consisted of atrophy of centrally located tubules and disturbed spermatogenesis in mice administered 1.1 mg Ni/kg as nickel sulfate (5 days/week) (Pandey et al. 1999). The significance of these findings is not known because the incidence data and statistical analysis were not reported. Käkälä et al. (1999) reported a statistically significant decrease in seminiferous tubule diameter in rats exposed to 3.6 mg Ni/kg/day as nickel chloride in drinking water for 28 or 42 days. A significant decrease in basal spermatogonia was also observed in the rats exposed for 28 days, but not in the rats exposed for 42 days. Although it was not discussed in the report, the final body weights of males exposed for 28 days appear to be lower than control body weights; this may have contributed to the histological findings. Other studies have not found histological alterations in male or female reproductive tissues in rats administered up to 25 mg Ni/kg/day as nickel chloride for 91 days (American Biogenic Corp 1988), rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 90 days (Obone et al. 1999), rats exposed to 2.2 mg Ni/kg/day as nickel sulfate administered via gavage for 18 weeks (Springborn Laboratories 2000a), rats exposed to 187.5 mg Ni/kg/day as nickel sulfate in the

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diet for 2 years (Ambrose et al. 1976), or dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976).

Significant decreases in sperm count and sperm motility and sperm abnormalities (banana and detached head; acrosome up, down, or missing; curved neck and curved, bent, round, loop, and folded tail) were observed in mice administered ≥ 2.2 mg Ni/kg as nickel sulfate (decreased sperm count significant at 4.5 mg Ni/kg) or 2.5 mg Ni/kg as nickel chloride 5 days/week for 35 days (Pandey and Srivastava 2000); no sperm effects were observed at 1.1 or 1.2 mg Ni/kg as nickel sulfate or nickel chloride, respectively. Although the route of administration was not reported, it is assumed that the nickel chloride and nickel sulfate were administered via gavage. The investigators reported a dose-related decrease in body weight gain and decreases in absolute and relative testes, epididymis, seminal vesicle, and prostate gland weights at the two highest dose levels (2.2 and 4.5 mg Ni/kg as nickel sulfate and 2.5 and 4.9 mg Ni/kg as nickel chloride). Similarly, Pandey et al. (1999) reported decreases in sperm count and motility in mice administered 2.2 mg Ni/kg as nickel sulfate, 5 days/week for 35 days; an increase in sperm abnormalities was also observed at 1.1 mg Ni/kg. Although Pandey et al. (1999) did not report alterations in body weight gain, significant decreases in testes, epididymis, seminal vesicle, and prostate gland weights were observed. In both studies by Pandey and associates, there were no significant alterations in the occurrence of a particular sperm abnormality; the total number of abnormalities was increased. Sobti and Gill (1989) reported increases in sperm head abnormalities in mice receiving a single gavage dose of 23, 28, or 43 mg/kg as nickel nitrate, nickel sulfate, or nickel chloride, respectively; it should be noted that this study was poorly reported and no information on number of animals tested was given. No alterations in sperm count, concentration, motility, or morphology were observed in the F0 or F1 rats administered 2.2 mg Ni/kg/day as nickel sulfate via gavage for 18 weeks (Springborn Laboratories 2000a).

In addition to the histological alterations and sperm alterations, alterations in fertility were observed in some studies, but not in all studies. Male-only exposure or male and female exposure to 3.6 mg Ni/kg/day as nickel chloride in drinking water resulted in decreased fertility in rats exposed for 28 days prior to mating (Käkelä et al. 1999). However, male rats exposed to 3.6 mg Ni/kg/day for 42 days prior to mating with unexposed females resulted in a small decrease in fertility (83 versus 100%) (Käkelä et al. 1999); suggesting regeneration of damaged tissues. Female-only exposure to concentrations as high as 13 mg/kg/day as nickel chloride in drinking water did not adversely affect fertility in rats (Käkelä et al. 1999). Interpretation of this study is limited by the small number of animals tested (six gender/group) and the limited reporting of the results. No adverse effects on fertility were observed in a multigeneration study in which male and female rats exposed to doses as high as 55 mg Ni/kg/day as nickel chloride in

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drinking water for 11 weeks prior to mating (RTI 1988a, 1988b), in a single generation study in which rats were administered 16.7 mg Ni/kg/day as nickel sulfate via gavage for 2-weeks prior to mating, during mating, and during gestation (Springborn Laboratories 2000b), in a two-generation study involving gavage administration of up to 2.2 mg Ni/kg/day for 10 weeks prior to mating, during mating, gestation, and lactation (Springborn Laboratories 2000a), or in a multilitter study in which female rats were exposed to doses as high as 31.6 mg Ni/kg/day (Smith et al. 1993).

The highest NOAEL value and all LOAEL values from each reliable study for reproductive effects in each species, duration category, and nickel compound are recorded in Table 3-8 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to nickel.

The available animal data on developmental toxicity provide suggestive evidence that the developing fetus and neonates are sensitive targets of nickel toxicity. The most commonly reported end point is fetal loss and decreased survival observed in the rat and mouse offspring in studies involving male-only exposure, female-only exposure, and combined male and female exposure in single generation, multilitter, and multigeneration studies. The developmental effects were often reported at maternally toxic doses. Other developmental end points that have been examined include body weights, gross necropsy for abnormalities, and neurodevelopmental toxicity.

Male-only exposure to 3.6 mg Ni/kg/day as nickel chloride in drinking water for 28 days resulted in decreases in the number of pups born alive (2.7/dam versus 10.2/dam in controls), the number of pups surviving until postnatal day 4 (56% versus 100% in controls), and litter size at postnatal day 21 (1.3 pups versus 9.2 pups in controls) (Käkelä et al. 1999). However, when the male rats were exposed to 3.6 mg Ni/kg/day for 42 days, no significant alterations in pup viability or survival were observed (Käkelä et al. 1999). A NOAEL was not identified in this study.

Several studies examined female-only exposure to nickel (Berman and Rehnberg 1983; Käkelä et al. 1999; Smith et al. 1993). An increase in spontaneous abortions was observed in female mice exposed to 160 mg Ni/kg/day as nickel chloride in drinking water on gestational days 2–17 (Berman and Rehnberg 1983); no effects were observed at 80 mg Ni/kg/day. In contrast, no effects on the average number of neonates per litter were observed when mouse dams were treated by gavage on gestation days 8–12 with

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90.6 mg Ni/kg/day as nickel chloride (a dose that resulted in a significant decrease in maternal body weight) (Seidenberg et al. 1986). Exposure of rats to 13 mg Ni/kg/day as nickel chloride in drinking water for 14 days prior to mating, during mating, gestation, and lactation resulted in a decreased pup survival from birth to postnatal day 4 (87 versus 100% in controls) and from postnatal day 4 to 21 (52 versus 90% in controls) (Käkelä et al. 1999); no significant alterations were observed at 4.0 mg Ni/kg/day. Pup mortality was also observed in a multilitter study in which rats were exposed to 0, 1.3, 6.8, or 31.6 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to breeding and during two successive gestation and lactation periods (Smith et al. 1993). In the first litter, the percentages of dead pups per litter at postnatal day 1 were 1.7, 3.1, 0, and 13.2% (statistically significant at the high dose only); no significant alterations were observed in the number of dead pups at postnatal day 21. In the second litter, the number of litters with dead pups at birth (2, 7, 6, and 10%; statistically significant at high dose only), the percentages of dead pups per litter at postnatal day 1 (1.0, 4.3, 4.6, and 8.8%; statistically significant at all three dose levels), and the percentage of dead pups at postnatal day 21 (12.5, 13.4, 19.4, and 29.2%; significant at high dose only) were increased.

Offspring mortality was also observed in four studies involving combined male and female exposure (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Springborn Laboratories 2000b). Exposure of rats to 3.6–4.0 mg Ni/kg/day as nickel chloride in drinking water for 28 days prior to mating, during mating, gestation, and lactation adversely affected the litter size at postnatal day 21 (2.7/dam versus 9.2/dam in controls) and pup survival from postnatal day 4 to 21 (44 versus 90% in controls) (Käkelä et al. 1999); a NOAEL was not identified. Significant increases in post-implantation losses were observed in the offspring of rats administered 6.7 mg Ni/kg/day as nickel sulfate via gavage for 14 days prior to mating, during mating, and gestation (Springborn Laboratories 2000b); at 16.7 mg Ni/kg/day, an increased number of dead pups at lactation day 0 and a decreased mean litter size were observed. This study identified a NOAEL of 4.5 mg Ni/kg/day. In a multigeneration study (Ambrose et al. 1976) involving exposure of rats to 0, 22.5, 45, or 90 mg Ni/kg/day as nickel chloride in the diet for 11 weeks prior to mating, during mating, gestation, and lactation, a dose-related increase in the number of stillborn pups was observed. An independent statistical analysis of the data using the Fisher Exact Test found significant increases in the total number pups born dead at 22.5 mg Ni/kg/day and higher for the F1a generation, 45 and 90 mg Ni/kg/day for the F1b generation, 90 mg Ni/kg/day for the F2a generation, 22.5 mg Ni/kg/day for the F2b generation, and 45 and 90 mg Ni/kg/day for the F3b generation. The study authors noted that the number of offspring (dead and alive) was progressively less with increasing nickel levels above 45 mg/kg/day (10.3, 10.6, 9.8, and 9.0 for 0, 22.5, 45, and 90 mg/kg/day, respectively); the number of offspring weaned per litter was also decreased with increasing nickel levels (8.1, 7.2, 6.8, and

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6.4 for 0, 22.5, 45, and 90 mg/kg/day, respectively). The third study (RTI 1988a, 1998b) is a two-generation study in which the P0 generation was exposed to nickel chloride in drinking water for 11 weeks before mating and during gestation and lactation, and the F1b generation animals were mated to produce the F2 generations. A reduction in live litter size was observed in the F1a, F1b, and F2a offspring of rats exposed to 55 mg Ni/kg/day. Increases in mortality were also observed in the F1b rats on postnatal days 22 through 42; these increases were statistically significant in males at 30 and 55 mg Ni/kg/day and in females at 55 mg Ni/kg/day. No adverse developmental effects were observed in the cesarean delivered F2b rats, suggesting that the nickel-induced decrease in live litter size occurred postnatally. No alterations in offspring mortality or survival were observed in a two-generation study in which rats were administered up to 2.2 mg Ni/kg/day as nickel sulfate via gavage for approximately 18 weeks (Springborn Laboratories 2000a).

Decreases in pup body weights were reported in the offspring of rats exposed to 90 mg Ni/kg/day (Ambrose et al. 1976), 30, and 55 mg Ni/kg/day (RTI 1988a, 1988b). Neither the Ambrose et al. (1976) nor the RTI (1988a, 1988b) multigeneration studies found significant, nickel-related gross abnormalities in the surviving offspring of rats exposed to nickel. Käkälä et al. (1999) noted that the pups that died during lactation were runts: the heads were disproportionately large and the posteriors of the bodies were underdeveloped. No effects on figure eight maze reactive locomotor activity levels were observed in the offspring of mice treated by gavage at 45.3 mg Ni/kg/day as nickel chloride on gestation days 8–12 (Gray et al. 1986).

In summary, these data provide suggestive evidence that exposure to nickel prior to mating and during gestation and lactation results in decreased survival (Ambrose et al. 1976; Käkälä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). Decreased survival was also observed in the offspring of male rats exposed prior to mating to unexposed females (Käkälä et al. 1999) and increased spontaneous abortions were observed following gestation-only exposure of mice (Berman and Rehnberg 1983). Interpretation of these data is complicated by the maternal toxicity, in particular, a decrease in maternal body weight gain, which was also observed at these dose levels (Ambrose et al. 1976; Käkälä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). Decreases in food and water intake have also been observed (RTI 1988a, 1988b; Smith et al. 1993).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species, duration category, and nickel compound are recorded in Table 3-8 and plotted in Figure 3-2.

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3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to nickel.

In lifetime drinking water studies in rats and mice, nickel acetate (0.6 mg Ni/kg/day for rats; 0.95 mg Ni/kg/day for mice) was found to be noncarcinogenic (Schroeder et al. 1964, 1974). The incidence of tumors was comparable to that observed in controls.

3.2.3 Dermal Exposure**3.2.3.1 Death**

No studies were located regarding death in humans or animals after dermal exposure to nickel.

3.2.3.2 Systemic Effects

No studies were located regarding adverse cardiovascular, gastrointestinal, musculoskeletal, or ocular effects in humans or animals after dermal exposure to nickel.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects for each species, duration category, and nickel compound are recorded in Table 3-9.

Respiratory Effects. Scratch tests and intradermal tests were performed on a patient diagnosed with nickel-related asthma (McConnell et al. 1973). Nonasthmatic controls were also tested. Testing resulted in respiratory distress in the patient but not in the controls, with a more severe response resulting from the scratch test.

No studies were located regarding adverse respiratory effects in animals after dermal exposure to nickel.

Hematological Effects. No studies were located regarding adverse hematological effects in humans after dermal exposure to nickel.

Table 3-9 Levels of Significant Exposure to Nickel - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Human	once	Dermal	0.01 Percent (%)	0.0316 Percent (%)	(contact dermatitis in sensitive individuals)	Emmett et al. 1988 sulfate
Human	once	Dermal		0.04 Percent (%)	(allergic dermatitis in sensitive individuals)	Eun and Marks 1990 sulfate
Human	once	Dermal	0.01 Percent (%)	0.1 Percent (%)	(skin reaction in nickel sensitive individuals)	Menne and Calvin 1993 chloride
Human	once	Dermal		1 mg/cm2/week	(contact dermatitis)	Menne et al. 1987 nickel alloys
Immuno/ Lymphoret						
Mouse (C3H:Hej)	once occluded for 7d			1 F Percent (%)	(development of dermal sensitization)	Siller and Seymour 1994 sulfate
INTERMEDIATE EXPOSURE						
Systemic						
Rat (NS)	15 or 30d daily	Hepatic	40 M mg/kg/day	60 M mg/kg/day	(focal necrosis)	Mathur et al. 1977 sulfate
		Renal	100 M mg/kg/day			
		Dermal		40 M mg/kg/day	(slight hyperkeratosis)	60 M mg/kg/day (degeneration of basal layer)

Table 3-9 Levels of Significant Exposure to Nickel - Dermal

(continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
Gn Pig (NS)	15 or 30d	Hemato	100 mg/kg/day			Mathur and Gupta 1994 sulfate
		Hepatic		100 mg/kg/day	(increased Mg ²⁺ ATPase, acid phosphatase, and glucose-6-phosphatase activities)	
		Renal		100 mg/kg/day	(increased Mg ²⁺ ATPas activity)	
		Endocr		100 mg/kg/day	(increased blood glucose)	
Reproductive						
Rat (NS)	30 d daily		40 M mg/kg/day		60 M mg/kg/day	(degeneration and edema of seminiferous tubules)
						Mathur et al. 1977 sulfate

d = day(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million

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Hematocrit and hemoglobin levels were not affected in guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994). Only one dose level was used in this study.

Hepatic Effects. No studies were located regarding adverse hepatic effects in humans after dermal exposure to nickel.

Effects on the liver were observed in rats treated dermally (lateral abdominal area) with daily doses of 60 mg Ni/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). The effects included swollen hepatocytes and feathery degeneration after 15 days and focal necrosis and vacuolization after 30 days.

In this study, there was no indication that the rats were prevented from licking the nickel from the skin; therefore, these effects could have resulted from oral exposure. Increased Mg^{2+} ATPase activity was observed in the livers of guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994). Acid phosphatase and glucose-6-phosphatase activities were increased only after 30 days of treatment.

Renal Effects. Proteinuria was not observed in electroforming industry workers exposed to nickel. No information was provided on exposure level or nickel compound (Wall and Calnan 1980).

No gross or microscopic lesions were observed in the kidneys of rats treated dermally with ≤ 100 mg Ni/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). In this study, there was no indication that the rats were prevented from licking the nickel from the skin; therefore, the animals could have been orally exposed. Increased Mg^{2+} ATPase activity was observed in the kidneys of guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 30 days (Mathur and Gupta 1994). No adverse effect was noted at 15 days, and dermal nickel exposure had no effect on kidney acid phosphatase or glucose-6-phosphatase activities.

Endocrine Effects. No studies were located regarding adverse endocrine effects in humans after dermal exposure to nickel.

Blood glucose levels were significantly increased in guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994).

