CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

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

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; dermal data are presented in Table 2-3.

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

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

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

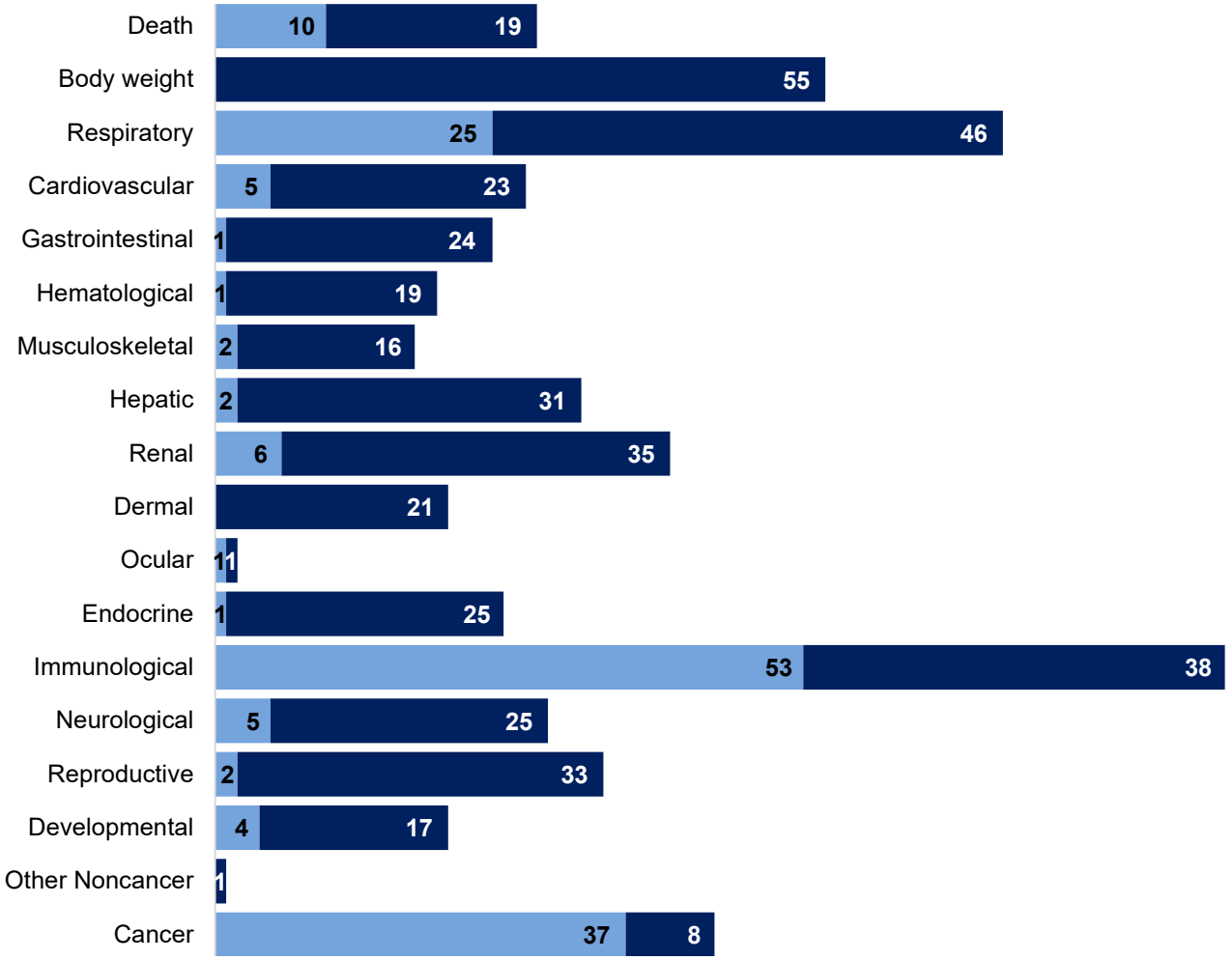
The health effects of nickel and compounds have been evaluated in epidemiological and laboratory animal studies. A large number of epidemiological studies have evaluated the toxicity of nickel; study types include case reports/case series, controlled oral exposure, and occupational exposure. In addition, there are general population studies of nickel as a constituent of ambient particulate matter. Studies discussed in this toxicological profile are restricted to studies with known nickel exposure to above background levels (e.g., occupational exposure) and controlled exposure studies; case reports and case series are included if there was clear evidence that exposure was primarily to nickel. As illustrated in Figure 2-1, most of the epidemiological studies included in the profile have evaluated immunological effects (primarily allergic contact dermatitis), cancer effects, and respiratory effects. Animal data are available for all health effects and all exposure duration categories. The most examined endpoints were body weight, respiratory, immunological, and reproductive effects. Approximately half of the animal studies involved inhalation exposure. The toxicity of a number of nickel compounds, including nickel sulfate, nickel chloride, nickel subsulfide, nickel oxide, and metallic nickel, was evaluated. 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 approximately 100 seconds (Stedman and Hikade 1980). Additionally, nickel carbonyl is not very soluble in water; therefore, it will not likely be found in drinking water.

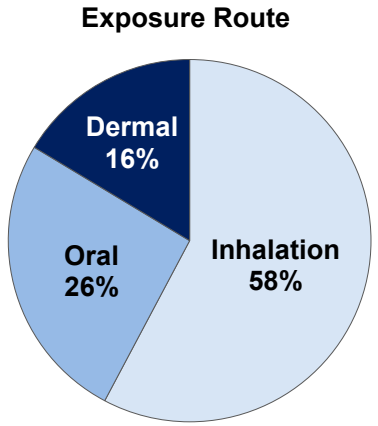
The human and animal studies suggest several sensitive targets of nickel toxicity (see Appendix C for details on the systematic review):

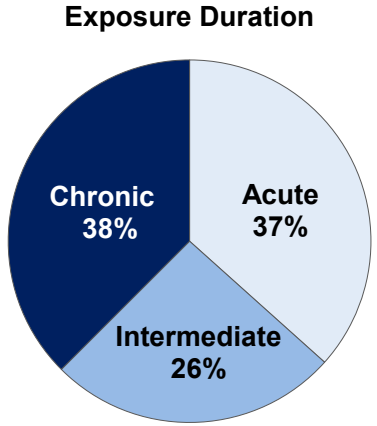
- **Respiratory Endpoints:** Respiratory effects are a presumed health effect for humans based on low-level evidence in occupational exposure studies and high level of evidence of lung inflammation and nasal lesions in animals following acute-, intermediate-, or chronic-duration exposure to several nickel compounds. Lung effects have also been observed in animals following oral exposure.
- **Immunological Endpoints:** Immunological effects are a presumed health effect for humans based on low-level evidence in epidemiological studies and high level of evidence in animal inhalation and oral exposure studies. Allergic contact sensitivity is a well-established health effect of nickel in humans sensitized to nickel. Animal studies have reported lymphoid hyperplasia in bronchial lymph nodes following inhalation exposure and impaired immune function following inhalation or oral exposure.
- **Reproductive Endpoints:** Reproductive effects are not classifiable as to whether they are a human effect based on low-level evidence in epidemiological studies and low-level evidence in animal studies. A small number of epidemiological studies have evaluated reproductive endpoints and the findings are inconsistent. A number of inhalation and oral exposure animal studies have examined reproductive endpoints; however, the level of evidence is low due to the conflicting results as to whether nickel induces male reproductive effects.
- **Developmental Endpoints:** Developmental effects are a presumed health effect in humans. This is based on low-level evidence in the small number of studies with inconsistent findings. There is high-level evidence from animal inhalation and oral exposure studies.

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

Most studies examined the potential respiratory and cancerous effects of nickel exposure.
More studies have evaluated health effects in humans than animals (counts represent studies examining endpoint).







*Includes studies discussed in Chapter 2. A total of 210 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Benson et al. 1995b									**Nickel subsulfide**
1	Rat (Fischer-344) 4–6 B	1, 2, 4, 7, or 12 days 6 hours/day	0, 0.44, 1.83	BC, BW, HP	Bd wt	0.44	1.83		Decreased body weight after 7 days of exposure (17–19%)
					Resp		0.44		Alveolitis after 7 days of exposure
Efremenko et al. 2014									**Nickel subsulfide**
2	Rat (Fischer-344) 5 M	5 days 6 hours/day	0, 0.03, 0.06, 0.11, 0.44	BW, BI	Resp		0.44		Peribronchiolar/perivascular inflammation and increased LDH in BALF (>250%)
Efremenko et al. 2017a, 2017b									**Nickel sulfate hexahydrate**
3	Rat (Fischer-344) 5 M	5 days 6 hours/day	0, 0.2244	CS, BW, BI, HP	Resp		0.2244[b]		Bronchiole epithelial degeneration/hyperplasia
Hirano et al. 1994									**Nickel sulfate**
4	Rat (Wistar) 28 M	2 hours	36.5	LE	Death			36.5	4/28 died
NTP 1996a									**Nickel oxide**
5	Rat (Fischer-344) 5 M, 5 F	12 days in 16-day period 6 hours/day	0, 0.9, 2.0, 3.9, 7.9, 23.6	BW, CS, HE, HP, LE, OW	Bd wt	23.6			
					Resp	3.9	7.9		Lung inflammation
					Cardio	23.6			
					Gastro	23.6			
					Musc/skel	23.6			
					Hepatic	23.6			
					Renal	23.6			
					Dermal	23.6			
					Endocr	23.6			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	23.6			
					Neuro	23.6			
					Repro	23.6			
NTP 1996b									**Nickel subsulfide**
6	Rat (Fischer-344) 5 M, 5 F	12 days in 16-day period 6 hours/day	0, 0.44, 0.88, 1.83, 3.65, 7.33	BW, CS, HE, HP, LE, OW	Bd wt	1.83		3.65	22–28% decrease in body weight gain
					Resp		0.44		Chronic lung inflammation and atrophy of olfactory epithelium
								3.65 F	Labored respiration
								7.33 M	Labored respiration
					Cardio	7.33			
					Gastro	7.33			
					Hepatic	7.33			
					Renal	7.33			
					Dermal	7.33			
					Endocr	7.33			
					Immuno	7.33			
					Neuro	7.33			
					Repro	7.33			
NTP 1996c									**Nickel sulfate hexahydrate**
7	Rat (Fischer-344) 5 M, 5 F	12 days in 16-day period 6 hours/day	0, 0.7, 1.4, 3.1, 6.1, 12.2	BW, HE, HP, LE, OW	Death			12.2 F	5/5 died
					Bd wt			0.7 M	Final body weights 28% lower than controls

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Resp			0.7	Labored breathing and increased respiration rates; chronic lung inflammation, and degeneration of bronchiolar epithelium and atrophy of olfactory epithelium
					Cardio	12.2			
					Gastro	12.2			
					Musc/skel	12.2			
					Hepatic	12.2			
					Renal	12.2			
					Dermal	12.2			
					Endocr	12.2			
					Immuno	0.7 F	1.4 F		Hyperplasia in bronchial and mediastinal lymph nodes
					Neuro	3.1 F			
					Repro	12.2			
Oller et al. 2023									**Nickel sulfate hexahydrate**
8	Rat (Fischer-344) 13 M	1 week 5 days/week 6 hours/day	0, 0.44	BW, CS, GN, HP, OW	Death			0.44	12 of 13 rats died
					Resp			0.44	Severe pulmonary edema and labored breathing
Adkins et al. 1979									**Nickel chloride**
9	Mouse (CD-1) 113 F	2 hours	0, 0.66	BI, CS	Immuno		0.66		Decreased ability to clear bacteria from lungs

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Adkins et al. 1979									**Nickel chloride**
10	Mouse (CD-1) 80-–160 F	2 hours	0, 0.288, 0.292, 0.37, 0.5, 0.51	BI, CS	Immuno	0.37	0.5		Increased susceptibility to Streptococcal infection (reduced mean survival time by 2.73 days)
Adkins et al. 1979									**Nickel sulfate**
11	Mouse (CD-1) 120 F	2 hours	0, 0.46	BI, CS	Immuno		0.46		Increased susceptibility to Streptococcal infection (reduced mean survival time by 2 days)
Buxton et al. 2021									**Nickel chloride hexahydrate**
12	Mouse (ICR) 10–15 F	24 hours	0, 0.016, 0.044, 0.081	BW, CS, FI, GN, HP, OW, WI, IX	Bd wt	0.081			
					Immuno	0.081			
Graham et al. 1978									**Nickel chloride**
13	Mouse (Swiss) 14–29 F	2 hours	0, 0.1, 0.25, 0.35, 0.5	OF, OW	Immuno	0.1	0.25		Impaired humoral immunity
NTP 1996a									**Nickel oxide**
14	Mouse (B6C3F1) 5 M, 5 F	12 days in 16-day period 6 hours/day	0, 0.9, 2.0, 3.9, 7.9, 23.6	BW, CS, HE, HP, LE, OW	Bd wt	23.6			
					Resp	3.9	7.9		Alveolar macrophage hyperplasia
					Cardio	23.6			
					Gastro	23.6			
					Hepatic	23.6			
					Renal	23.6			
					Dermal	23.6			
					Endocr	23.6			
					Immuno	23.6			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	23.6			
					Repro	23.6			
NTP 1996b									**Nickel subsulfide**
15	Mouse (B6C3F1) 5 M, 5 F	12 days in 16-day period 6 hours/day	0, 0.44, 0.88, 1.83, 3.65, 7.33	BW, HE, HP, LE, OW	Death			7.33	10/10 died
					Bd wt	3.65 F			
						1.83 M	3.65 M		Decreased terminal body weight (14%)
					Resp	0.44	0.88	7.33	SLOAEL: Labored breathing, necrosis in alveolar and bronchiolar epithelium, extensive vascular congestion and edema LOAEL: Atrophy of olfactory epithelium. Lung inflammation at 1.83 mg Ni/m^3
					Cardio	3.65			
					Gastro	3.65			
					Hemato	3.65			
					Musc/skel	3.65			
					Hepatic	3.65			
					Renal	3.65			
					Dermal	3.65			
					Endocr	3.65			
					Immuno	0.44	0.88		Lymphoid hyperplasia in bronchial lymph nodes in 3/3 males and 1/2 females
					Neuro	3.65			
					Repro	3.65			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1996c									**Nickel sulfate hexahydrate**
16	Mouse (B6C3F1) 5 M, 5 F	12 days in 16-day period 6 hours/day	0, 0.7, 1.4, 3.1, 6.1, 12.2	BW, CS, HE, HP, LE, OW	Death			1.4	10/10 died
					Bd wt	0.7			
					Resp		0.7	1.4	LOAEL: Chronic lung inflammation; atrophy of olfactory epithelium SLOAEL: Necrotizing inflammatory lesions with edema, vascular congestion; rapid respiration rates
					Cardio	1.4			
					Gastro	1.4			
					Musc/skel	1.4			
					Hepatic	1.4			
					Renal	1.4			
					Dermal	1.4			
					Endocr	1.4			
					Immuno	3.1			
					Neuro	0.7			
					Repro	1.4			
INTERMEDIATE EXPOSURE									
Benson et al. 1995a									**Nickel sulfate**
17	Rat (Fischer-344) 90 M	2–6 months 5 days/week 6 hours/day	0, 0.03, 0.11	BW, CS, HP, OW	Resp	0.03	0.11		Alveolitis
Benson et al. 1995a									**Nickel oxide**
18	Rat (Fischer-344) 90 M	2–6 months 5 days/week 6 hours/day	0, 0.49, 1.96	BW, CS, HP, OW	Bd wt	1.96			
					Resp	0.49	1.96		Alveolitis

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Benson et al. 1995b									**Nickel subsulfide**
19	Rat (Fischer-344) 45–66 M, 45–66 F	22 days 6 hours/day	0, 0.44, 1.83	BI, BW, HP, OW	Bd wt	1.83			Decreased body weight (~10–19%)
					Resp		0.44		Alveolitis, alveolar proteinosis; olfactory epithelium degeneration
Efremenko et al. 2014									**Nickel subsulfide**
20	Rat (Fischer-344) 26 M (5 M for HP)	4 weeks 5 days/week 6 hours/day	0, 0.03, 0.06, 0.11, 0.44	BW, BI, CS, GN, HP	Resp	0.06	0.11		Lung inflammation; increased lymphocytes, macrophages, total protein, and LDH in BALF
Efremenko et al. 2017a, 2017b									**Nickel sulfate hexahydrate**
21	Rat (Fischer-344) 5 M	4 weeks 5 days/week 6 hours/day	0.00066, 0.0304, 0.05412, 0.1104, 0.2209	CS, BW, BI, HP	Resp	0.05412	0.1104		Alveolus inflammation
Evans et al. 1995									**Nickel sulfate**
22	Rat (Long-Evans) 5–14 M	16 days 6 hours/day	0, 0.635	BW, HP, NX, OW	Bd wt	0.635			
					Resp		0.635		Atrophy of olfactory epithelium
Horie et al. 1985									**Nickel oxide**
23	Rat (Wistar) 2–8 M	1 month 5 days/week 6 hours/day	0, 0.5, 1.1, 5.1, 5.5, 6.3	CS, HP	Resp		0.5		Bronchial gland hyperplasia and squamous metaplasia

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Morimoto et al. 1995									**Nickel oxide**
24	Rat (Wistar) 5 M	4 weeks 5 days/week 8 hours/day	0, 9.2	BC	Immuno		9.2		Increased production of tumor necrosis factor by alveolar macrophages
NTP 1996a									**Nickel oxide**
25	Rat (Fischer-344) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.4, 0.9, 2.0, 3.9, 7.9	BW, CS, HE, HP, LE, OW, RX	Bd wt	7.9			
					Resp	2	3.9		Chronic active lung inflammation, granulomatous inflammation, and lung interstitial infiltrate
					Cardio	7.9			
					Gastro	7.9			
					Musc/skel	7.9			
					Hepatic	7.9			
					Renal	7.9			
					Dermal	7.9			
					Endocr	7.9			
					Immuno	2	3.9		Lymphoid hyperplasia in mediastinal lymph nodes
					Neuro	7.9			
					Repro	7.9 F			
						3.9 M	7.9 M		Decreased epididymal spermatozoa concentration

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1996b									**Nickel subsulfide**
26	Rat (Fischer-344) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.11, 0.22, 0.44, 0.88, 1.83	BW, CS, HE, HP, LE, OW, RX	Bd wt	1.83			
					Resp	0.21	0.22	1.83	LOAEL: Chronic active lung inflammation; olfactory epithelial atrophy at 0.44 mg Ni/m^3 SLOAEL: Labored breathing during weeks 2–7
					Cardio	1.83			
					Gastro	1.83			
					Hemato	0.44 F	0.88 F		Increased erythrocyte levels
						0.88 M	1.83 M		Increased erythrocyte and hemoglobin levels
					Musc/skel	1.83			
					Hepatic	1.83			
					Renal	1.83			
					Dermal	1.83			
					Endocr	1.83			
					Immuno	0.22	0.44		Lymphoid hyperplasia in bronchial and mediastinal lymph nodes
					Neuro	1.83			
					Repro	1.83			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1996c									**Nickel sulfate hexahydrate**
27	Rat (Fischer-344) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.03, 0.06, 0.11, 0.22, 0.44	BW, CS, HE, HP, LE, OW, RX	Bd wt	0.44			
					Resp	0.06 F	0.11 F		Chronic lung inflammation and interstitial infiltrates. Atrophy of olfactory epithelium at 0.22 mg Ni/m^3
						0.11 M	0.22 M		Chronic lung inflammation and interstitial infiltrates; atrophy of olfactory epithelium
					Cardio	0.44			
					Gastro	0.44			
					Hemato	0.44			
					Musc/skel	0.44			
					Hepatic	0.44			
					Renal	0.44			
					Dermal	0.44			
					Endocr	0.44			
					Immuno	0.11	0.22		Lymphoid hyperplasia in bronchial and mediastinal lymph nodes
					Neuro	0.44			
					Repro	0.44			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Oller et al. 2023									**Nickel subsulfide**
28	Rat (F344) 13 M	13 weeks 5 days/week 6 hours/day	0.01, 0.04, 0.11, 0.43	BW, CS, GN, HP, OW	Bd wt	0.43			
					Resp		0.04[c]		Alveolitis and perivascular/peribronchiolar inflammation ($BMCL_{10}$ = 0.0014 mg Ni/m^3)
Oller et al. 2023									**Nickel sulfate hexahydrate**
29	Rat (F344) 13 M	13 weeks 5 days/week 6 hours/day	0, 0.03, 0.11, 0.22	BW, CS, GN, HP, OW	Bd wt	0.22			
					Resp	0.03	0.11		Alveolitis, perivascular/peribronchiolar inflammation, and bronchiolar epithelial degeneration
Oller et al. 2023									**Nickel sulfate hexahydrate**
30	Rat (F344) 13 M	3 weeks, 5 days/week, 6 hours/day	0, 0.03, 0.11, 0.22	BW, OW, HP	Bd wt	0.22			
					Resp	0.11	0.22		Alveolitis, perivascular inflammation, and bronchiolar epithelial degeneration
Oller et al. 2023									**Nickel subsulfide**
31	Rat (F344) 13 M	3 weeks, 5 days/week, 6 hours/day	0, 0.04, 0.11, 0.44	BW, OW, HP	Bd wt	0.44			
					Resp	0.11	0.44		Alveolitis and perivascular inflammation
Spiegelberg et al. 1984									**Nickel oxide**
32	Rat (Wistar) 12 M	4 weeks continuous	0, 0.047, 0.093, 0.216, 0.404, 0.818	CS, IX	Immuno	0.093	0.216		Impaired response to sRBC exposure
Spiegelberg et al. 1984									**Nickel oxide**
33	Rat (Wistar) 12 M	4 months continuous	0, 0.025, 0.145	CS, IX	Immuno	0.025	0.145		Impaired response to sRBC exposure

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Tanaka et al. 1988									**Nickel oxide**
34	Rat (Wistar) 4–5 M	6 months 5 days/week 7 hours/day	0, 0.23, 0.94	BW, OW, HP	Bd wt	0.94			
					Resp		0.23		Pneumonia
					Hepatic	0.94			
					Renal	0.94			
Weischer et al. 1980									**Nickel oxide**
35	Rat (Wistar) 10–13 F	21 days 23.6 hours/day	0, 0.8, 1.6, 3.2	BC, BW, DX, OW	Bd wt			0.8	36% decrease in body weight gain
					Resp		0.8		Increased lung weight
					Hemato		0.8		Increased hematocrit and hemoglobin
Weischer et al. 1980									**Nickel oxide**
36	Rat (Wistar) 10–13 F	GDs 1–21 23.6 hours/day	0, 0.8, 1.6, 3.2	BC, BW, DX, OW, RX	Develop	0.8	1.6		Decreased fetal body weights (9%)
Weischer et al. 1980									**Nickel oxide**
37	Rat (Wistar) 10 M	28 days 23.6 hours/day	0, 0.178, 0.385, 0.784	BC, BW, OW	Bd wt	0.178		0.385	30% decrease in body weight gain
					Resp		0.178		Increased lung weight
					Hemato	0.784			
					Renal	0.784			Decreased blood urea
					Endocr	0.178	0.385		Increased serum glucose
Benson et al. 1995a									**Nickel sulfate**
38	Mouse (B6C3F1) 108 M	2–6 months 5 days/week 6 hours/day	0, 0.06, 0.22	BW, CS, HP, OW	Resp	0.06	0.22		Interstitial pneumonia
Benson et al. 1995a									**Nickel oxide**
39	Mouse (B6C3F1) 108 M	2–6 months 5 days/week 6 hours/day	0, 0.98, 3.9	BW, CS, HP, OW	Bd wt	3.9			
					Resp		0.98		Interstitial pneumonia

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Haley et al. 1990									**Nickel oxide**
40	Mouse (B6C3F1) 40 F	65 days 5 days/week 6 hours/day	0, 0.47, 2.0, 7.9	BI CS	Immuno		0.47		Decreased alveolar macrophage activity
Haley et al. 1990									**Nickel subsulfide**
41	Mouse (B6C3F1) 40 F	65 days 5 days/week 6 hours/day	0, 0.11, 0.45, 1.8	OF, OW	Immuno	0.11	0.45		Decreased alveolar macrophage phagocytic activity
Haley et al. 1990									**Nickel sulfate hexahydrate**
42	Mouse (B6C3F1) 40 F	65 days 5 days/week 6 hours/day	0, 0.027, 0.11, 0.45	CS, OF, OW	Immuno	0.11	0.45		Decreased resistance to tumor challenge
NTP 1996a									**Nickel oxide**
43	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.4, 0.9, 2.0, 3.9, 7.9	BW, HE, HP, LE, OW, RX	Bd wt	7.9			
					Resp	2 F	3.9 F		Perivascular lymphocytic infiltrates
						3.9 M	7.9 M		Perivascular lymphocytic infiltrates
					Cardio	7.9			
					Gastro	7.9			
					Musc/skel	7.9			
					Hepatic	7.9			
					Renal	7.9			
					Dermal	7.9			
					Endocr	7.9			
					Immuno	3.9	7.9		Bronchial lymph node hyperplasia
					Neuro	7.9			
					Repro	7.9			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1996b									**Nickel subsulfide**
44	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.11, 0.22, 0.44, 0.88, 1.83	BW, CS, HE, HP, LE, OW, RX	Bd wt	1.83			
					Resp	0.22	0.44		Atrophy of olfactory epithelium. Chronic lung inflammation and fibrosis at 0.88 mg Ni/m^3
					Cardio	1.83			
					Gastro	1.83			
					Hemato	1.83			
					Musc/skel	1.83			
					Renal	1.83			
					Dermal	1.83			
					Endocr	1.83			
					Immuno	0.44 F	0.88 F		Bronchial lymph node hyperplasia
						0.88 M	1.83 M		Bronchial lymph node hyperplasia
					Neuro	1.83 F			
					Repro	1.83			
NTP 1996c									**Nickel sulfate hexahydrate**
45	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.03, 0.06, 0.11, 0.22, 0.44	BW, CS, HE, HP, LE, OW, RX	Bd wt	0.44			
					Resp	0.22	0.44		Chronic lung inflammation, fibrosis, and interstitial infiltrate
					Cardio	0.44			
					Gastro	0.44			
					Musc/skel	0.44			
					Hepatic	0.44			
					Renal	0.44			
					Dermal	0.44			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	0.44			
					Immuno	0.22	0.44		Bronchial lymph node hyperplasia
					Neuro	0.44			
					Repro	0.44			
Johansson et al. 1987									**Nickel chloride**
46	Rabbit (NS) 8 M	4–6 weeks 5 days/week 6 hours/day	0, 0.6	HP, CS	Immuno		0.6		Decreased lysozyme activity in alveolar macrophages
Johansson et al. 1988a, 1989									**Nickel chloride**
47	Rabbit (NS) 8 M	4 months 5 days/week 6 hours/day	0, 0.6	GN, HP	Resp		0.6		Interstitial inflammation and intra-alveolar accumulation of macrophages
					Immuno		0.6		Decreased macrophage lysosomal activity
CHRONIC EXPOSURE									
Hueper 1958									**Nickel metallic**
48	Rat (Bethesda Black) 60 F	21 months 4–5 days/week 6 hours/day	15.0	CS, LE	Death			15	100% mortality
Hueper 1958									**Nickel metallic**
49	Rat (Wistar) 50 M, 50 F	21 months 4–5 days/week 6 hours/day	15.0	CS, LE	Death			15	100% mortality
NTP 1996a									**Nickel oxide**
50	Rat (Fischer-344) 65 M, 65 F	2 years 5 days/week 6 hours/day	0, 0.5, 1, 2	BW, CS, HE, HP, LE, OW	Bd wt	2			
					Resp		0.5		Chronic lung inflammation and lung alveolus pigmentation

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cardio	2			
					Gastro	2			
					Hemato	2			
					Musc/skel	2			
					Hepatic	2			
					Renal	2			
					Dermal	2			
					Endocr	1 F	2 F		Benign pheochromocytoma and adrenal medulla hyperplasia
						2 M			
					Immuno		0.5		Lymphoid hyperplasia and pigmentation in bronchial lymph nodes
					Neuro	2			
					Repro	2			
					Cancer			1	CEL: Alveolar/bronchiolar adenoma or carcinoma
NTP 1996b									**Nickel subsulfide**
51	Rat (Fischer-344) 63 M, 63 F	2 years 6 hours/day 5 days/week	0, 0.11, 0.73	BW, CS, HE, HP, LE, OW	Bd wt	0.11	0.73		11–12% decrease in body weight gain
					Resp			0.11	Rapid shallow breathing, chronic lung inflammation and lung fibrosis. Nasal olfactory epithelial atrophy at 0.73 mg Ni/m^3
					Cardio	0.73			
					Gastro	0.73			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hemato	0.11	0.73		Increased hematocrit and hemoglobin in both sexes and increased erythrocytes in males
					Musc/skel	0.73			
					Hepatic	0.73			
					Renal	0.73			
					Endocr		0.11 M		Benign pheochromocytoma
					Immuno		0.11		Lymphoid hyperplasia in bronchial lymph nodes
					Neuro	0.73			
					Repro	0.73			
					Cancer			0.73	CEL: Alveolar/bronchiolar adenoma or carcinoma, malignant pheochromocytomas
NTP 1996c									**Nickel sulfate hexahydrate**
52	Rat (Fischer-344) 65 M, 65 F	2 years 5 days/week 6 hours/day	0, 0.03, 0.06, 0.11	BW, CS, HE, HP, LE, OW	Bd wt	0.11			
					Resp	0.03	0.06		Chronic inflammation, fibrosis, and alveolar proteinosis in lung. Atrophy of olfactory epithelium at 0.11 mg Ni/m^3
					Cardio	0.11			
					Gastro	0.11			
					Hemato	0.11			
					Hepatic	0.11			
					Renal	0.11			
					Dermal	0.11			
					Endocr	0.11			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	0.06	0.11		Lymphoid hyperplasia in bronchial lymph nodes
					Neuro	0.11			
					Repro	0.11			
Oller et al. 2008									**Nickel metallic**
53	Rat (Wistar) 50 M, 50 F	104 weeks 5 days/week 6 hours/day	0, 0.1, 0.4, 1.0	BW, CS, FI, GN, HE, HP, LE, OW	Death			0.4	Reduced survival by week 103, 72% survival in males and 48% survival in females
					Bd wt		0.1 M	0.4 M	LOAEL: Decreased body weight gain (11%) SLOAEL: Decreased body weight gain (27%)
					Resp			0.1	Labored breathing; alveolar proteinosis, histiocytosis, chronic lung inflammation, and bronchiolar alveolar hyperplasia (females)
					Hemato	0.1 F	0.4 F		Moderate hypercellularity of the sternum and femoral bone marrows; extramedullary hematopoiesis in the spleen
							0.1 M		Increased hemoglobin and hematocrit levels at week 78
					Renal		0.1 M		Increased incidence of granular brown pigment in kidneys consistent with hemosiderin
					Endocr	0.1 M	0.4 M		Benign pheochromocytoma
					Immuno		0.1		Minimal-to-severe histiocyte infiltrate in bronchial lymph node

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cancer			0.4	CEL: Malignant pheochromocytoma in males and adrenal cortex carcinoma in females
Ottolenghi et al. 1975									**Nickel sulfide**
54	Rat (Fischer-344) 22–39 M, 24–32 F	78–80 weeks 5 days/week 6 hours/day	0, 0.63	BW, CS, GN, HP	Death			0.63	Less than 5% of rats survived
					Bd wt			0.63	Body weight 20–30% less than controls
					Resp			0.63	Pneumonitis, bronchitis, emphysema, and lung hyperplasia
					Cardio	0.63			
					Gastro	0.63			
					Hepatic	0.63			
					Renal	0.63			
					Endocr	0.63			
					Immuno	0.63			
					Neuro	0.63			
					Cancer			0.63	CEL: Lung adenomas, adenocarcinomas, squamous cell carcinoma
Takenaka et al. 1985									**Nickel oxide**
55	Rat (Wistar) 20–40 M	31 months 7 days/week 23 hours/day	0, 0.06, 0.2	BW, CS, GN, HP	Death			0.06	Decreased mean survival time (88 weeks; 125 weeks for controls)
					Bd wt	0.06			
					Resp		0.06		Increased lung weight, congestion, and alveolar proteinosis

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Tanaka et al. 1988									**Nickel oxide**
56	Rat (Wistar) 4–5 M	12 months 5 days/week 7 hours/day	0, 0.23, 0.94	BW, HP, OW	Bd wt	0.94			
					Resp			0.23	Pneumonia and bronchiolar metaplasia
					Hepatic	0.94			
					Renal	0.94			
Hueper 1958									**Nickel metallic**
57	Mouse (C57) 20 F	21 months 4–5 days/week 6 hours/day	15.0	CS, LE	Death			15	20/20 died
NTP 1996a									**Nickel oxide**
58	Mouse (B6C3F1) 79 M, 76 F	2 years 5 days/week 6 hours/day	0, 1.0, 2.0, 3.9	BW, CS, HE, HP, LE, OW	Bd wt	3.9			
					Resp		1		Chronic lung inflammation, bronchiolization, and alveolar proteinosis
					Cardio	3.9			
					Gastro	3.9			
					Hemato	3.9			
					Musc/skel	3.9			
					Hepatic	3.9			
					Renal	3.9			
					Dermal	3.9			
					Endocr	3.9			
					Immuno		1		Bronchial lymph node hyperplasia
					Neuro	3.9			
					Repro	3.9			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cancer			2 F	CEL: Alveolar/bronchiolar adenoma
NTP 1996b									**Nickel subsulfide**
59	Mouse (B6C3F1) 80 M, 80 F	2 years 6 hours/day 5 days/week	0, 0.44, 0.88	BW, CS, HE, HP, LE, OW	Bd wt	0.88			
					Resp		0.44		Chronic active lung inflammation, bronchiolization, alveolar proteinosis, and fibrosis; atrophy of olfactory epithelium
					Cardio	0.88			
					Gastro	0.88			
					Hemato	0.44 F	0.88 F		Increased hematocrit
						0.88 M			
					Hepatic	0.88			
					Renal	0.88			
					Dermal	0.88			
					Endocr	0.88			
					Immuno		0.44		Lymphoid hyperplasia and macrophage hyperplasia in bronchial lymph nodes
					Neuro	0.88			
					Repro	0.88			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1996c									**Nickel sulfate hexahydrate**
60	Mouse (B6C3F1) 80 M, 80 F	2 years 5 days/week 6 hours/day	0, 0.06, 0.11, 0.22	BW, HE, HP, LE, OW	Bd wt	0.11 F 0.22 M	0.22 F		12% decreased body weight
					Resp		0.06 F		Chronic active lung inflammation and bronchiolization
						0.06 M	0.11 M		Chronic active lung inflammation and bronchiolization; atrophy of olfactory epithelium
					Cardio	0.22			
					Gastro	0.22			
					Hemato	0.22			
					Hepatic	0.22			
					Renal	0.22			
					Dermal	0.22			
					Endocr	0.22			
					Immuno	0.06	0.11		Bronchial lymph node macrophage hyperplasia
					Neuro	0.22			
					Repro	0.22			

Table 2-1. Levels of Significant Exposure to Nickel – Inhalation (mg Ni/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hueper 1958									**Nickel metallic**
61	Guinea pig (strain 13) 32 M, 10 F	21 months 4–5 days/week 6 hours/day	15.0	CS, LE	Death			15	42/42 died

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration inhalation MRL of 1x10^{-4} mg Ni/m^3 for nickel based on a LOAEL of 0.2244 mg Ni/m^3, adjusted to continuous duration exposure and converted to a human equivalent concentration (LOAEL$_{HEC}$) of 0.0403 mg Ni/m^3, and divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive an intermediate-duration inhalation MRL of 3x10^{-6} mg Ni/m^3 for nickel based on a BMCL$_{10}$ of 0.0014 mg Ni/m^3, adjusted to continuous duration exposure and converted to a human equivalent concentration (BMCL$_{HEC}$) of 0.0000982 mg Ni/m^3, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

ADJ = adjusted; B = both males and females; BALF = bronchoalveolar lavage fluid; Bd wt and BW= body weight; BC = serum (blood) chemistry; BI = biochemical changes; BMCL = 95% lower confidence limit on the benchmark concentration; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematological; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = minimal risk level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect level; sRBC = sheep red blood cell

Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

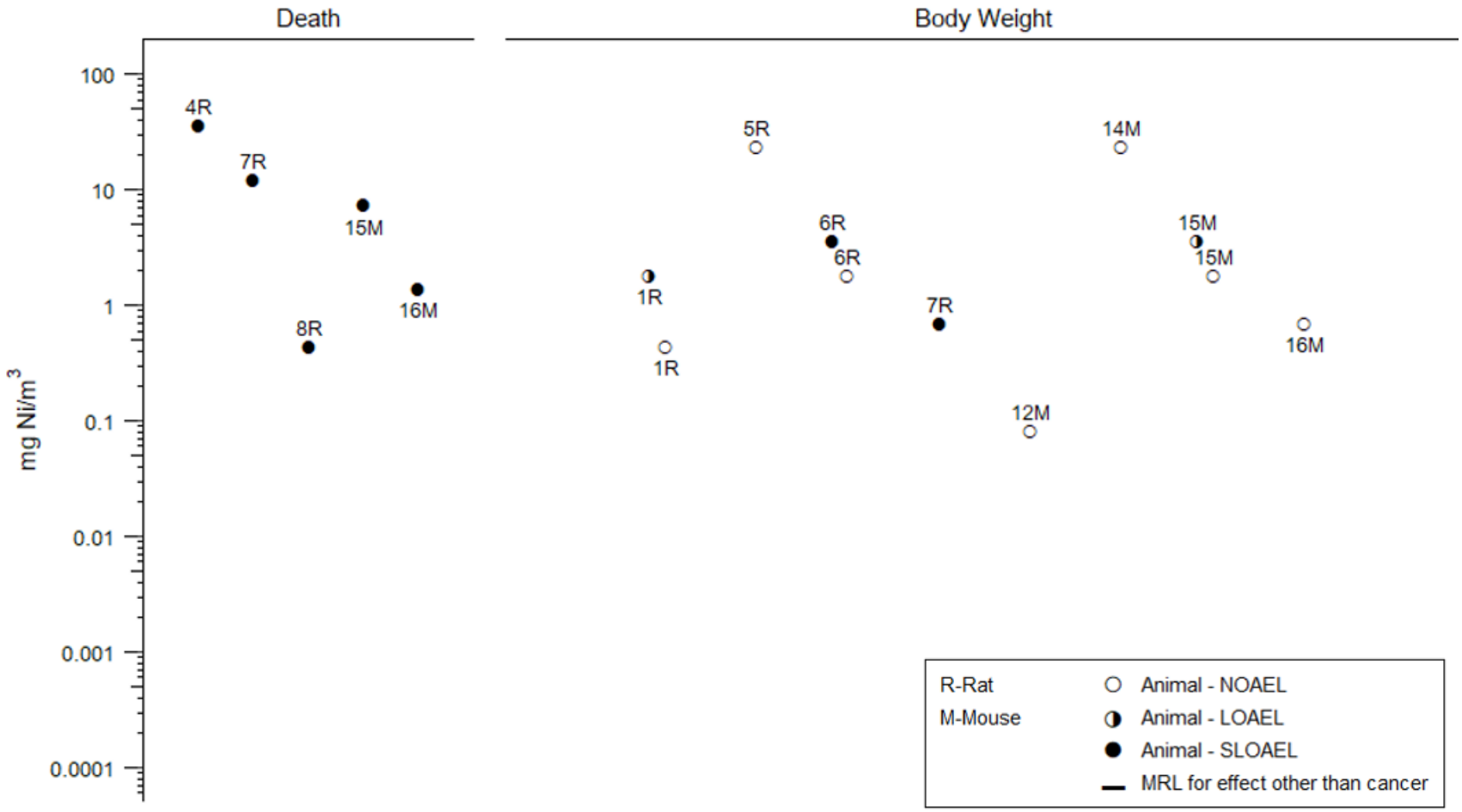


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

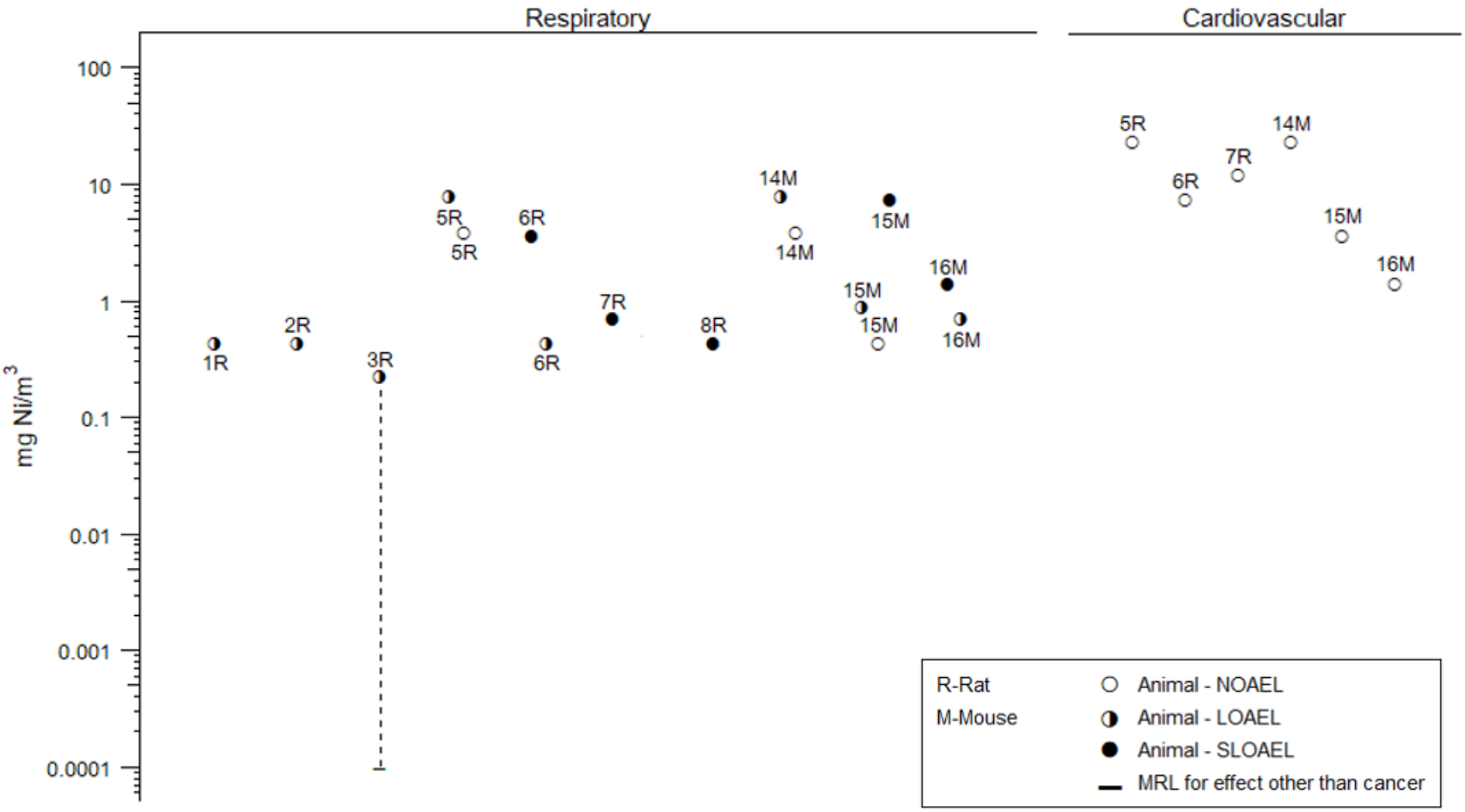


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

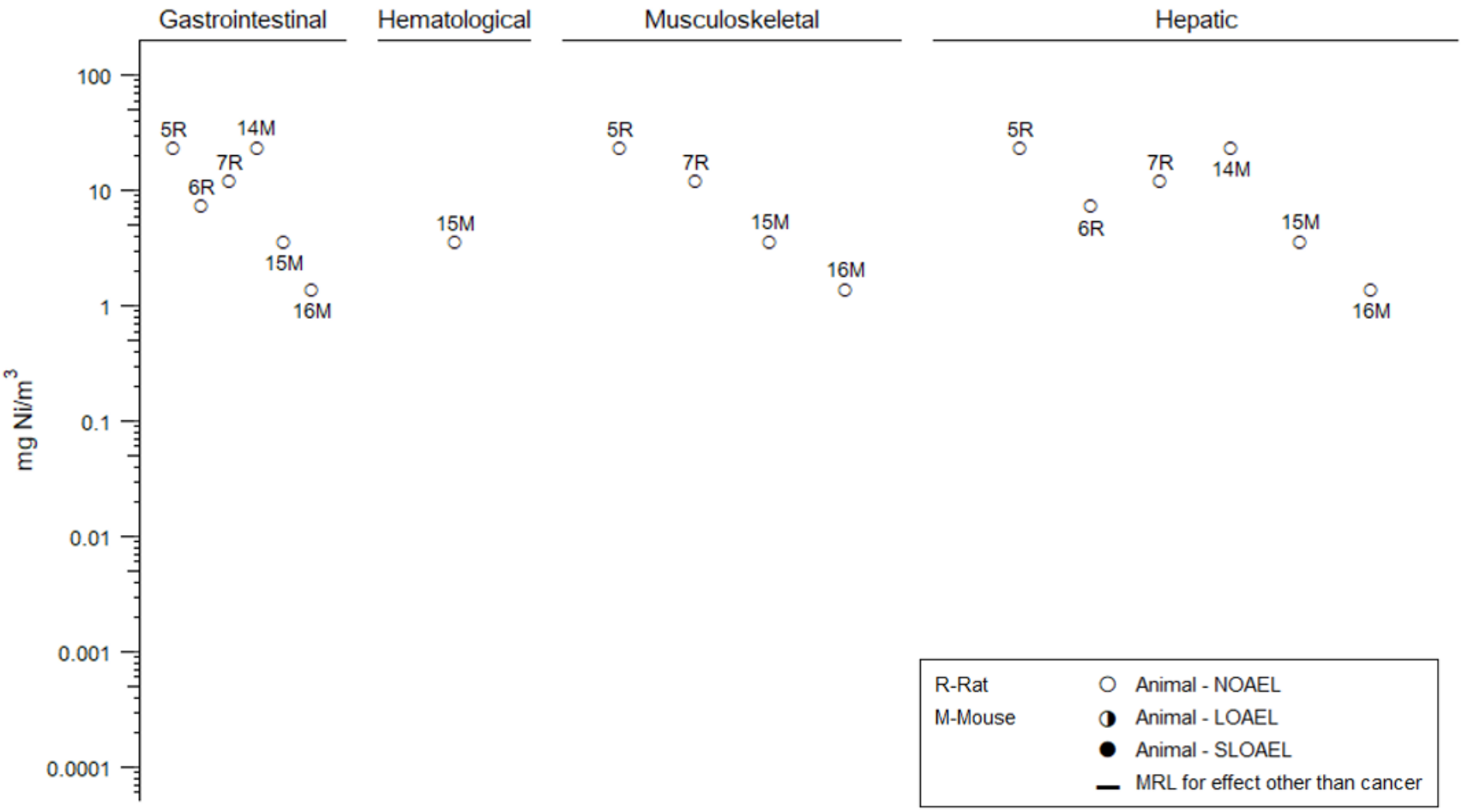


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

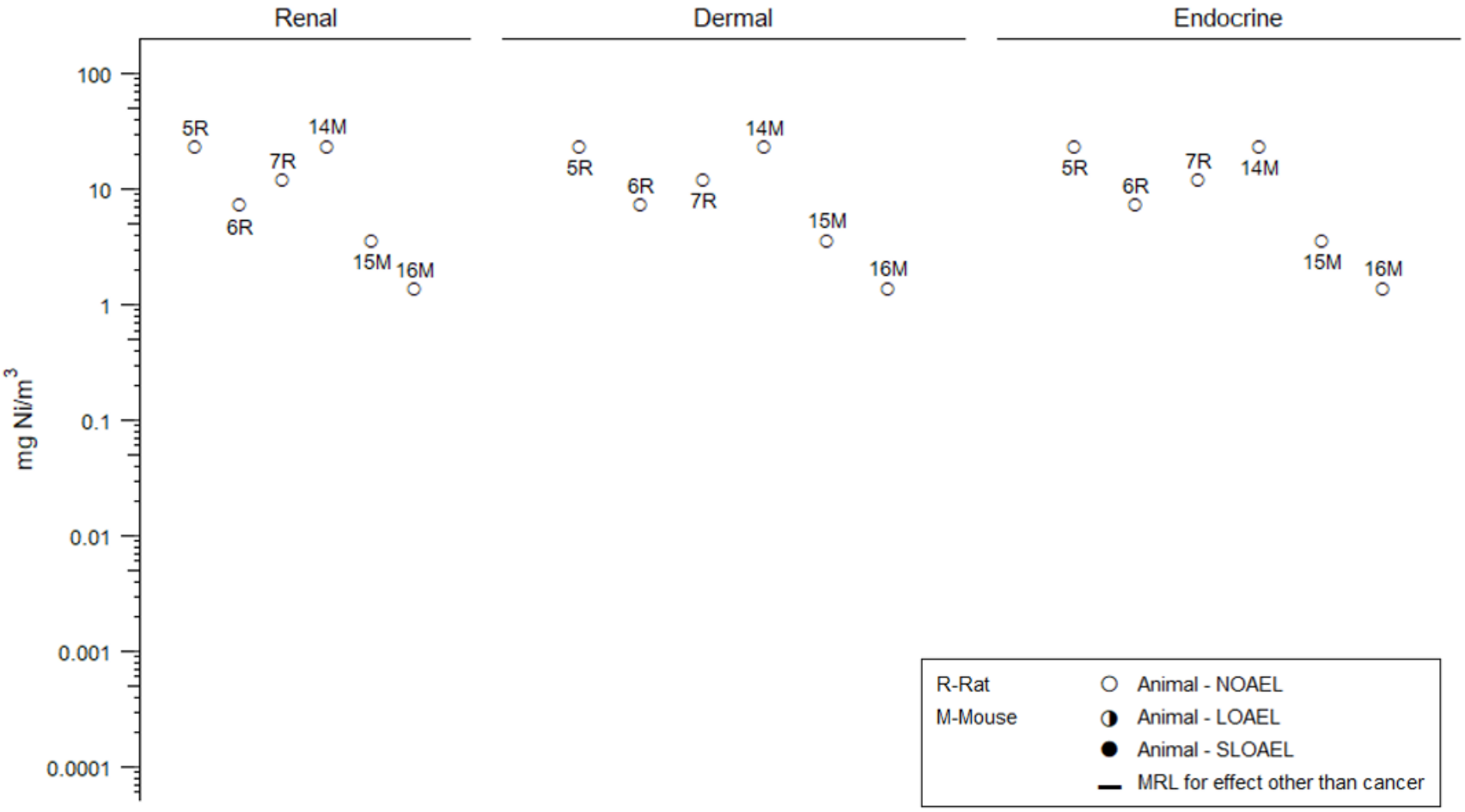


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

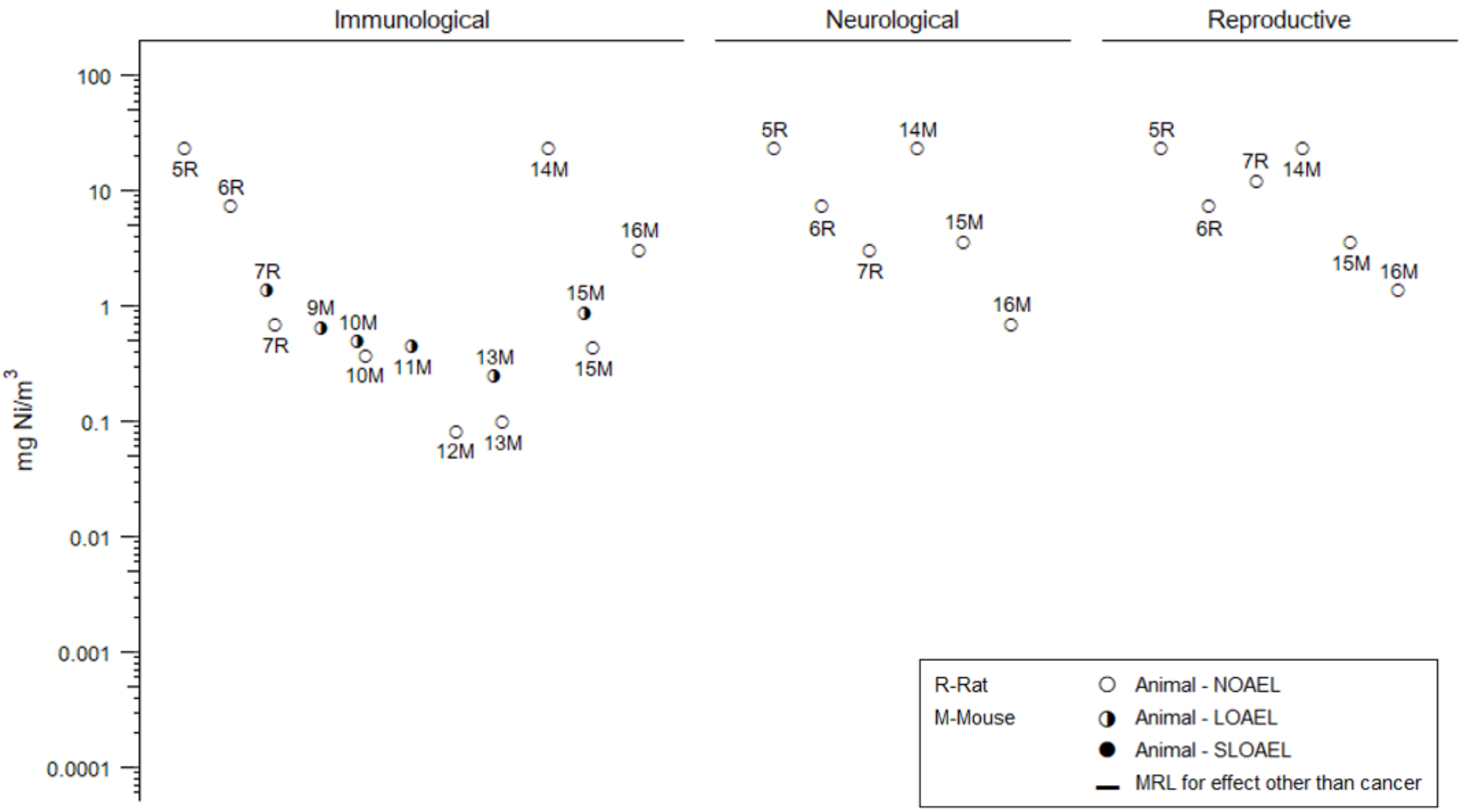


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

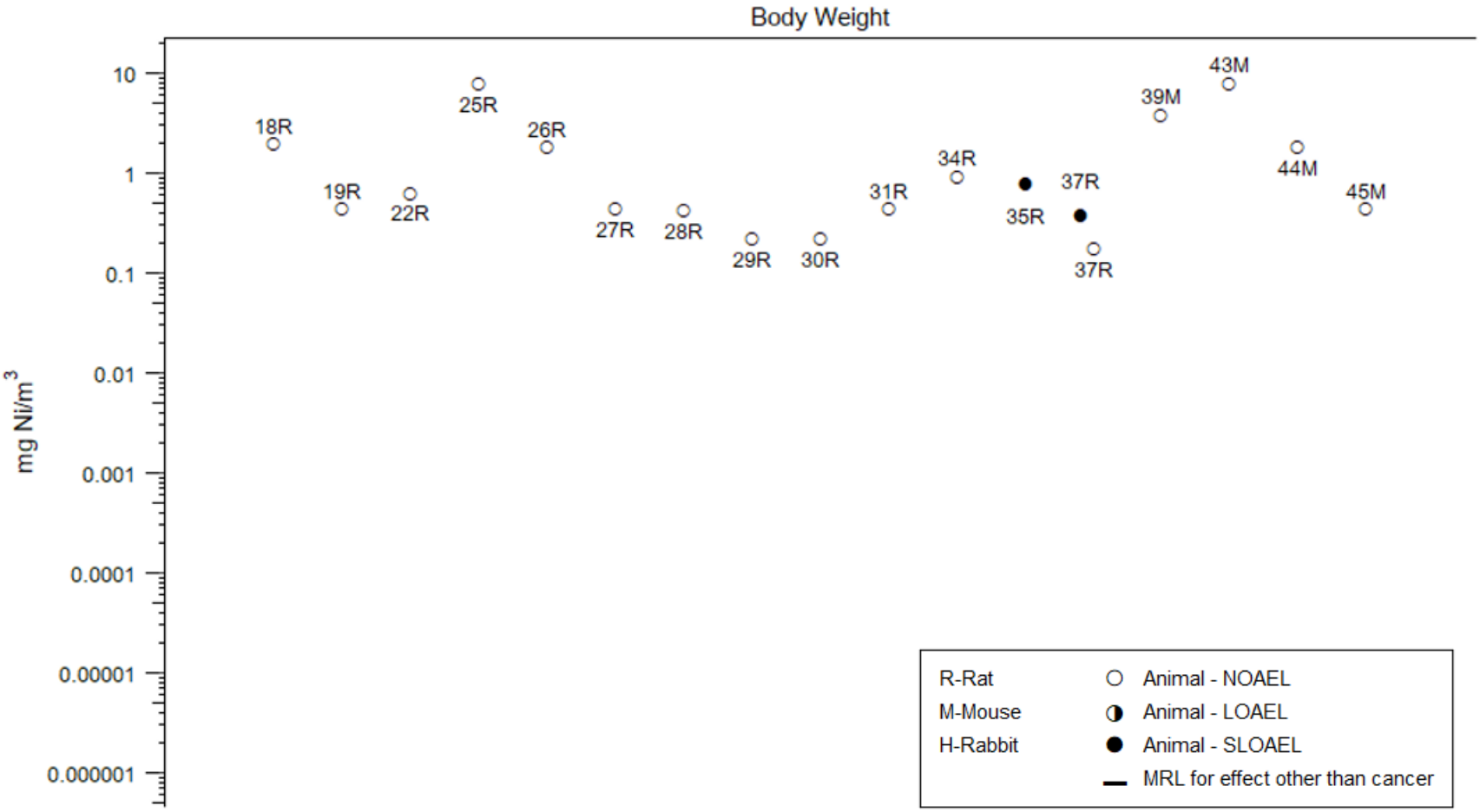


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

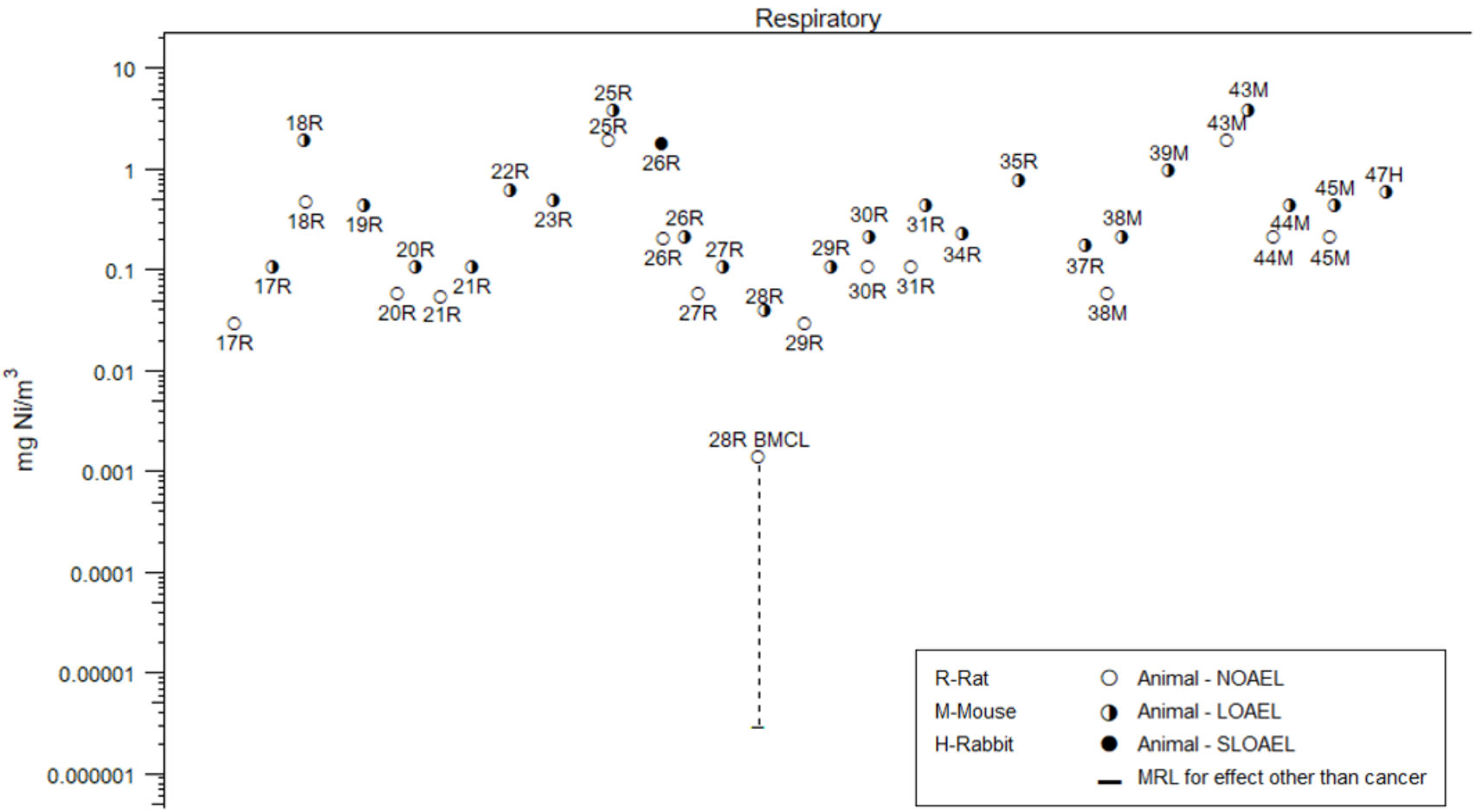


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

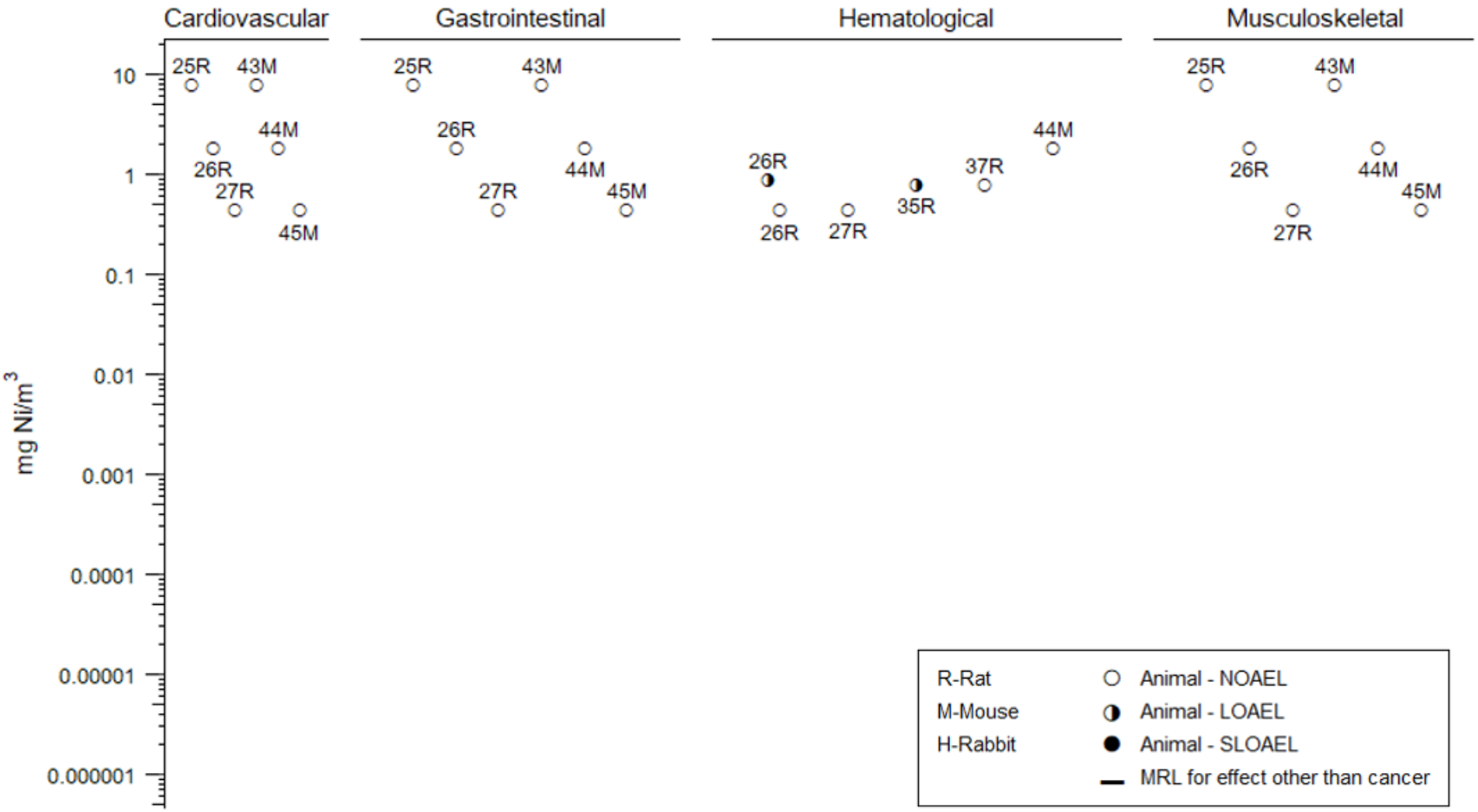


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

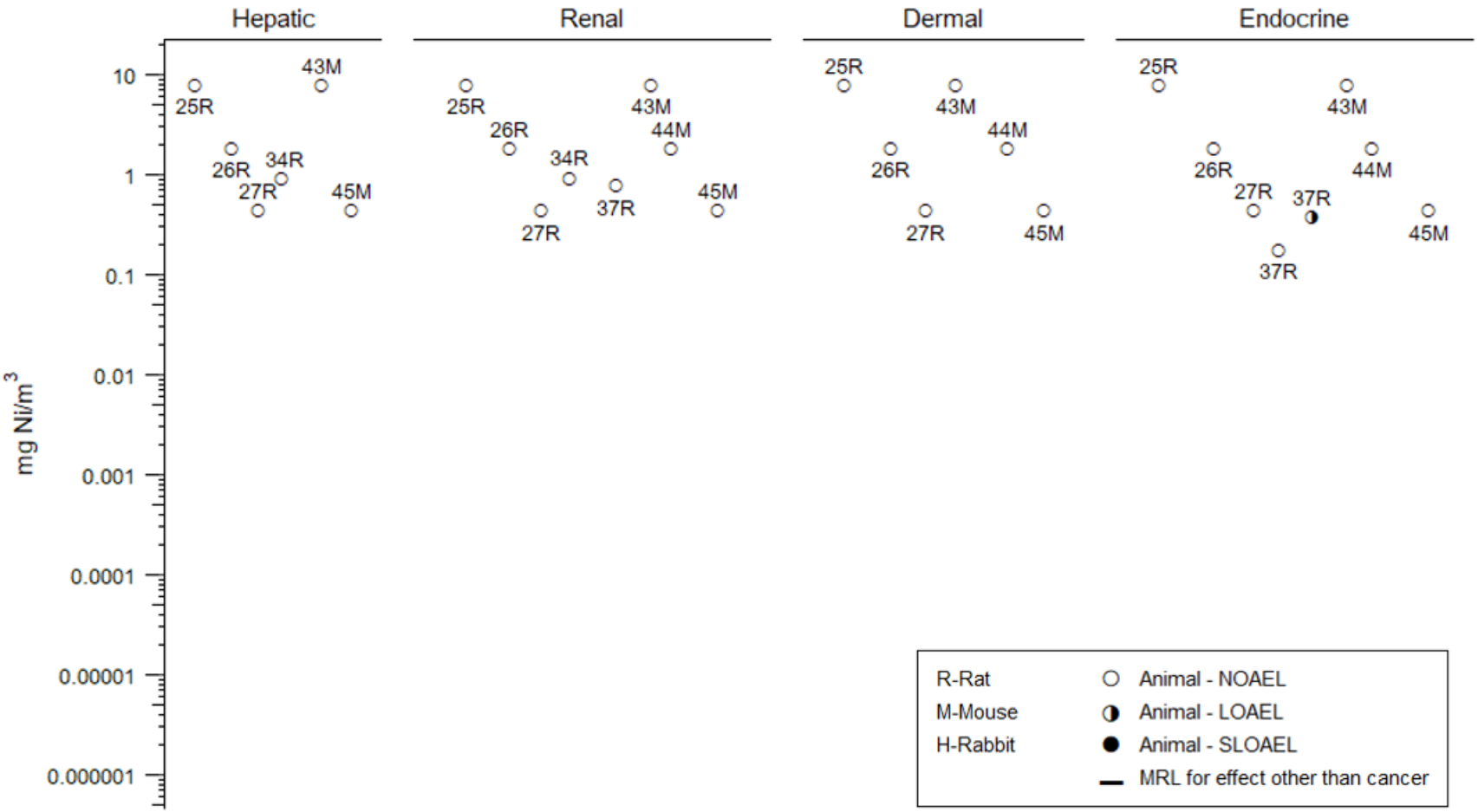


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

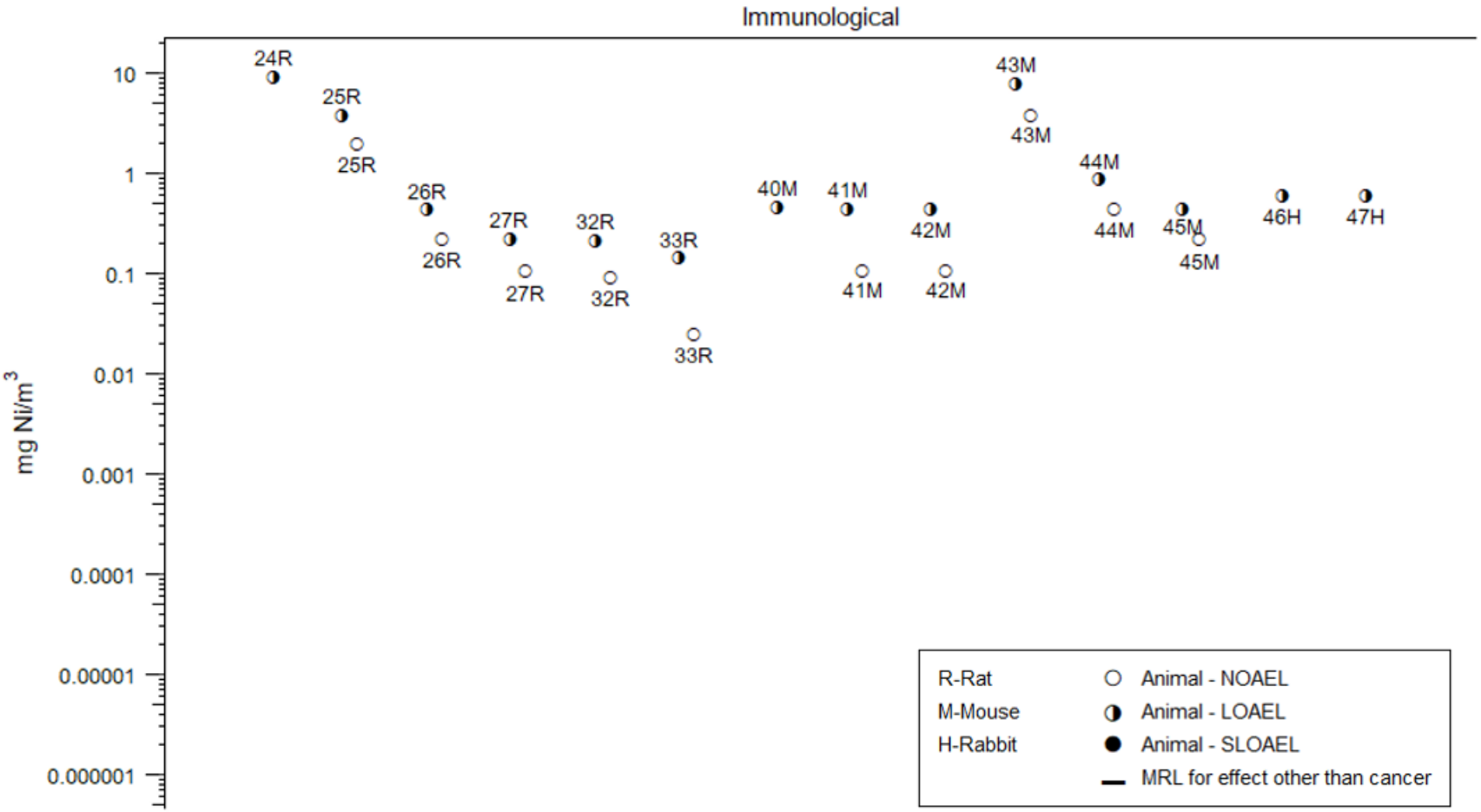


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

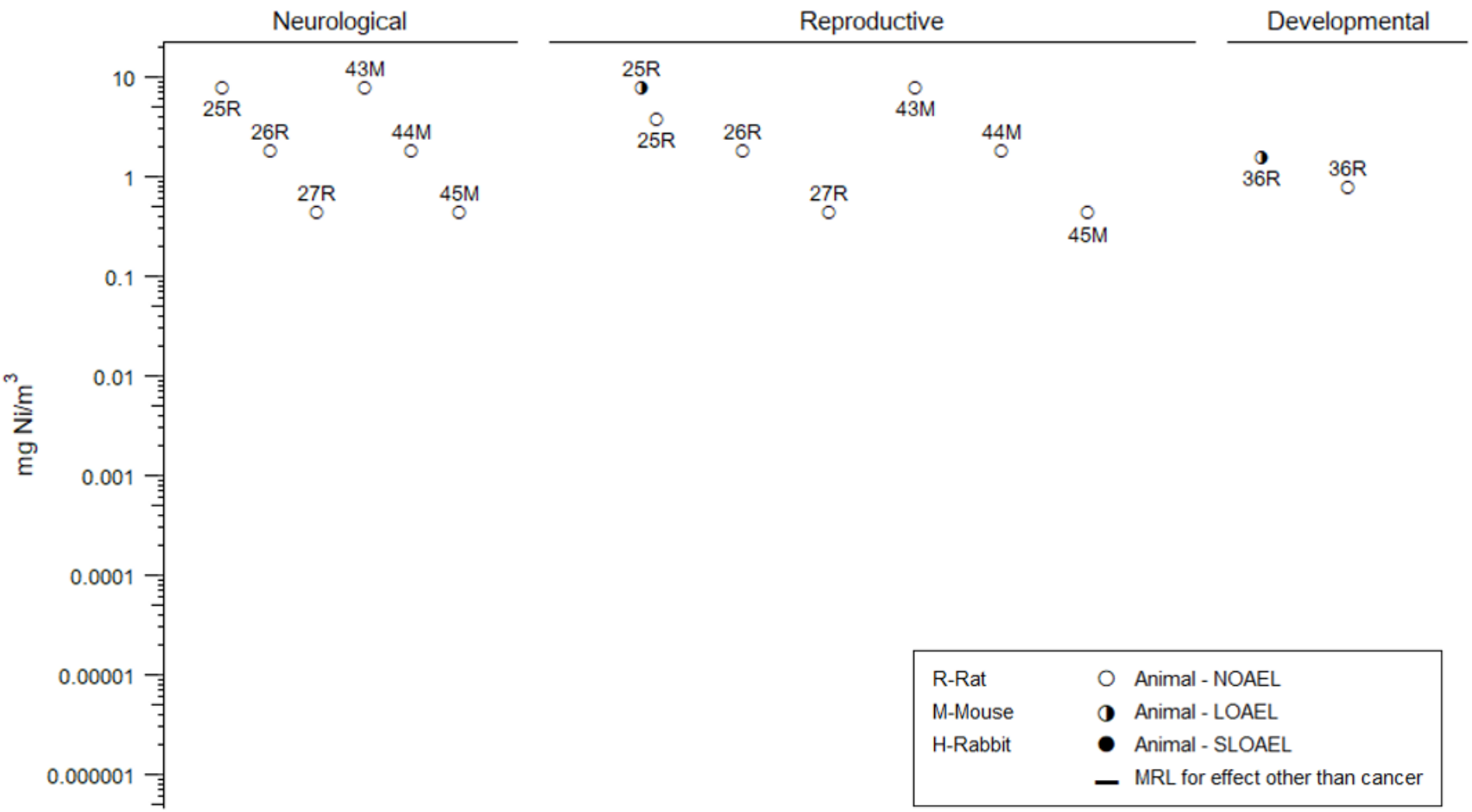


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

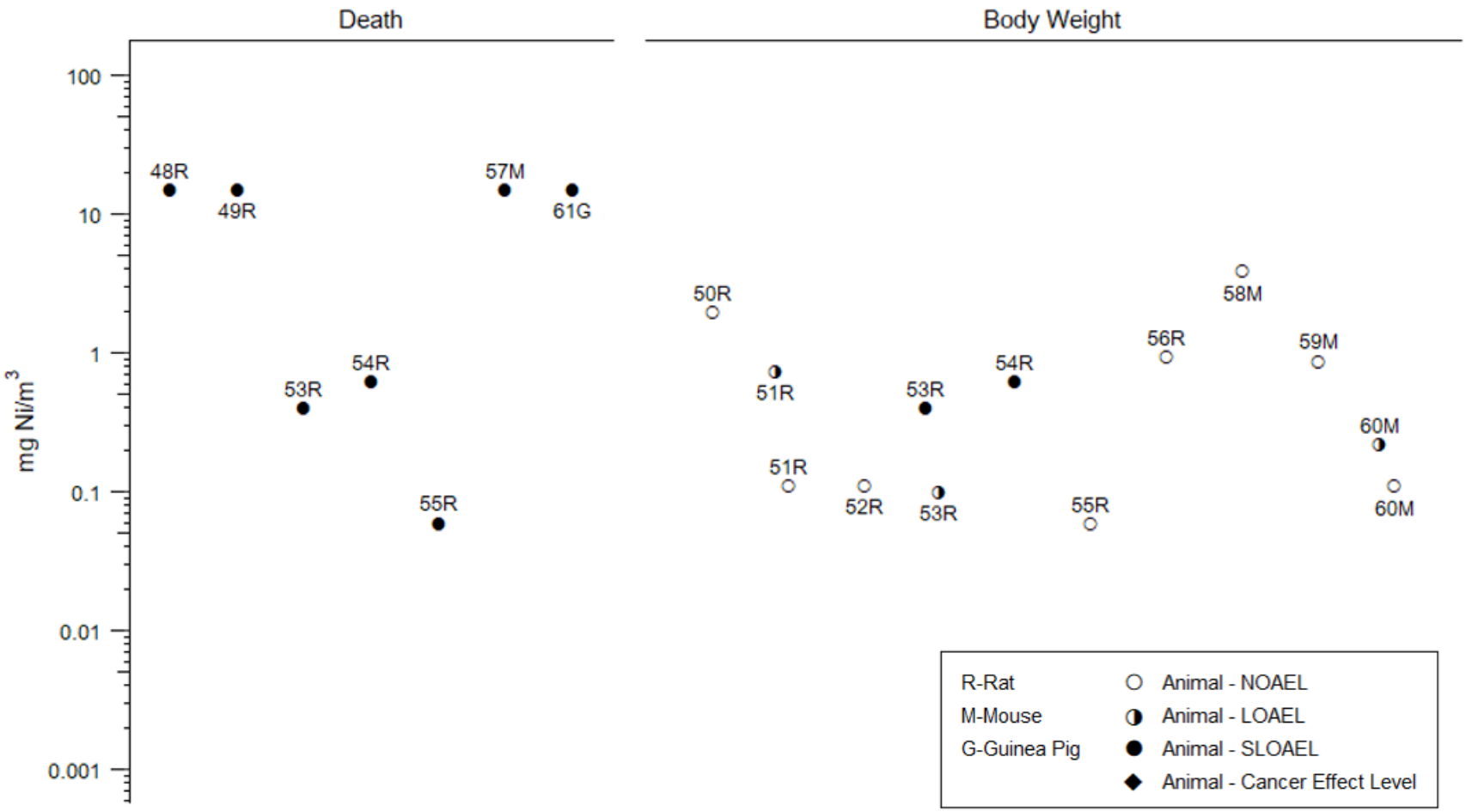


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

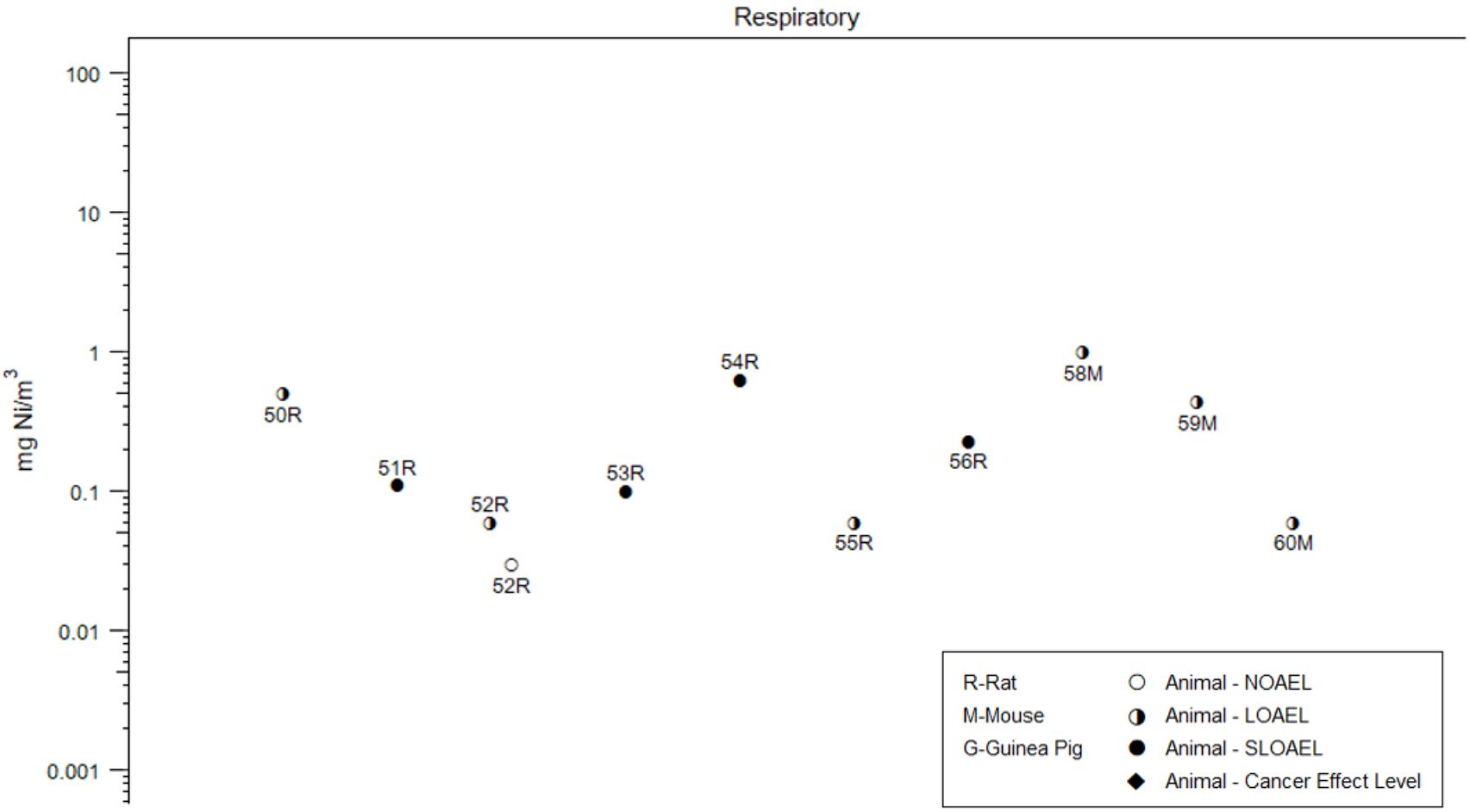


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

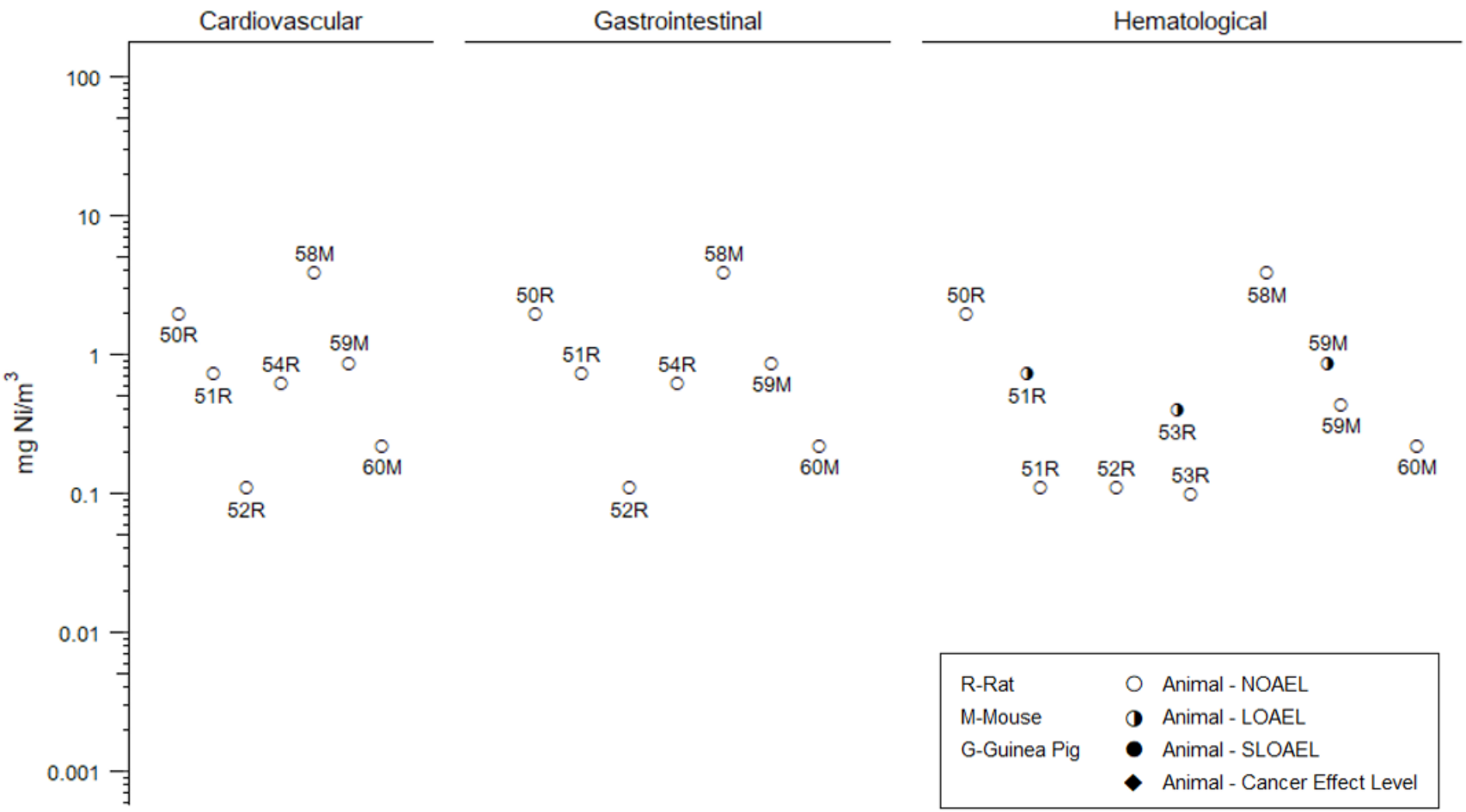


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

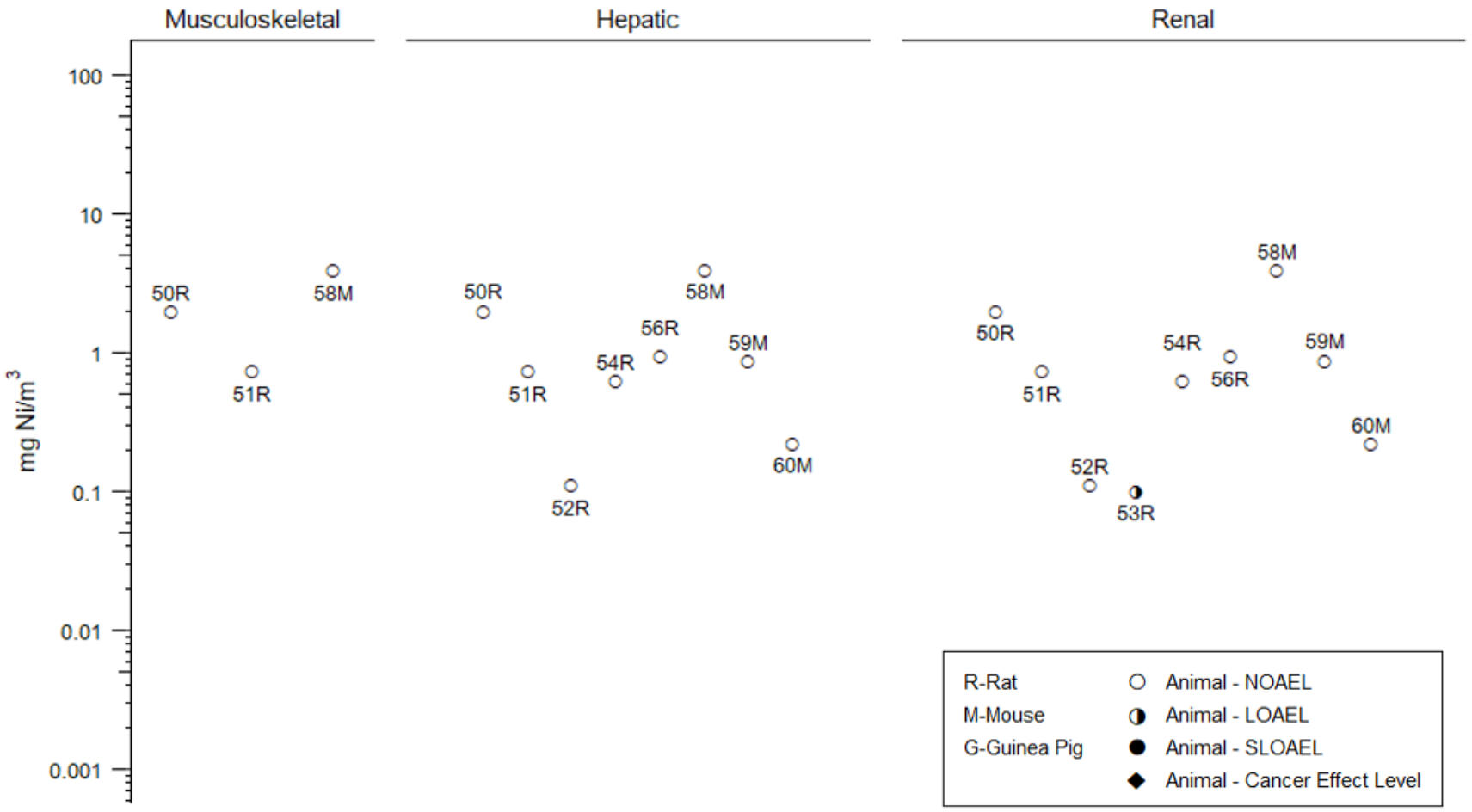


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

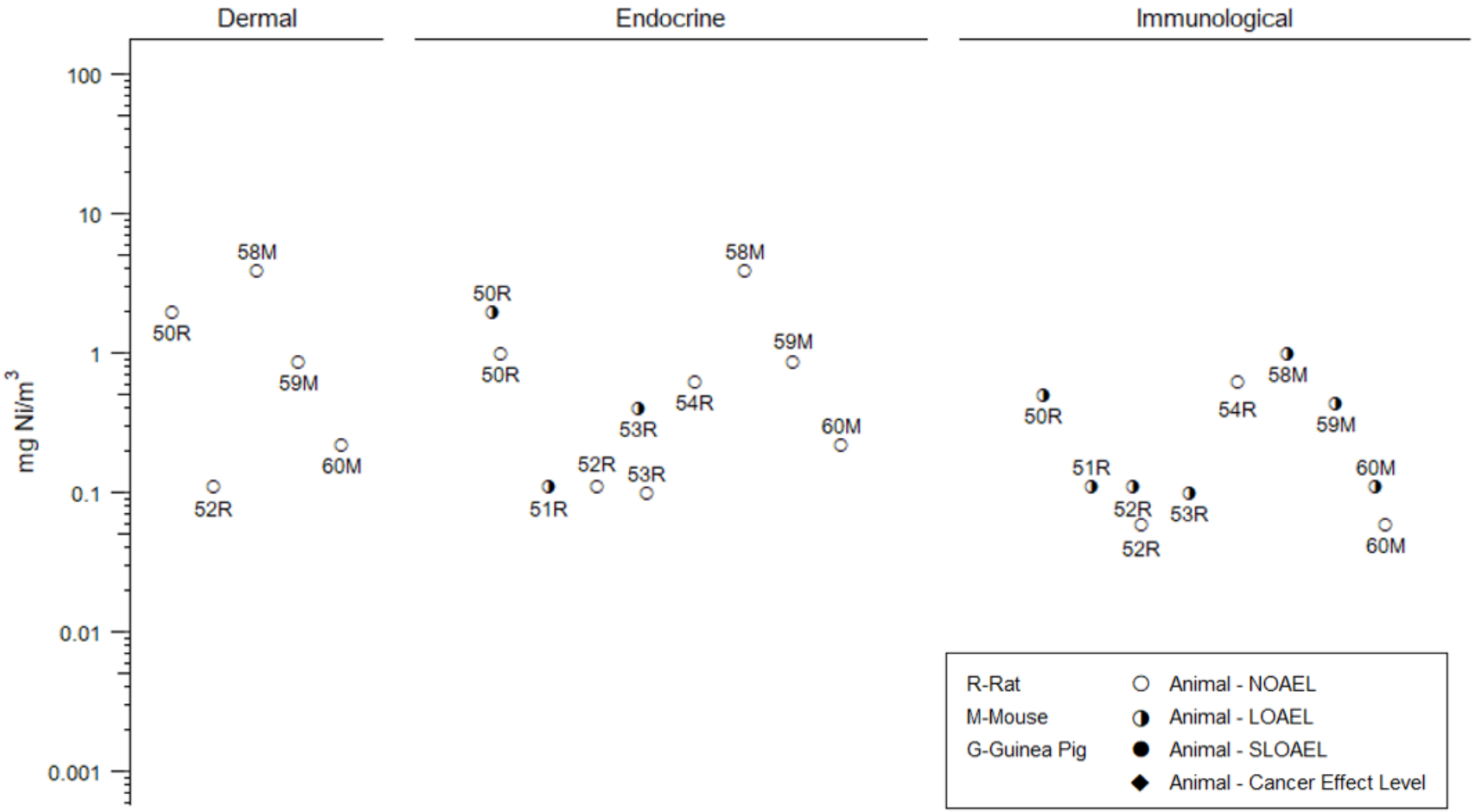


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

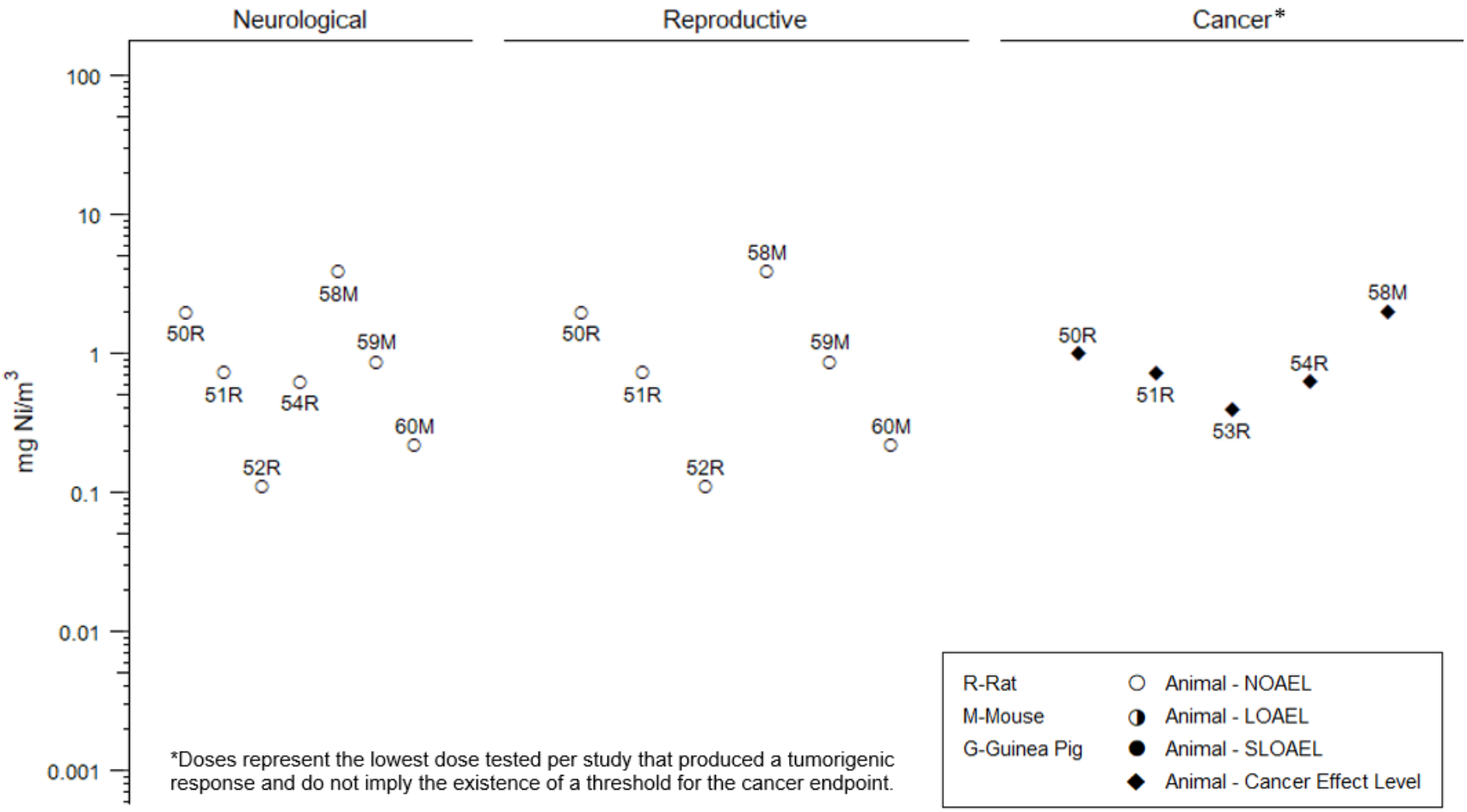


Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Burrows et al. 1981									**Nickel sulfate**
1	Human 22 NS	2 days 2 times/day (C)	0, 0.01, 0.03	CS	Dermal	0.03			
Gawkrodger et al. 1986									**Nickel sulfate heptahydrate**
2	Human 20 B	2 days Once/day (C)	0, 0.007, 0.043	CS	Dermal	0.043 F			
Gawkrodger et al. 1986									**Nickel sulfate heptahydrate**
3	Human 6 B	Once (C)	0, 0.097	CS	Dermal		0.097 F		Allergic dermatitis in sensitized individuals
Hindsén et al. 2001									**Nickel sulfate**
4	Human 9–10 F	Once (C)	0, 0.014, 0.057	CS	Dermal	0.014	0.057		Allergic dermatitis in nickel sensitive subjects
Jensen et al. 2003									**Nickel sulfate**
5	Human 10 F	Once (C)	0, 0.0043, 0.014, 0.057	CS	Dermal	0.014	0.057		Allergic dermatitis in nickel sensitive subjects
EPA 1988a, 1988b									**Nickel chloride**
6	Rat (CD) 30–32 M, 30–31 F	14 days (W)	F: 0, 7, 30, 55, 140; M: 0, 4, 20, 40, 140	BW, CS, FI, GN, HP, WI	Death			140	7/64 died
Haro et al. 1968									**Nickel acetate**
7	Rat (Fischer-344) 10 M, 10 F	Once (G)	66.4, 99.6, 132.8, 165.9, 199.2, 232.4, 265.6	CS, GN, HP	Death			116 F 120 M	LD_{50} LD_{50}

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Oller and Erexson 2007									**Nickel sulfate hexahydrate**
8	Rat (Sprague-Dawley) 6 M	3 days, 1 time/day (G)	0, 28, 56, 110, 170, 220, 280, 330, 390	BC, CS, HE, LE	Death			170	4/6 died
El-Sekily et al. 2020									**Nickel chloride hexahydrate**
9	Mouse (albino) 10 F	GDs 6–13, 1 time/day (G)	0, 46.125, 92.25, 184	CS DX	Develop			46.125	Increased resorption sites; incomplete ossification of skull, vertebrae, ribs, sternum, fore and hind limbs, carpals, metacarpals, and phalanges; and supernumerary ribs
Gray et al. 1986									**Nickel chloride**
10	Mouse (CD-1) NS F	GDs 8–12 Once, daily (G)	0, 45.3	DX	Develop	45.3			
Haro et al. 1968									**Nickel acetate**
11	Mouse (Swiss-Webster) 10 M, 10 F	Once (G)	66.4, 99.6, 132.8, 165.9, 199.2, 232.4, 265.6	CS, HP	Death			139 F 136 M	LD_{50} LD_{50}
He et al. 2013									**Nickel chloride hexahydrate**
12	Mouse (Kunming) 8 M	Once (GW)	0, 5, 50	BI, NX	Neuro	5	50		Reduced spatial memory performance indicated by increased escape latencies 3 hours after exposure; reduced locomotor activity indicated by reduced distance traveled

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Saini et al. 2013									**Nickel chloride hexahydrate**
13	Mouse (Swiss) 10 F	GDs 6–13, 1 time/day (GW)	0, 46.125, 92.25, 184.5	BW, DX, FI, LE, RX	Bd wt	46.125		92.25	Decreased maternal body weight (28%)
					Develop		46.125	92.25	LOAEL: Skeletal anomalies SLOAEL: Decreased fetal weight (12%)
Saini et al. 2014a									**Nickel chloride hexahydrate**
14	Mouse (Swiss) 10 F	GDs 0–5, 1 time/day (GW)	0, 46, 92, 185	BW, DX, FI, LE, RX, WI	Bd wt	46	92	185	LOAEL: Decreased maternal body weight (16%) SLOAEL: Decreased maternal body weight (30%)
					Repro			46	Decreased number of implantation sites and number of live fetuses/dam
					Develop		46	92	LOAEL: Increased incidence of skeletal abnormalities SLOAEL: Decreased fetal weight (10%)
Saini et al. 2014b									**Nickel chloride hexahydrate**
15	Mouse (Swiss) 15 F	GDs 6–13 1 time/day (GW)	0, 46.125, 92.25, 184.5	BW, DX	Develop	46.125		92.25	Pup mortality (9.52%) and decreased birth weight (16%)
Saini et al. 2014b									**Nickel chloride hexahydrate**
