Toxicological Profile for Nickel

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health-related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
August 2023	Draft for public comment released
August 2005	Final toxicological profile released
September 1997	Final toxicological profile released
October 1993	Final toxicological profile released
October 1988	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Nickel (Ni) is a chemical element that exists as a silvery-white metal and occurs naturally in the earth's crust. Due to nickel's strength, resistance to corrosion, and ability to withstand high temperatures, nickel is useful in a variety of applications. In the United States, nickel is primarily used for stainless and alloy steels, nonferrous alloys and superalloys, and electroplating (USGS 2021). Alloys are used in medical devices such as dental appliances and tools, orthopedic implants, birth control implants, and cardiovascular prosthesis; batteries, including electronic vehicle batteries; and equipment and parts for chemical plants, petroleum refineries, jet engines, power generation facilities, and offshore installations. The National Academy of Sciences reported that there are insufficient data to determine a Recommended Dietary Allowance for nickel (Institute of Medicine 2001). The Tolerable Upper Intake Level for nickel reported by the National Academies of Sciences, Engineering, and Medicine (NASEM) is 1.0 mg/day as soluble salts for humans 14 years and older, 0.6 mg/day for 9 to 13 year olds, 0.3 mg/day for 4 to 8 years of age, and 0.2 mg/day for 1 to 3 year olds (NASEM 2019). The Institute of Medicine (2001) estimates that the general population has a nickel intake of less than 0.5 mg/day. The general population is primarily exposed to nickel by food and water intake. While not considered an essential trace element in humans, it is essential for other animals, microorganisms, and especially plants. Elevated levels of nickel in drinking water can result in excess nickel consumption and possibly toxicity. Additionally, occupational exposures can occur following inhalation of dusts or powders containing elevated levels of nickel or nickel compounds. According to the Cleveland Clinic, nickel allergy and sensitivity, typically observed as contact dermatitis, is estimated to affect about 10% of the U.S. population (Cleveland Clinic 2018). Studies indicate that the prevalence of nickel allergy globally is between 11-16% (Alinaghi et al. 2019; Uter et al. 2003) and is more prevalent among females (Thyssen and Menne 2010). Nickel is released in the environment from natural sources such as windblown soil particles and weathering of rocks and from anthropogenic sources such as coal and oil combustion and waste incineration. There is evidence that nickel accumulates in plants. Thus, the public is exposed to nickel daily from many sources including air, food, water, and products containing nickel such as cooking utensils and jewelry. In ambient air in 2020, the mean nickel concentration across 22 U.S. sites ranged from 0.000078 to 0.16 $\mu g/m^3$ (EPA 2020a). The mean concentration of nickel in food products in the U.S. ranges from 0.0004 to 3.2 mg/kg, and nickel was not detected in bottled drinking water (FDA 2017a). The concentration of nickel in samples reported to the Water Quality Portal in which nickel was detected ranged from 0 to 18,200 µg/L in groundwater and 0 to 6,390 µg/L in surface water (WQP 2021). Nickel is also present in tobacco products and e-cigarettes at concentrations ranging from 1.19 to 27.67 µg/g in cigarettes and

smokeless tobacco products, and up to 22,600 µg/L in e-cigarette liquid (see Table 5-13). People who work in industries producing nickel or using nickel products may be exposed to nickel dermally or through inhalation. Nickel has been measured in blood, breastmilk, exhaled breath condensate, feces, hair nasal mucosa, saliva, serum, sweat, toenails, and urine.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of nickel and nickel compounds comes primarily from inhalation studies in both animals and humans exposed to nickel compounds. Human studies primarily consist of epidemiological studies examining the effect of inhalation-exposure to nickel on individuals or groups occupationally exposed indoors. Population-level studies examine associations between nickel levels in ambient air and various health outcomes among the population. Experimental studies in humans primarily test dermal reactions to nickel, particularly as a concern of allergic contact dermatitis (further described in 2.11 and 2.14). Experimental studies in animals examining inhalation exposure looked at various endpoints, mainly the respiratory and immunological endpoints, and contact dermatitis was a commonly reported effect. A limited number of studies in both humans and animals have examined nickel toxicity due to oral exposure. The genotoxicity of nickel and nickel compounds has been tested using a variety of species and protocols, as described in Section 2.20. Figure 1-3 and Figure 1-4 summarize the health effects observed in human and animal inhalation and oral studies, respectively. Taken together, the nickel database demonstrates that the respiratory and immunological systems are the most sensitive to nickel toxicity following inhalation or oral exposure. Subsequently, a systematic review was conducted on these endpoints. The weight-of-evidence conclusions are defined and summarized in Appendix C. The review resulted in the following hazard identification[1] conclusions:

- Respiratory effects are a presumed health effect of nickel exposure.
- Immunological effects are a presumed health effect of nickel exposure.

Respiratory Effects. Respiratory toxicity due to inhalation exposure to nickel or nickel compounds is reported in several occupational cohort studies. Supported by findings of respiratory toxicity in

[1] For additional details on the definitions on the hazard identification categories the reader is referred to Appendix C.

experimental animal studies, the respiratory system is the primary target of nickel toxicity. Several studies of nickel refinery workers have reported no increased death due to respiratory diseases (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Redmond 1984; Roberts et al. 1989a; Shannon et al. 1984b; Shannon et al. 1991). These studies are limited due to a possible healthy worker effect and co-exposure to other respiratory toxicants. A single case of death from adult respiratory distress syndrome (ARDS) has been reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994). Several other studies of welders and refinery workers reported that higher levels of nickel exposure in air was associated with respiratory systems effects, reduced vital capacity, and higher risk of pulmonary fibrosis (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990). However, these workers were also exposed to other metals and cigarette smoking may also be a confounder. Additionally, asthma relating to occupational exposure possibly as an allergic response is reported (Dolovich et al. 1984; Novey et al. 1983; Shirakawa et al. 1990). Case studies in workers exposed acutely to high concentrations of nickel-containing powders or fumes support epidemiological findings in the respiratory system (Bolek et al. 2017; Bowman et al. 2018; Kunimasa et al. 2011; Peric and Durdevic 2020). Several population studies in children and adults have reported associations between higher levels of nickel in ambient air and hospitalizations or incidence of asthma symptoms (Bell et al. 2009; Bell et al. 2014; Rosa et al. 2016; Schachter et al. 2020). Acute-duration inhalation studies in rats and mice further indicate respiratory toxicity at concentrations as low as 0.43 mg Ni/m^3 reporting chronic lung inflammation, labored breathing, bronchiolar epithelium degeneration, and alveolitis among other findings in the respiratory system (Bai et al. 2013; Benson et al. 1995b; Efremenko et al. 2014; NTP 1996b, 1996c). Similar findings, including interstitial pneumonia and histological changes in the lungs, are reported in similarly designed intermediate-duration studies in rats and mice at concentrations as low as 0.11 mg Ni/m^3 (Benson et al. 1995a; Bingham et al. 1972; Evans et al. 1995; Horie et al. 1985; NTP 1996a, 1996b, 1996c; Weischer et al. 1980). In chronic-duration studies where rats and mice were exposed to concentrations as low as 0.06 mg Ni/m^3 for 2 years, lung inflammation is the most reported effect following exposure to nickel sulfate, sulfate hexahydrate, subsulfide, and oxide (NTP 1996a, 1996b, 1996c ; Ottolenghi et al. 1975). Oral doses of nickel compounds in rats as low as 5.75 mg Ni/kg/day also induce respiratory effects including emphysema, bronchiectasis, irregular respiration, pneumonitis, increased lung weight, and altered lung enzyme levels (American Biogenics Corporation 1988; Obone et al. 1999; Oller and Erexson 2007; RTI 1988a, 1988).

Immunological Effects. Immunological effects following nickel exposure are evaluated in human studies. Contact dermatitis resulting from an allergic response, or sensitivity, to nickel is a prevalent adverse effect among the general population and workers. An allergic response can occur from exposure to

airborne nickel, ingestion of nickel-containing solutions, or dermal contact, and sensitization is reported following nickel ingestion or dermal contact. Nickel exposure induced significant changes in the levels of various antibodies in both production workers exposed to unknown amounts of nickel in air and in individuals with hard-metal asthma (Bencko et al. 1983; Bencko et al. 1986; Shirakawa et al. 1990). Nickel sensitivity is evaluated in individuals (non-workers) who tested positive for a dermal allergic reaction, and sensitivity appeared to be related to increased prevalence of human lymphocyte antigens (Kapsenberg et al. 1988; Mozzanica et al. 1990). In animal studies, nickel inhalation exposure appears to induce alteration in both innate and acquired immunity. At the lowest concentration tested of 0.00017 mg Ni/m^3, mice exposed to nickel sulfate for 3 months showed increased macrophages in epididymal white adipose tissue and in lung tissue sections (Xu et al. 2012). Rats exposed for 104 weeks to 0.1 mg Ni/m^3 showed an increased incidence of minimal-to-severe histiocyte infiltrate in bronchial lymph nodes and extramedullary hematopoiesis in the spleen Oller et al. 2008). At concentrations as low as 0.45 mg Ni/m^3, alveolar macrophage alterations are reported in rats exposed to nickel chloride, mice exposed to nickel subsulfide, and in rabbits exposed to nickel chloride (Bingham et al. 1972; Johansson et al. 1989; Johansson et al. 1987; Johansson et al. 1988). Alterations in macrophage production of tumor necrosis factor in rats both increased and decreased in two different studies, likely due to differing exposure conditions (Goutet et al. 2000; Morimoto et al. 1995). Impaired immune response is seen in inhalation exposure studies of mice exposed to nickel compounds for 2 hours (Adkins et al. 1979a, 1979b, 1979c; Graham et al. 1978), rats exposed for 4 months (Spiegelberg et al. 1984), and mice exposed for 65 days (Haley et al. 1990). However, a recent study in mice exposed 24-hours to concentrations up to 0.0801 mg Ni/m^3 reported no exposure-related immunosuppressive effects (Buxton et al. 2021). Inhalation exposure studies in rats and mice by the National Toxicology Program indicate lymph node damage from nickel compound exposure, likely due to the removal of some nickel from the lung to the lymphatic system (NTP 1996a, 1996b, 1996c). Oral studies in animals are mixed on the effect of nickel exposure to immune function. A limited number of alterations were reported in immune function tests in mice (Dieter et al. 1988) and in rats (Obone et al. 1999) in addition to splenic changes including atrophy. The spleens of rats exposed to nickel sulfate did not show any gross or microscopic changes following 2 years of exposure (Ambrose et al. 1976). Enhanced inflammatory response in the heart of mice exposed to nickel chloride is also reported (Ilbäck et al. 1994).

Dermal. Contact dermatitis is commonly observed in individuals allergic to nickel or who have become sensitized to it. As previously noted, adverse immune responses to airborne nickel are reported in workers. In controlled human studies, dermatitis is reported in individuals who were sensitized to nickel dermally and then ingested single oral challenges of nickel-containing solution (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). Prolonged dermal exposure to nickel, such as by wearing nickel-containing jewelry, may lead to nickel sensitization (Akasya-Hillenbrand and Ozkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widström 1985; Meijer et al. 1995; Uter et al. 2003). Increased ingestion of nickel through diet for 4 days was also found to aggravate hand eczema (dermatitis) in women already diagnosed (Nielsen et al. 1990). Patch tests with nickel sulfate on sensitive individuals indicates a concentration-response relationship between contact dermatitis severity and nickel exposure (Emmett et al. 1988; Eun and Marks 1990). Some evidence suggests that acute or intermediate exposure to nickel orally may reduce sensitization (Jordan and King 1979; van Hoogstraten et al. 1991).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Nickel

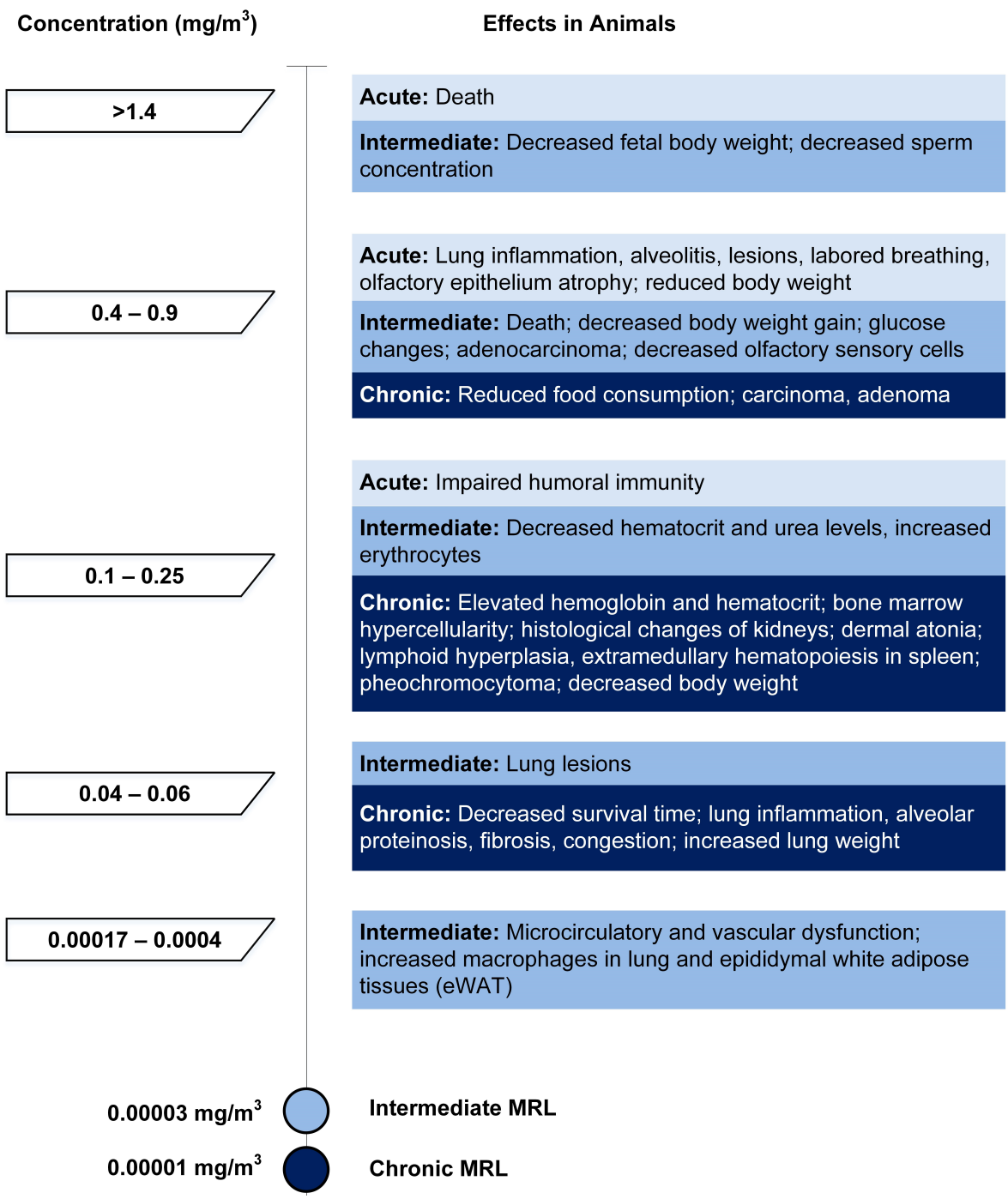
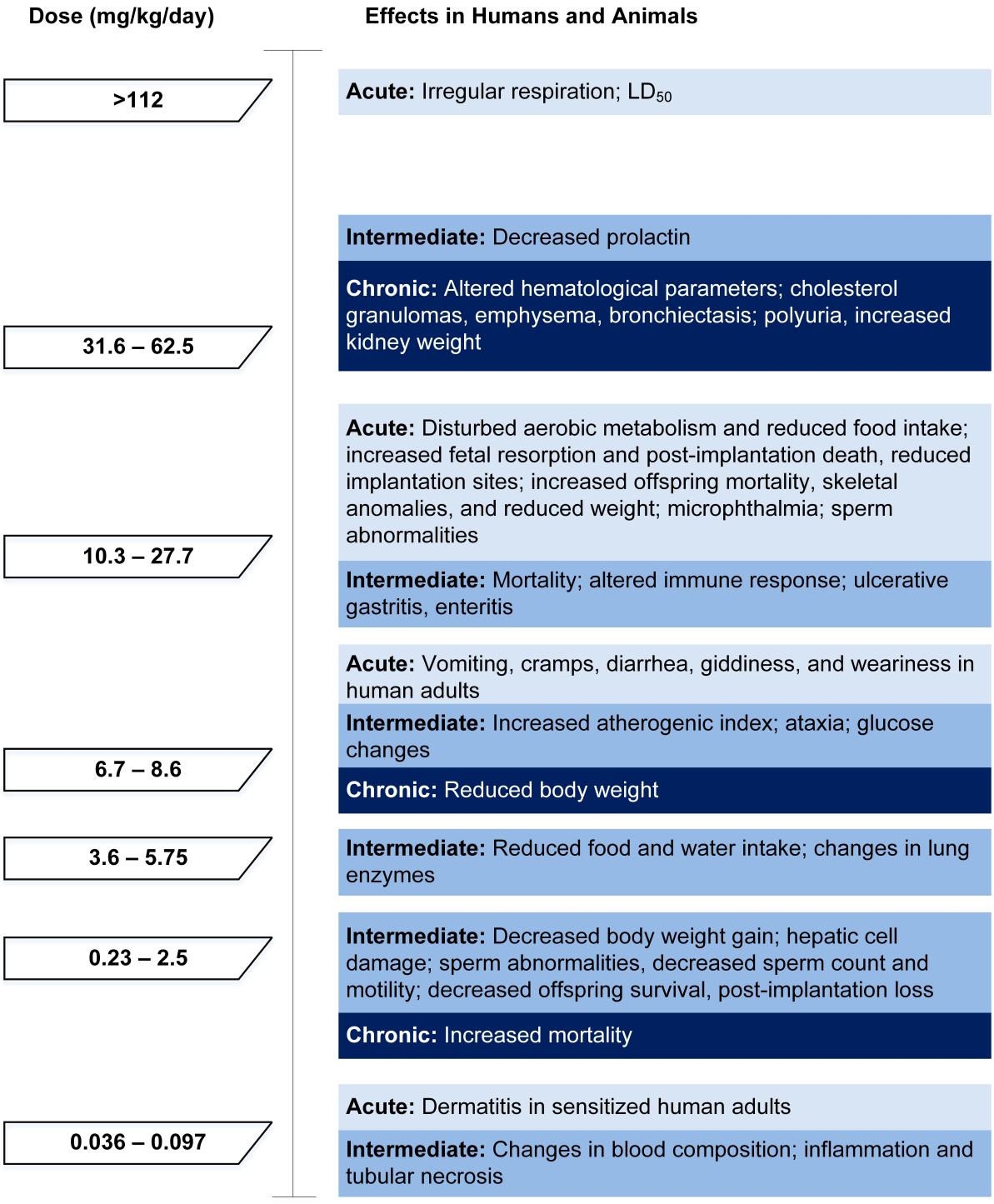


Figure 1-2. Health Effects Found in Humans* and Animals Following Oral Exposure to Nickel



*All effects listed were observed in animals unless otherwise specified.

1.3 MINIMAL RISK LEVELS (MRLS)

As presented in Figure 1-3, following inhalation exposure to nickel the respiratory and immunological systems appear to be the most sensitive to nickel toxicity. The acute-duration inhalation database was insufficient for derivation of an MRL. The inhalation database was adequate for the derivation of intermediate- and chronic-duration inhalation MRLs for nickel. The dermal endpoint appears to be the most sensitive target of oral nickel toxicity in humans, while in animals the hematological and renal endpoints appear to be the most sensitive. The oral exposure database was insufficient for the derivation of oral MRLs for any exposure duration. The inhalation MRLs derived for nickel are summarized in Table 1-1 and are discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Nickel – Inhalation

The immunological and respiratory systems are the most sensitive targets of Nickel inhalation exposure.

Numbers in circles are the lowest LOAELs among health effects in animals.

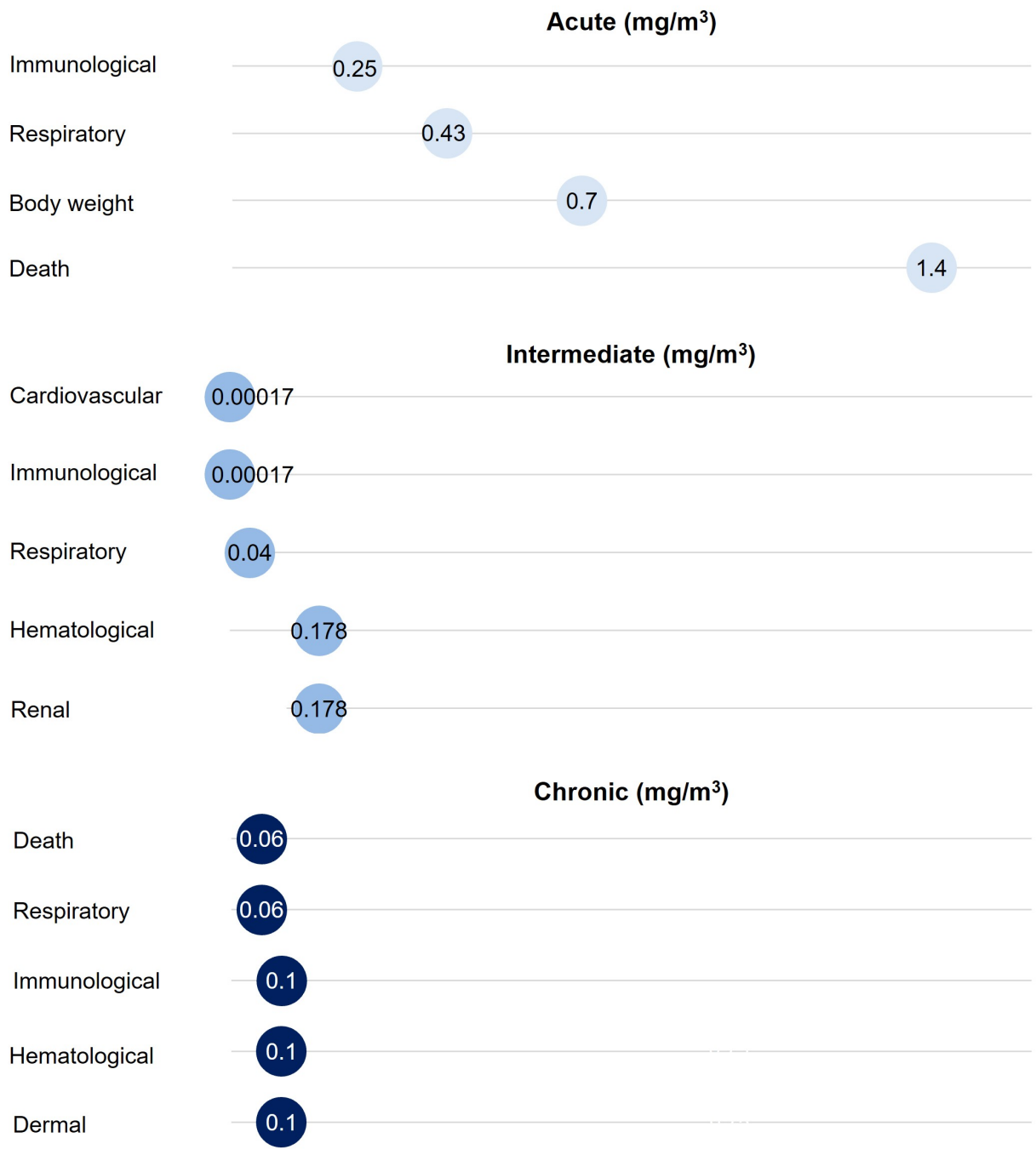


Figure 1-4. Summary of Sensitive Targets of Nickel – Oral

The dermal, hematological, and renal systems are the most sensitive targets of Nickel oral exposure.

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.

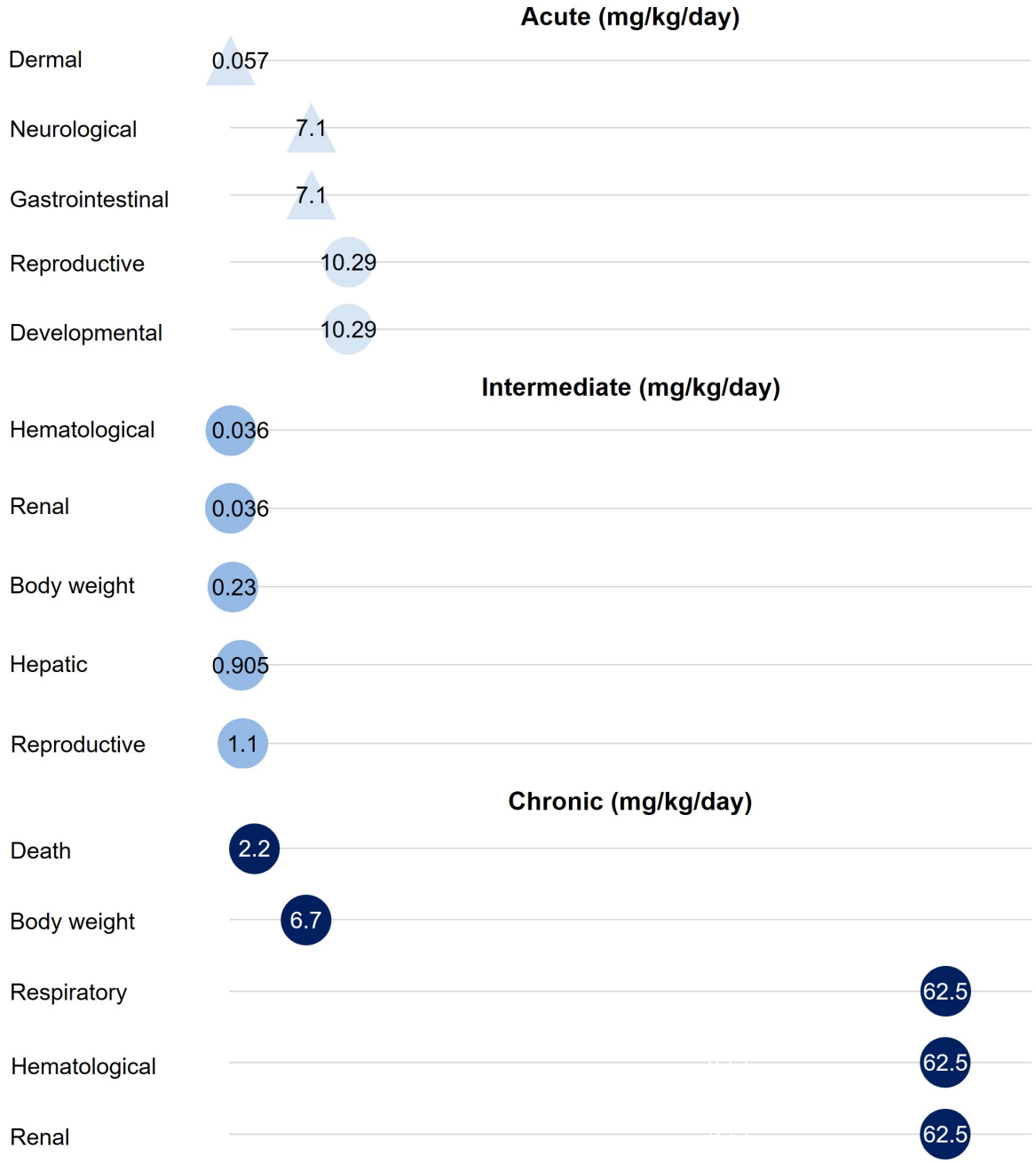


Table 1-1. Minimal Risk Levels (MRLs) for Chemical Nickel[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	None	–	–	–	–	–
	Intermediate	**$3x10^{-5}$ mg Ni/m^3**	Chronic lung inflammation	$NOAEL_{HEC,ADJ}$	$1x10^{-3}$ mg Ni/m^3	UF: 30	NTP 1996c
	Chronic	**$1x10^{-5}$ mg Ni/m3**	Chronic lung inflammation, fibrosis, alveolar proteinosis	$NOAEL_{HEC,ADJ}$	$3.6x10^{-4}$ mg Ni/m^3	UF: 30	NTP 1996c
Oral	**No Oral MRLs were derived for any duration.**						

[a]See Appendix A for additional information.

ADJ = adjusted for intermittent exposure; BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; MF = modifying factor; NOAEL = no-observed-adverse-effect level; LOAEL = lowest observed adverse effect level; MF = modifying factor; POD = point of departure; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

OVERVIEW

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.

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.

Summaries of cardiovascular human epidemiological studies are presented in Table 2-4. Animal inhalation studies are presented in Table 2-1 and Figure 2-2; and human and animal oral studies are presented in Table 2-2 and Figure 2-21; dermal data are presented in Table 2-3.

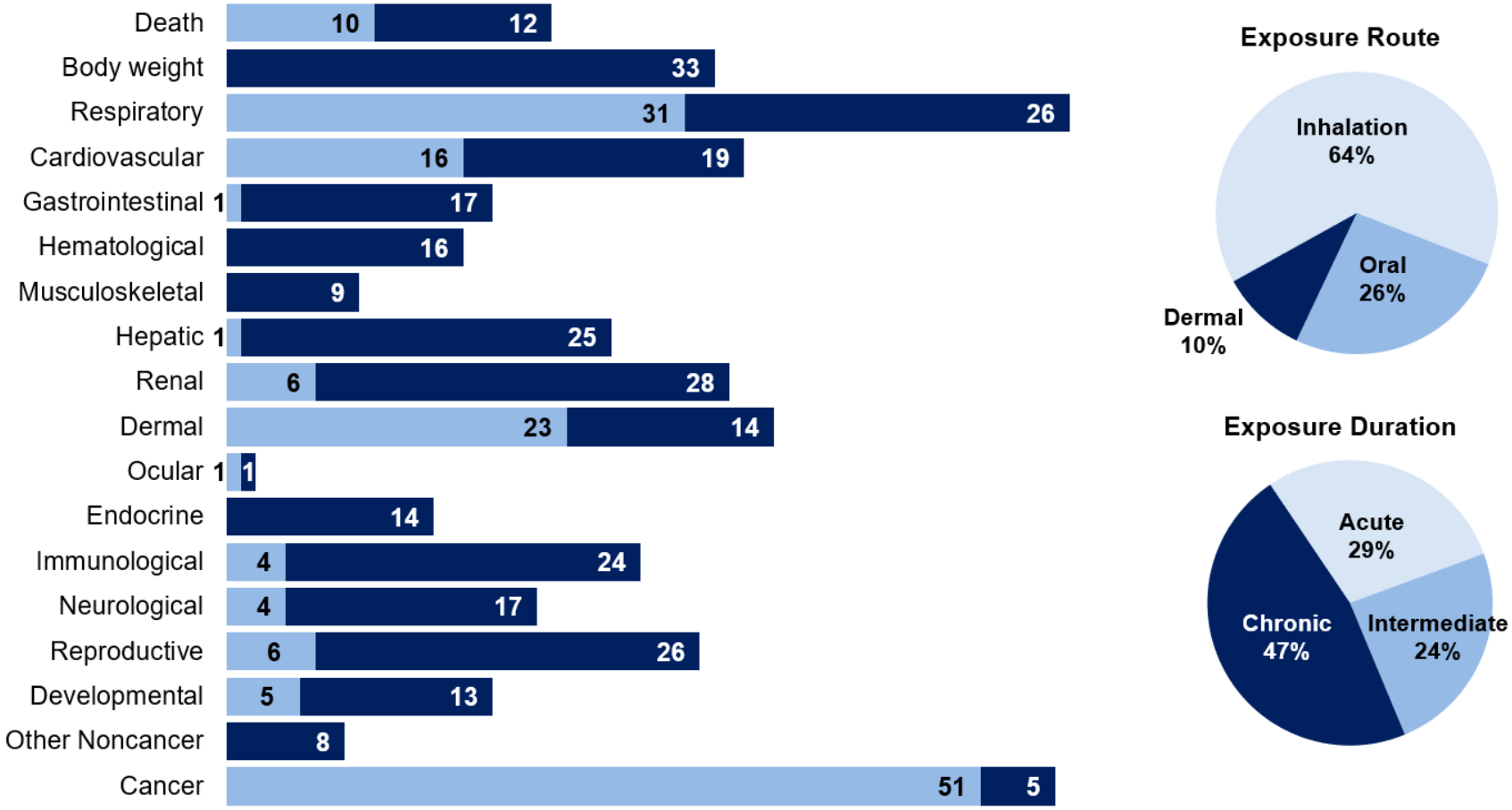
Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an 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 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.

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									
Bai et al. 2013									**Nickel carbonyl**
1	RAT (Sprague-Dawley) 40B	30 minutes (NS)	0, 6.88, 46.47, 85.94	HP	Resp		6.88	85.94	Damage of type II alveolar epithelial cells in rat lung tissue at 6.88 mg Ni/m^3 Pulmonary tissue edema, decreased peroxidation of pulmonary tissue lipid at 85.94 mg Ni/m^3
Benson et al. 1995b									**Nickel subsulfide**
2	RAT (Fischer-344) 4-6B	1, 2, 4, 7, or 12 days 6 hours/day	0, 0.44, 1.83	BC BW HP	Bd wt	0.44	1.83		~17-19% less body weight at day 7 of exposure
					Resp			0.44	Alveolitis in 6/6 rats, type II cell hypertrophy in 1/6 rats among other lung lesions after 7 days of exposure
Efremenko et al. 2014									**Nickel subsulfide**
3	RAT (Fischer-344) 5M	1 week 5 days/week 6 hours/day	0, 0.03, 0.06, 0.11, 0.43	BW BI	Bd wt	0.43			
					Resp	0.11	0.43		Over 250% increase of LDH in BALF
Efremenko et al. 2014									**Nickel subsulfide**
4	RAT (Fischer-344) 5M	1 week 5 days/week 6 hours/day	0, 0.43	BI GN HP	Resp		0.43		Peribronchiolar/perivascular inflammation in 5/5 rats
Hirano et al. 1994									**Nickel sulfate**
5	RAT (Wistar) 28M	2 hours	36.5	LE	Death			36.5	4/28 died
NTP 1996a									**Nickel oxide**

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
6	RAT (Fischer-344) 5M, 5F	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 in 2/5 male rats and 5/5 female rats
					Cardio	23.6			
					Gastro	23.6			
					Musc/skel	23.6			
					Hepatic	23.6			
					Renal	23.6			
					Dermal	23.6			
					Endocr	23.6			
					Immuno	23.6			
					Neuro	23.6			
					Repro	23.6			
NTP 1996b									**Nickel subsulfide**
7	RAT (Fischer-344) 5M, 5F	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 (10/10 rats), atrophy of olfactory epithelium (6/10 rats)
								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			

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	7.33			
					Immuno	7.33			
					Neuro	7.33			
					Repro	7.33			
NTP 1996c									**Nickel sulfate hexahydrate**
8	RAT (Fischer-344) 5M, 5F	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
					Resp			0.7	Labored breathing and increased respiration rates; chronic lung inflammation, degeneration of bronchiolar epithelium, and atrophy of olfactory epithelium in 10/10 rats
					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 (7/9 rats) and mediastinal (5/8 rats) lymph nodes
					Neuro	3.1 F			
					Repro	12.2			
Adkins et al. 1979a									**Nickel chloride**

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
9	MOUSE (CD-1) 113F	2 hours	0, 0.66	BI CS	Immuno			0.66	Decreased ability to clear bacteria from lungs resulting in a significant increase in mortality (>20% higher than controls) and increased incidence of sepsis
Adkins et al. 1979b									**Nickel sulfate**
10	MOUSE (CD-1) 120F	2 hours	0, 0.46	BI CS	Immuno			0.46	Increased susceptibility to Streptococcal infection resulting in a significant increase in mortality (21% higher than controls) and reduced mean survival time (2 days less than controls)
Adkins et al. 1979c									**Nickel chloride**
11	MOUSE (CD-1) 80-160F	2 hours	0, 0.288, 0.292, 0.369, 0.5, 0.51	BI CS	Immuno	0.37		0.5	Increased susceptibility to Streptococcal infection resulting in a significant increase in mortality (26% higher than controls) and reduced mean survival time (2.73 days less than controls)
Buxton et al. 2021									**Nickel chloride hexahydrate**
12	MOUSE (ICR) 10-15F	24 hours	0, 0.02, 0.04, 0.08	BW CS FI GN HP OW WI	Bd wt	0.08			
					Immuno	0.08			
Graham et al. 1978									**Nickel chloride**
13	MOUSE (Swiss) 14-29F	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**

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
14	MOUSE (B6C3F1) 5M, 5F	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		Elevated incidence of alveolar macrophage hyperplasia in 5/10 males and 3/10 females
					Cardio	23.6			
					Gastro	23.6			
					Hepatic	23.6			
					Renal	23.6			
					Dermal	23.6			
					Endocr	23.6			
					Immuno	23.6			
					Neuro	23.6			
					Repro	23.6			
NTP 1996b									**Nickel subsulfide**
15	MOUSE (B6C3F1) 5M, 5F	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		14% less body weight
					Resp	0.44	0.88	7.33	Atrophy of olfactory epithelium in 5/10 mice at 0.88 mg Ni/m^3 Necrosis in alveolar and bronchiolar epithelium, extensive vascular congestion, and edema at 7.33 mg Ni/m^3
					Gastro	3.65			
					Hemato	3.65			
					Musc/skel	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
					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			
NTP 1996c									**Nickel sulfate hexahydrate**
16	MOUSE (B6C3F1) 5M, 5F	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	Chronic lung inflammation in 9/10 mice and olfactory epithelium atrophy in 10/10 mice at 0.7 mg Ni/m^3 Necrotizing inflammatory lesions with edema, vascular congestion in all mice; rapid respiration rates at 1.4 mg Ni/m^3
					Cardio	1.4			
					Gastro	1.4			
					Musc/skel	1.4			
					Hepatic	1.4			
					Renal	1.4			
					Dermal	1.4			
					Endocr	1.4			

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	3.1			
					Neuro	0.7			
					Repro	1.4			
Muggenburg et al. 2003									**Nickel sulfate**
17	DOG (Beagle) 4B	3 hours	0.05, 0.1	CS	Cardio	0.1			
Muggenburg et al. 2003									**Nickel oxide**
18	DOG (Beagle) 4B	3 hours	0.06	CS	Cardio	0.06			
INTERMEDIATE EXPOSURE									
Benson et al. 1995a									**Nickel oxide**
19	RAT (Fischer-344) 90M	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		Moderate alveolitis that persisted at least 4 months after the exposure
Benson et al. 1995a									**Nickel sulfate**
20	RAT (Fischer-344) 90M	2-6 months 5 days/week 6 hours/day	0, 0.03, 0.11	BW CS HP OW	Resp	0.03	0.11		Alveolitis that persisted for 4 months after exposure
Benson et al. 1995b									**Nickel subsulfide**
21	RAT (Fischer-344) 4-6B	22 days 6 hours/day	0, 0.44, 1.83	BI BW HP OW	Bd wt	0.44	1.83		~10-19% less body weight
					Resp			0.44	Alveolitis in 6/6 rats, alveolar proteinosis in 5/6 rats, and olfactory epithelium degeneration in 3/4 rats; 18-27% increase in lung weight

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
Bingham et al. 1972									**Nickel oxide**
22	RAT (Wistar) 10M	> 2 weeks 6 days/week 12 hours/day	0, 0.12	BI CS HP	Resp		0.12		Alveolar wall thickening
Bingham et al. 1972									**Nickel chloride**
23	RAT (Wistar) 10M	>2 weeks 6 days/week 12 hours/day	0, 0.109	BI CS HP	Resp		0.11		Hyperplasia of the bronchial epithelium and peribronchial lymphocytic infiltration
Efremenko et al. 2014									**Nickel subsulfide**
24	RAT (Fischer-344) 26M (5M for HP)	4 weeks 5 days/week 6 hours/day	0, 0.03, 0.06, 0.11, 0.45	BW BI CS GN HP	Bd wt	0.45 M			
					Resp	0.06 M	0.11 M		Lung alveolus inflammation in 5/5 rats; significantly increased lymphocytes and macrophages
Evans et al. 1995									**Nickel sulfate**
25	RAT (Long-Evans) 5-14M	16 days 6 hours/day	0, 0.635	BW HP NX OW	Bd wt	0.64			
					Resp		0.64		Atrophy of olfactory epithelium; significant 20% increase in relative lung weight
					Renal	0.64			
					Neuro		0.64		Decrease in number of bipolar receptor cells in nasal olfactory epithelium
Horie et al. 1985									**Nickel oxide**
26	RAT (Wistar) 2-8M	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 in 5/6 rats, and squamous metaplasia in 3/6 rats
					Cancer			0.5	Adenocarcinoma in 1/6 rats

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**
27	RAT (Wistar) 5M	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**
28	RAT (Fischer-344) 10M, 10F	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 (17/20 rats), granulomatous inflammation (7/20 rats), and lung interstitial infiltrate in all rats
					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		Chronic active lung inflammation in 17/20 rats
					Neuro	7.9			
					Repro	7.9 F			
						3.9 M		7.9 M	20.5% decrease in sperm concentration
NTP 1996b									**Nickel subsulfide**
29		13 weeks 5 days/week			Bd wt	1.83			
					Resp	0.11	0.22		Chronic inflammation in 9/10 rats

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
	RAT (Fischer-344) 10M, 10F	6 hours/day	0, 0.11, 0.22, 0.44, 0.88, 1.83	BW CS HE HP LE OW RX				1.83 M	Labored breathing during weeks 2-7
					Cardio	1.83			
					Gastro	1.83			
					Hemato	0.11 F	0.22 F		3% increase in erythrocytes (p<=0.01)
						0.44 M	0.88 M		4 and 4.5% increase of erythrocyte and hemoglobin levels, respectively
					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 (19/20 rats) and mediastinal (14/19 rats) lymph nodes
					Neuro	1.83			
					Repro	1.83			
NTP 1996c									**Nickel sulfate hexahydrate**
30	RAT (Fischer-344) 10M, 10F	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[b]	0.11 F		Chronic lung inflammation in 4/10 rats and interstitial infiltrates in 6/10 rats ($NOAEL_{HEC,ADJ}$=0.001 mg/m^3)
						0.11 M	0.22 M		Atrophy of olfactory epithelium
					Cardio	0.44			
					Gastro	0.44			
					Musc/skel	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
					Hepatic	0.44			
					Renal	0.44			
					Dermal	0.44			
					Endocr	0.44			
					Immuno	0.11	0.22		Lymphoid hyperplasia in bronchial (17/19 rats) and mediastinal (17/20 rats) lymph nodes
					Neuro	0.44			
					Repro	0.44			
Oller et al. 2022									**Nickel subsulfide**
31	RAT (Fischer-344) 13M	3 - 13 weeks 5 days/week 6 hours/day	0, 0.04, 0.11, 0.44	BW CS GN HP OW	Bd wt	0.44			
					Resp		0.04		Increased incidence and severity of lung lesions including alveolitis (7/13 rats) and perivascular/ peribronchiolar inflammation (7/13 rats)
Oller et al. 2022									**Nickel sulfate hexahydrate**
32	RAT (Fischer-344) 13M	3 - 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		Increased incidence and severity of lung lesions including alveolitis (7/13 rats) and perivascular/ peribronchiolar inflammation (8/13 rats)
Oller et al. 2022									**Nickel sulfate hexahydrate**
33		3 - 13 weeks 5 days/week	0, 0.44	BW CS GN HP OW	Death			0.44	12 of 13 rats died within 1 week of 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
	RAT (Fischer-344) 13M	6 hours/day			Resp			0.44	Severe pulmonary edema, labored breathing
Spiegelberg et al. 1984									**Nickel oxide**
34	RAT (Wistar) 12M	4 weeks continuous	0, 0.047, 0.093, 0.216, 0.404, 0.818	CS OF	Immuno	0.093	0.216		Impaired humoral immunity
Spiegelberg et al. 1984									**Nickel oxide**
35	RAT (Wistar) 12M	4 months continuous	0, 0.025, 0.145	CS OF	Immuno		0.025		Increased number of macrophages and phagocytic activity increase to 130%
Weischer et al. 1980									**Nickel oxide**
36	RAT (Wistar) 10M	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 (31%)
					Hemato		0.178		4% decrease in hematocrit levels
					Hepatic	0.784			
					Renal		0.178		16% decrease in urea
					Other noncancer	0.178	0.385		Increased serum glucose (13%)
Weischer et al. 1980									**Nickel oxide**
37	RAT (Wistar) 10-13F	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 (40%)
					Hemato		0.8		Increased hematocrit (9%) and hemoglobin (10%)
					Hepatic	3.2			
					Renal		0.8		Increased urea (94%)

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
					Other noncancer		0.8		Decreased serum glucose level (19%)
Weischer et al. 1980									**Nickel oxide**
38	RAT (Wistar) 10-13F	GD 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%)
Benson et al. 1995a									**Nickel oxide**
39	MOUSE (B6C3F1) 108M	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
Benson et al. 1995a									**Nickel sulfate**
40	MOUSE (B6C3F1) 108M	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
Haley et al. 1990									**Nickel oxide**
41	MOUSE (B6C3F1) 40F	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 sulfate hexahydrate**
42	MOUSE (B6C3F1) 40F	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
Haley et al. 1990									**Nickel subsulfide**