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Dermal Effects. Allergic contact dermatitis is a commonly reported effect in humans exposed to nickel. Contact dermatitis was found in 15.5% of approximately 75,000 individuals undergoing patch tests with nickel sulfate (5% in petrolatum) (Uter et al. 2003). Smaller scale studies reported a similar frequency: 19.1% of 542 subjects (Akasya-Hillenbrand and Özkaya-Bayazit 2002), 21.2% of 1,729 subjects (Wantke et al. 1996), and 20.13% of 3,040 subjects (Simonetti et al. 1998). In the general population (a random sample of 567 people aged 15–69 years responding to a mailed screening questionnaire on respiratory allergy symptoms), 11% of the subjects had a positive reaction to nickel patch tests (Nielsen et al. 2002). Contact dermatitis in response to nickel exposure is more frequently observed in females, particularly younger females, than in males or older individuals (Uter et al. 2003; Wantke et al. 1996). This increased prevalence appears to be related to previous nickel exposure rather than increased susceptibility. Prolonged exposure to nickel in consumer products, especially jewelry, rather than occupational exposure, is often the sensitizing source. An association has been observed between ear piercing and nickel sensitivity (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995; Uter et al. 2003). The prevalence of nickel allergy was 9% among girls (age 8, 11, and 15; n=960) with pierced ears compared to 1% among girls without pierced ears. Girls with more than one hole in each ear were also more likely to be sensitive to nickel than girls with only one hole in each ear (19 versus 11%) (Larsson-Stymne and Widstrom 1985). In a study in schoolchildren age 7–12, the frequency of nickel allergy was 30.8% among girls with pierced ears and 16.3% among girls who did not have pierced ears (Dotterud and Falk 1994). Similarly, 14% of females with pierced ears developed nickel allergy compared to 4% in females without pierced ears (Nielsen et al. 2002). Among a group of Swedish men (age 18–24) completing military service, 4.6% with pierced ears reacted to nickel, while 0.8% who did not have pierced ears had a positive reaction to nickel (Meijer et al. 1995). Keczkes et al. (1982) have shown that sensitivity to nickel remains for many years. Fourteen people who tested positively for nickel sensitivity using nickel sulfate also tested positive 10 years later. However, the time interval between exposures can influence the degree of reactivity (Hindsén et al. 1997). A stronger reaction was found in nickel sensitized women when there was a 1-month period between nickel sulfate exposures compared to a 4-month period. This study also found a stronger reaction when nickel sulfate was applied to an area with previous allergic contact dermatitis.

Patch test studies in sensitive individuals using nickel sulfate have shown a dose-response relationship between the amount of nickel and the severity of the test response (Emmett et al. 1988; Eun and Marks 1990). In a study of 12 individuals, a nickel concentration of 0.0316% (316 ppm) in petrolatum resulted

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in dermatitis, while a concentration of 0.01% (100 ppm) did not produce adverse effects (Eun and Marks 1990). In aqueous solution, the nickel concentration of 0.0316% (316 ppm) did not result in dermatitis.

Although most patch testing is done with nickel sulfate because it is less irritating than nickel chloride, nickel alloys on the skin interact with human sweat, resulting in the release of nickel chloride. Therefore, nickel chloride is the more relevant form of nickel for examining threshold concentrations (Menne 1994). Menne and Calvin (1993) examined skin reactions to various concentrations of nickel chloride in 51 sensitive and 16 nonsensitive individuals. Although inflammatory reactions in the sweat ducts and hair follicles were observed at 0.01% and lower, positive reactions to nickel were not observed. To be scored as a positive reaction, the test area had to have both redness and infiltration, while the appearance of vesicles and/or a bullous reaction were scored as a more severe reaction. At 0.1%, 4/51 and 1/51 tested positive with and without 4% sodium lauryl sulfate. Menne et al. (1987) examined the reactivity to different nickel alloys in 173 nickel-sensitive individuals. With one exception (Inconel 600), alloys that released nickel into synthetic sweat at a rate of $<0.5 \mu\text{g}/\text{cm}^2/\text{week}$ showed weak reactivity, while alloys that released nickel at a rate of $>1 \mu\text{g}/\text{cm}^2/\text{week}$ produced strong reactions.

Nickel sensitivity has been induced in guinea pigs following skin painting or intradermal injection with nickel sulfate (Turk and Parker 1977; Wahlberg 1976; Zissu et al. 1987). As discussed in Section 3.2.2.2, nickel sensitivity can also be induced in mice if oral exposure to nickel is reduced (Moller 1984; van Hoogstraten et al. 1991).

Adverse effects on the skin were observed in rats treated dermally with $\geq 40 \text{ mg Ni/kg/day}$ as nickel sulfate for 15 or 30 days (Mathur et al. 1977). The effects included distortion of the epidermis and dermis after 15 days and hyperkeratinization, vacuolization, hydropic degeneration of the basal layer, and atrophy of the epidermis at 30 days. Biochemical changes in the skin (enzymatic changes, increased lipid peroxidation, and an increase in the content of sulfhydryl groups and amino nitrogen) were observed in guinea pigs dermally exposed to nickel sulfate for up to 14 days (Mathur et al. 1988, 1992). Additive effects were observed when nickel sulfate was given in combination with sodium lauryl sulfate.

3.2.3.3 Immunological and Lymphoreticular Effects

Contact dermatitis resulting from nickel allergy is well reported in the literature (see Section 3.2.3.2 for further discussion of allergic reactions to nickel following dermal exposure). A relationship between human lymphocyte antigens (HLA) and nickel sensitivity was observed in individuals who had contact

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allergic reactions and positive results in the patch test (Mozzanica et al. 1990). The individuals had not been occupationally exposed to nickel. The HLA typing found a significantly greater prevalence of HLA-DRw6 antigen in the nickel-sensitive group compared to normal controls. The relative risk for individuals with DRw6 to develop a sensitivity to nickel was approximately 3.3. In individuals with allergic contact dermatitis to nickel, nickel directly bound and activated T-cells (Kapsenberg et al. 1988).

The dose-response relationship for the development of nickel sensitivity has been examined in a mouse model (Siller and Seymour 1994). The sensitization exposure involved placing a 6-mm pad containing 45 µL of a 0, 1, 5, 10, 15, or 20% nickel sulfate solution on the shaved abdominal skin of mice. This pad was left on the skin under occlusion for 7 days. Seven days after the sensitization procedure, the mice were challenged with 10 µL of a 0.4% aqueous nickel sulfate solution injected into the footpad. Saline was injected into the opposite footpad as a control. Contact hypersensitivity, indicated by footpad swelling, was elicited at all doses, although the degree of swelling was minimal at the 1% concentration. Footpad swelling increased as the sensitizing dose increased and generally peaked between 24 and 48 hours after the challenge. In a comparison of the responses between male and female mice, males showed a weaker and more variable response than females, and the response peaked at 72 hours in males compared to 48 hours in females. The LOAEL for sensitization in mice is recorded in Table 3-9.

3.2.3.4 Neurological Effects

No studies were located regarding adverse neurological effects in humans or animals after dermal exposure to nickel.

3.2.3.5 Reproductive Effects

No studies were located regarding adverse reproductive effects in humans after dermal exposure to nickel.

Tubular degeneration of the testes was observed in rats treated dermally with nickel sulfate at 60 mg Ni/kg/day for 30 days (Mathur et al. 1977). No effects were found at 40 mg Ni/kg/day after 30 days or at doses of ≤ 100 mg Ni/kg/day after 15 days of treatment. In this study, there was no indication that the rats were prevented from licking the nickel sulfate from the skin; therefore, these effects could have resulted from oral exposure. Consequently, these values do not appear in Table 3-9.

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3.2.3.6 Developmental Effects

No studies were located regarding adverse developmental effects in humans or animals after dermal exposure to nickel.

3.2.3.7 Cancer

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

3.3 GENOTOXICITY

A number of studies have examined the genotoxicity of a variety of nickel compounds; the results of these *in vivo* and *in vitro* tests are presented in Tables 3-10 and 3-11, respectively. The available weight of evidence suggests that nickel does not alter the frequency of gene mutations in nonmammalian organisms (Arlauskas et al. 1985; Biggart and Costa 1986; Green et al. 1976; Marzin and Phi 1985; Rasmuson 1985; Wong 1988), although some studies have found gene mutations (Ogawa et al. 1994; Pikalek and Necasek 1983; Rodriguez-Arnaiz and Ramos 1986). Mixed results for gene mutations have been found in mammalian test systems. Increases in the frequency of gene mutations have been found at the HGPRT locus in Chinese hamster V79 cells (Hartwig and Beyersmann 1989; Miyaki et al. 1979) but not in Chinese hamster ovary cells (Hsie et al. 1979). An increase in gene mutation frequency has also been found in Chinese hamster ovary AS52 cells (*grp* locus) (Fletcher et al. 1994), mouse lymphoma cells (Amacher and Paillet 1980; McGregor et al. 1988), and virus-infected mouse sarcoma cells (Biggart and Murphy 1988; Biggart et al. 1987). Gene mutation frequency was not affected in transgenic mouse and rat respiratory tissue following inhalation exposure to nickel subsulfide (Mayer et al. 1998).

There is some evidence to suggest that nickel is clastogenic and can damage DNA. Chromosome gaps or chromosome aberrations have been reported in lymphocytes from nickel refinery workers (Waksvik and Boysen 1982), mouse bone marrow cells following intraperitoneal injection (Dhir et al. 1991), and in *in vitro* assays using hamster cells (Conway and Costa 1989; Larramendy et al. 1981; Sen and Costa 1986b; Sen et al. 1987), human lymphocytes (Larramendy et al. 1981; Lechner et al. 1984), and human bronchial epithelial cells (Lechner et al. 1984). No alterations in the occurrence of sister chromatid exchange were observed in lymphocytes from nickel refinery workers (Waksvik and Boysen 1982), but increases were found in *in vitro* assays of human lymphocytes (Andersen 1983; Arrouijal et al. 1992; Larramendy et al.

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Table 3-10. Genotoxicity of Nickel *In Vivo*

Species (test system)	End point	Results	Reference	Compound
<i>Drosophila melanogaster</i>	Gene mutation	–	Rasmuson 1985	Nickel nitrate or chloride
<i>D. melanogaster</i>	Recessive lethal	+	Rodriguez-Arnaiz and Ramos 1986	Nickel sulfate
<i>D. melanogaster</i>	Gene mutation (wing spot test)	±	Ogawa et al. 1994	Nickel chloride
Mammalian cells:				
Human lymphocytes	Chromosome gaps	+	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
Human lymphocytes	Sister chromatid exchange	–	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
Rat bone marrow and spermatogonial cells	Chromosome aberrations	–	Mathur et al. 1978	Nickel sulfate
Mouse bone marrow cells	Chromosome aberrations (ip)	+	Dhir et al. 1991	Nickel chloride
Mouse bone marrow cells	Micronucleus test (ip)	–	Morita et al. 1997	Nickel chloride, nickel sulfate, nickel oxide
Rat bone marrow cells	Micronucleus test (oral)	–	Covance Laboratories, Inc. 2003	Nickel sulfate
Mouse bone marrow cells	Micronucleus test (ip)	–	Deknudt and Leonard 1982	Nickel chloride
Mouse lung, mouse nasal mucosa, rat lung, rat nasal mucosa	Gene mutation (inhalation)	–	Mayer et al. 1998	Nickel subsulfide
Mouse	Dominant lethal (ip)	–	Deknudt and Leonard 1982	Nickel acetate

– = negative result; + = positive result; ± = weakly positive; (ip) = intraperitoneal

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Table 3-11. Genotoxicity of Nickel *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Prokaryotic organisms:				
<i>Salmonella typhimurium</i>	Gene mutation frequency	–	Arlauskas et al. 1985; Biggart and Costa 1986; Marzin and Phi 1985; Wong 1988	Nickel chloride, nickel nitrate, nickel sulfate
<i>Escherichia coli</i> WP2	Gene mutation frequency	–	Green et al. 1976	Nickel chloride
<i>Cornebacterium sp.</i>	Gene mutation frequency	+	Pikalek and Necasek 1983	Nickel chloride
<i>E. coli</i>	DNA replication rate	+	Chin et al. 1994	Nickel chloride
<i>Bacillus subtilis</i>	DNA damage (rec assay)	–	Kanematsu et al. 1980	Nickel oxide and trioxide
Eukaryotic organisms				
Fungi				
<i>Saccharomyces cerevesiae</i>	Reverse mutation	–	Singh 1984	Nickel sulfate
Mammalian cells:				
CHO cells	Gene mutation at HGPRT locus	–	Hsie et al. 1979	Nickel chloride
Virus-infected mouse sarcoma cells	Induction of revertant foci	+	Biggart and Murphy 1988; Biggart et al. 1987	Nickel chloride
Mouse lymphoma cells	Forward mutation	+	Amacher and Paillet 1980; McGregor et al. 1988	Nickel chloride, nickel sulfate
Chinese hamster V79 cells	Gene mutation at HGPRT locus	+	Harwig and Beyersmann 1989; Miyaki et al. 1979	Nickel chloride
Chinese hamster ovary AS52 cells	Gene mutation at <i>grp</i> locus	+	Fletcher et al. 1994	Nickel oxide (black and green); amorphous nickel sulfide; nickel subsulfide nickel chloride; nickel sulfate; nickel acetate
CD2F1 mouse lung and nasal mucosa cells	DNA fragmentation	+	Mayer et al. 1998	Nickel subsulfide
Chinese hamster ovary cells	DNA protein crosslinks/single strand breaks	+	Hamilton-Koch et al. 1986; Patierno and Costa 1985	Crystalline NiS, nickel chloride
Human diploid fibroblasts	DNA single strand breaks	–	Hamilton-Koch et al. 1986	Nickel chloride

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Table 3-11. Genotoxicity of Nickel *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Human gastric mucosal cells	DNA damage (comet analysis)	— ^a	Pool-Zobel et al. 1994	Nickel sulfate
Human HeLa cells	DNA replication	+	Chin et al. 1994	Nickel chloride
Hamster cells	Sister chromatid exchange	+	Andersen 1983; Larramendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981	Nickel sulfate, nickel chloride; crystalline NiS
Human lymphocytes	Sister chromatid exchange	+	Andersen 1983; Larramendy et al. 1981; Saxholm et al. 1981; Wulf 1980	Nickel sulfate, nickel sulfide
Hamster cells	Chromosome aberration	+	Conway and Costa 1989; Larramendy et al. 1981; Sen and Costa 1986b; Sen et al. 1987	Nickel sulfate, nickel chloride, nickel mono-sulfide
Human lymphocytes	Chromosome aberration	+	Larramendy et al. 1981	Nickel sulfate
Human lymphocytes	Sister chromatid exchange	+	Arrouijal et al. 1992	Nickel subsulfide
	Metaphase analysis	+		
	Micronucleus formation	+		
Human bronchial epithelial cells	Chromosome aberration	+	Lechner et al. 1984	Nickel sulfate
Hamster cell and C3H/10T1/2 cells	Cell transformation	+	Conway and Costa 1989; Costa and Heck 1982; Costa and Mollenhauer 1980; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stern 1984; Saxholm et al. 1981	Nickel monosulfide, nickel subsulfide, nickel chloride, nickel, nickel oxide or trioxide
Mouse embryo fibroblasts	Cell transformation	—	Miura et al. 1989	Nickel sulfate, nickel chloride
Mouse embryo fibroblasts	Cell transformation	+	Miura et al. 1989	Nickel subsulfide, nickel monosulfide, nickel oxide
Human foreskin cells	Cell transformation	+	Biedermann and Landolph 1987	Nickel subsulfide, nickel oxide, nickel sulfate, nickel acetate

^aNickel was genotoxic and cytotoxic at the same concentration (9.5 µmol/mL), so it was not a selective genotoxicant.

— = negative result; + = positive result; DNA = deoxyribonucleic acid; NiS = nickel sulfide

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1981; Ohno et al. 1982; Saxholm et al. 1981; Wulf 1980) and hamster cells (Andersen 1983; Larramendy et al. 1981; Saxholm et al. 1981). Micronucleus formation was not affected in rat or mouse bone marrow cells following oral or intraperitoneal exposure (Covance Laboratories 2003; Deknudt and Leonard 1982; Morita et al. 1997). DNA damage consisted of fragmentation in mouse lung and nasal mucosal cells (Mayer et al. 1998) and DNA protein crosslink and/or single strand breaks in Chinese hamster ovary cells (Hamilton-Koch et al. 1986; Patierno and Costa 1985). However, DNA single strand breaks and damage (as assessed using comet analysis) were not found in human diploid fibroblasts (Hamilton-Koch et al. 1986) or human gastric mucosal cells (Pool-Zobel et al. 1994), respectively.