16	Mouse (Swiss) 15 F	GDs 14–18 daily (GW)	0, 46.125, 92.25, 184.5	BW, DX	Develop	46.25		92.25	Pup mortality (11.11%), decreased birth weight (14%)
Saini et al. 2014b									**Nickel chloride hexahydrate**
17	Mouse (Swiss) 15 F	GDs 0–5 daily (GW)	0, 46.125, 92.25, 184.5	BW, DX, RX	Develop	46.125		92.25	Decreased litter size/dam

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Seidenberg et al. 1986									**Nickel chloride**
18	Mouse (ICR) 28 F	GDs 8–12 (GW)	0, 90.6	BW, DX, RX	Bd wt			90.6	Decreased maternal weight gain (50%)
					Develop	90.6			
Ambrose et al. 1976									**Nickel sulfate**
19	Dog (Beagle) 3 M, 3 F	3 days (F)	0, 2.5, 25, 62.5	BW, CS, FI, GN, HP, OW, UR	Gastro	25	62.5		Vomiting (six of six dogs)
INTERMEDIATE EXPOSURE									
Santucci et al. 1994									**Nickel sulfate**
20	Human 8 F	91–178 days (nickel-sensitized individuals) (W)	0.01–0.03	CS	Dermal	0.02			
Adeyemi and Elebiyo 2014									**Nickel sulfate**
21	Rat (Wistar) 5 M	21 days, 1 time/day (G)	0, 7.6	BC, BI, BW, OW	Bd wt	7.6			
					Renal		7.6		Increased plasma creatinine and urea
Adeyemi et al. 2017									**Nickel sulfate**
22	Rat (Wistar) 6 M	21 days, 1 time/day (GW)	7.6	BC, BI, BW, HE, HP, OW	Bd wt			7.6	Decreased average body weight (25%)
					Hepatic		7.6		Increased liver enzymes levels (ALT, AST, and ALP) and altered serum lipid levels (increased total cholesterol, triglyceride, LDL cholesterol and decreased HDL cholesterol)

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ambrose et al. 1976									**Nickel sulfate**
23	Rat (Wistar) 30 M, 30 F	3-generation study; F0 and F1 generation each exposed for 11 weeks (F)	0, 22.5, 45, 90	BW, CS, DX, GN, HP, RX	Bd wt	90 F 45 M	90 M		Decreased body weight of F0 generation (<13%)
					Develop			22.5	Increased number of stillborns in F1a generation
American Biogenics Corporation 1988									**Nickel chloride**
24	Rat (Sprague-Dawley) 30 M, 30 F	91 days (GW)	0, 1.2, 8.6, 25	BC, BW, CS, HP, LE	Death			25	100% mortality
					Bd wt	1.2 F	8.6 F		Decreased body weight gain (12%)
					Resp		8.6		Pneumonitis
					Cardio	8.6			
					Gastro	8.6		25	Ulcerative gastritis, enteritis, and abnormal intestinal contents
					Hemato	1.2 F	8.6 F		Increased platelet count
					Hepatic	8.6			
					Renal	8.6			
					Dermal	8.6			
					Ocular	8.6			
					Endocr	1.2 F	8.6 F		Decreased blood glucose level
					Neuro	1.2		8.6	Ataxia, prostration, hypothermia
Anyachor et al. 2023									**Nickel chloride**
25	Rat (Sprague-Dawley) 7 M	90 days 3 days/week (GW)	0, 0.2	BW, FI, WI, NX	Neuro		0.2		Impaired performance on test of learning and spatial memory

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
EPA 1988a, 1988b									**Nickel chloride**
26	Rat (CD) 30–32 M, 30–31 F	P0 generation exposure began 11 weeks prior to breeding; total exposure: F: 27–30 weeks M: 21– 4 weeks (W)	F: 0, 7, 30, 55; M: 0, 4, 20, 40	BW, CS, FI, GN, HP, WI	Resp	4 M	20 M		Histiocytic cellular infiltration in lungs in F1 generation
					Renal	55 F			
					Repro	7 F	30 F		Increased gestation length in first P0 pregnancy
					Develop	7 F		30 F	Increased mortality in F1b rats on PNDs 22–42
Käkelä et al. 1999									**Nickel chloride**
27	Rat (Wistar) 6 M, 6 F	28–76 days daily (W)	M: 0, 3.6; F: 0, 4.0	DX, RX	Repro			3.6	Decreased fertility
					Develop			3.6	Decreased number of pups born alive per dam, decreased litter size at PND 21
Käkelä et al. 1999									**Nickel chloride**
28	Rat (Wistar) 6 M	28 or 42 days before mating daily (W)	0, 3.6	DX, HP, RX	Repro			3.6	Decreased fertility (28-day exposure), decreased seminiferous tubule diameter, number of basal spermatogonia (28-day exposure)
					Develop			3.6	Decreased number of pups born alive per dam, decreased litter size at PND 21

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Käkelä et al. 1999									**Nickel chloride**
29	Rat (Wistar) 6 F	14 or 100 days before mating through LD 48 daily (W)	0, 1.3, 4.0, 13	DX, RX	Repro	13			Significantly decreased litter size by lactation day 21 (56.5% less than controls)
					Develop	4		13	Structural abnormalities in pups that died including underdeveloped posteriors of the bodies, slow movement, and disproportionately large heads; Decreased litter size on PND 21
Kamal et al. 2012									**Nickel sulfate hexahydrate**
30	Rat (albino) 6 M	28 days (W)	0, 17.06, 44.82	BI, BW, FI	Bd wt		17.06		Decreased terminal body weight (10%)
					Hepatic		17.06		Increased serum ALT and AST
Mahmoud et al. 2011									**Nickel sulfate heptahydrate**
31	Rat (albino) 4 M	21 days (W)	0, 17.05	BC, BI, BW, CS, FI, WI	Bd wt		17.05		Decreased terminal body weight (10%)
					Hepatic		17.05		Increased serum ALT and AST
Obone et al. 1999									**Nickel sulfate**
32	Rat (Sprague-Dawley) 8 M	13 weeks (W)	0, 5.75, 14.4, 28.8	BI, BW, HP, LE, OW	Bd wt	28.8			
					Resp		5.75		Decreased ALP activity in BALF
					Cardio	28.8			
					Gastro	28.8			
					Hepatic	28.8			
					Renal	5.75	14.4		Decreased urine volume and urine glucose
					Immuno		5.75		Increased spleen and thymus lymphocyte CD^{8+} T-cells and decreased CD4:CD8 ratio
					Neuro	28.8			
					Repro	28.8			