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
43	MOUSE (B6C3F1) 40F	65 days 5 days/week 6 hours/day	0, 0.11, 0.45, 1.8	OF OW	Immuno	0.11	0.45		Pulmonary alveolar macrophage phagocytic activity decreased by approximately 66%
NTP 1996a									**Nickel oxide**
44	MOUSE (B6C3F1) 10M, 10F	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 in 6/10 females
						3.9 M	7.9 M		Perivascular lymphocytic infiltrates in 8/10 males
					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		Increased incidence of bronchial lymph node hyperplasia (5/9 males, 7/9 females)
					Neuro	7.9			
					Repro	7.9			
NTP 1996b									**Nickel subsulfide**
45	MOUSE (B6C3F1) 10M, 10F	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
					Cardio	1.83			
					Gastro	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
					Hemato	1.83			
					Musc/skel	1.83			
					Renal	1.83			
					Dermal	1.83			
					Endocr	1.83			
					Immuno	0.44 F	0.88 F		Lymphoid hyperplasia in bronchial lymph nodes of 5/7 mice
						0.88 M	1.83 M		Lymphoid hyperplasia in bronchial lymph nodes of 8/8 mice
					Neuro	1.83 F			
					Repro	1.83			
NTP 1996c									**Nickel sulfate hexahydrate**
46	MOUSE (B6C3F1) 10M, 10F	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 F		0.44 F	Chronic lung inflammation (9/10 females), fibrosis (all males and 8/10 females), and interstitial infiltrate (8/10 males; 8/10 females)
					Cardio	0.44			
					Gastro	0.44			
					Musc/skel	0.44			
					Hepatic	0.44			
					Renal	0.44			
					Dermal	0.44			
					Endocr	0.44			
					Immuno	0.22	0.44		Hyperplasia of bronchial lymph nodes in 8/10 females and 5/8 males

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	0.44 F			
					Repro	0.44			
Xu et al. 2012									**Nickel sulfate**
47	MOUSE (ApoE-/-) 5-6M	3 months 5 days/week 6 hours/day (Environ)	0, 0.00017	BC BI OW	Bd wt	0.00017			
					Cardio		0.00017		Induced microcirculatory dysfunction indicated by increases in adherent and rolling monocytes in the microcirculation
					Hemato	0.00017			
					Endocr	0.00017			
					Immuno		0.00017		Increased macrophages in lung and eWAT tissues
Ying et al. 2013									**Nickel metallic**
48	MOUSE (ApoE-/-) 6M	14 weeks 6 hours/day, 5 days/week (Environ)	0, 0.0004	BI OF	Cardio		0.0004		Vascular endothelial dysfunction indicated by increased aortic relaxation response to acetylcholine
Johansson and Camner 1986									**Nickel metallic**
49	RABBIT (NS) NR M	1-8 months 5 days/week 6 hours/day	0.2, 1	HP	Resp		0.2		Increased volume density of alveolar type II cells
					Immuno		0.2		Increased number of alveolar macrophages
Johansson and Camner 1986									**Nickel metallic**
50	RABBIT (NS) NR M	1-8 months 5 days/week 6 hours/day	0.3	HP	Resp		0.3		Increased volume density of alveolar type II cells
					Immuno		0.3		Increased number of alveolar macrophages

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
Johansson et al. 1980									**Nickel metallic**
51	RABBIT (NS) 6M	3 or 6 months 5 days/week 6 hours/day	0, 1.0	HP	Immuno		1		Inactive macrophage surfaces
Johansson et al. 1987									**Nickel chloride**
52	RABBIT (NS) 8M	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**
53	RABBIT (NS) 8M	4 months 5 days/week 6 hours/day	0, 0.6	GN HP	Immuno		0.6		Decreased macrophage lysosomal activity
CHRONIC EXPOSURE									
Hueper 1958									**Nickel metallic**
54	RAT (Wistar) 50M 50F	21 months 4-5 days/week 6 hours/day	15.0	CS LE	Death			15	100/100 died
Hueper 1958									**Nickel metallic**
55	RAT (Bethesda Black) 60F	21 months 4-5 days/week 6 hours/day	15.0	CS LE	Death			15	60/60 died
NTP 1996a									**Nickel oxide**
56	RAT	2 years	0, 0.5, 1, 2		Bd wt	2			

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
	(Fischer-344) 65M, 65F	5 days/week 6 hours/day		BW CS HE HP LE OW	Resp		0.5		Chronic lung inflammation and lung alveolus pigmentation in 105/106 rats
					Cardio	2			
					Gastro	2			
					Hemato	2			
					Musc/skel	2			
					Hepatic	2			
					Renal	2			
					Dermal	2			
					Endocr	1 F	2 F		Benign pheochromocytoma (adjusted rate=57%) and adrenal medulla hyperplasia in 22/53 rats
						2 M			
					Immuno		0.5		Lymphoid hyperplasia (7/71 males) and pigmentation (88/101 males and females) in bronchial lymph nodes
					Neuro	2			
					Repro	2			
					Cancer			1	CEL: Increased incidence of alveolar/bronchiolar adenoma or carcinoma
NTP 1996b									**Nickel subsulfide**
57	RAT (Fischer-344) 63M, 63F	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 inflammation of lung in 104/106 rats and lung fibrosis in 98/106 rats

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	0.73			
					Gastro	0.73			
					Hemato	0.11	0.73		Increased hematocrit (6-9%), hemoglobin (5-10%) in both sexes and 7% increase of erythrocyte in males
					Musc/skel	0.73			
					Renal	0.73			
					Endocr		0.11		Increased incidence of benign pheochromocytoma in males (adjusted rate=85%)
					Immuno		0.11		Lymphoid hyperplasia in bronchial lymph nodes (25/106 rats)
					Neuro	0.73			
					Repro	0.73			
					Cancer			0.73	CEL: increased incidence of alveolar/bronchiolar adenoma or carcinoma
NTP 1996c									**Nickel sulfate hexahydrate**
58	RAT (Fischer-344) 65M, 65F	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[c]		0.06	Chronic inflammation (91/106 rats), fibrosis (80/106), and alveolar proteinosis (34/106) in lung; ($NOAEL_{HEC,ADJ}$=0.00036 mg Ni/m^3)
					Cardio	0.11			
					Gastro	0.11			
					Hemato	0.11			
					Hepatic	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
					Renal	0.11			
					Dermal	0.11			
					Endocr	0.11			
					Immuno	0.06	0.11		Lymphoid hyperplasia in bronchial lymph nodes (21/101 rats)
					Neuro	0.11			
					Repro	0.11			
Oller et al. 2008									**Nickel metallic**
59	RAT (Wistar) 50M, 50F	104 weeks 5 days/week 6 hours/day (Environ)	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
					Resp			0.1	Labored breathing; alveolar proteinosis, histiocytosis, and chronic lung inflammation
					Hemato		0.1 F		Moderate hypercellularity of the sternum and femoral bone marrows
							0.1 M		7.5 and 8.3% increase in hemoglobin and hematocrit levels, respectively, at week 78
					Renal		0.1 F		Increased incidence of granular brown pigment in kidneys
						0.1 M	0.4 M		Increased incidence of granular brown pigment in kidneys
					Dermal		0.1		Dermal atonia (decrease in normal skin elasticity)
					Immuno		0.1		Minimal-to-severe histiocyte infiltrate in bronchial lymph node and increased incidence of

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
									extramedullary hematopoiesis in the spleen
					Other noncancer	0.1	0.4		Lower mean food consumption reduced in males from week 58-end of study and in females from weeks 66 to 87
					Cancer			0.4	CEL: Increased incidence of malignant pheochromocytoma in males (5/50) and adrenal cortex carcinoma in females (3/54)
Ottolenghi et al. 1974									**Nickel sulfide**
60	RAT (Fischer-344) 22-39M, 24-32F	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; lung hyperplasia in 133/208 rats
					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 (15/208 rats), adenocarcinomas (10/208), squamous cell carcinoma (3/208)
Takenaka et al. 1985									**Nickel oxide**

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
61	RAT (Wistar) 20-40M	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	Six-fold increase in lung weight, congestion, and alveolar proteinosis
Tanaka et al. 1988									**Nickel oxide**
62	RAT (Wistar) 1-5M	3, 6, or 12 months 5 days/week 7 hours/day	0, 0.235, 0.942	BW HP OW	Bd wt	0.942			
					Resp			0.235	Increased incidence of pneumonia and 21% increase in lung weight
					Hepatic	0.942			
					Renal	0.942			
Hueper 1958									**Nickel metallic**
63	MOUSE (C57) 20F	21 months 4-5 days/week 6 hours/day	15.0	CS LE	Death			15	20/20 died
NTP 1996a									**Nickel oxide**
64	MOUSE (B6C3F1) 79M, 76F	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 (64/133 mice), bronchiolization (59/133), and alveolar proteinosis (20/133)
					Cardio	3.9			
					Gastro	3.9			
					Hemato	3.9			
					Musc/skel	3.9			
					Hepatic	3.9			
					Renal	3.9			
					Dermal	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
					Endocr	3.9			
					Immuno		1		Bronchial lymph node hyperplasia
					Neuro	3.9			
					Repro	3.9			
					Cancer			2 F	CEL: increased incidence of alveolar/bronchiolar adenoma (10 mice)
NTP 1996b									**Nickel subsulfide**
65	MOUSE (B6C3F1) 80M, 80F	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 (98/118 mice), bronchiolization (106/118), alveolar proteinosis (111/118), and fibrosis in 7/59 females; olfactory epithelium atrophy (38/118 mice)
					Cardio	0.88			
					Gastro	0.88			
					Hemato	0.44 F 0.88 M	0.88 F		6.5% increase of hematocrit
					Hepatic	0.88			
					Renal	0.88			
					Dermal	0.88			
					Endocr	0.88			
					Immuno		0.44		Lymphoid hyperplasia (86/110 mice) and macrophage hyperplasia (91/110) in bronchial lymph nodes
					Neuro	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
					Repro	0.88			
NTP 1996c									**Nickel sulfate hexahydrate**
66	MOUSE (B6C3F1) 80M, 80F	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 (7/60 rats) and bronchiolization (9/60)
						0.06 M	0.11 M		Chronic active lung inflammation (8/62 rats), bronchiolization (19/62), and olfactory epithelium atrophy (12/61)
					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 (22/103 rats)
					Neuro	0.22			
					Repro	0.22			
Hueper 1958									**Nickel metallic**
67	GN PIG (strain 13) 32M, 10F	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.

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

[b]Used to derive a provisional intermediate-duration inhalation minimal risk level of 0.00003 mg/m^3; the $NOAEL_{HEC,ADJ}$ of 0.001 mg/m^3 was divided by an uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).
[c]Used to derive a provisional chronic-duration inhalation minimal risk level of 0.00001 mg/m^3; the $NOAEL_{HEC,ADJ}$ of 0.00036 mg/m^3 was divided by an uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

B = both sexes; BALF = bronchoalveolar lavage fluid; Bd wt and BW= body weight; BC = serum (blood) chemistry; BI =biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; DX = developmental toxicity; Endocr = endocrine; Environ = environmental; eWAT = epididymal white adipose tissue; F= female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematological; HEC = human equivalent concentration; HP = histopathology; Immuno = immunological; LDH = lactate dehydrogenase; LE = lethality; LC50 = concentration producing 50% death; LOAEL = lowest-observed-adverse-effect-level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect-level; NR = not reported; 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