3.4 TOXICOKINETICS

Following inhalation exposure, about 20–35% of nickel deposited in the lungs of humans is absorbed into the bloodstream. Absorption from the respiratory tract is dependent on the solubility of the nickel compound, with higher urinary nickel levels observed in workers exposed to soluble nickel compounds (nickel chloride, nickel sulfate) than in those exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide). Following oral exposure, about 27% of the nickel given to humans in drinking water was absorbed, while only about 1% was absorbed when nickel was given with food. Nickel applied directly to the skin can be absorbed into the skin where it may remain rather than entering the bloodstream.

Autopsy data from nonoccupationally exposed individuals indicate that the highest concentrations of nickel are found in the skin, adrenal glands, and intestines. Following inhalation exposure, nickel also tends to accumulate in the lungs. The pituitary may accumulate nickel if exposure occurs during pregnancy. Nickel has been shown to cross the placenta, and nickel can accumulate in milk, resulting in exposure of the offspring. In human serum, the exchangeable pool of nickel is bound to albumin, L-histidine, and α_2 -macroglobulin. There is also a nonexchangeable pool of nickel in the serum, which is tightly bound to nickeloplasmin. Regardless of the route of exposure, absorbed nickel is excreted in the urine. Nickel that is not absorbed from the gastrointestinal tract is excreted in the feces.

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3.4.1 Absorption**3.4.1.1 Inhalation Exposure**

Inhaled nickel particles are deposited in the upper and lower respiratory tract and are subsequently absorbed by several mechanisms. The deposition pattern in the respiratory tract is related to particle size, which determines the degree to which particles are affected by inertial impaction, sedimentation, and diffusion. Large particles (5–30 μm) deposit in the nasopharyngeal area where higher airstream velocities and airway geometry promote inertial impaction (Gordon and Amdur 1991). Smaller particles (1–5 μm) enter the trachea and bronchiolar region where they deposit principally by sedimentation. The smallest particles (<1 μm) enter the alveolar region of the lungs where diffusion and electrostatic precipitation of the particles occurs. Fractional deposition can be expected to vary considerably with age and breathing patterns.

In humans, about 20–35% of the inhaled nickel that is retained in the lungs is absorbed into the blood (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991). The remainder is either swallowed, expectorated, or remains in the respiratory tract. Nickel is detected in the urine of workers exposed to nickel (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Higher concentrations of urinary nickel were found in workers exposed to soluble nickel compounds (nickel chloride, nickel sulfate) than in those exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide), indicating that the soluble compounds were more readily absorbed from the respiratory tract (Torjussen and Andersen 1979). A man who died of adult respiratory distress syndrome 13 days after being exposed to a very high concentration of metallic nickel fume (approximately 380 mg/m^3) had very high concentrations of nickel in his urine (700 $\mu\text{g}/\text{L}$) (Rendall et al. 1994). This case report indicates that metallic nickel can be absorbed from the lungs if levels are high enough to result in lung damage.

The half-life of nickel in the lungs of rats exposed by inhalation has been reported to be 32 hours for nickel sulfate (mass median aerodynamic diameter [MMAD] 0.6 μm) (Hirano et al. 1994b), 4.6 days for nickel subsulfide ($^{63}\text{Ni}_3\text{S}_2$ activity median aerodynamic diameter [AMAD] 1.3 μm), and 120 days for green nickel oxide (^{63}NiO , AMAD 1.3 μm) (Benson et al. 1994). Elimination half-times from the lung of rats of 7.7, 11.5, and 21 months were calculated for green nickel oxide with MMADs of 0.6, 1.2, and 4.0 μm , respectively (Tanaka et al. 1985, 1988).

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Following exposure to green nickel oxide, nickel was only excreted in the feces indicating that the dominant mechanism for removing nickel oxide from the lungs is macrophage-mediated rather than dissolution-absorption (Benson et al. 1994). Following exposure to nickel subsulfide, nickel was excreted in both the urine and the feces, with greater amounts in the urine on days 6–14 post-exposure. These results indicate that dissolution-absorption plays an important role in the removal of nickel subsulfide in the lungs, and the study authors concluded that in the lungs, nickel subsulfide acts more like a soluble compound (Benson et al. 1994).

3.4.1.2 Oral Exposure

A human study using a stable nickel isotope estimated that 29–40% of the ingested label was absorbed (based on fecal excretion data) (Patriarca et al. 1997). Other human absorption studies show that 40 times more nickel was absorbed from the gastrointestinal tract when nickel sulfate was given in the drinking water ($27 \pm 17\%$) than when it was given in food ($0.7 \pm 0.4\%$) (Sunderman et al. 1989b). The bioavailability of nickel, as measured by serum nickel levels, was elevated in fasted subjects given nickel sulfate in drinking water (peak level of 80 µg/L after 3 hours), but not when nickel was given with food (Solomons et al. 1982). The bioavailability of nickel increased when nickel was administered in a soft drink, but decreased when nickel was given with whole milk, coffee, tea, or orange juice. In another study (Nielsen et al. 1999) examining the relationship between nickel absorption and food intake, the highest nickel absorption (11.07–37.42% of dose), as evidenced by the amount excreted in urine, was found when the subjects were administered 12 µg Ni/kg 4 hours after ingestion of a scrambled egg meal. The lowest absorption level (2.83–5.27%) was found when nickel was administered at the same time as the meal. Ethylenediamine tetraacetic acid (EDTA) added to the diet decreased nickel bioavailability to below fasting levels (Solomons et al. 1982). These data indicate that the presence of food profoundly reduced the absorption of nickel. The observation of a decreased serum-nickel to urine-nickel ratio with increasing nickel doses in nickel-sensitive individuals suggests that at least some sensitive people adapt to increasing oral doses of nickel by reducing absorption by the gastrointestinal tract (Santucci et al. 1994). Urinary excretion of nickel following a single oral dose given to women after an overnight fast was found to decrease with increasing age, suggesting that nickel absorption may decrease with age (Hindsen et al. 1994).

Studies in rats and dogs indicate that 1–10% of nickel, given as nickel, nickel sulfate, or nickel chloride in the diet or by gavage, is rapidly absorbed by the gastrointestinal tract (Ambrose et al. 1976; Ho and Furst 1973; Tedeschi and Sunderman 1957). In a study in which rats were treated with a single gavage dose of

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a nickel compound (10 mg nickel) in a 5% starch saline solution, the absorption was found to be directly correlated with the solubility of the compound (Ishimatsu et al. 1995). The percentages of the dose absorbed were 0.01% for green nickel oxide, 0.09% for metallic nickel, 0.04% for black nickel oxide, 0.47% for nickel subsulfide, 11.12% for nickel sulfate, 9.8% for nickel chloride, and 33.8% for nickel nitrate. Absorption was higher for the more-soluble nickel compounds. Unabsorbed nickel is excreted in the feces.

3.4.1.3 Dermal Exposure

Human studies show that nickel can penetrate the skin (Fullerton et al. 1986; Norgaard 1955). In a study in which radioactive nickel sulfate was applied to occluded skin, 55–77% was absorbed within 24 hours, with most being absorbed in the first few hours (Norgaard 1955). It could not be determined whether the nickel had been absorbed into the deep layers of the skin or into the bloodstream. Compared to normal subjects, nickel absorption did not differ in nickel-sensitive individuals. In a study using excised human skin, only 0.23% of an applied dose of nickel chloride permeated skin after 144 hours when the skin was not occluded, while 3.5% permeated occluded skin (Fullerton et al. 1986). Nickel(II) ions from a chloride solution passed through the skin ≈ 50 times faster than nickel(II) ions from a sulfate solution (Fullerton et al. 1986). Application of nickel chloride in a sodium lauryl sulfate solution (0.25, 2, or 10%) to excised human skin resulted in a dose-related increase in the penetration of nickel during a 48-hour period (Frankild et al. 1995).

Studies in animals also indicate that nickel can penetrate the skin (Lloyd 1980; Norgaard 1957). Radioactive nickel sulfate was absorbed through the depilated skin of rabbits and guinea pigs after 24 hours and appeared primarily in the urine (Norgaard 1957). A small percentage of radioactive nickel chloride was absorbed through the skin of guinea pigs 4–24 hours after application, as indicated by radioactivity in the blood and urine (0.005–0.51%) (Lloyd 1980). Most of the nickel remained in the skin, primarily in the highly keratinized areas. Increased levels of nickel in the liver and kidneys in guinea pigs treated dermally with nickel sulfate for 15 or 30 days also indicate that nickel can be absorbed through the skin (Mathur and Gupta 1994).

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3.4.2 Distribution

An autopsy study of individuals not occupationally exposed to nickel has shown the highest concentrations of nickel ($\mu\text{g/kg}$ dry weight) in the lungs (174 ± 94), followed by the thyroid (141 ± 83), adrenals (132 ± 84), kidneys (62 ± 43), heart (54 ± 40), liver (50 ± 31), whole brain (44 ± 16), spleen (37 ± 31), and pancreas (34 ± 25) (Rezuke et al. 1987). In an autopsy study, median levels of 0.046, 0.084, and $0.33 \mu\text{g Ni/g}$ wet weight were found in the adrenal glands, colon, and skin, respectively (Tipton and Cook 1963). The total amount of nickel found in the human body has been estimated as 6 mg or $86 \mu\text{g/kg}$ for a 70-kg person (Sumino et al. 1975).

3.4.2.1 Inhalation Exposure

Workers occupationally exposed to nickel have higher lung burdens of nickel than the general population. Dry weight nickel content of the lungs at autopsy was $330\pm380 \mu\text{g/g}$ in roasting and smelting workers exposed to less-soluble compounds, $34\pm48 \mu\text{g/g}$ in electrolysis workers exposed to soluble nickel compounds, and $0.76\pm0.39 \mu\text{g/g}$ in unexposed controls (Andersen and Svenes 1989). In an update of this study, Svenes and Andersen (1998) examined 10 lung samples taken from different regions of the lungs of 15 deceased nickel refinery workers; the mean nickel concentration was $50 \mu\text{g/g}$ dry weight. Nickel levels in the lungs of cancer victims did not differ from those of other nickel workers (Kollmeier et al. 1987; Raithel et al. 1989). Nickel levels in the nasal mucosa are higher in workers exposed to less-soluble nickel compounds relative to soluble nickel compounds (Torjussen and Andersen 1979). These results indicate that, following inhalation exposure, less-soluble nickel compounds remain deposited in the nasal mucosa.

Higher serum nickel levels have been found in occupationally exposed individuals compared to nonexposed controls (Angerer and Lehnert 1990; Elias et al. 1989; Torjussen and Andersen 1979). Serum nickel levels were found to be higher in workers exposed to soluble nickel compounds compared to workers exposed to less-soluble nickel compounds (Torjussen and Andersen 1979). Concentrations of nickel in the plasma, urine, and hair were similar in nickel-sensitive individuals compared to nonsensitive individuals (Spruit and Bongaarts 1977).

Following a single 70-minute inhalation exposure of rats to green nickel oxide (^{63}NiO ; 9.9 mg Ni/m^3 ; AMAD $1.3 \mu\text{m}$), the fraction of the inhaled material deposited in the total respiratory tract was 0.13, with 0.08 deposited in the upper respiratory tract and 0.05 deposited in the lower respiratory tract (Benson et

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al. 1994). During the 180 days postexposure, nickel was not detected in extrapulmonary tract tissues. Following a single 120-minute inhalation exposure of rats to nickel subsulfide ($^{63}\text{Ni}_3\text{S}_2$; 5.7 mg Ni/m³; AMAD 1.3 μm), the fraction of inhaled material deposited in the upper respiratory tract was similar to that observed for nickel oxide (0.14 in the total respiratory tract, 0.09 in the upper respiratory tract, and 0.05 in the lower respiratory tract). In contrast to nickel from nickel oxide, nickel from nickel subsulfide was detected in the blood, kidneys, and carcass between 4 and 24 hours after the exposure.

Data in rats and mice indicate that a higher percentage of less-soluble nickel compounds was retained in the lungs for a longer time than soluble nickel compounds (Benson et al. 1987, 1988; Dunnick et al. 1989; Tanaka et al. 1985) and that the lung burden of nickel decreased with increasing particle size ($\leq 4 \mu\text{m}$) (Kodama et al. 1985a, 1985b). Nickel retention was ≈ 6 times (mice) to 10 times (rats) greater in animals exposed to less-soluble nickel subsulfide compared to soluble nickel sulfate (Benson et al. 1987, 1988). The lung burdens of nickel generally increased with increasing exposure duration and increasing levels of the various nickel compounds (Dunnick et al. 1988, 1989). From weeks 9 to 13 of exposure, lung levels of nickel sulfate and nickel subsulfide remained constant while levels of nickel oxide continued to increase (Dunnick et al. 1989).

Slow clearance of nickel oxide from the lungs was also observed in hamsters (Wehner and Craig 1972). Approximately 20% of the inhaled concentration of nickel oxide was retained in the lungs at the end of exposure for 2 days, 3 weeks, or 3 months. The retention was not dependent on the duration of exposure or exposure concentration. By 45 days after the last exposure to nickel oxide (2-day exposure), 45% of the initial lung burden was still present in the lungs (Wehner and Craig 1972). The nickel oxide used in this study was not further identified.

The clearance of nickel compounds from the lungs was studied following intratracheal injection (Carvalho and Ziemer 1982; Valentine and Fisher 1984). Nickel subsulfide (less soluble) was cleared from the lungs of mice in two phases: 38% of the dose was cleared with a half-time of 1.2 days, and 42% was cleared with a half-time of 12.4 days. After 35 days, 10% of the dose remained in the lungs (Valentine and Fischer 1984). Soluble nickel chloride was cleared from the lungs much faster: 71% of the dose was cleared from the lungs in 24 hours, and only 0.1% remained in the lungs by day 21 (Carvalho and Ziemer 1982).

In a study that examined the effect of green nickel oxide and nickel sulfate on the clearance of nickel from the lungs, rats and mice were exposed 6 hours/day, 5 days/week, for up to 6 months and then given a

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single nose-only exposure to a ^{63}Ni -labeled compound (Benson et al. 1995a). Nickel sulfate at concentrations up to 0.11 mg Ni/m^3 had no effect on lung clearance of nickel sulfate. Nickel oxide exposure did reduce the lung clearance of nickel oxide. When measured 184 days after the single exposure, a 6-month exposure of rats to nickel oxide at 0, 0.49, and 1.96 mg Ni/m^3 was found to result in the retention of 18, 33, and 96% of the dose, respectively. In mice exposed to nickel oxide at 0, 0.98, or 3.93 mg/m^3 for 6 months, 4, 20, and 62%, respectively, of the dose was retained 214 days after the single exposure to radiolabelled compound.

3.4.2.2 Oral Exposure

Serum nickel levels peaked 1.5 and 3 hours after ingestion of nickel (Christensen and Lagesson 1981; Patriarca et al. 1997; Sunderman et al. 1989b). In workers who accidentally ingested water contaminated with nickel sulfate and nickel chloride, the mean serum half-time of nickel was 60 hours (Sunderman et al. 1988). This half-time decreased substantially (27 hours) when the workers were treated intravenously with fluids.

In animals, nickel was found primarily in the kidneys following both short- and long-term oral exposure to various soluble nickel compounds (Ambrose et al. 1976; Borg and Tjalve 1989; Dieter et al. 1988; Ishimatsu et al. 1995; Jasim and Tjalve 1986a, 1986b; Oskarsson and Tjalve 1979; Whanger 1973). Substantial levels of nickel were also found in the liver, heart, lung, and fat (Ambrose et al. 1976; Dieter et al. 1988; Jasim and Tjalve 1986b; Schroeder et al. 1964; Whanger 1973) as well as in the peripheral nerve tissues and in the brain (Borg and Tjalve 1989; Jasim and Tjalve 1986a). Following a 2-year study in rats in which nickel levels were measured in bone, liver, kidneys, and fat, Ambrose et al. (1976) concluded that there were no important storage sites for nickel. In control rats, bone nickel was 0.53 ppm in female rats and $<0.096 \text{ ppm}$ in male rats. An explanation for the difference in bone nickel between male and female rats was not provided. Nickel was found to cross the placenta, as indicated by increases in the levels of nickel in the fetuses of mice given nickel during gestation (Jasim and Tjalve 1986a; Schroeder et al. 1964).