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Smith et al. 1993									**Nickel chloride**
33	Rat (Long-Evans) 34 F	11 weeks (breeding-lactation) two litters (W)	0, 1.3, 6.8, 31.6	BC, BW, CS, DX, FI, WI	Bd wt	31.6			
					Repro	6.8	13.6		Decreased maternal prolactin levels
					Develop			1.3	Increased number of dead pups on PND 1
Springborn Laboratories 2000a									**Nickel sulfate hexahydrate**
34	Rat (Sprague-Dawley) 8 M, 8 F	2 weeks prior to mating and during gestation and lactation (GW)	0, 2.2, 4.5, 6.7, 11.2, 16.8	CS, BW, FI, WI, RX, DX	Bd wt	16.8			
					Repro	16.8			
					Develop	4.5		6.7	Increased post-implantation loss
Springborn Laboratories 2000b									**Nickel sulfate hexahydrate**
35	Rat (Sprague-Dawley) 28 M, 28 F	2-generation study, 10 weeks prior to mating and during gestation and lactation (GW)	0, 0.22, 0.56, 1.1, 2.2	CS, BW,GN, OW, HP, RX, DX	Bd wt	2.2			
					Hepatic	2.2			
					Renal	2.2			
					Endocr	2.2			
					Neuro	2.2			
					Repro	2.2			
					Develop	2.2			
Springborn Laboratories 2002									**Nickel chloride hexahydrate**
36	Rat (Fischer-344) 10 M, 10 F	90 days, 1 time/day (GW)	M: 0, 11, 17, 22, 13, 13; F: 0, 11, 17, 22, 28, 33	CS, HP	Bd wt	11 M	17 M		12.2% decrease in final body weight
					Resp	22 M			
					Cardio	22 M			
					Gastro	22 M			
					Hepatic	22 M			
					Renal	22 M			
					Endocr	22 M			

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Vyskocil et al. 1994b									**Nickel sulfate**
37	Rat (Wistar) 10 M, 10 F	3 or 6 months (W)	0, M: 6.9, F: 7.6	BW, UR	Bd wt	7.6 F			
					Renal		7.6 F		Increased urinary albumin
Weischer et al. 1980									**Nickel chloride**
38	Rat (Wistar) 10 M	28 days (W)	0, 0.23, 0.49, 0.97	BC,HE, BW, OW, WI	Bd wt			0.23	Decreased body weight gain (20%)
					Hemato	0.97			
					Hepatic	0.97			
					Renal	0.97			
Whanger 1973									**Nickel acetate**
39	Rat (OSU brown) 6 M	6 weeks (F)	0, 5, 25, 50	BI, BW, HE	Bd wt	5		25	88% decrease in body weight gain
					Hemato	50			
Dahdouh et al. 2016									**Nickel sulfate**
40	Mouse (Swiss) 8 M	28 days (F)	0, 36	BC, BI, BW, FI, HE, HP, OW, WI	Hemato		36		Decreased RBCs, platelet counts, and packed cell volume and increased WBCs
					Renal			36	Increased serum urea, creatinine, and uric acid levels; proximal tubule degeneration with tubular necrosis and inflammation
Dieter et al. 1988									**Nickel sulfate**
41	Mouse (B6C3F1) 10 F	180 days (W)	0, 44, 108, 150	BI, BW, HP, OW, WI, IX	Bd wt	44	108	150	SLOAEL: Decreased body weight (26%) LOAEL: Decreased body weight (10%)
					Hepatic	150			
					Renal	44	108		Nephrosis
					Immuno		44		Mild thymic atrophy, impaired B-cell immune function, decreased granulocyte macrophage progenitor cell levels

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
EPA 1983									**Nickel chloride**
42	Mouse (CD-1) 12–24 F	GDs 2–17 (W)	0, 80, 160	DX, RX	Develop	80		160	Increased spontaneous abortions
Ilbäck et al. 1994									**Nickel chloride**
43	Mouse (BALB/c) 8 F	10–11 weeks (W)	0, 20.3	BW, HP, LE, OF, IX	Immuno		20.3		Enhanced inflammatory response in the hearts of mice challenged with coxsackie virus B3
Pandey and Srivastava 2000									**Nickel chloride**
44	Mouse (NS) 6 M	35 days 5 days/week (GW)	0, 1.2, 2.5, 4.9	RX	Repro	1.2	2.5		Decreased sperm motility and count and increased sperm abnormalities
Pandey and Srivastava 2000									**Nickel sulfate**
45	Mouse (NS) 6 M	35 days 5 days/week (GW)	0, 1.1, 2.2, 4.5	RX	Repro	1.1	2.2		Decrease of sperm count and motility and increase in sperm head, tail, and neck abnormalities
Pandey et al. 1999									**Nickel sulfate**
46	Mouse (Swiss) 20 M	35 days 5 days/week (GW)	0, 2.2	DX, RX	Repro			2.2	Increased post-implantation loss
Pandey et al. 1999									**Nickel sulfate**
47	Mouse (Swiss) 20 M	35 days 5 days/week (GW)	0, 1.1, 2.2	BI, BW, HP, OW, RX	Bd wt	2.2			
					Repro		1.1		Decrease in sperm motility and total sperm count; increased percent of morphological sperm abnormalities; decreased relative testis, seminal vesicle, and prostate gland weights

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Toman et al. 2012									**Nickel chloride**
48	Mouse (ICR) 5 M	3–12 weeks (F)	0, 4.5	BW, CS, HP, LE, OW	Repro		4.5		Degeneration of seminiferous epithelium, decreased relative volume of germinal epithelium, interstitium, blood vessels and increased relative volume of lumen, empty spaces in the epithelium and whole tubules of testes
CHRONIC EXPOSURE									
Heim et al. 2007									**Nickel sulfate hexahydrate**
49	Rat (Fischer-344) 60 M, 60 F	104 weeks, 1 time/day (GW)	0, 2.2, 6.7, 11.2	BC, BW, CS, FI, GN, HE, LE	Death			6.7 F	Increased mortality (43%)
					Bd wt	6.7 F	11.2 F		Decreased terminal body weight (10%)
						2.2 M	6.7 M		Decreased terminal body weight (11%)
					Hemato	11.2			
Ambrose et al. 1976									**Nickel sulfate**
50	Dog (Beagle) 3 M, 3 F	2 years (F)	0, 2.5, 25, 62.5	BW, CS, FI, GN, HP, OW, UR	Bd wt	25	62.5		10% decrease in body weight gain
					Resp	25		62.5	Cholesterol granulomas, emphysema, bronchiolectasis
					Cardio	62.5			
					Gastro	62.5			
					Hemato	25	62.5		Unspecified decrease of hematocrit and hemoglobin levels suggestive of simple hypochromic anemia
					Musc/skel	62.5			
					Hepatic	62.5			
					Renal	25	62.5		Polyuria in two of six dogs, increased kidney weight
					Dermal	62.5			

Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	62.5			
					Immuno	62.5			
					Neuro	62.5			
					Repro	62.5			

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

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; B = both males and females; BALF = bronchiolar lavage fluid; Bd wt and BW = body weight; BC = serum (blood) chemistry; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = dietary exposure; F = female(s); FI = food intake; (G) = gavage; (GW) = gavage with aqueous vehicle); Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HDL = high-density lipoprotein; HE = hematological; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LD = lactation day; LD_{50} = dose producing 50% death; LDL = low-density lipoprotein; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PND = postnatal day; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis; (W) = drinking water; WBC = white blood cell; WI = water intake

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

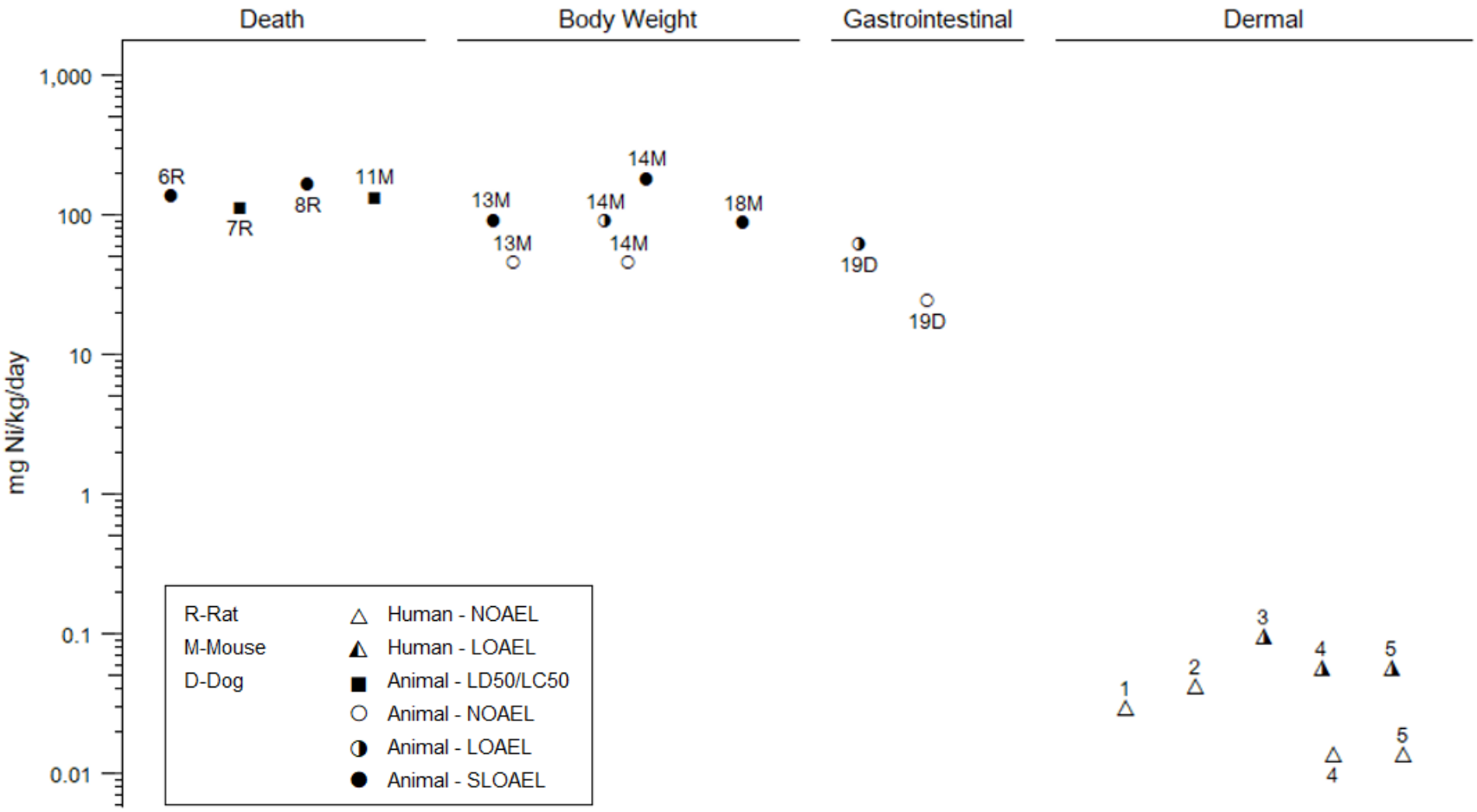


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Acute (≤14 days)