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

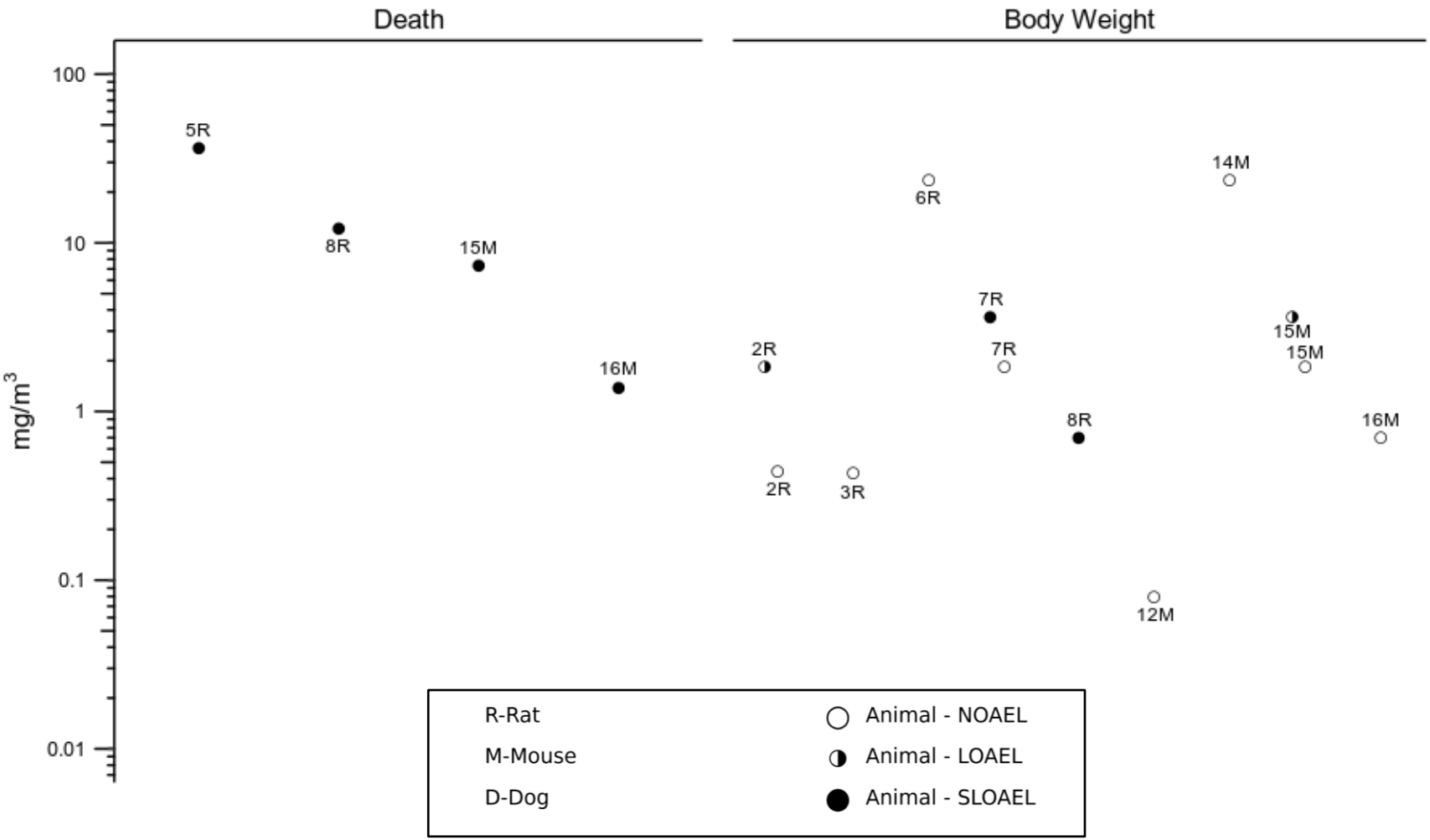


Figure 2-3. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

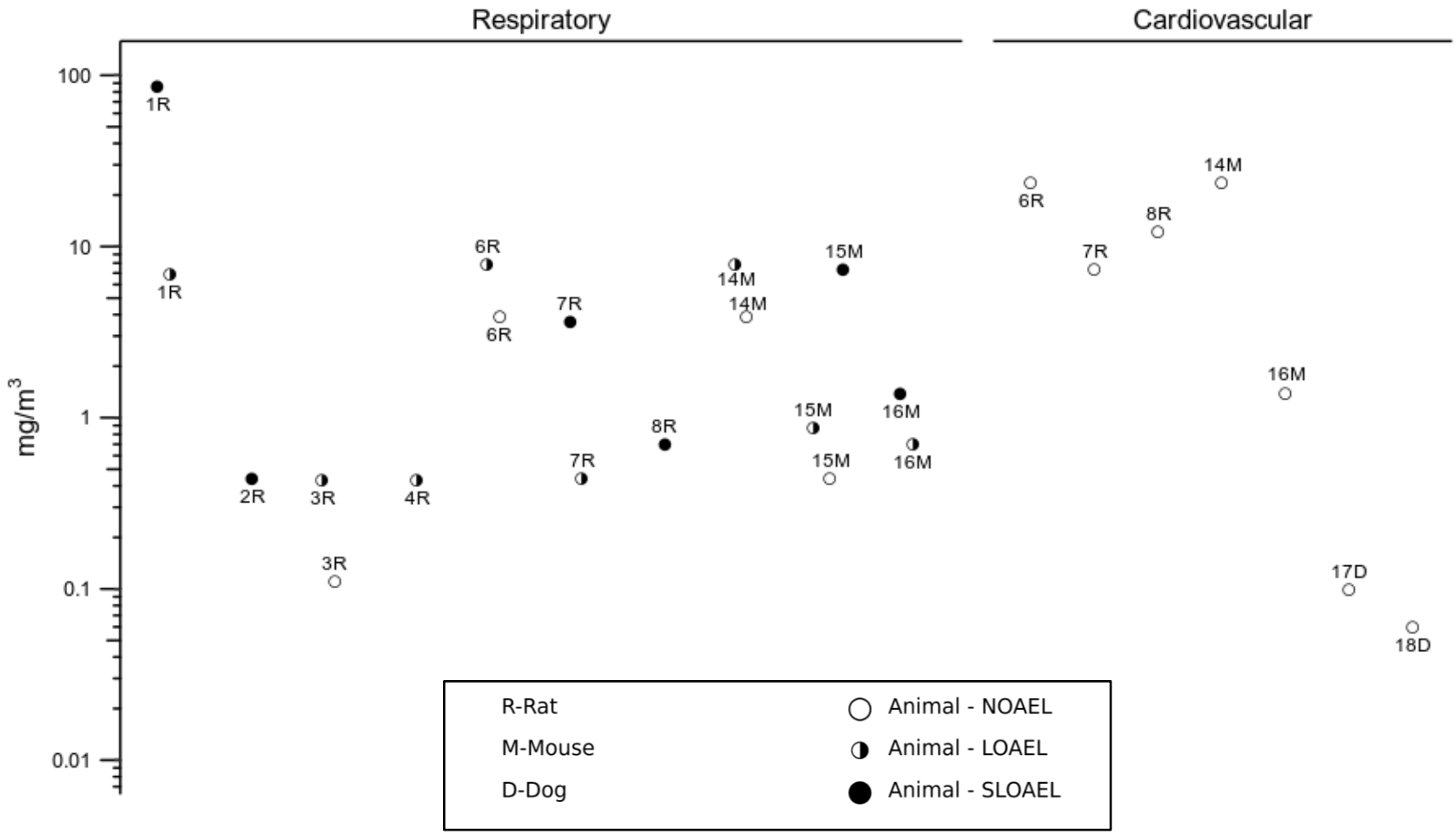


Figure 2-4. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

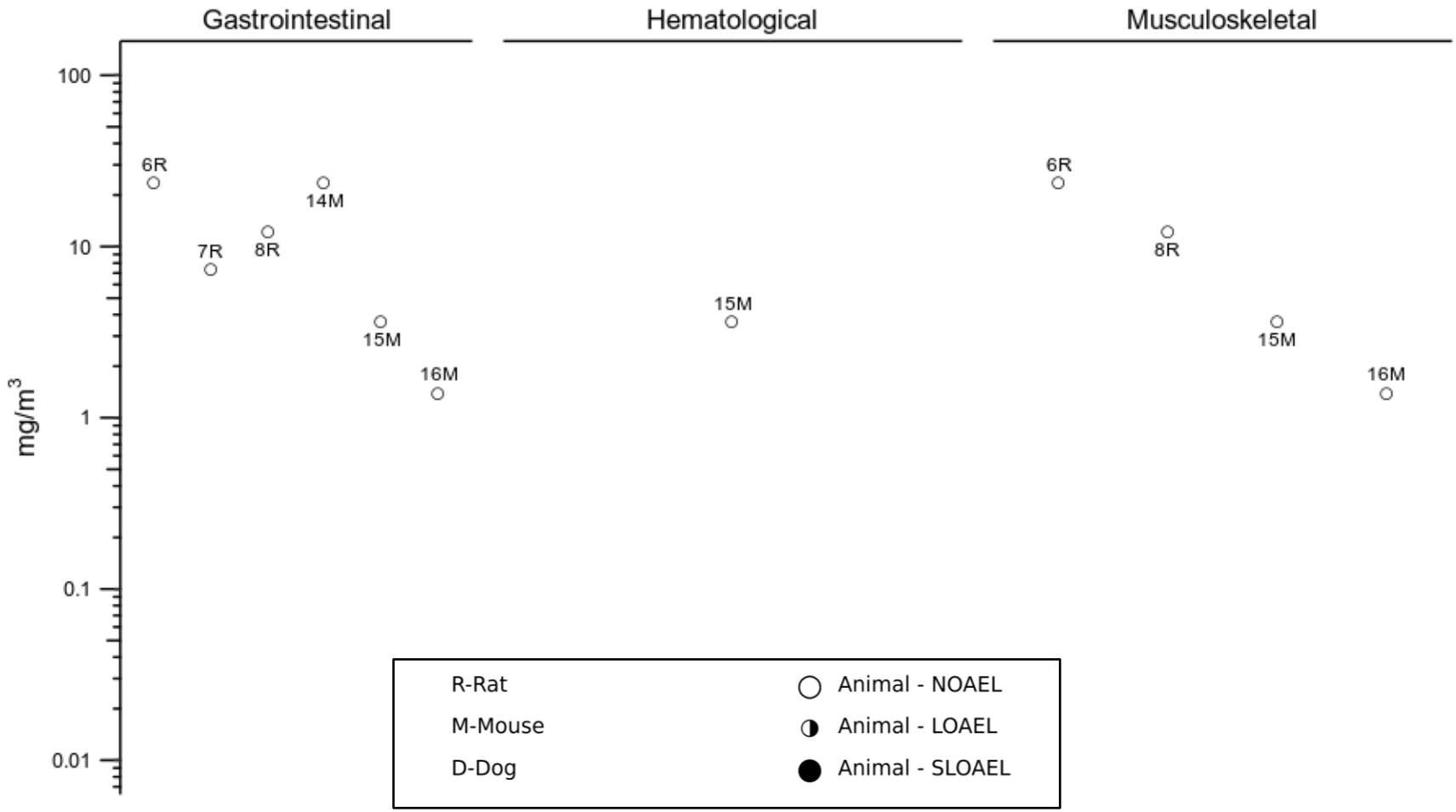


Figure 2-5. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

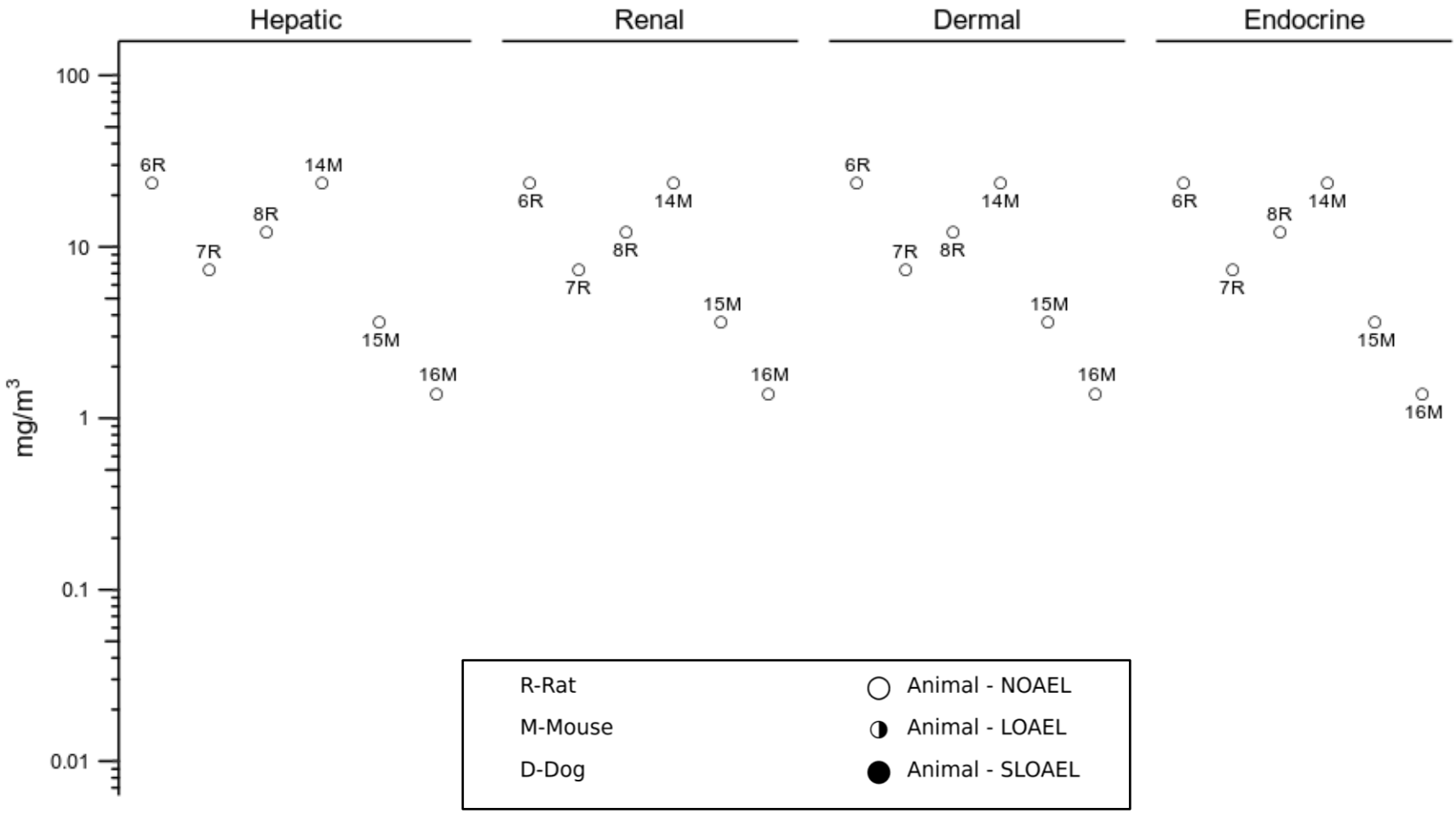


Figure 2-6. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

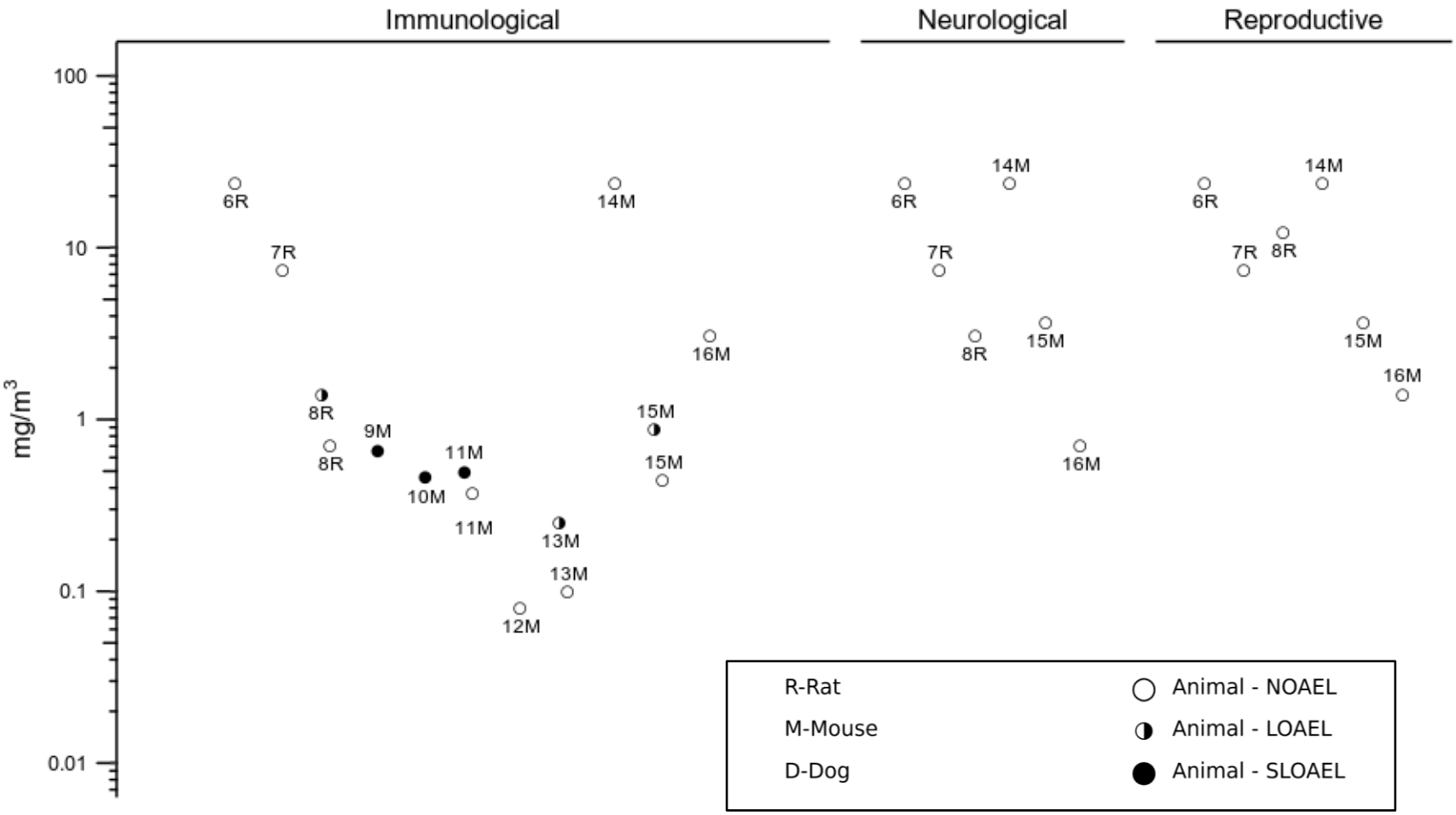


Figure 2-7. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

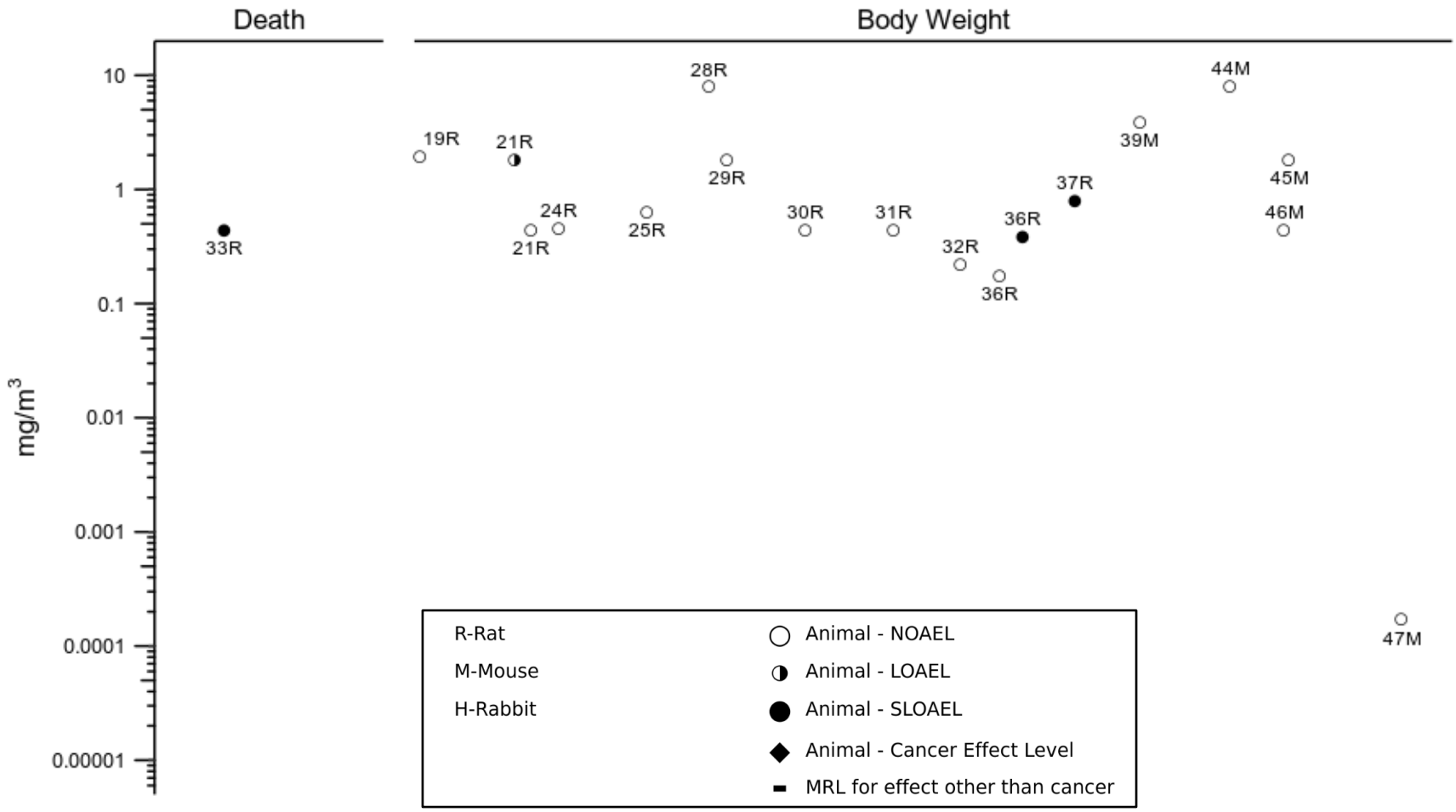


Figure 2-8. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

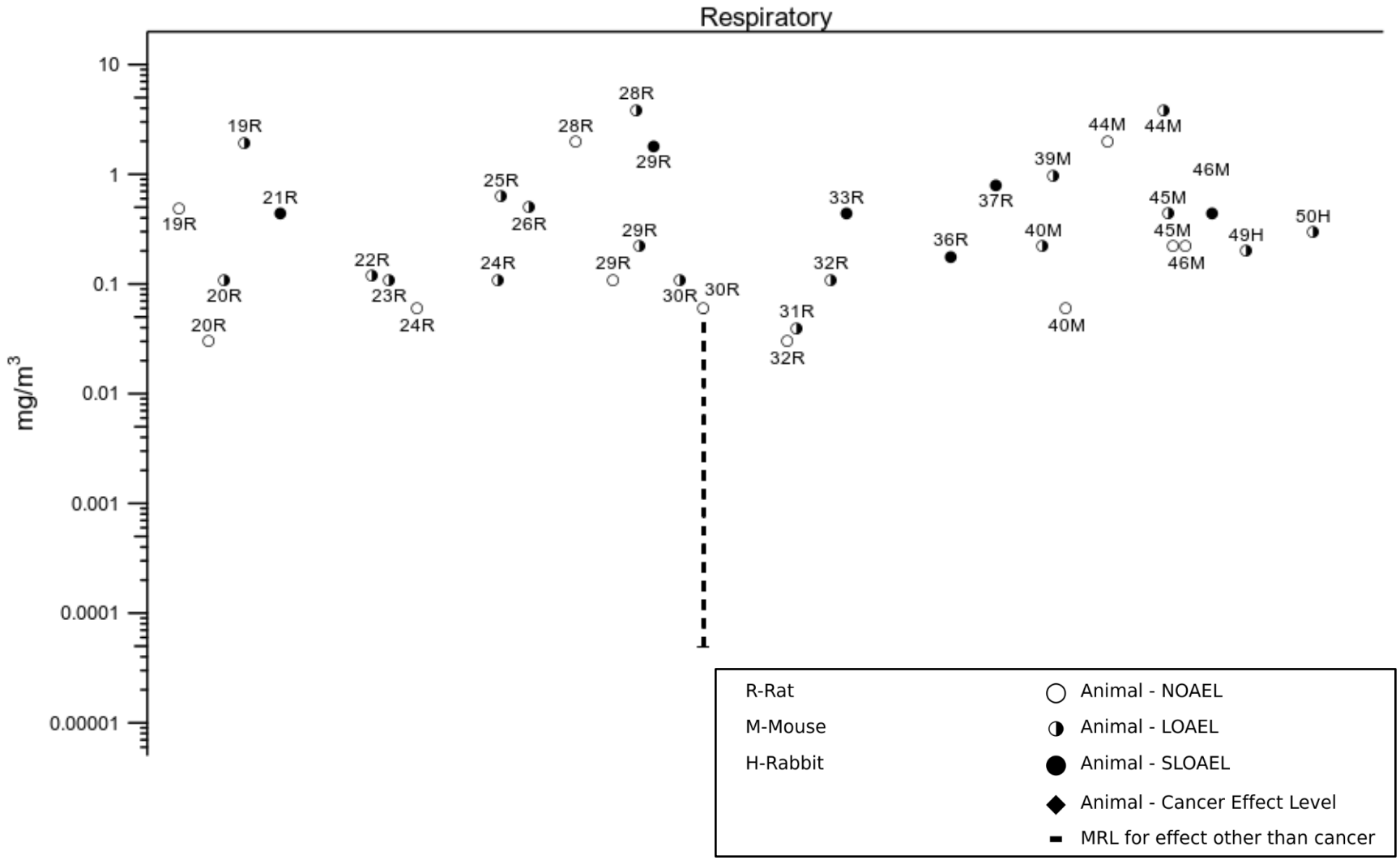


Figure 2-9. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

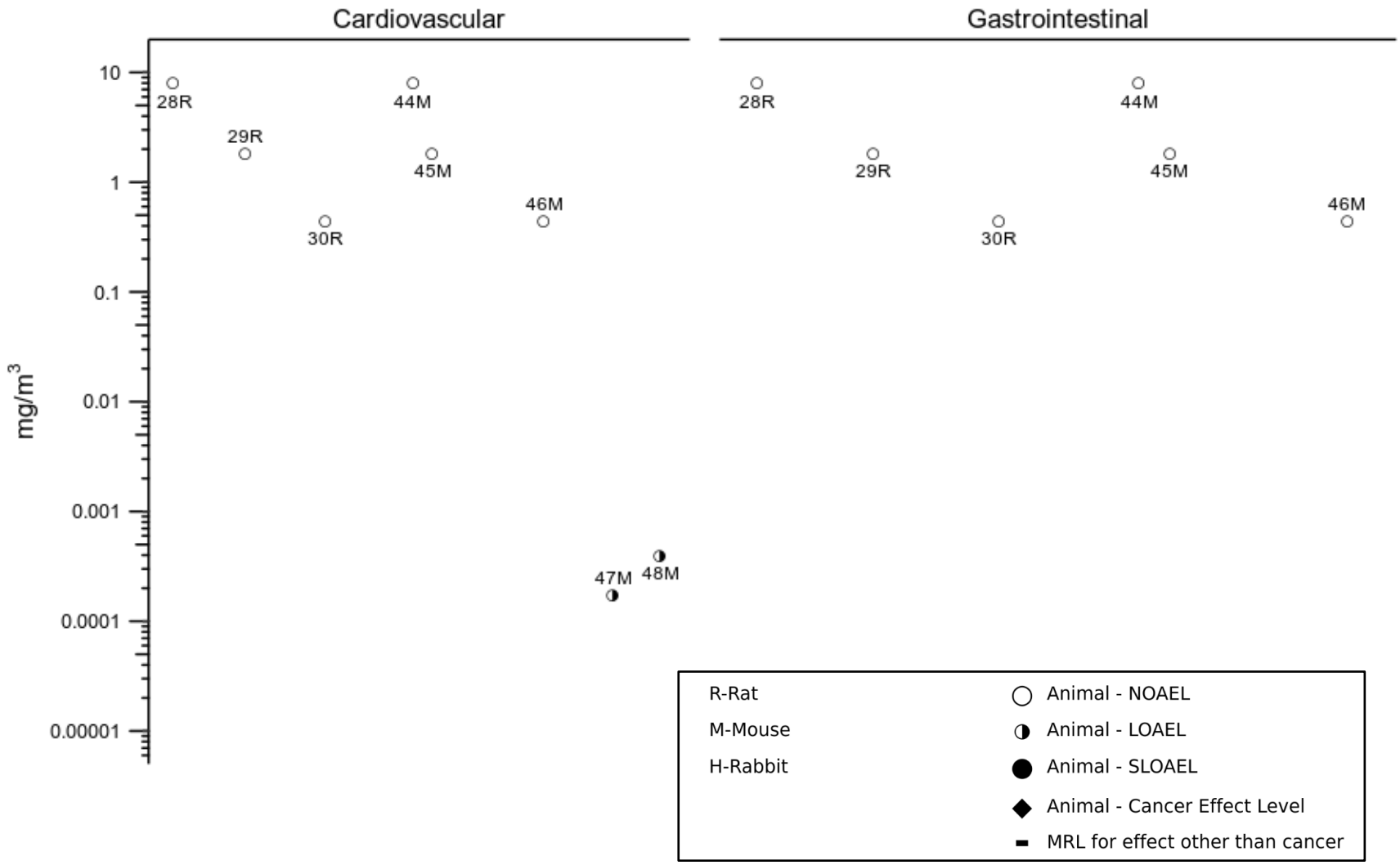


Figure 2-10. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

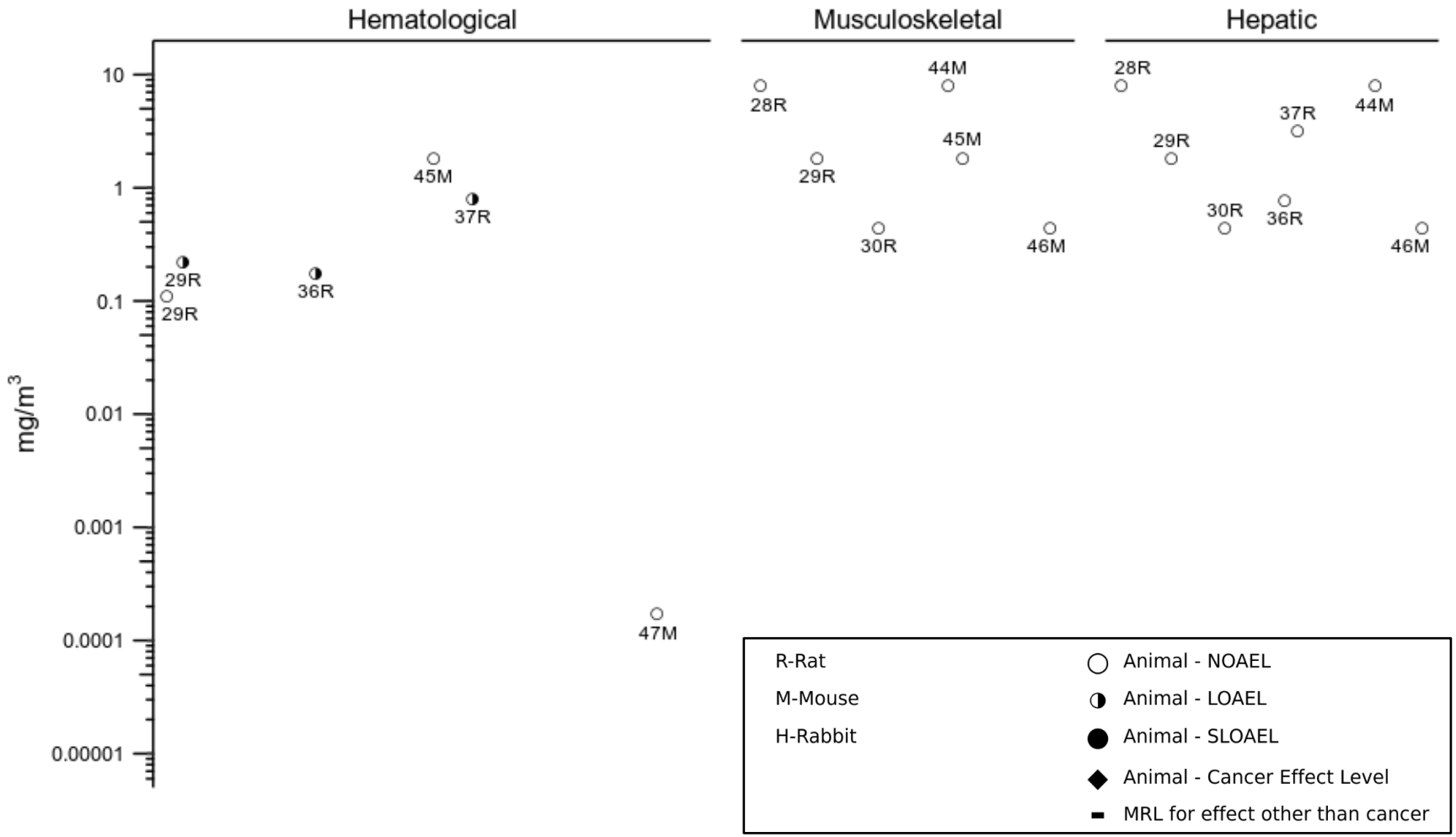


Figure 2-11. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

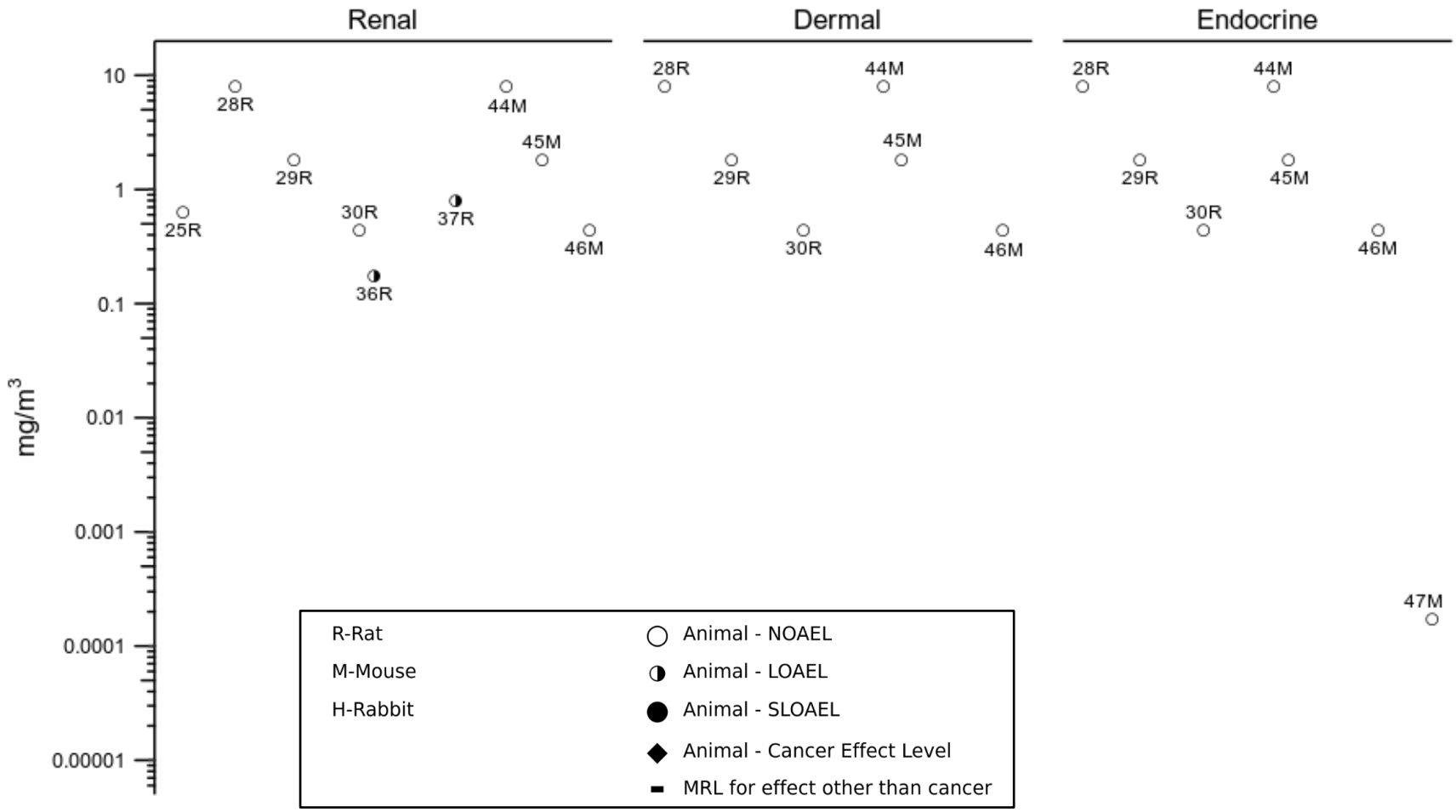


Figure 2-12. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

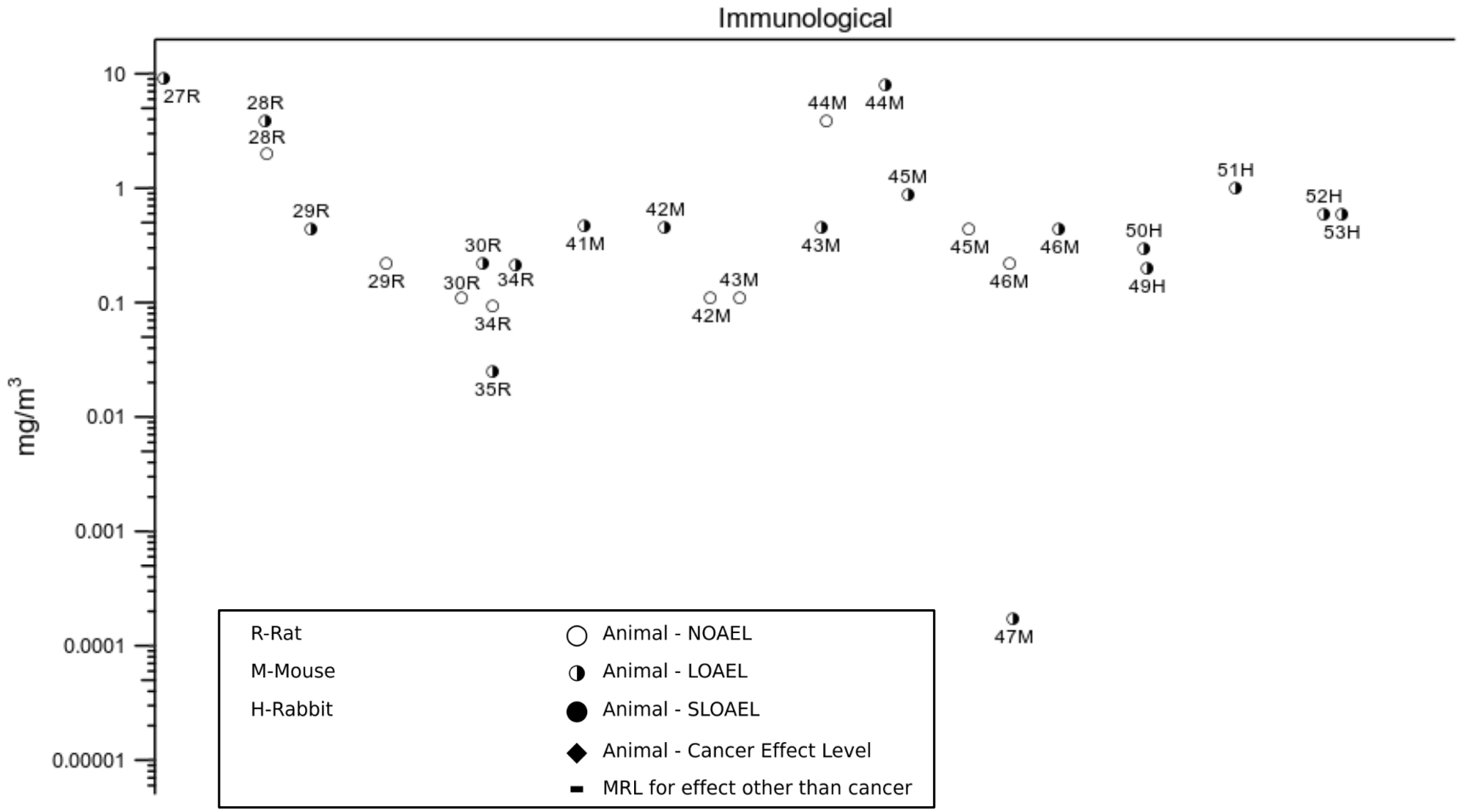


Figure 2-13. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

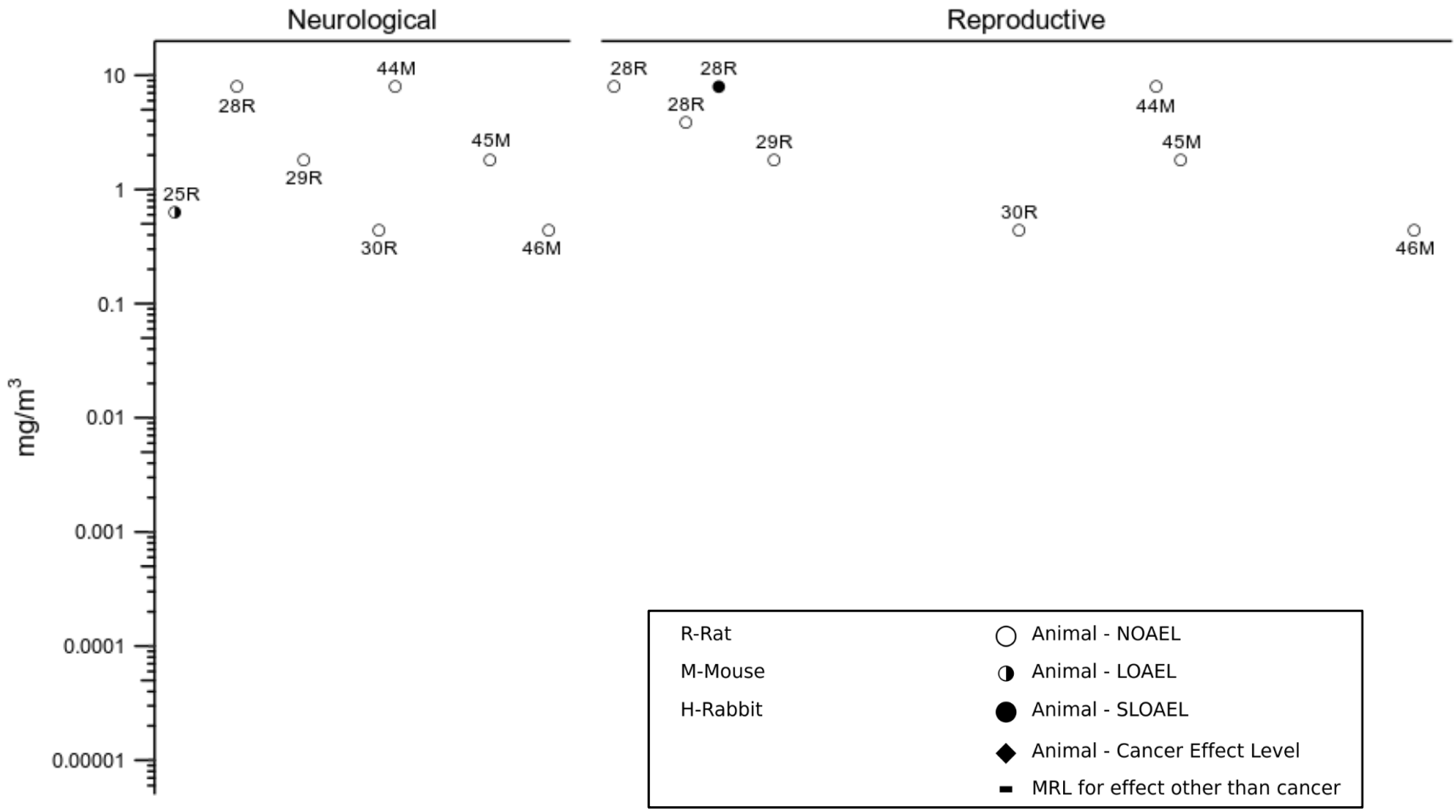


Figure 2-14. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15-364 days)

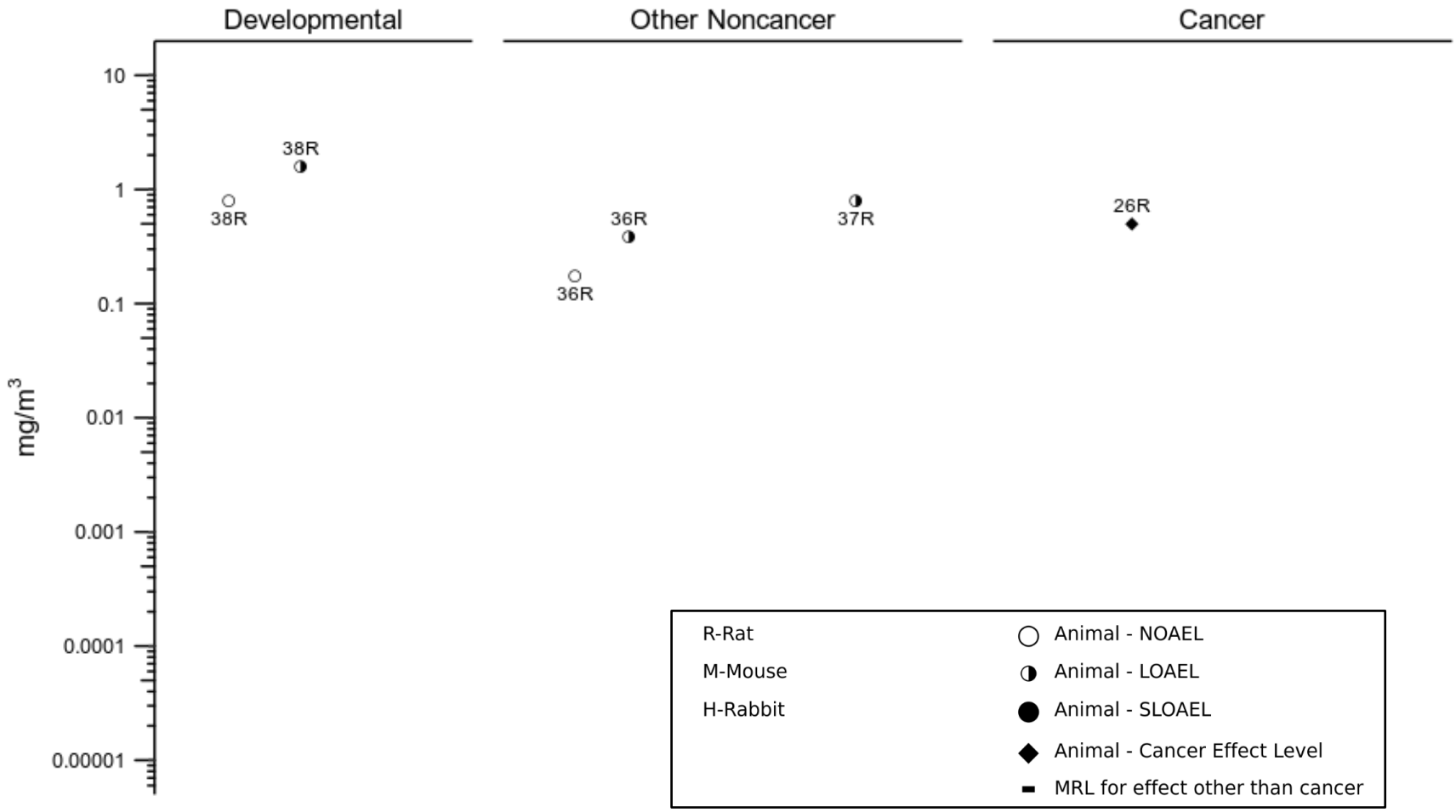


Figure 2-15. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

Figure 2-16. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

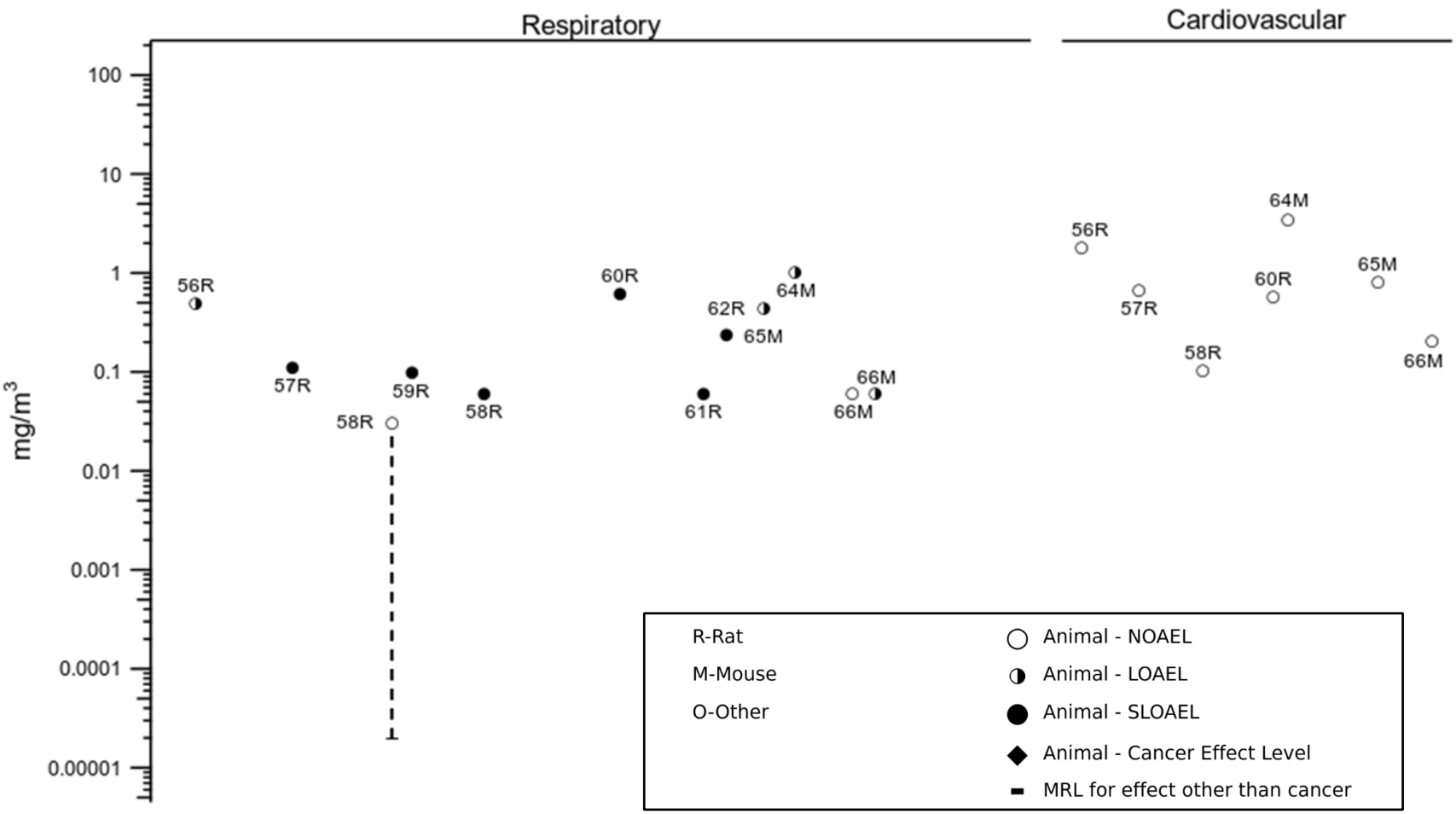


Figure 2-17. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

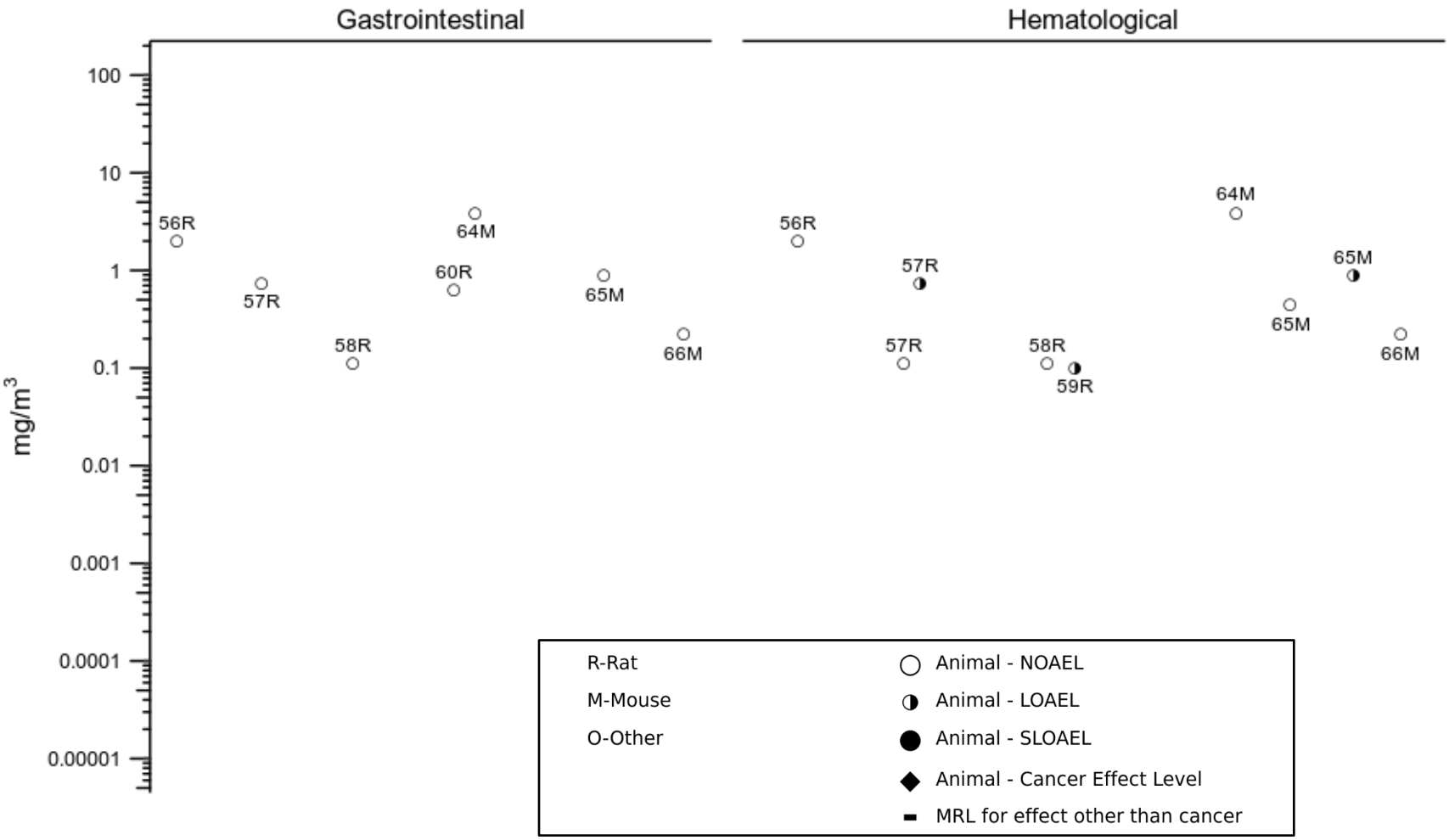


Figure 2-18. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

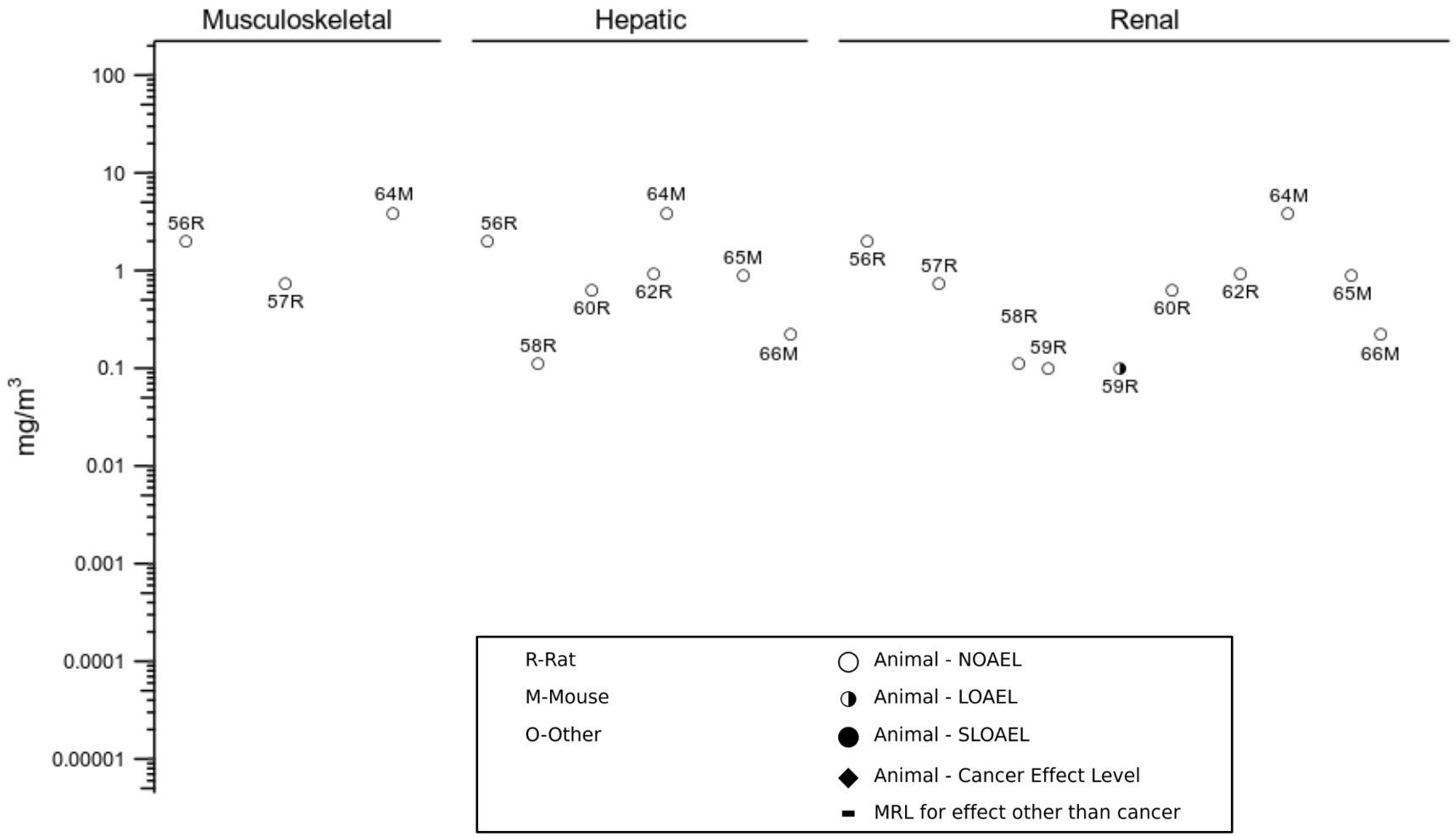


Figure 2-19. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

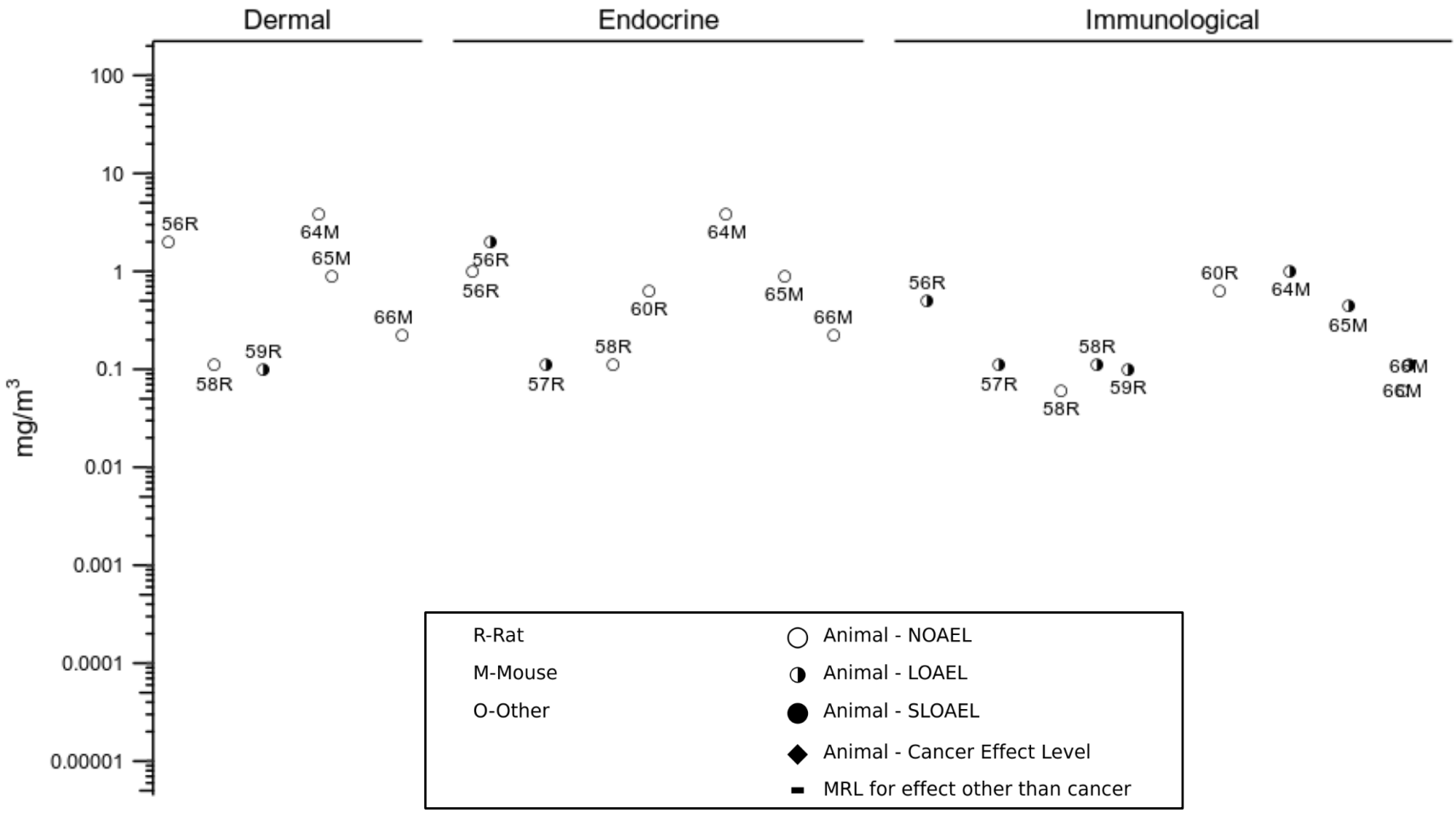


Figure 2-20. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

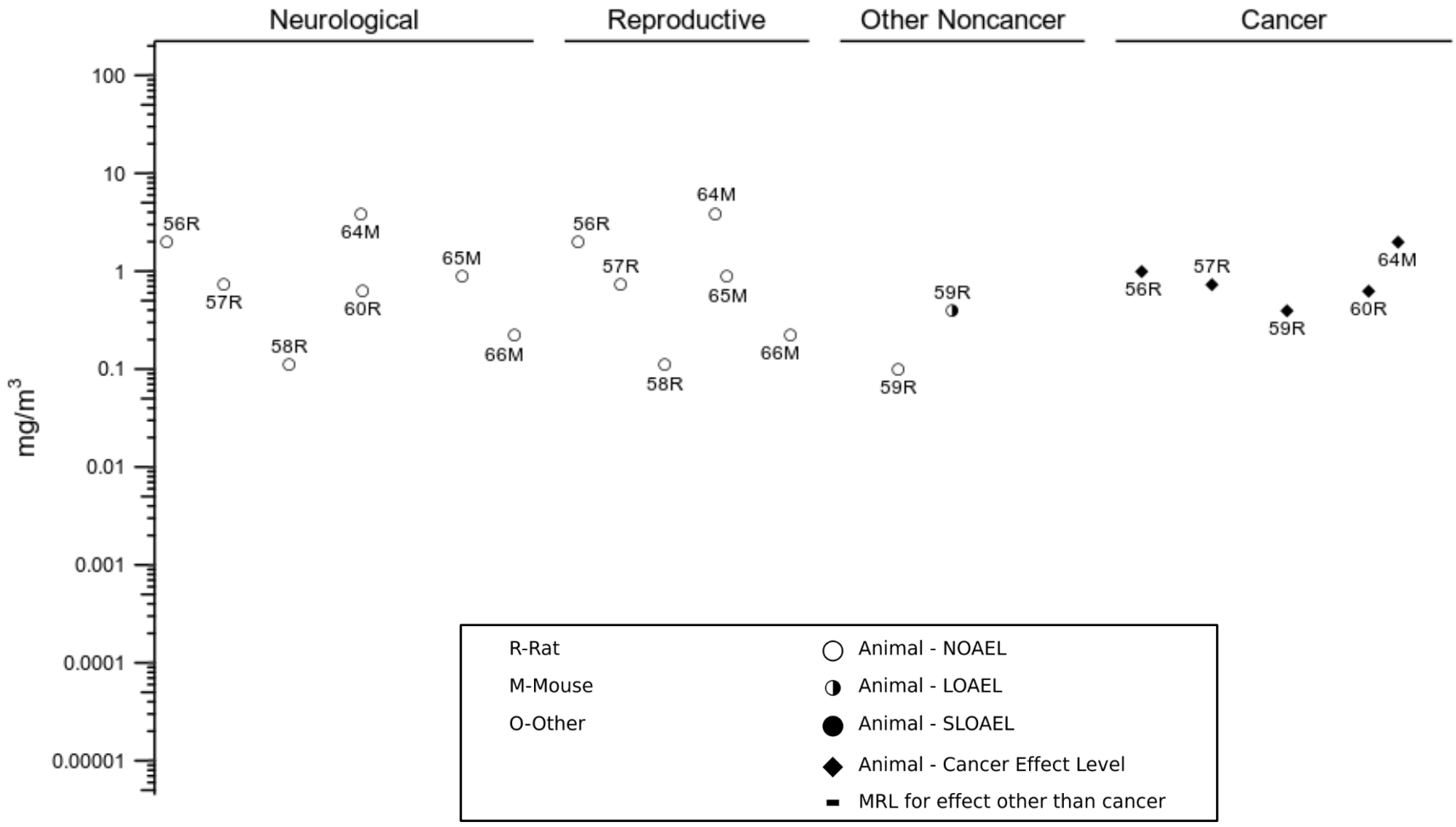


Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

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 22NS	2 days 2 times/day (C)	0, 0.01, 0.03	CS	Dermal	0.03			
Gawkrodger et al. 1986									**Nickel sulfate heptahydrate**
2	HUMAN 6B	Once (C)	0, 0.097	CS	Dermal		0.097 F		Allergic dermatitis in sensitized individuals
Gawkrodger et al. 1986									**Nickel sulfate heptahydrate**
3	HUMAN 20B	2 days Once/day (C)	0, 0.007, 0.043	CS	Dermal	0.043 F			
Hindsen et al. 2001									**Nickel sulfate**
4	HUMAN 9-10F	Once (C)	0, 0.014, 0.057	CS	Dermal	0.014	0.057		Dermatitis in nickel sensitive subjects
Jensen et al. 2003									**Nickel sulfate**
5	HUMAN 10F	Once (C)	0, 0.0043, 0.014, 0.057	CS	Dermal	0.014	0.057		Dermatitis in nickel sensitive subjects
Sunderman et al. 1988									**Nickel**
6	HUMAN 32M	1 day (W)	0, 7.1 - 35.7 (estimated doses)	BC CS	Gastro		7.1		Vomiting (3/20 workers), cramps (14/20), and diarrhea (4/20)
					Neuro		7.1		Giddiness (7/20 workers), headache (5/20) and weariness (6/20)
Haro et al. 1968									**Nickel acetate**
7	RAT (Fischer-344) 10M, 10F	Once (G)	66.4, 99.6, 132.8, 165.9, 199.2, 232.4, 265.6	CS GN HP	Death			116 F	Calculated LD50
								120 M	Calculated LD50

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) 6M	3 days daily (G)	0, 27.91, 55.82, 111.6, 167.4, 223.2, 279.1, 334.9, 390.7	BC CS HE LE	Death			167.4	4/6 died
					Resp		111.6		Irregular respiration in 4/6 rats
					Neuro		27.91		Hypoactivity and/or salivation
RTI 1988a, 1988b									**Nickel chloride**
9	RAT (CD) 30-32M, 30-31F	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
El Sekily et al. 2020									**Nickel chloride hexahydrate**
10	MOUSE (albino) 10F	8 days daily (G)	0, 10.29, 20.59, 41.08	CS DX	Develop			10.29	Significant increase in fetal resorption and skeletal abnormalities including incomplete ossification of skull, vertebrae, ribs, sternum, fore and hind limbs, carpals, metacarpals, and phalanges; supernumerary ribs
Gray et al. 1986									**Nickel chloride**
11	MOUSE (CD-1) NS F	GD 8-12 Once daily (G)	0, 45.3	DX	Develop	45.3			
Haro et al. 1968									**Nickel acetate**
12	MOUSE (Swiss-Webster) 10M, 10F	Once (G)	66.4, 99.6, 132.8, 165.9, 199.2, 232.4, 265.6	CS HP	Death			139 F	Calculated LD50
								136 M	Calculated LD50

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
He et al. 2013									**Nickel chloride hexahydrate**
13	MOUSE (Kunning) 8M	Once (G)	0, 1.234, 12.34	BI NX	Neuro	1.234		12.34	Reduced spatial memory performance indicated by increased escape latencies 3 hours after exposure; reduced locomotor activity indicated by reduced distance traveled
					Other noncancer	1.234	12.34		Disturbance to aerobic metabolism indicated by reduced oxygen consumption, decreased superoxide dismutase activity, and decreased aconitase activity at 3 hours post-exposure
Saini et al. 2013									**Nickel chloride hexahydrate**
14	MOUSE (Swiss Albino) 10F	GD 6-13 daily	0, 11.38, 22.77, 45.55	BW DX FI LE RX	Repro			11.38	4.16% embryos resorbed/post-implantation death
					Develop			11.38	5% of offspring with microphthalmia, and 22.7% with skeletal anomalies including reduced or fused sternebrae, absence or gap between the ribs, and reduced ossification
					Other noncancer	11.38	22.77		14% reduction in food consumption
Saini et al. 2014a									**Nickel chloride hexahydrate**
15	MOUSE (Swiss Albino) 10F	GD 0-5 daily (W)	0, 11.35, 22.71, 45.68	BW DX FI LX RX WI	Neuro	45.68			
					Repro			11.35	25 and 28.5% reduction in mean number of implantation sites/dam and mean number of live fetuses/dams, respectively

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
					Develop		11.35		Increased incidence of skeletal anomalies (in 12% of fetuses) including reduced ossification of intraparietal skull bones, metatarsals, and phalanges, and reduced number of ribs
					Other noncancer		45.68		11% reduction in diet consumption and water intake
Saini et al. 2014b									**Nickel chloride hexahydrate**
16	MOUSE (Swiss Albino) 15F	GD 0-5 daily (G)	0, 10.29, 20.59, 41.19	BW DX RX	Repro		10.29	20.59	Reduced gestation index (75%) at 10.29 mg Ni/kg/day 16% reduction in average litter size/dam during preimplantation at 20.59 mg Ni/kg/day
					Develop	10.29	20.59	41.19	Significant 27% and 9% decrease of offspring body weight in postpartum week 1 and 6 (end of study period), respectively at 20.59 mg Ni/kg/day 11.75% offspring mortality at 41.19 mg Ni/kg/day
Saini et al. 2014b									**Nickel chloride hexahydrate**
17	MOUSE (Swiss Albino) 15F	GD 6-13 daily (G)	0, 10.29, 20.59, 41.19	BW DX RX	Repro	20.59		41.19	Reduced mean litter size/dam (24%)
					Develop		10.29	20.59	14% less offspring bodyweight at birth at 10.29 mg Ni/kg/day 9.5% offspring mortality and microphthalmia in 5% of offspring at 20.59 mg Ni/kg/day

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. 2014b									**Nickel chloride hexahydrate**
18	MOUSE (Swiss Albino) 15F	GD 14-18 daily (G)	0, 10.29, 20.59, 41.19	BW DX RX	Repro	20.59		41.19	Reduced mean litter size/dam (27%)
					Develop	10.29		20.59	11.11% offspring mortality
Seidenberg et al. 1986									**Nickel chloride**
19	MOUSE (ICR) 28F	GD 8-12 (GW)	0, 90.6	BW DX RX	Repro	90.6			
					Develop	90.6			
Sobti and Gill 1989									**Nickel sulfate**
20	MOUSE (lacca) NS M	Once (GW)	0, 27.68	CS HP	Repro			27.68	3-fold increase in sperm head abnormalities
Sobti and Gill 1989									**Nickel nitrate**
21	MOUSE (lacca) NS M	Once (GW)	0, 23	CS HP	Repro			23	3.7-fold increase in sperm head abnormalities
Sobti and Gill 1989									**Nickel chloride**
22	MOUSE (lacca) NS M	Once (GW)	0, 43	CS HP	Repro			43	2.6-fold increase in sperm head abnormalities
Ambrose et al. 1976									**Nickel sulfate**
23	DOG (Beagle) 3M, 3F	3 days (F)	0, 2.5, 25, 62.5	BW CS FI GN HP OW UR	Gastro	25	62.5		Vomiting (6/6 dogs)

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
INTERMEDIATE EXPOSURE									
Santucci et al. 1994									**Nickel sulfate**
24	HUMAN 8F	91-178 days (Ni-sensitized individuals) (W)	0.01-0.03	CS	Dermal	0.02			
Adeyemi and Elebiyo 2014									**Nickel sulfate**
25	RAT (Wistar) 5M	21 days daily (G)	0, 7.585	BC BI BW OW	Bd wt	7.585			
					Renal		7.585		Increased plasma creatinine and urea and renal cell alterations including swollen tubules and mild necrosis
Adeyemi et al. 2017									**Nickel sulfate**
26	RAT (Wistar) 6M	21 days daily (GW)	7.585	BC BI BW HE HP OW	Cardio		7.585		Increased atherogenic index
					Hemato		7.585		Altered blood chemistry (reduced plasma protein and GSH, increased MDA, TC, TAG, and LDL-C).
					Hepatic		7.585		Significantly increased liver enzyme levels: ALT (>300%), AST (>400%), and ALP (>100%) with liver inflammation and cellular degeneration
Ambrose et al. 1976									**Nickel sulfate**
27	RAT (Wistar) 30M, 30F	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		13% decrease in body weight of F1 generation compared to controls
					Repro			22.5	Increased incidence in number of stillborn (23 stillborn) in F1 generation (8 stillborn among controls)
					Develop	90			

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
American Biogenics Corp 1988									**Nickel chloride**
28	RAT (Sprague-Dawley) 30M, 30F	91 days daily (GW)	0, 1.2, 8.6, 25	BC BW CS HP LE	Death			25	100% mortality due to exposure by study day 76 for males and study day 78 for females
					Bd wt	1.2 F	8.6 F		12% decrease in body weight gain
					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			
					Neuro	1.2		8.6	Ataxia, prostration, hypothermia
					Other noncancer	1.2 F	8.6 F		Decreased blood glucose level
Heim et al. 2007									**Nickel sulfate hexahydrate**
29	RAT (Fischer-344) NS M, NS F	90 days (G)	0, 11.16, 16.74, 22.32, 27.91, 33.49	BW HP	Bd wt	22.32 F	27.91 F		~10% decrease in body weight
						11.16 M	16.74 M		~12% decrease in body weight
Kakela et al. 1999									**Nickel chloride**
30	RAT (Wistar) 6M	28 or 42 days before copulation Daily (W)	0, 3.6	DX HP RX	Repro			3.6	Significantly decreased gestation index (73.5% less compared to controls) and decreased litter size by lactation day 21 (86% less than controls)

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
					Develop			3.6	Structural abnormalities in pups that died including underdeveloped posteriors of the bodies, slow movement, and disproportionately large heads
Kakela et al. 1999									**Nickel chloride**
31	RAT (Wistar) 6F	62 days: 14 or 100 days before copulation 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			13	Structural abnormalities in pups that died including underdeveloped posteriors of the bodies, slow movement, and disproportionately large heads; lower relative kidney and liver weights
Kakela et al. 1999									**Nickel chloride**
32	RAT (Wistar) 6M, 6F	28-76 days daily (W)	M: 0, 3.6; F: 0, 4.0	DX RX	Repro			3.6	Significantly decreased litter size by lactation day 21 (71% less than controls); 44% pup survival
					Develop			3.6	Structural abnormalities in pups that died including underdeveloped posteriors of the bodies, slow movement, and disproportionately large heads
Kamal et al. 2012									**Nickel sulfate hexahydrate**
33	RAT (albino) 6M	28 days daily (W)	0, 3.81, 10.00	BI BW FI	Hepatic		3.81		Increased ALT (248%), AST (56%), MDA (29%), and decreased SOD (29%), GST (20%)

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
Mahmoud et al. 2011									**Nickel sulfate heptahydrate**
34	RAT (albino) 4M	21 days daily (W)	0, 3.563	BC BI BW CS FI WI	Hepatic		3.563		Altered liver enzymes, including increased MDA content (30%), serum ALT (248%) and AST (56%), and reduced SOD (30%) activity
					Renal		3.563		Increased SOD (25%) and GSH (60%) activity in kidney tissue
					Other noncancer		3.563		13.5% and 8% reduction in fluid and food intake, respectively
Obone et al. 1999									**Nickel sulfate**
35	RAT (Sprague-Dawley) 8M	13 weeks daily (W)	0, 5.75, 14.4, 28.8	BI BW HP LE OW	Bd wt	28.8			
					Resp		5.75		66% decrease of alkaline phosphatase activity in bronchioalveolar lavage fluid compared to controls
					Cardio	28.8			
					Gastro	28.8			
					Hepatic	28.8			
					Renal	5.75	14.4		Decreased urine volume and urine glucose
					Immuno	5.75	14.4		63 and 80% increase in absolute %CD8+ T-cells in the spleen and thymus; 34% decrease of CD4:CD8 ratio compared to controls
					Neuro	28.8			
					Repro	28.8			
RTI 1988a, 1988b									**Nickel chloride**
36		PO generation exposure		BW CS FI GN HP WI	Resp	4 M	20 M		Histiocytic cellular infiltration in lungs in F1 generation

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
	RAT (CD) 30-32M, 30-31F	began 11 weeks prior to breeding; total exposure: F: 27-30 weeks M: 21-24 weeks (W)	F: 0, 7, 30, 55; M: 0, 4, 20, 40		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 PND 22-42
Smith et al. 1993									**Nickel chloride**
37	RAT (Long-Evans) 34F	11 weeks (breeding-lactation) 2 litters (W)	0, 1.3, 6.8, 31.6	BC BW CS DX FI WI	Bd wt	31.6			
					Endocr	6.8	31.6		21% decreased prolactin
					Repro	31.6			
					Develop			1.3	Decreased pup survival
Springborn Laboratories 2000a									**Nickel sulfate hexahydrate**
38	RAT (Sprague-Dawley) 28M, 28F	18 weeks Daily F1 generation (GW)	0, 0.22, 0.56, 1.1, 2.2	BW CS DX FI GN HP LE OW RX	Bd wt	2.2			
					Resp	2.2			
					Cardio	2.2			
					Gastro	2.2			
					Hepatic	2.2 F			
						0.56 M	1.1 M		Significant 7.3% decrease in relative liver weight
					Renal	2.2			
					Dermal	2.2			
					Endocr	2.2			
					Immuno	2.2			
					Neuro	2.2			
					Repro	2.2			
					Develop	2.2			

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
					Other noncancer	2.2			No treatment-related changes in food consumption, hair loss, or discolorations
Springborn Laboratories 2000a									**Nickel sulfate hexahydrate**
39	RAT (Sprague-Dawley) 28M, 28F	16 weeks Daily F0 generation (GW)	0, 0.22, 0.56, 1.1, 2.2	BW CS DX FI GN HP LE OW RX	Bd wt	2.2			
					Resp	2.2			
					Gastro	2.2			
					Hemato	2.2			
					Hepatic	2.2 F			
						1.1 M	2.2 M		Significant 9% decrease in relative liver weight
					Renal	2.2			
					Dermal	2.2			
					Endocr	2.2			
					Immuno	2.2			
					Neuro	2.2			
					Repro	2.2			
					Other noncancer	2.2			No treatment-related changes in food consumption, hair loss, or discolorations
Springborn Laboratories 2000a									**Nickel sulfate hexahydrate**
40	RAT (Sprague-Dawley) 325-394B	exposure in utero and during lactation; both parents exposed (GW)	0, 0.22, 0.56, 1.1, 2.2	DX	Develop	2.2			