When administered as part of a mixture of nickel, cadmium, arsenic, chromium, and vanadium in drinking water or food, elevated levels of nickel were found in the small intestines, kidneys, pancreas, and femur (only tissues examined) (Radike et al. 2002). The highest levels were found in the small intestine and kidney. When administered in water, significant elevations in nickel levels were found in the small

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intestine after 8 weeks of exposure; maximum levels were reached after 20 weeks. In the kidneys, the nickel levels were only significantly higher than controls at week 20.

In pregnant rats not exposed to nickel, maternal and fetal blood concentrations of nickel were 3.8 and 10.6 µg/L, respectively (Szakmary et al. 1995). Twenty-four hours after a single gavage dose of 5.4, 11.3, or 22.6 mg Ni/kg as nickel chloride was given to pregnant rats (gestation day 19), nickel levels in µg/L were 18.5, 90, and 91.5, respectively, in maternal blood, 14.5, 65.5, and 70.5, respectively, in fetal blood, and 16.5, 20, and 17, respectively, in amniotic fluid. This study showed that at higher doses, nickel reached a plateau in maternal and fetal blood, and that nickel concentrations in amniotic fluid were relatively well controlled in that they were similar at all three doses.

3.4.2.3 Dermal Exposure

No data were located regarding the distribution of nickel in humans after dermal exposure.

One hour after application of nickel chloride to the shaved skin of guinea pigs, nickel had accumulated in keratinaceous areas and in hair sacs (Lloyd 1980). After 4 hours, nickel was found in the stratum corneum and stratum spinosum. Twenty-four hours after treatment of depilated skin in rabbits and guinea pigs with nickel-57, radioactivity was detected in the blood, kidneys, and liver with the greatest amounts found in the blood and kidneys (Norgaard 1957). Quantitative data were not provided. Concentrations of nickel in the liver were 2.4 ± 0.1 µg/g following 15 daily dermal treatments of guinea pigs with nickel sulfate at 100 mg Ni/kg/day and 4.4 ± 0.5 µg/g following 30 days of treatment with the same dose, compared to 0.2 ± 0.01 µg/g before treatment (Mathur and Gupta 1994). In the kidneys, nickel levels were 0.4 ± 0.2 µg/g before treatment, 1.5 ± 0.12 µg/g at 15 days, and 3.52 ± 0.42 µg/g at 30 days.

3.4.2.4 Other Routes of Exposure

Several researchers have examined the distribution of nickel in pregnant and lactating rats following its injection (Dostal et al. 1989; Mas et al. 1986; Sunderman et al. 1978). Half-lives of nickel in whole blood following intraperitoneal treatment of pregnant and nonpregnant rats were similar (3.6–3.8 hours), while the half-life for nickel in fetal blood was 6.3 hours following treatment on gestation days 12 or 19 (Mas et al. 1986). Intramuscular injection of nickel chloride (12 mg Ni/kg/day) into pregnant and nonpregnant rats resulted in a greater accumulation of nickel in the pituitary of pregnant rats (Sunderman et al. 1978).

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Wet weight nickel concentrations in the pituitary were 0.13 µg/g in nonpregnant rats and 1.1 and 0.91 µg/g in pregnant rats treated on gestation days 8 and 18, respectively. Following subcutaneous exposure of lactating rats to nickel chloride, Dostal et al. (1989) found that peak nickel concentrations in the milk were reached 12 hours after treatment. Relative to treatment with a single dose, four daily subcutaneous doses of nickel resulted in higher nickel concentrations in milk, while serum nickel levels were the same as following a single dose (Dostal et al. 1989). This study suggests that nickel can accumulate in the milk, which would result in exposure of the offspring.

Using whole-body autoradiography, Ilback et al. (1992, 1994) examined the distribution of an intravenous dose of nickel given to mice with and without Coxsackie virus B3 infection. Virus infection changed nickel distribution, resulting in accumulation in the pancreas and the wall of the ventricular myocardium. The investigators suggested that the change in distribution may result from repair and immune mechanisms activated in response to the virus.

3.4.3 Metabolism

The extracellular metabolism of nickel consists of ligand exchange reactions (Sarkar 1984). In human serum, nickel binds to albumin, L-histidine, and α_2 -macroglobulin. Binding in animals is similar. The principal binding locus of nickel to serum albumins is the histidine residue at the third position from the amino terminus in humans, rats, and bovines (Hendel and Sunderman 1972). Dogs do not have this binding locus, and most of the nickel (>85%) in dog serum was not bound to protein. A proposed transport model involves the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and L-histidine. The low molecular weight L-histidine nickel complex can then cross biological membranes (Sarkar 1984). In the serum, there is also a nonexchangeable pool of nickel tightly bound to nickeloplasmin, which is an α -macroglobulin (Sunderman 1986).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Absorbed nickel is excreted in the urine, regardless of the route of exposure (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). In nickel workers, an increase in urinary excretion was found from the beginning to the end of the shift, indicating a fraction that was rapidly eliminated. An increase in urinary excretion was also found as the workweek

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progressed, indicating a fraction that was excreted more slowly (Ghezzi et al. 1989; Tola et al. 1979). Nickel was also excreted in the feces of nickel workers, but this probably resulted from mucociliary clearance of nickel from the respiratory system to the gastrointestinal tract (Hassler et al. 1983). Among electrolysis and refinery workers exposed to soluble nickel compounds (nickel sulfate aerosols), nickel concentrations in the urine were 5.2–22.6 µg/L for those exposed to concentrations of 0.11–0.31 mg Ni/m³, and 3.2–18 µg/L for those exposed to 0.08–0.2 mg Ni/m³ (Chashschin et al. 1994). Higher nickel levels were found in the urine of workers exposed to soluble nickel compounds, indicating that the soluble compounds are more readily absorbed than the less-soluble compounds (Bernacki et al. 1978; Torjussen and Andersen 1979). Although high levels of nickel were found in the urine of a man who died of adult respiratory distress syndrome 13 days after being exposed to a very high concentration of metallic nickel (Rendall et al. 1994), it is not clear if metallic nickel would be absorbed from healthy lungs.

In animals, the route of excretion following intratracheal administration of nickel depends on the solubility of the nickel compound. In rats given soluble nickel chloride or nickel sulfate, ≈70% of the given dose was excreted in the urine within 3 days (Carvalho and Zeimer 1982; Clary 1975; English et al. 1981; Medinsky et al. 1987). By day 21, 96.5% of the given dose of nickel chloride had been excreted in the urine (Carvalho and Zeimer 1982). Following intratracheal administration of less-soluble compounds (nickel oxide, nickel subsulfide), a greater fraction of the dose was excreted in the feces as a result of mucociliary clearance. Following administration of black nickel oxide to rats or nickel subsulfide to mice, approximately equal amounts of the initial dose were excreted in the urine and the feces (English et al. 1981; Valentine and Fischer 1984). A total of 90% of the initial dose of nickel subsulfide was excreted within 35 days (Valentine and Fischer 1984), and 60% of the initial dose of black nickel oxide was excreted within 90 days (English et al. 1981). This is consistent with nickel oxide being less soluble and not as rapidly absorbed as nickel subsulfide (English et al. 1981; Valentine and Fischer 1984).

3.4.4.2 Oral Exposure

In humans, most ingested nickel is excreted in the feces; however, this represents unabsorbed nickel (Patriarca et al. 1997; Sunderman et al. 1989b). However, the nickel that is absorbed from the gastrointestinal tract is excreted in the urine. Nickel administered in the drinking water was absorbed much more readily than when administered in the food (27% absorption in water versus 0.7% absorption in food, respectively) (Sunderman et al. 1989b). By 4 days post-treatment, 26% of the dose given in water was excreted in the urine and 76% in the feces, and 2% of the dose given in food was excreted in the urine and 102% in the feces (Sunderman et al. 1989b). The elimination half-time for absorbed nickel

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averaged 28 ± 9 hours (Sunderman et al. 1989b). These data are consistent with a nickel tracer study that found that 51–82% of the administered label was excreted in the urine over the 5 days (Patriarca et al. 1997).

In animals, the majority of the ingested dose of nickel is excreted in the feces. One day after administration of nickel chloride in rats, 94–97% had been excreted in the feces and 3–6% had been excreted in the urine (Ho and Furst 1973). In dogs fed nickel sulfate in the diet for 2 years, only 1–3% of the ingested nickel was excreted in the urine (Ambrose et al. 1976). Because dogs lack a major binding site in serum albumin that is found in humans (Hendel and Sunderman 1972), the relevance of dog data to humans is unclear.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of nickel in humans or animals after dermal exposure to nickel.

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewett 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 and Krishnan 1994; Andersen et al. 1987). 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

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PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

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

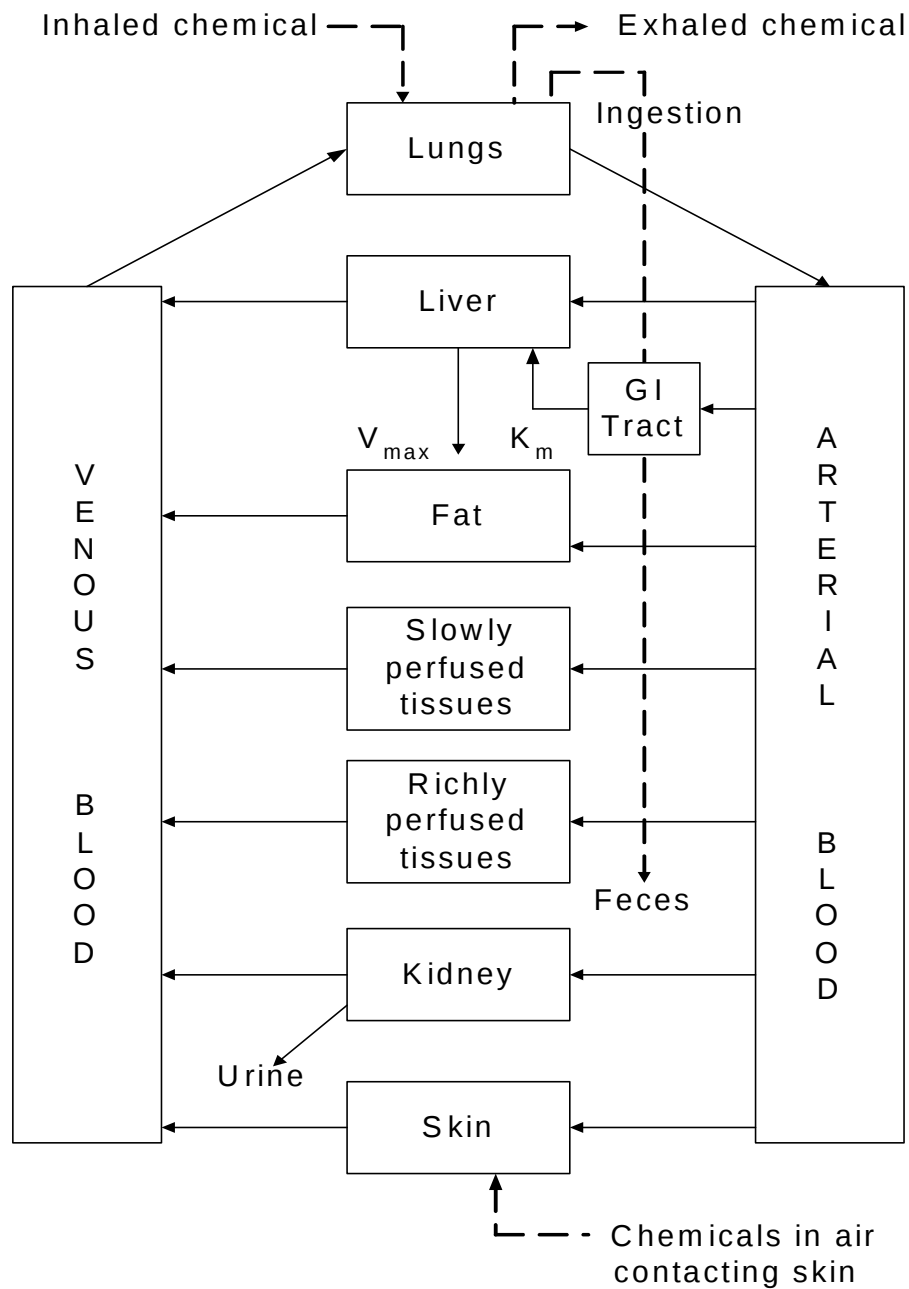
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many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

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

If PBPK models for nickel 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.

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



Source: adapted from Krishnan et al. 1994

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

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Sunderman et al. (1989b) Model

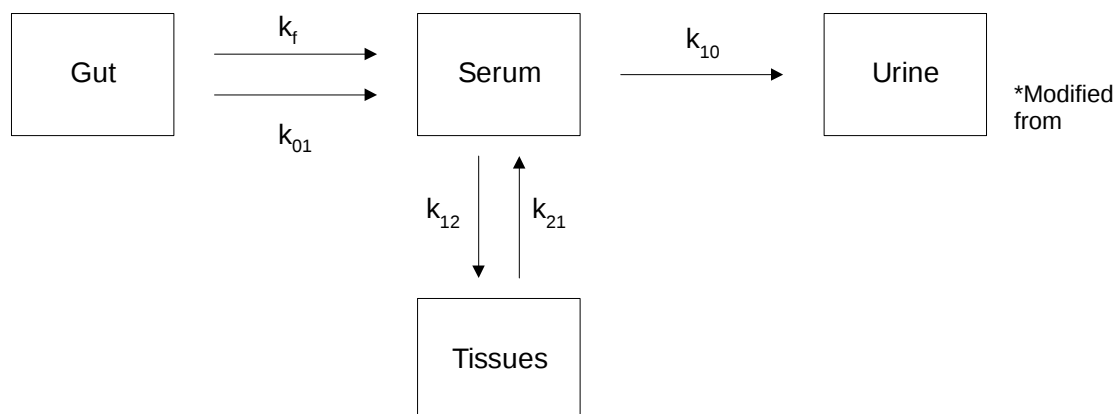
Description of the Model. Sunderman et al. (1989b) developed a model to predict nickel absorption, serum levels, and excretion following oral exposure to nickel in water and food. The model was developed based on two experiments in humans in which serum nickel levels and urinary and fecal excretion of nickel were monitored for 2 days before and 4 days after eight subjects were given an oral dose of nickel as nickel sulfate (12, 18, or 50 µg Ni/kg) in water (experiment 1) or in food (experiment 2). The data were then analyzed using a linear, compartmental, toxicokinetic model (Figure 3-4). Two inputs of nickel, the single oral dose, in which uptake was considered to be a first-order process, and the baseline dietary ingestion of nickel, in which uptake was considered to be a pseudo-zero order process, were included in the model. Parameters determined for the model from the two experiments are shown in Table 3-12. The only parameter that was significantly different between exposure in water and exposure in food was the fraction of nickel absorbed from the gastrointestinal tract. The absorption rate constant was not different at the different doses, but the investigators indicated that the observations do not exclude the possibility that nickel absorption from the gastrointestinal tract could be saturated at higher doses. At doses low enough to be in the deficiency range, the absorption rate and percentage absorbed are probably larger.

Validation of the Model. The model has been shown to predict serum nickel and cumulative nickel levels in subjects receiving a single dose of nickel in drinking water or food. The study authors (Sunderman et al. 1989b) noted that the model was going to be analyzed using data on individuals accidentally ingesting nickel from a contaminated drinking fountain (toxicity data described in Sunderman et al. 1988); however, it does not appear that this validation of the model has been published.

Risk Assessment. Currently, there are no oral exposure MRLs for nickel. Because the model evaluates the absorption of nickel from different media (food and water), the model can be used in conjunction with MRLs during the assessment of potential health hazards associated with nickel in different environmental media (e.g., soil, water).

Target Tissues. This model was designed to predict nickel absorption. It did not measure nickel in target tissues.