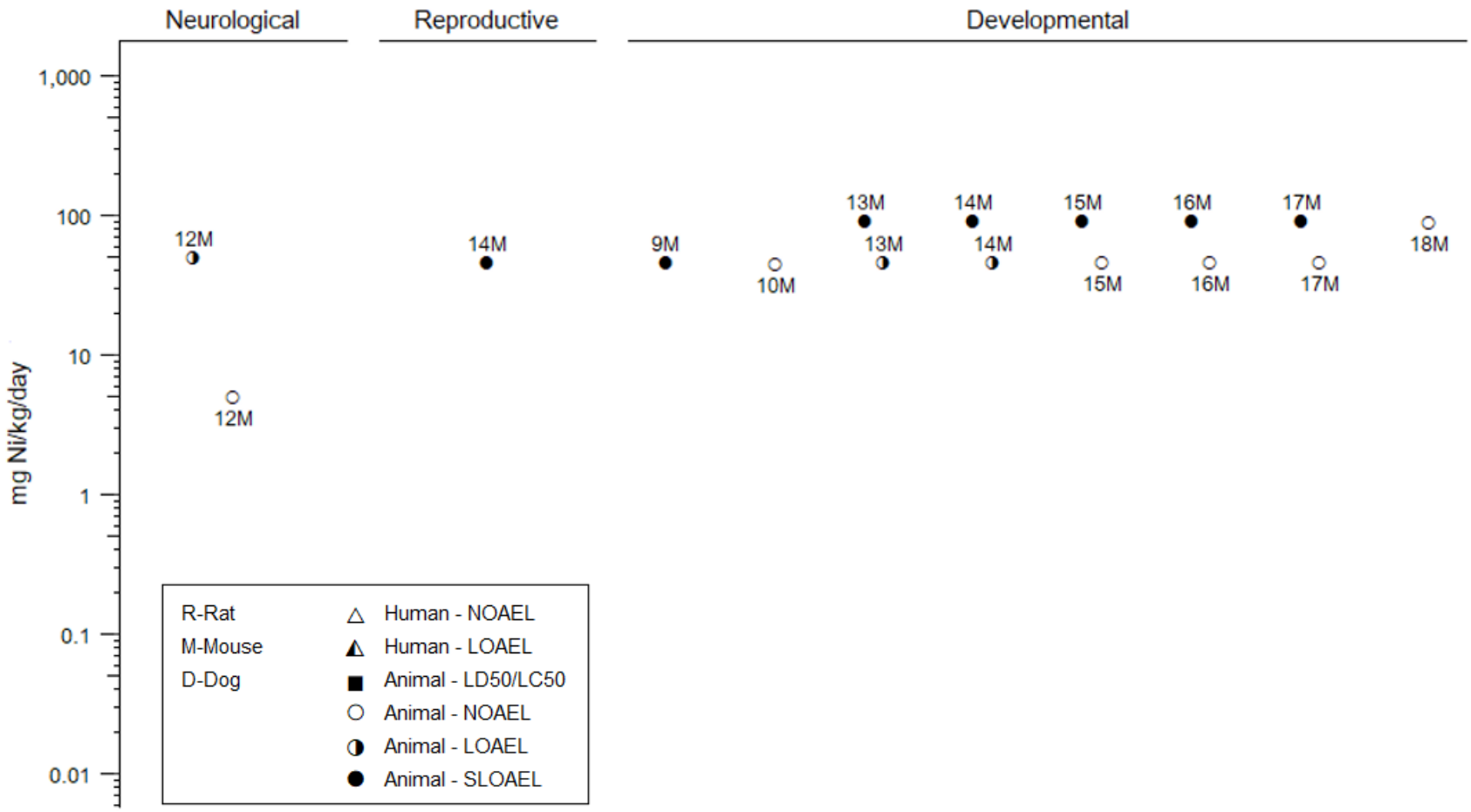


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

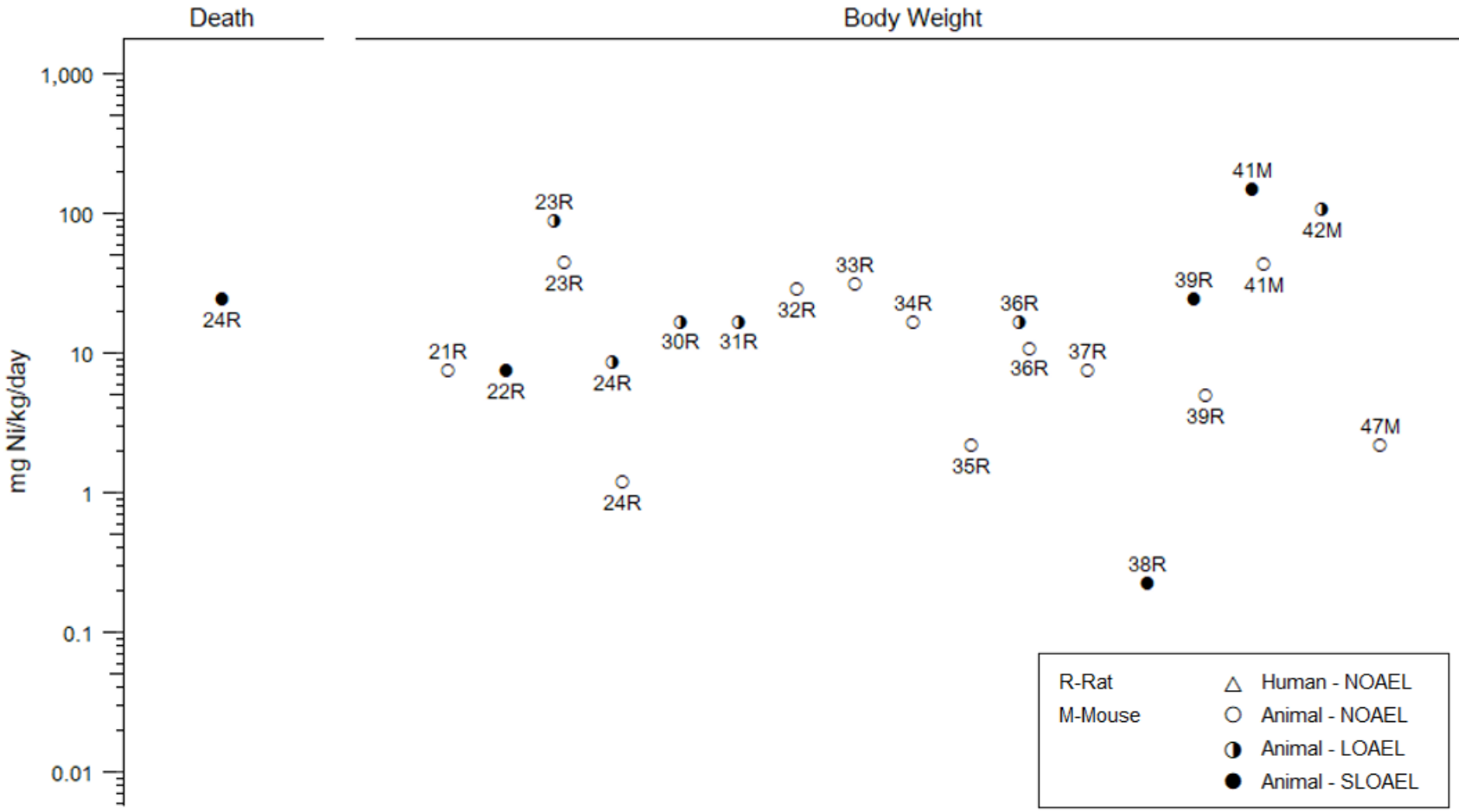


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

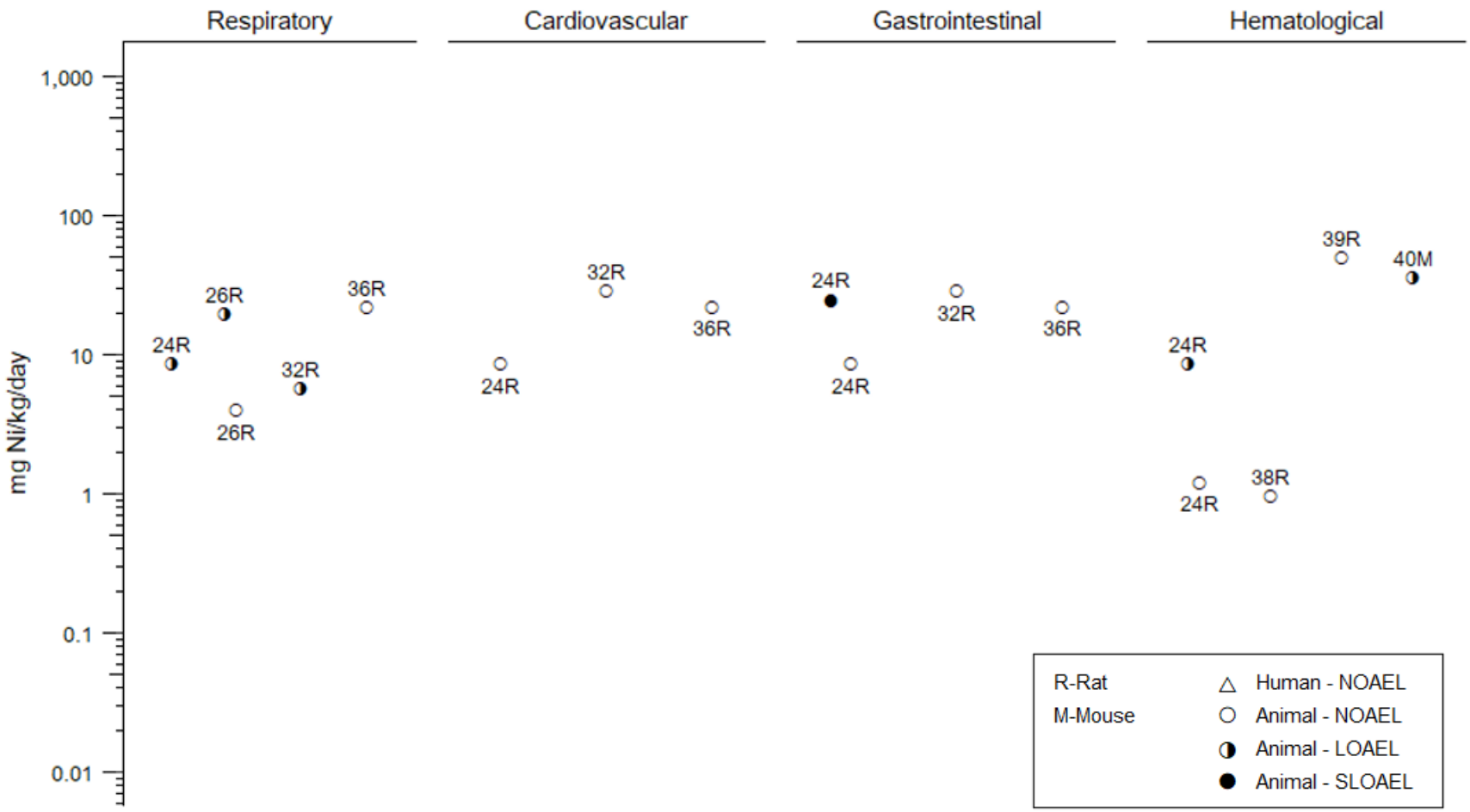


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

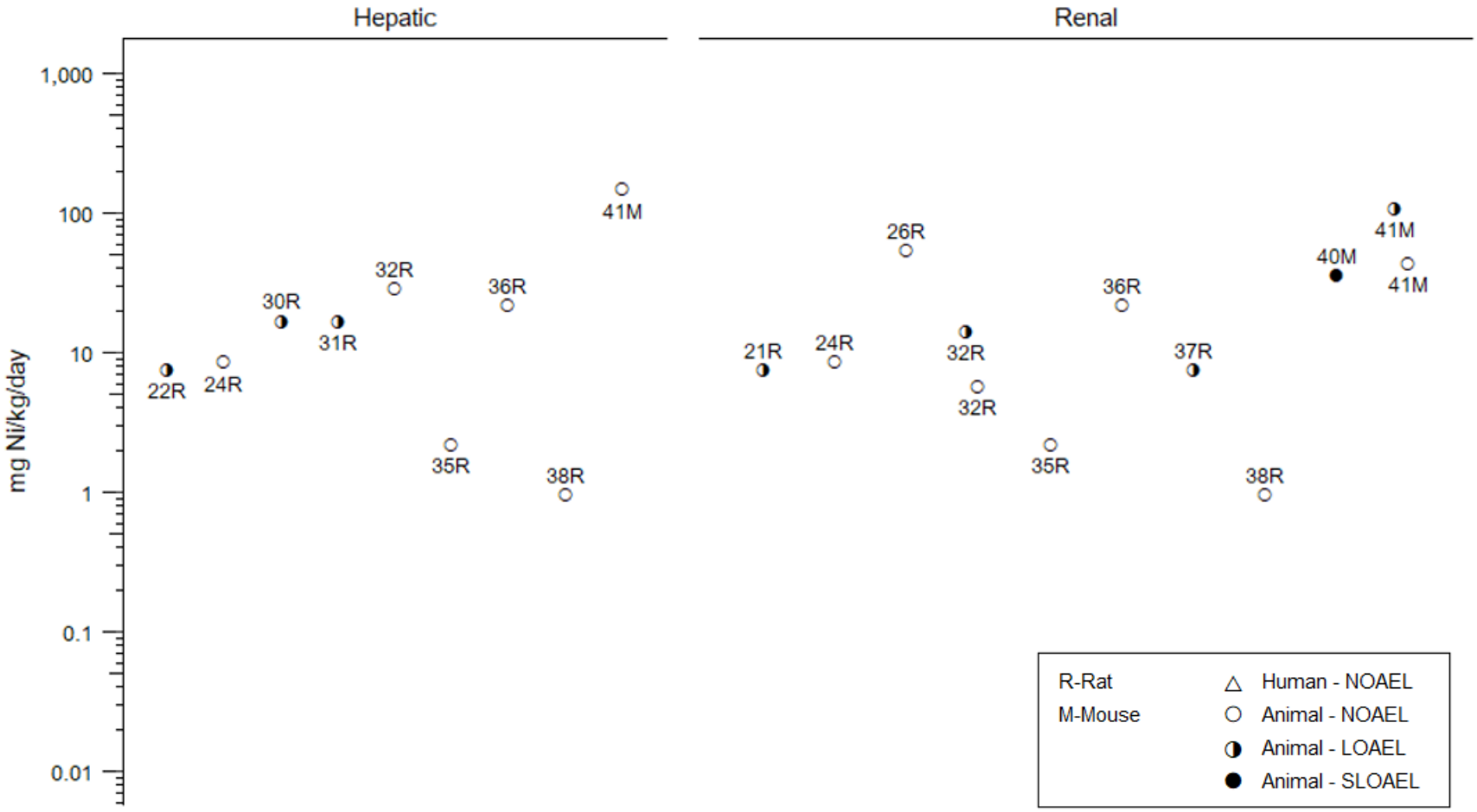


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

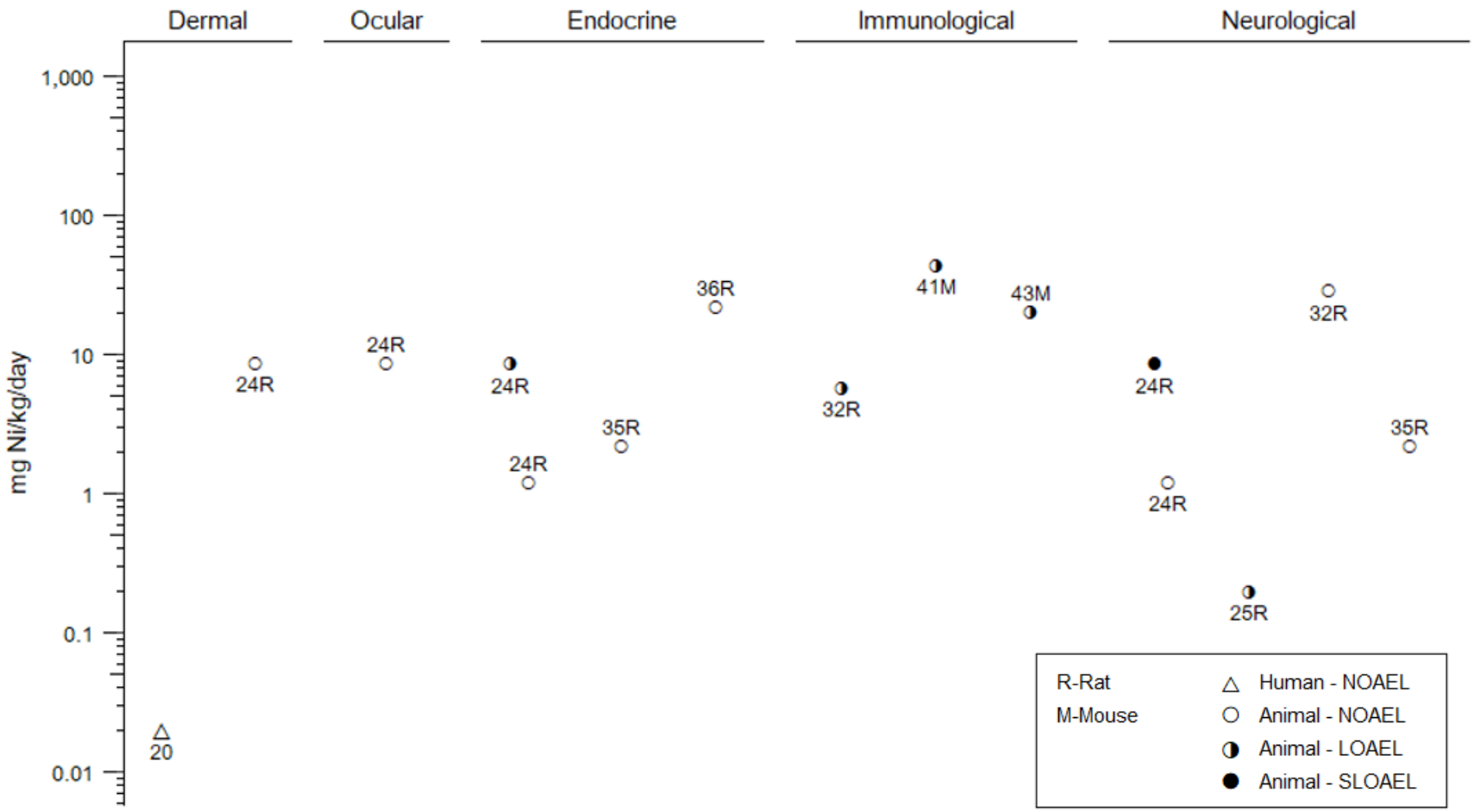


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

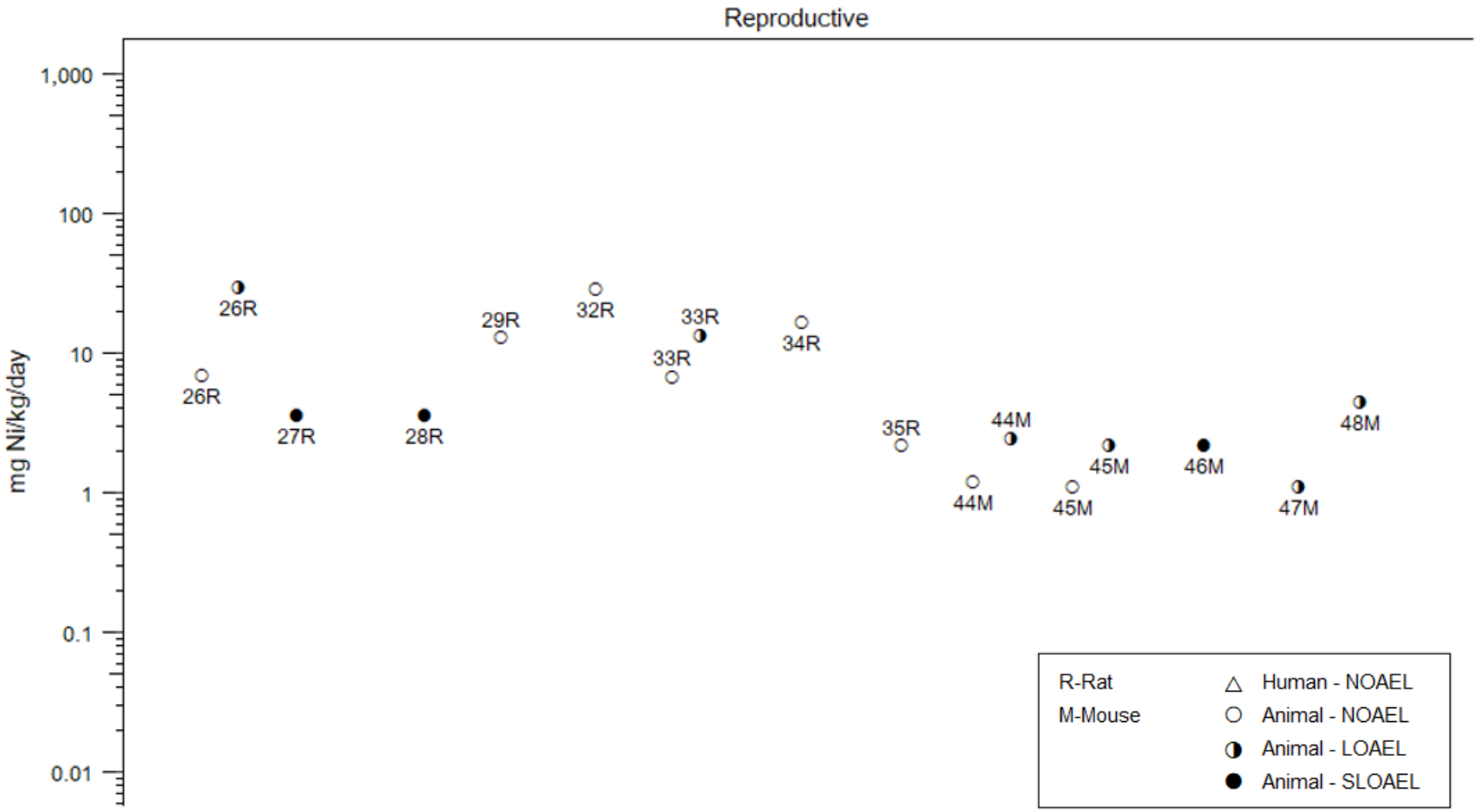


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

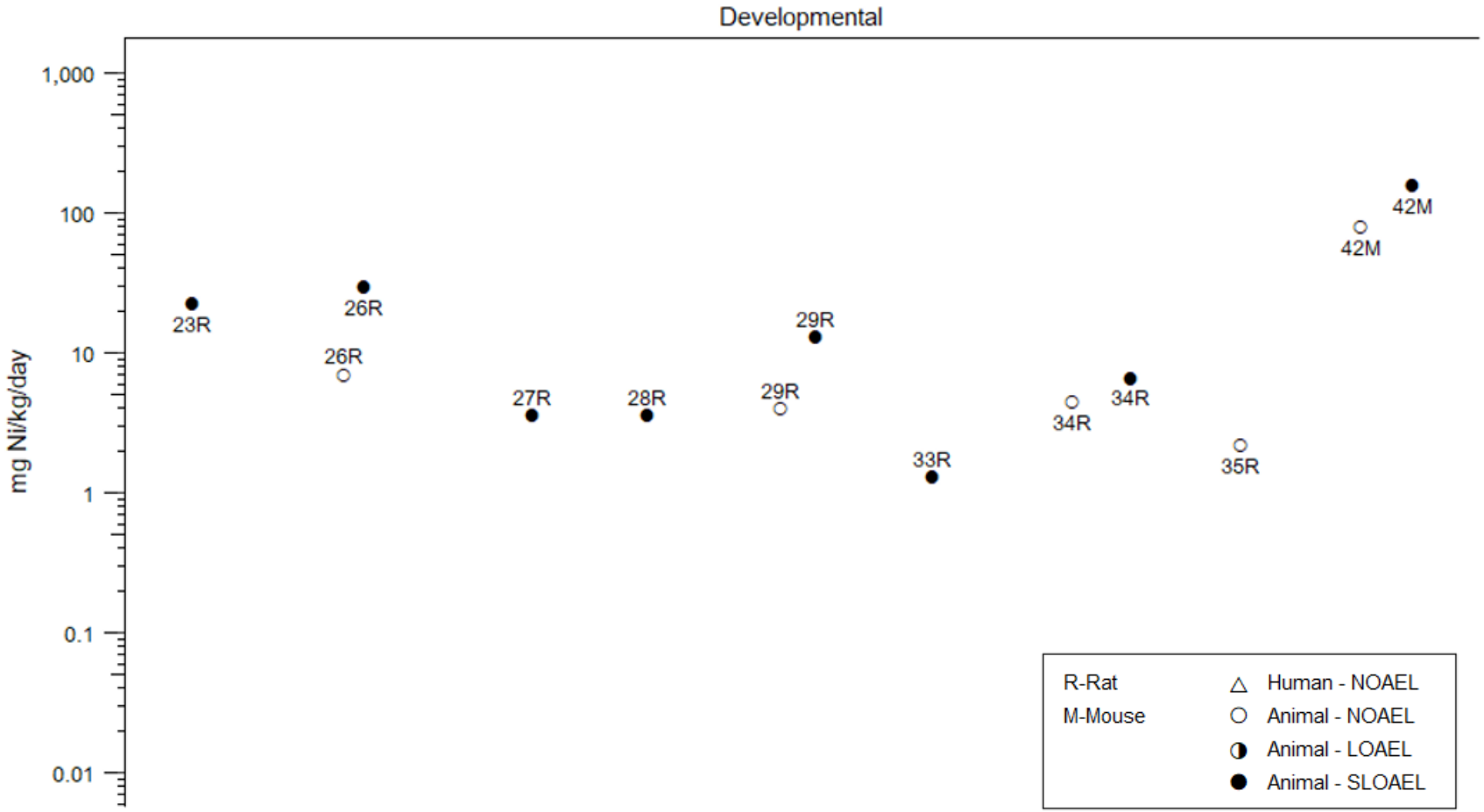


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

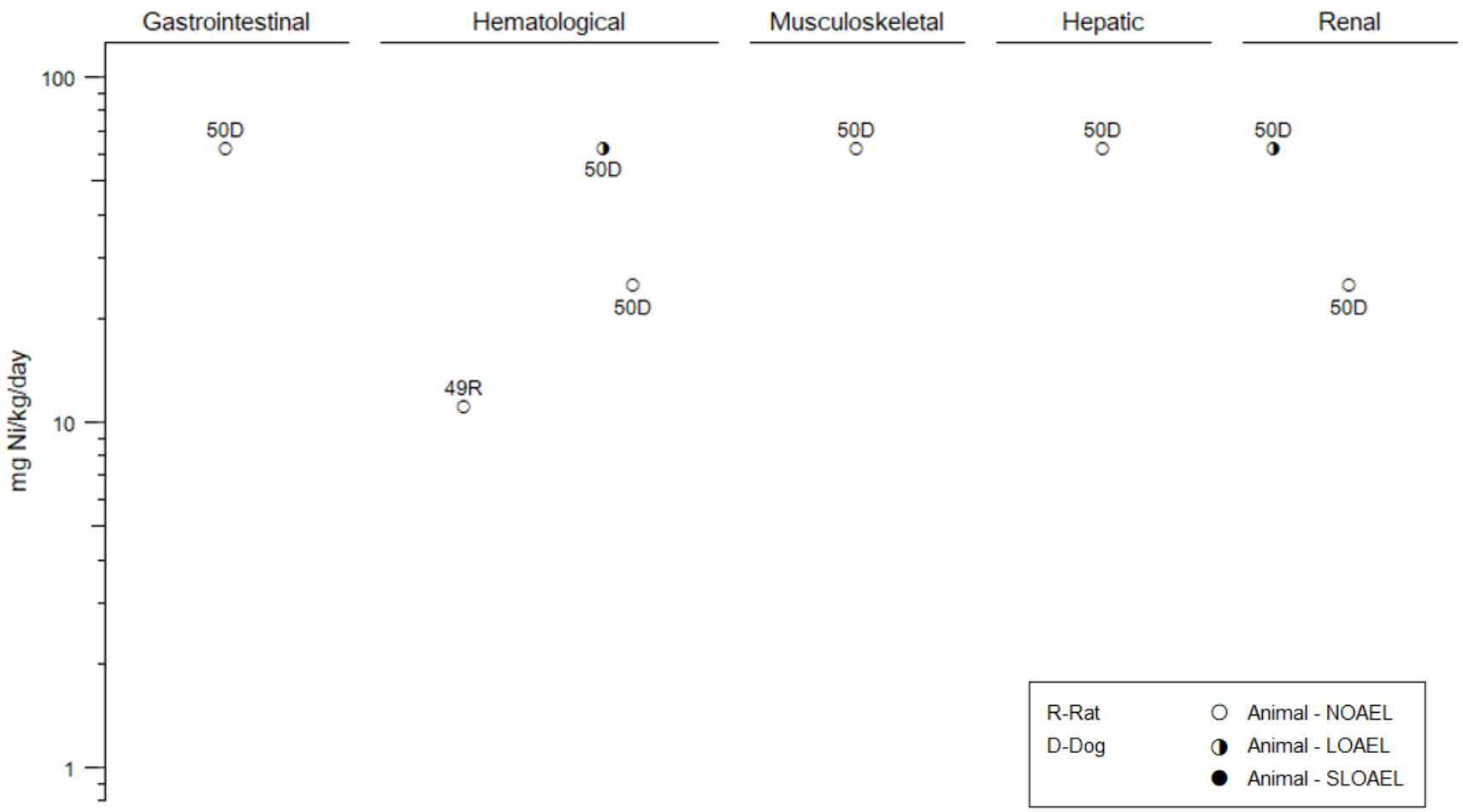


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

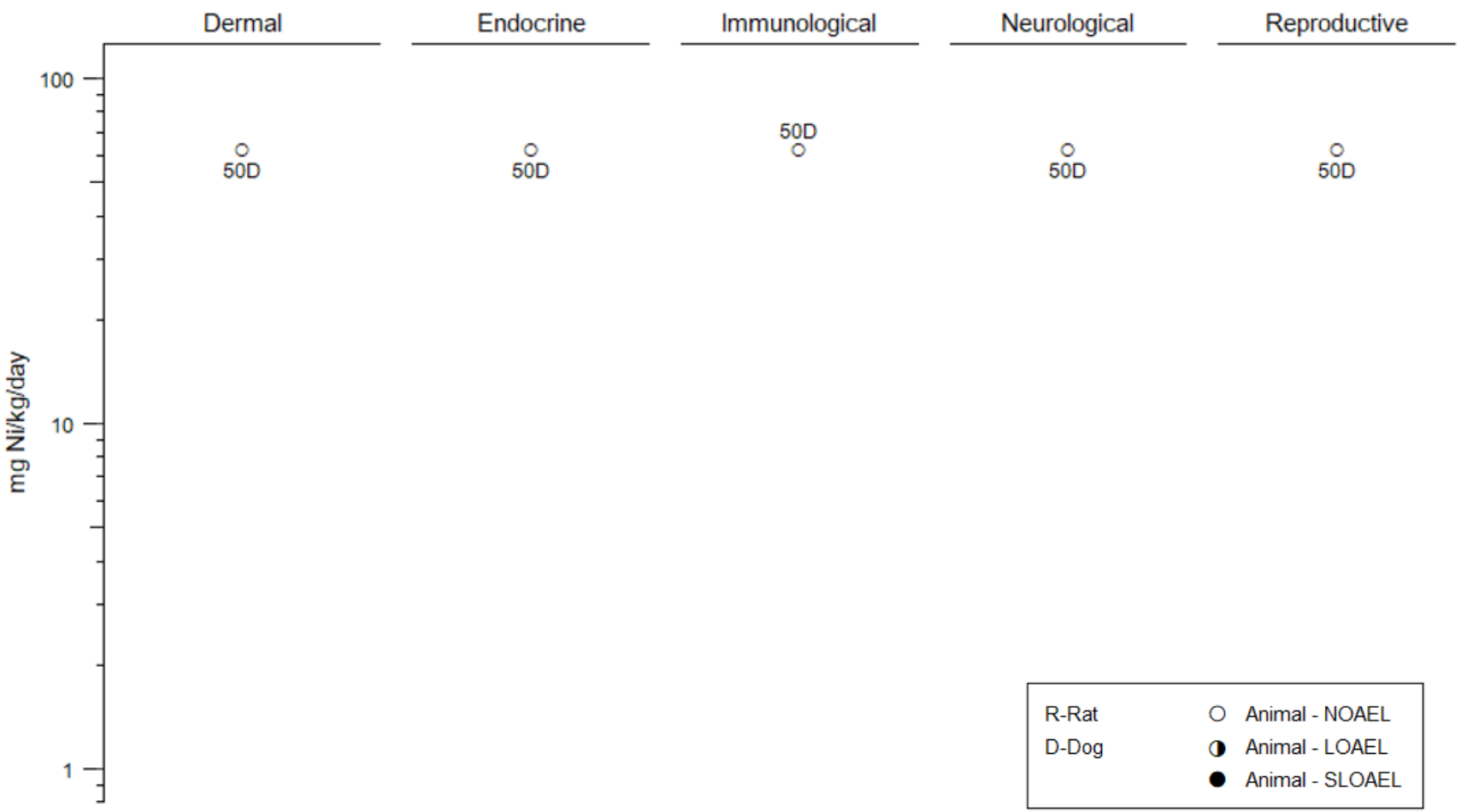


Table 2-3. Levels of Significant Exposure to Nickel – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Emmett et al. 1988								**Nickel sulfate**
Human 12 NS	Once	0.47 mg (0.01%)–5.2mg (2.5%)	CS	Dermal	0.01	0.0316		Contact dermatitis in sensitive individuals
Eun and Marks 1990								**Nickel sulfate**
Human 20 NS	Once	0.04–5%	CS	Dermal		0.04		Allergic dermatitis in sensitive individuals
Menné and Calvin 1993								**Nickel chloride**
Human 16–51 NS	Once	0, 0.1, 1, 10, 100, 1,000, 4,000 ppm	CS	Dermal	0.01	0.1		Skin reaction in nickel sensitive individuals
Menné et al. 1987								**Nickel alloys**
Human 164 F, 9 M	Once	1	CS	Dermal		1		Contact dermatitis
Siller and Seymour 1994								**Nickel sulfate**
Mouse (C3H:Hej) 4 F	Once for 7 days	0, 1, 5, 10, 15, 20%	CS	Immuno		1		Development of dermal sensitization
INTERMEDIATE EXPOSURE								
Mathur et al. 1977								**Nickel sulfate**
Rat (NS) 8 M	15 or 30 days, 1 time/day	0, 40, 60, 100 mg/kg	CS, GN, HP, RX	Hepatic	40	60		Focal necrosis
				Renal	100			
				Dermal		40		Slight hyperkeratosis
				Repro	40		60	Degeneration and edema of seminiferous tubules

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mathur and Gupta 1994								**Nickel sulfate**
Guinea pig (NS) 12 NS	15 or 30 days	0, 100 mg/kg	BC	Hemato	100			
				Renal		100		Increased Mg^{2+} ATPase activity
				Other noncancer		100		Increased blood glucose

ATP = adenosine triphosphate; BC = serum (blood) chemistry; CS = clinical signs; F = female(s); GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Repro = reproductive; RX = reproductive function

2.2 DEATH

Death from adult respiratory distress syndrome (ARDS) was reported in one person who sprayed nickel with a metal arc process without wearing personal protective equipment (Rendall et al. 1994). Death occurred 13 days after a 90-minute exposure to an estimated concentration of 382 mg Ni/m^3 of principally metallic nickel with the majority of particle sizes of <1.4 µm (Sunderman 1993). 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-duration inhalation exposure to nickel are limited to occupational exposure studies. Most of these studies analyzed the toxicity of nickel, usually in the form of nickel oxide, metallic nickel, or nickel refinery dust, by calculating standardized mortality ratios (SMRs) for all causes of death. Generally, the studies reported a higher incidence of cancer deaths from lung and nasal cancers in the exposed workers (see Section 2.19 Cancer). Two studies 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) and non-metallic substances, 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. 1984a, 1984b, 1991).

During the first 2 days after a single 2-hour exposure, 4 out of 28 Fischer-344 rats died after exposure to nickel sulfate at 36.5 mg Ni/m^3 (Hirano et al. 1994). Severe hemorrhage of the lungs was observed in the lungs of the rats that died. No deaths were observed in rats exposed to 0.00672 mg Ni/m^3 as nickel oxide for 4 hours followed by a 14-day observation period (Lyons-Darden et al. 2023). Significant mortality was observed during the last 26 weeks of a 31-month inhalation study of Fischer-344 rats exposed to 0.63 mg Ni/m^3 as nickel sulfide (Ottolenghi et al. 1975). 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. 1975). A significant decrease in mean survival time was observed in Wistar rats exposed 23 hours/day for life to 0.06 mg Ni/m^3 as nickel oxide (Takenaka et al. 1985); the average survival times for rats exposed to 0 or 0.06 mg Ni/m^3 were 125.2 and 87.7 weeks, respectively. Male and female Wistar rats showed reduced survival by 72 and 48%, respectively, by 103 weeks of continuous exposure 0.11 mg Ni/m^3 as metallic nickel (5 days/week, 6 hours/day) (Oller et al. 2008).

NTP studies observed that B6C3F1 mice were more sensitive to lethality from nickel exposure than Fischer-344 rats. At 1.4 mg Ni/m^3 as nickel sulfate hexahydrate, all mice and no rats died, and at 7.33 mg Ni/m^3 as nickel subsulfide, all mice and only 2 of 10 rats died following exposure for 6 hours/day, 5 days/week, for up to 12 exposures (NTP 1996b, 1996c). No rats or mice died following exposure to 23.6 mg Ni/m^3 as nickel oxide (NTP 1996a). 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/m^3 as nickel oxide, nickel subsulfide, or nickel sulfate, respectively (NTP 1996a, 1996b, 1996c). 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/m^3, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c) or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c).

All rats (Bethesda Black), guinea pigs (Strain 13), and mice (C57) exposed to 15 mg Ni/m^3 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 (Hueper 1958). Lung lesions, including edema, hyperemia, and hemorrhage, were the principal causes noted. A major study deficiency was the lack of control animals, the study instead compared exposure groups to data of same-species controls from previous carcinogenic studies (Hueper 1958).

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

Oral LD_{50} values of 116 and 139 mg Ni/kg as nickel acetate in Fischer-344 female rats and male Swiss-albino mice, respectively, have been reported for nickel acetate (Haro et al. 1968). Single-dose oral lethality studies indicate that soluble nickel compounds are more toxic than less-soluble nickel compounds. A study conducted by Henderson et al. (2012) evaluated the acute lethality of a number of nickel compounds. The oral LD_{50} values estimated in this study are presented in Table 2-4.

Table 2-4. Acute Lethality of Nickel Compounds Following a Single Dose Administration to Female Sprague-Dawley Rats

Compound	LD_{50} (95% CI) (mg Ni/kg)
Nickel acetate tetrahydrate	132 (46–403)
Nickel chloride hexahydrate	125 (99–156)
Nickel dihydroxide	2,700 (1,830–3,132)
Nickel fluoride tetrahydrate	99 (56–160)
Nickel hydroxycarbonate	980[a]
Nickel oxide (green)	>8.910
Nickel oxide (black)	7,492 (6,581–8,325)
Nickel subsulfide	>7,700
Nickel sulfamate tetrahydrate	307 (14–560)
Nickel sulfate hexahydrate	94[a]

[a]95% CI was not calculated.

CI = confidence interval; LD_{50} = lethal dose at which lethality is expected in 50% of animals

Source: Henderson et al. 2012

Increases in mortality were observed in Sprague-Dawley rats administered via gavage 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, increases in mortality in Sprague-Dawley rats were observed within 2 weeks of exposure to 140 mg Ni/kg/day as nickel chloride (EPA 1988a). Over a 2-year study, increases in mortality were observed in female Fischer-344 rats exposed to 6.7 mg Ni/m^3 as nickel sulfate hexahydrate (Heim et al. 2007). No exposure-related response was seen in male rats exposed during the same period. In other studies, no deaths were observed in Sprague-Dawley rats given 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999), Fischer-344 rats administered 22 mg Ni/kg/day (males) or 33 mg Ni/kg/day (females) as nickel sulfate hexahydrate for 90 days (Springborn Laboratories 2002), or B6C3F1 mice exposed 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 (EPA 1988a, 1988b) in which CD 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 (EPA 1988a, 1988b) are confounded by a decrease in food and water intake observed in the exposed animals. Deaths in offspring before weaning have also been reported in multigeneration, multi-littered studies (EPA 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 were 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-duration studies in Wistar rats or Beagle 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).

No studies were identified that examined death in humans or animals after dermal exposure to nickel.

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans after inhalation, oral, or dermal exposure to nickel.

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 exposures. 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/m^3 and in mice exposed to 1.4 mg Ni/m^3 6 hours/day for 12 days in a 16-day period (NTP 1996c); no alterations in body weight gain were observed in mice exposed to 0.7 mg Ni/m^3. No significant alterations in body weight gain were observed in rats or mice exposed to ≤0.44 mg Ni/m^3 for 13 weeks (NTP 1996c; Oller et al. 2023), rats exposed to 0.11 mg Ni/m^3 for 2 years (NTP 1996c), or mice exposed to 0.22 mg Ni/m^3 for 2 years (NTP 1996c).

For nickel subsulfide, serious decreases in body weight gain (22–28%) and emaciation were observed in rats and mice exposed to 3.65 mg Ni/m^3 for 6 hours/day for 12 days in a 16-day period (NTP 1996b); a NOAEL of 1.85 mg Ni/m^3 was identified. No alterations in body weight were observed at ≤1.83 mg Ni/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 1996b; Oller et al. 2023). Exposure to approximately 0.7 mg Ni/m^3 6 hours/day, 5 days/week for chronic duration resulted in 11–30% decreases in body weight

gains in rats (NTP 1996b; Ottolenghi et al. 1975). No alterations were observed in mice exposed to 0.88 mg Ni/m^3 6 hours/day, 5 days/week for 2 years.

Most studies did not find significant body weight alterations in rats and mice exposed to inhaled nickel oxide. A NOAEL of 23.6 mg Ni/m^3 was identified in rats and mice exposed 6 hours/day for 12 days in a 16-day period (NTP 1996a). For intermediate-duration exposure, NOAELs of 1.9–7.9 mg Ni/m^3 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/m^3, respectively, continuously for 21–28 days. In pregnant rats, an 11% decrease in body weight gain was observed at 0.8 mg Ni/m^3 compared to the 36% decrease observed in similarly exposed nonpregnant rats. NTP (1996a) did not find alterations in body weight gain in rats or mice exposed to 2 or 3.9 mg Ni/m^3, respectively, 6 hours/day, 5 days/week for 2 years; a NOAEL of 0.9 mg Ni/m^3 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/m^3 for 31 months; the weight loss began after 13 months of exposure. These data suggest that continuous exposure is more toxic than intermittent exposure (the duration-adjusted NOAEL for the rat NTP [1996a] study is 0.36 mg Ni/m^3). Continuous exposure resulted in higher lung burdens than intermittent exposure, which would lead to increased lung damage.

There are more limited data on other nickel compounds. No alterations in body weight were observed in ICR mice exposed to 0.081 mg Ni/m^3 as nickel chloride for 24 hours (Buxton et al. 2021). Exposure to 0.1 mg Ni/m^3 as metallic nickel resulted in decreases of 11% body weight gain in rats exposed 6 hours/day, 5 days/week for 2 years (Oller et al. 2008); at 0.4 mg Ni/m^3, a 27% decrease in body weight gain was observed.

Decreases in body weight gain have been observed in a number of oral exposure studies of soluble nickel compounds. In several studies, the decreased body weight was associated with decreased food and/or water intake. Dose-related reductions in body weight gain with decreased food and/or water intake were reported in rats orally exposed to 0.23– 0.97 mg Ni/kg/day as nickel chloride in drinking water for 28 days (Weischer et al. 1980), rats treated by gavage with 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988) or 55 mg Ni/kg/day for 30 weeks (EPA 1988a), and rats treated with 75 mg Ni/kg/day of nickel sulfate for 2 years in the diet (Ambrose et al. 1976). The concomitant decreases in food and/or water consumption limit the interpretation of these results.

Other studies of nickel sulfate have reported decreased body weight without consistent alterations in food intake. Decreased terminal body weights of 10–13% have been observed in male and female rats administered via gavage 17 or 28 mg Ni/kg/day, respectively, for 90 days (Springborn Laboratories 2002) or 6.7 or 11.2 mg Ni/kg/day, respectively, for 2 years (Heim et al. 2007). In studies not reporting food intakes, decreased body weight gain of 10% was observed in mice exposed to 108 mg Ni/kg/day as nickel sulfate in drinking water for 180 days and in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate for 2 years (Ambrose et al. 1976). Decreases in body weight gain of ≥25% were observed in rats administered 7.6 mg Ni/kg/day as nickel sulfate for 21 days (Adeyemi et al. 2017), rats exposed to 25 mg Ni/kg/day as nickel acetate in the diet for 6 weeks (Whanger 1973), and in mice exposed to 150 mg Ni/kg/day as nickel sulfate for 180 days (Dieter et al. 1988). Other studies have not found decreases in body weight gain in rats exposed to nickel sulfate for intermediate durations at doses of ≤28.8 mg Ni/kg/day (Adeyemi and Elebiyo 2014; Obone et al. 1999; Springborn Laboratories 2000a). Decreases in maternal body weight gain have also been observed in rats administered approximately 92 mg Ni/kg/day as nickel chloride (Saini et al. 2013, 2014a), with both studies reporting decreased food and water consumption, and in mice administered 90.6 mg Ni/kg/day as nickel chloride with no information of feed intake (Seidenberg et al. 1986). There is considerable overlap in the NOAEL and LOAEL values and interpretation of the data is limited by inconsistent reporting of food and water intake data.

No studies were identified that examined body weight in humans or animals after dermal exposure to nickel.

2.4 RESPIRATORY

Human studies have examined the potential of nickel and nickel compounds to induce respiratory effects. Epidemiological studies of respiratory effects are summarized in Table 2-5. 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; the excess was associated with the duration of foundry employment, regardless of exposure to nickel (Cornell and Landis 1984). Other studies of workers exposed to nickel 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; Moulin et al. 2000; Polednak 1981; Redmond 1984; Roberts et al. 1989a; Shannon et al. 1984a, 1984b, 1991). A common limitation of the cohort mortality studies is that the numbers of observed deaths from all causes were lower (significantly lower in many cases) than the numbers of 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 ARDS was reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall 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.

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Nickel and Respiratory Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Mortality studies			
Arena et al. 1998 Retrospective cohort, 31,165 male and female high nickel alloys workers (United States)	Range of average air concentrations by work area: 0.008–1.5 mg Ni/m^3	Death from nonmalignant respiratory disease	↔
Cornell and Landis 1984 Retrospective cohort, 4,487 male stainless and low nickel alloy production workers (United States)	Not reported	Death from nonmalignant respiratory disease	↑
Cox et al. 1981 Retrospective cohort, 1,925 male nickel alloy production workers (United Kingdom)	Range of average air concentrations by operating area: 0.04–0.84 mg Ni/m^3	Death from nonmalignant respiratory disease	↔
Cragle et al. 1984 Retrospective cohort, 814 male workers exposed to metallic nickel powder and 7,552 male workers in the same facility without exposure (United States)	Range of air concentrations in exposure areas: 0.1–1.0 mg Ni/m^3	Death from nonmalignant respiratory disease	↔
Egedahl et al. 2001 Retrospective cohort, 1,649 male hydrometallurgical nickel refinery workers (Canada)	Range of average air concentrations for different areas and sampling methods: 2–95 mg Ni/m^3	Death from nonmalignant respiratory disease	↔
Enterline and Marsh 1982 Retrospective cohort, 1,855 male nickel refinery workers (United States)	Range of historic air concentrations by department: 0.01–5 mg Ni/m^3	Death from nonmalignant respiratory disease	↔

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Nickel and Respiratory Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Moulin et al. 2000 Retrospective cohort, 4,897 male and female stainless and alloyed steel production workers (France)	Not reported; exposure assessed using job-exposure matrix	Death from nonmalignant respiratory disease	↔
Polednak 1981 Retrospective cohort, 1,059 male welders (United States)	Range of TWA air concentrations by welding procedure: 0.04–0.57 mg Ni/m^3	Death from nonmalignant respiratory disease	↔
Redmond 1984 Retrospective cohort, 28,261 male and female high nickel alloys workers (United States)	Not reported	Death from nonmalignant respiratory disease	↔
Roberts et al. 1989a Retrospective cohort, 54,509 nickel mining, smelting, and refining workers (Canada)	Not reported	Death from nonmalignant respiratory disease	↔
Shannon et al. 1984a, 1984b Retrospective cohort, 11,594 nickel mining, milling, and smelting workers (Canada)	Not reported	Death from nonmalignant respiratory disease	↔
Shannon et al. 1991 Retrospective cohort, 11,567 nickel mining, milling, and smelting workers (Canada)	Range of air concentrations by department: 0.01–0.22 mg Ni/m^3	Death from nonmalignant respiratory disease	↔
Other respiratory endpoints			
Berge and Skyberg 2003 Cohort, 1,046 male nickel refinery workers (Norway)	Mean cumulative exposure, mg Ni/m^3-years: All species: 4.49	Risk of pulmonary fibrosis	↔
	Soluble: 1.43		↑
	Sulfidic: 0.55		↑
	Metallic: 0.52		↔
	Oxidic: 3.09		↔

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Nickel and Respiratory Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Fishwick et al. 2004 Cross-sectional, 49 welders and 26 non-welders (mean age 39.2 years) (New Zealand)	Range of air concentrations of nickel by site and exposure category: 0.001–0.038 mg Ni/m^3	Self-reported work-related respiratory symptoms	↑
Kilburn et al. 1990 Cross-sectional, 90 male welders in stainless steel fabricating plant (mean age 44 years), compared with predictions for unexposed men (United States)	Not reported	Prevalence of chronic bronchitis	↑
		Pre-shift FVC, FEV_1, $FEF_{25–75}$, and $FEF_{75–85}$	↓
		Alveolar volume and diffusing capacity for carbon monoxide, single breath (DLCOsb)	↔
	Mean serum level: 1.1 µg Ni/L	Cross-shift change in FEV, FVC, and DLCOsb (subset of 31 welders)	↔
Muir et al. 1993 Cross-sectional, 745 nickel sinter plant workers compared with data from published studies (Canada)	Air concentrations reportedly as high as 100 mg Ni/m^3	Prevalence of small opacities on chest radiograph	↔
Syurin and Vinnikov 2022 Prospective cohort, 1,424 nickel pyrometallurgical production workers, followed for 14 years (Russia)	Range of mean annual air concentrations by job: 0.198–6.760 mg Ni/m^3	Compensation claims for occupational bronchitis	↑
		Compensation claims for occupational asthma	↑
Wu et al. 2022 Cross-sectional, 186 welders (mean age 41.04 years) (China)	Median urine concentration: 3.58 µg Ni/L	PEF	↓
		FVC, FEV_1	↔

↑ = association; ↓ = inverse association; ↔ = no association; DLCOsb = single-breath diffusing capacity of the lungs for carbon monoxide; FEV_1 = forced expiratory volume in the first second; $FEF_{25–75}$ = forced expiratory flow at 25–75% of the pulmonary volume; $FEF_{75–85}$ = forced expiratory flow at 75–85% of the pulmonary volume; FVC = forced vital capacity; PEF = peak expiratory flow; TWA = time-weighted average

A small number of occupational studies have examined nonlethal respiratory tract effects and observed associations with respiratory symptoms, spirometry parameters, and pulmonary changes (see Table 2-5). As with the mortality studies, workers in these studies often were exposed to other airborne metals. An industrial hygiene survey reported an association between self-reported, work-related respiratory

symptoms among welders in New Zealand compared with non-welders (Fishwick et al. 2004). The welders were exposed to airborne nickel concentrations in the range of 0.001–0.002 mg/m^3 (Fishwick et al. 2004). Reduced vital capacity and expiratory flows were observed in 90 stainless steel welders exposed to elevated levels of nickel and chromium without respiratory protection or local area ventilation devices (Kilburn et al. 1990). Ninety welders were selected to participate in the study and results were compared against the predicted values obtained through regression analysis of a random population of men (reference population). When results in welders were stratified based on smoking status, among nonsmokers, only the forced expiratory flow at 25–75% of the pulmonary volume ($FEF_{75–85}$) was significantly different from the predicted measurement based on the reference population, thus suggesting that current smoking status may have contributed to the observed effects. The study also found that the prevalence of chronic bronchitis was higher among all exposed welders regardless of smoking status when compared to predicted values from the reference population. Although these data provide suggestive evidence of respiratory effects in welders, the study is limited by co-exposure to chromium as well as the use of predicted population values for comparison, rather than a comparison group of non-nickel-exposed welders.

In a cross-sectional study of 186 welders in China, end-of-shift spirometry was assessed along with urinary nickel concentration as a measure of exposure (Wu et al. 2022). Peak expiratory flow (PEF) was inversely related to urinary concentration of nickel, while neither forced vital capacity (FVC) nor forced expiratory volume in the first second (FEV_1) was associated with urinary nickel concentration. Based on reported concentrations of 16 metals in urine, the welders had co-exposures to several metals; however, statistical models accounting for other metals also showed the association between nickel and PEF (Wu et al. 2022). Air exposure levels of nickel and other metals were not reported.

Examination of chest radiographs of nickel sinter plant workers exposed to nickel while wearing protective masks at concentrations as high as 100 mg/m^3 did not reveal an increase in small irregular opacities, which would be indicative of an inflammatory or fibrogenic response in the lungs (Muir et al. 1993). Another study, which did not state if personal protective equipment was used, found an increased risk of moderate pulmonary fibrosis (defined as median International Labour Organization [ILO] score ≥1/0) among nickel refinery workers with cumulative exposure to soluble nickel or sulfidic nickel (Berge and Skyberg 2003). Although there were indications of dose-response trends for cumulative exposures to either soluble or sulfidic nickel, the odds ratios were no longer significant after adjusting for age, smoking, and exposure to asbestos (Berge and Skyberg 2003).

In a cohort study of 1,424 nickel pyrometallurgical workers in Russia, Syurin and Vinnikov (2022) reported higher worker compensation claims for occupational bronchitis and occupational asthma among workers with higher nickel exposures. The mean annual air concentrations to which the workers were exposed ranged from 0.198 to 6.670 mg Ni/m^3 depending on the job category. The study did not control for tobacco use, and cigarette smoking was also a strong independent predictor for both bronchitis and asthma claims. The use of worker compensation claims for outcome evaluation is a significant limitation of this study.

Several case studies of workers exposed to nickel corroborate the respiratory system as a sensitive endpoint of inhalation exposure. Asthma induced by occupational exposure to nickel has been documented in a small number of case reports (Dolovich et al. 1984; Novey et al. 1983; Shirakawa et al. 1990). Asthma can result from either primary irritation or an allergic response. Lung injury was seen in a 50-year-old welder who accidentally inhaled an unknown concentration of nickel fumes that were being sprayed while not wearing any personal protective equipment (Kunimasa et al. 2011). The patient immediately developed a persistent strong cough and a chest radiograph 3 days later showed reticular opacities in middle and lower lung fields, while a computed tomography (CT) scan of the chest showed bilateral nonsegmental ground-glass opacities. A 29-year-old metallic coating and nickel-plating worker, exposed for 5 years, presented with nasal septal perforation; exposure was further indicated by elevated nickel concentrations in serum and urine samples (Bolek et al. 2017). A 27-year-old male metalworker presented with nasal obstruction and mild right-sided epistaxis and reported 6 years of exposure to a dry furnace dust of "nickel matte" (50% nickel, 30% copper, 20% sulfur, and trace amounts of other metals) (Peric and Vukomanovic Durdevic 2020). Histological examination of a lesion in the paranasal sinuses showed an inflammatory nasal polyp.

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 Fischer-344 rats, chronic lung inflammation was observed at the lowest nickel sulfate (0.7 mg Ni/m^3) and 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); the results of the NTP (1996a, 1996b, 1996c) studies are also presented in Dunnick et al. (1988). 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 were also present. Peribronchiolar/perivascular

inflammation was also observed in rats exposed to 0.44 mg Ni/m^3 as nickel subsulfide for 5 days (6 hours/day) (Efremenko et al. 2014). Exposure to ≥0.7 mg Ni/m^3 as nickel sulfate also resulted in bronchiolar epithelium degeneration in rats (Efremenko et al. 2017a, 2017b; NTP 1996c). Consistent with these findings is the observation of alveolitis in Fischer-344 rats exposed to 0.44 mg Ni/m^3 as nickel subsulfide 6 hours/day for 7 days (Benson et al. 1995b). Additionally, exposure to 1.83 mg Ni/m^3 as nickel subsulfide resulted in alveolitis and alveolar proteinosis after 4 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 mg Ni/m^3 as nickel sulfate, nickel subsulfide, and nickel oxide, respectively (NTP 1996a, 1996b, 1996c).

When exposed for 20 days over 4 weeks, five of five rats exposed to 0.11 mg Ni/m^3 had minimal to mild alveolar inflammation. No effects were seen at 4 weeks of exposure to concentrations ≤0.06 mg Ni/m^3 (Efremenko et al. 2014).

As with acute-duration 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) NTP 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. Similar lung effects (alveolitis, perivascular/peribronchiolar inflammation, and bronchiolar epithelial degeneration) were observed in rats exposed to 0.04 mg Ni/m^3 as nickel subsulfide or 0.11 mg Ni/m^3 as nickel sulfate 6 hours/day, 5 days/week for 4 or 13 weeks (Efremenko et al. 2017a, 2017b; Oller et al. 2023). Comparison of lesions showed that the incidence and severity of perivascular/peribronchiolar lesions and alveolar type II cell hyperplasia was higher in rats exposed to nickel subsulfide (Oller et al. 2023). 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). Similarly, localized interstitial pneumonia, represented by lymphoid infiltration and fibrosis of alveolar septa, emphysema, and atelectasis of varying degrees, was seen in rats exposed to 0.5 mg Ni/m^3 as nickel oxide for 1 month (Horie et al. 1985).

Several 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 evaluated (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 part of the normal physiologic response to inhaled particles, and it is not believed to compromise the lung's ability to clear foreign matter. This is supported by results from Oller et al. (2023) where the incidence of alveolar macrophage hyperplasia was similar between controls and groups of rats exposed to concentrations of nickel sulfate or nickel subsulfide up to 0.22 and 0.44 mg Ni/m^3, respectively. However, the increased severity of this lesion appears to be concentration related (Oller et al. 2023). At higher nickel concentrations, mild to moderate changes in alveolar macrophage hyperplasia were found. 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), granulomatous inflammation was observed in rats exposed to 3.9 mg Ni/m^3 as nickel oxide (NTP 1996a), and alveolar wall thickening was observed in rats exposed to 0.12 mg Ni/m^3 as nickel oxide (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 0.03 mg Ni/m^3 (NTP 1996c), 0.11 mg Ni/m^3 (NTP 1996b), and 0.49 mg Ni/m^3, respectively (Benson et al. 1995a).

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/m^3 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/m^3 (NTP 1996a); however, perivascular lymphocyte infiltrates were observed at 3.9 and 7.9 mg Ni/m^3 (NTP 1996a). Interstitial pneumonia has also been observed in mice exposed to 0.22 or 0.98 mg Ni/m^3 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/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c), interstitial infiltrates at ≥0.44 or 0.44 mg Ni/m^3 as nickel subsulfide or nickel sulfate, respectively (NTP 1996b, 1996c), and fibrosis at 0.44 and 0.88 mg Ni/m^3 as nickel sulfate or nickel subsulfide, respectively (NTP 1996b, 1996c). As with 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 3.9 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c).

Chronic-duration exposure to nickel (6 hours/day, 5 days/week for 2 years) resulted in chronic active lung inflammation (e.g., pneumonitis) in rats and mice at 0.06 mg Ni/m^3 as nickel sulfate, in rats at ≥0.11 mg

Ni/m^3 as nickel sulfide (NTP 1996b; Ottolenghi et al. 1975), in mice at ≥0.44 mg Ni/m^3 as nickel subsulfide (NTP 1996b), in rats at ≥0.2 mg Ni/m^3 as nickel oxide (NTP 1996a; Tanaka et al. 1988), and in mice at 1 mg Ni/m^3 as nickel oxide (NTP 1996a); the results of the NTP (1996a, 1996b, 1996c) studies are also presented in Dunnick et al. (1995). Additional lung effects that were found at the same dose levels as inflammation included alveolar epithelium hyperplasia (or bronchiolization), fibrosis in rats and mice exposed to nickel subsulfide (NTP 1996b), and bronchiolization and/or alveolar proteinosis in mice exposed to nickel oxide (NTP 1996a; Takenaka et al. 1985). Apart from the NTP (1996c) study of nickel sulfate in rats, NOAEL values for respiratory effects following chronic-duration exposure were not identified.