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
Springborn Laboratories 2000b									**Nickel sulfate hexahydrate**
41	RAT (Sprague-Dawley) 8M, 8F	F1 generation began on PND 22 for 1, 2, or 3 weeks (GW)	0, 2.2, 4.5. 6.7, 11.2, 16.7	BW CS DX GN LE	Develop	4.5		6.7	Significantly increased incidence of stillborn pups on lactation day 0 (23 dead vs 1 dead in controls) and significantly reduced mean live litter size (29%)
Springborn Laboratories 2000b									**Nickel sulfate hexahydrate**
42	RAT (Sprague-Dawley) 8M, 8F	Began 2 weeks before mating to LD 21 for F0 generation Daily (GW)	0, 2.2, 4.5. 6.7, 11.2, 16.7	CS BW FI GN LE RX WI	Bd wt	16.7			
					Resp	16.7			
					Gastro	16.7			
					Hepatic	16.7			
					Renal	16.7			
					Endocr	16.7			
					Neuro	16.7			
					Repro	4.5		6.7	Significantly increased post-implantation loss (475% more than controls)
					Other noncancer	16.7			No exposure-related changes in food or water intake
Springborn Laboratories 2002									**Nickel sulfate**
43	RAT (Fischer-344) 10M, 10F	90 days daily (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**
44	RAT (Wistar) 10M, 10F	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**
45	RAT (Wistar) 10M	28 days (W)	0, 0.23, 0.49, 0.97	BC BW OW WI	Bd wt			0.23	20% decreased body weight gain
					Hemato	0.23	0.49		Increased leukocytes (36%)
					Hepatic	0.97			
					Renal		0.23		Decreased urea (15%)
Whanger 1973									**Nickel acetate**
46	RAT (OSU brown) 6M	6 weeks (F)	0, 5, 25, 50	BI BW HE	Bd wt	5		25	88% decrease in body weight gain
					Hemato	50			
Berman and Rehnberg 1983									**Nickel chloride**
47	MOUSE (CD-1) 12-24F	GD 2-17 (W)	0, 80, 160	DX RX	Develop	80		160	Increased spontaneous abortions
Dahdouh et al. 2016									**Nickel sulfate**
48	MOUSE (Swiss albino) 8M	28 days daily (F)	0, 0.036	BC BI BW FI HE HP OW WI	Hemato		0.04		Significant changes in blood composition including 25, 26, and 24% reductions in RBCs, PVC%, and hemoglobin, and 33% increase WBC count all compared to controls
					Renal			0.04	Proximal tubule degeneration with tubular necrosis and inflammation

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
Dieter et al. 1988									**Nickel sulfate**
49	MOUSE (B6C3F1) 10F	180 days daily (W)	0, 44, 108, 150	BI BW HP OW WI	Bd wt	44	108	150	Body weight 10% lower than controls at 108 mg Ni/kg/day Body weight 26% lower than controls at 150 mg Ni/kg/day
					Hepatic	150			
					Renal	44	108		Hyaline casts, loss of tubular epithelial cells
					Immuno		44		Mild thymic atrophy, impaired B-cell immune function, decreased granulocyte macrophage progenitor cell levels
Gathwan et al. 2013									**Nickel chloride**
50	MOUSE (BALB/c) 5M	40 days daily (NS)	0, 0.905, 3.714, 7.246	BI BW FI HP OW WI	Bd wt	7.246			
					Hepatic		0.905	7.246	Diffused cytoplasm and damaged nuclei in hepatic cells at 0.905 mg Ni/kg/day Hepatocellular degeneration with hypertrophy of nuclei and blood in the central canal of the liver at 7.246 mg Ni/kg/day
Ilback et al. 1994									**Nickel chloride**
51	MOUSE (BALB/c) 8F	10-11 weeks (W)	0, 20.3	BW HP LE OF	Immuno		20.3		Enhanced inflammatory response in the hearts of mice challenged with coxsackie virus B3
Pandey and Srivastava 2000									**Nickel chloride**
52	MOUSE (NS) 6M	35 days 5 days/week (GW)	0, 1.2, 2.5, 4.9	RX	Repro	1.2		2.5	24 and 25% decreased in sperm motility and count, respectively; increased sperm abnormalities

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
Pandey and Srivastava 2000									**Nickel sulfate**
53	MOUSE (NS) 6M	35 days 5 days/week (GW)	0, 1.1, 2.2, 4.5	RX	Repro	1.1		2.2	12.5 and 15% decrease of sperm count and motility, respectively; significant dose-related increase in sperm head, tail, and neck abnormalities in 24% of mice
Pandey et al. 1999									**Nickel sulfate**
54	MOUSE (Swiss) 20M	35 days 5 days/week (GW)	0, 2.2	DX RX	Repro			2.2	Significant post-implantation loss (3.33% in controls vs 19.20% in treated)
Pandey et al. 1999									**Nickel sulfate**
55	MOUSE (Swiss) 20M	35 days 5 days/week (GW)	0, 1.1, 2.2	BI BW HP OW RX	Bd wt	2.2			
					Repro			1.1	7% decrease in sperm motility and 37% decrease in total sperm count; significantly reduced relative weight of testis (14%), seminal vesicle (30%), and prostate gland (25%); 117% increase in percent morphological sperm abnormalities
Toman et al. 2012									**Nickel chloride**
56	MOUSE (ICR) 5M	3-12 weeks daily (F)	0, 4.53	BW CS HP LE OW	Repro			4.53	Degeneration of seminiferous epithelium, decrease in relative volume of germinal epithelium, interstitium, blood vessels and increased relative volume of lumen, empty spaces in the epithelium and whole tubules of testes

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
CHRONIC EXPOSURE									
Heim et al. 2007									**Nickel sulfate hexahydrate**
57	RAT (Fischer-344) 60M, 60F	2 years (104 weeks) daily (G)	0, 2.232, 6.698, 11.16	BC BW CS FI GN HE LE	Death			2.232 F	Exposure-response trend in mortality, 33% mortality
					Bd wt	6.698 F	11.16 F		10% reduction in body weight
						2.232 M	6.698 M		11% reduction in bodyweight
					Hemato	11.16			
Ambrose et al. 1976									**Nickel sulfate**
58	DOG (Beagle) 3M, 3F	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, bronchiectasis
					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 2/6 dogs, increased kidney weight
					Dermal	62.5			
					Endocr	62.5			
					Immuno	62.5			
					Neuro	62.5			
					Repro	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

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

ALP = Alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; B = both sexes; 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; GSH = glutathione; GST = glutathione-s-transferase; HE = hematological; HP = histopathology; Immuno = immunological; LD50 = dose producing 50% death; LDL-C = low-density lipoprotein cholesterol; LE = lethality; LOAEL = lowest-observed-adverse-effect-level; M = male(s); MDA = malondialdehyde; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect-level; NS = not specified; NX = neurological function; OW = organ weight; PVC =packed cell volume; RBCs = red blood cells; Repro = Reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect-level; SOD = superoxide dismutase; TAG = triacylglycerol; TC = total cholesterol; UR = urinalysis; (W) = drinking water; WBC = white blood cells; WI = water intake.

Figure 2-21. Levels of Significant Exposure to Nickel – Oral
Acute (≤14 days)

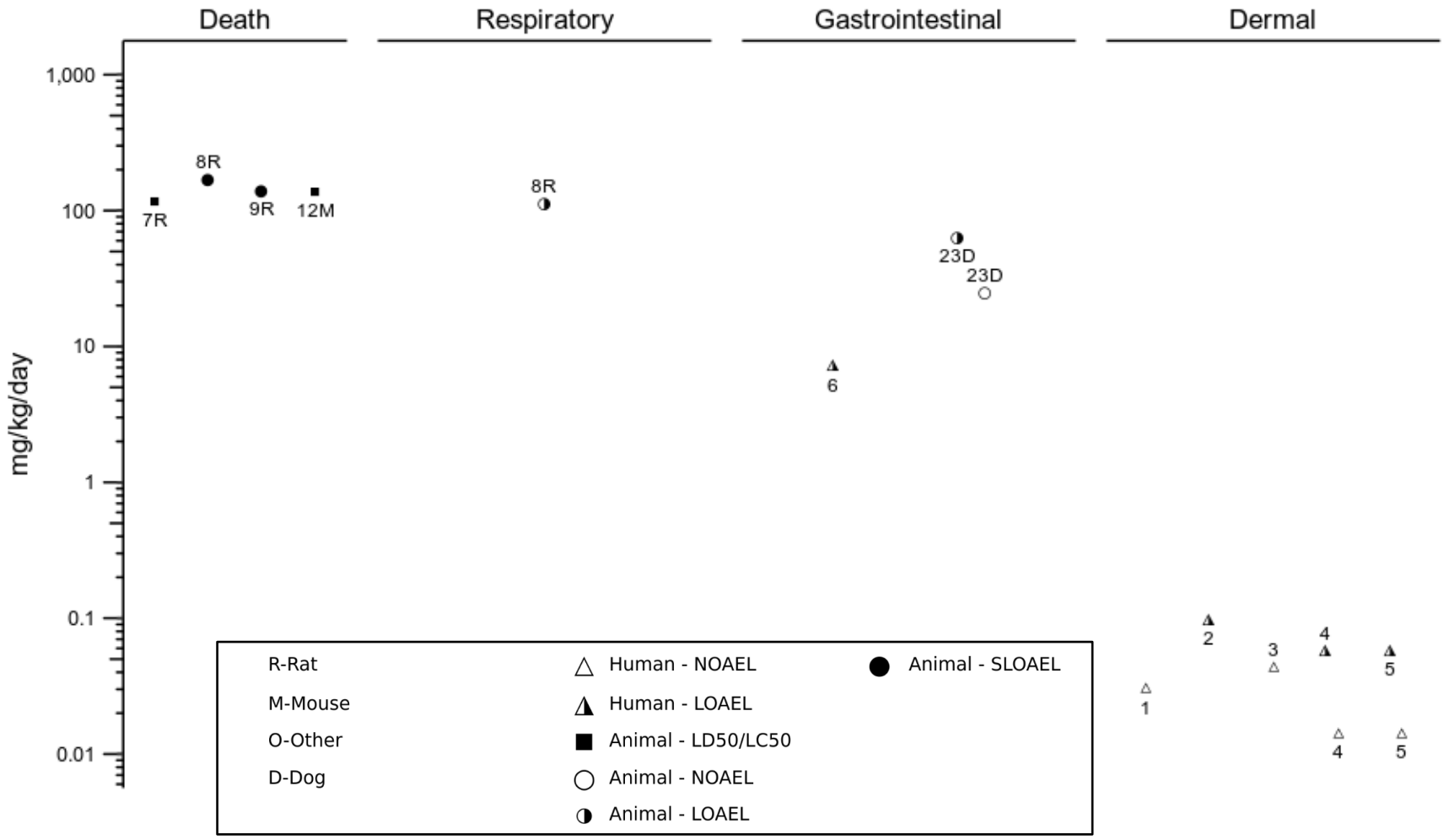


Figure 2-22. Levels of Significant Exposure to Nickel – Oral
Acute (≤14 days)

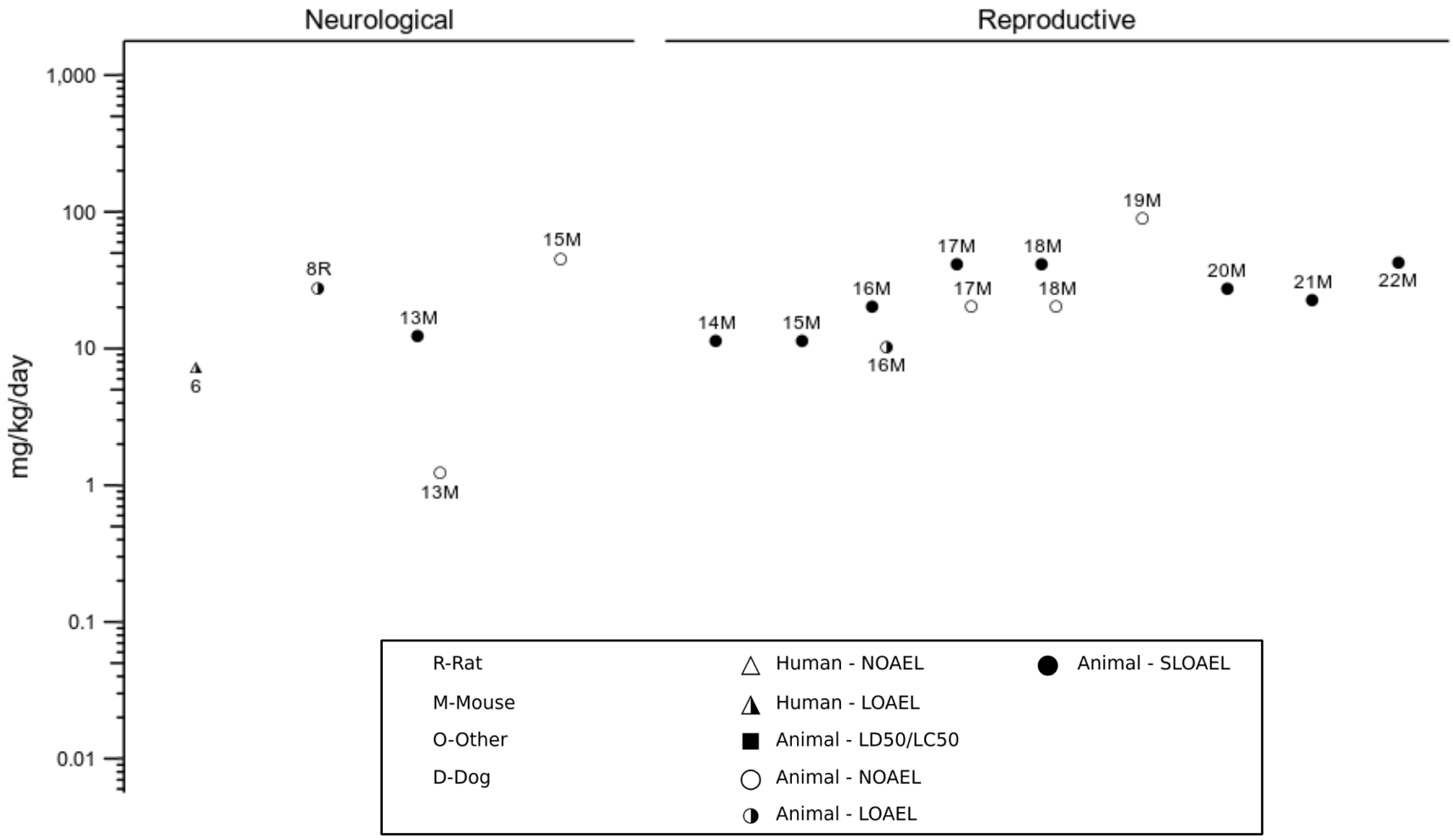


Figure 2-23. Levels of Significant Exposure to Nickel – Oral
Acute (≤14 days)

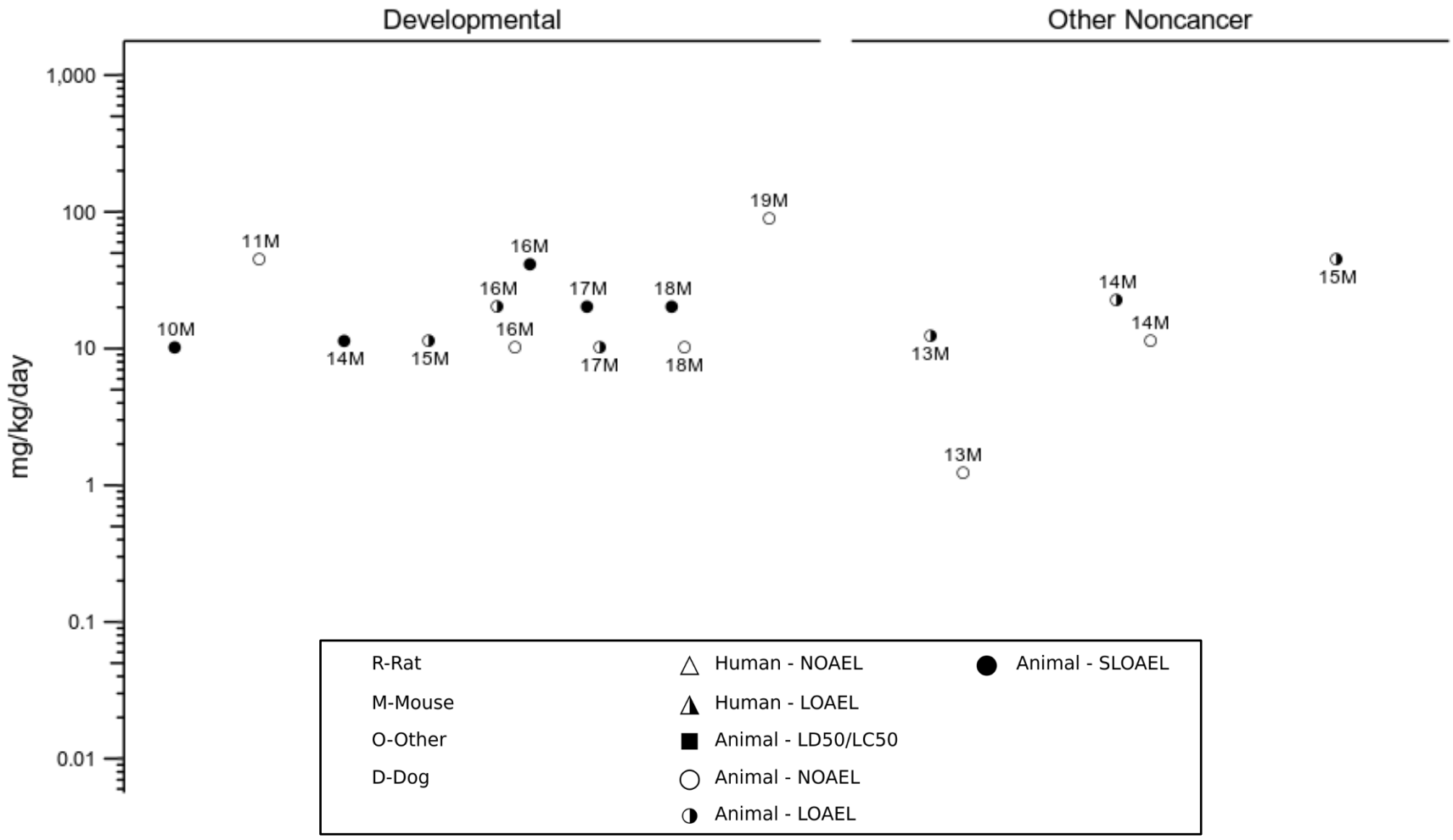


Figure 2-24. Levels of Significant Exposure to Nickel – Oral
Intermediate (15-364 days)

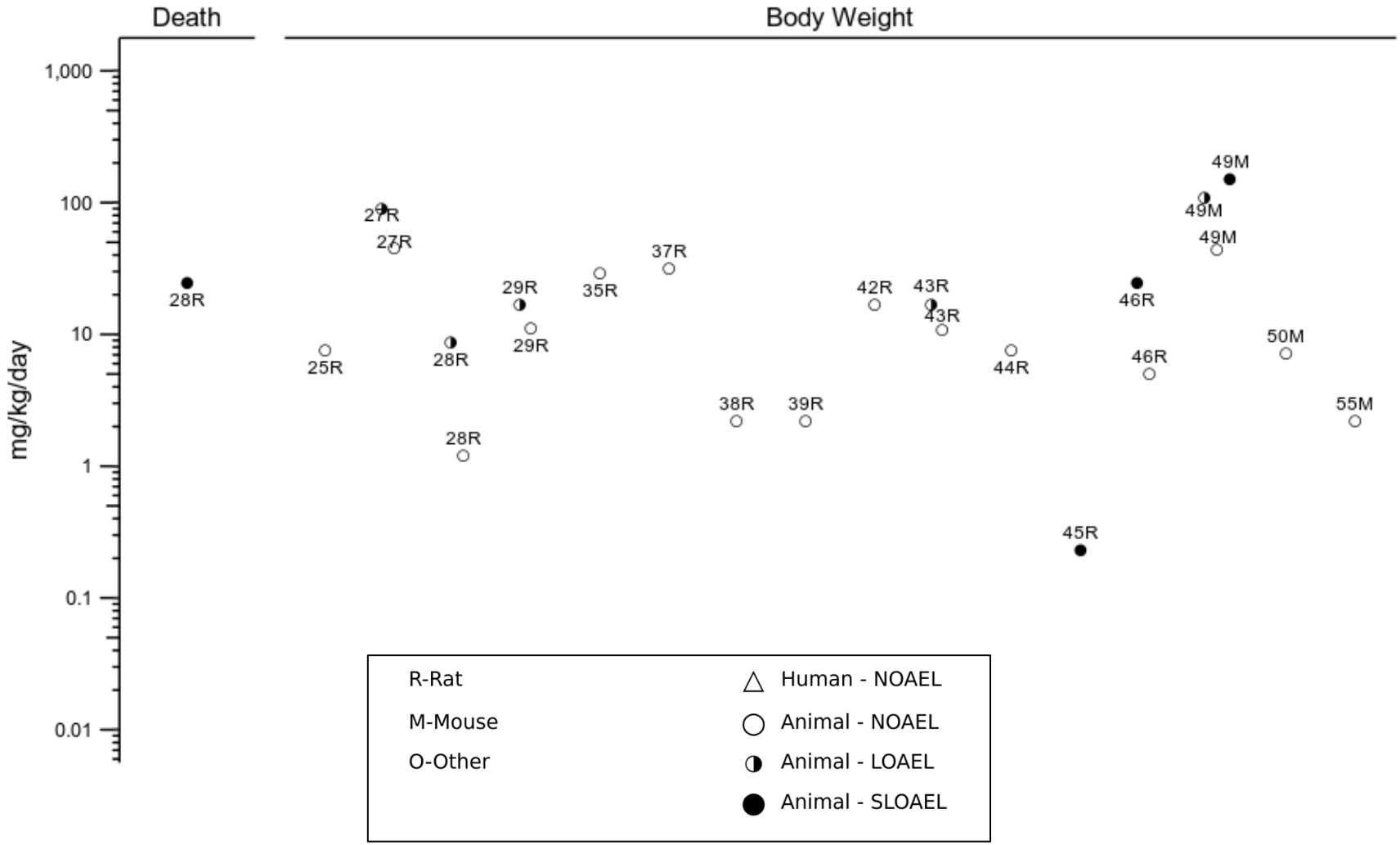


Figure 2-25. Levels of Significant Exposure to Nickel – Oral
Intermediate (15-364 days)

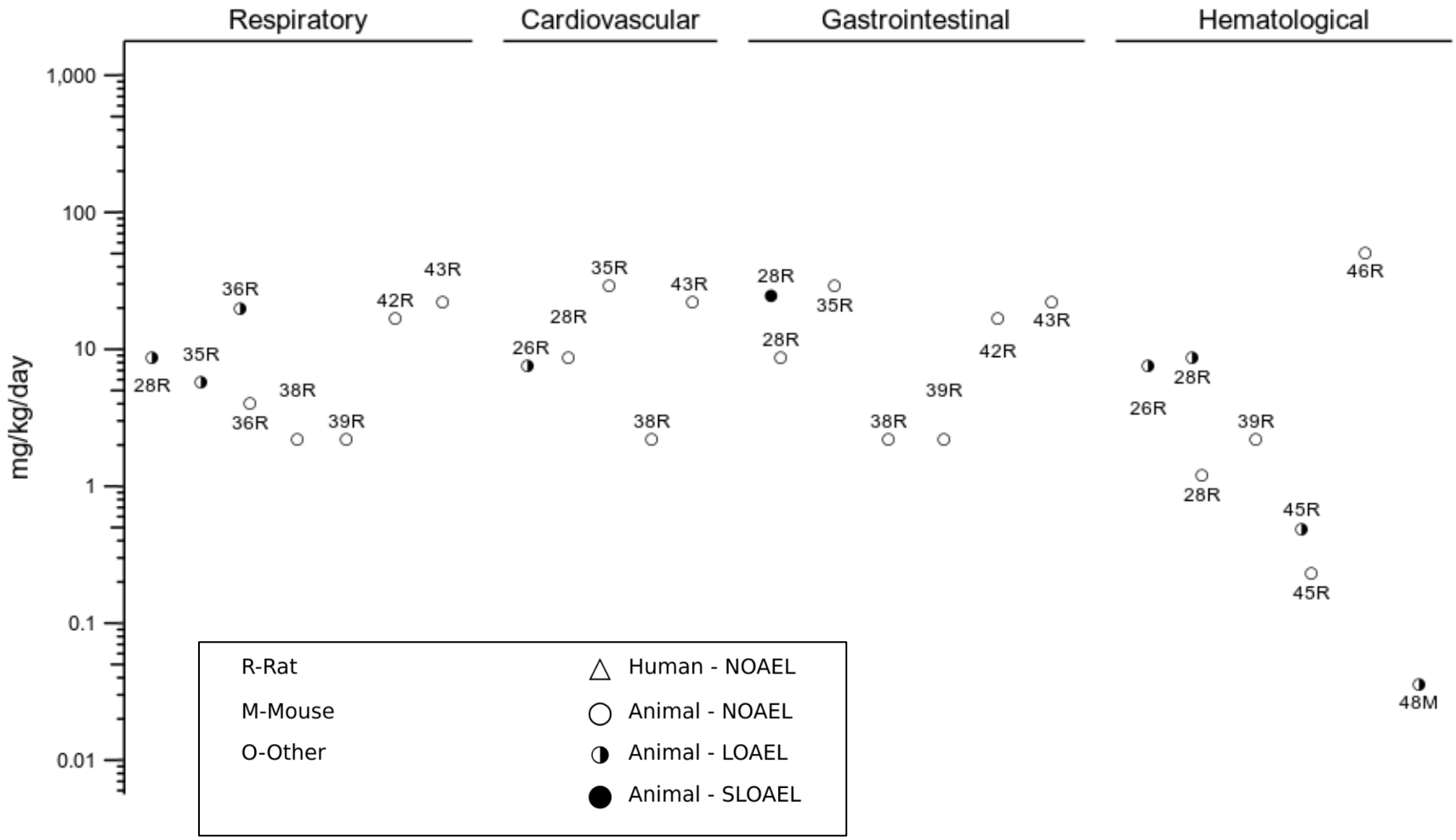


Figure 2-26. Levels of Significant Exposure to Nickel – Oral
Intermediate (15-364 days)

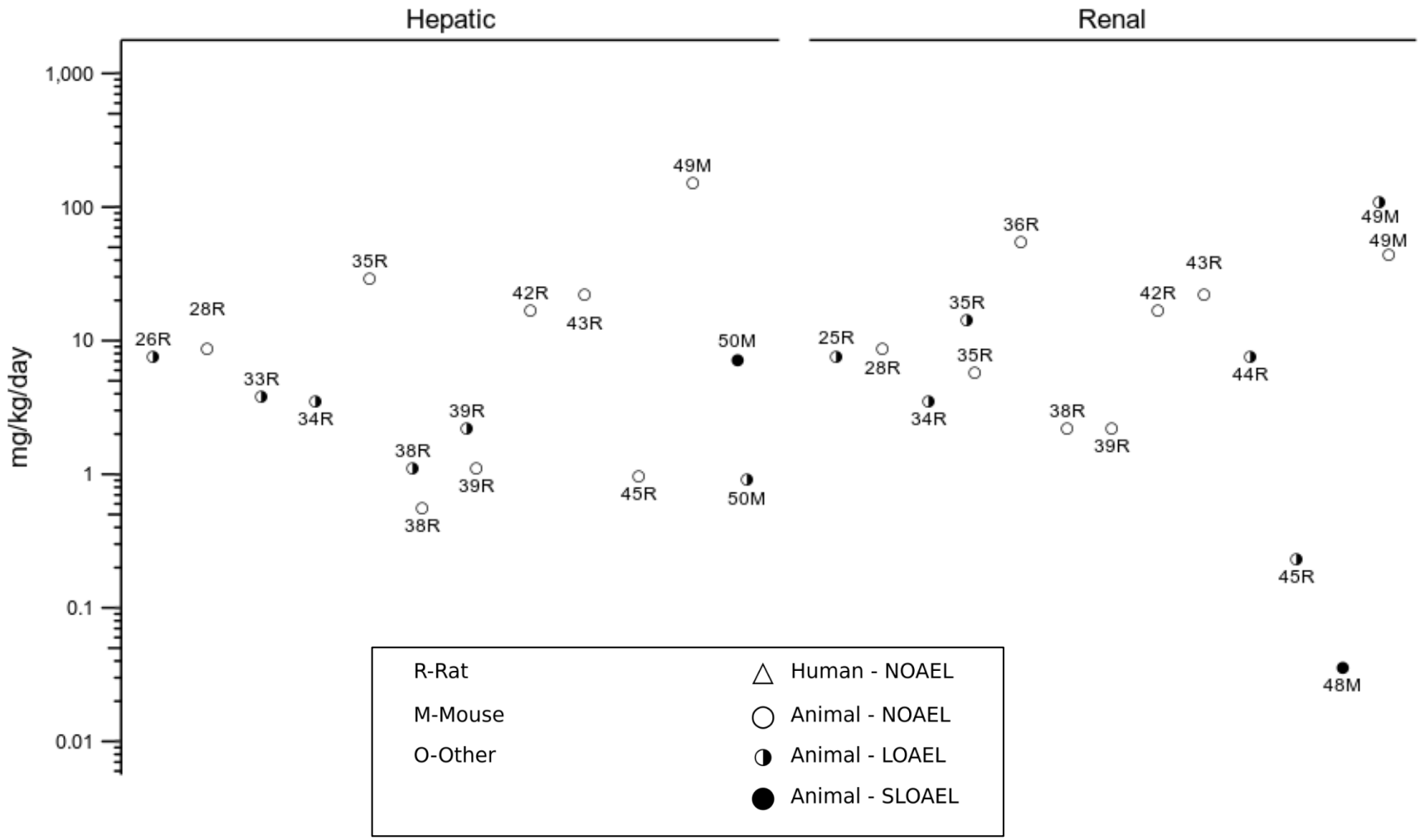


Figure 2-27 Levels of Significant Exposure to Nickel – Oral

Intermediate (15-364 days)

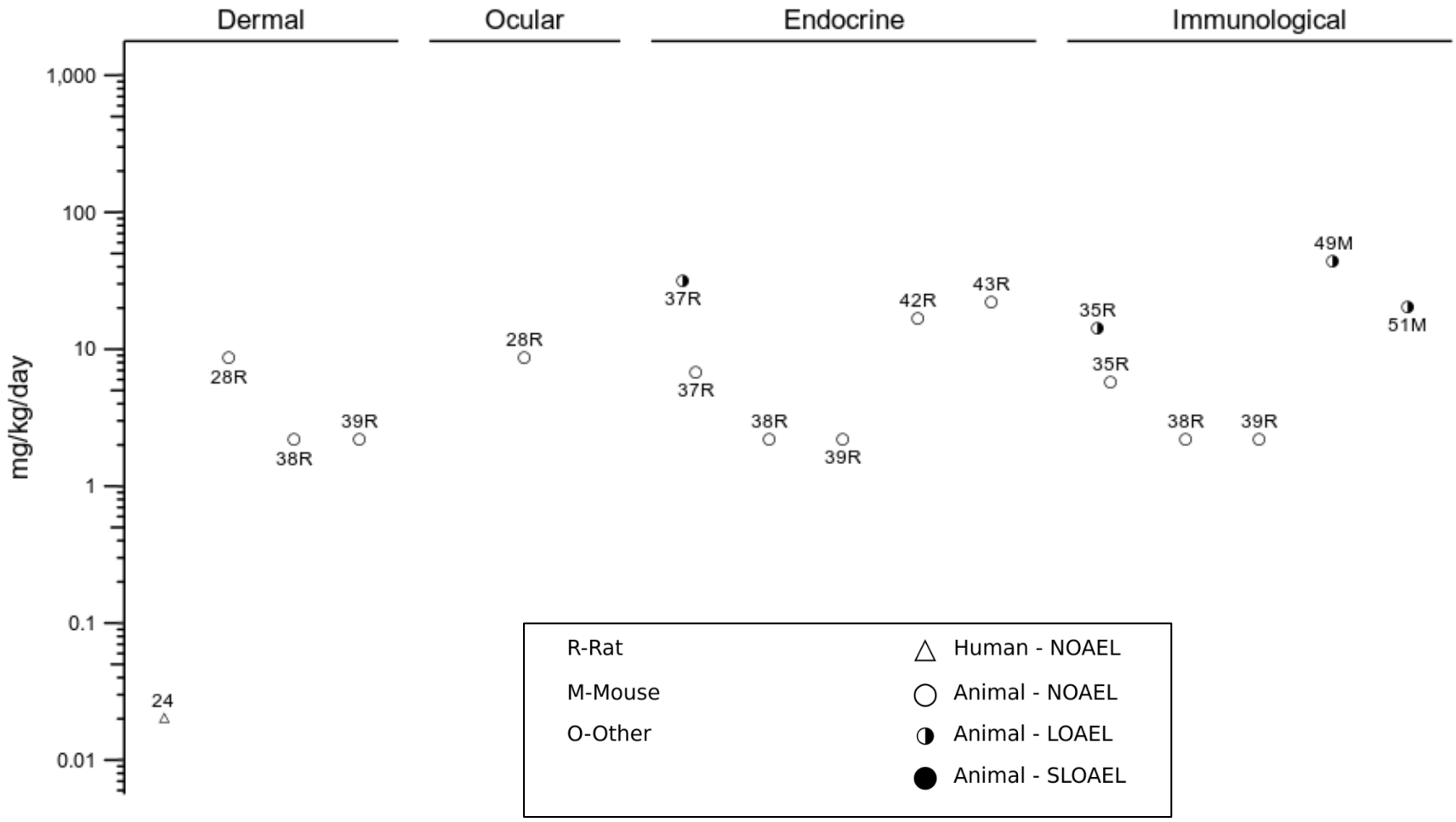


Figure 2-28 Levels of Significant Exposure to Nickel – Oral

Intermediate (15-364 days)

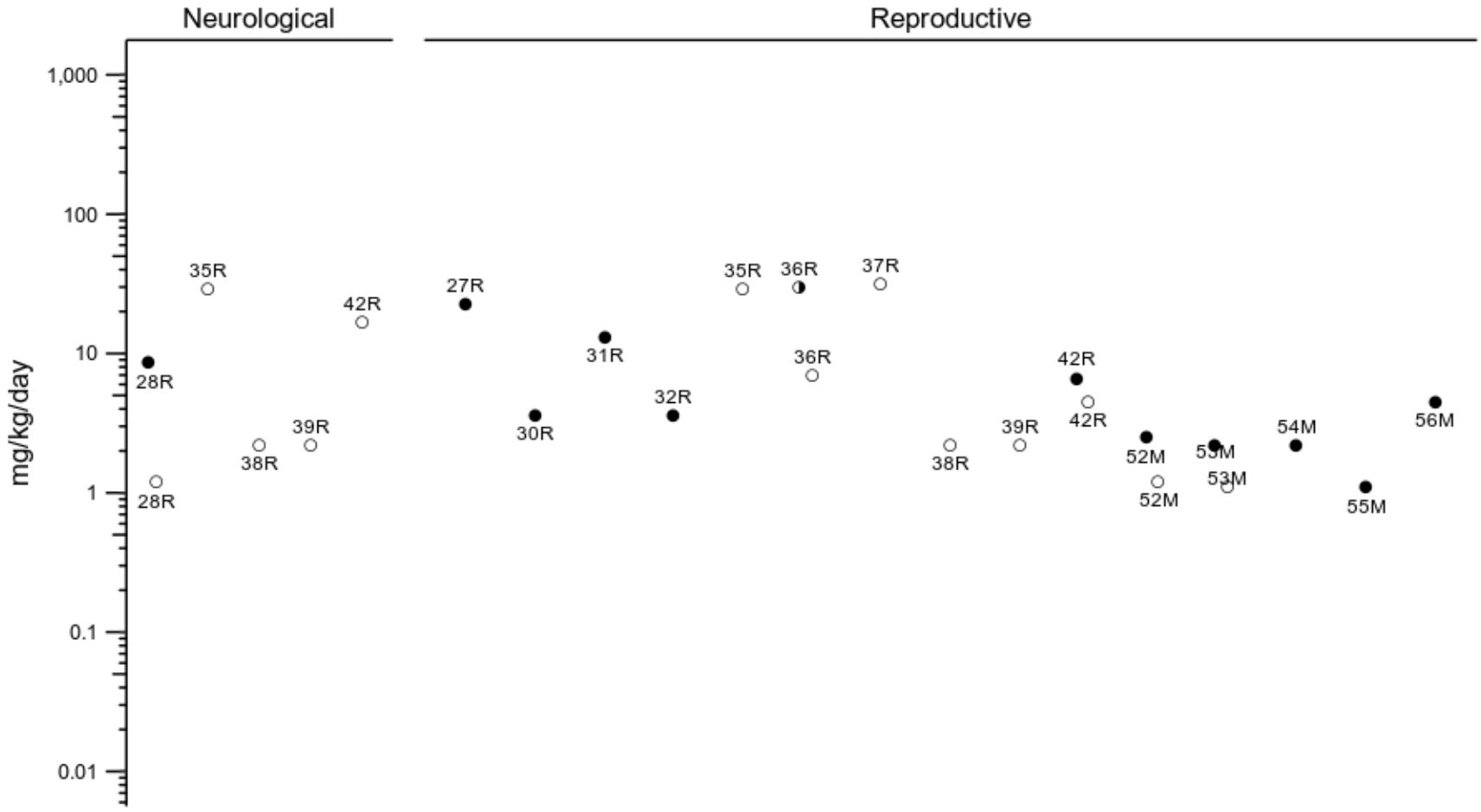


Figure 2-29 Levels of Significant Exposure to Nickel – Oral
Intermediate (15-364 days)