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Figure 3-4. Diagram of the Compartmental Model of Nickel Metabolism*

Sunderman et al. 1989b

k_f = zero-order rate constant for fractional absorption of dietary nickel
 k_{01} = first-order rate constant for intestinal absorption of nickel from oral NiSO_4
 k_{12} = first-order rate constant for nickel transfer from serum to tissues
 k_{21} = first-order rate constant for nickel transfer from tissue to serum
 k_{10} = first-order rate constant for nickel excretion in urine

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Table 3-12. Kinetic Parameters of Nickel Sulfate Absorption, Distribution, and Elimination in Humans^a

Parameters (symbols and units)	Experiment 1 (nickel sulfate in water)	Experiment 2 (nickel sulfate in food)
Mass fraction of nickel dose absorbed from the gastrointestinal tract (F, percent)	27±17	0.7±0.4 ^b
Rate constant for alimentary absorption of nickel from the nickel dose (k_{01} , hour ⁻¹)	0.28±0.11	0.33±0.24
Rate constant for alimentary absorption of dietary nickel intake (k_f , µg/hour)	0.092±0.051	0.105±0.036
Rate constant for nickel transfer from serum to tissues (k_{12} , hour ⁻¹)	0.38±0.17	0.37±0.34
Rate constant for nickel transfer from tissue to serum (k_{21} , hour ⁻¹)	0.08±0.03	— ^c
Rate constant for urinary elimination of nickel (k_{10} , hour ⁻¹)	0.21±0.05	0.15±0.11
Rate clearance of nickel (C_{Ni} , mL/minute/1.73 mg/m ²)	8.3±2.0	5.8±4.3
Rate clearance of creatinine ($C_{creatinine}$, mL/minute/1.73 mg/m ²)	97±9	93±15
Nickel clearance as percent of creatinine clearance ($C_{Ni}/C_{creatinine}$, x100)	8.5±1.8	6.3±4.6

^aData (mean ± standard deviation) from Sunderman et al. 1989b^bp<0.001 relative to exposure in food computed by analysis of variance^cNo value was determined because of the small mass of nickel absorbed from the gastrointestinal tract and transferred from the serum into the tissues.

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Species Extrapolation. This model was designed for application to humans; the study authors noted that studies to use this model for absorption, distribution, and excretion in laboratory animals are being initiated. No publications of these data were located.

Interroute Extrapolation. This model is designed to simulate oral absorption of nickel and cannot be used for other routes of exposure.

Dosimetric Model for Lung Burden (Hsieh et al. 1999a, 1999b; Yu et al. 2001)

Description of the Model. Hsieh et al. (1999a) describe a dosimetric model of nickel deposition and clearance from the lung. This model was derived using lung burden data from the rat NTP studies of nickel sulfate (NTP 1996c), nickel subsulfide (NTP 1996b), and nickel oxide (NTP 1996a) and existing models of lung deposition. The model considers the alveolar region of the lung as a single compartment; removal of nickel from the compartment occurs via macrophage phagocytosis and migration (mechanical clearance) and/or via dissolution. For nickel sulfate and nickel oxide, dissolution and mechanical clearance, respectively, are assumed to be the primary clearance mechanisms; clearance of nickel subsulfide occurs via both mechanisms. The accumulation of nickel in the lung over time was described by the following equations:

$$(1) \quad \frac{dM}{dt} = \dot{r} - \lambda M$$

$$(2) \quad \dot{r} = \text{concentration} \times \eta \times MV$$

$$(3) \quad \lambda = a \exp \left[-b \left(\frac{m_s}{m_{s0}} \right)^c \right]$$

where M is the mass burden, r is the deposition rate, λ is the total alveolar clearance rate coefficient; η is the alveolar deposition fraction, MV is the minute ventilation, a , b , c are clearance rate coefficient constants, $m_s = M/S$ in which M is the lung mass burden and S is the total alveolar surface area ($m_s = 5.38 \times 10^3 \text{ cm}^2$ for rats), and $m_{s0} = 1 \text{ mg/cm}^2$ is the dimensional constant introduced to normalize m_s .

The clearance rate coefficients constants in rats for the three nickel compounds examined are presented in Table 3-13.

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Hsieh et al. (1999b) modified the rat model to develop a model of deposition and clearance of nickel in humans. Deposition rates were calculated for six scenarios: nose-breathing at rest, nose-breathing at light work, nose breathing at moderate work, mouth breathing at rest, mouth breathing at light work, and mouth breathing at moderate work. The clearance rate coefficient constants for humans were modified from the rat values. For nickel oxide, clearance rate coefficient constant *a* was estimated to be 1/7.6 times the rat value; constants *b* and *c* were assumed to be the same as rats. For nickel subsulfide, clearance is due to mechanical transport and dissolution; the clearance rate coefficient constant *a* was estimated to be the sum of the clearance rate coefficient constant *a* for insoluble nickel (nickel oxide) and the difference between the clearance rate coefficient constant *a* for nickel oxide and for nickel subsulfide for rats. For nickel sulfate, clearance rate coefficient constants in humans were assumed to be the same as in rats. The human coefficient constants are presented in Table 3-13.

Yu et al. (2001) further expanded this human model to incorporate three additional factors: inhalability, mixed breathing mode, and clearance rate coefficient of a mixture of nickel compounds.

Validation of the Model. To validate the Hsieh et al. (1999a) model, lung burdens for the nickel concentrations used by NTP were compared with measured lung burdens. In general, there was good agreement between the predicted lung burdens and measured burdens. Some differences were noted, particularly for the shorter term studies (16 days and 13 weeks). Hsieh et al. (1999a) noted that the differences may be due to assumptions used in the model (e.g., average body weight, constant respiratory parameters), using lung geometry data for Long Evans rats rather than for the Fischer rats used by NTP, or shortcomings in the experimental data.

The Hsieh et al. (1999b) model modification was not verified.

The Yu et al. (2001) modification of the model was used to predict lung burdens in nickel refinery workers; the predicted burdens were compared to measured lung burdens in deceased nickel refinery workers (Andersen and Svenes 1989). Good agreement between predicted and measured body burdens was found.

Risk Assessment. Currently, the intermediate- and chronic-duration inhalation MRLs for nickel are based on lung effects in rats. Further development of this model (Hsieh et al. 1999a) and the modifications of the model (Hsieh et al. 1999b; Yu et al. 2001) would allow for the model to be used to

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Table 3-13. Clearance Rate Coefficient Constants of Nickel Compounds

Species	Nickel compound	Clearance rate coefficient constant		
		<i>a</i>	<i>b</i>	<i>c</i>
Rat ^a	Nickel sulfate	10.285	17.16	0.105
	Nickel subsulfide	0.00768	-20.135	0.266
	Nickel oxide	0.0075	300	0.95
Human ^b	Nickel sulfate	10.285	17.16	0.105
	Nickel subsulfide	0.00117	-20.135	0.266
	Nickel oxide	0.00099	300	0.95

^aData from Hsieh et al. 1999a^bData from Hsieh et al. 1999b

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extrapolate from rats to humans with greater certainty than using the standard dosimetric approach. This model could also be used for estimating human equivalent concentrations following low-dose extrapolation of the animal carcinogenicity data, similar to that conducted by Seilkop and Oller (2003).

Target Tissues. Based on limited human data and extensive animal data, the lung has been identified as the critical target of nickel toxicity. Further development of this model would allow nickel lung burdens to be predicted.

Species Extrapolation. The modifications of the Hsieh et al. (1999a) model allow for estimation of human lung burdens.

Interroute Extrapolation. This model is designed to simulate deposition and clearance of nickel from the lung and cannot be used for other routes of exposure.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Nickel is thought to be absorbed from the gastrointestinal tract as a lipophilic, low molecular weight compound (Kenney and McCoy 1992). The absorption of nickel from the gut is dependent on the various ligands and ions that are present. For example, food greatly decreases the absorption of nickel (Sunderman et al. 1989b). The results of an *in situ* perfusion study in rats (Arnich et al. 2000) suggest that at low concentrations (≤ 10 mg Ni/L), nickel is absorbed via active transport and facilitated diffusion; at higher concentrations, the carriers become saturated and nickel is absorbed via passive diffusion. These results are consistent with *in vitro* data showing that nickel is actively absorbed in the jejunum, but may cross the ileum by passive diffusion (Tallkvist and Tjalve 1994).

In the plasma, nickel is transported by binding to albumin and ultrafiltrable ligands, which include small polypeptides and amino acids; for example, histidine (Sunderman and Oskarsson 1991). The nickel binding site on albumin consists of the terminal amino group, the first two peptide nitrogen atoms at the *N*-terminus, and the imidazole nitrogen of the histidine at the third position from the *N*-terminus. Nickel competes with copper for this albumin binding site. In the plasma, nickel is also found bound to nickeloplasmin, an α -macroglobulin, but the nickel associated with nickeloplasmin is not readily exchangeable, and this protein is not thought to play a role in the transport of nickel (Sunderman and

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Oskarsson 1991). An *in vitro* study of rat hepatocytes found that the calcium channels are involved in nickel uptake by the liver (Funakoshi et al. 1997). At physiological levels, no tissue significantly accumulates orally administered nickel (Nielsen 1990).

Nickel that is absorbed is excreted primarily in the urine. In the urine, nickel is primarily associated with low molecular weight complexes that have free amino acids as indicated by the ninhydrin reaction (Sunderman and Oskarsson 1991). In humans nickel is also eliminated in hair, skin, milk, and sweat.

The physiological role of nickel in animals and humans has not yet been identified. The most likely roles are as cofactors in metalloenzymes or metalloproteins, or as a cofactor that facilitates the intestinal absorption of iron (Fe^{3+} ion) (Nielsen 1982). Support for a role of nickel in enzymes comes from the identification of nickel-containing enzymes in plants and microorganisms. The types of nickel-containing enzymes that have been identified are urease, hydrogenase, methylcoenzyme M reductase, and carbon monoxide dehydrogenase (Nielsen 1990). Nickel may also have a role in endocrine gland function as suggested by its effect on prolactin levels.

3.5.2 Mechanisms of Toxicity

The mechanism of adverse respiratory effects following lung exposure of rabbits to metallic nickel or nickel chloride has been examined (Johansson and Camner 1986; Johansson et al. 1980, 1981, 1983, 1987, 1988a, 1989). In these studies, an accumulation of macrophages and granular material (primarily phospholipids) in the alveoli and an increase in volume density of alveolar type II cells were observed. The type II cells contained large amounts of lamellar bodies. Similar results were found following exposure to metallic nickel and nickel chloride, indicating that nickel ions apparently had a direct effect on type II cells (Johansson and Camner 1986). At the end of 6 months, all of the rabbits had foci of pneumonia, indicating an increased susceptibility to infection (Johansson et al. 1981). This may have been a result of the decreased function of the alveolar macrophages.

The substitution of nickel for other essential elements may also contribute to the adverse effects of nickel. Nickel can replace magnesium in certain steps in the activation of complement (McCoy and Kenney 1992). For example, the replacement of nickel for magnesium can increase the formation of C3b, Bb enzyme by 40 times, which amplifies activation of the complement pathway. Nickel has also been shown to activate calcineurin, a phosphatase that binds zinc and iron, and is usually activated by manganese.

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There is some evidence that nickel may have a role in the release of prolactin from the pituitary. *In vitro* studies have shown that nickel could directly inhibit the release of prolactin by the pituitary, and it has been suggested that nickel may be part of a prolactin inhibiting factor (LaBella et al. 1973). Intravenous exposure to nickel chloride has been shown to reduce serum levels of prolactin in male rats that were pretreated with chlorpromazine, which itself produces hyperprolactinemia (LaBella et al. 1973). The effect was not observed in rats that had not been pretreated with chlorpromazine. Nickel has also been shown to accumulate more in the pituitaries of pregnant rats than nonpregnant rats (Sunderman et al. 1978), suggesting that a toxicological effect through prolactin may only be manifested during maximum prolactin production. A subcutaneous injection study has also shown that nickel can change the quality of the milk produced, resulting in increased milk solids (42%) and lipids (110%), and decreased protein (29%) and lactose (61%) (Dostal et al. 1989). Because these changes were noted in comparison to pair-fed rats, they were not considered to be a result of changes in food intake.

The mechanism of nickel carcinogenicity has not been firmly established; it is likely that the carcinogenic effects result from a variety of mechanisms. The available evidence suggests that, mechanistically, nickel carcinogenicity is probably the result of genetic factors and/or direct (e.g., conformational changes) or indirect (e.g., generation of oxygen radicals) epigenetic factors. Additionally, certain nickel compounds promote cell proliferation, which would convert repairable DNA lesions into nonrepairable mutations. Nickel is considered to be genotoxic, but has a low mutagenic potential (Kasprzak et al. 2003b). The nickel-induced DNA damage has resulted in the formation of chromosomal aberrations (Conway and Costa 1989; Dhir et al. 1991; Larramendy et al. 1981; Lechner et al. 1984; Sen and Costa 1986b; Sen et al. 1987; Waksvick and Boysen 1982) that could result in deletion of senescence or tumor suppressor genes. Nickel compounds have also been found to be weak inducers of sister chromatid exchanges (Andersen 1983; Arrouijal et al. 1992; Larramendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981; Wulf 1980).

Although nickel has a relatively weak affinity for DNA, it has a high affinity for chromatin proteins, particularly histones and protamines (Costa et al. 1994; Kasprzak et al. 2003b; Oller et al. 1997). The complexing of nickel ions with heterochromatin results in a number of alterations including condensation, DNA hypermethylation, gene silencing, and inhibition of histone acetylation. These alterations have been shown to disturb gene expression (Costa et al. 1994; Kasprzak et al. 2003b; Lee et al. 1995; Oller et al. 1997; Zoroddu et al. 2002). Methylation of DNA may result in critical genes becoming incorporated into heterochromatin where they can no longer be expressed (Costa 1995). Some of the alterations in gene expression may be mediated by activated transcription factors. Nickel has been shown to alter several

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transcription factors including hypoxia-inducible transcription factor (HIF-1), activating transcription factor (ATF-1) involved in inactivation of thrombospondin-1, which suppresses angiogenesis, and NF- κ B transcription factor involved in the inducible expression of adhesion molecules (Kasprzak et al. 2003b). The strongest epigenetic effects on nickel have been associated with HIF-1. The HIF-1 transcription factor is involved in the regulation of hypoxia-inducible genes involved in cell transformation, tumor promotion, and progression, angiogenesis, altered metabolism, and apoptosis. HIF-1 α , one of the HIF-1 subunits, is over-expressed in both primary and metastatic tumors. It is induced in response to hypoxia and exposure to nickel (Li et al. 2004; Salnikow et al. 2000b). Both soluble and insoluble nickel compounds have also been shown to induce Cap43 (also called NDRG2) gene expression, which requires HIF-1 α activation (Costa et al. 2003; Li et al. 2004; Salnikow et al. 2000b). There is also evidence that nickel ions inhibit DNA repair (Hartwig et al. 1994). Nickel enhances the genotoxicity of ultraviolet light, x-rays, *cis*- and *trans*-platinum, and mitomycin C. *In vitro* studies in HeLa cells suggest that nickel inhibits the incision step in excision repair (Hartwig et al. 1994), while studies using Chinese hamster ovary cells suggest that nickel inhibits the ligation step of excision repair (Lee-Chen et al. 1994). The underlying mechanism of how nickel affects DNA repair is unclear. Sunderman and Barber (1988), Sunderman (1989b), and Hartwig et al. (1994) suggest that nickel ions may compete with zinc ions for binding to zinc-finger DNA binding proteins, resulting in structural changes in DNA that prevent repair enzymes from binding. Nickel may also directly interact with enzymes required for DNA repair (Hartwig et al. 1994).

The binding of nickel to the histone protein within heterochromatin could result in the generation of oxygen radicals. These oxygen radicals could subsequently induce damage bases, DNA strand breaks, and DNA protein crosslinks (Costa et al. 1994; Oller et al. 1997). The available evidence suggests that this mechanism would play a minor (if any) role in nickel carcinogenicity because the damage would be confined to heterochromatin regions of DNA, which lack active genes (Oller et al. 1997). However, nickel ions can complex with a number of cellular ligands including amino acids, peptides, and proteins resulting in the generation of oxygen radicals. The reactive oxygen species (ROS) generated could nonselectively damage DNA, possibly resulting in genetic changes in active genes (Kasprzak et al. 2003b; Oller et al. 1997).