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-duration 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 evaluated, 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/m^3 as nickel sulfate and 1.96 mg Ni/m^3 as nickel oxide at the end of the 6-month exposure period and 4 months after exposure termination. Horie et al. (1985) reported localized interstitial pneumonia in rats exposed 6 hours/day, 5 days/week to 0.5 mg Ni/m^3 as nickel oxide for 1 month. At 12 and 20 months after termination of exposure to 6.3 mg Ni/m^3, 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). In studies examining the lungs and nasal cavity, the nasal lesions were 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/m^3 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. After a recovery period of 22 days, the only change that remained was fewer sensory cilia, indicating that the effects of an intermediate-duration exposure to nickel were reversible.

A case-series examined 20 female patients who presented with chronic rhinitis (nasal inflammation); upon allergen testing, all females only had a positive reaction to nickel sulfate in patch testing (Brera and Nicolini 2005). The study authors suggested that the rhinitis was due to nickel allergy, further demonstrated by reduced nasal and bronchial symptoms in patients who had accepted a "strict and prolonged diet low in nickel content."

Respiratory effects have also been observed in animals following oral exposure to nickel. Irregular respiration was one of several clinical signs of nickel toxicity observed in rats administered doses of nickel sulfate ≥111.6 mg Ni/kg/day for 3 days (Oller and Erexson 2007). Pneumonitis was observed in 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 fluid (BALF) and lung tissues, including increases in protein levels in BALF at ≥14.4 mg Ni/kg/day, decreases in alkaline phosphatase (ALP) activity in BALF at ≥5.75 mg Ni/kg/day, and decreases in ALP 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 ALP activity was indicative of decreased activity of type II alveolar cells and that the increased total protein was indicative of increased air-blood barrier permeability. In a multigeneration study (EPA 1988a, 1988b), increased relative lung weights were observed in rats provided with nickel chloride in 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. Emphysema, bronchiectasis, 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).

Scratch tests and intradermal tests performed on a patient diagnosed with nickel-related asthma resulted in respiratory distress indicated by a more severe response to the tests when compared to the results from non-asthmatic controls (McConnell et al. 1973).

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

2.5 CARDIOVASCULAR

No increases in the number of deaths from cardiovascular diseases were reported in standardized mortality studies of workers exposed to nickel (Cornell and Landis 1984; Cox et al. 1981; Cragle et al. 1984). In addition, a panel study of 26 male boilermaker construction workers exposed to welding fumes observed no association between nickel concentration in airborne $PM_{2.5}$ (particulate matter with diameter ≤2.5 μm) during the day and nighttime heart rate variability (a measure of cardiovascular autonomic control) (Cavallari et al. 2008).

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. No studies were identified that examined cardiovascular effects in humans after dermal exposure to nickel.

Inhalation and oral exposure studies in animals have not reported cardiovascular effects. No histopathological alterations were observed in the hearts of rats or mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate 6 hours/day, 5 days/week for acute, intermediate, or chronic durations. In rats, the highest NOAEL values for nickel oxide, nickel subsulfide, and nickel sulfate were 23.6, 7.33, and 12.2 mg Ni/m^3, respectively, for a 16-day exposure (NTP 1996a, 1996b, 1996c); 7.9, 1.83, and 0.44 mg Ni/m^3, respectively, for 13-week exposure (NTP 1996a, 1996b, 1996c); and 2, 0.73, and 0.11 mg Ni/m^3, respectively, for 2 years (NTP 1996a, 1996b, 1996c). The highest NOAEL in rats exposed to nickel sulfide for 78–80 weeks was 0.63 mg Ni/m^3 (Ottolenghi et al. 1975). In mice, the highest NOAEL values for nickel oxide, nickel subsulfide, and nickel sulfate were 23.6, 3.65, or 1.4 mg Ni/m^3, respectively, for a 16-day exposure (NTP 1996a, 1996b, 1996c); 7.9, 1.83, and 0.44 mg Ni/m^3, respectively, for 13-week exposure (NTP 1996a, 1996b, 1996c); and 3.9, 0.88, and 0.22 mg Ni/m^3, respectively, for 2 years (NTP 1996a, 1996b, 1996c).

Cardiovascular effects were observed in transgenic mice exposed to nickel sulfate. Exposure of male mice to metallic nickel at 0.0004 mg Ni/m^3 6 hours/day, 5 days/week for 14 weeks resulted in vascular endothelial dysfunction indicated by increased aortic relaxation in $ApoE^{-/-}$ mice (Ying et al. 2013). At similar lower concentrations of exposure in ApoE mice, exposure induced microcirculatory dysfunction indicated by increases in adherent and rolling monocytes in the microcirculation was also observed in another study of $ApoE^{-/-}$ mice exposed to 0.00017 mg Ni/m^3 as nickel sulfate 6 hours/day, 5 days/week for 3 months (Xu et al. 2012). $ApoE^{-/-}$ mice are deficient in apolipoprotein E, which is implicated in cardiovascular diseases (Meir and Leitersdorf 2004). The relevance of these findings in humans is not known.

The results of oral exposure studies do not suggest that the heart is a target of nickel toxicity. Decreased heart weight was observed in rats administered via gavage 8.6 mg Ni/kg/day as nickel chloride for 91 days (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 (EPA 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).

No studies were identified that examined adverse cardiovascular effects in humans or animals after dermal exposure to nickel.

2.6 GASTROINTESTINAL

No studies were identified that examined gastrointestinal effects in humans after inhalation or dermal exposure to nickel. Symptoms of gastrointestinal distress were most frequently 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). The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. Of the 32 workers exposed, 20 reported symptoms including nausea (15 workers), abdominal cramps (14 workers), diarrhea (4 workers), and vomiting (3 workers).

The gastrointestinal symptoms persisted 1–2 days in 10 workers who were then hospitalized. Although the actual contribution of boric acid to these effects is not known, the study authors indicated 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 (Sunderman et al. 1988).

Histopathological examinations of the gastrointestinal tract of mice and rats exposed to airborne nickel sulfate, nickel subsulfide, or nickel oxide for 6-hour exposures over 12 days did not reveal any changes at concentrations as high as 12.2, 7.33, or 23.6 mg Ni/m^3, respectively, in rats and 1.4, 3.65, or 23.6 mg Ni/m^3, 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/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic-duration exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice to 0.22, 0.88, or 3.9 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, did not result in microscopic changes in the gastrointestinal tract (NTP 1996a, 1996b, 1996c). Continuous chronic-duration exposure (6 hours/day, 5 days/week) of rats to 0.63 mg Ni/m^3 as nickel sulfide for 78 weeks also did not affect the microscopic appearance of the intestines (Ottolenghi et al. 1975).

Discolored gastrointestinal contents, ulcerative gastritis, and enteritis 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). 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 2000a, 2002) have not reported gastrointestinal effects.

No studies were identified that examined adverse gastrointestinal effects in humans or animals after dermal exposure to nickel.

2.7 HEMATOLOGICAL

No studies were identified that examined hematological effects in humans after inhalation or dermal exposure to nickel. A transient increase in blood reticulocytes was observed in 10 workers who were hospitalized for gastrointestinal symptoms after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). These workers were among 20 workers who reported symptoms following exposure and were hospitalized due to the 1–2-day persistence of clinical gastrointestinal symptoms. 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.

Several 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/m^3 as nickel oxide for 28 days (Weischer et al. 1980); no significant alterations were observed at 0.785 mg Ni/m^3. The biological significance of a decrease in hematocrit level in the absence of hemoglobin or erythrocyte alterations is not known and lacks a clear dose-response. In nonpregnant females continuously exposed to nickel oxide for 21 days, increases in hematocrit and hemoglobin levels were observed at ≥0.8 mg Ni/m^3; an increase in mean cell volume and a decrease in erythrocyte levels were observed at ≥1.6 mg Ni/m^3 (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/m^3 6 hours/day, 5 days/week for 2 years (NTP 1996b). Chronic-duration exposure of rats to nickel oxide or nickel sulfate at concentrations up to 2 or 0.11 mg Ni/m^3, respectively, and chronic-duration exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in significant hematological effects (NTP 1996a, 1996b, 1996c). Oller et al. (2008) observed increases in hemoglobin and hematocrit levels in rats after 78 weeks of exposure to concentrations ≥0.1 mg Ni/m^3 as metallic nickel. These same rats showed labored breathing and chronic lung inflammation. As noted by NTP (1996b), increases in hematocrit, hemoglobin, and erythrocytes are consistent with erythropoietin production in response to tissue hypoxia, possibly because of the nickel-induced lung damage.

Hematological effects have also been reported in animals orally exposed to nickel. Rat studies have indicated that intermediate-duration exposure to ≥0.7 mg Ni/kg/day as various nickel salts produces hematological effects. Effects included a decreased hemoglobin level in rats exposed to 25 mg Ni/kg/day as nickel acetate in the diet for 6 weeks (Whanger 1973), decreased erythrocytes and platelet counts, and increased white blood cell (WBC) levels in mice exposed to 36 mg Ni/kg/day as nickel sulfate in the diet for 28 days (Dahdouh et al. 2016), increased 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 increased platelet counts in rats administered via gavage 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988). Two years of daily exposure to doses of nickel sulfate hexahydrate up to 11.16 mg Ni/kg/day in rats did not result in significant exposure-related changes in hematological parameters including hemoglobin and hematocrit levels (Heim et al. 2007). No hematological effects were observed in rats administered via gavage 11.2 mg Ni/kg/day as nickel sulfate (Heim et al. 2007) or in rats exposed to 187.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976). Low hematocrit levels were observed in dogs after chronic-duration dietary exposure to 62.5 mg Ni/kg/day as nickel sulfate (Ambrose et al. 1976).

No studies were identified that examined adverse hematological effects in humans after dermal exposure to nickel.

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

2.8 MUSCULOSKELETAL

Few studies were identified that examined musculoskeletal effects in humans after exposure to nickel. In a prospective cohort study of 1,424 male workers involved in pyrometallurgical nickel production, Syurin and Vinnikov (2022) observed no association between nickel exposure and workers' compensation claims for "musculoskeletal disorders of vertebral origin." The use of compensation claims to assess outcomes is a significant limitation of this study. 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). This worker was among 20 workers who reported symptoms, primarily gastrointestinal, after 32 workers 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.

No histological alterations were observed in the bone of rats and mice exposed to nickel sulfate 6 hours/day for 12 or 16 days (highest NOAEL is 12.2 mg Ni/m^3), 5 days/week for 13 weeks (0.44 mg Ni/m^3) or 5 days/week for 2 years (0.11 and 0.22 mg Ni/m^3 for rats and mice, respectively) (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/m^3 for 16 days (12 or 16 days), 7.9 mg Ni/m^3 for 13 weeks, or 2 (rats) or 3.9 mg Ni/m^3 (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/m^3 for 13 weeks or 0.73 mg Ni/m^3 for 2 years, or mice at 7.33 mg Ni/m^3 for 16 days, 1.83 mg Ni/m^3 for 13 weeks, or 0.88 mg Ni/m^3 for 2 years (NTP 1996b).

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).

No studies were identified that examined adverse musculoskeletal effects in humans or animals after dermal exposure to nickel.

2.9 HEPATIC

A prospective cohort study of nickel-plating workers found that nickel exposure affects hepatic inflammatory function (Kalahasthi et al. 2006). Workers (n=69) were grouped by no, moderate, or high exposure indicated by nickel levels in blood, and the highest exposed group had significantly elevated serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) levels (Kalahasthi et al. 2006). Only AST was elevated among workers in the moderate exposure group. This study is limited by lack of information on the exposure levels and the study authors did not provide information on possible exposure length.

A transient increase in serum bilirubin levels was observed in 3 of 10 workers who were hospitalized with primarily gastrointestinal symptoms 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 or who were hospitalized (20 of 32) 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.

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/m^3, respectively, in rats and 1.4, 12.2, or 23.6 mg Ni/m^3, 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/m^3 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Following chronic-duration exposure, no histological changes were observed in the livers of rats exposed to nickel sulfide at 0.63 mg Ni/m^3 (Ottolenghi et al. 1975) or 0.73 mg Ni/m^3 (NTP 1996b), to nickel oxide at 0.9 mg Ni/m^3 (Tanaka et al. 1988) or 2 mg Ni/m^3 (NTP 1996a), or to nickel sulfate at 0.11 mg Ni/m^3 (NTP 1996c). Chronic-duration exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the liver (NTP 1996a, 1996b, 1996c).

Oral exposure studies do not provide strong evidence that the liver is a target of nickel toxicity. Increased serum enzymes (ALT and AST) were observed in rats administered 7.6 mg Ni/kg/day as nickel sulfate for 21 days (Adeyemi et al. 2017), 17.06 mg Ni/kg/day as nickel sulfate in drinking water (Kamal et al. 2012), and 17.05 mg Ni/kg/day as nickel sulfate in drinking water for 21 days (Mahmoud et al. 2011). Altered serum lipid levels (increased total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol) were also observed in the Adeyemi et al. (2017) rat study.

However, no histological alterations have been observed in rats administered 22 mg Ni/kg/day as nickel sulfate via gavage for 90 days (Springborn Laboratories 2002), rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water (Obone et al. 1999), rats administered 2.2 mg Ni/kg/day as nickel sulfate for 16 weeks (Springborn Laboratories 2000b), or mice exposed to 150 mg Ni/kg/day as nickel sulfate in drinking water for 180 days (Dieter et al. 1988).

No studies were identified that examined 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.

Focal necrosis was observed in rats dermally exposed to 60 mg Ni/kg as nickel sulfate for 30–60 days (Mathur et al. 1977). There was no indication that the animals were prevented from licking the nickel from the skin; therefore, these effects could have resulted from oral exposure.

2.10 RENAL

Marked tubular necrosis was observed in the kidneys of a man who died of ARDS 13 days after a 90-minute exposure to a very high concentration, simulated by the study authors to be 382 mg/m^3 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 >100 μg/L; urinary β2-microglobulin levels were not significantly altered in workers with urine nickel levels <100 μg/L. Urinary levels of total proteins, β2-microglobulin, retinol binding protein, and N-acetyl-β-D-glycosaminidase (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/m^3 (Vyskocil et al. 1994a). Although the average exposure concentration was the same for women and men, women may have been 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 biomarkers of effect 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 <60 μg/L. Multiple 24-hour urine collections were collected from each participant. 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 three or more voids (multiple samples from a participant), the average levels were within the normal range. 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).

A transient increase in urine albumin levels was observed in 3 of 10 workers who were hospitalized with primarily gastrointestinal symptoms after drinking water during one work shift from a water fountain

contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Among 32 exposed workers, 20 reported symptoms and 10 had to be hospitalized due to the persistence of gastrointestinal symptoms. 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.

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/m^3, respectively, for 16 days (12 days in a 16-day period) (NTP 1996a, 1996b, 1996c), ≤0.44, 1.83, or 7.9 mg Ni/m^3, respectively, for 13 weeks (NTP 1996a, 1996b, 1996c), or 0.9 mg Ni/m^3 as nickel oxide for 12 months (Tanaka et al. 1988). Chronic-duration exposure of rats to nickel oxide (NTP 1996a; Tanaka et al. 1988), nickel subsulfide (NTP 1996b), nickel sulfate (NTP 1996c), or nickel sulfide at concentrations up to 2, 0.73, 0.11, or 0.63 mg Ni/m^3, 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/m^3, respectively (NTP 1996a, 1996b, 1996c).

Changes in serum urea are reported in 21- and 28-day studies in male rats exposed to concentrations of 0.8 and 0.178 mg Ni/m^3 as nickel oxide, respectively (Weischer et al. 1980); however, the findings were inconsistent, with increased urea levels after 21 days of exposure and decreased levels after 28 days of exposure. The study did not include a histopathological examination of the kidney. In a chronic-duration, 104-week study, granular brown pigment consistent with hemosiderin was observed in the kidneys of rats exposed to 0.4 mg Ni/m^3 as metallic nickel (Oller et al. 2008).

Renal effects have been reported in animals orally exposed to nickel. The effects included alterations in serum and urine parameters suggestive of impaired renal function and histological alterations. 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 (LDH) and NAG levels and β2-microglobulin levels) were observed in male and female rats exposed to 6.9 and 7.6 mg Ni/kg/day, respectively, as nickel sulfate in the drinking water for 3–6 months (Vyskocil et al. 1994b). Urinary albumin levels, a marker of glomerular barrier dysfunction, were 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 study

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. A 28-day study in rats exposed to 36 mg Ni/kg/day as nickel sulfate in the diet reported proximal tubule degeneration with tubular necrosis and inflammation (Dahdouh et al. 2016). Renal dysfunction was further indicated by increases in serum urea, uric acid, and creatinine. Another intermediate-duration oral study reported increased plasma creatinine and urea levels in rats administered 7.6 mg Ni/kg/day as nickel sulfate for 21 days (Adeyemi and Elebiyo 2014). The study investigators also reported thickening of the glomerular wall, mild nephrosis, and necrosis; however, no incidence data were provided to assess whether the incidence was significantly different from controls. No histopathological lesions were observed in the kidneys of rats administered 2.2 mg/kg/day as nickel sulfate for 16 weeks (Springborn Laboratories 2000b), administered 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988), administered 22 mg Ni/kg/day as nickel sulfate for 90 days (Springborn Laboratories 2002), or exposed to 55 mg Ni/kg/day as nickel chloride in drinking water for 27–30 weeks (EPA 1988a, 1988b).

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; EPA 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).

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).

2.11 DERMAL

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 common effects of nickel exposure. Immunological studies indicate that dermatitis is an allergic response to nickel; therefore, studies of contact dermatitis in humans are discussed in Section 2.14.

There are limited data on the dermal effects in animals resulting from inhalation exposure. 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/m^3, 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/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic-duration exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice at concentrations up to 0.22, 0.88, or 3.9 mg Ni/m^3, respectively, did not result in microscopic changes in the skin (NTP 1996a, 1996b, 1996c).

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 (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.

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). Nickel sensitivity can also be induced in mice if oral exposure to nickel is reduced (Möller 1984; van Hoogstraten et al. 1991).

Adverse effects on the skin were observed in rats treated dermally with ≥40 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; Mathur et al. 1992). Additive effects were observed when nickel sulfate was given in combination with sodium lauryl sulfate.

2.12 OCULAR

No studies were identified that examined ocular effects in humans or animals after inhalation or dermal exposure to nickel.

In a pharmacokinetic study in humans, transient left homonymous hemianopsia (loss of sight in the same corresponding two left halves of the visual fields of both 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).

2.13 ENDOCRINE

Only one study pertaining to endocrine effects in humans exposed to nickel was located. Lai et al. (2021) examined 49 welders and 20 office workers in a shipyard in Taiwan on two occasions 1 year apart and measured urinary nickel and cortisol concentrations. A significant association between higher urinary nickel concentration and decreased urinary cortisol (β = -0.161 for a 1-µg/g increase in creatinine-adjusted urinary nickel concentration) was observed (Lai et al. 2021). The study authors suggested that decreases in cortisol levels could be associated with adrenal gland dysfunction; however, no other studies were located regarding effects on cortisol, adrenal glands, or other endocrine effects in humans following 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 days (6-hour exposure) 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/m^3 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/m^3, respectively, for the 13-week study. Alterations in serum glucose levels were observed in rats exposed to airborne nickel oxide 23.6 hours/day for 21–28 days (Weischer et al. 1980). In female rats, decreased serum glucose levels were observed at 0.8 and 1.6 mg Ni/m^3 but not at 3.2 mg Ni/m^3, whereas increased serum glucose levels were observed in males exposed to 0.385 mg Ni/m^3.

Some endocrine effects have been observed following chronic-duration inhalation exposure. Increased incidences of benign pheochromocytoma were observed in female rats exposed to 2 mg Ni/m^3 as nickel oxide 6 hours/day, 5 days/week for 2 years (NTP 1996a) and male rats exposed 0.11 mg Ni/m^3 as nickel subsulfide 6 hours/day, 5 days/week for 2 years (NTP 1996b). An increase in benign pheochromocytomas was also observed in male rats exposed to metallic nickel at 0.4 mg Ni/m^3 6 hours/day, 5 days/week for 104 weeks (Oller et al. 2008). The study investigators noted that the pheochromocytomas may be secondary to nickel-induced lung damage rather than a direct effect on the adrenal gland. The investigators also noted that there was an increased incidence of angiectasis in the adrenal glands in female rats exposed to 0.4 mg Ni/m^3 (Oller et al. 2008). No endocrine effects were observed in rats exposed chronically to nickel sulfate at concentrations up to 0.11 mg Ni/m^3, in rats exposed to 0.63 mg Ni/m^3 as nickel sulfide 6 hours/day, 5 days/week for 78 weeks (Ottolenghi et al. 1975), or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations of 3.9, 0.88, or 0.22 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c).

Decreased blood glucose levels were observed in female rats administered 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988).

No histological alterations were observed in the endocrine glands of rats administered 2.2 mg Ni/kg/day as nickel sulfate for 16 weeks (Springborn Laboratories 2000b) or 22 mg Ni/kg/day as nickel sulfate for 90 days (Springborn Laboratories 2002), or in rats and dogs exposed to 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).

2.14 IMMUNOLOGICAL

Several immunological effects have been reported in humans 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 were observed (Bencko et al. 1983, 1986). Significant increases in other serum proteins, which may be involved in cell-mediated immunity (including α1-antitrypsin, α2-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 eight workers with hard metal asthma attributed to cobalt exposure and who then underwent a bronchial provocation challenge to nickel sulfate

(Shirakawa et al. 1990). A relationship between nickel and cobalt sensitization is further supported by the finding that nickel-reactive IgE antibodies were observed in all of the workers (Shirakawa et al. 1990).

Contact dermatitis, which results from dermal exposure to nickel, is the most prevalent effect of nickel in the general population. Several studies indicated that a single oral dose of nickel given as nickel sulfate can result in a flare up of dermatitis in nickel-sensitive individuals (Burrows et al. 1981; Christensen and Möller 1975; Cronin et al. 1980; Gawkrodger 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 effects at low doses (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 studies have used many 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, soybeans, 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 of 12 women by day 4 after the start of the challenge, and although excess nickel was excreted 2 days after the last treatment, further exacerbation of hand eczema was observed in 10 of 12 women by day 11. Diet was no longer tracked after day 4 of the challenge period; therefore, it is not known whether participant diet affected the reported outcomes. In a second study by this group (Nielsen et al. 1999), 20 nickel-sensitized women with hand eczema were given water containing 0.012 mg Ni/kg. A flare-up of hand eczema was observed in 9/20 nickel sensitized subjects which began within 12 hours of exposure. In the control group, there was no change in the hand eczema.

Intermediate-duration studies suggest that longer-term oral exposure can be tolerated by some nickel-sensitive individuals. For example, Jordan and King (1979) found flaring of dermatitis in only 1/10 nickel-sensitive women given nickel sulfate orally at 0.007 mg/kg/day for 2 weeks. Repeated oral exposure may even serve to desensitize some individuals. Patch test responses to nickel were reduced in nickel-sensitive women given one weekly dose of 0.05 or 0.07 mg Ni/kg, but not 0.007 mg Ni/kg, as nickel sulfate for 6 weeks (Sjövall 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 sulfates every other day, or daily for up to 2–3 years, 7 subjects stopped the treatment for unspecified reasons and 7 subjects had reactivation of symptoms; complete (29) or partial (1) disappearance of symptoms for 2–4 years was observed in 30 subjects.

Oral exposure before 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 study authors 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 (nonsensitizing contacts) before oral exposure was also shown to interfere with oral tolerance induction.

Allergic contact dermatitis is a commonly reported effect in humans exposed to nickel. There are many studies reporting the prevalence of positive patch tests to nickel among clinical patients suspected of allergic contact dermatitis, but few recent studies of the prevalence of positive results among the general

population as a whole (e.g., including non-sensitized individuals). However, in a meta-analysis of 44 studies (of nonclinical populations), the pooled data from 34,102 subjects patch tested for nickel allergy indicated a prevalence of 11.4% (95% confidence interval [CI] 9.4–14.5%) among the general population (Alinaghi et al. 2019), with prevalences in females and males estimated at 15.7% (14,873 women tested) and 4.3% (11,157 men tested), respectively.

The prevalence of nickel allergy among metalworkers has also been studied. Alinaghi et al. (2023) conducted a meta-analysis of 21 studies of metalworkers and estimated a pooled (n=3,908 subjects) prevalence for positive nickel patch test results of 13.5% (95% CI 9.6–18.0%).

Table 2-6 shows recent studies reporting the prevalence of positive results to nickel sulfate patch testing among patients with suspected allergic contact dermatitis or other allergic conditions. As Table 2-6 indicates, the prevalence of positive results in these studies ranged between 13 and 41%. Bach et al. (2022) observed differing results (29–41%) depending on the formulation tested, with higher prevalence observed with 5% nickel sulfate in petrolatum compared with 2.5%. As discussed below, both age and gender modify the prevalence of nickel allergy.

Table 2-6. Prevalence of Positive Nickel Sulfate Patch Test Results in Dermatology/Allergy Patients[a]

Reference	Number of subjects (sex)	Study population (location and years of study)	Overall prevalence
Bach et al. 2022	192 (M and F, all ages)	Patients at dermatology and allergy center (Denmark, 2020)	29–41% depending on test preparation
Barwari et al. 2023	439 children (M and F)	Patients with suspected allergic contact dermatitis (Netherlands, 2015–2021)	20.3%
Cai et al. 2021	122 adults (M and F) in Russia 126 adults (M and F) in China	Patients with allergic dermatosis (Russia and China, year[s] of study not specified)	25.2% (Russia) 30.7% (China)
Coşgun et al. 2023	50 adult cases (M and F) 40 healthy adults (M and F)	Patients with IBS (Turkey, 2018)	38% (IBS patients) 17.5% (healthy subjects)
DeKoven et al. 2023	4,121 (M and F, all ages)	Patients undergoing patch testing at North American Contact Dermatitis Group (United States and Canada, 2019–2020)	18.2%
Dugonik et al.2020	15,171 (M and F, all ages)	Patients undergoing patch testing (Slovenia, 2008–2017)	16.33%
Isaksson et al. 2021	1,356 (M and F)	Patients undergoing patch testing (Sweden, 2018)	13.3%

Table 2-6. Prevalence of Positive Nickel Sulfate Patch Test Results in Dermatology/Allergy Patients[a]

Reference	Number of subjects (sex)	Study population (location and years of study)	Overall prevalence
Johnson and Yu 2023	1438 (M and F, all ages)	Patients with suspected allergic contact dermatitis (United States, 2017–2022)	21.5%
Kazan et al. 2023	61 children (M and F)	Patients undergoing patch testing (Turkey, 2013–2021)	13.1%
Koumaki et al. 2020	75 (M and F, all ages)	Patients undergoing patch testing (Greece, 2014–2018)	17.3%
Mukovozov et al. 2022	3,263 (M and F, all ages)	Patients at contact dermatitis clinic (Canada, 2008–2020)	24.3%
Rizzi et al. 2020	140 (M and F, all ages)	Patients with lipid transfer protein allergy (Italy, 2019)	25.7%
Sahu et al. 2022	111 (M and F, all ages)	Patients with allergic contact dermatitis (India, year[s] of study not specified)	18.84%
Tam et al. 2020a	2,373, (M and F, all ages)	Patients with suspected allergic contact dermatitis (United States, 1990–2016)	19.8%
Tam et al. 2020b	150 (M and F, all ages)	Patients with suspected metal allergy (United States, 2007–2016)	26.2%
Uter et al. 2021	51,914 (M and F, all ages)	Patients undergoing patch testing at participating practices in European Surveillance System on Contact Allergies (Europe, 2015–2018)	17.6%
Warshaw et al. 2019	7,928 (M and F, all ages)	Patients undergoing patch testing at North American Contact Dermatitis Group (United States and Canada, 1998–2016)	18.2%

[a]This table includes a selection of the most recent studies (published during or after 2019) identified in the literature searches and is not intended to be a comprehensive summary of the available data.

F = females; IBS = irritable bowel syndrome; M = males;

Contact dermatitis and/or positive patch test results in response to nickel exposure are more frequently observed in females, particularly younger females, than in males or older individuals (Cherry and Galarneau 2021; Mukovozov et al. 2022; Thyssen and Menne 2010; Uter et al. 2003; Wantke et al. 1996). For example, a prospective cohort study of 554 men and 447 women entering the welding trade observed higher odds (relative to those entering electrical trades) of developing new onset dermatitis among women, but not among men (Cherry and Galarneau 2021). This difference appears to be related to previous nickel exposure rather than increased susceptibility. Prolonged exposure to nickel in consumer products, especially jewelry, is often a sensitizing source. An association has been observed between skin piercing and nickel sensitivity (Akasya-Hillenbrand and Ozkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widström 1985; Meijer et al. 1995; Uter et al. 2003; Warshaw et al. 2017). For

example, a large analysis of patch test results from 17,912 patients in North America reported that the prevalence of positive nickel patch test results was related to the number of piercings: 14.3% of patients with a single piercing tested positive while 34.0% of patients with five or more piercings tested positive (Warshaw et al. 2017). The prevalence of nickel allergy was 9% among girls (aged 8, 11, and 15 years; 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 Widström 1985). In a study in school children aged 7–12 years, 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 years) 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) has 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 have shown a dose-response relationship between the amount of nickel and the prevalence and/or severity of the test response (Emmett et al. 1988; Eun and Marks 1990; Fischer et al. 2005, 2007). Fischer et al. (2005) synthesized the findings of eight dose-response studies of single occluded nickel patch tests and reported that 5 and 10% of sensitized individuals responded positively to concentrations of 0.44 and 1.04 µg Ni/cm^2, respectively. Menné 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%, positive reactions to nickel were not observed. At 0.1%, 4/51 and 1/51 tested positive with and without 4% sodium lauryl sulfate, respectively. Menné et al. (1987) examined the nickel release into synthetic sweat from 111 different nickel alloys and the reactivity to these alloys in 173 nickel-sensitive individuals. With one exception (Inconel 600), alloys that released nickel into synthetic sweat at a rate of at least 1 µg/cm^2/week produced "strong" reactions. For those alloys releasing at least 1 µg/cm^2/week, the prevalence of positive patch test results (any reaction) ranged from 30 to 55% in this study (Menné et al. 1987).

Fischer et al. (2007) showed that the total nickel dose also influenced the patch-test response in sensitive individuals. These study authors applied the same nickel dose per unit area (6.6, 15, 66, or 150 µg Ni/cm^2) to differing skin surface areas (patch sizes of 0.5 or 1.13 cm^2), resulting in total doses of 3.3–169.5 µg Ni. Each of 20 patients (18 women and 2 men) with previously confirmed nickel allergy was tested simultaneously with all four concentrations and both patch sizes under occlusion on the skin of the back. The mean score obtained 2 days after application was significantly higher when a dose of 15 µg Ni/cm^2 was applied to the larger surface area (total dose of 17 µg Ni) compared with the smaller surface area (total dose of 7.5 µg Ni). At higher doses, there were no differences (between patch sizes) in response score, and prevalence of skin reactions did not differ significantly at any dose. In testing of the same patients using repeated open application of aqueous nickel sulfate, patients reacted sooner to application of 6.64 µg Ni/cm^2 when a large area was exposed (mean 4.3 days to reaction) than when a small area was exposed (mean 5.1 days to reaction). There were no differences by exposed area when the dose per area was 15 µg Ni/cm^2 (Fischer et al. 2007). Based on these findings, the study authors suggested that the exposed area (and therefore the total dose of nickel to the skin) could influence allergic response when the dose per unit area is in the range of the elicitation threshold concentration.

Some studies have suggested that nickel allergy may be linked to respiratory symptoms. In a case-series of 20 female patients who presented with chronic rhinitis (nasal inflammation), the patients exhibited positive reactions to nickel, but not chromium or cobalt, in patch testing; prick tests for nickel were positive for 7 of the 20 patients (Brera and Nicolini 2005). The patients were also subjected to nasal provocation with nickel sulfate solution on a piece of cotton wool; this provocation yielded rhinorrhea, sneezing, and mucosal edema within 30 minutes. In a prospective cohort study of 2,051 young adults, self-reported nickel allergy was associated with higher odds of developing wheezing during ~5 years of follow-up (compared with those not reporting nickel allergy) (Kolberg et al. 2020). Male subjects also exhibited higher odds of incident asthma (Kolberg et al. 2020). However, the study authors relied only on self-reported nickel allergy and did not perform confirmatory testing.

Animal studies have evaluated several aspects of immune function following inhalation, oral, or dermal exposure to nickel. Alveolar macrophage function was evaluated in several inhalation studies. A significant reduction in pulmonary alveolar macrophage phagocytic activity was observed in mice exposed to 0.5–0.66 mg Ni/m^3 as nickel chloride for 2 hours (Adkins et al. 1979) or exposed to 0.47 mg Ni/m^3 as nickel oxide or 0.45 mg Ni/m^3 as nickel subsulfide 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/m^3 as nickel chloride 6 hours/day, 5 days/week for 4– 6 weeks (Bingham et al.

1972; 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/m^3 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/m^3 as metallic nickel 6 hours/day, 5 days/week for 3–6 months (Johansson et al. 1980) or 0.6 mg Ni/m^3 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).

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/m^3 as nickel sulfate (NTP 1996c) and mice exposed to 0.88 mg Ni/m^3 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/m^3 as nickel subsulfide (NTP 1996b), rats or mice exposed to 23.5 mg Ni/m^3 as nickel oxide (NTP 1996a), or mice exposed to 3.1 mg Ni/m^3 as nickel sulfate (NTP 1996c). In intermediate-duration studies, exposure for 6 hours/day, 5 days/week resulted in lymphoid hyperplasia in bronchial lymph nodes of rats exposed to 0.22, 0.22, or 2 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.44, 0.88, or 2 mg Ni/m^3 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/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.22, 0.44, or 1 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c). Exposure of rats to 0.1 mg Ni/m^3 as metallic nickel for 104 weeks resulted in increased incidence of minimal-to-severe histiocyte infiltrate in bronchial lymph nodes (Oller et al. 2008).

Several studies have examined the relationship between nickel exposures and acquired immune function. A concentration-related increase in susceptibility to *Streptococci* infection was seen in mice exposed to nickel chloride (≤0.5 mg Ni/m^3) for 2 hours and then infected either immediately or after a 24-hour recovery period (Adkins et al. 1979). Increased susceptibility was indicated by an exposure-related increase in mortality and decrease in relative mean survival time in exposure groups when compared to simultaneously infected non-nickel-exposed controls (Adkins et al. 1979). Increased mortality and

reduced survival time were also observed following a 2-hour exposure to 0.46 mg Ni/m^3 as nickel sulfate (Adkins et al. 1979). An additional group of mice, exposed to 0.66 mg Ni/m^3 as nickel chloride, developed septicemia from the *Streptococci* infection and had a reduced ability to clear the inhaled bacteria 96 hours after infection (Adkins et al. 1979). Other studies have found an impaired response to sRBCs in mice exposed to 0.25 mg Ni/m^3 as nickel chloride for 2 hours (Graham et al. 1978) or rats continuously exposed to 0.2 mg Ni/m^3 as nickel oxide for 4 weeks or 0.15 mg Ni/m^3 for 4 months (Spiegelberg et al. 1984). At lower concentrations, no immunosuppressive response to sRBCs was observed in mice exposed to 0.081 mg Ni/m^3 as nickel chloride for 24 hours (Buxton et al. 2021). A decreased resistance to a tumor challenge was also observed in mice exposed to 0.45 mg Ni/m^3 as nickel sulfate 6 hours/day, 5 days/week for 65 days (Haley et al. 1990).

Oral exposure studies have evaluated histological alterations in immune tissues, alterations in lymphocytes, and immune function. Effects on the immunological system following exposure to ≥44 mg Ni/kg/day 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 mild splenic atrophy was observed at ≥108 mg Ni/kg/day. 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) at ≥44 mg Ni/kg/day; a marginal response to sRBCs 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/k g/day, decreases in granulocyte macrophage progenitor cells (CFU-GM) at ≥44 mg Ni/kg/day, and multipotential stem cells (CFU-S) at ≥108 mg Ni/kg/day. 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- 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 CD^{4+} T cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; increases in CD^{8+} 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 CD^{4+} T cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; a decrease in the ratio of CD^{4+} T cells to total cells at 28.8 mg Ni/kg/day; increases in CD^{8+} 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 CD^{8+} T cells to total cells at ≥5.75 mg Ni/kg/day; 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 (Ilbäck 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 dogs fed 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976).

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.