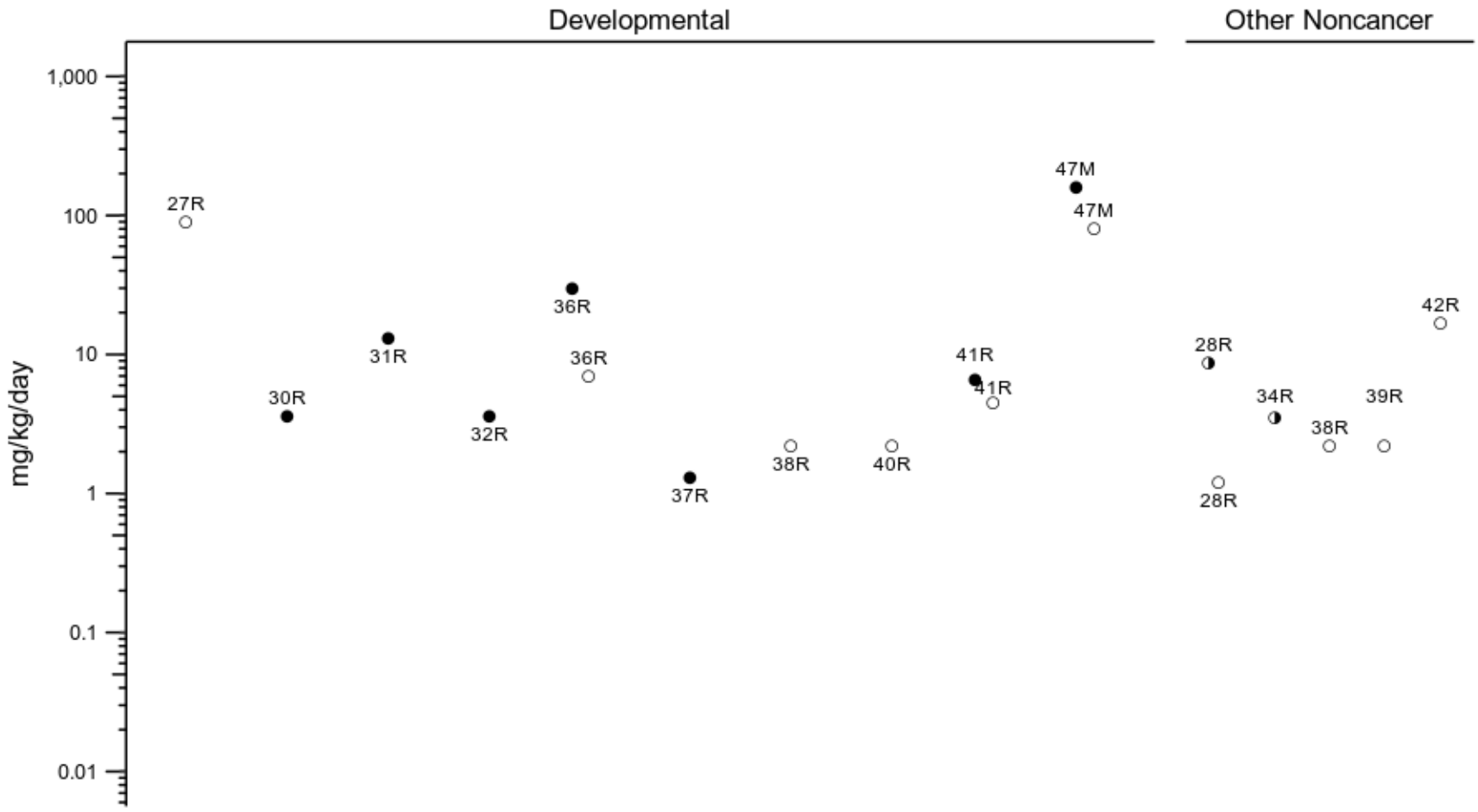


Figure 2-30. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

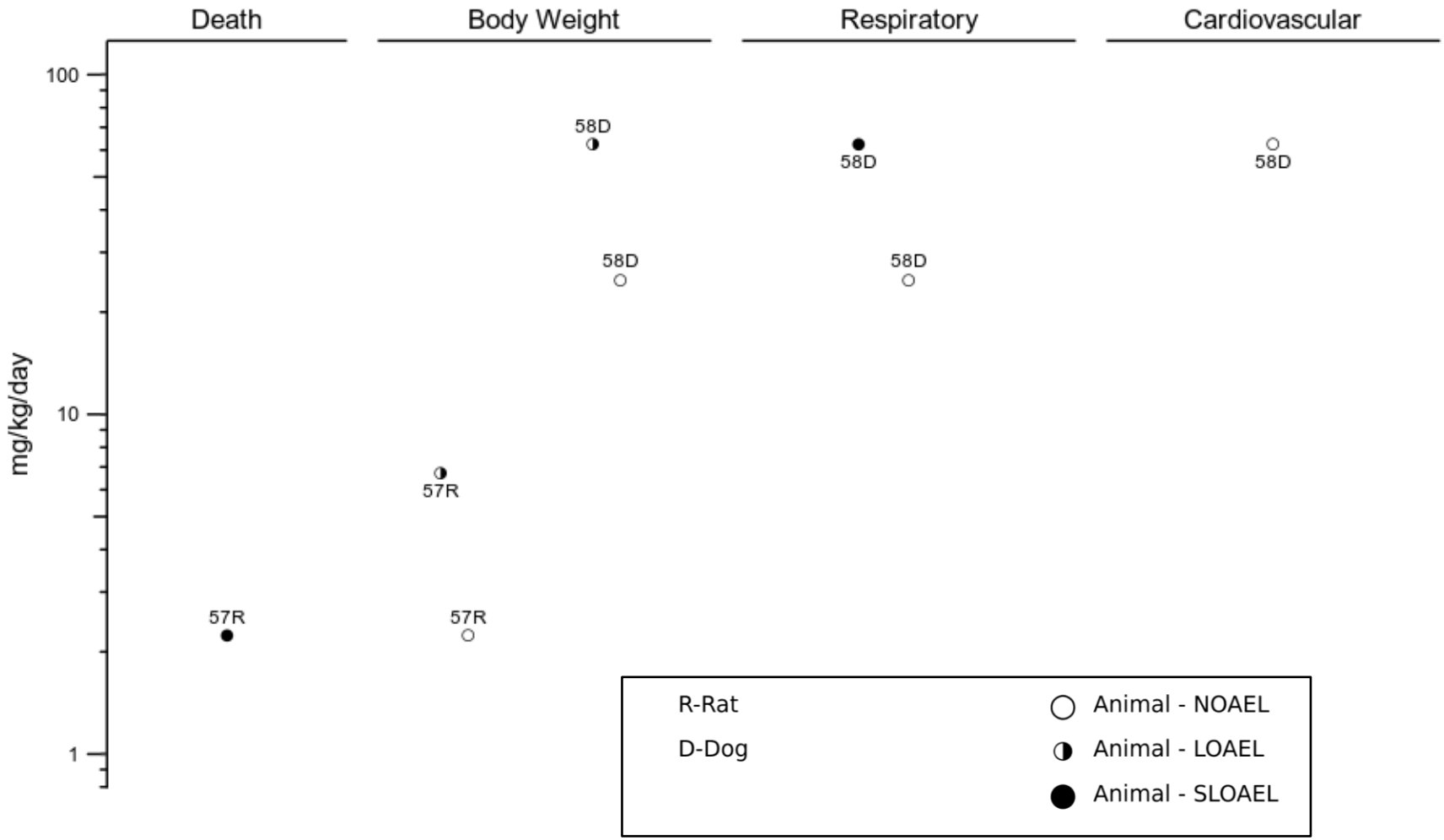


Figure 2-31. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

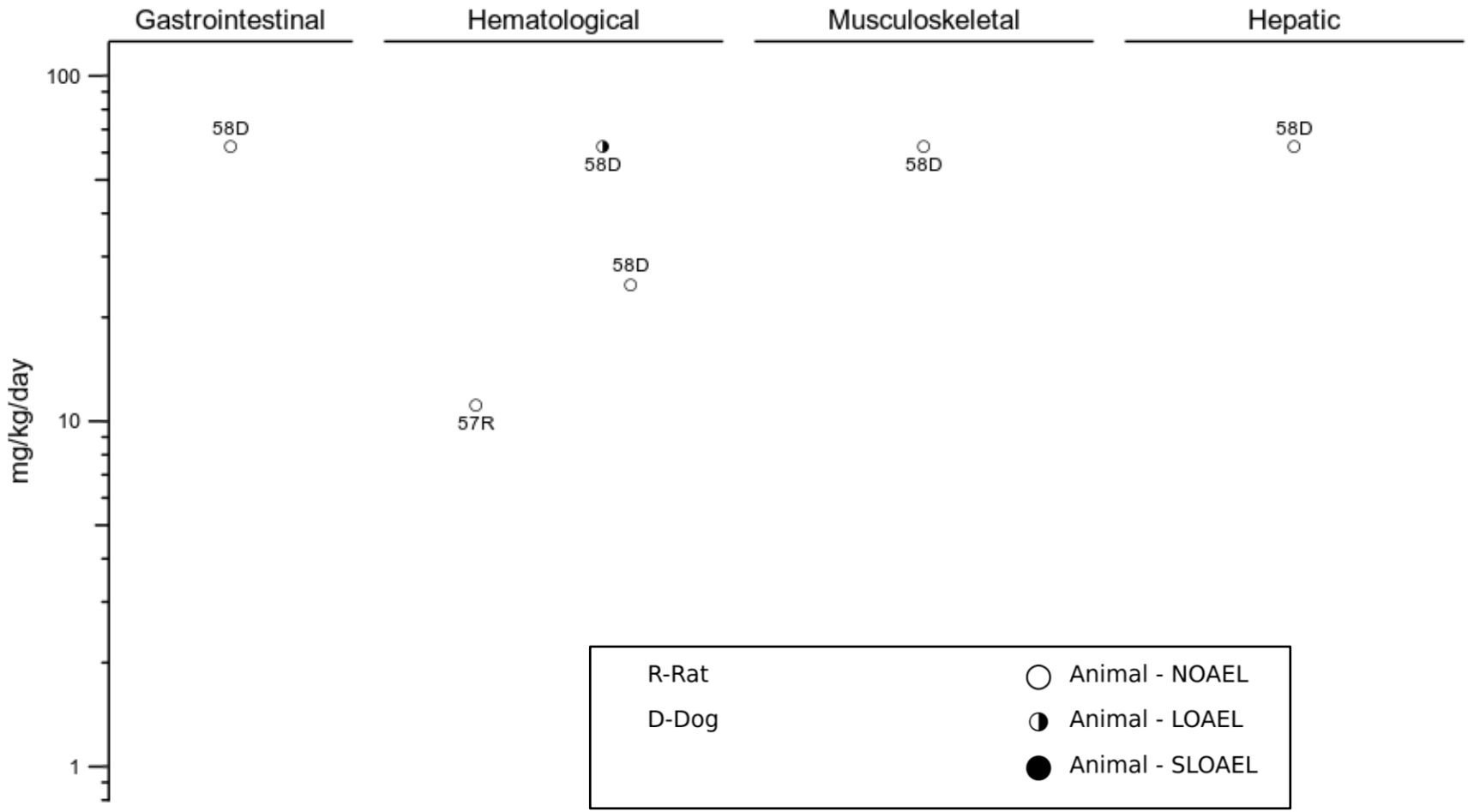


Figure 2-32. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

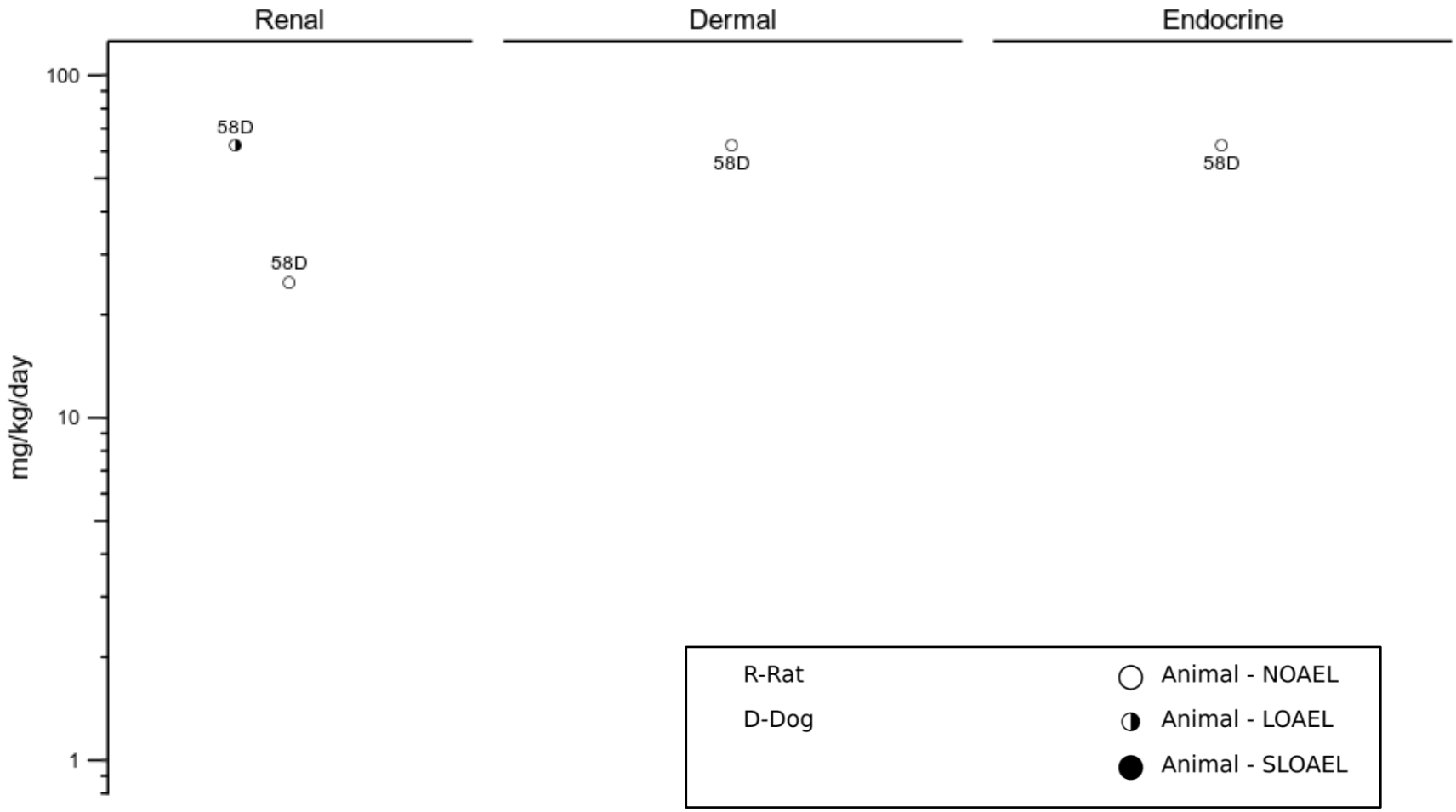


Figure 2-33. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

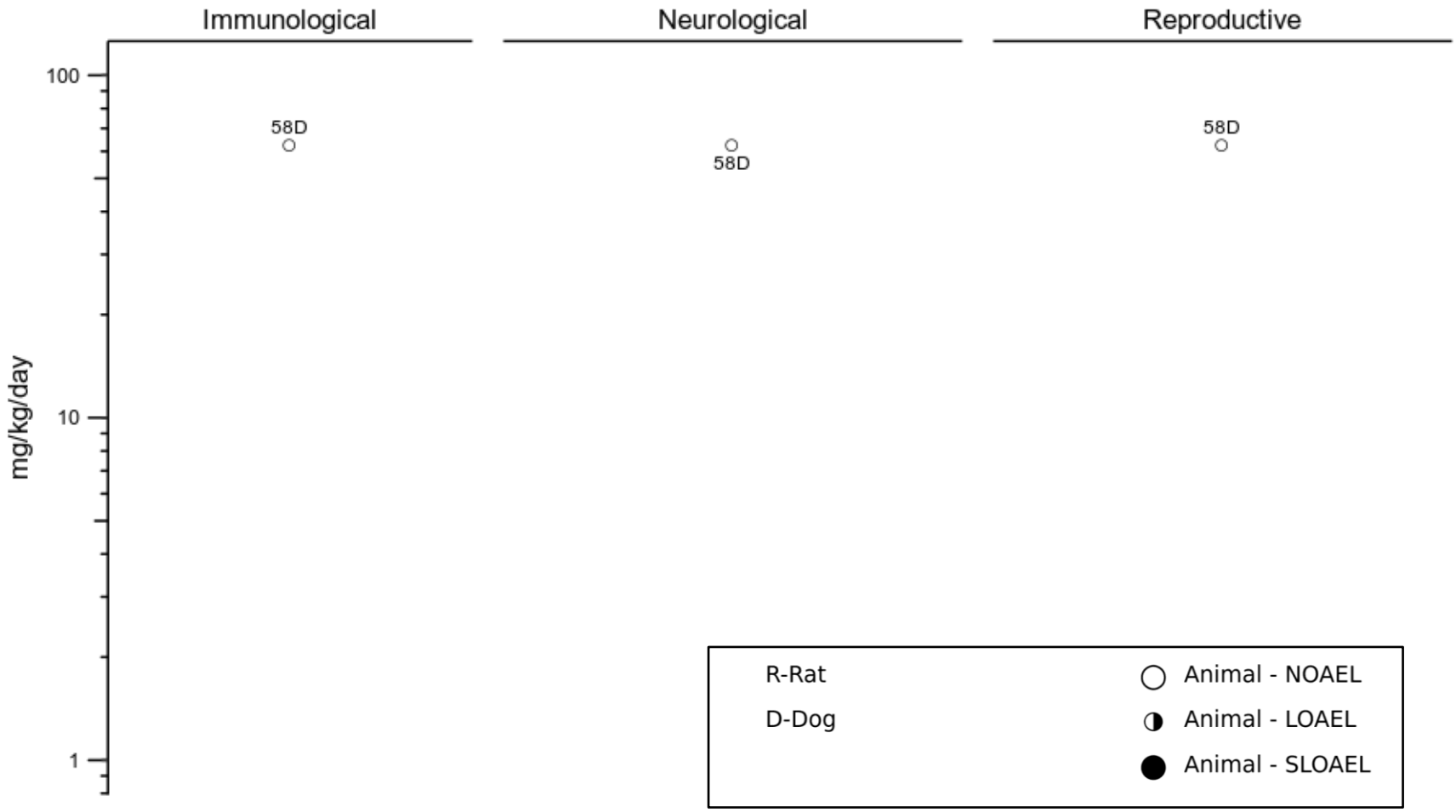


Figure 2-34. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

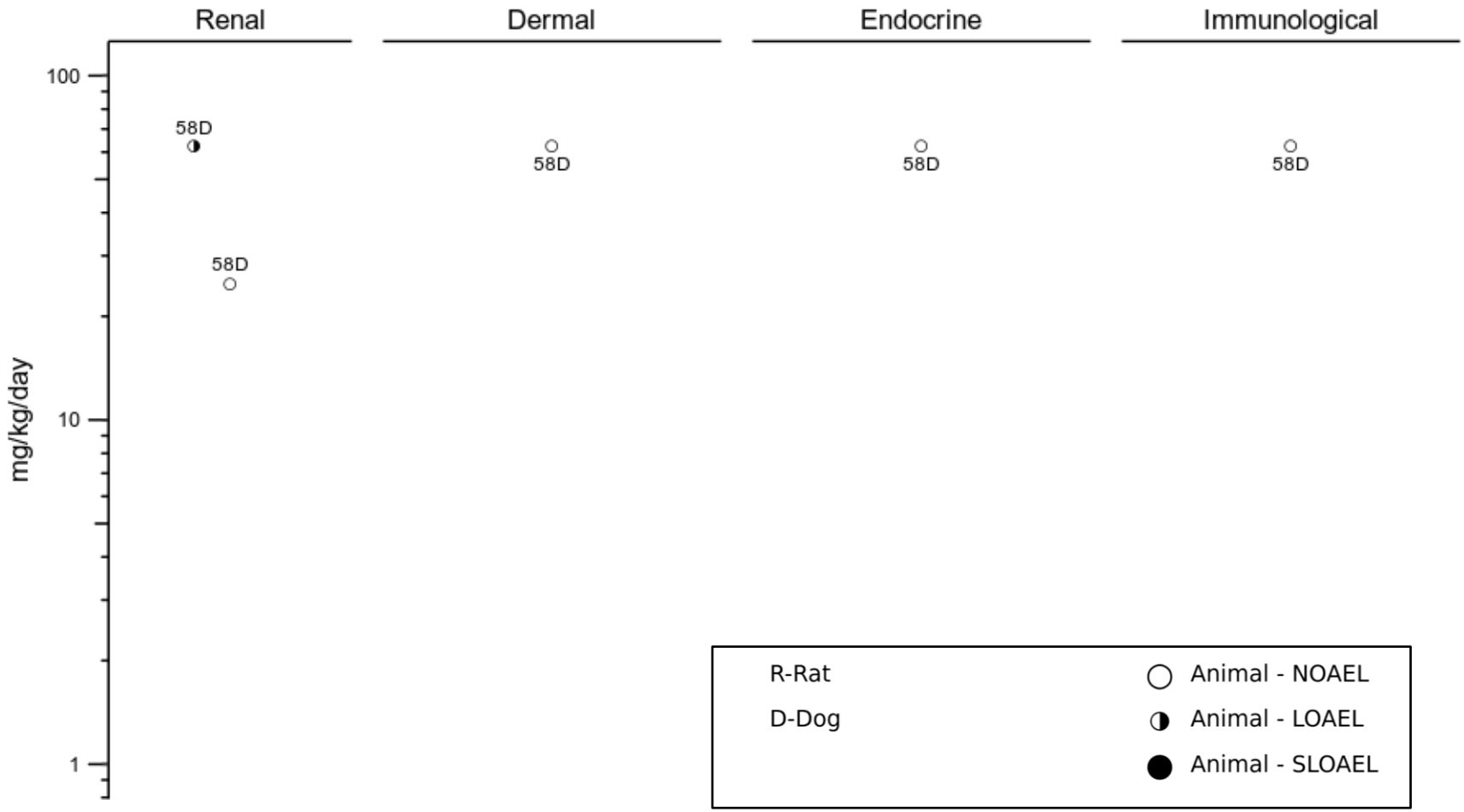


Figure 2-35. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

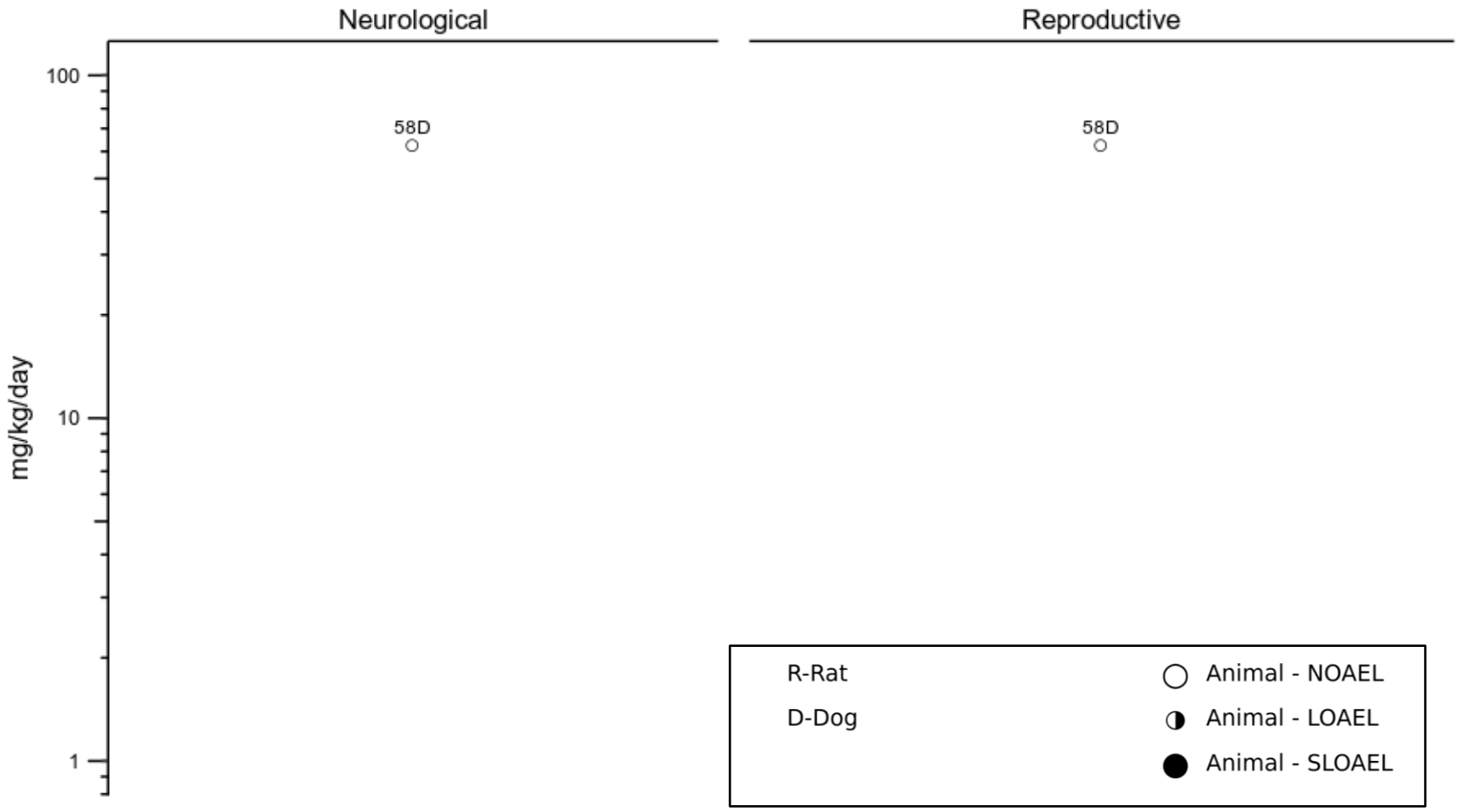


Table 2-3. Levels of Significant Exposure to Nickel – Dermal

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%) - 5.2 mg (2.5%)	CS	Dermal	0.01%	0.03%		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
Menne and Calvin 1993								**Nickel chloride**
HUMAN 16-51 NS	Once	0, 0.1, 1, 10, 100, 1000, 4000 ppm	CS	Dermal	0.01 ppm	0.1 ppm		Skin reaction in nickel sensitive individuals
Menne et al. 1987								**Nickel alloys**
HUMAN 164F 9M	Once	1 mg/cm^2/week	CS	Dermal		1 mg/cm^2/week		Contact dermatitis
Siller and Seymour 1994								**Nickel sulfate**
MOUSE (C3H:Hej) 4F	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) 8M	15 or 30 days daily	0, 40, 60, 100 mg/kg	CS GN HP RX	Hepatic	40 mg/kg	60 mg/kg		Focal necrosis
				Renal	100 mg/kg			
				Dermal		40 mg/kg		Slight hyperkeratosis
				Repro	40 mg/kg		60 mg/kg	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**
GN PIG (NS) 12NS	15 or 30 days	0, 100 mg/kg	BC	Hemato	100 mg/kg			
				Hepatic		100 mg/kg		Increased Mg2+ ATPase, acid phosphatase, and glucose-6-phosphatase activities
				Renal		100 mg/kg		Increased Mg2+ ATPase activity
				Other noncancer		100 mg/kg		Increased blood glucose

ATP = adenosine triphosphate; CS = clinical signs; F= female(s); HE = hematological; 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; SLOAEL = serious lowest-observed-adverse-effect-level

2.2 DEATH

Inhalation

Death from 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. A case-series detailing 7 workers of a waste-processing factory who were admitted to the hospital following nickel carbonyl poisoning reported 3 deaths with autopsies revealing interstitial lung fibrosis (Seet et al. 2005). In a fatal case of an adult male worker exposed to nickel carbonyl vapor for an estimated 30 minutes to several hours, imaging showed pneumonitis following presentation with dyspnea and hypoxia (Rusin et al. 2019).

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 Standard Mortality Ratios (SMR) for all causes of death. Generally, the studies report a higher incidence of cancer deaths from lung and nasal cancers in the exposed workers (see Section 2.19 Cancer). Two studies have also reported a higher incidence of deaths resulting from nonmalignant respiratory disease (Cornell and Landis 1984; Polednak 1981). However, all of the workers were exposed to other metals (arsenic, uranium, iron, lead, chromium) 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. 1984b; Shannon et al. 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. 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). Male and female Wistar rats showed reduced survival by 72% and 48% respectively by 103 weeks of continuous exposure (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 1996a, 1996b, 1996c). No rats or mice died following exposure to 23.6 mg Ni/m^3 as nickel oxide. No deaths were reported in rats or mice following 13 weeks of exposure (6 hours/day, 5 days/week) to nickel at 7.9, 1.83, or 0.44 mg Ni/m^3 as nickel oxide, nickel subsulfide, or nickel sulfate, respectively (NTP 1996a, 1996b, 1996c). The average survival times for rats exposed to 0 or 0.06 mg Ni/m^3 were 125.2 and 87.7 weeks, respectively. Survival was not affected in rats exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c). Survival of mice was also not affected by exposure to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/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).

Oral

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 136 mg Ni/kg as nickel acetate in Fischer-344 female rats and male Swiss-albino mice, respectively have been reported for soluble nickel compounds (Haro et al. 1968). Single-dose oral lethality studies indicate that soluble nickel compounds are more toxic than less-soluble nickel compounds.

Increases in mortality (6/52, 60/60) were observed in Sprague-Dawley rats administered via gavage 8.6 or 25 mg Ni/kg/day as nickel chloride hexahydrate for 91 days (American Biogenics Corporation 1988). Clinical signs observed included lethargy, ataxia, irregular breathing, hypothermia, salivation, squinting, and loose stools. As part of a longer-term study, Sprague-Dawley rats were provided with drinking water containing 1,000 ppm nickel as nickel chloride (approximately 140 mg/kg/day) (RTI 1988a). Within 2 weeks, 7/62 died and the dose was eliminated from the study. Over a 2-year study, mortality in female Fischer-344 rats exposed to 2.232 mg Ni/m^3 as nickel sulfate hexahydrate was 33% and the increase with

dose was an exposure-response to nickel (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), or Fischer-344 rats given 22 mg Ni/kg/day (males) or 33 mg Ni/kg/day (females) as nickel sulfide administered via gavage for 90 days (Springborn Laboratories 2002); no deaths were observed in B6C3F1 mice provided with nickel sulfate in the drinking water at doses up to 150 mg Ni/kg/day for 180 days (Dieter et al. 1988).

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

An increase in mortality was not observed in chronic-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).

Dermal

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

2.3 BODY WEIGHT

Inhalation

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

No exposure-related body weight changes are observed in female ICR mice exposed 24-hours whole body to concentrations up to 0.0801 mg Ni/m^3 as nickel chloride hexahydrate (Buxton et al. 2021). Acute continuous exposure of 23.6 mg Ni/m^3 as nickel oxide for 12 days in a 16-day period did not affect body weight in Fischer-344 rats and B6C3F1 mice of both sexes (NTP 1996a). Subsequent studies from the

National Toxicology program observed significant decreases in body weight (22-28%) of Fischer-344 rats after 12 days of continuous exposure to 0.7 to 1.83 mg Ni/m^3 nickel sulfate hexahydrate and nickel subsulfide (NTP 1996b, 1996c). Male and female B6C3F1 mice exposed for a similar duration to 1.4 mg Ni/m^3 of nickel sulfate appeared emaciated (NTP 1996c) while a similar study observed male mice final body weight from exposure to 3.65 mg Ni/m^3 of nickel subsulfide was 14% less than controls (NTP 1996b). Based on these NTP studies, body weight changes appear to be sensitive to an acute low dose exposure to nickel (NTP 1996a, 1996b, 1996c). Acute-duration exposure in Fischer-344 rats to nickel subsulfide at concentrations of 0.3 to 0.43 mg Ni/m^3 for 1 week (5 days/week, 6 hours/day) did not result in any body weight changes (Efremenko et al. 2014). When Fischer-344 rats of both sexes were exposed to 1.83 mg Ni/m^3 of metallic nickel, body weight decreased by 17-19 % after 7 days of exposure (Benson et al. 1995b).

Intermediate-duration continuous exposure of 7.9, 1.83, 0.44 mg Ni/m^3 for 13 weeks (5 days/week, 6 hours/day) did not affect body weight in Fischer- 344 rats and B6C3F1 mice of both sexes (NTP 1996a, 1996b, 1996c). No exposure-related body weight changes were seen in male Fischer-344 rats exposed continuously to 1.96 mg Ni/m^3 metallic nickel for 2-6 months (Benson et al. 1995a) and exposed to 0.03 to 0.45 mg Ni/m^3 as nickel subsulfide for 4 weeks, 5 days/week, 6 hours/day (Efremenko et al. 2014). Similarly, no effect on body weight was reported in Long-Evans rats exposed to 0.635 mg Ni/m^3 nickel sulfate hexahydrate for 16 days (Evans et al. 1995). Conversely, other studies in rats have observed exposure-related body weight changes at concentrations ranging from 0.385 to 1.83 mg Ni/m^3 as nickel oxide, nickel chloride, or nickel subsulfide (Benson et al. 1995b; Weischer et al. 1980). Male and female Fischer-344 rats showed a 10-19% decrease in body weight follow exposure to 1.83 mg Ni/m^3 for 22 days, 6 hours/day (Benson et al. 1995b). Weischer et al. (1980) reported 30–36% decreases in body weight gain in male and female Wistar 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 non-pregnant rats (Weischer et al. 1980).

Two intermediate-duration studies in mice did not find exposure related changes in body weight (Benson et al. 1995a; Xu et al. 2012). Neither exposure to 0.00017 mg Ni/m^3 for 3 months, 5 days/week, 6 hours/day in ApoE-/- mice (Xu et al. 2012) nor continuous exposure to 3.9 mg Ni/m^3 in B6C3F1 mice for 2-6 months resulted in body weight changes (Benson et al. 1995a).

Chronic-duration continuous exposure of 2 mg Ni/m^3 for 2 years (5 days/week, 6 hours/day) did not affect body weight in Fischer- 344 rats of both sexes (NTP 1996a). Under identical exposure conditions a concentration of 3.9 mg Ni/m^3 as metallic nickel did not change body weight in B6C3F1 mice of both sexes (NTP 1996a). In NTP (1996b), chronic-duration exposure to metallic nickel at 0.73 mg Ni/m^3

resulted in a 11-12% decrease in body weight in Fischer-344 rats of both sexes but had no effect in B6C3F1 mice at a concentration of 0.88 mg Ni/m^3. In NTP (1996c), chronic-duration continuous (5 days/week, 6 hours/day) exposure to nickel sulfate hexahydrate at 0.22 mg Ni//m^3 decreased body weight by 12% in female B6C3F1 mice but not in male mice. Similar duration of exposure at 0.11 mg Ni/m^3 had no effect on body weight in Fischer-344 rats of both sexes (NTP 1996c). Ottolenghi et al. (1975) observed a 20-30% decrease in body weight in male and female Fischer-344 rats compared to controls after exposure to metallic nickel at 0.63 mg Ni/m^3. Chronic-duration exposure to metallic nickel at 0.06 to 0.942 mg Ni/m^3 in male Wistar rats did not affect body weight (Takenaka et al. 1985; Tanaka et al. 1988).

Oral

No studies were identified that examined body weight effects in humans after oral exposure to nickel.

A dose-dependent reduction in body weight gain was observed in treated animals compared to the control group. This reduction of body weight gain was associated with reduced food and/or water intake reported in Wistar rats orally exposed to 0.23 to 0.97 mg Ni/kg/day as nickel chloride in drinking water for 28 days (Weischer et al. 1980); in Sprague-Dawley 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 (RTI 1988a); and in Wistar rats treated with 75 mg Ni/kg/day of nickel sulfate hexahydrate 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. Decreases (10–13%) in body weight gain were also observed in male and female Fischer-344 rats administered via gavage 17 or 28 mg Ni/kg/day, respectively, as nickel sulfate (Springborn Laboratories 2002); however the decreases in body weight gain were not associated with consistent alterations in food intake (water consumption data were not reported). Male and female Fischer-455 rats exposed to 6.69 and 11.16 mg Ni/kg/day as nickel sulfate hexahydrate, respectively, for 2 years daily showed an average body weight decrease of 10-11% compared to controls (Heim et al. 2007). In the 90-day intermediate-duration study by Heim et al. (2007) similar body weight decreases were reported in rats when males and females were exposed to 16.74 and 27.91 mg Ni/kg/day, respectively. In brown rats, no body weight changes were reported following a 6-week exposure to 5 mg Ni/kg/day as nickel acetate in feed (Whanger 1973). However, body weight gain was significantly decreased by 88% compared to controls at doses ≥25 mg Ni/kg/day.

Decreases in body weight gain of 10% or more were not observed in various studies in rats, including Sprague-Dawley rats exposed to nickel sulfate in drinking water at 28.8 mg Ni/kg/day for 13 weeks (Obone et al. 1999), in Wistar rats exposed by gavage at 7.58 mg Ni/kg/day for 21 days (Adeyemi et al. 2017), or in Sprague-Dawley rats by gavage at up to 2.2 mg Ni/kg/day for 18 weeks daily (Springborn

Laboratories 2000a). Similarly, no exposure related effects were reported in rats treated with nickel chloride in drinking water at 31.6 mg Ni/kg/day for 11 weeks (Smith et al. 1993), nickel sulfate in drinking water at 28.8 mg Ni/kg/day for 13 weeks (Obone et al. 1999), or nickel sulfate at a dose of 7.6 mg Ni/kg/day for 3 or 6 months (Vyskocil et al. 1994b).

Decreased body weight gain has also been reported in mice treated with nickel chloride in feed at 4.53 mg Ni/kg/day for 3-12 weeks daily (Toman et al. 2012), nickel sulfate in drinking water at a dose of 108 mg Ni/kg/day for 180 days (Dieter et al. 1988), and in dogs treated with nickel sulfate in the diet at a dose of 62.4 mg/kg/day for 2 years (Ambrose et al. 1976). Female ICR mice treated with 90.6 mg Ni/kg/day as nickel chloride during gestation days 8-12 showed weight gain 49% lower than controls (Seidenberg et al. 1986). Male BALB/c mice exposed to doses ranging from 0.9 to 7.2 mg Ni/kg/day as nickel chloride did not show any exposure-related changes in body weight (Gathwan et al. 2013).

Dermal

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

2.4 RESPIRATORY

Inhalation

Numerous human studies have examined the potential of nickel and nickel compounds to induce respiratory effects. Most of these studies were cohort mortality studies in nickel exposed workers. A significant excess of deaths from nonmalignant respiratory system disease was found among foundry workers that was associated with the duration of foundry employment, regardless of exposure to nickel (Cornell and Landis 1984). Other studies of refinery workers or workers exposed to nickel alloys have not found increases in deaths from respiratory disease (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Redmond 1984; Roberts et al. 1989a; Shannon et al. 1984b; Shannon et al. 1991). Two studies of welders also did not find significant increases in the risk of nonmalignant respiratory disease deaths (Moulin et al. 2000; Polednak 1981). A common limitation of the cohort mortality studies is that the number of observed deaths from all causes were lower (in many cases significantly lower) than the number expected deaths, suggesting a healthy worker effect. Additionally, the workers were exposed to other respiratory toxicants; this is particularly true for welders exposed to elevated levels of chromium. A single case of death from ARDS has been reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 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.

A small number of studies have examined potential respiratory tract effects, not associated with lethality. An industrial hygiene survey of welders in New Zealand reported a significant odds ratio for workers currently exposed to high nickel levels (0.001-0.002 mg/m^3) and work-related respiratory symptoms (adjusted OR=7.0, 1.3-36.6) (Fishwick et al. 2004). Study authors reported that detailed exposure information was not available however exposure to welding fumes considered workplace factors, respiratory protection, and ventilation (Fishwick et al. 2004). Reduced vital capacity and expiratory flows were observed in stainless steel welders exposed to elevated levels of nickel and chromium (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). Welders did not wear respiratory protection nor were local area ventilation devices used. When results in welders were stratified based on smoking status, among non-smokers, only the forced expiratory volume (FEV_{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 this study provides suggestive evidence of respiratory effects in welders, establishing a causal relationship between nickel and the observed effects is limited by co-exposure to chromium. Additional limitations include use of predicted population values based on a random sample of men as the comparison group, rather than a comparison group of non-nickel-exposed welders. 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, after controlling for age and smoking, among nickel refinery workers with cumulative exposure to soluble nickel or sulfidic nickel (Berge and Skyberg 2003). A dose-response trend was also found for soluble nickel among cases in the three highest cumulative exposure categories (0.04–≤0.15, 0.15–≤0.6, and >0.6 mg/m^3 x years), after adjusting for age, smoking, and exposure to asbestos. Asthma induced by occupational exposure to nickel has been documented in a small number of individuals (Dolovich et al. 1984; Novey et al. 1983; Shirakawa et al. 1990). Asthma can result from either primary irritation or an allergic response. Interpretation of these data is limited by the small number of cases, as well as by possible exposure to other sensitizing metals.

Several case studies of workers exposed to nickel corroborate the respiratory system as a sensitive endpoint of inhalation exposure. A 55-year-old male who had cleaned a nickel carbonyl reaction vessel had sought medical care 2 days after exposure and imaging showed pneumonitis following presentation with dyspnea and hypoxia (Rusin et al. 2019). The worker died 44 days after exposure and had also developed diarrhea, acute kidney injury, and leukocytosis during treatments; an investigation by OSHA indicated that the worker had likely inhaled nickel carbonyl vapor for 30 minutes to several hours (Rusin et al. 2019). Nausea, myalgia, and cough was reported by a 50-year-old industrial worker who presented to the hospital 12-24 hours after exposure to an unknown concentration of nickel carbonyl (Bowman et al. 2018). Additional testing revealed that forced expiratory volume (FEV1) and forced vital capacity (FVC) were lower than predicted. The patient's urine nickel level on admission was 692 µg/L (reference value: <10 mcg/L) (Bowman et al. 2018). Lung injury was seen in a 50-year-old welder who accidentally inhaled an unknown concentration of nickel fumes that was 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 three days later showed reticular opacities in middle and lower lung fields, while a CT scan of the chest showed bilateral non-segmental 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 Durdevic 2020). Histological examination of a lesion in the paranasal sinuses showed an inflammatory nasal polyp.

Several population studies have also examined associations of nickel in ambient air and various respiratory system effects. Two studies specifically looked at respiratory and cardiovascular hospitalizations in adults over 65 years old and found an association with higher nickel in $PM_{2.5}$ (Bell et al. 2009; Bell et al. 2014). Bell et al. (2009) looked at hospitalizations in 106 U.S. counties from 1999 to 2005, while Bell et al. (2014) analyzed 4 counties in the Northeast from 2000 to 2004.

Several other studies have examined respiratory effects in children. Increases in ambient air nickel concentrations were significantly associated with increased probability of wheeze among a cohort of children up to 24 months of age living in New York City between 1998 and 2006 (Patel et al. 2009). In a separate prospective case-control study of thirty-six 6-to-14 year old children in New York City, nickel in air was significantly associated with maximum asthma symptoms including cough and wheeze in the winter; odds ratio of 1.94 (1.08-3.49) (Schachter et al. 2020). Additionally, increased albuterol use (asthma inhaler) was significantly associated with nickel (odds ratio=2.27; 1.02-5.07), however this effect

disappeared when adjusted for ozone. In a single pollutant model, reports of asthma in children 11-14 years of age were associated with nickel exposure, as a relative risk of 1.11 was calculated per 4 ng/m^3 increase (Rosa et al. 2016). A prospective birth cohort which followed children from birth up 12 years of age found no associations between Ni $PM_{2.5}$ or Ni PM_{10} and parent-reported asthma symptoms or incidents (Gehring et al. 2015).

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). 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. Bronchiolar epithelium degeneration was also observed in rats exposed to 0.7 mg Ni/m^3 as nickel sulfate (NTP 1996c). Consistent with these findings, is the observation of alveolitis in 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). Bai et al. (2013) exposed Sprague-Dawley rats to concentrations of 6.88, 46.47, and 85.94 mg Ni/m^3 as nickel carbonyl for 30 minutes in an inhalation chamber and damage of type II alveolar epithelial cells was apparent in rat lung tissue of all exposure groups. A dose-effect relationship was indicated based on the increasing severity of damage. The highest exposure group showed pulmonary tissue edema and decreased peroxidation of pulmonary tissue (Bai et al. 2013). Lung histopathology in 5 out of 5 Fischer-344 rats exposed to 0.43 mg Ni/m^3 as nickel subsulfide showed peribronchiolar/perivascular inflammation following 1 week of exposure (5 days/weeks for 6 hours/day) (Efremenko et al. 2014). Inflammation was characterized by “peribronchiolar and perivascular edema, lymphocytes and occasional neutrophils.” When exposed for 20 days over 4 weeks, 5 out of 5 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.

Oller et al. (2022) reported increased incidence of alveolitis, proteinosis, and perivascular/peribronchiolar inflammation in Fischer-344 rats exposed to 0.04 mg Ni/m^3 as nickel subsulfide for 13 weeks (6 hours/day, 5 days/week). The incidence and severity of lung lesions at 3 and 13 weeks of exposure showed that increases in both are concentration dependent. Rats exposed under similar conditions to nickel sulfate hexahydrate showed similar concentration-dependent results in pulmonary lesions (Oller et al. 2022). At a NOAEL of 0.03 mg Ni/m^3 as nickel sulfate hexahydrate, there was no difference between the exposed rats and controls for incidence of lung inflammation or lesions, or changes in lung weight. At 0.11 mg Ni/m^3 as nickel sulfate hexahydrate, the incidence of alveolitis, perivascular/peribronchiolar inflammation, and bronchiolar epithelial degeneration and apoptosis was high. In addition, increases in LDH levels in bronchoalveolar lavage fluid (BALF) were significant at 0.11 mg Ni/m^3 as nickel sulfate hexahydrate (Oller et al. 2022). 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. 2022). 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 degree, was seen in rats exposed to 0.5 mg Ni/m^3 as nickel oxide for 1 month (Horie et al. 1985). In the study by Oller et al. (2022), one group of rats was exposed to a high dose of nickel sulfate hexahydrate (0.44 mg Ni/m^3) but died within the first week of exposure, and the deaths were attributed to respiratory toxicity. Rats showed labored breathing and nasal discharge; gross necropsy showed severe pulmonary edema as the likely cause of death (Oller et al. 2022).

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. (2022) where the incidence of alveolar macrophage hyperplasia was similar between controls and groups of rats

exposed to concentrations of nickel sulfate hexahydrate 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. 2022). 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) or 0.109 mg Ni/m^3 as nickel chloride (Bingham et al. 1972), granulomatous inflammation was observed in rats exposed to 3.9 mg Ni/m^3 as nickel oxide (NTP 1996a), alveolar wall thickening was observed in rats exposed to 0.12 mg Ni/m^3 as nickel oxide (Bingham et al. 1972), and hyperplasia of the bronchial epithelium was observed in rats exposed to 0.109 mg Ni/m^3 as nickel chloride (Bingham et al. 1972). The highest NOAEL values for respiratory effects in rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for intermediate-durations were 0.06 mg Ni/m^3 (NTP 1996c), 0.11 mg Ni/m^3 (NTP 1996b), and 0.49 mg Ni/m^3, respectively (Benson et al. 1995a). An intermediate-duration inhalation MRL was derived from the NOAEL (0.06 mg Ni/m^3) and LOAEL (0.11 mg Ni/m^3) identified from the NTP (1996c) study of nickel sulfate.

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 and higher as nickel sulfide (NTP 1996b; Ottolenghi et al. 1975), in mice at 0.44 mg Ni/m^3 and higher as nickel subsulfide (NTP 1996b), in rats at 0.2 mg Ni/m^3 and higher as nickel oxide (NTP 1996a; Tanaka et al. 1988), and in mice at 1 mg Ni/m^3 as nickel oxide (NTP 1996a). 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 NOAEL of 0.03 mg Ni/m^3 and LOAEL of 0.06 mg Ni/m^3 identified in rats exposed to nickel sulfate (NTP 1996c) were used to derive a chronic-duration inhalation MRL for nickel.

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. Twelve 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). The nasal lesions are typically observed at higher concentrations than the lung effects. In a study designed specifically to examine the effects of nickel on the olfactory system, rats were exposed to nickel sulfate at 0 or 0.635 mg Ni/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, fewer sensory cilia were the only change that remained, indicating that the effects of an intermediate-duration exposure to nickel were reversible.

Oral

A case-series examined 20 female patients who presented with chronic rhinitis (nasal inflammation) and upon allergen testing all females only had a positive reaction to nickel sulfate in patch testing (Brera and Nicolini 2005). Authors suggest 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.”

Irregular respiration was one of several clinical signs of nickel toxicity observed in 4 out of 6 rats exposed to doses of nickel sulfate hexahydrate ≥111.6 mg Ni/kg/day for 3 days (Oller and Erexson 2007). Pneumonitis was observed in 6/19 male rats and 9/17 female rats treated for 91 days by gavage with 8.6 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988). Significant increases in absolute and relative lung weights were observed in rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999). This study also found alterations in enzyme activity in bronchoalveolar lavage (BAL) fluid and lung tissues, including increases in protein levels in BAL fluid at 14.4 mg Ni/kg/day and higher, decreases in alkaline phosphatase activity in BAL fluid at 5.75 mg Ni/kg/day and higher, and decreases in alkaline phosphatase activity in lung tissue at 28.8 mg Ni/kg/day. No histological alterations were observed in the lungs. The study authors suggested that the decrease in alkaline phosphatase activity was indicative of decreased activity of type II alveolar cells and the increased total protein was indicative of increased air-blood barrier permeability. In a multigeneration study (RTI 1988a, 1988b), increased 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).

Dermal

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

Inhalation

No increases in the number of illness or deaths from cardiovascular diseases were reported in workers exposed to nickel (Cavallari et al. 2008; Cornell and Landis 1984; Cox et al. 1981; Cragle et al. 1984). A cross-sectional population level study in southern California reported a correlation between nickel concentrations in ambient air and mortality from ischemic heart disease (Cahill et al. 2011). Several population-level studies report an association of nickel concentration in air and cardiovascular hospitalizations, illness, and indicators (Bell et al. 2009; Bell et al. 2014; Huang et al. 2017; Jacobs et al. 2012; Niu et al. 2013; Occelli et al. 2020; Spiezia et al. 2016; Wu et al. 2012). In other epidemiological studies, no evidence of an association between nickel exposure and pulmonary embolism was seen (Spiezia et al. 2014), and between nickel exposure in ambient air and coronary events (Wolf et al. 2015). Epidemiological studies examining cardiovascular effects and exposure to nickel in ambient air are summarized in Table 2-4.

Microscopic examinations of the hearts of Fischer-344 rats exposed to nickel oxide, nickel subsulfide, or nickel sulfate for 12 6-hour exposures over 16 days did not reveal any changes at concentrations as high as 23.6, 7.33, or 12.2 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c). Similarly, no changes were observed in B6C3F1 mice exposed to nickel oxide or nickel sulfate at concentrations as high as 23.6 or 1.4 mg Ni/m^3, respectively (NTP 1996a, 1996c). Acute-duration exposure in beagle dogs to nickel sulfate and nickel oxide at 0.1 and 0.06 mg Ni/m^3, respectively did not cause any effects in the cardiovascular system based on electrocardiogram test evaluations (Muggenburg et al. 2003).

No cardiovascular effects were observed in rats or 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). Continuous exposure to metallic nickel at 0.0004 mg Ni/m^3 in male ApoE mice for 14 weeks (5 days/week, 6 hours/day) caused vascular endothelial dysfunction indicated by increased aortic relaxation (Ying et al. 2013). At similar lower concentrations of exposure to 0.00017 mg Ni/m^3 as nickel sulfate in ApoE mice, exposure induced microcirculatory dysfunction indicated by increases in adherent and rolling monocytes in the microcirculation after a 3-month continuous exposure (5 days/week, 6 hours/day) (Xu et al. 2012).

Chronic-duration exposure (6 hours/day, 5 days/week) of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice to, 0.22, 0.88, or 3.9 mg Ni/m^3, respectively, did not result in microscopic changes in the heart (NTP 1996a, 1996b, 1996c). Continuous exposure (6 hours/day, 5 days/week) of Fischer-344 rats to 0.63 mg Ni/m^3 as

nickel sulfide for 78 weeks also did not affect the microscopic appearance of the heart (Ottolenghi et al. 1975).

Overall, cardiovascular effects of exposure to any form of nickel for any duration did not show an effect in rats and mice of different strains except $ApoE^{-/-}$ mice (Ying et al. 2013; Xu et al. 2012). This strain of mice is deficient in apolipoprotein E which is implicated in cardiovascular diseases, and is used to study cardiovascular diseases (Meir and Leitersdorf 2004).