3.5.3 Animal-to-Human Extrapolations

The available data on the toxicity of inhaled nickel provide strong evidence that the respiratory tract, in particular the lung, is the most sensitive target of nickel toxicity in humans and animals. There are

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limited exposure-response data for noncarcinogenic effects in humans; several well-designed animal studies (Benson et al. 1995a, 1995b; NTP 1996a, 1996b, 1996c) provide good exposure-response data that can be used to predict the thresholds of toxicity. One of these studies (NTP 1996c) was used to derive intermediate- and chronic-duration inhalation MRLs for nickel. A PBPK model (Hsieh et al. 1999a, 1999b) of lung deposition and clearance of inhaled nickel found a higher deposition of nickel in the alveolar region of humans compared to rats; however, adjustment for differences in lung weights resulted in a lower alveolar deposition of nickel in humans than in rats. This model, as described in more detail in Section 3.4.5, allows for prediction of human lung burdens. A cancer bioassay in rats and mice conducted by NTP (1996c) did not find significant increases in the occurrence of lung tumors. However, several occupational exposure studies have reported increases in the occurrence of nasal and lung tumors in workers exposed to soluble nickel compounds (primarily nickel sulfate and nickel chloride) in combination with exposures to other nickel compounds and/or carcinogenic agents (Anttila et al. 1998; Grimsrud et al. 2001, 2002; International Committee on Nickel Carcinogenesis in Man 1990). It is not known if the apparent species differences are due to differences in carcinogenic potential, co-exposure to other nickel compounds or other metals, or differences in exposure concentrations.

The available data on the oral toxicity of nickel are insufficient for comparing sensitive targets of toxicity and dose-response relationships between humans and laboratory animals. With the exception of dogs, the toxicokinetic properties of nickel did not differ between species. In dogs, the serum albumin lacks the histidine residue at the third position from the amino terminus (Hendel and Sunderman 1972); thus, dogs would not be a good model for the disposition of nickel in humans. In the absence of data to the contrary, it is assumed that most laboratory animals are a good model for humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for “...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...”. To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine*

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

There is no evidence to suggest that nickel disrupts the normal functioning of the neuroendocrine axis. However, nickel-induced endocrine effects have been observed in laboratory animals. Several studies have found decreases in prolactin levels in lactating animals following oral (Smith et al. 1993), subcutaneous (Dostal et al. 1989), or intravenous (LaBella et al. 1973) administration. Additionally, *in vivo* and *in vitro* studies (Forgács et al. 1998, 2001) reported an inhibitory effect of nickel on stimulated testosterone production in mouse Leydig cells.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

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

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

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

There are limited data on the toxicity of nickel in children. Several surveys of nickel-induced dermatitis found higher incidences of nickel sensitivity among young girls (Uter et al. 2003; Wantke et al. 1996). This apparent age-related increase in nickel-induced dermatitis is likely the result of increased nickel exposure in this segment of the population rather than an increase in sensitivity. For most of the general population, the sensitizing exposure is through consumer products, particularly jewelry. The higher prevalence of ear piercing in young women probably results in a higher prevalence of nickel sensitivity (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995; Uter et al. 2003). With the exception of nickel sensitization, there are limited toxicity data on age-related differences in toxicity in humans or animals. Zhang et al. (2000) found that elderly rats (aged 20 months) were more susceptible to the proinflammatory effects in the lungs of inhaled ultrafine nickel as compared to juvenile rats (aged 2 months).

A number of inhalation and oral exposure studies in rats and mice provide suggestive evidence that the fetus and neonate are targets of nickel toxicity. Increases in spontaneous abortions and stillbirths and decreases in neonatal survival have been observed in rats (Ambrose et al. 1976; Käkälä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993) and mice (Berman and Rehnberg 1983) following oral exposure to nickel. Decreases in pup body weight have also been observed in rats following inhalation (Weischer et al. 1980) or oral (Ambrose et al. 1976; RTI 1988a, 1988b) exposure.

No human or animal data on the toxicokinetic properties of nickel in children or immature animals or studies examining possible age-related differences in the toxicokinetics of nickel were located. Studies with other metals, notably lead and cadmium (Bhattacharyya 1983), have found higher absorption rates in suckling animals, as compared to adults; it is not known if this is also true for nickel. Parenteral administration studies in rats and mice demonstrate that water-soluble nickel compounds are transferred across the placenta (Olsen and Jonsen 1979) and via maternal milk (Dostal et al. 1989). Subsequent sections of this chapter (Sections 3.8, 3.10, and 3.11) discuss the available information on biomarkers, interactions, and methods for reducing toxic effects. The available information is from adults and mature animals; no child-specific information was identified. It is likely that this information will also be applicable to children.

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3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic 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 nickel are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by nickel are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

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biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations that are Unusually Susceptible."

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Nickel

Biological monitoring data are available primarily from occupational settings. Determination of nickel in the urine, feces, serum, hair, and nasal mucosa has been used to demonstrate human exposure to nickel compounds (Angerer and Lehnert 1990; Bencko et al. 1986; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Based on an extensive review of biological monitoring data, Sunderman et al. (1993) concluded that serum and urine nickel levels were the most useful biomarkers of nickel exposure. Levels of nickel in urine and serum can provide the most information about levels of nickel exposure if the route, sources, and duration of exposure are known, if the chemical identities and physical-chemical properties of the nickel compounds are known, and if physiological information (e.g., renal function) of the exposed population is known (Sunderman 1993). In the general population, average nickel concentrations in serum and urine are 0.2 and 1–3 µg/L, respectively (Templeton et al. 1994).

Significant correlations have been found between occupational exposure to less-soluble nickel compounds (breathing zone samples) and the levels of nickel in the urine and serum in various groups of workers (Morgan and Rouge 1984). Nickel levels in urine and serum of workers inhaling nickel powder, alloys, or slightly soluble compounds reflect the combined influences of long-term accumulation and recent exposures (Sunderman et al. 1986). Correlations between exposure concentration and levels in the urine and serum were found only in groups and not in individual workers. A relationship between exposure concentrations of soluble nickel compounds and levels of nickel in the urine and serum has also been reported (Bernacki et al. 1980). Urine and serum levels of nickel in workers inhaling soluble nickel compounds reflect the amount of nickel absorbed in the previous 1 or 2 days (Sunderman et al. 1986). With respect to monitoring nickel following exposure to soluble compounds, the best correlations between exposure concentration and urine levels were found with "end-of-shift" urine sampling (Bernacki et al. 1980) or "next morning" urine sampling (Tola et al. 1979). A correlation was found between urinary nickel and plasma nickel in workers, with nickel levels in urine being about 8-fold higher than plasma levels (Angerer and Lehnert 1990; Bernacki et al. 1978). Bavazzano et al. (1994) did not find significant correlations between urinary nickel concentrations in nickel electroplating workers and air concentrations of soluble nickel compounds. Among nickel refinery workers, there was a significant correlation between urinary nickel levels (unadjusted or adjusted for creatinine levels) and soluble nickel

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concentrations in air; the correlation coefficients were approximately 0.35 and 0.55 for unadjusted and adjusted urine (Werner et al. 1999). Adding insoluble nickel air concentrations into the regression analysis as a predictor value resulted in a negligible change. Similarly, Oliveira et al. (2000) found significant correlations between postshift urinary nickel levels (adjusted for creatinine excretion) and nickel concentrations in the air among workers at a galvanizing facility exposed to soluble nickel compounds. A lower correlation coefficient was found for the relationship between preshift adjusted urinary levels and airborne nickel concentrations.

Higher concentrations of nickel in the urine and the plasma and lower concentrations of nickel in the nasal mucosa were observed in workers exposed to soluble nickel compounds when compared to workers exposed to less-soluble compounds (Bernacki et al. 1978; Torjussen and Andersen 1979). Less-soluble nickel compounds tended to remain in the nasal mucosa (half-life of ≈ 3.5 years); therefore, urinary and plasma levels were relatively low (Torjussen and Andersen 1979).

In workers exposed to nickel at a battery factory, a positive correlation was also found between air concentrations of nickel and concentrations of nickel in the feces (Hassler et al. 1983). High concentrations of nickel were found in the feces of workers exposed to nickel dusts containing large particles (as a result of greater mucociliary clearance from the lungs to the gastrointestinal tract) (Hassler et al. 1983).

It has been questioned whether or not levels of nickel in urine or serum are indicators of specific adverse health effects in humans. After reviewing monitoring data in occupationally exposed workers, Sunderman (1993) concluded that with the exception of nickel carbonyl, a relationship between nickel levels in body fluids and a specific health risk could not be established.

Exposure to nickel has also been monitored by assessing the content of nickel in the hair (Bencko et al. 1986). Analysis of the nickel content of hair provides evidence of past exposure and not changes in recent exposure to nickel. Correlations between exposure concentration and the level of nickel in hair were not reported.

Sensitization to nickel produces changes in serum antibodies (an increase in IgG, IgA, and IgM and a decrease in IgE) that may be monitored to determine if exposure to nickel has occurred (Bencko et al. 1983, 1986; Novey et al. 1983). These changes were found in both sensitized (Novey et al. 1983) and

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nonsensitized (Bencko et al. 1983, 1986) individuals. Information regarding the exposure concentration of nickel needed to produce serum antibody changes was not reported.

3.8.2 Biomarkers Used to Characterize Effects Caused by Nickel

Antibodies to hydroxymethyl uracil, an oxidized DNA base, were determined in workers exposed to nickel and cadmium, and in welders (Frenkel et al. 1994). Compared to controls, a significant increase in these antibodies was noted in the most highly exposed workers. Personal monitoring of 12 workers exposed to nickel and cadmium showed correlation coefficients between exposure concentrations and the antibodies of 0.4699 for cadmium and 0.7225 for nickel. Antibodies to hydroxymethyl uracil were not increased among welders. The levels of antibodies in the control populations for the nickel cadmium workers and for the welders were different, indicating the importance of determining the distribution of a new biomarker in controls for each population that is studied. This preliminary study suggests that antibodies to oxidized DNA products may be useful biomarkers for nickel and other metals that induce oxidative stress.

A preliminary study using imaging cytometry of nasal smears obtained from nickel workers indicates that this method may be useful to detect precancerous and cancerous lesions (Reith et al. 1994). With this method in which the cells were obtained by brushing the inside of the nose, the investigators were able to distinguish between nickel-exposed workers with non-dysplastic normal and suspicious mucosa smears and those with dysplastic lesions.

Although increases in oxidized DNA products and precancerous and cancerous lesions in the nose have been associated with nickel exposure, these effects are not specific to nickel. There are no specific biomarkers for nickel adverse health effects.

3.9 INTERACTIONS WITH OTHER CHEMICALS

A number of interactions of nickel with other chemicals are reported in the literature. The toxicity of nickel has been mitigated by treatment with chelating agents (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). Chelation treatment stimulates the excretion of nickel, thereby mitigating its toxicity. Lipophilic chelating agents, such as triethylenetetramine (TETA) and Cyclam (1,4,8,11-tetraaza-cyclotetradecane), were more effective than hydrophilic chelating agents such as EDTA,

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cyclohexanediamine tetraacetic acid (CDTA), diethylenetriamine pentaacetic acid (DTPA), and hydroxyethylenediamine triacetic acid (HEDTA) (Misra et al. 1988). The higher efficacy of the lipophilic agents may be due to their ability to bind to nickel both intracellularly and extracellularly, while the hydrophilic agents can only bind extracellularly.

A cross-reactivity between nickel and cobalt in sensitive individuals has been noted. For example, eight patients with asthma resulting from cobalt exposure also developed asthma when challenged with nickel sulfate (Shirakawa et al. 1990).

Nickel has also been found to interact with other metals such as iron, chromium, magnesium, manganese, zinc, and cadmium. The toxicity of nickel was mitigated by treatment with zinc (Waalkes et al. 1985) and magnesium (Kasprzak et al. 1986). The data suggest that magnesium, but not zinc, acted by altering the pharmacokinetics of nickel. The mechanism of action for zinc could not be determined from the study (Waalkes et al. 1985). Nickel absorption is increased during iron deficiency (Müller-Fassbender et al. 2003; Talkvist and Tjälve 1997), suggesting that iron deficiency may result in increased nickel toxicity. Coadministration of magnesium and nickel resulted in increased urinary excretion of nickel and decreased deposition of nickel in the lung, liver, and kidneys (Kasprzak et al. 1986). Manganese dust inhibited nickel subsulfide-induced carcinogenesis following simultaneous intramuscular injection of the two compounds (Sunderman and McCully 1983). The inhibition by manganese was a local and not a systemic effect.

Pretreatment of animals with cadmium 1 week before nickel treatment enhanced the nephrotoxicity and hepatotoxicity of nickel (Khandelwal and Tandon 1984). The mechanism of interaction could not be determined from these studies. Pretreatment of mice with cadmium 24 hours before nickel treatment has also been shown to decrease nickel-induced lethality and lipid peroxidation in the liver (Srivastava et al. 1995). The investigators suggested that a cadmium-induced production of ceruloplasmin, which prevented a nickel-induced reduction of ceruloplasmin, provided the protection against nickel toxicity.

More severe respiratory effects (increases in lung weight, in the accumulation of alveolar macrophages, and in the density of type II cell volumes) were observed in rabbits exposed by inhalation to both nickel and trivalent chromium than in rabbits exposed to nickel only (Johansson et al. 1988b).

In iron-deficient rats, nickel enhanced the absorption of iron (Nielsen 1980; Nielsen et al. 1980, 1984). This effect of nickel was only observed when ferric sulfate was given. No interaction was observed when

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iron was given as a 60% ferric/40% ferrous sulfate mixture. It has been proposed that nickel facilitates the passive diffusion of ferric ions by stabilizing the transport ligand (Nielsen 1980).

Veien and Menne (1990) have suggested that vasoactive substances found in food can enhance nickel sensitivity reactions. Foods that they suggested that nickel-sensitive people should avoid include beer, wine (especially red wine), herring, mackerel, tuna, tomatoes, onions, carrots, apples, and citrus fruits. The vasoactive substances may increase the amount of nickel that is able to reach the skin.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Individuals sensitized to nickel may be unusually susceptible because exposure to nickel by any route may trigger an allergic response. Epidemiology studies indicate that African-Americans have a higher nickel sensitivity than Caucasians and that women of both racial groups have higher reaction rates than men (Nethercott and Holness 1990; North American Contact Dermatitis Group 1973; Prystowsky et al. 1979). The incidence of reactions may be higher in women because they generally wear more metal jewelry than men. Further studies are required to determine if there are true gender and racial differences in nickel sensitivity, or if it is indeed a difference in exposure.

A relationship between HLA and nickel sensitivity was observed in individuals who had a contact allergy and positive results in a patch test for nickel (Mozzanica et al. 1990). The nickel-sensitive group had a significant elevation in HLA-DRw6 antigen, compared to controls with no history of atopy or contact dermatitis. The relative risk for individuals with DRw6 to develop a sensitivity to nickel was approximately 3.3. The presence of DRw6 may be monitored to determine the potential risk of individuals to become sensitized to nickel.

Nickel that has been absorbed into the blood stream is primarily excreted in the urine. Therefore, individuals with kidney dysfunction are likely to be more sensitive to nickel. The increased sensitivity of

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persons with kidney dysfunction is also suggested by increased serum concentrations of nickel in dialysis patients (Hopfer et al. 1989). Because diabetics often have kidney damage, and because of the hyperglycemic effects of nickel observed in animal studies, the sensitivity of diabetics to nickel is also likely to be increased.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Bronstein AC, Currance PL. 1988. Emergency care for hazardous material exposure. Washington, DC: The CV Mosby Company, 147-148.

Gosselin RE, Smith RP, Hodge HC. 1984. Clinical toxicology of commercial products, 5th ed. Baltimore, MD: Williams & Wilkins, II, 145.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries--a handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 218-219.

3.11.1 Reducing Peak Absorption Following Exposure

General recommendations for reducing absorption of nickel following acute inhalation exposure have included moving the patient to fresh air and monitoring for respiratory distress (HSDB 2003). About 20–35% of less-soluble nickel deposited in the lungs is absorbed into the blood from the respiratory tract (see Section 3.4.1.1). The nickel that is not absorbed into the blood is removed by mucociliary action and is expectorated or swallowed. Since the oral toxicity of metallic nickel is low, treatment with fluid and electrolyte replacement has been considered necessary only in cases with severe vomiting and diarrhea (HSDB 2003), which can occur as a result of nickel-induced gastrointestinal irritation (Sunderman et al. 1988). Thus, further induction of emesis is seldom necessary. EDTA added to the diet of humans decreased the bioavailability of orally administered nickel (Solomons et al. 1982). The presence of food in the stomach also reduced the gastrointestinal absorption of nickel (Christensen and Lagesson 1981). Oral administration of water or milk helps to dilute caustic nickel compounds in the stomach (Bronstein

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and Currance 1988; Stutz and Janusz 1988). In cases of dermal or ocular exposure, the skin or eyes should be thoroughly washed to prevent absorption by the skin or irritation of the eyes (Bronstein and Currance 1988; Stutz and Janusz 1988). Topical application of chelating agents and barrier creams has also been used to reduce dermal absorption in nickel-sensitive subjects (Gawkrödger et al. 1995). The most effective topical ligand for nickel yet described is 5-chloro-7-iodoquinolin-8-ol, but its use may be limited by its toxicity. Propylene glycol, petrolatum, and lanolin have been shown to reduce the dermal absorption of nickel.