Mechanisms of Skin Sensitization. The mechanisms by which skin sensitization in humans is induced by dermal contact with nickel were reviewed by Petersen et al. (2018) and Saito et al. (2016) and are briefly summarized here. During the sensitization phase, nickel is absorbed into the skin where it activates keratinocytes to release pro-inflammatory cytokines. The cytokines upregulate and activate dendritic cells, which subsequently migrate to draining lymph nodes, where the dendrocytes present nickel in association with a major histocompatibility complex (MHC) peptide to naïve T-cells. Differentiation and proliferation of nickel-specific T-cells is followed by their migration to the skin, where these cells promote the allergic reaction upon re-exposure (elicitation phase) to nickel (Petersen et al. 2018; Saito et al. 2016).

The innate response to nickel may be mediated by the human toll-like receptor 4 (TLR4) (Saito et al. 2016). In experiments using TLR4-deficient mice, contact allergy was demonstrated in mice expressing the transgenic human TLR4 but not the mouse TLR4. Activation of TLR4 by nickel induces several

proinflammatory cell signaling pathways including NFκB, MAPK p38, and interferon regulatory factor 3, initiating the inflammatory response (Saito et al. 2016).

Experiments with different CD^{4+} T-cell clones from nickel-sensitive patients have identified several molecular interactions that result in presentation of nickel to CD^{4+} T-cells (Petersen et al. 2018). For example, the functional ligand for ANi-2.3 CD4+ T-cells is a complex of nickel with an MHC restriction element identified as HLA-DR52c and an unknown peptide produced by B-cells. In contrast, in SE9 CD^{4+} T-cells, nickel recognition does not depend on a specific MHC-associated peptide, but rather is believed to occur via direct linking and/or stabilization of intra-molecular bridges between the receptor and MHC-associated peptides. In other nickel-reactive CD^{4+} T-cell clones, nickel presentation was dependent on active antigen processing. While available information on nickel antigen presentation was obtained with CD^{4+} T-cells, similar mechanisms may operate in presentation to CD^{8+} T-cells (Petersen et al. 2018).

Differentiation of T-cells in response to nickel exposure leads to proliferation of several T-cell subtypes (Petersen et al. 2018). Comparisons between the T-cells in blood or skin obtained from healthy and nickel-allergic subjects have shown that allergic subjects have higher numbers of T-cells producing IL-17, IL-22, IFN-γ, and CCR6. Tc1, Th1, and Th17 cells have been identified as the primary effector cells in nickel allergy. Tolerance to nickel exposure, in contrast, appears to result from the induction of suppressor/regulatory T-cells (Treg, Tr1). The cell-mediated mechanism for tolerance was shown when naïve animals that received spleen and lymph node cells from animals that had been fed nickel also exhibited tolerance. In humans, tolerance to nickel was correlated with production of IL-10. This finding is consistent with the observation that T-cell clones from healthy individuals produced greater amounts of IL-10 than those from individuals allergic to nickel (Petersen et al. 2018).

2.15 NEUROLOGICAL

Few epidemiological studies of neurological effects in humans exposed occupationally to nickel were located. Syurin and Vinnikov (2022) observed no association between nickel exposure and workers' compensation claims for sensorineural deafness in a prospective cohort study of 1,424 male workers involved in pyrometallurgical nickel production. The use of compensation claims to assess the outcome is a significant limitation of this study. A cross-sectional study of 186 welders in China reported nonlinear dose-response relationships between urinary nickel concentration and three serum biomarkers of neural damage (neurofilament light chain, sphingosine-1-phosphate, and dopamine) but not a fourth

(prolactin) (Wu et al. 2023). The study authors reported that these biomarkers are involved in the development of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Wu et al. 2023); however, no studies examining neurological diseases in workers exposed to nickel were located.

A single case of generalized tonic-clonic seizure was reported in a 43-year-old with no prior history to indicate a cause, and upon further examination, that patient had elevated levels of nickel in urine (Denays et al. 2005). Acute nickel poisoning was then suspected as a coworker from the same workshop had been admitted a week prior with a first-time seizure and respiratory complaints.

Neurological effects of giddiness and weariness were observed among 20 of 32 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). It was estimated that the workers were exposed to 7.1–35.7 mg Ni/kg. Seven workers reported giddiness and six workers reported weariness within hours of the exposure. 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 man developed left homonymous hemianopsia (loss of sight in the same corresponding two left halves of the visual fields of both eyes) 7 hours after ingesting a single dose of 0.05 mg Ni/kg as nickel sulfate in drinking water. The condition lasted for 2 hours (Sunderman et al. 1989b). The appearance of the visual defect involving the same two left halves of the visual fields in both eyes occurred soon after the peak serum concentration of nickel was reached, leading the study authors to suspect a causal relationship between nickel exposure and the loss of sight/visual field defect. The doses given to other subjects were lowered to 0.018 and 0.012 mg Ni/kg with no adverse effects.

No studies were identified that examined adverse neurological effects in humans after dermal exposure to nickel.

Evaluation of the potential neurotoxicity of nickel in animals has primarily focused on histopathology and overt signs of toxicity; only one study evaluated neurobehavior. Microscopic examinations did not reveal any changes in the whole brains of rats or mice exposed to nickel as nickel sulfate hexahydrate, nickel oxide, or nickel subsulfide for 12 days (6-hour/day) 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/m^3 in Fischer-344 rats for nickel sulfate hexahydrate, nickel oxide, and nickel subsulfide, respectively, and 0.7, 23.6, and 3.65 mg/m^3 in B6C3F1 mice for nickel sulfate hexahydrate, nickel oxide,

and nickel subsulfide, respectively. Reduced spatial memory performance and reduced motor activity were observed in mice following a single exposure to 50 mg Ni/kg as nickel chloride (He et al. 2013).

In intermediate-duration studies, no histological alterations were observed in the whole brains of Fischer-344 rats and B6C3F1 mice exposed to 0.44, 7.9, or 1.83 mg Ni/m^3 as nickel sulfate hexahydrate, nickel oxide, or nickel subsulfide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Exposure of rats to 0.635 mg Ni/m^3 as nickel sulfate 6 hours/day for 16 days resulted in a nonsignificant decrease in bipolar receptor cells and atrophy in the septal olfactory epithelium (Evans et al. 1995). However, no changes of olfactory function were noted following completion of behavioral studies for olfactory absolute threshold (odor detection) and discrimination. Thinning (atrophy) of the epithelium appeared normal after 12 days of recovery, and carnosine, a neurochemical marker, was reduced in the olfactory epithelium only at 12 days of exposure. Carnosine levels in the olfactory bulb were reduced up to the 12^{th} day of exposure and returned to control levels by the 16^{th} exposure day. The study authors attributed the recovery of carnosine levels during the exposure period to a defensive response against continued exposure (Evans et al. 1995). In rats exposed to nickel sulfide at 0.63 mg Ni/m^3 for 78 weeks (6 hours/day, 5 days/week), histological changes were not observed in the brain (Ottolenghi et al. 1975). Chronic-duration exposure of Fischer-344 rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, or exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the whole brain (NTP 1996a, 1996b, 1996c).

A small number of oral exposure studies evaluate neurological endpoints. In a 90-day study, lethargy, ataxia, prostration, irregular breathing, and reduce 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 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. Hypoactivity and/or salivation was also observed in an unspecified number of rats administered ≥28 mg Ni/kg/day for 3 days (Oller and Erexson 2007). Microscopic examinations of whole brains did not reveal any changes in the brains of dogs treated with nickel sulfate at doses ≤62.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976). Two studies have evaluated neurobehavior. In mice administered a single dose of 50 mg Ni/kg as nickel chloride, increases in escape latency in the Morris water maze test, indicating impaired learning and spatial memory, and decreased total distance traveled in the open field test were observed (He et al. 2013). A study in rats exposed to 0.2 mg Ni/kg as nickel

chloride for 90 days (3 days/week) reported increased time to locate the escape hole in the Barnes maze test, which is indicative of impaired learning and spatial memory (Anyachor et al. 2023).

No studies were identified that examined adverse neurological effects in humans or animals after dermal exposure to nickel.

2.16 REPRODUCTIVE

Epidemiological studies of reproductive effects in humans exposed to nickel in the workplace are limited to two studies of nickel refinery operations in the Kona peninsula region of Russia. In addition to nickel exposure, the population in this region was exposed to "large" emissions of sulfur dioxide, dust, and copper (Vaktskjold et al. 2006). A higher rate of spontaneous abortions (15.9%) was reported among a group of 356 women who worked in a nickel hydrometallurgy refining plant in the Kola peninsula of Russia as compared to the rate (8.5%) in 342 local female construction workers (Chashschin et al. 1994). The analysis by Chashschin et al. (1994) did not account for potential confounders (e.g., tobacco or alcohol use or underlying disease), and the study authors did not provide any details of the control population of construction workers, precluding conclusions based on the results. In a case-control study of the same region, there was no significant association between maternal occupational exposure to nickel in early pregnancy and the risk of spontaneous abortion (Vaktskjold et al. 2008b). In this study of 474 cases and 4,571 controls, exposure was categorized as background, low, or high nickel based on maternal occupation and workplace at the beginning of pregnancy coupled with quantitative nickel air and urine measurements for representative workers (Vaktskjold et al. 2008b). As a sensitivity analysis, spontaneous abortion was evaluated using either the Kola Birth Registry or maternal questionnaire responses, and the results did not differ.

The potential reproductive toxicity of nickel has been examined in animal inhalation, oral, and dermal exposure studies. No histological alterations in reproductive tissues were observed in male rats exposed at 23.6, 7.33, and 12.2 mg Ni/m^3, or mice exposed at 23.6, 3.65 and 1.4 mg Ni/m^3 for 12-day exposure (6 hours/day) to nickel oxide, nickel subsulfide, and nickel sulfate hexahydrate, respectively (NTP 1996a, 1996b, 1996c). In intermediate-duration studies, sperm concentration was decreased by 21% in rats exposed to nickel oxide at 7.9 mg Ni/m^3, with no effects at 3.9 mg/m^3 (NTP 1996a). No effects on sperm motility, morphology, or concentration were observed in rats and mice exposed to nickel subsulfide or nickel sulfate at concentrations up to 1.83 and 0.44 mg Ni/m^3, respectively, or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate at concentrations up to 7.9, 1.83, or 0.44 mg Ni/m^3,

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 hexahydrate at ≤0.44 mg Ni/m^3, nickel oxide at ≤7.9 mg Ni/m^3, or nickel subsulfide at ≤1.83 mg Ni/m^3 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic-duration exposure of rats and mice to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, and exposure of mice to nickel oxide, nickel subsulfide, respectively, or nickel sulfate hexahydrate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the reproductive organs (NTP 1996a, 1996b, 1996c).

Several 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. Histological alterations have been observed in male reproductive tissues in some studies. Pandey et al. (1999) reported regressed epithelium and vacuolated cells 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. Additionally, interpretation of Pandey et al. (1999) is impeded by limited methodological details and possible improper tissue fixation. Käkelä et al. (1999) reported a statistically significant decrease in seminiferous tubule diameter in Wistar 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 appeared to be lower than control body weights; this may contribute to the histological findings in the maturing rats (Rehm et al. 2008). Toman et al. (2012) did not observe any exposure-related changes in relative testis weight in mice following 3–12 weeks of exposure to 4.5 mg Ni/kg/day as nickel chloride; however, histological alterations, including degeneration of seminiferous epithelium and empty spaces in the epithelium, indicating spermatogenesis disruption were observed (Toman et al. 2012). 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 Biogenics Corporation 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 16 weeks (Springborn Laboratories 2000b), 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 study authors 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 (Pandey and Srivastava 2000; Pandey et al. 1999), there were no significant alterations in the occurrence of a particular sperm abnormality; the total number of abnormalities was increased. Toman et al. (2012) did not observe any exposure-related changes in relative testis weight following 3–12 weeks of exposure to 4.5 mg Ni/kg/day as nickel chloride; however, significant changes were observed in the testis upon histological examination. The study authors observed signs of degeneration of seminiferous epithelium and empty spaces in the epithelium indicating spermatogenesis disruption (Toman et al. 2012). Sobti and Gill (1989) reported increases in sperm head abnormalities in mice administered via gavage of 23, 28, or 43 mg Ni/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 or the exposure duration were 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 16–18 weeks (Springborn Laboratories 2000b).

Nickel-induced alterations in fertility were evaluated in oral studies involving male-only, female-only, or male and female exposure. Male-only 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, when the exposure to 3.6 mg Ni/kg/day was extended to 42 days, there was a smaller impact on fertility; the fertility index was 83% in rats exposed for 42 days compared to 50% in rats exposed for 28 days (fertility index in the controls was 100%) (Käkelä et al. 1999). Female-only exposure to doses as high as 13 mg Ni/kg/day as nickel chloride in drinking water for 100 days prior to mating did not adversely affect

fertility in rats (Käkelä et al. 1999). In a study in which male and female rats were exposed to 3.6 (males) or 4.0 (females) mg Ni/kg/day as nickel chloride in drinking water for 28–76 days, decreased fertility was observed (Käkelä et al. 1999). In contrast to these findings, better reported studies have not found effects on fertility. No adverse effects on fertility were observed in a multigeneration study in which male and female rats were exposed to doses as high as 55 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to mating (EPA 1988a, 1988b), in a 1-generation study in which rats were administered 16.8 mg Ni/kg/day as nickel sulfate via gavage for 2-weeks prior to mating, during mating, and during gestation (Springborn Laboratories 2000a), in a 2-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 2000b), or in a multi-litter study in which female rats were exposed to doses as high as 31.6 mg Ni/kg/day (Smith et al. 1993).

Other reproductive effects that have been reported include an increased gestation length in the first P0 pregnancy in rats exposed to 30 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to mating and during gestation (EPA 1988a, 1988b) and decreased maternal prolactin levels in rats exposed to 31.6 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks (Smith et al. 1993). Several studies examined possible associations between nickel exposure and post-implantation loss and the occurrence of still births; these effects are discussed in the Section 2.17 (Developmental).

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.

2.17 DEVELOPMENTAL

A series of studies examined developmental effects in offspring of adults exposed to nickel from a nickel refinery in the Kola peninsula of Russia. In addition to nickel exposure, the population in this region was exposed to “large” emissions of sulfur dioxide, dust, and copper (Vaktskjold et al. 2006). An early investigation reported a higher incidence of unspecified structural malformations (16.9%) in the offspring of female nickel hydrometallurgy refining plant workers as compared to the incidence (5.8%) in female construction workers (Chashschin et al. 1994). However, this study did not consider potential confounders (e.g., tobacco or alcohol use or underlying disease) and did not provide any details of the

control population of construction workers, significantly limiting the information that can be obtained from the study. Subsequent, more rigorous epidemiological studies of birth outcomes based on data obtained from the Kola Birth Registry observed no association between maternal nickel exposure and the risk of delivering a small-for-gestational-age (SGA) newborn (Vaktskjold et al. 2007), delivering a newborn with a genital malformation (Vaktskjold et al. 2006), or delivering a newborn with musculoskeletal defects (Vaktskjold et al. 2008a) after adjustment for potential confounders. Maternal exposure in these studies was categorized as background, low, or high nickel based on maternal occupation and workplace at the beginning of pregnancy coupled with quantitative nickel air and urine measurements for representative workers (Vaktskjold et al. 2006, 2007, 2008a).

No studies were identified that examined developmental effects in humans after oral or dermal exposure to nickel.

One animal study evaluated the developmental toxicity of nickel following inhalation exposure. A decrease in fetal body weight was observed in the offspring of Wistar rats exposed to 1.6 mg Ni/m^3 as nickel oxide 23.6 hours/day on gestation days (GDs) 1–21 (Weischer et al. 1980). No effect on fetal body weight was observed at 0.8 mg Ni/m^3, although decreased maternal body weight gain was observed at this concentration. No effects on the number of fetuses or on the weight of the placenta were observed (Weischer et al. 1980).

The available animal data on developmental toxicity provide suggestive evidence that the developing fetus and neonates are sensitive targets of toxicity of soluble nickel compounds; developmental toxicity has not been evaluated following oral exposure to metallic nickel or insoluble nickel compounds. The most reported endpoint was 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, multi-litter, and multigeneration studies. The developmental effects were often reported at maternally toxic doses. Other developmental endpoints 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 (PND) 4 (56% versus 100% in controls), and litter size at PND 21 (1.3 pups versus 9.2 pups in controls) (Käkelä et al. 1999). However, when the male rats were exposed to

3.6 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 that examined female-only exposure to nickel also examined fetal loss and postnatal survival (El-Sekily et al. 2020; EPA 1983; Käkelä et al. 1999; Saini et al. 2013, 2014a, 2014b; Seidenberg et al. 1986; Smith et al. 1993). Increased fetal resorption sites were observed in mice administered 46.125 mg Ni/kg/day as nickel chloride on GDs 6–18 (El-Sekily et al. 2020). The study also reported an increase in stillborn fetuses at 184 mg Ni/kg/day. Decreased number of live fetuses per dam and reduced number of implantation sites were observed in mice administered nickel chloride at 46 mg Ni/kg/day on GDs 0–5 (Saini et al. 2014a) or at 184.5 mg Ni/kg/day on GDs 6–13 (Saini et al. 2013). Similarly, nickel chloride exposure to 92.25 mg Ni/kg/day on GDs 0–5 or 184.5 mg Ni/kg/day on GDs 6–13 or 14–18 resulted in decreased average litter size per day (Saini et al. 2014b). An increase in spontaneous abortions was observed in female mice exposed to 160 mg Ni/kg/day as nickel chloride in drinking water on GDs 2–17 (EPA 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 GDs 8–12 with 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 and during mating, gestation, and lactation resulted in decreased pup survival from birth to PND 4 (87 versus 100% in controls) and from PND 4 to 21 (52 versus 90% in controls) (Käkelä et al. 1999); no significant effects were observed at 4.0 mg Ni/kg/day. Pup mortality was also observed in a multi-litter study in which rats were exposed to 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 PND 1 was increased at 31.6 mg Ni/kg/day; no significant alterations were observed in the number of dead pups at PND 21. In the second litter, the number of litters with dead pups at birth was increased at 31.6 mg Ni/kg/day, the percentages of dead pups per litter at PND 1 was increased at ≥1.3 mg Ni/kg/day, and the percentage of dead pups at PND 21 was increased at 31.6 mg Ni/kg/day.

Offspring mortality was also observed in studies involving combined male and female exposure (Ambrose et al. 1976; EPA 1988a, 1988b; Käkelä et al. 1999; 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 and during mating, gestation, and lactation adversely affected the litter size at PND 21 and pup survival from PND 4 to 21 (Käkelä et al. 1999). 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, and 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 nickel chloride in the diet for 11 weeks prior to mating and 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 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 numbers of offspring (dead and alive) were progressively less with increasing nickel levels >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 6.4 for 0, 22.5, 45, and 90 mg/kg/day, respectively). In a 2-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 (EPA 1988a, 1988b). Increases in mortality were also observed in the F1b rats on PNDs 22–42; 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, including no effect on litter size, 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 another 2-generation study in which rats were administered up to 2.2 mg Ni/kg/day as nickel sulfate via gavage for 10 weeks prior to mating and during gestation and lactation (Springborn Laboratories 2000b).

Decreased fetal body weight was observed in the offspring of mice administered 92.25 mg Ni/kg/day as nickel chloride on GDs 6–13 (Saini et al. 2013). A study comparing birth weight in the offspring of mice administered nickel chloride at different stages of gestation suggests that the timing of the nickel exposure influences body weight (Saini et al. 2014b). The LOAELs for decreased birth weight were 46.125, 92.25, and 184.5 mg Ni/kg/day when the nickel chloride was administered on GDs 6–13, 14–18, and 0–5, respectively. With one exception, the lower pup body weights were maintained throughout the 6-week postnatal observation period. In postnatal week 6, the body weights of the pups of mice administered 92.25 mg Ni/kg/day on GDs 0–5 were also lower than controls (Saini et al. 2014b). Decreases in pup body weights were also reported in offspring in a multiple mating rat study of nickel chloride (EPA 1988a, 1988b). Decreased pup body weight was observed at 55 mg Ni/kg/day in the F1a pups, at 30 and 55 mg Ni/kg/day in the F1b pups, and at 55 mg Ni/kg/day in the F2a pups. Decreased pup body weight was also observed in the offspring of rats exposed to 90 mg Ni/kg/day as nickel sulfate in the diet

(Ambrose et al. 1976). Although decreases in growth have been observed, no alterations in the timing of developmental landmarks (pinna detachment, hair appearance, eye opening, vaginal opening, or testes descent) were observed in the offspring of mice administered up to 184.5 mg Ni/kg/day as nickel chloride on GDs 0–5, 6–13, or 14–18 (Saini et al. 2014b).

Several studies have reported increases in occurrence of skeletal abnormalities. Maternal exposure of mice to 46.125 mg Ni/kg/day as nickel chloride on GDs 6–13 resulted increased incidence of skeletal anomalies including reduced or fused sternebrae, absence or gap between the ribs, and reduced ossification (Saini et al. 2013). Maternal mouse administration to 46 mg Ni/kg/day as nickel chloride on GDs 0–5 also resulted in an increased incidence of reduced ossification of metatarsals and phalanges (Saini et al. 2014a). In another study by this group, increases in the occurrence of total limb anomalies and total tail anomalies were observed in the offspring of mice administered 184.5 mg Ni/kg/day as nickel chloride on GDs 6–13 (Saini et al. 2014b). Skeletal abnormalities were also reported in offspring of mice administered 46.125 mg Ni/kg/day as nickel chloride on GDs 6–13; abnormalities included incomplete ossification of the skull, vertebrae, ribs, and limbs, and unossified carpals, metacarpals, tarsals, metatarsals, and phalanges (El-Sekily et al. 2020). Neither the Ambrose et al. (1976) nor the EPA (1988a, 1988b) multigeneration study found a significant increase in the incidence of gross abnormalities in the surviving offspring of rats exposed to nickel. Käkelä et al. (1999) noted that the pups that died during lactation were runts (smaller or weaker animals in a litter): the heads were disproportionately large and the posteriors of the bodies were underdeveloped.

In the only study evaluating neurodevelopmental behavior, no effect on locomotor activity was observed following a figure 8 maze test in the offspring of mice treated by gavage at 45.3 mg Ni/kg/day as nickel chloride on GDs 8–12 (Gray et al. 1986).

2.18 OTHER NONCANCER

No data were located on other noncancer effects in humans or animals following inhalation, oral, or dermal exposure to nickel.

2.19 CANCER

The database of epidemiological studies evaluating cancer in nickel-exposed workers is extensive. IARC (1990, 2012) conducted an in-depth evaluation of the data for cancer in nickel refinery and smelter

cohorts from epidemiological studies published through ~2009. Their review concluded that nickel refinery workers exhibited increased risks of lung and nasal sinus cancers and that nickel smelter workers exhibited increased risks of lung cancer, based on studies included in IARC's (1990) review in addition to studies by Andersen et al. (1996), Anttila et al. (1998), and Grimsrud and Peto (2006). These studies, in addition to several others by Grimsrud et al. (2002, 2003, 2005), provided the basis for IARC's conclusion that the risk for lung cancer could be attributed to the following specific nickel compounds: nickel chloride, nickel sulfate, nickel oxides, and nickel sulfides, as well as more general nickel compounds of a range of solubilities (water-soluble, insoluble, and mostly insoluble) (IARC 2012). A study was published by Pavela et al. (2017) after IARC (2012) analyzed workers employed from 1967 to 2011 at a nickel refinery and smelter in Finland that had been studied previously (Anttila et al. 1998; Karjalainen et al. 1992). Pavela et al. (2017) added 16 years of follow-up to the cohort and confirmed that exposure to nickel compounds contributed to excess risk of lung and sinonasal cancers among refinery workers, reporting standardized incidence ratios (SIRs) of 2.01 (95% CI 1.10–3.36) and 26.68 (95% CI 5.50–77.97), respectively. Risks for lung and sinonasal cancers were not increased among maintenance or smelter workers (95% CIs included unity).

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.

Studies of workers in other nickel-exposed occupations have not shown consistent findings of increased risk of lung cancers. In cohort studies of lung cancer, most studies in other groups of nickel workers have not found significant increased risks, including workers in mines (Shannon et al. 1984a, 1984b, 1991), nickel alloy and stainless steel production facilities (Cornell 1984; Cornell and Landis 1984; Cox et al. 1981; Enterline and Marsh 1982; Jakobsson et al. 1997; Moulin et al. 1993; Sorahan 2004), stainless steel welders (Danielsen et al. 1996; Gérin et al. 1993; Hansen et al. 1996; Simonato et al. 1991), workers involved in nickel-chromium electroplating (Pang et al. 1996), workers of a barrier production facility (Cragle et al. 1984; Godbold and Tompkins 1979), and hard metal production workers (Marsh et al. 2017a, 2017b). Although some studies of these workers did report significant increases in mortality from respiratory tract cancers (Becker 1999; Moulin et al. 1990), the increased risks were attributed to

exposure to other carcinogenic agents, such as polycyclic aromatic hydrocarbons (PAHs) or asbestos. Redmond (1984) and Arena et al. (1998) reported significant increases in mortality from lung cancer among exposed nickel alloy production workers as compared to the general U.S. population. However, when the local population was used as the comparison group, the increase was no longer statistically significant (Arena et al. 1998). It is important to note that IARC (2018) conducted an extensive evaluation of the epidemiology data on cancer in welders and concluded that there was sufficient evidence that welding fumes cause lung cancer in humans. Their analysis included studies of a range of welding processes including those with and those without significant nickel exposure.

Population-based, case-control studies have reported mixed findings for nickel exposure and lung cancer; however, studies of this design are generally less robust than occupational cohort studies in which there is less chance of exposure misclassification. A pooled analysis of two population-based, case-control studies in Germany reported that welding regularly in processes with high nickel exposure was associated with an increased risk of lung cancer after adjusting for exposure to welding fumes and hexavalent chromium (Pesch et al. 2019). A multicenter population-based, case-control study in Europe did not find an association between risk of lung cancer and exposure to nickel dust or fumes in occupational settings (Mannetje et al. 2011).

Occupational cohort studies have not shown consistent associations between exposure to nickel compounds and risks of cancers outside the respiratory tract. In contrast to an earlier study reporting a significant increase in the incidence of stomach cancer among nickel refinery workers in Finland (Anttila et al. 1998), the updated evaluation of this cohort reported no significant increased risk of stomach cancer among refinery, maintenance, or smelter workers (Pavela et al. 2017). A study of nickel platers (Pang et al. 1996) reported an increased SMR for stomach cancer (SMR 322, 95% CI 139–634). Pang et al. (1996) also observed a higher (albeit not statistically significant) relative risk for stomach cancer among those working with nickel for more than a year (relative to those exposed less than a year); however, the total number of stomach cancer cases in the cohort was only eight and the cohort itself was quite small (n=284), limiting the precision of this analysis.

Population-based, case-control studies have not shown associations between reported occupational exposure to nickel and cancers, including cancers occurring in childhood. A case-control study of pancreatic cancer patients from the Mayo Clinic did not find a significant relationship between self-reported nickel exposure in the work environment and pancreatic cancer risk (Antwi et al. 2015). A seven-country, case-control study of glioma cases did not find that occupational exposure to nickel or

welding fumes increased the risk of disease development, even when accounting for cumulative exposure (Parent et al. 2017). Two case-control studies of individuals with testicular germ cells tumors found that neither paternal nor maternal occupational exposure to solvents and heavy metals including nickel increased the risk of tumors (Olsson et al. 2018; Togawa et al. 2016). A pooled analysis of case-control studies in Europe reported no association between paternal or maternal workplace exposure to nickel and risk of childhood leukemia (Onyije et al. 2022). In a similar case-control study in Sweden that evaluated childhood cancers together and by individual type, no significant association was observed between paternal or maternal occupational nickel exposure and any childhood cancer (individually or as a group) (Rossides et al. 2023).

Several animal studies have examined the carcinogenic potential of nickel and nickel compounds. Chronic-duration exposure to nickel oxide resulted in increases in the combined incidences of alveolar/bronchiolar adenoma or carcinoma in the lungs of rats exposed to 1 or 2 mg Ni/m^3 6 hours/day, 5 days/week for 2 years (NTP 1996a). No increases in lung tumors were observed in rats exposed to up to 6.3 mg Ni/m^3 as nickel oxide for 6 hours/day, 5 days/week for 1 month followed by a ≤20-month observation period (Horie et al. 1985). Increases in the combined incidences of alveolar/bronchiolar adenoma or carcinoma were observed in male rats exposed to 0.11 mg Ni/m^3 and in female rats exposed to 0.73 mg Ni/m^3 as nickel subsulfide, 6 hours/day, 5 days/week for 2 years (NTP 1996b). Increases in the incidence of lung tumors (adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcomas) were observed in rats exposed to 0.63 mg Ni/m^3 as nickel sulfide for 78 weeks, 6 hours/day, 5 days/week (Ottolenghi et al. 1975). In contrast, rats exposed to metallic nickel at concentrations up to 1 mg Ni/m^3 for 24 months, 6 hours/day, 5 days/week did not show increased incidence of respiratory tract neoplasms, but other signs of lung toxicity were present (Oller et al. 2008). Similarly, no increases in lung tumors were observed in rats exposed to concentrations up to 0.11 mg Ni/m^3 as nickel sulfate 6 hours/day, 5 days/week for 2 years (NTP 1996c); as with the metallic nickel study, nonneoplastic lung effects were observed in these rats.

In addition to increases in lung tumors, several studies have found increases in the adrenal tumors in rats. Increases in the combined incidence of benign or malignant adrenal gland pheochromocytomas were observed in male and female rats at 0.11 and 0.73 mg Ni/m^3, respectively, as nickel subsulfide (NTP 1996b) and in male and female rats exposed to 2 mg Ni/m^3 as nickel oxide for 2 years (NTP 1996a). Oller et al. (2008) also reported increases in the combined incidence of benign and malignant adrenal gland pheochromocytoma in male rats and cortical adenoma/carcinomas in female rats at 0.4 mg Ni/m^3 as metallic nickel. However, the study authors noted that the incidence of cortical adenoma/carcinomas in

females fell within historical ranges for control and could not be definitely linked to the nickel exposure. Ozaki et al. (2002) examined the possible relationship between lung lesions and adrenal pheochromocytomas in rats exposed to nickel oxide, nickel subsulfide, nickel sulfate, and six other particulate compounds examined in NTP studies. The study found statistical evidence that the severity of lung fibrosis and inflammation was associated with the incidence of pheochromocytomas; this association was also found in control animals. These results suggest that the pheochromocytomas may be secondary to the lung lesions rather than a direct effect of nickel.

No increases in neoplastic lesions were observed in mice exposed 6 hours/day, 5 days/week for 2 years to ≤0.88 mg Ni/m^3 as nickel subsulfide (NTP 1996b) or ≤0.22 mg Ni/m^3 as nickel sulfate (NTP 1996c). NTP (1996a) considered there to be equivocal evidence of carcinogenicity of nickel oxide in female mice exposed 6 hours/day, 5 days/week for 2 years based on an increased incidence of alveolar/bronchiolar adenomas observed at 2 mg Ni/m^3 but not at 3.9 mg Ni/m^3. No increases in neoplastic lesions were observed in male mice exposed to ≤3.9 mg Ni/m^3 as nickel oxide (NTP 1996a). No increases in the incidence of lung tumors were observed in mice following weekly intratracheal injections of ≤0.8 mg Ni/m^3 as nickel subsulfide for ≤15 weeks, followed by observation for ≤27 months (Fisher et al. 1986; McNeill et al. 1990).

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. Similarly, no increases in neoplastic lesions related to nickel exposure were observed in 344 rats administered doses up to 11.2 mg Ni/kg/day for 2 years (Heim et al. 2007).

The U.S. Department of Health and Human Services (NTP 2016) 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, 2021) 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 1987a, 1987b); other nickel compounds have not been classified by EPA.

2.20 GENOTOXICITY

A number of studies have examined the genotoxicity of nickel and nickel compounds; the results of these *in vivo* and *in vitro* tests are presented in Tables 2-7 and 2-8, 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; Pikálek and Necásek 1983; Rodríguez-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 exposed to nickel (Hartwig and Beyersmann 1989; Miyaki et al. 1979; Ohshima 2003). Two studies on V79 cells (Åkerlund et al. 2018; Buxton et al. 2020) and another in Chinese hamster ovary cells (Hsie et al. 1979) failed to find evidence of gene mutations at this locus. An increase in gene mutation frequency has also been found in Chinese hamster ovary AS52 cells (hprt 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). Kargacin et al. (1993) observed increased mutant frequencies in response to nickel exposure (crystalline nickel sulfide, nickel subsulfide, nickel oxides, and nickel chloride) in V79 cells transfected with the gpt gene from *E. coli*. Subsequent work showed that the mechanism for nickel-induced mutation in this model was epigenetic, occurring via nickel-mediated deoxyribonucleic acid (DNA) condensation and hypermethylation resulting in silencing of the gpt transgene (Klein and Costa 1997). Gene mutation frequency was not affected in transgenic mouse and rat respiratory tissue following inhalation exposure to nickel subsulfide (Mayer et al. 1998). Dominant lethal mutations were not affected by intraperitoneal exposure of nickel acetate in mice (Deknudt and Léonard 1982). Nickel acetate exposure ranging from 0.5 to 5 mg/kg was associated with increased frequency of dominant lethal mutations in germline cells of mice (Domshlak et al. 2005). Additionally, increased frequency of gene mutations was observed in pigment cells of first-generation mice at doses >1.0 mg/kg (Domshlak et al. 2005). There is evidence to suggest that nickel is clastogenic and can damage DNA. Chromosome gaps or chromosome aberrations have been reported in several studies of lymphocytes from nickel refinery workers (Deng et al. 1988; Waksvik and Boysen 1982; Waksvik et al. 1984). Welding fumes are a complex mixture of several metals including nickel and have been shown to cause cytotoxic and genotoxic effects such as DNA methylation and telomere alterations (Shoeb et al. 2017, 2021, 2024). Workers in a welding factory exposed to high concentrations of nickel (0.340–10.129 mg/m^3) showed significant increases in chromosomal aberrations relative to unexposed controls, though the controls were co-exposed to chromium and PAHs (Borská et al. 2003). *In vivo* studies show that intraperitoneal injection resulted in

chromosomal aberrations in mouse bone marrow cells following nickel chloride exposure (Dhir et al. 1991; El-Habit and Abdel Moneim 2014), and in rat bone marrow and spermatogonial cells following nickel sulfate exposure (Mathur et al. 1978). *In vitro* assays have found chromosomal abnormalities using hamster cells (Conway and Costa 1989; Larramendy et al. 1981; Ohshima 2003; Sen and Costa 1986; Sen et al. 1987), mouse embryo cells (Clemens and Landolph 2003; Terpilowska and Siwicki 2018), human lymphocytes (Larramendy et al. 1981; Lechner et al. 1984), human bronchial epithelial cells (Holmes et al. 2013; Lechner et al. 1984), and human liver cancer cells (Terpilowska and Siwicki 2018). In a metaphase analysis of human lymphocytes from nickel-hypersensitized and nickel-unsensitized subjects, positive evidence of genotoxicity was observed (Arrouijal et al. 1992).