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
Bell et al. 2009 **Study Type/Population:** Time-series population study linking two national datasets by county and by season and analyzed the long-term average concentrations of $PM_{2.5}$ chemical components for 2000 to 2005 and the risk ratios (RRs) of cardiovascular and respiratory hospitalizations for persons 65 or older associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ total mass on the same day for 106 US counties from 1999 to 2005.	**Exposure:** Analyzed long-term average concentrations of $PM_{2.5}$ chemical components for 2000-2005 and RRs of cardiovascular and respiratory hospitalizations for persons 65 years or older associated with a 10 ug/m^3 increase in PM2.5 total mass on the same day for 106 US counties for 1999 through 2005. 20 metals were analyzed in total. **Inclusion/Exclusion Criteria:** Counties were selected based on data availability for $PM_{2.5}$ total mass and chemical components and had populations of 200,000 or more. **Covariates Considered/Other Regression Adjustments:** Analysis adjusted for daily temperature and dew point temperature for the previous 3 days' temperatures. Percent increase in nickel, elemental carbon, and vanadium were adjusted by other chemical components in the regression analysis and reported both with and without co-pollutants.	**Outcomes:** Counties with higher $PM_{2.5}$ content of nickel were found to have higher risk of cardiovascular and respiratory hospitalizations associated with short-term exposure to $PM_{2.5}$. Reported percent increases in health effects estimates for $PM_{2.5}$ lag 0 and risk of cardiovascular hospitalizations (19% increase) and respiratory hospitalizations (223%) per interquartile range increase in the fraction of $PM_{2.5}$ total mass for each component, with and without co-pollutant adjustment (listed without co-pollutant adjustment here). **Limitations:** The population criterion results in more urban counties. The analysis also includes 19 other metals, in addition to nickel. The result found in the outcome is true for elemental carbon (EC) and vanadium as well.
Bell et al. 2014 **Study Type/Population:** Time series population study analyzing the relative risks of cardiovascular and respiratory	**Exposure:** Filter samples for four counties in Connecticut and Massachusetts were analyzed for $PM_{2.5}$ elements. Source apportionment was used to estimate daily $PM_{2.5}$ contributions from sources (traffic, road dust, oil combustion, and sea salt, and regional sources, e.g., coal	**Outcomes:** Found association between nickel in $PM_{2.5}$ exposure and cardiovascular and respiratory illness hospitalizations. Higher contribution of nickel strengthens associations between $PM_{2.5}$ mass and cardiovascular hospitalization rates. A higher risk of

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Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
hospitalizations associated with short-term exposure to $PM_{2.5}$ constituents and sources for the Medicare population (> 330,000 persons ≥ 65 years old) in a time-series analysis between February 2000 and August 2004 in 4 counties in Connecticut (3) and Massachusetts (1). Effect was measured supplementing EPA's Chemical Speciation Network for the 4 counties with data from X-ray fluorescence elemental analysis of $PM_{2.5}$ filters collected at five EPA monitoring sites in the sample states.	combustion). Associations between daily $PM_{2.5}$ constituents and sources and risk of cardiovascular and respiratory hospitalizations for the Medicare population (< 330,000 persons > 65 years of age) were estimated with time-series analyses between August 2000 and February 2004. 12 metals were analyzed in total. Mean nickel exposure was found to be 0.003, median 0.0020. Mean nickel exposure was 0.003, median 0.0020, and $PM_{2.5}$ total mass was 0.02%. **Inclusion/Exclusion Criteria:** Exposure for $PM_{2.5}$, constituents, and sources by analyzing filters used by regulatory agencies to measure $PM_{2.5}$ total mass and used those data to source apportionment analysis. Estimated weather variables for each county. Identified at-risk population of Medicare beneficiaries (≥ 65 years old) who resided in the counties studied and were enrolled in the Medicare fee-for-service plan during August 2000 – February 2004. Included only emergency hospitalizations and used date of admission to calculate daily number of admissions and used the principal discharge diagnosis code as cause of admission. Days with missing data were omitted from the analysis.	respiratory hospitalizations was associated with higher levels of nickel, more than other pollutants examined. **Limitations:** Samples were taken every 3 days in some monitoring sites, and every day, missing some periods, in others. The authors cited several limitations, including the limited period of the data set prohibited the authors' extensive analysis by season; lack of key data for particle sources and constituents (e.g., ammonium sulfate); and minimum detection limits hindered the authors' ability to estimate exposure for all constituents and incorporate them in source-apportionment methods. Authors cited limitations also include confounding by covarying constituents and $PM_{2.5}$ in situations where $PM_{2.5}$ is associated with the health outcome. Nickel did not remain statistically significant when adjusted by black carbon.

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
	Covariates Considered/Other Regression Adjustments: Analysis adjusted for co-pollutants.	
Cahill et al. 2011 **Study Type/Population:** Cross-sectional study analyzing the association of wintertime $PM_{2.5}$ mass with mortality associated with cardiovascular and specifically ischemic heart disease (IHD) in southern California Central Valley. Conducted an aerosol sampling transect in the study area during a 17-day period of strong stagnation. Mass and elemental components were measured.	**Exposure:** Authors conducted an aerosol sampling transect from Redding to Bakersfield during a 17-day period of strong stagnation, January 5-22, 2009. Mass and elemental components were measured every 3 hours in eight particle size modes, ranging from 10 to 0.09 µm, while ultrafine particles (<0.09 µm) were collected on Teflon filters. 32 elements were analyzed in this study. Over 6,400 measurements were made of mass and inorganic elements in nine size modes for the study period. **Inclusion/Exclusion Criteria:** Using meteorological predictions, the authors simultaneously sampled continuously by size, time, and composition for 17 days starting on January 5, 2009, at five sites from the extreme north to the extreme south of the study area. The study included three components, all conducted in winter conditions using the same equipment: 1) an initial year-long study of the DRUM sampler and the ARB's FRM to establish equivalency 2) a simultaneous transect across a heavily traveled secondary street to identify very fine and ultrafine aerosols from roadways, and 3) the main transect study in winter, 2009.	**Outcomes:** A correlation ($r^2 = 0.95$) was found between nickel and IHD mortality for concentration (ng/m^3) of very fine (0.09-0.26 µm) aerosols, and $r^2 = 0.70$ for concentration of ultrafine (<0.09µm) aerosols. **Limitations:** The authors state that the evidence they present in the study is not conclusive, but strongly supports the hypothesis that very fine and ultrafine transition metals (including nickel) are a causal factor in IHD in the Central Valley of California. The authors cited limited information on ultrafine metals from vehicular exhaust.

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
	Covariates Considered/Other Regression Adjustments: Authors did not explicitly list any covariates or adjustments, though ancillary studies were performed including direct upwind-downwind profile across a heavily traveled secondary street near a stoplight (in which there would be braking, therefore exposure to brake drums and pads).	
Cavallari et al. 2008 **Study Type/Population:** Prospective panel study (cohort) examining the association between daytime exposure to the metal content of $PM_{2.5}$ and night heart rate variability (HRV) in a panel study of 26 male boilermaker construction workers exposed to metal-rich welding fumes. Authors recruited boilermakers between 1999 and 2006 at an apprentice welding school to participate in ECG monitoring over two 24-hour periods on both a workday and a non-workday.	**Exposure:** 26 male workers in boilermaker construction were monitored by ambulatory electrocardiogram (ECG) on a workday while exposure to welding fume and a non-workday (baseline) from 2004-2006. Exposure was analyzed by x-ray fluorescence for elemental content. Mean nickel exposure (n=31) was 0.11 $\mu g/m^3$ for personal, workday $PM_{2.5}$ measurement. 8 metals were analyzed. Each metal was modeled separately due to the small sample size. **Inclusion/Exclusion Criteria:** Included boilermaker construction workers exposed to metal-rich welding fumes. **Covariates Considered/Other Regression Adjustments:** Metal exposure was assessed both with and without adjustment for total $PM_{2.5.}$ Authors controlled for individual cardiac risk	**Outcomes:** The study did not observe a statistically significant association between nickel exposure and altered heart rate variability. Mean nickel exposure (n=31) was 0.11 $\mu g/m^3$ for personal, workday $PM_{2.5}$ measurement. The authors reported a regression coefficient (β) expressed as change in msec of night rMSSD (square root of the mean squared differences of successive intervals) per 1 $\mu g/m^3$ increase in exposure after adjusting for baseline HRV, smoking status, and with or without adjustment for total $PM_{2.5}$. Authors report β = -4.76 (not statistically significant) for nickel, adjusted for baseline night rMSSD and smoking status; β=1.03 (not statistically significant) with nickel and $PM_{2.5}$, adjusted for baseline night rMSSD and smoking status, and -0.006 (statistically significant with $p<0.05$) for particulates.

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Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
From 2004 to 2006, 26 boilermakers were selected for monitoring for workday $PM_{2.5}$ exposure, which was then analyzed by x-ray fluorescence for elemental content. The 26 boilermakers were monitored a total of 31 times.	factors such as age and health status. All models were adjusted for cigarette smoking. Since metal and total $PM_{2.5}$ mass exposure covaried, authors investigated the effect of each metal, independent of $PM_{2.5}$ by including $PM_{2.5}$ in the model along with the metals.	**Limitations:** Of the 31 exposure measurements, 12 (39%) nickel samples had concentrations below the limit of detection. The authors cite exposure source as a major limitation of the study because it differs substantially from ambient $PM_{2.5}$ or other sources of $PM_{2.5}$. The metal component alone did not account for the observed declines in night HRV, suggesting the importance of other PM elemental components. Due to the small sample size, authors were unable to investigate the potential modifying effects of hypertension or cardiac compromises. A self-reported questionnaire was used to collect information on medical history, current cardiopulmonary symptoms, medication use, demographics, occupational history, and lifestyle factors such as smoking history.
Huang et al. 2017 **Study Type/Population:** A time-stratified case crossover study between fine particulate matter ($PM_{2.5}$) elemental composition and emergency admission to Third Xiangya Hospital of Central south	**Exposure:** Authors analyzed the correlation between emergency admissions for cerebral hemorrhage, cerebral infarction, TIA, coronary heart disease and $PM_{2.5}$, concentrations of chemical element compositions ($PM_{2.5}$), and PM_{10} in Changsha city from June 1, 2009, to October 31, 2009. The analysis of $PM_{2.5}$ elemental composition was performed by Energy Dispersive	**Outcomes:** Concentration rises of nickel for $PM_{2.5}$ in Changsha city were related to the increase of emergency admissions with hypertensive cerebral hemorrhage. The average mass concentration levels of $PM_{2.5}$ in Changsha city for nickel was reported as 40.72 ng/m^3. $PM_{2.5}$ element concentrations of nickel and emergency treatment OR values of hypertension associated with cardiovascular

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
University with cardiovascular disease in Changsha city, China. The study analyzes data of emergency admissions from June 1, 2009, to October 31, 2009, and meteorological data from routine monitoring within the same time period. N = 1,027, with 86 cases of hypertension, 99 cases of cerebral hemorrhage, 353 cases of cerebral infarction, 242 cases of transient ischemic attack (TIA), and 246 cases of coronary heart disease.	X-Ray Fluorescence (EDXRF). 18 elements were measured in this analysis. **Inclusion/Exclusion Criteria:** Emergency admissions to Third Xiangya Hospital of Central South University with cardiovascular disease, including cerebral hemorrhage, cerebral infarction, TIA, and coronary heart disease from June 1, 2009, to October 31, 2009. **Covariates Considered/Other Regression Adjustments:** Authors adjusted for everyday air temperature, air pressure, and maximum wind speed for the selected $PM_{2.5.}$ Control cases were matched by day of the week to control any weekly patterns in emergency admissions and air pollution levels.	disease for each additional one IQR were reported. For hypertension, OR = 1.016; cerebral hemorrhage, OR = 1.826 (significant at p <0.5); cerebral infarction, OR = 1.169; TIA, OR = 1.277; coronary heart disease, OR = 1.184; total cardiovascular diseases, OR = 1.204. **Limitations:** Cases came from a single location. The study did not take socio-economic factors into account. The study did not adjust for body mass index, smoking, or comorbidities. $PM_{2.5}$ was only monitored for 5 months, a comparatively short time frame.
Jacobs et al. 2012 **Study Type/Population:** Cross-section panel study in persons living in five elderly homes in Antwerp, Belgium between June 2007, and October 2009. N = 88 non-smoking persons. Authors collected blood pressure and a blood sample two times on	**Exposure:** $PM_{2.5}$ samples were collected indoors, in a common room, and outdoors over approximately 24 hours. $PM_{2.5}$ samples were collected on glass or quartz filters immediately outside each elderly home. Authors performed pollutant-specific, exposure-response analysis. Data for $PM_{2.5}$ samples were collected over 39 days. The mean concentration of nickel in outdoor settings over 24 hours was 3.5 ng/m^3, and in indoor settings it was 2.5 ng/m^3.	**Outcomes:** in Model 2, nickel was significantly associated with elevated systolic blood pressure and pulse pressure among individuals on antihypertensive medication. The estimated mean change in systolic blood pressure values for an IQR increase in outdoor $PM_{2.5}$ elemental concentrations was reported in both model analyses. Among individuals with no antihypertensive medication, nickel concentration of outdoor $PM_{2.5}$ was related to

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
two separate days. Authors also measured the elemental content of indoor and outdoor $PM_{2.5}$ and outdoor PM_{10}. Results were separated by persons taking antihypertensive medication (n=57) and in persons not using antihypertensive medication (n=31). Study staff measured systolic and diastolic blood pressure and heart rate on two separate visits. Pulse pressure (systolic blood pressure minus diastolic blood pressure) was also considered in the analyses. The analyses used the average of the last three of five consecutive blood pressure measurements.	**Inclusion/Exclusion Criteria:** Lived in one of five elderly homes under the same organization. Participants were 65 or older, non-smoking, and able to provide informed consent. **Covariates Considered/Other Regression Adjustments:** Two analyses were conducted: Model 1 and Model 2. The Model 1 analysis was adjusted for sex, age, body-mass index, period (the visit a measurement was taken), and outdoor temperature. The Model 2 analysis was adjusted for all factors included in Model 1, in addition to systolic and diastolic blood pressure.	non-significant decreases in systolic blood pressure. Estimated mean changes of 0.41 ng/m^3 (Model 1) and a 0.81 ng/m^3 (Model 2) were estimated for an IQR increase in outdoor nickel PM concentration. Among those on antihypertensive medication, the estimated mean systolic blood pressure change was 2.4 $\mu g/m^3$ (Model 1; non-significant) and 2.5 $\mu g/m^3$ (Model 2; significant). **Limitations:** 74 of the 88 participating people had a second clinical visit. The study did not have personal exposure measurements. The authors state they had a rather low number of participants and could not analyze the effects of PM on blood pressure for different medications. Authors also could not know for sure that participants took their antihypertensive medication the day of the examination.
Niu et al. 2013 **Study Type/Population:** Cross-sectional population study of non-smoking and healthy female 60–65-year-old residents in Jinchang and	**Exposure:** Daily $PM_{2.5}$ samples were collected from downtown areas of both Jinchang and Zhangye for a 12-month period. Personal sampling of $PM_{2.5}$ mass concentrations was conducted for the 60 subjects by use of a backpack containing a personal pump to collect $PM_{2.5}$ samples for 24 hours on days when blood	**Outcomes:** Nickel was significantly associated with ICAM-1 (a cardiovascular inflammatory biomarker), as was living in Jingchang which had a higher nickel concentration in air compared to Zhangye.

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
Zhangye, China. Thirty women were recruited from each city. Authors conducted an examination of the difference in inflammatory biomarkers in subjects living in the two cities as a function of the levels of personal exposures to $PM_{2.5}$ and its chemical components, adjusting for individual risk factors. $PM_{2.5}$ measurements were collected over 12 months and from personal air monitoring. Blood samples were collected from each participant on the same day as personal air sampling however study authors did not specify the timing or frequency of collection.	samples were collected. Central ambient exposure monitoring in Jingchang resulted in Ni=204.8 ng/m^3, and 2.7 ng/m^3 in Zhangye. Personal exposure monitoring results were Ni=71.28 ng/m^3 and 4.88 ng/m^3, respectively. **Inclusion/Exclusion Criteria:** Elderly, non-smoking female residents ages 60-65 were first targeted. Men were excluded from this study because it was difficult to find non-smoking male subjects in these communities. Subjects with abnormal blood sugar and lipid profiles and who had diagnosed diseases, including CVD, diabetes and hypertension were excluded. **Covariates Considered/Other Regression Adjustments:** The authors adjusted models for individual risk factors, which included age, cotinine level, BMI, blood sugar, LDL, HDL, triglycerides, systolic and diastolic blood pressure. Metal concentrations were log-transformed.	**Limitations:** Relatively small sample size and males were excluded.
Occelli et al. 2020 **Study Type/Population:** Retrospective cohort population-level study. Authors assessed the	**Exposure:** Authors compared the spatial distributions of a composite air pollution index (SEnv) and the CHD rate after adjusting for the level of social deprivation. SEnv was calculated for neighborhoods from 20 spatialized environmental indicators, which included analysis	**Outcomes:** Overall, higher SEnv was positively associated with greater CHD risk (p=0.0151), and median nickel levels were positively associated with higher SEnv (SP = 0.22, p<0.0001). In the single-pollutant analysis, after adjustment of FDep, the relative

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
relationship between exposure to multiple air pollutants and the incidence of coronary heart disease (CHD) in a general population sample collected in the Lille MONICA registry (2008-2011) on 3,268 incident cases (men and women 35-74 years old) from the French WHO. This data records all fatal and non-fatal CHD events, regardless of hospitalization. Authors derived a composite environmental score (SEnv) for cumulative exposure to air pollution, then used Poisson regression models to analyze associations between CHD rates and SEnv. Authors studied the Lille urban area in northern France; 473 neighborhoods were included in the analysis.	from lichen biomonitoring data to assess 16 metal loads and eutrophication, which together served as a guide to long-term overall air quality. Higher SEnv (tertile 3 the highest) indicate greater air pollution. Authors used the Fdep index, a deprivation index reflecting the spatial socioeconomic heterogeneity, validated in the French context that uses median household income, percentage of high school graduates aged 15 and over, percentage of blue-collar workers, and unemployment rate. The higher the Fdep index, the greater the level of deprivation. The median level of nickel for n=473 was reported as 2.86 µg/g. **Inclusion/Exclusion Criteria:** Authors only included incident coronary events. Of 5,448 cases from 2008-2011, n= 3,268. **Covariates Considered/Other Regression Adjustments:** Model was adjusted for age, sex area-level socio deprivation, and neighborhood spatial structure. Models included ecological covariates as fixed effects.	risk of CHD was 11% higher in neighborhoods in the highest tertile for nickel, compared to those in the lowest tertile (RR = 1.11, 95% CI: 1.00, 1.23). **Limitations:** Data on atmospheric pollutants (including heavy metals) came from different sources and were provided in various formats and units on various spatiotemporal scales. Authors could not take account of certain individual risk factors for CHD, such as smoking or diet. Study only uses data from women. Authors did not have data on incident cases' workplaces, which prevented authors from assessing their exposure to air pollution during the day.
Spiezia et al. 2014 **Study Type/Population:** Retrospective case-control	**Exposure:** Average mean concentrations of 10 pollutants were obtained from monitors located at 2 different sites in Padua. Nickel levels were evaluated using ambient concentration averages	**Outcomes:** There was no statistically significant difference in exposure between cases and controls. Authors report tertiles of exposure to air pollutants of the study

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
study examining the associations between one month's exposure to elevated levels of different pollutants and the development of acute isolated pulmonary embolism (PE). The study group was 33 patients consecutively admitted to Padua Hospital with an objectively proven diagnosis of acute unprovoked isolated PE between January 2008 and October 2012. The control group consisted of 72 consecutive patients with objectively proven acute provoked isolated PE.	over the month preceding the index date (date of PE diagnosis). Nickel exposure was recorded in tertiles: $\leq$ 2.86 ng/m^3, 2.87-4.64 ng/m^3, and $\geq$ 4.65 ng/m^3 **Inclusion/Exclusion Criteria:** Only subjects with a "high probability" of PE at ventilation-perfusion scan were enrolled in the study. Patients were excluded if they were under anticoagulant treatment at the time of the diagnosis of PE, if they were under 18, if they exhibited a previous episode of PE, or if they were a resident outside the city of Padua. **Covariates Considered/Other Regression Adjustments:** The multivariate model was adjusted for age, gender, chronic obstructive pulmonary disease (COPD), smoking status, educational level, distance from monitoring stations, season, and temperature.	population during the month before enrollment. Tertiles were reported as $\leq$ 2.86 ng/m^3, accounting for 10 cases, 24 controls; 2.87-4.64 ng/m^3 accounted for 13 cases and 24 controls, and $\geq$ 4.65 ng/m^3 accounted for 10 cases (30%) and 24 controls (33%), all with p = 0.76. Study reported OR for isolated PE associated with an exposure to elevated air pollutants. At 4.65 ng/m^3, OR = 1.07 for univariate model, and OR = 0.60 for multivariate model. **Limitations:** Study has a relatively small sample size. Because of the number of variables included in the logistic regression analysis, the authors note the specific weight of each variable is questionable. The evaluation of the environmental air pollution was used as a surrogate measurement, which may result in an underestimation or overestimation of the personal exposure for each patient. The monitoring station does not fully consider the individual differences in the time spent at home and in other environments, such as workplaces or in traffic while commuting. Data on $PM_{2.5}$ levels were not available. Information on specific sources of pollution (e.g., factories, major roads) close to

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
		the patient's home was not included in this study.

Table 2-4. Epidemiological Studies Examining Cardiovascular Outcomes in Humans Exposed to Nickel in Ambient Air

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
Spiezia et al. 2016 **Study Type/Population:** Authors performed a retrospective case-control study to evaluate the association between short-term exposure to elevated levels of air pollution and the risk of developing an acute idiopathic proximal deep vein thrombosis (DVT) in the legs. All eligible patients were admitted between April 2010 and December 2012 to the thrombosis unit of the University of Padua (Italy) with acute symptoms indicative of DVT in the legs. 233 subjects with a diagnosis of acute proximal DVT in the legs were evaluated, and n = 220 patients were enrolled: 86 (39%) experienced unprovoked DVT, and 134 (61%) presented a provoked DVT (control group).	**Exposure:** All eligible patients were admitted between April 2010 and December 2012. Pollutants were measured over the month and trimester preceding the DVT diagnosis from two monitoring sites in Padua, which were obtained from the Regional Agency for Environmental Protection. Month = 4.00 ng/m^3 and trimester = 4.44 ng/m^3. Nickel was one of ten environmental pollutants studied (including metals). **Inclusion/Exclusion Criteria:** Patients under anticoagulant treatment at the time of the diagnosis of venous thromboembolism, or younger than 18, or with a previous episode of PE or DVT, or who were residents outside of the city of Padua were excluded. **Covariates Considered/Other Regression Adjustments:** Multivariate analysis was adjusted for age, gender, smoking status, educational level, distance from monitor stations, season, and temperature.	**Outcomes:** Authors reported estimated OR for unprovoked proximal DVT associated with elevated air pollutants (nickel) exposure. Month = 4.00 ng/m^3 and trimester = 4.44 ng/m^3. OR = 2.52 and 0.85 for univariate models for month and trimester, respectively. OR = 2.49 and 0.79 for multivariate for month and trimester estimates, respectively. Using the upper limit of the second tertile measured in controls in the month before DVT diagnosis as a cut-off point, authors found a 2.5-fold increase in the risk of unprovoked proximal DVT for individuals who were exposed to nickel levels equal/above the cutoff point in the month before DVT. **Limitations:** Study has relatively small sample size that can affect the precision of estimations. Evaluation of environmental air pollution was used as a surrogate measurement, causing a possible error in the estimation of personal exposure for each patient.

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Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
Wang et al. 2014 **Study Type/Population:** Retrospective cohort study. Analysis included 19 cohorts for 12 countries where PM measurements were available from north to south Europe (Finland, Norway, Sweden, Denmark, the Netherlands, Germany, the UK, Austria, Switzerland, France, Italy, and Greece). Population = 322,291 participants with 9,545 CVD deaths. CVD mortality was defined based on underlying cause of death recorded on death certificates. Three two-week measurements of PM2.5 and PM10 were conducted during different seasons between October 2008 and May 2011 at 20 sites in each cohort study area (1 year per study area). Land Use Regression (LUR) models were developed	**Exposure:** Authors a priori selected 8 elements (including other metals) reflecting major anthropogenic sources. Annual average elemental concentrations at the baseline residential addresses of study participants were estimated by LUR models. Model 1 (see **Covariates**) presents hazard ratios (HR) for an increase of 1 ng/m^3 for $PM_{2.5}$ Ni and 2 ng/m^3 for PM_{10} Ni. **Inclusion/Exclusion Criteria:** In a sensitivity analysis, authors excluded cohorts with a weight larger than 50% in the meta-analysis. **Covariates Considered/Other Regression Adjustments:** Model 1 was adjusted for age, gender, and calendar time. Model 2 added adjustments for smoking status, smoking intensity, smoking duration, environmental tobacco smoke, fruit intake, vegetable intake, alcohol consumption, body mass index, education level, occupational class, employment status, marital status. Model 3 as in model 2 also adjusting for area-level socioeconomic status.	**Outcomes:** Study reports no significant associations between CVD mortality and exposure to neither $PM_{2.5}$ nor PM_{10} Ni elemental constituents. Hazard ratios for all associations between PM Ni and CVD mortality included 1 in confidence intervals. **Limitations:** LUR models used for exposure assessment were based on air pollution measurements in the period 2009-2011 while cohort studies included in ESCAPE started in the past (1985-2007). Predictions for nickel $PM_{2.5}$ in LUR models were poor in several study areas due to lack of identification of a major nickel source in the analysis which may have underestimated effect estimates. General explanations for a lack of association between CVD mortality and PM may apply, including better medication and medical treatment and less incidence of smoking. Site selection was designed for estimating especially the health effects on traffic pollution, which may restrict the power to detect other emission sources.

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Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
for each element to explain annual concentrations.		
Wolf et al. 2015 **Study Type/Population:** Retrospective cohort study of 11 European cohorts. 5,157 incident coronary events were identified within 100,166 persons followed for 1,154,386 person-years. Enrollment period was between 1992 and 2007. Mean age was between 44 and 74. Long-term residential concentrations of PM_{10} and $PM_{2.5}$ were estimated with land use regression models.	**Exposure:** A PM was measured based on standardized methodology between 2008 and 2011. In each study region, authors performed three 14-day measurement periods at 20 monitoring sites over approximately 1 year. Authors developed land use regression models for each area and each exposure variable. Authors used Cox proportional hazard models adjusted for a common set of confounders to estimate cohort-specific component effect. Other metals were analyzed in this analysis. **Inclusion/Exclusion Criteria:** The analyses were restricted to persons with no missing information in both the exposure variables and the covariates of the main model. Authors excluded persons with prevalent events. **Covariates Considered/Other Regression Adjustments:** The main model included year of enrollment, sex, marital status education, occupation, smoking status, smoking duration, smoking intensity among current smokers, and an area-level socioeconomic indicator.	**Outcomes:** Authors reported the association between incidence of coronary events and elemental composition in 11 European cohorts. However, incidence of coronary events did not appear associated with PM_{10} Ni or $PM_{2.5}$ Ni. The PM_{10} hazard ratios in the single and PM-adjusted constituent models were 1.13 (1.00,1.28) and 1.09 (0.94, 1.28), respectively. The $PM_{2.5}$ hazard ratios in the single and PM-adjusted constituent models were 1.10 (0.89, 1.37) and 1.07 (0.82, 1.39), respectively. **Limitations:** Specific predictor variables for sources such as biomass combustion were not available in the geographic databases that authors had access to. Fewer sites were included to capture differences in other sources, such as industry or ports. Many models did not contain specific source predictor variables, so authors could not disentangle effects of related elements. Because elements may stand for different sources in different regions, meta-analysis may not always be meaningful.

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Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, and Covariates Considered/Other Regression Adjustments:	Outcomes and Limitations
Wu et al. 2012 **Study Type/Population:** In a prospective panel study of 17 nonsmoking male mail carriers recruited from the Sin-Jhuang Post Office, Taipei County, Taiwan. Subjects were followed for 5-6 days while delivering mail on motorcycles. The weekly campaigns were conducted over 7 weeks in February and March of 2007.	**Exposure:** Authors applied linear mixed-effects models with repeated health measurements to assess the relationship between cardiovascular effects and personal air pollution exposure. Each mail carrier wore a personal cascade impactor sampler with the air inlet in the breathing zone. The sampling pump was turned on only during periods where participants were delivering mail outdoors. Ambient PM samples were also collected at a central monitoring site near the post office. Mean exposure is between 0.8 and 2.4 ng/m^3 for subject and central monitoring sites. 20 metals were included in this analysis. **Inclusion/Exclusion Criteria:** Individuals with existing cardiovascular disease were excluded from participation in the study. **Covariates Considered/Other Regression Adjustments:** Authors controlled for fixed covariates of the subjects' age, body mass index, frequency of secondhand smoke exposure, and ambient temperature during the working period.	**Outcomes:** Nickel exposure was associated with a 2% decline in LF/HF ratio (an indicator of heart rate variability). There was no significant association with any of the other four heart rate indicators measured. **Limitations:** The exposure data of the 17 subjects were not representative of all mail carriers. The potential lag effects of PM exposures were not evaluated due to the limitation of having time-integrated filter samples. The study mainly focused on metal components of PM samples, when other hazardous compounds may be absorbed onto the surface of these particles and lead to certain health effects. Having only metal data limited the number of sources that could be separated by source apportionment models. It is possible some of the identified associations occurred by chance.

Oral

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

Rats exposed to 8.6 mg Ni/kg/day as nickel chloride for 91 days had decreased heart weight (American Biogenics Corporation 1988), whereas rats exposed to 75 mg Ni/kg/day as nickel sulfate for 2 years had increased heart weight (Ambrose et al. 1976). Because the changes in heart weight were not accompanied by histological changes and decreases in body weight gain were also observed, the significance of these changes is not known. Rats exposed by gavage for 21 days to 7.6 mg Ni/kg/day as nickel sulfate had an increase of atherogenic index, an index of triglycerides and high-density lipoprotein cholesterol, serving as indicators of cardiovascular disease (Adeyemi et al. 2017). Histological changes in the heart were not observed in rats treated with nickel chloride in the drinking water at 40 mg/kg/day for up to 30 weeks (RTI 1988a), rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water (Obone et al. 1999), rats exposed to 187.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976), rats administered via gavage 22 mg Ni/kg/day (males) or 33 mg Ni/kg/day (females) as nickel sulfate for 90 days (Springborn Laboratories 2002), or dogs provided with nickel sulfate in the diet at a dose of 62.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976). No heart lesions were reported during gross necropsy of male and female rats exposed to 2.2 mg Ni/kg/day as nickel sulfate daily for 18 weeks (Springborn Laboratories 2000a).

Dermal

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

2.6 GASTROINTESTINAL

Inhalation

No studies were identified that examined gastrointestinal effects in humans after inhalation exposure to nickel.

Histopathological examinations of the gastrointestinal tract of mice and rats exposed to 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).

Oral

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 investigators (Sunderman et al. 1988) indicate that the intake of 20–200 mg boric acid probably did not contribute to the observed effects because the effects of boric acid are generally observed only following ingestion of ≥4 g by adults.

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.

Singla et al. (2006) exposed Wistar Albino male rats to 18.96 mg Ni/kg/day as nickel sulfate for 7 days daily and observed several changes in the intestines. Nickel-exposed animals had altered enzyme activity levels, specifically brush border enzymes along the crypt–villus axis, in the intestines compared to controls indicating an effect on digestive gut function.

Dermal

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

2.7 HEMATOLOGICAL

Inhalation

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

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 non-pregnant females continuously exposed to nickel oxide for 21 days, increases in hematocrit and hemoglobin levels were observed at 0.8 mg Ni/m^3 and higher; an increase in mean cell volume and a decrease in erythrocyte levels were observed at 1.6 mg Ni/m^3 and higher (Weischer et al. 1980). Similarly, increases in hematocrit, hemoglobin, and erythrocyte levels were observed in rats exposed to nickel subsulfide at 0.73 mg Ni/m^3 6 hours/day, 5 days/week for 2 years (NTP 1996b). As noted by NTP (1996b), increases in hematocrit, hemoglobin, and erythrocytes are consistent with erythropoietin production in response to tissue hypoxia, possibly because of the nickel-induced lung damage. 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/mg^3 of metallic nickel. These same rats showed labored breathing and chronic lung inflammation.

Oral

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.

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 decrease in hemoglobin level in rats exposed to 25 mg Ni/kg/day as nickel acetate in the diet for 6 weeks (Whanger 1973), an increase in leukocyte levels in rats exposed to 0.49 mg Ni/kg/day as nickel chloride in drinking water for 28 days, but not at 0.97 mg Ni/kg/day (Weischer et al. 1980), and an increase in platelet counts in rats administered via gavage 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988). Rats exposed to 7.58 mg Ni/kg/day as nickel sulfate for 21 days showed altered blood chemistry including reduced plasma protein (Adeyemi et al. 2017). 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). Twenty-eight days of exposure to 0.036 mg Ni/kg/day as nickel sulfate in mice resulted in changes in blood composition including reduced red blood cells and hemoglobin and increased white blood cell count (Dahdouh et al. 2016). No hematological effects were observed in rats treated with nickel sulfate in the diet at a dose of 187.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976). Low hematocrit levels were observed in dogs after chronic-duration dietary exposure to 62.5 mg Ni/kg/day as nickel sulfate (Ambrose et al. 1976).

Dermal

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). Only one dose was examined in this study and 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.

2.8 MUSCULOSKELETAL

Inhalation

No studies were identified that examined musculoskeletal effects in humans after inhalation exposure to nickel.

No histological alterations were observed in the bone of rats and mice exposed to nickel sulfate 6 hours/day for 12 days 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) (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 days 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, 0.73 mg Ni/m^3 (rats) 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 (mice) for 2 years (NTP 1996b).

Oral

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 twenty 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.

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).

Dermal

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

2.9 HEPATIC

Inhalation

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 exposure, moderate, or high exposure indicated by nickel levels in blood, and the highest exposed group had significantly

elevated serum aspartate transaminase (AST) and serum alanine transaminase (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.

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. 1974) 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

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.

Decreased liver weight was observed in rats exposed to 0.97−75 mg Ni/kg/day as nickel chloride or nickel sulfate for 28 days to 2 years (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Weischer et al. 1980) and mice exposed to 150 mg Ni/kg/day as nickel sulfate in drinking water for 180 days (Dieter et al. 1988). Adeyemi et al. (2017) observed changes in liver enzymes and histopathological changes following daily exposure for 21 days to 7.58 mg Ni/kg/day as nickel sulfate. Kamal et al. (2012) observed altered liver enzyme levels in rats exposed for 28 days to 3.81 mg Ni/kg/day as nickel sulfate hexahydrate in drinking water. Livers from nickel-exposed rats showed inflammation and cellular degeneration, and significant increases in activity of alanine transaminase, aspartate transaminase, alkaline phosphatase, and malondialdehyde, and decreased glutathione (Adeyemi et al. 2017). In mice exposed to nickel chloride daily for 40 days, histological examination of the liver showed diffuse cytoplasm and nuclei damage in hepatic cells following exposure to 0.905 mg Ni/kg/day (Gathwan et al. 2013). Among mice exposed to the higher dose of 7.2 mg Ni/kg/day, the livers showed

more serious damage including hepatocellular degeneration and hypertrophy of nuclei and blood in the central canal of the liver (Gathwan et al. 2013).

No alterations in absolute liver weights were observed in male and female rats administered via gavage 22 or 33 mg Ni/kg/day as nickel sulfate, respectively, for 90 days (Springborn Laboratories 2002); no histological alterations were reported in this study. Similarly no histological changes were reported in the livers of rats exposed for 18 weeks to doses of up to 2.2 mg Ni/kg/day (Springborn Laboratories 2000a). A significant increase in relative liver weight, however, was observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate for 2 years (Ambrose et al. 1976). Since histological changes in the liver were not observed in these studies and decreases in body weight gain were often observed at the same dose levels, the significance of changes in the liver-to-body weight ratios are unclear.

Dermal

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.

Increased Mg2+ ATPase activity was observed in the livers of 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). Acid phosphatase and glucose-6-phosphatase activities were increased only after 30 days of treatment. In both of these studies, 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

Inhalation

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 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 exceeding 100 µg/L; urinary β2-microglobulin levels were not significantly altered in workers with urine nickel levels of less than 100 µg/L. Urinary levels of total proteins, β2-microglobulin, retinol binding protein, and N-acetyl-β-D-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 less than 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. A study of 17 electroforming workers did not find evidence of proteinuria (Wall and Calnan 1980).

No change in kidney weight was reported in rats exposed to 0.635 mg Ni/m^3 for 16 days, 6 hours/day, when compared to controls (Evans et al. 1995). 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), or ≤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), or nickel sulfate (NTP 1996c) at concentrations up to 2, 0.73, or 0.11 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). In a chronic-duration 104-week study, male and female rat histopathology showed granular brown pigment in the kidneys (Oller et al. 2008). Incidence in females was significantly higher at concentrations ≥0.1 mg Ni/m^3 metallic nickel, while in males incidence increased at concentrations ≥0.4 mg Ni/m^3. A separate 78-80 week study in rats

did not observe any histopathological changes in either males or females at 0.63 mg Ni/m^3 as nickel sulfide (Ottolenghi et al. 1975).

Oral

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.

Cellular changes were observed in kidney sections of rats exposed to 0.7585 mg Ni/m^3 as nickel sulfate for 21 days (Adeyemi and Elebiyo 2014). These changes included swollen renal tubules, necrosis, and nephritis, and further there was a 12% decline in kidney-to-body weight ratio and increases in plasma creatinine and urea (Adeyemi and Elebiyo 2014). A 28-day study in male Swiss albino rats exposed to 0.036 mg Ni/m^3 as nickel sulfate reported histological findings of tubule degeneration and tubular necrosis among other lesions (Dahdouh et al. 2016). Renal dysfunction was further indicated by increases in serum urea, uric acid, and creatinine.

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 and NAG levels and β2-microglobulin levels) were observed in rats exposed to nickel sulfate in the drinking water for 6 months at a concentration that supplied doses of 6.9 mg/kg/day for males and 7.6 mg/kg/day for females (Vyskocil et al. 1994b). Urinary albumin levels, a marker of glomerular barrier dysfunction, was significantly increased in nickel-exposed female rats. Albumin excretion also tended to be higher in male rats but did not reach statistical significance because of two control rats with very high values. The investigators noted that male rats develop a spontaneous nephrosis as they age and that this may have obscured the effect of nickel. Significant decreases in urine volume and urine glucose levels and increases in relative kidney weight at 14.4 or 28.8 mg Ni/kg/day and increases in blood urea nitrogen (BUN) at 28.8 mg Ni/kg/day were observed in rats exposed to nickel sulfate in drinking water for 13 weeks (Obone et al. 1999); no changes in γ-glutamyl transpeptidase activity, NAG activities, or histological alterations were observed.

In dogs, polyuria and increased kidney weight were observed after exposure to 62.5 mg Ni/kg/day as

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

Dermal

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

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

2.11 DERMAL

Inhalation

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. In addition, immunological studies indicate that dermatitis is an allergic response to nickel, and significant effects on the immune system have been noted in workers exposed to nickel.

Wistar rats exposed to ≥0.1 mg/m^3 for 104 weeks (5 days/week, 6 hours/day) showed exposure-related clinical signs including dermal atonia (Oller et al. 2008). 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).

Oral

Contact dermatitis, which results from dermal exposure to nickel, is the most prevalent effect of nickel in the general population. Several studies indicate 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 low LOAEL values (e.g., 0.009 mg Ni/kg), these studies have several design limitations including small sample size, the observation of placebo effects, and non-double-blind study designs (possibly introducing investigator bias). Two 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.

Intermediate-duration studies suggest that longer-term oral exposure can be tolerated by some nickel sensitive individuals and may even serve to desensitize some individuals. Jordan and King (1979) found flaring of dermatitis in only 1/10 nickel-sensitive women given nickel sulfate at 0.007 mg/kg/day for 2 weeks. Patch test responses to nickel were reduced in nickel-sensitive women given one weekly dose of

0.05 or 0.07 (but not 0.007) mg Ni/kg as nickel sulfate for 6 weeks (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, 7 had reactivation of symptoms, and 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 investigators hypothesized that the oral nickel exposure that occurred during orthodontic treatment helped prevent the sensitization that occurred following ear piercing with earrings containing nickel. Orthodontic treatment after ear piercing did not affect the risk of nickel sensitization. Further evidence that oral exposure to nickel before a sensitizing exposure can prevent hypersensitivity is provided by the observation that nickel sensitivity in mice could be consistently produced only when metal frames to cover the cages and metal water nipples that released nickel were replaced with glass covers and nipples free of nickel (van Hoogstraten et al. 1991). Oral treatment of guinea pigs with nickel sulfate (30 mg/week for 6 weeks) has also been shown to prevent dermal sensitization (van Hoogstraten et al. 1991). Skin exposure of guinea pigs to nickel (non-sensitizing contacts) before oral exposure was also shown to interfere with oral tolerance induction.

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

Dermal

Allergic contact dermatitis is a commonly reported effect in humans exposed to nickel. Contact dermatitis was found in 15.5% of approximately 75,000 individuals undergoing patch tests with nickel sulfate (5%

in petrolatum) (Uter et al. 2003). A pooled analysis of 20,107 patched tested individuals reported a prevalence of 11.4% among the general population (Alinaghi et al. 2019), indicating the prevalence is between 11-16%. Smaller scale studies report slightly higher frequencies: 19.1% of 542 subjects (Akasya-Hillenbrand and Ozkaya-Bayazit 2002), 21.2% of 1,729 subjects (Wantke et al. 1996), and 20.13% of 3,040 subjects (Simonetti et al. 1998). In the general population (a random sample of 567 people aged 15–69 years responding to a mailed screening questionnaire on respiratory allergy symptoms), 11% of the subjects had a positive reaction to nickel patch tests (Nielsen et al. 2002). Contact dermatitis in response to nickel exposure is more frequently observed in females, particularly younger females, than in males or older individuals (Thyssen and Menne 2010; Uter et al. 2003; Wantke et al. 1996). This increased prevalence appears to be related to previous nickel exposure rather than increased susceptibility. Prolonged exposure to nickel in consumer products, especially jewelry, rather than occupational exposure, is often a sensitizing source. An association has been observed between ear 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). The prevalence of nickel allergy was 9% among girls (age 8, 11, and 15; n=960) with pierced ears compared to 1% among girls without pierced ears. Girls with more than one hole in each ear were also more likely to be sensitive to nickel than girls with only one hole in each ear (19 versus 11%) (Larsson-Stymne and Widström 1985). In a study in schoolchildren age 7–12, the frequency of nickel allergy was 30.8% among girls with pierced ears and 16.3% among girls who did not have pierced ears (Dotterud and Falk 1994). Similarly, 14% of females with pierced ears developed nickel allergy compared to 4% in females without pierced ears (Nielsen et al. 2002). Among a group of Swedish men (age 18–24) completing military service, 4.6% with pierced ears reacted to nickel, while 0.8% who did not have pierced ears had a positive reaction to nickel (Meijer et al. 1995). Keczkes et al. (1982) 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 using nickel sulfate have shown a dose-response relationship between the amount of nickel and the severity of the test response (Emmett et al. 1988; Eun and Marks 1990). In a study of 12 individuals, a nickel concentration of 0.0316% (316 ppm) in petrolatum resulted in dermatitis, while a concentration of 0.01% (100 ppm) did not produce adverse effects (Eun and Marks 1990). In aqueous solution, the nickel concentration of 0.0316% (316 ppm) did not result in dermatitis. Although most patch testing is done with nickel sulfate because it is less irritating than nickel chloride,

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

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

Inhalation

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

Oral

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).

Dermal

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

2.13 ENDOCRINE

Inhalation

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

Histological examinations did not reveal any changes in the adrenal glands, pancreas, parathyroid, pituitary, or thyroid glands in rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 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. In Fischer-344 rats exposed intermittently to nickel sulfide at 0.63 mg Ni/m^3 for 78 weeks, no histological changes were observed in the thyroid or adrenal glands (Ottolenghi et al. 1975). Increased incidences of benign pheochromocytoma were observed in female Fischer-344 rats exposed to 2 mg Ni/m^3 as nickel oxide for 2 years (5 days/week, 6 hours/day) (NTP 1996a).

No effects were observed in Fischer-344 rats exposed chronically to nickel sulfate at concentrations up to 0.11 mg Ni/m^3, 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). Chronic-duration exposure to metallic nickel at 0.4 mg Ni/m^3 in male rats resulted in relative adrenal gland weight 89% higher than controls and correlated with increased incidence of pheochromocytomas (Oller et al. 2008). However, the authors noted that the pheochromocytomas were secondary to lung toxicity of nickel exposure. In female rats exposed to 0.4 mg Ni/m^3, the incidence of angiectasis in the adrenal glands was greater than controls (Oller et al. 2008).

Oral

No studies were identified that examined endocrine effects in humans after oral exposure to nickel.

Although histological changes were not observed, increases in pituitary weights were observed in male rats, but not female rats, treated with nickel chloride at doses ≥20 mg Ni/kg/day for up to 30 weeks (RTI 1986, 1988a, 1988b). The multigeneration study (RTI 1988a, 1988b) is confounded by a decrease in both food and water intake. Decreased prolactin levels were observed in female rats treated with 31 mg Ni/kg/day as nickel chloride in the drinking water throughout the breeding and lactation of two litters (11 weeks before breeding, 2-week rest period after weaning of the first litter, followed by a second breeding), but not at a 6.8-mg/kg/day dose (Smith et al. 1993). Histological examinations did not reveal any adverse effects in the pituitary, thyroid, and adrenal glands or in the pancreas of rats and dogs treated with nickel sulfate in the diet for 2 years at 187.5 mg Ni/kg/day for rats and 62.5 mg Ni/kg/day for dogs (Ambrose et al. 1976).

Dermal

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

2.14 IMMUNOLOGICAL

Inhalation

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; Bencko et al. 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).

Buxton et al. (2021) reported no nickel-exposure related immune effects in female ICR mice exposed whole-body 24-hours to concentrations ≤0.0801 mg Ni/m^3 as nickel chloride hexahydrate. Immune response was tested using sheep red blood cells (SRBC) in a splenic antibody forming cell (AFC) assay. Reductions in the number of spleen cells appeared concentration-dependent, however were not associated with decreases in spleen or thymus weight. Additionally, increases in Total Spleen Activity and Specific Activity were significant, however were normal and within biological variability for the mouse breed.