3.11.2 Reducing Body Burden

Once absorbed into the blood, nickel has been found to distribute to the kidneys, liver, heart, fat, peripheral nervous tissues, and brain of animals (see Section 3.4.2). A mean serum half-time of nickel of 60 hours was measured in humans after oral exposure to nickel sulfate and nickel chloride (Sunderman et al. 1988).

A number of methods to decrease the body burden of nickel have been used or suggested. As discussed in Section 3.9, chelation treatment with a number of agents has been helpful (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). Lipophilic chelating agents such as TETA and Cyclam were more effective than hydrophilic chelating agents such as EDTA, CDTA, DTPA, and HEDTA (Misra et al. 1988). This may reflect differences in the distribution of hydrophilic and lipophilic agents between the intracellular and extracellular compartments. The use of diethyldithiocarbamate (DDC) as a chelating agent has been suggested as the preferred agent (Goldfrank et al. 1990; HSDB 2003). Disulfiram, which is metabolized to two molecules of DDC, might also be effective if DDC is not available. Penicillamine has also been used as a chelating agent for nickel. Intravenous infusion of fluids reduced the half-time for serum clearance of nickel from 60 to 27 hours in humans accidentally exposed to nickel sulfate and nickel chloride in water (Sunderman et al. 1988). The use of chelating agents over the long term to reduce nickel body burden in nickel-sensitive individuals is not recommended because it would also result in the reduction of other essential metals (Veien and Menne 1990). A nickel-restricted diet is useful in some sensitive adults for reducing nickel dermatitis, but this diet must be used with caution in nickel-sensitive children because it may not provide sufficient levels of nutrients for growth (Veien and Menne 1990).

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3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Many toxic effects of both soluble nickel and some relatively less-soluble (in water) nickel compounds, which slowly dissolve in serum and cytosol, are due to nickel ions (Sunderman and Oskarsson 1991). In addition to reducing body burden of nickel, chelating agents may effectively mitigate toxicity by binding to nickel ions before toxic effects can be produced. For example, contact dermatitis is a prevalent allergic response to nickel, and disulfiram has been shown to be effective in clearing up cases of nickel dermatitis (Goldfrank et al. 1990; HSDB 2003).

Inhalation exposure to nickel or nickel compounds (along with other metals) in the workplace has resulted in such adverse respiratory effects as chronic bronchitis, emphysema, reduced vital capacity, and asthma (see Section 3.2.1.2). Studies in animals have indicated that the effects of nickel compounds on the respiratory system (chronic inflammation, fibrosis, macrophage hyperplasia) depend on the solubility of the compounds rather than on lung burden. Nickel oxide (low solubility) was less toxic than the soluble nickel sulfate but resulted in a higher lung burden. Nickel compounds have been shown to have effects on lung macrophages of animals, including accumulation of macrophages and granular material in the alveoli and an increase in volume density of alveolar type II cells. A decrease in alveolar macrophage activity was observed in animals after exposure to nickel compounds, and the more-soluble compounds had the greatest effect (Haley et al. 1990). The relationship between the effects on alveolar macrophages and respiratory toxicity is unknown, but since soluble nickel compounds appear to have greater effects, the involvement of the nickel ion is implicated.

The mechanisms of nickel carcinogenicity have not been established. There is a strong evidence that the mechanism involves the binding of nickel to biological macromolecules, including chromatin and proteins (Costa et al. 1994; Kasprzak et al. 2003b; Lee et al. 1995; Oller et al. 1997; Zoroddu et al. 2002). The complexing of nickel ions and chromatin can result in hypermethylation of DNA condensation, which alters gene expression. Additionally, the binding of nickel ions to proteins and peptides can result in the generation of oxygen radicals, which could indirectly damage DNA. Mechanisms that interfere with the binding of nickel ions to macromolecules may interfere with the carcinogenicity of nickel.

In conclusion, it appears that the toxicity of nickel and nickel compounds involves the binding of nickel ions to biological macromolecules. Chelation therapy appears to be effective both in reducing the body burden of nickel and interfering with the mechanism by which nickel exerts toxic effects by competing with the binding sites on biological molecules.

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3.12 ADEQUACY OF THE DATABASE

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

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

3.12.1 Existing Information on Health Effects of Nickel

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to nickel are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of nickel. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Humans have been exposed to nickel in nickel mines and processing plants, and numerous epidemiology studies have been performed to assess the cause of death in these workers. Accidental ingestion of nickel also has been documented in a small child and in electroplating workers. Nickel dermatitis is the most prevalent effect of nickel in humans.

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

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

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

● Existing Studies

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Several chronic inhalation and oral studies and acute dermal studies in animals are reported in the literature. These studies exposed several species of animals to both soluble and less-soluble nickel compounds. The target organs were found to be the respiratory system for inhalation exposure and the respiratory system, gastrointestinal tract, hematological system, and kidneys for oral exposure at high levels. Reproductive and developmental effects were observed in animals after inhalation exposure and after oral exposure to nickel. Nickel sensitivity and dermatitis were also observed.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Data on the acute toxicity of nickel come from case reports of individuals exposed to nickel via inhalation, ingestion, or dermal contact, studies of patch testing in humans, and animal inhalation, oral, and dermal exposure studies. Human inhalation data are limited to a study of a worker dying due to respiratory tract injury following a 90-minute exposure to a very high concentration of metallic nickel with a small particle size (Rendall et al. 1994). Adverse gastrointestinal and neurological effects were observed in workers who ingested drinking water contaminated with nickel and boric acid (Sunderman et al. 1988). The contribution of boric acid to these effects is not known. Patch testing and oral nickel challenge testing have been done on individuals with contact dermatitis to determine if an allergy to nickel exists (Christensen and Moller 1975; Cronin et al. 1980; Eun and Marks 1990; Gawkrödger et al. 1986; Jordan and King 1979; Kaaber et al. 1978; Nielsen et al. 1990; Sjøvall et al. 1987; Veien et al. 1987). With the exception of nickel sensitivity following dermal contact, the available human data are not sufficient for identifying the most sensitive targets of nickel toxicity.

Acute inhalation studies in animals of nickel sulfate, nickel subsulfide, and nickel oxide indicate that nickel sulfate as the most toxic of the three compounds tested (NTP 1996a, 1996b, 1996c). The most sensitive target of nickel toxicity in animals appears to be the respiratory tract. Alveolitis, chronic lung inflammation, alveolar macrophage hyperplasia, and atrophy of the nasal olfactory epithelium have been observed in rats exposed to nickel sulfate (Evans et al. 1995; NTP 1996c) or nickel subsulfide (Benson et al. 1995b; NTP 1996b), and active lung inflammation has been observed in rats exposed to nickel oxide (NTP 1996a). Chronic lung inflammation was also observed in mice acutely exposed to nickel sulfate (NTP 1996c) or nickel subsulfide (NTP 1996b). In addition to the respiratory effects, adverse immunological effects have been observed in mice exposed to nickel chloride (Adkins et al. 1979; Graham et al. 1978) or nickel sulfate (Adkins et al. 1979). Although the available acute-duration inhalation data are sufficient for identifying the critical target of nickel toxicity, the data were not

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considered adequate for derivation of an inhalation MRL because a serious LOAEL was identified at the lowest concentration tested in a study examining the respiratory tract (NTP 1996c). Although a NOAEL was identified for immunological effects; this study (Graham et al. 1978) was not suitable for MRL derivation due to the uncertainty of whether the NOAEL concentration would also be a no effect level for respiratory effects. A study involving exposure to low concentrations of a soluble nickel compound in which the respiratory tract was examined might provide data to derive an acute-duration inhalation MRL.

Acute oral studies in animals are limited to LD₅₀ studies (Haro et al. 1968; Mastromatteo 1986), a mouse study reporting increases in the occurrence of sperm head abnormalities (Sobti and Gill 1989), and a developmental toxicity screening study in mice that did not find adverse developmental effects (Seidenberg et al. 1986). Because of the limited number of end points examined, these studies do not provide sufficient information for identifying the most sensitive target of nickel toxicity following acute oral exposure, and are thus inadequate for MRL derivation. Acute oral exposure studies that examine a number of end points, including reproductive and development toxicity, would help to identify the most sensitive target of toxicity. Studies utilizing a number of doses would be useful for establishing the dose-response relationships for ingested nickel.

The development of nickel sensitivity in mice has been shown to be related to both the concentration of the nickel solution applied to the skin and the duration of exposure (Siller and Seymour 1994). Male mice showed a weaker response than females, and further studies regarding the gender difference in the development of nickel sensitivity would be useful. Additionally, dermal exposure studies examining a number of potential end points would be useful for identifying the most sensitive target of nickel toxicity following dermal exposure.

Intermediate-Duration Exposure. Intermediate-duration inhalation studies in humans were not located. Several studies examining the relationship between nickel ingestion and contact dermatitis were identified (Jordan and King 1979; Santucci et al. 1994; Sjobvall et al. 1987). These studies are not useful for identifying the critical target of nickel toxicity or the threshold of toxicity in nonsensitized individuals. No human studies examining the toxicity of nickel following dermal contact for an intermediate duration were located.

A number of adverse health effects have been observed in laboratory animals exposed to airborne nickel; the effects occurred in the respiratory tract (Benson et al. 1995a; Bingham et al. 1972; Horie et al. 1985;

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Johansson and Camner 1986; NTP 1996a, 1996b, 1996c; Tanaka et al. 1988), blood glucose levels (Weischer et al. 1980), immune and lymphoreticular system (Haley et al. 1990; Johansson et al. 1980, 1987, 1988a, 1989; Morimoto et al. 1995; NTP 1996a, 1996b, 1996c; Spiegelberg et al. 1984), reproductive system (NTP 1996a), and the developing organism (Weischer et al. 1980). The available inhalation data provide strong evidence that the respiratory tract is the most sensitive target of nickel toxicity following intermediate-duration exposure. Chronic active lung inflammation was the most sensitive respiratory effect and a NOAEL for this effect (NTP 1996c) was used to derive an intermediate-duration inhalation MRL.

A number of animal studies have assessed the toxicity of nickel following intermediate-duration oral exposure. Observed effects include decreases in body weight (American Biogenics Corporation 1988; Dieter et al. 1988; RTI 1988a, 1988b; Springborn Laboratories 2002; Weischer et al. 1980; Whanger 1973), kidney damage (Dieter et al. 1988), adverse lung effects (American Biogenics Corporation 1988; RTI 1988b), adverse reproductive effects (Käkelä et al. 1999; Pandey and Srivastava 2000; Pandey et al. 1999) and decreases in fetal/neonatal survival (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993; Springborn Laboratories 2000b). These data provide suggestive evidence that the developing organism may be a sensitive target of nickel toxicity following intermediate-duration exposure. As discussed in the sections on data needs for Reproductive Effects and Developmental Effects, additional studies are needed to confirm the identification of these effects as sensitive targets of nickel toxicity. Additional intermediate-duration studies would be useful for identifying sensitive targets of systemic toxicity and establishing dose-response relationships.

Dose-response data for dermal exposure of humans or animals to nickel were not identified. Dermal exposure studies would be useful for identifying sensitive targets of toxicity and establishing exposure-response relationships.

Chronic-Duration Exposure and Cancer. A number of epidemiology studies examining the inhaled toxicity of nickel in workers at nickel mines or nickel processing plants have been identified (Bencko et al. 1983, 1986; Berge and Skyberg 2003; Cornell 1984; Cornell and Landis 1984; Enterline and Marsh 1982; Godbold and Tompkins 1979; Kilburn et al. 1990; Muir et al. 1993; Pedersen et al. 1973; Polednak 1981; Redmond et al. 1994; Shannon et al. 1991; Sunderman and Horak 1981). In general, these studies were mortality studies and did not provide nickel monitoring data. Additionally, Chashschin et al. (1994) examined the potential of nickel to induce reproductive and developmental effects in female nickel workers. Chronic oral toxicity data in humans are limited to a study on nickel

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sensitized individuals (Panzani et al. 1995), which examined the occurrence of contact dermatitis. Three studies examined the occurrence of contact dermatitis in individuals chronically exposed to nickel via dermal contact (Lee and Lee 1990; Meijer et al. 1995; Wall and Calnan 1980).

The toxicity of nickel sulfate (NTP 1996c), nickel subsulfide (NTP 1996b; Ottolenghi et al. 1974), and nickel oxide (NTP 1996a; Takenaka et al. 1985, 1988) following chronic inhalation exposure has been investigated in a number of studies in laboratory animals. The results of these studies provide strong evidence that the lung is the most sensitive target of toxicity; inflammatory changes were observed in the lung at the lowest adverse effect levels. Other effects that have been observed include damage to the nasal olfactory epithelium (NTP 1996b, 1996c), decreases in body weight gain (Ottolenghi et al. 1974; Takanaka et al. 1985), and hyperplasia of the bronchial lymph nodes (NTP 1996a, 1996b, 1996c). A chronic-duration inhalation MRL was derived from the NTP (1996c) rat study of nickel sulfate. Data on the chronic toxicity of ingested nickel in laboratory animals are limited to a 2-year study in rats and dogs (Ambrose et al. 1976). The observed effects included decreases in body weight gain, lung damage, and adverse kidney effects. A chronic-duration oral MRL was not derived from this study because intermediate-duration studies provide suggestive evidence that the developing organism and possibly the reproductive system are sensitive targets of toxicity; these end points were not examined in chronic-duration studies. Additional oral exposure studies would be useful for identifying the critical targets of toxicity for ingested nickel; studies which examined the systemic toxicity of nickel would be useful in assessing whether the developing organism and/or the reproductive system are most sensitive targets. No chronic-duration dermal studies in laboratory animals were located. Studies by the dermal route of exposure would be useful for identifying the most sensitive targets of toxicity and establishing exposure-response relationships.

A number of occupational exposure studies have examined the carcinogenic potential of nickel. In general, these studies have found increased risks of lung and/or nasal cancer in workers exposed to less-soluble nickel compounds (Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; International Committee on Nickel Carcinogenesis in Man 1990; Magnus et al. 1982; Pedersen et al. 1973; Sunderman et al. 1989a) or soluble nickel compounds (Anttila et al. 1998; Grimsrud et al. 2002, 2003; International Committee on Nickel Carcinogenesis in Man 1990). No studies have examined the carcinogenicity of nickel in humans following oral or dermal exposure. A series of bioassays conducted by NTP (1996a, 1996b, 1996c) and Ottolenghi et al. (1974) examined the carcinogenic risk of inhaled nickel. Significant increases in the occurrence of lung tumors following exposure to nickel oxide (NTP 1996a) and nickel subsulfide (NTP 1996b; Ottolenghi et al. 1974), but not after nickel sulfate (NTP 1996c), were found. No

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additional inhalation studies in laboratory animals are needed at this time. Data on the carcinogenicity of ingested nickel are limited to a rat and mouse study conducted by Schroeder and associates (Schroeder and Mitchener 1975; Schroeder et al. 1974); no increases in the occurrence of malignant tumors were observed. These studies are inadequate for assessing carcinogenic potential because very low doses, below the MTD, were administered. Additional oral exposure carcinogenicity studies are needed to assess whether increased exposure to nickel could lead to an increased risk of developing cancer. Carcinogenicity studies using animals dermally exposed to nickel were not located. Cancer has been observed, however, after parental administration of less-soluble nickel compounds (e.g., nickel oxide, nickel subsulfide), but not soluble nickel compounds (Gilman 1962; Kasprzak et al. 1983; Lumb and Sunderman 1988; Smialowicz et al. 1985; Sunderman and Maenza 1976; Sunderman and McCully 1983).