Table 2-7. Genotoxicity of Nickel *In Vivo*

Species (test system)	Endpoint	Results	Reference	Compound
Drosophila melanogaster	Gene mutation	–	Rasmuson 1985	Nickel nitrate or chloride
	Recessive lethal	+	Rodríguez-Arnaiz and Ramos 1986	Nickel sulfate
	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
	Sister chromatid exchange	–	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
	Chromosome aberrations	+	Waksvik et al. 1984	Nickel
	Sister chromatid exchange	–	Waksvik et al. 1984	Nickel
	Chromosome aberrations	+	Deng et al. 1988	Nickel
	Sister chromatid exchange	+	Deng et al. 1988	Nickel
	Chromosome aberrations	+	Borská et al. 2003	Nickel
	DNA damage	+	Iarmarcovai et al. 2005	Nickel
	Micronuclei formation	+	Iarmarcovai et al. 2005	Nickel
Human blood cells	Oxidative DNA damage	+	Cheng et al. 2019	Nickel
Human umbilical cord blood	Oxidative DNA damage	+	Ni et al. 2014	Nickel
Human urine	Oxidative DNA damage	+	Kim et al. 2004	Nickel
Human plasma	Oxidative DNA damage	+	Wu et al. 2015	Nickel
Human buccal mucosa cells	DNA damage	–	Hafez et al. 2011	Nickel
Human sperm cells	DNA damage	–	Wang et al. 2016	Nickel

Table 2-7. Genotoxicity of Nickel *In Vivo*

Species (test system)	Endpoint	Results	Reference	Compound
Rat bone marrow and spermatogonial cells	Chromosome aberrations	–	Mathur et al. 1978	Nickel sulfate
Mouse bone marrow cells	Chromosome aberrations (i.p.)	+	Dhir et al. 1991	Nickel chloride
	Chromosome aberrations	+	El-Habit and Abdel Moneim 2014	Nickel chloride
	DNA damage	+	El-Habit and Abdel Moneim 2014	Nickel chloride
Mouse leukocytes	DNA damage	+	Danadevi et al. 2004	Nickel chloride
Rat type II lung epithelial cells	DNA damage	+	Oller et al. 2023	Nickel subsulfide
		–	Oller et al. 2023	Nickel sulfate hexahydrate
Mouse testis and epididymal sperm cells	DNA double-strand breaks	+	Doreswamy et al. 2004	Nickel chloride
Mouse germline sperm cells	DNA double-strand breaks	+	Domshlak et al. 2005	Nickel sulfate
Mouse blood mononuclear cells	DNA fragmentation	+	Jia and Chen 2008	Nickel chloride
Mouse bone marrow cells	Micronucleus test (i.p.)	–	Morita et al. 1997	Nickel chloride, nickel sulfate, nickel oxide
Rat bone marrow cells	Micronucleus test (oral)	–	Oller and Erexson 2007	Nickel sulfate
Mouse bone marrow cells	Micronucleus test (i.p.)	–	Deknudt and Léonard 1982	Nickel chloride
	Micronucleus test	+	El-Habit and Abdel Moneim 2014	Nickel chloride
Mouse lung, mouse nasal mucosa, rat lung, rat nasal mucosa	Gene mutation (inhalation)	–	Mayer et al. 1998	Nickel subsulfide
Mouse pigment cells	Gene mutations	+	Domshlak et al. 2005	Nickel sulfate
Mouse	Dominant lethal (i.p.)	–	Deknudt and Léonard 1982	Nickel acetate
Mouse germline sperm cells	Dominant lethal mutations	+	Domshlak et al. 2005	Nickel sulfate

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; i.p. = intraperitoneal

Table 2-8. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Prokaryotic organisms					
Bacillus subtilis	DNA damage (rec assay)	NT	–	Kanematsu et al. 1980	Nickel oxide, nickel trioxide
Escherichia coli	DNA replication rate	NT	+	Chin et al. 1994	Nickel chloride
Salmonella typhimurium	DNA damage	+	–	Keyhani et al. 2006	Nickel
E. coli WP2	Gene mutation frequency	NT	–	Green et al. 1976	Nickel chloride
S. typhimurium	Gene mutation frequency	NT	–	Arlauskas et al. 1985	Nickel chloride, Nickel sulfate
S. typhimurium	Gene mutation frequency	NT	–	Biggart and Costa 1986	Nickel chloride
S. typhimurium TA10	Gene mutation frequency	NT	–	Marzin and Phi 1985	Nickel nitrate
S. typhimurium	Gene mutation frequency	–	–	Wong 1988	Nickel chloride
Cornebacterium sp.	Gene mutation frequency	NT	+	Pikálek and Necásek 1983	Nickel chloride
Eukaryotic organisms					
Fungi:					
Saccharomyces cerevisiae	Reverse mutation	NT	–	Singh 1984	Nickel sulfate
Mammalian cells					
Human foreskin cells	Cell transformation	NT	+	Biedermann and Landolph 1987	Nickel subsulfide, nickel oxide, nickel sulfate, nickel acetate
Baby hamster kidney (BHK-21 cells)	Cell transformation	NT	+	Hansen and Stern 1984	Nickel powder, nickel acetate, nickel oxide, nickel subsulfide
CHE cells	Cell transformation	NT	+	Conway and Costa 1989	Nickel chloride, nickel sulfide
CHO cells	Cell transformation	NT	+	Costa and Heck 1982	Nickel sulfide, nickel subsulfide, nickel oxide, metallic nickel
		NT	+	Costa and Mollenhauer 1980	Nickel sulfide, nickel subsulfide
		NT	+	Costa et al. 1982	Nickel sulfide
SHE cells	Cell transformation	NT	+	Costa and Mollenhauer 1980	Nickel sulfide, nickel subsulfide
		NT	+	Costa et al. 1982	Nickel sulfide
		NT	+	DiPaolo and Casto 1979	Nickel sulfate, nickel subsulfide

Table 2-8. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Mouse embryo cells (C3H/10T1/2)	Cell transformation	NT	+	Saxholm et al. 1981	Nickel subsulfide
Mouse embryo fibroblasts	Cell transformation	NT	+	Miura et al. 1989	Nickel subsulfide, nickel monosulfide, nickel oxide
		NT	–	Miura et al. 1989	Nickel sulfate, nickel chloride
Mouse embryo cells	Cell transformation	NT	+	Clemens and Landolph 2003	Nickel arsenide
Human lymphocytes	Chromosome aberration	NT	+	Larramendy et al. 1981	Nickel sulfate
Human bronchial epithelial cells	Chromosome aberration	NT	+	Lechner et al. 1984	Nickel sulfate
		NT	+	Holmes et al. 2013	Nickel subsulfide
Human liver cancer cells	Chromosome aberration	NT	+	Terpilowska and Siwicki 2018	Nickel chloride
Mouse embryo cells	Chromosome aberration	NT	+	Clemens and Landolph 2003	Nickel arsenide
Mouse embryo fibroblasts	Chromosome aberration	NT	+	Terpilowska and Siwicki 2018	Nickel chloride
CHE cells	Chromosome aberration	NT	+	Conway and Costa 1989	Nickel chloride, nickel sulfide
CHO cells	Chromosome aberration	NT	+	Sen and Costa 1986	Nickel chloride, nickel sulfide
		NT	+	Sen et al. 1987	Nickel sulfate, nickel chloride
C3H/10T1/2 cells	Chromosome aberration	NT	+	Sen et al. 1987	Nickel sulfate, nickel chloride
SHE cells	Chromosome aberration	NT	+	Larramendy et al. 1981	Nickel sulfate
Chinese hamster V79 cells	Chromosome aberration	NT	+	Ohshima 2003	Nickel sulfate
CHO cells	Gene mutation at HGPRT locus	NT	–	Hsie et al. 1979	Nickel chloride
Chinese hamster V79 cells	Gene mutation at HGPRT locus	NT	+	Hartwig and Beyersmann 1989	Nickel chloride
		NT	+	Miyaki et al. 1979	Nickel chloride
		NT	–	Åkerlund et al. 2018	Nickel chloride
		NT	+	Ohshima 2003	Nickel sulfate
		NT	–	Buxton et al. 2020	Nickel metal powder

Table 2-8. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
CHO AS52 cells	Gene mutation at *grp* locus	NT	+	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	NT	+	Mayer et al. 1998	Nickel subsulfide
Human diploid fibroblasts	DNA single strand breaks	NT	–	Hamilton-Koch et al. 1986	Nickel chloride
Human gastric mucosal cells	DNA damage (comet analysis)	NT	–[a]	Pool-Zobel et al. 1994	Nickel sulfate
Human HeLa cells	DNA replication	NT	+	Chin et al. 1994	Nickel chloride
Human leukemic cells	DNA damage	NT	–	Cavallo et al. 2003	Nickel sulfate
Human leukemic cells	Inhibition of DNA repair	NT	+	Cavallo et al. 2003	Nickel sulfate
Human leukemic cells	DNA fragmentation	NT	+	Jia and Chen 2008	Nickel chloride
Human lymphoblastoid TK6 cells	DNA damage	NT	+	Guillamet et al. 2008	Nickel chloride
Human B lymphoblastoid cells	DNA damage	NT	+	Lou et al. 2013	Nickel chloride
Human lymphocytes	DNA single strand breaks	NT	+	Chen et al. 2003	Nickel chloride
Human lymphocytes	DNA damage	NT	+	Rao et al. 2008	Nickel chloride
Human peripheral lymphocytes	DNA single strand breaks	NT	+	M'Bemba-Meka et al. 2005	Nickel carbonate hydroxide, nickel subsulfide, nickel oxide
Human peripheral lymphocytes	DNA single strand breaks	NT	–	M'Bemba-Meka et al. 2005	Nickel sulfate
Human alveolar epithelial cells (A549)	DNA strand breaks	NT	+	Schwerdtle and Hartwig 2006	Nickel chloride, nickel oxide
Human alveolar epithelial cells	DNA damage	NT	–	Di Pietro et al. 2009	Nickel

Table 2-8. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Human umbilical cord endothelial cells	DNA damage	NT	+	Beck et al. 2014	Nickel
Human bronchial epithelial cells	DNA fragmentation	NT	+	Castorina and Giunta 2014	Nickel acetate
	DNA strand breaks	NT	+	Di Bucchianico et al. 2018	Nickel chloride
	DNA damage	NT	+	Gliga et al. 2020	Nickel chloride
	DNA damage	NT	–	Åkerlund et al. 2018	Nickel chloride
Human dermal fibroblast cells	DNA strand breaks	NT	+	Belliardo et al. 2018	Nickel chloride
Human colon cancer cells	DNA damage	NT	–	Kim and Seo 2011	Nickel acetate
		NT	–	Kim and Seo 2012	Nickel acetate
Human fetal fibroblast cells	DNA damage	NT	+	Qiao and Ma 2013	Nickel ions
Human liver cancer cells	DNA damage	NT	+	Terpilowska and Siwicki 2018	Nickel chloride
Human proximal tubule epithelial cells	DNA damage	NT	+	Wang et al. 2012	Nickel acetate
Mouse embryo fibroblast cells	DNA damage	NT	+	Terpilowska and Siwicki 2018	Nickel chloride
CHO cells	DNA protein crosslinks	NT	+	Patierno and Costa 1985	Crystalline nickel sulfide, nickel chloride
CHO cells	DNA strand breaks	NT	+	Hamilton-Koch et al. 1986	Nickel chloride
		NT	+	Patierno and Costa 1985	Crystalline nickel sulfide, nickel chloride
Rat kidney cells	DNA single strand breaks	NT	+	Chen et al. 2010	Nickel chloride
Human lymphocytes	Metaphase analysis	NT	+	Arrouijal et al. 1992	Nickel subsulfide
	Micronucleus formation	NT	+	Arrouijal et al. 1992	Nickel subsulfide
		NT	–	Gliga et al. 2020	Nickel chloride
		NT	–	Kim and Seo 2011	Nickel acetate
		NT	–	Buxton et al. 2020	Metallic nickel

Table 2-8. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Human lymphocytes	Sister chromatid exchange	NT	(+)	Andersen 1983	Nickel sulfate
		NT	+	Larramendy et al. 1981	Nickel sulfate
		NT	+	M'Bemba-Meka et al. 2007	Nickel carbonate hydroxide, nickel subsulfide, nickel oxide, nickel sulfate
		NT	+	Saxholm et al. 1981	Nickel subsulfide
		NT	+	Wulf 1980	Nickel sulfate
		NT	+	Arrouijal et al. 1992	Nickel subsulfide
Chinese hamster V79 cells	Sister chromatid exchange	NT	+	Hartwig and Beyersmann 1989	Nickel chloride
Chinese hamster DON cells	Sister chromatid exchange	NT	+	Ohno et al. 1982	Nickel sulfate, nickel chloride
SHE cells	Sister chromatid exchange	NT	+	Larramendy et al. 1981	Nickel sulfate
Virus-infected mouse sarcoma cells	Induction of revertant foci	NT	+	Biggart et al. 1987	Nickel chloride
		NT	+	Biggart and Murphy 1988	Nickel chloride
Mouse lymphoma (L5178Y/TK$^{+/-}$) cells	Forward mutation	NT	+	Amacher and Paillet 1980	Nickel chloride
		NT	+	McGregor et al. 1988	Nickel sulfate

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

– = negative result; + = positive result; (+) = weakly positive result; CHE = Chinese hamster embryo; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NT = not tested; SHE = Syrian hamster embryo

No alterations in the occurrence of sister chromatid exchange were observed in two studies of lymphocytes from nickel refinery workers (Waksvik and Boysen 1982; Waksvik et al. 1984), but another study found that nickel workers had significantly higher levels of sister chromatid exchange than unexposed controls (Deng et al. 1988). Increases were also found in *in vitro* assays of human lymphocytes (Andersen 1983; Arrouijal et al. 1992; Larramendy et al. 1981; M'Bemba-Meka et al. 2007; Saxholm et al. 1981; Wulf 1980) and hamster cells (Andersen 1983; Hartwig and Beyersmann 1989; Larramendy et al. 1981; Saxholm et al. 1981).

In vitro studies suggest that exposure to nickel leads to cell transformation in mammalian cells. Positive evidence for cell transformation has been observed in several types of hamster cells: Chinese hamster ovary cells (Conway and Costa 1989; Costa and Mollenhauer 1980; Costa et al. 1982), Chinese hamster embryo cells (DiPaolo and Casto 1979), Syrian hamster embryo cells (Conway and Costa 1989; Costa and Mollenhauer 1980; Costa et al. 1982), and baby kidney hamster cells (Hansen and Stern 1984). Cell transformation was also found in human foreskin (Biedermann and Landolph 1987) and mouse embryo cells (Clemens and Landolph 2003; Saxholm et al. 1981). Miura et al. (1989) observed cell transformation in mouse embryo cells exposed to nickel subsulfide, nickel monosulfide, and nickel oxide, but not in those exposed to nickel sulfate or nickel chloride.

Micronucleus formation was not affected in several studies of rat or mouse bone marrow cells following oral or intraperitoneal exposure (Deknudt and Léonard 1982; Morita et al. 1997; Oller and Erexson 2007). One study found increased micronuclei formation in bone marrow cells of mice exposed to nickel chloride via intraperitoneal injection (El-Habit and Abdel Moneim 2014). Exposed welders with a mean blood nickel concentration of approximately 5 μg/L had significantly higher frequency of micronuclei than controls, although it should be noted that co-exposures to chromium and lead occurred (Iarmarcovai et al. 2005). Increased micronuclei formation was observed in one *in vitro* study of human lymphocytes from nickel-unsensitized subjects, and the effect was dose-dependent and 50% greater than in nickel-sensitized subjects (Arrouijal et al. 1992). No evidence of increased micronuclei formation was found in several studies including an immortalized human bronchial epithelial cell line (BEAS-2B) (Gliga et al. 2020), human colon cancer cells (Kim and Seo 2011), and Chinese hamster V79 cells (Buxton et al. 2020).

DNA damage has been observed in several *in vivo* studies in mice and rats. In mice exposed to single nose-only inhalation doses of nickel subsulfide, DNA damage in lung and nasal mucosal cells consisted of fragmentation (Mayer et al. 1998). Significant DNA damage was observed at all doses in bone marrow cells of mice given intraperitoneal injections of nickel chloride from 40 to 120 μmol/kg body weight (El-Habit and Abdel Moneim 2014). Intraperitoneal administration for 2 weeks of 2 or 20 mg/kg also resulted in significant DNA fragmentation of peripheral blood mononuclear cells (Jia and Chen 2008). DNA damage was observed in leukocytes of mice orally exposed to nickel chloride at doses ranging from 3.4 to 108.8 mg/kg (Danadevi et al. 2004). Two studies observed significant increases in DNA double-strand breaks in mouse sperm cells following intraperitoneal administration to either nickel sulfate or nickel chloride (Domshlak et al. 2005; Doreswamy et al. 2004). In isolated lung cells from rats exposed to concentrations ≤0.22 mg Ni/m^3 as nickel sulfate hexahydrate, DNA damage was not increased after

3 weeks but appeared to increase after 13 weeks (Oller et al. 2023). Exposure to nickel subsulfide showed DNA damage increased with exposure concentration regardless of duration (Oller et al. 2023). Evidence from *in vivo* studies in humans has been mixed. DNA oxidative damage was observed in nickel smelting workers and correlated with length of employment (Cheng et al. 2019). Workers with a mean blood nickel concentration around 5 µg/L had significant increases in DNA damage of lymphocytes relative to controls (Iarmarcovai et al. 2005). Oxidative DNA damage, as assessed by levels of plasma 8-hydroxyguanosine, was significantly associated with nickel in umbilical cord blood in pregnant women (Ni et al. 2014), nickel urine in smelting workers (Wu et al. 2015), and employment length in nickel smelting workers (Wu et al. 2015). In a study of U.S. factory workers, urine 8-hydroxyguanosine was also significantly associated with air concentrations of nickel (Kim et al. 2004). A study of orthodontic treatments containing nickel and chromium found evidence of DNA damage in buccal mucosa, but linear regression analyses indicated these effects were unrelated to nickel content (Hafez et al. 2011). In a study of Chinese men (n=516), urine nickel (mean of 2.0 µg/L) was not associated with DNA damage in sperm cells (Wang et al. 2016).

Two studies of prokaryotic organisms—one in *Bacillus subtilis* (Kanematsu et al. 1980) and one in *Salmonella typhimurium* (Keyhani et al. 2006)—found no evidence of DNA damage upon exposure to nickel. Nickel significantly altered DNA replication rate in *E. coli* (Chin et al. 1994). One study of eukaryotic organisms was located, which found no evidence of reverse mutation in *Saccharomyces cerevisiae* after exposure to nickel (Singh 1984).

Most *in vitro* studies of nickel exposure have found positive evidence of DNA damage in mammalian cells. DNA damage was found in mouse fibroblast cells (Terpilowska and Siwicki 2018) and rat kidney cells (Chen et al. 2010). DNA protein crosslink and/or single-strand breaks have also been observed in Chinese hamster ovary cells (Hamilton-Koch et al. 1986; Patierno and Costa 1985). Several studies have noted DNA damage in human lymphocytes exposed to nickel (Chen et al. 2003; Rao et al. 2008; M'Bemba-Meka et al. 2005). DNA damage has also been observed in numerous types of epithelial cells following exposure to nickel: umbilical cord endothelial cells (Beck et al. 2014), alveolar epithelial cells (Di Pietro et al. 2009; Schwerdtle and Hartwig 2006), bronchial epithelial cells (Di Bucchianico et al. 2018; Castorina and Giunta 2014; Gliga et al. 2020), and human proximal tubule epithelial cells (Wang et al. 2012). DNA damage to fibroblasts has been found in dermal (Belliardo et al. 2018) and fetal (Qiao and Ma 2013) cell cultures. Additional evidence of DNA damage comes from *in vitro* studies of leukemic cells (Cavallo et al. 2003; Jia and Chen 2008), lymphoblastoid cells (Guillamet et al. 2008; Lou et al. 2013), colon cancer cells (Kim and Seo 2011, 2012), and liver cancer cells (Terpilowska and

Siwicki 2018). In a study of HeLa cells, exposure to nickel adversely affected DNA replication (Chin et al. 1994). 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.

2.21 NICKEL NANOPARTICLES

The following section provides a brief overview on toxicity of nickel nanoparticles and is focused on highlighting findings from experimental animal studies. No epidemiology studies using nickel nanoparticles were identified. A case report indicated that a worker developed nickel nanoparticle powder sensitization when working in a setting handling 1–2 g of nano nickel powder without any special respiratory protection or control measures (Journeay and Goldman 2014). In another case report of occupational inhalation exposure to nickel nanoparticles via spraying, death occurred 13 days after exposure; the cause of death at autopsy was determined to be ARDS (Phillips et al. 2010). The case report by Phillips et al. (2010) also identified high levels of nickel nanoparticles in the urine and kidneys, which were indicative of acute tubular necrosis. Several *in vivo* and *in vitro* studies have demonstrated that nickel nanoparticles increase the production of reactive oxygen species (ROS) and reactive nitrogen species which are both associated in other studies with serious adverse effects such as genotoxicity, inflammation, apoptosis, and fibrosis (Chang et al. 2017; Genchi et al. 2020).

The acute lethality of nickel oxide nanoparticles was evaluated after inhalation and oral exposure in male and female Sprague-Dawley rats (Lyons-Darden et al. 2023). No deaths occurred among 20 male and 20 female rats exposed by inhalation to measured concentrations of 5.41–5.42 mg/L nickel oxide nanoparticles (mass median aerodynamic diameter [MMAD] 3.01–3.42 mm) for 4 hours. Exposed rats showed lower body weights during the first week after exposure and hypoactivity and irregular respiration during the 2-week observation period. Gross necropsy showed discoloration of the lungs in the exposed animals. In the oral experiment using the up-and-down method, no deaths occurred within 14 days after doses up to 5,000 mg/kg, and there were no clinical signs, gross necropsy findings, or body weight differences (Lyons-Darden et al. 2023).

Many studies in animals have reported a wide range of adverse effects in the respiratory system following exposure to nickel nanoparticles. Single inhalation exposure to nickel oxide nanoparticles at a concentration of 0.00134 mg/m^3 in BALB/C mice for 4 hours resulted in nidal perivascular and peribronchial lymphoid infiltration in the lungs of the exposed mice (Zaitseva et al. 2018). This study

also observed changes in alveolar patterns in mice exposed to nickel nanoparticles. Single intratracheal instillation of nickel oxide nanoparticles in male Sprague-Dawley rats to a concentration of 800 μg (3.3 mg/kg) induced pulmonary inflammation with elevated neutrophil count (Cao et al. 2016). Single intratracheal instillation of nickel oxide nanoparticles in Wistar rats at the concentration of 0.5 mg/mL resulted in lung injury and oxidative stress over a period of 72 hours after the exposure (Horie et al. 2012). Whole-body inhalation exposure to nickel nanoparticles at a concentration of 500 $\mu g/m^3$ for 5 hours in C57BL/6 mice resulted in significantly increased circulating endothelial progenitor cells, indicating endothelial damage caused by nickel nanoparticles (Liberda et al. 2014). Whole-body inhalation exposure to nickel sulfate ($NiSO_4$) nanoparticles at a concentration of 558 $\mu g/m^3$ in mice for 4 hours resulted in pulmonary inflammation (Kang et al. 2011a). Whole-body inhalation exposure to nickel hydroxide nanoparticles at a concentration of 79 $\mu g/m^3$ for 5 hours/day, 5 days/week, for 1 week in hyperlipidemic, apoprotein E-deficient ($ApoE^{-/-}$) mice resulted in increased oxidative stress, cardiopulmonary inflammation, DNA damage in the aorta, significant signs of inflammation in bronchoalveolar lavage fluid, and changes in lung histopathology (Kang et al. 2011b). A 5-month exposure in the same study exacerbated the health effects observed in the 1-week exposure (Kang et al. 2011b). Whole-body inhalation of nickel hydroxide nanoparticles in C57BL/6 mice for 5 hours/day for 1 day induced acute endothelial disruption and caused vasoconstriction at 150 $\mu g/m^3$; this effect occurred after 3- and 5- day exposures as well (Cuevas et al. 2010). Male Fischer-344 rats received nickel oxide nanoparticles as four doses of 2 mg/kg body weight as intratracheal instillations, which caused pulmonary injury and inflammation, and nickel oxide particles were detected in the lung and lung associated lymph nodes (Senoh et al. 2017). Male Wistar rats were subjected to aerosol inhalation exposures of nickel oxide nanoparticles for 6 hours/day, 5 days/week for 4 weeks at 0.20 mg/m^3, which resulted in macrophage accumulation in the alveoli with infiltration of inflammatory cells (Kadoya et al. 2016). In a similar experiment, Morimoto et al. (2011) observed increased total cell count in BALF along with minimal pulmonary infiltration of neutrophils and alveolar macrophages in male Wistar rats 4 days after the end of a 4-week inhalation exposure to nickel oxide nanoparticles (daily mean particle number concentration of $1x10^5/cm^3$); the effects were no longer observed 1 month after the end of exposure. Albino rats were exposed to nickel oxide nanoparticles at 0.23 mg/m^3 for 4 hours/day, 5 times a week for up to 10 months and resulted in altered pulmonary cytology and biochemical characteristics of the bronchoalveolar lavage fluid (Sutunkova et al. 2019). Sutunkova et al. (2019) also observed damage to the liver and kidneys along with genotoxic effects assessed by the increased degree of DNA fragmentation. In male Wistar rats exposed to nickel oxide nanoparticles via intratracheal instillation, twice a week for 6 weeks at 0.24 mg/kg body weight, increased indicators of nitrative stress (nitric oxide, TNOS, and inducible nitric oxide synthase [iNOS]), inflammatory cytokines (tumor necrosis factor-alpha

[TNF-α], interleukin-2 [IL-2], and interleukin-10 [IL-10]), and cytokine induced neutrophil chemoattractants (CINC-1, CINC-2αβ, and CINC-3) were observed in lung tissue (Chang et al. 2017). Nickel oxide nanoparticles when intratracheally instilled into female Wistar rats at 200 cm^2/rat produced an acute neutrophilic inflammation (Lee et al. 2016). Male Wistar rats were exposed to 0.2 mg nickel oxide nanoparticles via intratracheal instillation once, which caused a transient increase in cytokine expression and persistent pulmonary inflammation (Morimoto et al. 2010, 2016). Intratracheal instillation of 0.1–2 mg nickel oxide nanoparticles in male Wistar rats caused pulmonary inflammation (Mizuguchi et al. 2013; Ogami et al. 2009). Lung inflammation and inflammatory hyperplasia were observed in Sprague-Dawley rats 14 days after intratracheal instillation of nickel oxide nanoparticles (≥5.6 mg/kg) (Magaye et al. 2016). A dose-dependent increase in acute lung inflammation and injury was seen in C57BL/6 mice after exposure to 50 µg nickel nanoparticles via intratracheal instillation (Mo et al. 2019).

Hepatic effects of intratracheal exposure to nickel nanoparticles were reported in two studies. Wistar rats were exposed to nickel oxide nanoparticles via intratracheal instillation twice a week for 6 weeks at 0.24 mg/kg body weight, which induced abnormal changes in hepatic enzymes (Yu et al. 2018). Single intratracheal instillation of nickel nanoparticles at 5.6 mg/kg in Sprague-Dawley rats caused hepatotoxicity consisting of hepatocellular hypertrophy and congestion (Magaye et al. 2016).

Oral exposure to nickel oxide nanoparticles in animals primarily targets both male and female reproductive organs and the immune system. Oral exposure to 100 mg/kg body weight nickel oxide nanoparticles in water to pregnant albino rats for 12–14 days of gestation significantly increased luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone hormones (Alsoltane and Altaee 2020b). Kong et al. (2019) orally dosed Sprague-Dawley rats with nickel nanoparticles via gavage for 10 weeks and examined reproductive toxicity in one generation. At 15 mg/kg body weight, nickel nanoparticles induced oxidative stress and caused morphological changes in the testis (Kong et al. 2019). At the same dose, female Sprague-Dawley rats showed slight swelling, cavitation, and crest disorders of mitochondria in primary follicles along with increased oxidative stress and cell apoptosis (Kong et al. 2016). Kong et al. (2014) observed transgenerational effects in F0 generation on reproductive toxicity in male and female rats dosed with 5–15 mg/kg body weight. Male rats showed morphological changes in the testis while female rats showed changes in hormone levels. Exposure to 5 mg/kg body weight nickel nanoparticles in male ICR mice by gavage for 30 days damaged the reproductive system by affecting spermatogenesis and testicular structure (Hu et al. 2020). Developmental toxicity was observed in the pups with a significant decrease in survival rates at birth and during feeding (Kong et al. 2014). Oral exposure to 10 mg/kg body weight nickel oxide nanoparticles in water to pregnant albino rats for 12–

14 days of gestation significantly decreased IgA, IgG, and IgM (Alsoltane and Altaee 2020b). A single oral nickel oxide nanoparticle dose of 500 mg/kg via intubation in adult Wistar rats resulted in increased WBC count (Dumala et al. 2018).

Effects in several other systems have been reported in various animal studies. In male Wistar rats orally exposed to nickel oxide nanoparticles at 2 mg/kg body weight/day, significant increases in chromosomal aberrations, micronuclei formation, and DNA damage were induced after 7- and 14-day exposures (Saquib et al. 2017). Oral exposure to 100 mg/kg body weight nickel oxide nanoparticles in water to pregnant albino rats for 12–14 days resulted in decreased maternal relative body weight. Exposed rats on GD 12 showed an increase in relative organ weight (lung, uterus, kidney) and decreases in heart, liver, eye, spleen, and brain weights. Similarly, decreases in relative weight of the heart, liver, eye, brain, and kidney and increases in lung, spleen, and uterus weight were observed in treated rats on GD 14 (Alsoltane and Altaee 2020a). At lower doses, Wistar rats exposed to nickel oxide nanoparticles once via gavage at 0.5 and 1 mg/kg body weight showed increases in relative weight of the brain, kidney, and liver, and increases in erythrocytes and hemoglobin levels (Ali 2019). Changes in kidney and liver enzymes were also noted. Hematological effects were observed in Wistar rats after 28 days of repeated oral exposure to nickel oxide nanoparticles, including decreased hemoglobin and hematocrit levels in male and female rats exposed to ≥50 mg/kg body weight (Dumala et al. 2019b).

Parenteral exposure to nickel nanoparticles targets the hematological system, heart, kidneys, and liver. Adult male Wistar rats exposed to 25 mg/kg body weight nickel nanoparticles and nickel chloride intraperitoneally daily for 1 week developed a significant increase in blood urea, creatinine, and WBC count (Seyedalipour et al. 2017). Wistar rats dosed with nickel oxide nanoparticles via intraperitoneal injection at 2.5 mg/kg for 3 times/week up to 18 injections, developed decreased hematocrit levels and lymphocytes and increased monocytes and reticulocytes along with morphological changes observed in the brain, kidney, liver, and spleen (Minigalieva et al. 2015). Intraperitoneal injections of 20–50 nickel oxide nanoparticles mg/mL for 14 days in albino mice induced oxidative stress that affected cardiac, hepatic, and renal systems. The effects were dose and sex dependent as they were more pronounced at higher doses and specifically in male mice (Hussain et al. 2020).

The genotoxic effects of nickel nanoparticles have been tested in *in vivo* and *in vitro* studies. DNA damage, increased polychromatic erythrocytes in the micronucleus test, and chromosomal aberrations were seen in female Wistar rats orally exposed to 2,000 mg/kg body weight of nickel oxide nanoparticles once (Dumala et al. 2017). Peripheral blood lymphocytes isolated from humans showed dose-dependent

cytotoxic and genotoxic effects when exposed to nickel oxide nanoparticles for 24 hours (Dumala et al. 2019a). No cytotoxicity was observed in human bronchial epithelial cells exposed to doses up to 50 µg/mL of nickel nanoparticles and nickel oxide nanoparticles for 24 hours (Åkerlund et al. 2018, 2019). In Åkerlund et al. (2018), nickel nanoparticles and nickel oxide nanoparticles induced DNA strand breaks at doses of 5–25 µg/mL. Nickel oxide nanoparticles appear to be more toxic; DNA damage began at 5 µg/mL compared to 10 µg/mL from nickel nanoparticle exposure (Åkerlund et al. 2018). However, double-strand breaks were not significantly increased. Significant differences in the frequencies of micronuclei, which is indicative of genotoxic potential, occurred in both Chinese hamster cell lines and *D. melanogaster* exposed to nickel oxide nanoparticles concentrations of 250 and 500 µg/mL for 4- and 24-hour treatment periods (De Carli et al. 2018). These effects were also seen at 125 µg/mL nickel oxide nanoparticles only in the 4-hour exposure period (De Carli et al. 2018). A comet assay of V79 cells revealed that 62, 125, 250, and 500 µg/mL nickel oxide nanoparticles induced a significant increase in DNA damage (De Carli et al. 2018). The results from De Carli et al. (2018) indicate that nickel oxide nanoparticles are genotoxic and mutagenic *in vitro* and *in vivo.* Exposure to nickel nanoparticles induced genotoxic effects and increased oxidized stress in immortalized human bronchial epithelial (BEAS-2B) cells at doses as low as 1 µg/mL after 48 hours (Di Bucchianico et al. 2018). Low-dose nickel nanoparticles and nickel oxide nanoparticle exposure at 0.5 µg/mL on BEAS-2B cells for 6 weeks resulted in DNA strand breaks on comet assay (Gliga et al. 2020). Cytotoxicity occurred in a Chinese hamster lung fibroblast cell line after a 48-hour exposure at ≥0.15 µg/cm^2 nickel nanoparticles (not further speciated) in the air-liquid interface, but no increase in HPRT mutation frequency was seen at exposures up to 0.32 µg/cm^2 (Latvala et al. 2017). In the same cell system, exposure to nickel nanoparticles (0.3–0.4 µg/cm^2) did not increase DNA strand breaks except in the presence of an inhibitor of base excision repair (Latvala et al. 2017). Lung tissues exposed to 5–25 µg/cm^2 nickel nanoparticles showed dose-dependent cytotoxicity (Magaye et al. 2016). Dose-dependent cyto- and genotoxicity of nickel nanoparticles, nickel oxide nanoparticles, and nickel ferrite nanoparticles were observed in human lung epithelial cells, liver HepG2 cells, human skin epidermal cells, intestinal epithelial cells, and breast MFC-7 cancer cells mediated through oxidative stress (Abudayyak et al. 2020; Ahamed 2011; Ahamed et al. 2015; Ahmad et al. 2015; Alarifi et al. 2014; Capasso et al. 2014; Duan et al. 2015; Latvala et al. 2016; Saquib et al. 2018). Dose-dependent genotoxicity to nickel nanomaterials was observed in *D. melanogaster* after 24 hours of exposure (Alaraby et al. 2018).

Research on the absorption of nickel nanoparticles is limited, but existing data show that smaller nickel particles are absorbed more readily than larger ones. This suggests that absorption rates may be higher for nickel nanoparticles than for other nickel compounds due to their small size. Solubility of nickel

nanoparticles may be related to shape. In a study of intratracheal exposure in rats, spherical nickel oxide nanoparticles dissolved less readily in artificial lysosomal fluid and had lower pulmonary clearance rates than wire-shaped nickel oxide nanoparticles, suggesting that wire-shaped nickel nanoparticles may be more readily absorbed by the lungs. The smallest nickel oxide nanoparticles also had the highest absorption and distribution rates (Shinohara et al. 2017). Nickel nanoparticle shape may also affect distribution rate. In a study of differently shaped nickel nanoparticles administered intratracheally to rats, distribution from the lungs to lymph nodes was time- and dose-dependent for spherical and irregular nickel oxide particles, but not for wire-shaped ones (Shinohara et al. 2017). Dumala et al. (2018) also observed that a single oral dose of 125 mg/kg body weight nickel oxide nanoparticles in rats accumulated in the blood, liver, and kidney and the 250 mg/kg body weight dose in the brain. Human neuronal (SH-SY5Y) cells exposed to nickel oxide nanoparticles 0–500 µg/mL for 24 hours exhibited a dose-dependent uptake of the nanoparticles and DNA damage, decreased cell viability, and increased oxidative stress (Abudayyak et al. 2017b). In another study, similar doses of nickel oxide nanoparticles in kidney epithelial cells resulted in DNA damage and apoptosis (Abudayyak et al. 2017a). Nickel nanoparticles accumulated in the liver and spleen of Wistar rats dosed with 2.5 mg/kg nickel oxide nanoparticles via intraperitoneal injection 3 times a week up to 18 injections (Minigalieva et al. 2015). In a study by Shinohara et al. (2017), pulmonary clearance rate constants were estimated using a one-compartment model in rats that demonstrated that the shape of nickel nanoparticles influenced the clearance. Research on nanoparticles in general suggest that particle size will influence respiratory distribution and deposition (Oberdörster et al. 2005). The percentage of regional deposition in the nasal, pharyngeal, and laryngeal regions decrease with increasing nanoparticle size and alveolar region deposition increases. Additionally, the translocation of nanoparticles to extrapulmonary sites appears to be greater for nanoparticles compared to larger particles.

There are little data about the metabolism of nickel nanoparticles, but research suggests that nickel nanoparticles have the same target organs as larger nickel compounds and exert toxicity in a similar manner (binding to ligands in serum).

In female Wistar rats, excretion of nickel via urine and feces increased with both dose and time when measured 18 and 24 hours after a single gavage dose (125–500 mg/kg body weight) of nickel oxide nanoparticles (Dumala et al. 2017). Wistar rats were dosed with nickel oxide nanoparticles via intraperitoneal injection at a dose of 2.5 mg/kg 3 times/week up to 18 injections and nickel oxide nanoparticles underwent renal excretion (Minigalieva et al. 2015). Whole-body inhalation exposure to nickel oxide nanoparticles for 6 hours/day for 4 weeks resulted in accumulation of nickel oxide

nanoparticles in the lungs; retained particles in rat lungs after inhalation exponentially decreased with a calculated biological half-time of 62 days (Oyabu et al. 2007). In a study of differently shaped nickel nanoparticles administered intratracheally to rats, wire-shaped nickel oxide nanoparticles were excreted in urine much more quickly (35% 24 hours after administration) than spherical and irregular particles (0.33–3.6% 24 hours after administration) (Shinohara et al. 2017).