Taken together, the assay did reveal immunosuppressive effects due to nickel chloride hexahydrate exposure (Buxton et al. 2021).

At higher concentrations, alterations in innate (or non-specific) and acquired immunity have been observed in animals. Several studies examined alveolar macrophage functions. A significant reduction in macrophage phagocytic activity was observed in mice exposed to 0.5 to 0.66 mg Ni/m^3 as nickel chloride for 2 hours (Adkins et al. 1979a, 1979c) 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). Haley et al. (1990) performed a pulmonary alveolar macrophage (PAM) phagocytosis immune function test to measure nickel immunotoxicity. 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. 1989; Johansson et al. 1987; Johansson et al. 1988), 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. 1989; Johansson et al. 1988) 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). Exposure to 0.1 mg Ni/m^3 metallic nickel for 104 weeks resulted in increased incidence of minimal-to-severe histiocyte infiltrate in bronchial lymph nodes and extramedullary hematopoiesis in the spleen (Oller et al. 2008). Xu et al. (2012) tested the lowest concentration in mice exposed to 0.00017 mg Ni/m^3 as nickel sulfate for 3 months, and immunohistochemical staining showed increased macrophages in epididymal white adipose tissue (eWAT) and in lung tissue sections.

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 ($\leq$ 0.5 mg Ni/m^3) for 2 hours and then infected either immediately or after a 24-hour recovery period (Adkins et al. 1979c). 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. 1979c). Increased mortality and reduced survival time was also observed following a 2-hour exposure to 0.46 mg Ni/m^3 as nickel sulfate

(Adkins et al. 1979b). 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. 1979a). Other studies have found an impaired response to sheep red blood cells (decrease in the number of antibody production spleen cells) 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). 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).

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) or 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 and mice exposed to 23.5 mg Ni/m^3 as nickel oxide (NTP 1996a), and mice exposed to 3.1 mg Ni/m^3 as nickel sulfate (NTP 1996c). In intermediate-duration studies, a 6 hour/day, 5 day/week exposure resulted in lymphoid hyperplasia in bronchial lymph nodes of rats exposed to 0.22, 0.22, or 2 mg Ni/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).

Oral

Dermatitis resulting from nickel allergy is well reported in the literature (see Section 2.11 for further discussion of allergic dermatitis following oral exposure).

Effects on the immunological system following exposure to 44 mg Ni/kg/day and higher as nickel sulfate in the drinking water for 180 days were assessed in mice (Dieter et al. 1988). Mild thymic atrophy was observed at 44 mg Ni/kg/day and higher and mild splenic atrophy was observed at 108 mg Ni/kg/day and higher. Although several tests of immune function were performed, only two alterations were found—decreased spleen cellularity at 150 mg Ni/kg/day and impaired lymphoproliferative response to the B-cell mitogen, Escherichia coli lipopolysaccharide (LPS), at 44 mg Ni/kg/day and higher; a marginal response to sheep red blood cells was also observed at 150 mg Ni/kg/day. No response to concanavalin A (con A), natural killer cell activity, or resistance to Listeria monocytogenes challenge were observed. In addition to

the immune function responses, exposure to nickel sulfate resulted in alterations in bone marrow, decreases in bone marrow cellularity at 108 mg Ni/k g/day and higher, decreases in granulocyte macrophage progenitor cells (CFU-GM) at 44 mg Ni/kg/day and higher, and multipotential stem cells (CFU-S) at 108 mg Ni/kg/day and higher. The stem cell alterations were associated with alterations in glucose-6-phosphate dehydrogenase activity—increased at 44 mg Ni/kg/day and decreased at 108 and 150 mg Ni/kg/day. Obone et al. (1999) reported alterations in T-cell and B-cell subpopulations in the thymus and splenic lymphocytes in rats exposed to nickel sulfate in drinking water for 13 weeks. In the spleen, the changes consisted of an increase in the total number of cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; an increase in 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 higher; and an increase in the number of B cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day. When challenged with Coxsackie virus B3, an enhanced inflammatory response was observed in the hearts of mice treated with nickel chloride in drinking water at 20.3 mg Ni/kg/day for 10–11 weeks (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. Springborn Laboratories (2000a) observed no gross necropsy changes in the spleen or thymus of rats following 16-to-18-week daily exposures to doses of 0.22 to 2.2 mg Ni/kg/day as nickel sulfate hexahydrate. 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).

Dermal

Contact dermatitis resulting from nickel allergy is well reported in the literature (see Section 2.11for further discussion of allergic reactions to nickel following dermal exposure). A relationship between human lymphocyte antigens (HLA) and nickel sensitivity was observed in individuals who had contact allergic reactions and positive results in the patch test (Mozzanica et al. 1990). The individuals had not been occupationally exposed to nickel. The HLA typing found a significantly greater prevalence of HLADRw6 antigen in the nickel-sensitive group compared to normal controls. The relative risk for individuals with DRw6 to develop a sensitivity to nickel was approximately 3.3. In individuals with allergic contact dermatitis to nickel, nickel directly bound and activated T-cells (Kapsenberg et al. 1988).

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

Nickel-activated nuclear factor-kappa B (NF-κB) transcription factor may explain immune response to nickel contact resulting in nickel sensitivity (Kasprzak et al. 2003). NF-κB is involved in the inducible expression of adhesion molecules which are involved in leukocyte recruitment to inflammation sites (Goebeler et al. 1993; Kasprzak et al. 2003). In a skin dendritic cell line, nickel-induced activation of NF-κB transcription factor stimulated inducible isoform of nitric oxide synthase (iNOS) expression (Cruz et al. 2004); iNOS is involved in the regulation of immune responses. NF-κB activation by nickel also induces interleukin-8 (IL-8) production (Freitas et al. 2010) which plays a role in recruiting immune cells to inflammation sites.

2.15 NEUROLOGICAL

Inhalation

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. A retrospective case-control study of autistic children in California reported a potential association between autism and concentration of heavy metals in air, including nickel (Windham et al. 2006). The exposure to each metal was individually categorized into quartiles based on participant location. The fourth quartile (highest nickel exposure) of participants had significantly elevated adjusted odds of autism (OR=1.46; 1.04 – 2.06). Since the concentrations of many metals and solvents were correlated, the reported effect cannot be attributed to any specific exposure, and the modeled estimates only apply to the general geographic area and are not accurate to individual exposure (Windham et al. 2006).

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.

In intermediate-duration studies, no histological alterations are 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 for 6 hours/day for 16 days to cobalt sulfate heptahydrate in male Long-Evans rats at 0.635 mg Ni/m^3 resulted in histological changes including decreased 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. Study authors attributed the recovery of carnosine levels during the exposure period to a defensive response against continued exposure (Evans et al. 1995). In Fischer-344 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 hexahydrate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, or exposure of B6C3F1 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).

Oral

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 between 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 male 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 investigators 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.

Hypoactivity and increased salivation were clinical signs of toxicity observed in rats exposed for 3 days to doses ≥27.91 mg Ni/kg/day as nickel sulfate hexahydrate (Oller and Erexson 2007). 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. Microscopic examinations of whole brains did not reveal any changes in the brains of dogs treated with nickel salts at doses ≤62.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976; American Biogenics Corporation 1988). No nickel-exposure related changes in relative brain weight were recorded in rats exposed for 13 weeks to doses of up to 28.8 mg Ni/kg/day as nickel sulfate (Obone et al. 1999). Multi-generation studies by Springborn Laboratories (2000a, 2000b) did not find any exposure-related changes in the brain following gross necropsy examination nor any clinical signs that would indicate neurotoxicity. Springborn Laboratories (2000a) exposed 2 generations of rat parents to 0.22 to 2.2 mg Ni/kg/day for 16 to 18 weeks.

Dermal

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

2.16 REPRODUCTIVE

Inhalation

An increase in the rate of spontaneous abortions (15.9%) was reported among a group of 356 women who worked in a nickel hydrometallurgy refining plant in the Arctic region of Russia as compared to the rate (8.5%) in 342 local female construction workers (Chashschin et al. 1994). Exposure concentrations were 0.08–0.196 mg Ni/m^3, primarily as nickel sulfate, and nickel concentrations in the urine of nickel workers were 3.2– 22.6 µg/L. Nickel levels in the urine of persons not occupationally exposed are generally <0.1

to 13.3 µg/L (Sunderman 1993). The investigators noted that the nickel-exposed women manually lifted heavy nickel anodes and that they may have experienced heat stress. These confounders, plus the lack of information on the selection of control group subjects, possible acute exposure to high concentrations of chlorine, and the lack of adequate control of possible confounding variables such as smoking habits, use of alcohol, and intercurrent disease, preclude establishing a causative relationship between nickel exposure and reproductive toxicity from this study. Several epidemiological studies examined the association between maternal occupational exposure to water soluble nickel at the start of pregnancy and the risk of varying fetal outcomes among a population living near a large complex of nickel, copper, and cobalt refineries operating in the Kola Peninsula (Vaktskjold 2006, 2007, 2008a, 2008b). Maternal occupation and birth outcomes were obtained from the Kola Birth Registry and used to categorize nickel exposure based on job (Vaktskjold 2006, 2007, 2008a). Exposure did not affect the risk of birthing a small for gestation age newborn (Vaktskjold et al. 2007), delivering a newborn with a genital malformation (Vaktskjold et al. 2006), or delivery of a newborn with musculoskeletal defects (Vaktskjold et al. 2008a). The adjusted odds ratio for per unit increase in maternal occupational exposure to water soluble nickel and birthing a small-for-gestation age (SGA) newborn is 0.84 (95% CI: 0.75-0.93) (Vaktskjold et al. 2007). The adjusted odds ratio for nickel-exposed women delivering a newborn with a genital malformation is 0.81 (95% CI: 0.52–1.26), and that for an undescended testicle is 0.76 (95% CI 0.40–1.47) (Vaktskjold et al. 2006). The adjusted odds ratio for per unit increases in maternal nickel exposure category and musculoskeletal defects is 0.96 (95% CI: 0.76–1.21) (Vaktskjold et al. 2008a). In a case-control study of the same population, workers of facilities within and outside of the refinery complex self-reported pregnancy outcomes and employment history (Vaktskjold et al. 2008b). There was no significant association between maternal occupational exposure to water soluble nickel in early pregnancy and the risk of spontaneous abortion; the adjusted odds ratio is 1.14 (95% CI: 0.95 – 1.37) (Vaktskjold et al. 2008b).

A cross-sectional study found nickel concentration in local air to be associated with decreased sperm concentration in men whose partners underwent assisted reproductive technology procedures (Huang et al. 2019). Study authors used $PM_{2.5}$ data from 2 monitoring stations from dates right before and during sperm sample collection, and the average nickel exposure was 2.72 ng/m^3. However, this study had severe limitations as most subjects only had one semen sample collected while others had up to 9 collections, additionally air monitoring data is not indicative of the true exposure, and there was limited consideration of exposure to other pollutants (Huang et al. 2019).

No reproductive effects were observed in male Fischer-344 rats exposed at 23.6, 7.33, and 12.2 mg Ni/m^3, and in B6C3F1 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 Fischer-344 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 Fischer-344 rats and B6C3F1 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 Fischer-344 rats and B6C3F1 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, 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).

Oral

No studies were identified that examined reproductive effects in humans after oral exposure to nickel.

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. Pandey et al. (1999) reported an accumulation of nickel (in descending order of concentration) in the epididymis, testes, seminal vesicles, and prostate gland in Swiss mice orally exposed to nickel sulfate for 35 days. The accumulation of nickel in male reproductive tissues resulted in histological damage in the epididymis and seminal vesicles and sperm damage. Regressed epithelium and vacuolated cells were observed in the epididymis of mice administered 1.1 mg Ni/kg as nickel sulfate via gavage 5 days/week for 35 day s (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. 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 appear to be lower than control body weights; this may contribute to the histological findings in the maturing rats (Rehm et al. 2008). 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 18 weeks (Springborn Laboratories 2000a), or dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976).

Significant decreases in sperm count and sperm motility and sperm abnormalities (banana and detached head; acrosome up, down, or missing; curved neck and curved, bent, round, loop, and folded tail) were observed in mice administered ≥2.2 mg Ni/kg as nickel sulfate (decreased sperm count significant at 4.5 mg Ni/kg) or 2.5 mg Ni/kg as nickel chloride 5 days/week for 35 days (Pandey and Srivastava 2000); no sperm effects were observed at 1.1 or 1.2 mg Ni/kg as nickel sulfate or nickel chloride, respectively. Although the route of administration was not reported, it is assumed that the nickel chloride and nickel sulfate were administered via gavage. The investigators reported a dose-related decrease in body weight gain and decreases in absolute and relative testes, epididymis, seminal vesicle, and prostate gland weights at the two highest dose levels (2.2 and 4.5 mg Ni/kg as nickel sulfate and 2.5 and 4.9 mg Ni/kg as nickel chloride). Similarly, Pandey et al. (1999) reported decreases in sperm count and motility in mice administered 2.2 mg Ni/kg as nickel sulfate, 5 days/week for 35 days; an increase in sperm abnormalities was also observed at 1.1 mg Ni/kg. Although Pandey et al. (1999) did not report alterations in body weight gain, significant decreases in testes, epididymis, seminal vesicle, and prostate gland weights were observed. In both studies by Pandey et al., 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 4.53 mg Ni/kg/day as nickel chloride, however significant changes were observed in the testis upon histological examination. 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 receiving a single gavage dose of 23, 28, or 43 mg/kg as nickel nitrate, nickel sulfate, or nickel chloride, respectively; it should be noted that this study was poorly reported and no information on number of animals tested was given. No alterations in sperm count, concentration, motility, or morphology were observed in the F0 or F1 rats administered 2.2 mg Ni/kg/day as nickel sulfate via gavage for 18 weeks (Springborn Laboratories 2000a).

In addition to the histological alterations and sperm alterations, alterations in fertility were observed in some studies, but not in all studies. Male-only exposure or male and female exposure to 3.6 mg Ni/kg/day as nickel chloride in drinking water resulted in decreased fertility in rats exposed for 28 days prior to mating (Käkelä et al. 1999). However, male rats exposed to 3.6 mg Ni/kg/day for 42 days prior to mating with unexposed females resulted in a small decrease in fertility (83 versus 100%) (Käkelä et al. 1999); suggesting regeneration of damaged tissues. In a single generation study in which rats were administered 6.7 mg Ni/kg/day as nickel sulfate hexahydrate via gavage for 2-weeks prior to mating, during mating, and during gestation, post-implantation loss was 475% greater than in controls (Springborn Laboratories 2000b). The severity of post-implantation loss appeared dose related as the mean incidence increased with doses up to 16.7 mg Ni/kg/day and the loss at 2.2 and 4.5 mg Ni/kg/day were not statistically different from the mean (Springborn Laboratories 2000b). In a 3-generation study in rats where the F0 and F1 generations were each exposed for 11 weeks, the F1 generation had a significantly higher number of stillbirths compared to controls at the lowest dose tested of 22.5 mg Ni/kg/day (Ambrose et al. 1976). These effects were not observed in the F0 generation exposed to the same doses.

Female-only exposure to concentrations as high as 13 mg/kg/day as nickel chloride in drinking water did not adversely affect fertility in rats (Käkelä et al. 1999). Interpretation of this study is limited by the small number of animals tested (six/gender/group) and the limited reporting of the results. No adverse effects on fertility were observed in a multigeneration study in which male and female rats exposed to doses as high as 55 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to mating (RTI 1988a, 1988b), in a single generation study in which rats were administered 16.7 mg Ni/kg/day as nickel sulfate via gavage for 2-weeks prior to mating, during mating, and during gestation (Springborn Laboratories 2000b), in a two-generation study involving gavage administration of up to 2.2 mg Ni/kg/day for 10 weeks prior to mating, during mating, gestation, and lactation (Springborn Laboratories 2000a), or in a multi-litter study in which female rats were exposed to doses as high as 31.6 mg Ni/kg/day (Smith et al. 1993).

Several acute-duration studies where pregnant mice were exposed to doses ranging from 10.29 to 41.19 mg Ni/kg/day as nickel chloride reported exposure-related reductions in fertility (Saini et al. 2013, 2014a, 2014b). Exposure to ≥11.38 mg Ni/kg/day on gestation days 6 to 13 resulted in increased post-implantation death and fetal resorption (Saini et al. 2013). Similarly, exposure to ≥11.35 mg Ni/kg/day on gestation days 0 to 5 resulted in reduced number of implantation sites and number of live fetuses per dam (Saini et al. 2014a). Lower doses were not tested in either of these studies therefore a NOAEL for these effects was not reported. Saini et al. (2014b) exposed mice to 10.29 to 41.19 mg Ni/kg/day on either gestation days 0 to 5, 6 to 13, or 14 to 18. Exposure on gestation days 0 to 5 resulted in reduced gestation

index compared to controls and fetal loss appeared to increase in severity with dose. No effects on reproduction were seen in mice exposed to doses ≤ 20.59 mg Ni/kg/day on gestation days 6 to 13, or 14 to 18. However, at the highest dose, litter size per dam was significantly less than controls (Saini et al. 2014b).

Dermal

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

Tubular degeneration of the testes was observed in rats treated dermally with nickel sulfate at 60 mg Ni/kg/day for 30 days (Mathur et al. 1977). No effects were found at 40 mg Ni/kg/day after 30 days or at doses of ≤100 mg Ni/kg/day after 15 days of treatment. In this study, there was no indication that the rats were prevented from licking the nickel sulfate from the skin; therefore, these effects could have resulted from oral exposure.

2.17 DEVELOPMENTAL

Inhalation

Several studies have reported developmental effects in offspring of adults exposed to nickel in occupational settings. Chashschin et al. (1994) reported an increase in the incidence of structural malformations (16.9%) in the offspring of female nickel hydrometallurgy refining plant workers as compared to the incidence (5.8%) in female construction workers. Although the specific structural malformations found were not stated, the investigators note that relative risks were 2.9 for all defects, 6.1 for cardiovascular system defects, and 1.9 for musculoskeletal defects. Exposure concentrations were 0.08–0.196 mg Ni/m^3, primarily as nickel sulfate, and nickel concentrations in the urine were 3.2–22.6 µg/L. Nickel levels in the urine of persons not occupationally exposed are generally <0.1 to 13.3 µg/L (Sunderman 1993). A number of possible confounders include heavy lifting, possible heat stress, lack of information on the selection of control group subjects, possible acute exposure to high concentrations of chlorine, and the lack of adequate control of possible confounding variables such as smoking habits, use of alcohol, and intercurrent disease, preclude establishing a causative relationship between nickel exposure and developmental toxicity from this study. A separate study of female refinery workers exposed to nickel found that there was a slight but non-significant association between maternal exposure to nickel and musculoskeletal defects at birth (adjusted OR=0.96; 0.76-1.21) (Arild et al. 2008). Authors noted that the study examined the risk of delivering a newborn with defects for women working in nickel-exposed areas, and not the fetal risk for these defects. Nickel exposure was determined by air sampling

and urine measurements obtained from facility records on air sampling and medical history, respectively, thus there is uncertainty on the concentrations to which workers were exposed (Arild et al. 2008).

Population level studies have indicated associations between exposure to nickel in ambient air and low birth weight in offspring. A cohort study in New England found higher levels of Ni $PM_{2.5}$ were associated with lower birth weight, and nickel exposure during pregnancy resulted in a mean birthweight decrease of 7 grams, and an 11% increase in risk of small-at-term birth (Bell et al. 2010). This study also examined differences between race and found that infants from African American mothers had a 12 gram decrease in birth weight per interquartile range while infants from white mothers had a 6 gram decrease in birthweight per interquartile range (Bell et al. 2010). Another study examined children born from 2000 to 2007 from the U.S. northeast and mid-Atlantic and authors reported a 5.7% risk increase of low birthweight per interquartile range of $PM_{2.5}$ nickel (Ebisu and Bell 2012). The mean gestational exposure to nickel across all locations was 0.006 µg/m^3. Additionally, the relative risk of low birthweight with an interquartile increase in $PM_{2.5}$ nickel was 10.2% lower among infants of African American mothers compared to white mothers (Ebisu and Bell 2012). Similarly, a European cohort of children born between 1994 and 2008 showed an increased risk of low birthweight with increased nickel $PM_{2.5}$ concentrations (Pedersen et al. 2016). This same study reported an increased risk of reduced mean head circumference with increasing nickel $PM_{2.5}$ and PM_{10} levels.

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 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).

Oral

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

The available animal data on developmental toxicity provide suggestive evidence that the developing fetus and neonates are sensitive targets of nickel toxicity. The most 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 4 (56% versus 100% in controls), and litter size at postnatal day 21 (1.3 pups versus 9.2 pups in controls) (Käkelä et al. 1999). However, when the male rats were exposed to 3.6 Ni/kg/day for 42 days, no significant alterations in pup viability or survival were observed (Käkelä et al. 1999). A NOAEL was not identified in this study.

Several studies examined female-only exposure to nickel (Berman and Rehnberg 1983; Käkelä et al. 1999; Smith et al. 1993). An increase in spontaneous abortions was observed in female mice exposed to 160 mg Ni/kg/day as nickel chloride in drinking water on gestational days 2–17 (Berman and Rehnberg 1983); no effects were observed at 80 mg Ni/kg/day. In contrast, no effects on the average number of neonates per litter were observed when mouse dams were treated by gavage on gestation days 8–12 with 90.6 mg Ni/kg/day as nickel chloride (a dose that resulted in a significant decrease in maternal body weight) (Seidenberg et al. 1986). Exposure of rats to 13 mg Ni/kg/day as nickel chloride in drinking water for 14 days prior to mating, during mating, gestation, and lactation resulted in a decreased pup survival from birth to postnatal day 4 (87 versus 100% in controls) and from postnatal day 4 to 21 (52 versus 90% in controls) (Käkelä et al. 1999); no significant 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 0, 1.3 , 6.8, or 31.6 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to breeding and during two successive gestation and lactation periods (Smith et al. 1993). In the first litter, the percentages of dead pups per litter at postnatal day 1 were 1.7, 3.1, 0, and 13.2% in rats exposed to 0,1.3, 6.8, or 31.6 mg Ni/kg/day, respectively, (statistically significant at the high dose only); no significant alterations were observed in the number of dead pups at postnatal day 21. In the second litter, the number of litters with dead pups at birth (2, 7, 6, and 10%; statistically significant at high dose only), the percentages of dead pups per litter at postnatal day 1 (1.0, 4.3, 4.6, and 8.8%; statistically significant at all three dose levels), and the percentage of dead pups at postnatal day 21 (12.5, 13.4, 19.4, and 29.2%; significant at high dose only) were increased in rats exposed to 0, 1.3, 6.8, or 31.6 mg Ni/kg/day, respectively.

Offspring mortality was also observed in four studies involving combined male and female exposure (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Springborn Laboratories 2000b). Exposure of rats to 3.6–4.0 mg Ni/kg/day as nickel chloride in drinking water for 28 days prior to mating, during mating, gestation, and lactation adversely affected the litter size at postnatal day 21 (2.7/dam versus 9.2/dam in controls) and pup survival from postnatal day 4 to 21 (44 versus 90% in controls) (Käkelä et al. 1999); a NOAEL was not identified. Significant increases in post-implantation losses were observed in the offspring of rats administered 6.7 mg Ni/kg/day as nickel sulfate via gavage for 14 days prior to

mating, during mating, and gestation (Springborn Laboratories 2000b); at 16.7 mg Ni/kg/day, an increased number of dead pups at lactation day 0 and a decreased mean litter size were observed. This study identified a NOAEL of 4.5 mg Ni/kg/day. In a multigeneration study (Ambrose et al. 1976) involving exposure of rats to 0, 22.5, 45, or 90 mg Ni/kg/day as nickel chloride in the diet for 11 weeks prior to mating, during mating, gestation, and lactation, a dose-related increase in the number of stillborn pups was observed. An independent statistical analysis of the data using the Fisher Exact Test found significant increases in the total number pups born dead at 22.5 mg Ni/kg/day and higher for the F1a generation, 45 and 90 mg Ni/kg/day for the F1b generation, 90 mg Ni/kg/day for the F2a generation, 22.5 mg Ni/kg/day for the F2b generation, and 45 and 90 mg Ni/kg/day for the F3b generation. The study authors noted that the number of offspring (dead and alive) was progressively less with increasing nickel levels above 45 mg/kg/day (10.3, 10.6, 9.8, and 9.0 for 0, 22.5, 45, and 90 mg/kg/day, respectively); the number of offspring weaned per litter was also decreased with increasing nickel levels (8.1, 7.2, 6.8, and 6.4 for 0, 22.5, 45, and 90 mg/kg/day, respectively). The third study (RTI 1988a, 1988b) is a two-generation study in which the P0 generation was exposed to nickel chloride in drinking water for 11 weeks before mating and during gestation and lactation, and the F1b generation animals were mated to produce the F2 generations. A reduction in live litter size was observed in the F1a, F1b, and F2a offspring of rats exposed to 55 mg Ni/kg/day. Increases in mortality were also observed in the F1b rats on postnatal days 22 through 42; these increases were statistically significant in males at 30 and 55 m g 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 a two-generation study in which rats were administered up to 2.2 mg Ni/kg/day as nickel sulfate via gavage for approximately 18 weeks (Springborn Laboratories 2000a).

Several acute-duration studies in pregnant mice where reproductive changes were observed also reported development abnormalities in offspring. Maternal exposure to ≥11.38 mg Ni/kg/day on gestation days 6 to 13 resulted increased incidence of skeletal anomalies including reduced or fused sternebrae, absence or gap between the ribs, and reduced ossification, and a 5% incidence of microphthalmia (born with small eyes resulting in vision loss or blindness) (Saini et al. 2013). Maternal exposure to ≥11.35 mg Ni/kg/day on gestation days 0 to 5 also resulted in an increased incidence of skeletal anomalies that increased with dose (Saini et al. 2014a). The incidence of skeletal anomalies and significance of reduced body weight compared to controls increased with dose. Saini et al. (2014b) exposed pregnant mice to 10.29 to 41.19 mg Ni/kg/day on either gestation days 0 to 5, 6 to 13, or 14 to 18. The lowest LOAEL for developmental effects in this study was among mice exposed on gestation days 6 to 13 where offspring body weight was significantly lower at birth than controls at 10.29 mg Ni/kg/day and >9% fetal mortality was reported at

higher doses. A 12% increase in fetal mortality was reported at 41.19 mg Ni/kg/day from exposure on gestation days 0 to 5, and an 11% increase at 20.59 mg Ni/kg/day from exposure on gestation days 14 to 18 (Saini et al. 2014b). El Sekily et al. (2020) similarly exposed pregnant female mice to 10.29 to 41.08 mg Ni/kg/day as nickel chloride on gestation days 6 to 13 and reported a significant increase in fetal resorption sites at all doses and a significant number of stillborn fetuses at 41.08 mg Ni/kg/day. Skeletal abnormalities are reported in offspring exposed to all doses, including incomplete ossification of the skull, vertebrae, ribs, and limbs, and unossified carpals, metacarpals, tarsals, metatarsals, and phalanges (El Sekily et al. 2020).

Decreases in pup body weights were reported in the offspring of rats exposed to 90 mg Ni/kg/day (Ambrose et al. 1976), 30, and 55 mg Ni/kg/day (RTI 1988a, 1988b). Neither the Ambrose et al. (1976) nor the RTI (1988a, 1988b) multigeneration studies found 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. 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 gestation days 8–12 (Gray et al. 1986).

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

Dermal

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

2.18 OTHER NONCANCER

Inhalation

This section on other noncancer effects includes discussion on metabolic effects, including discussion on serum glucose levels. Urinary and serum glucose levels may also be discussed in other sections of Chapter 2 as relevant to the discussed health effects. No studies were identified that examined noncancer effects in humans after inhalation exposure to nickel.

Significant increases (13%) in serum glucose levels were observed in male Wistar rats continuously exposed to 0.385 mg Ni/m^3 as nickel oxide for 28 days (23.6 hours/day) (Weischer et al. 1980). In females rats continuously (23.6 hours/day) exposed to nickel oxide, a 19% decrease in serum glucose levels was observed at 0.8 mg Ni/m^3 (Weischer et al. 1980). These data suggest that there may be a sex difference.

In male and female Wistar rats exposed to 0.4 mg Ni/m^3 metallic metal for 104 weeks (5 days/week, 6 hours/day), reduced mean food consumption was exposure-related (Oller et al. 2008). For males this occurred from week 58 to 104, and for females, from weeks 66 to 87.

Oral

No studies were identified that examined other noncancer effects in humans after oral exposure to nickel.

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

Dermal

Blood glucose levels were significantly increased 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). 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.

2.19 CANCER

Inhalation

The carcinogenic potential of nickel has been examined in many population and occupational studies. Associations between breast cancer and air exposure was analyzed in several studies using data from the EPA's Toxics Release Inventory (TRI) to estimate county-level exposures to nickel (Coyle et al. 2005; Kresovich et al. 2019; White et al. 2019). Using county-level estimates of nickel in air, Coyle et al. (2005) concluded that age-adjusted breast cancer rates were not associated with nickel release in women over 50 years of age. In a prospective study, White et al. (2019) followed 50,884 cancer-free women and did not find nickel concentrations in air to be associated with a higher risk of breast cancer. Kresovich et al. (2019) did not find that nickel ambient air exposure in Chicago, calculated by census-tract level from TRI data, increased the odds of developing ER/PR-negative breast tumors.

Several population-level studies have examined associations between nickel in ambient air and different types of cancers. A study in California analyzing cases of children diagnosed with retinoblastoma between 1990 and 2007 found a significantly increased risk of diagnosis associated with higher nickel exposures during pregnancy (Heck et al. 2015). A non-significant increased risk was also reported for exposure to nickel during a child's first year of life. Air concentration data was collected from several monitors during the same years of diagnosis and calculated a mean nickel air concentration of 5.08 ng/m^3 (Heck et al. 2015). A different study of children in California by Whitehead et al. (2015) specifically looked at exposure to nickel from carpet dust and found no significant association with development of acute lymphoblastic leukemia.

Two studies have found associations between increased risk of lung cancer and nickel exposures. Luo et al. (2011) analyzed TRI county-level data on on-site releases to air, water, surface land, and surface injection, and found an increased risk of lung cancer in counties with non-zero nickel releases. An analysis of 14 European cohort measured Ni $PM_{2.5}$ and PM_{10} in cohort areas from October 2008 to May 2011 and recorded a statistically significant association between risk of lung cancer among those who did not move away from the cohort area and PM_{10} nickel (Raaschou-Nielsen et al. 2016).

Several occupational studies have found statistically significant increases in the risk of nasal and/or lung cancer among nickel refinery workers generally employed between 1910 and 1985 at sulfidic nickel refineries, mines, and smelters (Andersen et al. 1996; Anttila et al. 1998; Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; Grimsrud et al. 2003; Karjalainen et al. 1992; Magnus et al. 1982; Muir et al. 1994; Pedersen et al. 1973; Peto et al. 1984; Roberts et al. 1989b). Sorahan and Williams (2005) provided an update on a cohort of 812 workers at the Clydach nickel carbonyl refinery in South Wales,

employed from 1953 to 1992; this facility was previously studied by Doll et al. (1977) and Peto et al. (1984). Among all workers, the standardized mortality ratio (SMR) was non-significant for excess lung cancer however it was significant among workers employed for at least 5 years in feed handling and nickel extraction (Sorahan and Williams 2005). The same study did not find increased cancer mortality for other sites among this cohort. Study authors concluded that lung cancer deaths could not be linked to nickel exposure however since previous studies at this refinery have found an association, further study is warranted (Sorahan and Williams 2005). A study by Pavela et al. (2017) analyzed workers employed from 1967 to 2011 at a previously studied nickel refinery and smelter in Finland (Anttila et al. 1998; Karjalainen et al. 1992). This study confirmed that exposure to nickel compounds primarily contributed to excess risk of lung cancer in both men and women working at this facility, reporting standardized incidence ratios (SIRs) of 1.05 and 1.22, respectively (Pavela et al. 2017). 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.

Two case-control studies of German male workers employed from 1988-1996 reported that among those welding regularly, high nickel exposure was associated with an increased risk of lung cancer when adjusting for exposure to welding fumes and hexavalent chromium (Pesch et al. 2019).

In contrast, most studies in other groups of nickel workers have not found significant increases in the risk of lung cancer among workers. This includes workers in mines (Shannon et al. 1984a; Shannon et al. 1991), hydrometallurgical refineries (Egedahl and Rice 1984; Egedahl et al. 2001; Egedahl et al. 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), or hard metal production workers (Marsh et al. 2017a; Marsh et al. 2017b). Although some studies of these workers did find significant increases in respiratory tract cancers (Becker 1999; Moulin et al. 1990), the increased risk was attributed to exposure to other carcinogenic agents, such as polycyclic aromatic hydrocarbons or asbestos. Redmond (1984) and Arena et al. (1998) reported significant increases in lung cancer risks among 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 in lung cancer risk was no longer statistically significant (Arena et al. 1998). In general, workers employed in these industries were exposed to lower levels of sulfidic or oxidic nickel than the nickel refinery workers who were primarily exposed to metallic nickel (Cragle et al. 1984; Godbold and Tompkins 1979) or soluble nickel (Pang et al. 1996). A broader population-based lung cancer case-control study in Europe did not find an increased risk from exposure to nickel dust or fumes in occupational settings (Mannetje et al. 2011).

Two studies found significant increases in the incidence of stomach cancer among nickel refinery workers (Anttila et al. 1998) and nickel platers (Pang et al. 1996). These data are insufficient to conclude whether the increases in stomach cancer risks are due to exposure to nickel, other agents, or chance. A meta-analysis of occupational exposure studies on pancreatic cancer (Ojajärvi et al. 2000) found a significant association between exposure to nickel and pancreatic cancer risk. However, the Ojajärvi et al. (2000) meta-analysis has been criticized (Seilkop 2001) for excluding a study of nickel mining and smelting workers (Shannon et al. 1991) and a study of nickel alloy production workers (Arena et al. 1998). The addition of these studies lowered the meta-analysis ratio from 1.9 (95% confidence interval 1.2–3.2) to 1.3 (95% confidence interval 0.9–1.9). A recent 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 7-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). Additionally, two case-control studies of individuals with testicular germ cells tumors found that neither paternal or maternal occupational exposure to solvents and heavy metals including nickel increased the risk of tumors (Olsson et al. 2018; Togawa et al. 2016). Overall, there does not appear to be sufficient evidence that exposure to airborne nickel is associated with increased cancer risks outside of the respiratory tract.

Several animal studies have examined the carcinogenic potential of nickel subsulfide, nickel oxide, and nickel sulfate hexahydrate. Chronic-duration exposure to nickel subsulfide resulted in significant increases in lung tumors in two rat studies. Adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcoma were observed in rats exposed to 0.63 mg Ni/m^3 as nickel sulfide for 78 weeks, 6 hours/day, 5 days/week (Ottolenghi et al. 1975). Similarly, significant increases in the combined incidences of alveolar/ bronchiolar adenoma or carcinoma were observed in male and female rats exposed to 0.11 or 0.73 mg Ni/m^3 as nickel subsulfide, 6 hours/day, 5 days/week for 2 years (NTP 1996b). In contrast, Wistar rats exposed to concentrations up to 1 mg Ni/m^3 as a nickel powder for 24 months, 6 hours/day, 5 days/weeks, did not show increased incidence of respiratory tract neoplasms, but other signs of lung toxicity were present (Oller et al. 2008). However, this same study found that the incidence of benign and

malignant adrenal gland pheochromocytoma in male rats and cortical adenoma/carcinomas in females were concentration-dependent to nickel metal exposure and increased tumor incidence was significant at 0.4 mg Ni/m^3 for both sexes (Oller et al. 2008). The study authors noted the incidence of cortical adenoma/carcinomas in females falls within historical ranges for control and cannot be definitely linked to the nickel exposure. Significant increases in the incidence of benign or malignant pheochromocytoma in the adrenal medulla were also observed in male rats at 0.11 or 0.73 mg Ni/m^3 and in females at 0.73 mg Ni/m^3 nickel subsulfide (NTP 1996b). In contrast to the findings in rats, no significant alterations in tumor incidences were observed in mice exposed to 0.44 or 0.88 mg Ni/m^3 as nickel subsulfide 6 hours/day, 5 days/week for 2 years (NTP 1996b) or 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). Acute-duration (6 hours/day, 5 days/week, for 1 month) inhalation exposure to ≤6.3 mg Ni/m^3 as nickel oxide resulted in no significant increase in lung cancer in rats ≤20 months after exposure (Horie et al. 1985). However, significant increases in the incidence of alveolar/bronchiolar adenoma or carcinoma were observed in male and female rats exposed to 1 or 2 mg Ni/m^3 as nickel oxide 6 hours/day, 5 days/week for 2 years (NTP 1996c), but not in rats exposed to 0.5 mg Ni/m^3 or in mice exposed to 1, 2, or 3.9 mg Ni/m^3. Significant increases in the incidence of benign or malignant pheochromocytoma in the adrenal medulla were also observed in rats exposed to 3.9 mg Ni/m^3 (NTP 1996c). In contrast to the less soluble nickel compounds, chronic-duration (6 hours/day, 5 days/week for 2 years) exposure to nickel sulfate did not result in significant increases in neoplasms in rats or mice (NTP 1996a); the highest concentrations tested were 0.11 and 0.22 mg Ni/m^3, respectively.

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 (IARC 1990b, 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) and nickel carbonyl in Group B2 (probable human carcinogen) (IRIS 1987c). Other nickel compounds have not been classified by the EPA. Based on the occupational data, inhalation unit risk levels of $2.4x10^{-4}$ $(\mu g/m^3)^{-1}$ and $4.8x10^{-4}$ $(\mu g/m^3)^{-1}$ were derived for nickel refinery dust and nickel subsulfide, respectively (IRIS 1987a, 1987b). The risk levels range from $4x10^{-1}$ to $4x10^{-4}$ $\mu g/m^3$ for a risk ranging from $1x10^{-4}$ to $1x10^{-7}$, respectively, for nickel refinery dust (IRIS 1987a) and from $2x10^{-1}$ to $2x10^{-4}$ $\mu g/m^3$ for a risk ranging from $1x10^{-4}$ to $1x10^{-7}$, respectively, for nickel subsulfide (IRIS 1987b).

Nickel-induced alterations in gene expression may be mediated by activated transcription factors. Nickel has been shown to alter several transcription factors including hypoxia-inducible transcription factor

(HIF-1) and activated transcription factor (ATF-1) (Kasprzak et al. 2003). Nickel exposure is associated with accumulation of HIF-1 which is involved in the regulation of hypoxia-inducible genes involved in cell transformation, tumor promotion, and progression, angiogenesis, altered metabolism, and apoptosis (Salnikow et al. 2003). HIF-1α, one of the HIF-1 subunits, is over-expressed in both primary and metastatic tumors, and is induced in response to hypoxia and exposure to nickel (Li et al. 2004; Salnikow et al. 2000). Both soluble and insoluble nickel compounds have also been shown to induce Cap43 (also called NDRG1) gene expression, a tumor marker, which requires HIF-1α activation (Costa et al. 2003; Li et al. 2004; Salnikow et al. 2000, 2003). Nickel (II) via reactive oxygen species (ROS) can imitate cellular hypoxia without activating HIF-1 dependent genes (Salnikow et al 1994). The ability of nickel to activate HIF-1α transcription factors may be attributed to nickel's capacity to substitute iron (II) in oxygen transport and formation of non-functional hemoglobin (Das et al. 2019). Nickel-transformed rat and mice cells show that the induction of ATF-1 transcription factor down-regulates thrombospondin-1 (TSP-1) expression (Kasprzak et al. 2003; Salnikow et al. 1997). TSP-1 suppresses angiogenesis; thus, the suppression of TSP-1 stimulates tumor growth.

Oral

No studies were identified that examined cancer in humans after oral exposure to nickel. A few studies have found a correlation between nickel levels in local farm soils and increased incidences of different cancers however these studies are very limited as exposure scenarios to soils are not established and other factors and exposures cannot be fully considered in the analyses (Huang et al. 2013; Lee et al. 2016a; Su et al. 2010).

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; Schroeder et al. 1974). The incidence of tumors was comparable to that observed in controls. Similarly, neoplastic and non-neoplastic findings in Fischer-344 rats exposed for 2 years to doses up to 11.16 mg Ni/kg/day were not related to nickel exposure and were similar to the control group (Heim et al. 2007).

Dermal

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

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 Table 2-5 and Table 2-6, 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 (Iyehara 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 (grp locus) (Fletcher et al. 1994), mouse lymphoma cells (Amacher and Paillet 1980; McGregor et al. 1988), and virus-infected mouse sarcoma cells (Biggart and Murphy 1988; Biggart et al. 1987). Gene mutation frequency was not affected in transgenic mouse and rat respiratory tissue following inhalation exposure to nickel subsulfide (Mayer et al. 1998). 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 mg/kg 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 above 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). 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).

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 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 (Covance Laboratories 2003; Deknudt and Léonard 1982; Morita et al. 1997). 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, though 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; Nordin et al. 2018).

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 BW (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. 2022). Exposure to nickel subsulfide showed DNA damage increased with exposure concentration regardless of duration (Oller et al. 2022). 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. 2016a).

Two studies of prokaryotic organisms – one in *Bacillus subtilis* (Kanematsu et al. 1980) and one in *S. 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; Wang et al. 2016b) 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) and V79 cells (Nordin et al. 2018). 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 are 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.

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

Species (test system)	Endpoint	Results	Reference	Compound
Drosophila melanogaster	Gene mutation	–	Rasmuson 1985	Nickel nitrate or chloride
D. melanogaster	Recessive lethal	+	Rodríguez-Arnaiz and Ramos 1986	Nickel sulfate
D. melanogaster	Gene mutation (wing spot test)	(+)	Iyehara Ogawa et al. 1994	Nickel chloride
Mammalian cells:				
Human lymphocytes	Chromosome gaps	+	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
Human lymphocytes	Sister chromatid exchange	–	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
Human lymphocytes	Chromosome aberrations	+	Waksvik et al. 1984	Nickel
Human lymphocytes	Sister chromatid exchange	–	Waksvik et al. 1984	Nickel
Human lymphocytes	Chromosome aberrations	+	Deng et al. 1988	Nickel
Human lymphocytes	Sister chromatid exchange	+	Deng et al. 1988	Nickel
Human lymphocytes	Chromosome aberrations	+	Borská et al. 2003	Nickel
Human lymphocytes	DNA damage	+	Iarmarcovai et al. 2005	Nickel
Human lymphocytes	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. 2016a	Nickel

Table 2-5. 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 (ip)	+	Dhir et al. 1991	Nickel chloride
Mouse bone marrow cells	Chromosome aberrations	+	El-Habit and Abdel Moneim 2014	Nickel chloride
Mouse bone marrow cells	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. 2022	Nickel subsulfide
Rat type II lung epithelial cells	DNA damage	–	Oller et al. 2022	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 (ip)	–	Morita et al. 1997	Nickel chloride, nickel sulfate, nickel oxide
Rat bone marrow cells	Micronucleus test (oral)	–	Covance Laboratories 2003	Nickel sulfate
Mouse bone marrow cells	Micronucleus test (ip)	–	Deknudt and Léonard 1982	Nickel chloride
Mouse bone marrow cells	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 (ip)	–	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; ip = intraperitoneal

Table 2-6. 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
S. typhimurium	DNA damage	+	–	Keyhani et al. 2006	Nickel
E. coli WP2	Gene mutation frequency	NT	–	Green et al. 1976	Nickel chloride
Salmonella 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 TA102	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
Chinese hamster embryo (CHE) cells	Cell transformation	NT	+	Conway and Costa 1989	Nickel chloride, Nickel sulfide
Chinese hamster ovary (CHO) cells	Cell transformation	NT	+	Costa and Heck 1982	Nickel sulfide, Nickel subsulfide, Nickel oxide, metallic Nickel
CHO cells	Cell transformation	NT	+	Costa and Mollenhauer 1980	Nickel sulfide, Nickel subsulfide
CHO cells	Cell transformation	NT	+	Costa et al. 1982	Nickel sulfide

Table 2-6. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Syrian hamster embryo (SHE) cells	Cell transformation	NT	+	Costa and Mollenhauer 1980	Nickel sulfide, Nickel subsulfide
SHE cells	Cell transformation	NT	+	Costa et al. 1982	Nickel sulfide
SHE cells	Cell transformation	NT	+	DiPaolo and Casto 1979	Nickel sulfate, Nickel subsulfide
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
Mouse embryo fibroblasts	Cell transformation	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
Human bronchial epithelial cells	Chromosome aberration	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, Ni sulfide
CHO cells	Chromosome aberration	NT	+	Sen and Costa 1986	Nickel chloride, Ni sulfide
CHO cells	Chromosome aberration	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

Table 2-6. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Chinese hamster V79 cells	Gene mutation at HGPRT locus	NT	+	Hartwig and Beyersmann 1989	Nickel chloride
Chinese hamster V79 cells	Gene mutation at HGPRT locus	NT	+	Miyaki et al. 1979	Nickel chloride
Chinese hamster V79 cells	Gene mutation at HGPRT locus	NT	–	Åkerlund et al. 2018	Nickel chloride
Chinese hamster V79 cells	Gene mutation at HPRT locus	NT	+	Ohshima 2003	Nickel sulfate
Chinese hamster V79 cells	Gene mutation at HPRT locus	NT	–	Buxton et al. 2020	Nickel metal powder
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

Table 2-6. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
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
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
Human bronchial epithelial cells	DNA strand breaks	NT	+	Di Bucchianico et al. 2018	Nickel chloride
Human bronchial epithelial cells	DNA damage	NT	+	Gliga et al. 2020	Nickel chloride
Human bronchial epithelial cells	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
Human colon cancer cells	DNA damage	NT	–	Kim and Seo 2012	Nickel acetate
Human fetal fibroblast cells	DNA damage	NT	+	Qiao and Ma 2013	Nickel
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	+	Wang et al. 2016b	Nickel
Mouse embryo fibroblast cells	DNA damage	NT	+	Terpilowska and Siwicki 2018	Nickel chloride
Chinese hamster V79 cells	DNA damage	NT	–	Nordin et al. 2018	Nickel

Table 2-6. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
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
CHO cells	DNA single strand breaks	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
Human lymphocytes	Micronucleus formation	NT	+	Arrouijal et al. 1992	Nickel subsulfide
Human bronchial epithelial cells	Micronucleus formation	NT	–	Gliga et al. 2020	Nickel chloride
Human colon cancer cells	Micronucleus formation	NT	–	Kim and Seo 2011	Nickel acetate
Chinese hamster V79 cells	Micronucleus formation	NT	–	Nordin et al. 2018	Nickel
Chinese hamster V79 cells	Micronucleus formation	NT	–	Buxton et al. 2020	Nickel
Human lymphocytes	Sister chromatid exchange	NT	(+)	Andersen 1983	Nickel sulfate
Human peripheral lymphocytes	Sister chromatid exchange	NT	+	Larramendy et al. 1981	Nickel sulfate
Human peripheral lymphocytes	Sister chromatid exchange	NT	+	M'Bemba-Meka et al. 2007	Nickel carbonate hydroxide, Nickel subsulfide, Nickel oxide, Nickel sulfate
Human lymphocytes	Sister chromatid exchange	NT	+	Saxholm et al. 1981	Nickel subsulfide
Human lymphocytes	Sister chromatid exchange	NT	+	Wulf 1980	Nickel sulfate
Human lymphocytes	Sister chromatid exchange	NT	+	Arrouijal et al. 1992	Nickel subsulfide
Chinese hamster V79 cells	Sister chromatid exchange	NT	+	Hartwig and Beyersmann 1989	Nickel chloride

Table 2-6. Genotoxicity of Nickel *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
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
Virus-infected mouse sarcoma cells	Induction of revertant foci	NT	+	Biggart and Murphy 1988	Nickel chloride
Mouse lymphoma (L5178Y/TK$^{+/-}$) cells	Forward mutation	NT	+	Amacher and Paillet 1980	Nickel chloride
Mouse lymphoma (L5178Y/TK$^{+/-}$) cells	Forward mutation	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; DNA = deoxyribonucleic acid; NiS = nickel sulfide

2.21 NICKEL NANOPARTICLES

The following section provides a brief overview on toxicity of nickel nanoparticles (NiNPs) and is focused on highlighting findings from experimental animal studies. No epidemiology studies using NiNPs were identified. A case report indicates that a worker developed NiNPs powder sensitization when working in a setting handling 1-2 grams of nano nickel powder without any special respiratory protection or control measures (Journeay and Goldman 2014). In another case report occupational inhalation exposure to NiNPs via spraying resulted in death 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 NiNPs in the urine and kidneys which were indicative of acute tubular necrosis. Occupational NiNPs inhalation is associated with increased risk of lung fibrosis, and high incidence of lung and nasal cancer is also reported (Genchi et al. 2020). Several *in vivo* and *in vitro* studies have demonstrated that NiNPs increase the production of reactive oxygen species 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).