Genotoxicity. Investigators conducting epidemiology studies have reported a higher incidence of chromosomal aberrations in nickel workers compared to controls (Elias et al. 1989; Waksvik and Boysen 1982). Both *in vitro* and *in vivo* studies in mammals indicate that nickel is genotoxic (Andersen 1983; Biedermann and Landolph 1987; Conway and Costa 1989; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stern 1984; Larramendy et al. 1981; Miura et al. 1989; Ohno et al. 1982; Saxholm et al. 1981; Sobti and Gill 1989; Wulf 1980), and the mechanism of action of nickel on cellular DNA has been studied (Ciccarelli and Wetterhahn 1982; Patierno and Costa 1985, 1987; Robinson and Costa 1982). Additional studies regarding the genotoxicity of nickel compounds are not needed at this time.

Reproductive Toxicity. Data on the reproductive toxicity of nickel in humans is limited to a study of women working at a nickel hydrometallurgy refining plant (Chashschin et al. 1994). However, interpretation of these study results is limited by the lack of information on the control of potential confounding variables, heavy lifting, and possible heat stress. Several oral exposure studies in animals suggest that nickel can result in testicular and epididymal damage (Käkelä et al. 1999; Pandey et al. 1999) and decreases in sperm motility, count, and sperm abnormalities (Pandy and Srivastava 2000; Pandey et al. 1999; Sobti and Gill 1999), or alterations in fertility (Käkelä et al. 1999; Pandey et al. 1999). Other oral studies have not found histological alterations in male or female reproductive tissues or impaired fertility following intermediate- or chronic- duration exposure (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; RTI 1988a, 1988b; Springborn Laboratories 2000a). Although testicular effects were also observed following inhalation exposure, the investigators (NTP 1996b, 1996c) considered the testicular effects to be secondary to emaciation. Additionally, fertility was not adversely affected in a single generation study (Springborn Laboratories 2000b) or two multigeneration studies (RTI 1988a, 1988b; Springborn Laboratories 2000a). The poor reporting of the study results, particularly

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incidence data and statistical analysis, limits the interpretation of the Käkälä et al. (1999), Pandey et al. (1999), and Pandey and Srivastava (2000) studies. An expert evaluation of the unpublished results of these studies, along with the other available reproductive toxicity studies (RTI 1988a, 1988b; Springborn Laboratories 2000a, 2000b), may provide insight on the apparent differences between the studies. Nickel treatment of rats during lactation has also been shown to change the quality of the milk (Dostal et al. 1989). Further studies concerning the role of physiological levels, as well as toxic levels, of nickel in the release of prolactin from the pituitary could provide useful information on potential reproductive and developmental effects of nickel.

Developmental Toxicity. There are limited data on the potential developmental toxicity of nickel in humans. An increase in structural malformations was observed in infants of women who worked in a nickel hydrometallurgy refining plant (Chashschin et al. 1994); however, the lack of information on control of potential confounding variables such as smoking and alcohol use and heavy lifting, and possible heat stress limits the interpretation of these results. Decreased fetal body weight was observed in offspring of rats exposed to high levels of nickel via inhalation during gestation (Weischer et al. 1980). Developmental effects such as increased pup mortality, decreased pup survival, and decreased pup body weight were observed in oral exposure single-generation studies involving male-only, female-only, or male and female exposure to nickel (Käkälä et al. 1999), multigeneration studies in rats (Ambrose et al. 1976; RTI 1988a, 1988b; Springborn Laboratories 2000b), and multilitter studies in rats (Smith et al. 1993). Although the available studies have consistently found decreases in pup survival, decreases in maternal body weight, food consumption, and water consumption often occur at the same dose levels. Thus, it is not known if the effects are due to nickel-induced damage to the offspring or are secondary to the maternal toxicity. Studies that controlled for maternal food intake and water consumption would be useful in understanding the mechanism of nickel toxicity. Developmental toxicity studies utilizing a number of dose levels would provide useful information in establishing the dose-response relationships for nickel. Studies assessing the developmental effects following dermal exposure were not located. Developmental effects have also been observed in animals following parental administration of nickel (Chernoff and Kavlock 1982; Lu et al. 1979; Sunderman et al. 1978).

Immunotoxicity. Human exposure to a large dose of nickel can result in sensitization manifested as contact dermatitis. Although there are limited data for the inhalation route, there are extensive data for the oral and dermal routes. Three studies examined immunological end points following inhalation exposure; two of these studies (Bencko et al. 1983, 1986) measured immunoglobulin levels in nickel workers and found significant alterations. The third study (Shirakawa et al. 1990) found positive results

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in patch tests of workers with hard metal lung disease. In nickel-sensitized individuals, oral exposure to fairly low doses of nickel can result in contact dermatitis; this has been tested in several acute-duration studies (Christensen and Moller 1975; Cronin et al. 1980; Gawkrödger et al. 1986; Veien et al. 1987) and two intermediate-duration studies (Jordan and King 1979; Sjøvall et al. 1987). There is extensive information on the immunotoxicity of nickel in humans following dermal exposure. In general, the dermal exposure studies fall into two main categories: patch testing in individuals with contact dermatitis (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Cavelier et al. 1988; Emmett et al. 1988; Eun and Marks 1990; Keczkes et al. 1982; Meijer et al. 1995; Menne et al. 1987; Simonetti et al. 1998; Uter et al. 2003; Wantke et al. 1996) and studies designed to assess the occurrence of nickel sensitivity in the general population (Dotterud and Falk 1994; Larsson-Stymme and Widstrom 1985; Menne and Holm 1983; Nielsen et al. 2002).

Animal studies demonstrate that nickel can induce immunological effects in nonsensitized individual. Alterations in nonspecific immunity (e.g., macrophage activity) (Adkins et al. 1979; Haley et al. 1990; Johansson et al. 1980) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) (Adkins et al. 1979; Graham et al. 1978; Morimoto et al. 1995; Spiegelberg et al. 1984) has been observed in animals following inhalation exposure. Similarly, oral exposure to nickel has resulted in alterations in natural killer cells (Ilback et al. 1994) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) (Dieter et al. 1988; Ilback et al. 1994). One dermal exposure study in mice examined the exposure-response relationship for nickel sensitization in mice (Siller and Seymour 1994). Studies designed to assess the dose-response relationship for contact dermatitis and oral dose are needed; the results of these studies should be considered during the derivation of oral MRLs for nickel. Additionally, studies that examined whether tolerance to nickel can develop and that assess cross sensitization of nickel with other metals would also be useful.

Neurotoxicity. No studies on the neurotoxicity of nickel in humans following inhalation or dermal exposure were located. Neurological effects (giddiness, weariness) were reported in individuals accidentally exposed to nickel and boric acid in drinking water (Sunderman et al. 1988). Temporary blindness in half of each eye occurred shortly after one person took a 0.05-mg/kg dose of nickel as nickel sulfate in drinking water (Sunderman et al. 1989b). There is limited information on the neurotoxicity of nickel in laboratory animals. No histological alterations were observed in the central nervous system following inhalation (NTP 1996a, 1996b, 1996c) or oral exposure (Ambrose et al. 1976; Obone et al. 1999). Although histological damage to the nasal olfactory epithelium was observed in animals following

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inhalation exposure to nickel sulfate or nickel subsulfide (Evans et al. 1995; NTP 1996b, 1996c), functional changes were not noted (Evans et al. 1995). Neurological signs (lethargy, ataxia, prostration) were observed in dying rats treated with nickel for 3 months; however, these effects were probably associated with overall toxicity (American Biogenics Corporation 1988). No animal dermal exposure studies examined neurological end points. The human data provide suggestive evidence that exposure to nickel may result in neurological effects; additional animal studies examining neurobehavioral performance would provide valuable information on the neurotoxic potential of nickel.

Epidemiological and Human Dosimetry Studies. A number of epidemiology studies regarding nickel toxicity are available in the literature. Most of these studies have focused on the carcinogenicity of inhaled nickel (Anttila et al. 1998; Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; Grimsrud et al. 2002, 2003; International Committee on Nickel Carcinogenesis in Man 1990; Magnus et al. 1982; Pedersen et al. 1973; Sunderman et al. 1989a) or nickel sensitivity following oral (Christensen and Moller 1975; Cronin et al. 1980; Gawkrödger et al. 1986; Jordan and King 1979; Sjøvall et al. 1987; Veien et al. 1987) or dermal (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Cavelier et al. 1988; Dotterud and Falk 1994; Emmett et al. 1988; Eun and Marks 1990; Keczkes et al. 1982; Larsson-Stymme and Widstrom 1985; Meijer et al. 1995; Menne and Holm 1983; Menne et al. 1987; Nielsen et al. 2002; Simonetti et al. 1998; Uter et al. 2003; Wantke et al. 1996) exposure. As nickel exposure levels in the occupational environments have been reduced, continued health monitoring of populations occupationally exposed to nickel would be useful to determine if more subtle adverse health effects occur in humans at lower concentrations. Continued monitoring of nickel sensitization in the general population is needed to assess whether the increased popularity of body piercing will result in increased occurrences of nickel sensitivity. Additional studies on the dose-response relationship of ingested nickel dose and contact dermatitis would be useful. Animal data provide some suggestive evidence that nickel may be a reproductive toxicant and maternal exposure may result in increases in neonatal mortality. Inclusion of these end points in occupational exposure studies may provide valuable information on whether these would also be end points of concern for humans.

Biomarkers of Exposure and Effect.

Exposure. Nickel is a naturally occurring component of the diet and can be detected in hair, blood, urine, and feces (Angerer and Lehnert 1990; Bencko et al. 1986; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). In persons exposed to nickel above background levels, positive qualitative correlations have been found between air concentrations of nickel

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and nickel levels in the feces (Hassler et al. 1983) and urine (Angerer and Lehnert 1990; Bavazzano et al. 1994; Bernacki et al. 1978, 1980; Morgan and Rouge 1984; Oliveira et al. 2000; Sunderman et al. 1986; Tola et al. 1979; Torjussen and Andersen 1979; Werner et al. 1999). Additional studies examining the relationship between levels of nickel in the urine and body burden levels and studies associating urinary nickel levels and the manifestation of adverse health effects would be useful in establishing biological exposure indices for nickel.

Effect. A relationship between human lymphocyte antigens and nickel sensitivity exists and predicts that individuals with this antigen have a relative risk of approximately 3.3 for developing nickel sensitivity (Mozzanica et al. 1990). Antibodies to hydroxymethyl uracil, an oxidized DNA base, have also been shown to be increased in some nickel-exposed workers (Frenkel et al. 1994). A preliminary study using imaging cytometry of nasal smears obtained from nickel workers indicates that this method may be useful to detect precancerous and cancerous lesions (Reith et al. 1994). Additional studies that examine markers of early biological effects, such as changes in gene expression measured by microarrays, could be piloted with *in vitro* cell lines to determine nickel-specific markers, followed by *in vivo* screening of people living near sites that contain elevated levels of nickel or who have occupational exposures to nickel. Studies that identify nickel-specific biomarkers may be helpful in alerting health professionals to nickel exposure before serious toxicological effects occur.

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetic studies in humans indicate that nickel is absorbed through the lungs (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991), gastrointestinal tract (Nielsen et al. 1999; Patriarca et al. 1997; Sunderman et al. 1989b), and skin (Fullerton et al. 1986; Norgaard 1955). Food greatly decreases the absorption of nickel from the gastrointestinal tract (Sunderman et al. 1989b). Following absorption from the lungs and the gastrointestinal tract, nickel is excreted in the urine (Angerer and Lehnert 1990; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Sunderman et al. 1989b; Torjussen and Andersen 1979). Increased levels of nickel were found in the lungs, nasal septum, liver, and kidneys of workers inhaling nickel (Andersen and Svenes 1989; Kollmeier et al. 1987; Raithel et al. 1988; Rezuke et al. 1987; Sumino et al. 1975; Svenes and Andersen 1998; Torjussen and Andersen 1979). Animal data indicate that after inhalation, nickel particles can remain in the lungs (nickel oxide) or be absorbed and then excreted in the urine (nickel sulfate). High levels of nickel have been found in the liver, kidneys, and spleen of animals after inhaling high levels of nickel (Benson et al. 1987, 1988, 1994, 1995a; NTP 1996a, 1996b, 1996c; Tanaka et al. 1985). Nickel that has been absorbed after oral exposure is primarily distributed to the kidneys before being excreted in the urine. High levels of nickel were also found in the

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liver, heart, lungs, fat, peripheral nervous tissue, and brain (Ambrose et al. 1976; Borg and Tjalve 1989; Dieter et al. 1988; Jasim and Tjalve 1986a, 1986b; Oskarsson and Tjalve 1979; Whanger 1973). Studies examining the bioavailability of nickel from soil following oral exposure would be useful for determining the absorbed dose from nickel-contaminated soil at a hazardous waste site. Further verification of the toxicokinetic models developed by Hsieh et al. (1999a, 1999b) and Sunderman et al. (1989b) would improve the ability to predict the absorbed dose following inhalation or oral exposure.

Comparative Toxicokinetics. Studies that examine the toxicokinetics of nickel in humans after occupational exposure, ingestion of nickel from food and water, and dermal exposure are available (Bennett 1984; Fullerton et al. 1986; Grandjean 1984; Norgaard 1955; Sunderman and Oskarsson 1991; Sunderman et al. 1989b). The toxicokinetics of both inhaled and ingested nickel have been examined in several species of animals (rats, mice, dogs, hamsters) (Ambrose et al. 1976; Benson et al. 1987, 1988; Borg and Tjalve 1989; Dieter et al. 1988; Jasim and Tjalve 1986a, 1986b; NTP 1996a, 1996b, 1996c; Oskarsson and Tjalve 1979; Tanaka et al. 1985; Whanger 1973). Dermal studies have been performed in guinea pigs and rabbits (Lloyd 1980; Norgaard 1957). The limited human data correlate well with the toxicokinetics observed in animals. Studies that compare the toxicokinetics of humans and animals using the same experimental protocol would be helpful in determining which species of animal is the best model for assessing the effects of nickel in humans.

Methods for Reducing Toxic Effects. Approximately 20–35% of inhaled less-soluble nickel is absorbed through the lungs (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991). Methods that would enhance the clearance of nickel from the lung, thus preventing or reducing the severity of lung damage (inflammation or fibrosis), would be useful. The administration of EDTA in food (Solomons et al. 1982) and the presence of food in the stomach (Christensen and Lagesson 1981) decrease the amount of nickel that is absorbed through the gastrointestinal tract. Several chelating agents (e.g., TETA, Cyclam, EDTA) have been shown to be effective in reducing the body's nickel burden (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). It is not known if other methods, such as dialysis, would be more effective in reducing the body burden. The mechanism of nickel toxicity involves the binding of nickel ions to macromolecules; chelating agents have been shown to bind to the nickel ions, thus mitigating the toxicity. Studies designed to determine if other methods would be more effective in binding nickel ions would be useful.

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Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are limited data on the toxicity of nickel in children. Several patch testing studies have included children (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995; Uter et al. 2003; Wantke et al. 1996), the results of which suggest that children may be more susceptible than adults. However, the increased susceptibility observed in children may be due to increased prolonged exposure to nickel-containing products such as earrings, rather than increased sensitivity; additional studies are needed to verify this assumption. Studies in laboratory animals provide evidence that the fetus and neonates are sensitive targets of nickel toxicity following inhalation or oral exposure (Ambrose et al. 1976; Berman and Rehnberg 1993; Käkälä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993; Weischer et al. 1980). As noted in the Developmental Toxicity section, additional studies are needed to verify this apparent sensitivity. No human or animal data on the toxicokinetic properties of nickel in children or immature animals or studies examining possible age-related differences in the toxicokinetics of nickel were located. Studies with other metals, notably lead and cadmium (Bhattacharyya 1983), have found higher absorption rates in suckling animals, as compared to adults; it is not known if this is also true for nickel. Additional studies examining potential age-related differences in nickel would provide valuable information on the susceptibility of children to nickel toxicity.

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

3.12.3 Ongoing Studies

Ongoing studies pertaining to nickel have been identified and are shown in Table 3-14.

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Table 3-14. Ongoing Studies on Nickel Health Effects

Investigator	Affiliation	Research area
Costa, M	New York University, School of Medicine	Examination of the epigenetic mechanisms of nickel carcinogenesis
Rokita, SE	University of Maryland	Mechanisms of nickel carcinogenicity
Kasprzak, KS	National Cancer Institute	Mechanisms of nickel carcinogenicity
Leikauf, GD	University of Cincinnati	Genetic determinants on nickel-induced lung toxicity
Warshaw, EM	Department of Veterans Affairs, Medical Center, Minneapolis	Treatment of nickel contact dermatitis

Source: FEDRIP 2004