Many studies in animals have reported a wide range of adverse effects in the respiratory system following exposure to NiNPs. Single inhalation exposure to NiO (nickel oxide) NPs 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. 2019). This study also observed changes in alveolar patterns in mice exposed to NiNPS. Wistar rats were exposed to NiO NPs via intratracheal instillation twice a week for 6 weeks at 0.24 mg/kg-bodyweight, which induced abnormal changes in hepatic enzymes (Yu et al. 2018). Single intratracheal instillation of NiO NPs 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 NiNPs at 5.6 mg/kg in Sprague-Dawley rats caused hepatotoxicity (Magaye et al. 2016). Single intratracheal instillation of NiO NPs in Wistar rats at the concentration of 5 mg/ml resulted in lung injury and oxidative stress over a period of 72 hours after the exposure (Horie et al. 2012). C57BL/6N mice inhaled 0.5 mg/ml NiO NPS mist by nasal exposure 4 times/day (10 min/day) for 8 days with a 1 week break after the first 4 days; this treatment induced pulmonary inflammation and an immune response by increasing the expression of IgE (Horie et al. 2016). Whole body inhalation exposure to NiNPs 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 NiNPs (Liberda et al. 2014). Whole body inhalation exposure to nickel sulfate ($NiSO_4$) NPs 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 (NH) NPs 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 aorta, significant signs of inflammation in bronchoalveolar lavage fluid, and changes in lung histopathology (Kang et al. 2011b). A five-month exposure in the same study exacerbated the health effects observed in the 1 week exposure (Kang et al. 2011b). Whole body inhalation of NH NPs in C57BL/6 mice for 5 hours/day for one 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 NiO NPs as 4 doses of 2 mg/kg/bw as intratracheal instillations which caused pulmonary injury and inflammation, and NiO particles were detected in the lung and lung associated lymph nodes (Senoh et al. 2017). Male Wistar rats were subjected to two aerosol inhalation exposures of NiO NPs 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). Albino rats were exposed to NiO NPs 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 NiO NPs via intratracheal instillation, twice a week for 6 weeks at 0.24 mg/kg bw, increased indicators of nitrative stress (NO, TNOS, and iNOS), inflammatory cytokines (TNF-a, IL-2, and IL-10), and cytokine induced neutrophil chemoattractants (CINC-1, CINC-2ab, and CINC-3) were observed in lung tissue (Chang et al. 2017). NiO NPs when intratracheally instilled into female Wistar rats at 200 cm^2/rat produced an acute neutrophilic inflammation (Lee et al. 2016b). Male Wistar rats were exposed to 0.2 mg NiO NPs via intratracheal instillation once which caused a persistent inflammatory effect, and a transient increase in cytokine expression and persistent pulmonary inflammation (Morimoto et al. 2011; Morimoto et al. 2016; Morimoto et al. 2010). A 4-week intratracheal instillation of 0.1-3 mg NiO NPs in male Wistar rats caused pulmonary inflammation (Mizuguchi et al. 2013; Ogami et al. 2009). A dose-dependent increase in acute lung inflammation and injury was seen in C57BL/6 mice after exposure to 50 µg NiNPs via intratracheal instillation (Mo et al. 2019).

Oral exposure to NiO NPs in animals primarily targets both male and female reproductive organs and the immune system. Oral exposure to 100 mg/kg-bodyweight nickel oxide NPs in water to pregnant albino rats for 12 to 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 NiNPs via food for 10 weeks and examined reproductive toxicity in one generation. At 15 mg/kg-bw, NiNPs 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 to 15 mg/kg-bw. Male rats showed morphological changes in the testis while female rats showed changes in hormone levels. 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 100 mg/kg bodyweight NiO NPs in water to pregnant albino rats for 12 to 14 days of gestation significantly decreased IgA, IgG, and IgM (Alsoltane and Altaee 2020b). A single oral NiO NP dose of 500 mg/kg via intubation in adult Wistar rats resulted in increased white blood cell count (Dumala et al. 2018).

Effects in several other systems have been reported in various animal studies. In male Wistar rats orally exposed to NiO NPs at 2 mg/kg-bw/day, significant increases in chromosomal aberrations, micronuclei formation, and DNA damage were induced after 7-day and 14-day exposures (Saquib et al. 2017). Oral

exposure to 100 mg/kg-bw NiO NPs in water to pregnant albino rats for 12 to 14 days resulted in decreased maternal relative body weight. Exposed rats on gestation day 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 gestation day 14 (Alsoltane and Altaee 2020a). At lower doses, Wistar rats exposed to NiO NPs via food for 14 days at 0.5 and 1 mg/kg-bw 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 NiO NPs, including decreased hemoglobin and hematocrit levels in male and female rats exposed to ≥50 mg/kg-bw (Dumala et al. 2019b).

Parenteral exposure to NiNPs targets the hematological system, heart, kidneys, and liver. Exposure to 5 mg/kg-bw NiNPs in male ICR mice by intraperitoneal injection damages the reproductive system by affecting spermatogenesis and testicular structure (Hu et al. 2020). Adult male Wistar rats exposed to 25 mg/kg-bw NiNPs and nickel chloride intraperitoneally daily for 1 week developed a significant increase in blood urea, creatinine, and white blood cell count (Seyedalipour et al. 2017). Wistar rats dosed with NiO NPs via intraperitoneal injection at 2.5 mg/kg for 3 times a 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 NiO NPs 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 NiNPs 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/bw of NiO NPs once (Dumala et al. 2017). Peripheral blood lymphocytes isolated from humans showed dose-dependent cytotoxic and genotoxic effects when exposed to NiO NPs 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 NiNPs and NiO NPs for 24 hours (Åkerlund et al. 2018, 2019). In Åkerlund et al. (2018), NiNPs and NiO NPs induced DNA strand breaks at doses of 5 to 25 µg/ml. NiO NPs appear more toxic; DNA damage began at 5 µg/ml compared to 10 µg/ml from NiNP 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 NiO NPs 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 NiO NPs 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 NiO NPs induced a significant increase in DNA damage (De Carli et al. 2018). The results from De Carli et al. (2018) indicate that NiO NPs are genotoxic and mutagenic *in vitro* and *in vivo.* Exposure to NiNPs 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 NiNPs and NiO NPs 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 and DNA strand breaks in a Chinese hamster lung fibroblast cell line occurred after a 48-hour exposure at 0.15 µg/cm^2 and oxidative stress in a human type II alveolar epithelial cell line exposed to 10 µg/ml NiNPs (Latvala et al. 2017; Latvala et al. 2016). Lung tissues exposed to 5-25 µg/cm^2 NiNPs showed dose-dependent cytotoxicity (Magaye et al. 2016). Dose-dependent cyto- and geno- toxicity of NiNPs and NiO NPs was 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; 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 NiNPs is limited, but existing data shows that smaller nickel particles are absorbed more readily than larger ones. This suggests that absorption rates may be higher for NiNPs than for other nickel compounds due to their small size. Solubility of NiNPs may be related to shape. In a study of intratracheal exposure in rats, spherical NiO NPs dissolved less readily in artificial lysosomal fluid and had lower pulmonary clearance rates than wire-shaped NiO NPs, suggesting that wire-shaped NiNPs may be more readily absorbed by the lungs. The smallest NiO NPs also had the highest absorption and distribution rates (Shinohara et al. 2017). NiNP shape may also affect distribution rate. In a study of differently shaped NiNPs administered intratracheally to rats, distribution from the lungs to lymph nodes was time- and dose-dependent for spherical and irregular NiO 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-bw NiO NPs in rats accumulated in the blood, liver, and kidney and the 250 mg/kg-bw dose in the brain. Rat neuronal cells exposed to NiO NPs 0-500 µg/ml for 24 hours resulted in a dose-dependent uptake of the nanoparticles and DNA damage, decreased cell viability, and oxidative stress (Abudayyak et al. 2017b). In another study, similar doses of NiO NPs in kidney epithelial cells resulted in DNA damage and apoptosis (Abudayyak et al. 2017a). NiNPs accumulated in the liver and spleen of Wistar rats dosed with 2.5 mg/kg NiO NPs 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 which demonstrated that the shape of NiNPs influenced the clearance.

Spherical and irregular shaped NiO NPs showed time- and dose-dependent increases in translocation from lungs to the thoracic lymph nodes, but wire-like NiO NPs did not (Shinohara et al. 2017).

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

NiO NPs appear to be excreted via urine and feces and appear to be dose- and time-dependent (Dumala et al. 2018). In this study, the excretion of nickel in urine was significant at all doses of NiO NPs at all sampling times in a dose- and time-dependent manner. In feces, the maximum amount of NiO NPs was cleared significantly and clearance was rapid from 18 to 24 hours (Dumala et al. 2017). Wistar rats were dosed with NiO NPs via intraperitoneal injection at a dose of 2.5 mg/kg 3 times a week up to 18 injections and NiO NPs underwent renal excretion (Minigalieva et al. 2015). Whole body inhalation exposure to NiO NPs for 6 hours/day for 4 weeks resulted in accumulation of NiO NPs 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 NiNPs administered intratracheally to rats, wire-shaped NiO NP 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).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Absorption: Nickel absorption following deposition to the lungs is dependent on the form and bioavailability. Insoluble nickel forms may clear from the lungs and undergo gastrointestinal absorption if coughed up and swallowed. Soluble forms may be absorbed into the bloodstream. An estimated 20-35% of inhaled nickel is absorbed into the bloodstream. Estimates of absorption following oral exposure in humans range from 12-40% after fasting, and 1-37% when consumed with a meal. Dermal absorption of nickel through the skin is slow and minimal.
- Distribution: Following absorption, nickel enters and distributes in the bloodstream. Less soluble forms of nickel appear to remain in the lungs more than soluble forms. Nickel appears to distribute primarily to the lungs then to the thyroid, adrenals, kidneys, heart, liver, brain, spleen, and pancreas. The total amount of nickel found in the human body has been estimated as 6 mg or 86 μg/kg for a 70-kg person.
- Metabolism: Nickel does not undergo any metabolism prior to excretion.
- Excretion: Urine is the main form of excretion of absorbed nickel through all exposure routes, while unabsorbed nickel is primarily excreted through feces. Nickel is also eliminated via sweat and breast milk. The elimination half-time of nickel administered in either water or food is 28 hours.

3.1.1 Absorption

In general, after inhalation exposures, deposition location in the lungs depends on both biological and physical characteristics such as particulate size, breathing patterns, and airstream velocity (James et al. 1994). Deposition of particulates greater than 2.5 μm predominantly occurs in the nasopharyngeal area, whereas particulates less than 2.5 μm are predominantly deposited in the bronchioalveolar region of the lungs. Absorption of deposited nickel is dependent on its form and bioavailability. Insoluble nickel deposited in the upper region of the lung is cleared by phagocytosis and/or mucociliary transport, subsequently swallowed and may undergo gastrointestinal absorption. More soluble forms of nickel may be absorbed into the bloodstream through the alveolar or bronchial walls via phagocytosis or dissolution. Particle dissolution rates in lung fluids, in secretions, or in macrophages as well as biochemical reactions and binding to tissue components affect the rate of absorption (Bailey and Roy 1994).

While quantitative human data regarding absorption are not available, estimates of absorption have been reported. These reported estimates of absorption of inhaled nickel into the blood range from 20-35% (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991). Other indicators of absorption are nickel levels in urine and serum. Nickel has been detected in the urine of workers exposed to nickel, with higher urinary concentrations in workers exposed to the more soluble nickel compounds compared to workers exposed to the less soluble forms, indicating that the more soluble forms are more readily absorbed from the lungs (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Similarly, serum levels may also be an indication of absorption as higher serum levels have been reported in exposed workers compared to controls and serum levels were also higher in works exposed to more soluble nickel forms compared to workers exposed to the less soluble forms (Angerer and Lehnert 1990; Elias et al. 1989; Torjussen and Andersen 1979). Elevated urinary nickel levels (700 µg/L) were reported in a case study where a man was exposed to a high level of metallic nickel fumes, 380 mg/m^3, which subsequently resulted in his death (Rendall et al. 1994).

Kodama et al. (1985a) reported a fractional lung deposition of 0.145 in male Wistar rats exposed to 6.5 NiO mg/m^3 for two months. Following a single acute-duration exposure to either nickel oxide or nickel subsulfide, Benson et al. (1994) reported total respiratory tract fractional depositions of 0.13 and 0.14 for nickel oxide and nickel subsulfide, respectively in Fischer-344/N rats. Fractional deposition in both the upper and lower respiratory tracts were similar for both compounds: nickel oxide upper 0.08, 0.05 lower; and nickel subsulfide upper 0.09 and lower 0.05. Fractional deposition of nickel chloride was reported to be 0.107 for acute-duration single exposures and 0.069 for repeated exposures in male Sprague-Dawley rats (Menzel et al. 1987). The difference in fractional deposition may be due to the estimation of the fractional deposition using all data points in the repeated exposures, with the latter exposures weighted more heavily than the single initial exposure (Menzel et al. 1987). Hirano et al. (1994) reported almost complete absorption into the lung tissue of Wistar rats following nickel sulfate deposition into the lungs 12 hours post inhalation. Serita et al. (1999) exposed male Wistar rats to 0.15, 1.14, and 2.54 mg/m^3 of ultrafine metallic nickel for five hours and reported deposition rates of 23.5%, 23.4%. and 33.9%, respectively. Retention times were similar for all three doses.

Clearance times of nickel from the lungs may give an indication of the absorption rate as the more soluble forms dissolve faster than the less soluble forms. As insolubility increases, the half-life of nickel in the lungs also increases. The half-life of nickel in the lungs of rats exposed by inhalation has been reported to be 32 hours for nickel sulfate (Hirano et al. 1994), 4.6 days for nickel subsulfide, and 120 days for green nickel oxide (Benson et al. 1994). Benson et al. (1995a) reported that most of the highly soluble nickel sulfate deposited in the lungs cleared within 1-3 days. Tanaka et al. (1985, 1988) calculated elimination

half-time from the lung of rats of 7.7, 11.5, and 21 months for green nickel oxide that increased with increasing particle diameter.

Nickel absorption is also observed after oral exposures, and results from various studies provide a wide range of absorption rates. Diamond et al. (1998) calculated oral nickel absorption in humans using data from several studies and found that absorption was inconsistently affected by fasting. Oral absorption in fasting humans ranged from 12-29% compared to a much lower absorption rate of 1-6% when nickel was consumed with food or water. Other studies not included in the analysis of Diamond et al. (1998) support these results (Nielsen et al. 1999; Patriarca et al. 1997; Solomons et al. 1982; Sunderman et al. 1989b). Based on fecal excretion data, Patriarca et al. (1997) reported that 29-40% of the ingested dose, given in drinking water after fasting, was absorbed. Nielsen et al. (1999) reported that based on the amount of nickel measured in urine that the highest nickel absorption, 11.07–37.42% of dose, was found when the subjects were administered 12 μg Ni/kg four hours after a meal; whereas when nickel was administered with a meal the absorption rate was 2.83–5.27%. Forty times more nickel was absorbed from the gastrointestinal tract when nickel was given in drinking water (27%) than in food (0.7%) (Sunderman et al. 1989b). Absorption rate appears to be rapid with peak serum levels occurring one to three hours after ingestion and is affected by whether nickel is consumed in water or food, with water having a faster rate (Christensen and Lagesson 1981; Nielsen et al. 1999; Solomons et al. 1982; Sunderman et al. 1989b). Beverage type also appears to affect bioavailability with increased bioavailability when nickel was administered in a soft drink, but decreased when nickel was given with whole milk, coffee, tea, or orange juice. In another study Ethylenediamine tetraacetic acid (EDTA, a chelating agent with poor GI absorption) added to the diet decreased nickel bioavailability to below fasting levels (Solomons et al. 1982).

Nickel-sensitive individuals exposed to increasing oral doses of nickel showed a decrease in the serum to urine nickel ratios which may be indicative of an adaption by reducing gastrointestinal absorption (Santucci et al. 1994).

Animal studies demonstrate the solubility of the ingested nickel affects gastrointestinal absorption, with the more soluble compounds exhibiting a higher absorption rate. Ishimatsu et al. (1995) reported that in rats exposed to various forms of nickel, the absorption was much higher with the soluble compounds nickel sulfate (11%), nickel chloride (9.8%), and nickel nitrate (33.8%), compared to the less soluble compounds nickel subsulfide (0.47%) and green nickel oxide (0.01%). The reported absorption rates correlate with the relative aqueous solubilities of the nickel compounds. Other animal studies in rats and dogs also report similar absorption rates of between 1–10% for nickel, nickel sulfate, or nickel chloride in the diet or by gavage (Ambrose et al. 1976; Ho and Furst 1973; Tedeschi and Sunderman 1957). The

results of an *in situ* intestinal perfusion study in rats (Arnich et al. 2000) suggest that at concentrations less than or equal to 10 mg Ni/L, nickel is absorbed via active transport and facilitated diffusion; however, the carriers become saturated at concentrations greater than 10 mg Ni/L and nickel absorption also occurs via passive diffusion. *In vitro* data also show similar results in that nickel is actively absorbed in the jejunum but may cross the ileum by passive diffusion (Tallkvist and Tjälve 1994).

Dermal absorption of nickel through the skin is slow and minimal. In tape stripping experiments on the skin of human volunteers most of the applied nickel dose was found on the skin surface or adsorbed into the stratum corneum 24 hours after application, indicating limited potential for absorption (Ahlstrom et al. 2019; Hostýnek et al. 2001a). In another study using sequential tape stripping on the skin of human volunteers, Hostýnek et al. (2001b) measured dermal absorption of nickel ions after exposing the skin to nickel metal powder at exposure durations of 5 minutes, 30 minutes, 3 hours, 24 hours, and 96 hours. Dermal absorption rates increased with exposure duration, but the amount of nickel removed after 10-20 strips was similar across durations. After five minutes dermal absorption was 0.07% and after 96 hours the absorption was 0.2%. Similarly, Tanojo et al. (2001) evaluated dermal absorption of nickel salts using human cadaver skin and report that less than 1% of nickel permeates beyond the stratum corneum after 96 hours, with the highest 0.95% for nickel nitrate. Whether the skin is intact or damaged appears to affect absorption. Filon et al. (2009) report absorption percentages of 0.03 for intact skin and 1.27% for damaged skin for nickel powder applied to human abdominal skin. Absorption following dermal exposure exhibits a considerable lag time. Larese et al. (2007) reported a lag time of 14 hours for nickel powder dissolved in synthetic sweat and applied to human abdominal skin. Fullerton et al. (1986) reported a lag time of 50 hours for nickel salts applied under occlusion to human breast or leg skin. Norgaard (1955) conducted an experiment using radiolabeled nickel sulfate which showed that nickel resorption is similar between individuals with and without nickel-hypersensitivity. Fullerton et al. (1986) report that the absorption rate depends on which form of nickel is used. Nickel ions penetrated occluded human skin *in vitro* about 50 times faster when aqueous nickel chloride is used than the absorption rate of the nickel ions when aqueous nickel sulfate is used. Fullerton et al. (1986) also report that the absorption rate is affected by whether occlusion of the skin is used. Only 0.23% of an applied dose of nickel chloride permeated skin after 144 hours when the skin was not occluded, while 3.5% permeated occluded skin. Application of nickel chloride in a sodium lauryl sulfate solution (0.25, 2, or 10%) to excised human skin resulted in a dose-related increase in the penetration of nickel during a 48-hour period (Frankild et al. 1995).

Studies in animals also indicate that nickel can penetrate the skin (Lloyd 1980; Norgaard 1957). Radioactive nickel sulfate was absorbed through the depilated skin of rabbits and guinea pigs after 24 hours and appeared primarily in the urine (Norgaard 1957). However, only a small percentage of

radioactive nickel chloride was absorbed through the skin of guinea pigs 4–24 hours after application, with most of the nickel remaining in the highly keratinized areas, the stratum corneum, and hair shafts (Lloyd 1980). Increased levels of nickel in the liver and kidneys in guinea pigs treated dermally with nickel sulfate for 15 or 30 days also appear to indicate that nickel can be absorbed through the skin (Mathur and Gupta 1994).

3.1.2 Distribution

Once absorbed, nickel enters the bloodstream and is transported by binding to albumin and ultra-filterable ligands (e.g., small polypeptides and L-histidine). Nickel also binds to nickeloplasmin; however, the nickel associated with nickeloplasmin is not readily exchangeable, and this protein is not thought to play a role in the transport of nickel (Sunderman and Oskarsson 1991). Nickel competes with copper for the albumin binding site, which consists of a terminal amino group with the first two peptide nitrogen atoms at the *N*-terminus, and the imidazole nitrogen of the histidine at the third position from the *N*-terminus (Sunderman and Oskarsson 1991). An *in vitro* study of rat hepatocytes found that the calcium channels are involved in nickel uptake by the liver (Funakoshi et al. 1997). Nickel is also known to accumulate in hair (Buxton et al. 2019).

Autopsy results of non-occupationally exposed individuals shows the highest concentrations of nickel (μg/kg dry weight) in the lungs (174±94), thyroid (141±83), adrenals (132±84), kidneys (62±43), heart (54±40), liver (50±31), whole brain (44±16), spleen (37±31), and pancreas (34±25) (Buxton et al. 2019; Rezuke et al. 1987). Generally, inhaled nickel particles of sufficiently small size (<100 μm) enter the respiratory tract and particle size dictates the region of deposition (Buxton et al. 2019). Particles with an aerodynamic diameter <4 μm are expected to enter the lower respiratory tract regions, while particles >4 μm will deposit in higher regions (Buxton et al. 2019). The total amount of nickel found in the human body has been estimated as 6 mg or 86 μg/kg for a 70-kg person (Sumino et al. 1975).

Studies examining nickel distribution in human tissues of workers suggest that less soluble forms of nickel remain in the lungs when compared to more soluble forms. Dry weight nickel content of the lungs at autopsy was 330±380 μg/g in roasting and smelting workers exposed to less-soluble nickel compounds, 34±48 μg/g in electrolysis workers exposed to soluble nickel compounds, and 0.76±0.39 μg/g in unexposed controls (Andersen and Svenes 1989). Svenes and Andersen (1998) reported a mean nickel concentration of 50 μg/g dry weight from 10 lung samples collected from different regions of the lungs of 15 deceased nickel refinery workers. Nickel levels in the lungs of cancer victims did not differ from those of nickel workers (Kollmeier et al. 1987; Raithel et al. 1989). Nickel levels in the nasal mucosa are higher

in workers exposed to less-soluble nickel compounds relative to soluble nickel compounds (Torjussen and Andersen 1979).

Higher serum nickel levels have been found in occupationally exposed individuals compared to non-exposed controls and serum nickel levels were higher in workers exposed to the more soluble forms of nickel than in works exposed to the less soluble forms, which correlates with the faster clearance of the more soluble forms (Angerer and Lehnert 1990; Elias et al. 1989; Torjussen and Andersen 1979). Concentrations of nickel in the plasma, urine, and hair were similar in nickel-sensitive individuals compared to non-sensitive individuals (Spruit and Bongaarts 1977). The amount of nickel in the hair, plasma, and urine of individuals occupationally exposed was ten times that of the controls (non-occupationally exposed).

Similar to human data, a higher percentage of less-soluble nickel compounds was retained in the lungs for a longer time than soluble nickel compounds in rats and mice (Benson et al. 1987; Benson et al. 1988; Dunnick et al. 1989; Goodman et al. 2011; Tanaka et al. 1985). The lung burden of nickel also decreased with increasing particle size (≤4 μm) (Kodama et al. 1985a; Kodama et al. 1985b). As summarized by Buxton et al. (2019), deposition is dependent on particle size where larger particles are expected to deposit in higher regions of the respiratory tract (e.g., tracheobronchial or nasopharyngeal regions) thereby reducing lung burden. Nickel retention was higher in rats (10 times) and mice (almost six times) exposed to less-soluble nickel subsulfide compared to soluble nickel sulfate (Benson et al. 1987; Benson et al. 1988). The lung burdens of nickel increased with increasing exposure duration and increasing concentrations (Benson et al. 1988; Dunnick et al. 1989; Goodman et al. 2011; NTP 1996a). Equilibrium levels in the lungs were reached for both nickel sulfate and nickel subsulfide while levels of nickel oxide continued to increase by week 13 (Dunnick et al. 1989). Benson et al. (1988) also reports that the lung nickel burden may rise to a steady state level as the lung nickel burdens were almost similar in rats exposed to 15 or 30 mg/m^3.

Solubility affects the lung burden and distribution to the kidneys (Buxton et al. 2019). Lung burdens in rats exposed to nickel oxide at durations of 16 days, 13 weeks, 7 months, and 15 months increased as concentrations increased, especially for the longer exposure durations (NTP 1996a). In mice, nickel oxide was only measurable in the lungs for the 13-week study (NTP 1996a). Levels in other tissues were measured in the kidney only and showed minor accumulation. Although nickel levels in the kidneys were elevated for rats, the results were not statistically significant from background levels and in mice the nickel levels in the kidney were not different from background levels (NTP 1996a). NTP performed similar studies using nickel subsulfide and nickel oxide, which are less soluble than nickel sulfate. Serum

nickel levels in both rats and mice were higher than those reported for nickel sulfate and lung burdens were higher for nickel oxide than for nickel subsulfide (NTP 1996b, 1996c).

Wehner and Craig (1972) report that approximately 20% of the inhaled concentration of nickel oxide was retained in the lungs at the end of exposure for either 2 days, or 3 weeks, or 3 months and was not dependent on the duration of exposure or exposure concentration. By 45 days after the last exposure to nickel oxide (2-day exposure), 45% of the initial lung burden was still present in the lungs (Wehner and Craig 1972).

Benson et al. (1995a) designed a study to examine the effect of green nickel oxide and nickel sulfate on the clearance of nickel from the lungs. In rats exposed to nickel oxide 0, 0.49, and 1.96 mg Ni/m^3 for six months, 18, 33, and 96% of the dose was retained, respectively, 184 days after the single exposure. In mice exposed to nickel oxide at 0, 0.98, or 3.93 mg/m^3 for 6 months, 4, 20, and 62%, respectively, of the dose was retained 214 days after the single exposure to radiolabeled compound.

Medinsky et al. (1987) reported nickel tissue concentrations following intratracheal installation of nickel sulfate in rats. The distribution was similar to that of inhalation studies with the lungs (also including the trachea and larynx) having the highest amount of nickel followed by the kidneys. Nickel distribution in animals may vary based on solubility of the nickel compound. Following intratracheal administration of either radiolabeled soluble nickel chloride or insoluble nickel oxide, English et al. (1981) found that the lungs had the highest concentration of nickel. However, the tissue distribution after the lungs varies between the soluble and insoluble form. The tissue distribution (in descending order) for the soluble form was kidneys, femur, heart, and duodenum. The tissue distribution (in descending order) for the insoluble form was heart, femur, duodenum, and kidneys.

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

In mice and rats, nickel was found primarily in the kidneys following both short- and long-term oral exposure to various soluble nickel compounds (Ambrose et al. 1976; Dieter et al. 1988; Ishimatsu et al. 1995; Whanger 1973). In studies that included analysis of nickel in the lung, the lung typically had the next highest levels after the kidney. Nickel was also found in the liver, heart, and fat (Ambrose et al. 1976; Dieter et al. 1988; Schroeder et al. 1964; Whanger 1973) as well as in the peripheral nerve tissues and in the brain (Borg and Tjälve 1989; Jasim and Tjälve 1986).

Szakmáry et al. (1995) exposed pregnant rats to nickel via gavage. Nickel levels were measured in maternal and fetal blood. Nickel levels in maternal and fetal blood in the control group were 3.8 and 10.6 µg/L, respectively. In the exposed animals, nickel levels showed a dose dependent increase in both maternal and fetal blood. Nickel was also detected in amniotic fluid. Nickel concentrations increased in both the placenta and fetuses of mice administered nickel during gestation, indicating that nickel can cross the placenta (Jasim and Tjälve 1986; Schroeder et al. 1964). In fetal tissue, nickel levels were the highest in the kidneys (Jasim and Tjälve 1986).

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

Twenty-four hours after treatment of depilated skin in rabbits and guinea pigs with nickel^{57}, radioactivity was detected in the blood, kidneys, and liver (Norgaard 1957). Quantitative data were not provided. Nickel concentrations increased in both the liver and kidneys of guinea pigs following 15 days or 30 days of dermal treatments with nickel sulfate (Mathur and Gupta 1994).

Several researchers have examined the distribution of nickel in pregnant and lactating rats following its injection (Dostal et al. 1989; Mas et al. 1986; Sunderman et al. 1978). The half-lives of nickel in whole blood following intraperitoneal treatment of pregnant and nonpregnant rats were similar (3.6–3.8 hours), while the half-life for nickel in fetal blood was 6.3 hours following treatment on gestation days 12 or 19 (Mas et al. 1986). Intramuscular injection of nickel chloride (12 mg Ni/ kg/day) into pregnant and nonpregnant rats resulted in a greater accumulation of nickel in the pituitary of pregnant rats. The kidneys had the highest concentrations of nickel and nickel was found in the embryos and embryonic membranes. Autoradiography of the fetuses and placentas showed nickel in the bladders, basal laminae, and yolk sacs, indicating that nickel can cross the placenta and into the fetus (Sunderman et al. 1978). Dostal et al. (1989) report that following subcutaneous exposure of lactating rats to nickel chloride, peak nickel concentrations in the milk were reached 12 hours after treatment. Compared to a single dose, four daily subcutaneous doses of nickel resulted in higher nickel concentrations in milk, while serum nickel levels were the same as following a single dose (Dostal et al. 1989). Parenteral administration of nickel via intraperitoneal injections in outbred white female rats lead nickel accumulation in brain, kidney, and spleen with the highest retention in the brain (Minigaliyeva et al. 2014).

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

3.1.3 Metabolism

Nickel does not undergo any metabolism prior to excretion and is primarily excreted in the urine or feces. The extracellular metabolism of nickel consists of ligand exchange reactions (Sarkar 1984). In humans, the exchangeable pool of nickel is bound to albumin, L-histidine, and α2-macroglobulin. The location where nickel binds to serum albumins is the same in humans, rats, and bovines with nickel binding to serum albumins at the histidine residue located at the third position from the amino terminus (Hendel and Sunderman 1972). Sarkar (1984) proposed a transport model involving the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and L-histidine, which allows the nickel complex to cross biological membranes. In the serum, there is also a nonexchangeable pool of nickel tightly bound to nickeloplasm, which is an α-macroglobulin (Sunderman 1986).

3.1.4 Excretion

Absorbed nickel is excreted in the urine, regardless of the route of exposure (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979) and unabsorbed nickel is excreted through feces (Buxton et al. 2019). Nickel is also eliminated via sweat and breast milk (Buxton et al. 2019). Several studies measured nickel in urine to assess inhalation exposures. Urinary levels in workers reflect recent exposures as suggested by comparing pre-shift and post-shift nickel urinary levels, with levels increasing from beginning to end of shift and returning to baseline levels the next morning, indicating rapid absorption and excretion (Ghezzi et al. 1989; Tola et al. 1979). However, as the workweek progressed an increase in urinary excretion was reported, suggesting that some nickel was absorbed and excreted more slowly (Ghezzi et al. 1989; Tola et al. 1979). Nickel was detected in the feces of nickel workers, but this probably resulted from mucociliary clearance of nickel from the respiratory system to the gastrointestinal tract (Hassler et al. 1983). Among electrolysis and refinery workers exposed to soluble nickel compounds (nickel sulfate aerosols), nickel concentrations in the urine were higher in workers exposed to higher air levels of nickel than those exposed to lower nickel levels (Chashschin et al. 1994). Workers exposed to more soluble forms of nickel had higher nickel levels in their urine, indicating that the soluble compounds are more readily absorbed than the less-soluble compounds (Bernacki et al. 1978; Torjussen and Andersen 1979). Yokota et al. (2007) reported no difference in nickel urine levels measured pre- and post-shift in battery workers exposed to nickel hydroxide. The nickel levels in urine were lower than more soluble nickel and suggest that nickel hydroxide may not be as soluble.

No studies were located on the excretion of inhaled soluble nickel salts by animals; however, intratracheal installation studies are available. Excretion depends on the solubility of the nickel compound. In rats

given soluble nickel chloride or nickel sulfate, approximately 70% of the administered dose was excreted in the urine within three days (Carvalho and Ziemer 1982; Clary 1975; English et al. 1981; Medinsky et al. 1987) and by day 21, 96.5% of the given dose of nickel chloride had been excreted in the urine (Carvalho and Ziemer 1982). In rats administered doses of nickel chloride, biliary excretion was negligible (<0.5%) 24-hours after injection (Marzouk and Sunderman Jr. 1985). Administration of the less soluble compounds, nickel oxide or nickel subsulfide, resulted in a greater fraction of the dose excreted in the feces likely as a result of mucociliary clearance compared to the more soluble forms. Equal amounts of the initial dose were found in the urine and feces of rats and mice exposed to black nickel oxide or nickel subsulfide, respectively (English et al. 1981; Valentine and Fisher 1984). Within 35 days 90% of the initial dose of nickel subsulfide had been excreted (Valentine and Fisher 1984). However, only 60% of the initial dose of black nickel oxide had been excreted within 90 days (English et al. 1981). This is consistent with nickel oxide being less soluble and not as rapidly absorbed as nickel subsulfide (English et al. 1981; Valentine and Fisher 1984). Medinsky et al. (1987) reports that in rats exposed to nickel sulfate, the amount excreted in the urine was dependent on the dose, with higher amounts excreted in the urine associated with a higher dose. The clearance half-time was also dose dependent with the shortest half-time associated with the highest dose and the longer half-time with the lowest dose. A higher percentage of the dose was excreted in the feces at the lowest dose (Medinsky et al. 1987).

Nickel administered in the drinking water was absorbed much more readily than when administered in the food, also affecting the amount excreted. Approximately 25% of nickel administered in water was excreted in urine, but only 1% was excreted in urine if nickel was administered in food (Sunderman et al. 1989b). Elimination half-time, 28 hours, was not affected by administration in either water or food and renal clearances were similar as well, 8.3 ± 2.0 ml/1.73 m^2 for water and 5.8 ± 4.3 ml/min/1.73 m^2 for food. Nielsen et al. (1999) report similar elimination median half-times of 19.9 to 26.7 hours and median clearances of 8.15 – 8.4 ml/min. Patriarca et al. (1997) report similar findings from a nickel tracer study in which 51-82% of the administered label was excreted in urine over five days.

Studies of animals are limited. Following oral intubation of nickel chloride in rats, 94–97% had been excreted in the feces and 3–6% had been excreted in the urine after 24 hours (Ho and Furst 1973). In dogs fed nickel sulfate in the diet for 2 years, only 1–3% of the ingested nickel was excreted in the urine (Ambrose et al. 1976). Because dogs lack a major binding site in serum albumin that is found in humans (Hendel and Sunderman 1972), the relevance of dog data to humans is unclear. Heim et al (2007) found that nickel levels in the urine and feces of Fischer-344 rats exposed to nickel sulfate hexahydrate via oral gavage increased in a dose dependent manner with most of the administered dose excreted in the feces.

Parenteral administration of nickel via intraperitoneal injections in outbred white female rats was excreted via urine (Minigaliyeva et al. 2014).

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

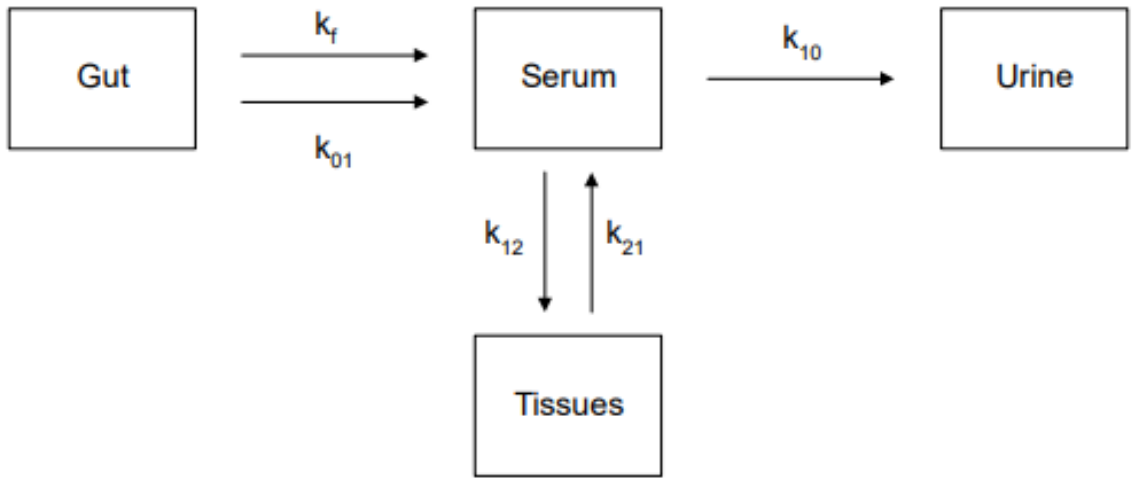
3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

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

Oral Toxicokinetic Model (Sunderman et al. 1989b and Dede et al. 2018)

Sunderman et al. (1989b) developed a model to predict nickel absorption, serum levels, and excretion following oral exposure in human volunteers to nickel in water and food. Two experiments were conducted, the first administering an oral dose of nickel as nickel sulfate (12, 18, or 50 µg/kg) in water and the second an oral dose of nickel as nickel sulfate in food. Serum nickel levels and both urinary and fecal excretion of nickel were monitored for 2 days before and 4 days after exposure. The data were then analyzed using a four compartment (gut, serum, urine, and tissues) linear model. The model used two inputs of nickel: the first based on a single oral dose, in which uptake was assumed to be a first-order process; and the second based on baseline dietary ingestion of nickel, in which uptake was assumed to be a pseudo-zero order process. Parameters determined for the model from the two experiments are shown in Table 3-1. The fraction of nickel absorbed was higher when administered in water than in food. However, dose had no effect on the absorption rate, suggesting that nickel absorption from the gastrointestinal tract could be saturated at higher doses. At doses low enough to be in the deficiency range, the absorption rate and percentage absorbed are probably larger. The model has been shown to predict serum nickel and cumulative nickel levels in subjects receiving a single dose of nickel in drinking water or food. However, validation with independent data were not described and the model does not predict tissue concentrations.

Figure 3-1. Diagram of the Compartment Model of Nickel Metabolism



Modified from Sunderman et al. 1989b

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

Table 3-1. Kinetic Parameters of Nickel Sulfate Absorption, Distribution, and Elimination in Humans[a]

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

[a]Data (mean ± standard deviation) from Sunderman et al. (1989b).

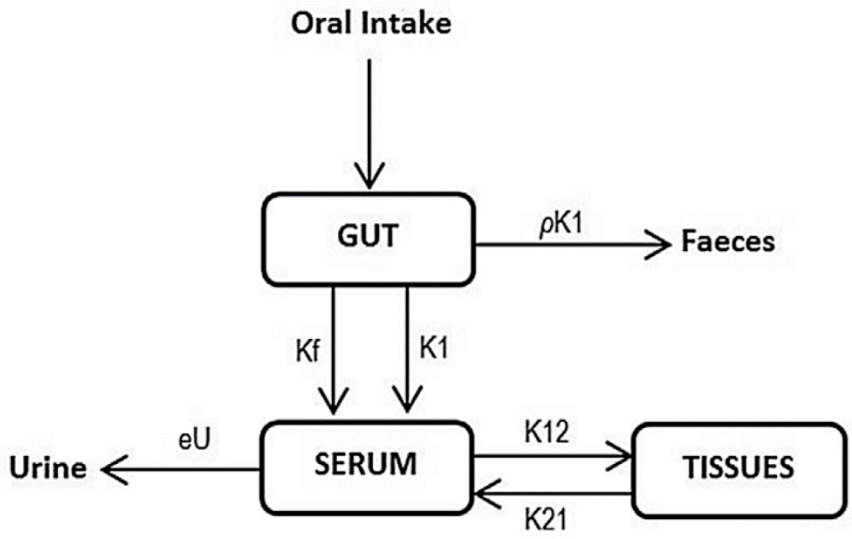
Table 3-1. Kinetic Parameters of Nickel Sulfate Absorption, Distribution, and Elimination in Humans[a]

Parameters (symbols and units)	Experiment 1 (nickel sulfate in water)	Experiment 2 (nickel sulfate in food)

[b]p<0.001 relative to exposure in food computer by analysis of variance.
[c]No value was determined because of the small mass of nickel absorbed from the gastrointestinal tract and transferred from the serum into the tissues.

Dede et al. (2018) modified the Sunderman et al. (1989b) model to evaluate nickel exposures from food. Since the Sunderman et al. (1989b) model for food did not include a nickel transfer rate from tissues to serum, Dede et al. (2018) used the nickel transfer rate from the drinking water model of Sunderman et al. (1989b). To account for the unabsorbed nickel, Dede et al. (2018) added a feces compartment. The model is depicted in Figure **3-2**.

Figure 3-2. Dede et al. 2018 modified Sunderman et al. 1989b model



Where:
K1, Kf, K12 and K21 = transfer rates of Ni between compartments.
eU is the rate constant for urinary elimination.
Agut is the absorbed fraction in the gut (0.011), as determined by Sunderman et al. (1989b).
ρK1 is the fecal excretion and ρ was calculated as (1-Agut)/Agut.

Source: Dede et al. 2018

The model was tested using the Sunderman et al. (1989b) data and data from Nielsen (1990). The model predictions showed good agreement with the Sunderman data. However, the model underpredicted the cumulative urinary excretion of nickel compared to the Nielsen (1990) data. The authors suggest that the underprediction may be due to the higher oral absorption (2.95%) reported by Nielsen (1990) compared to the reported oral absorption of 0.7% by Sunderman et al. (1989b).

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

Hsieh et al. 1999a developed a dosimetric model of nickel deposition and clearance from the lung using lung burden data from the rat NTP studies of nickel sulfate (NTP 1996c), nickel subsulfide (NTP 1996b), and nickel oxide (NTP 1996a) and using previously developed models. The model consists of a single compartment with removal of nickel occurring either via macrophage phagocytosis and migration (mechanical clearance) and/or via dissolution depending on the solubility of the nickel compound. Since nickel sulfate is soluble most of the clearance occurs by dissolution, nickel oxide on the other hand is not very soluble and the primary clearance is mechanical, and the clearance of nickel subsulfide occurs via both mechanisms. The accumulation of nickel in the lung over time was described by the following equations:

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

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

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

where M is the mass burden, r is the deposition rate, λ is the total alveolar clearance rate coefficient; η is the alveolar deposition fraction, MV is the minute ventilation, a, b, c are clearance rate coefficient constants, ms=M/S in which M is the lung mass burden and S is the total alveolar surface area (m_s=5.38x10^3 cm^2 for rats), and m_{s0}=1 mg/cm^2 is the dimensional constant introduced to normalize m_s.

Hsieh et al. (1999b) modified the rat model to develop a model of deposition and clearance of nickel in the alveolar region of the lungs in humans. Six scenarios were evaluated, and deposition rates calculated for each one: nose-breathing at rest, nose-breathing at light work, nose breathing at moderate work, mouth breathing at rest, mouth breathing at light work, and mouth breathing at moderate work. Clearance rate coefficient constants for humans were estimated using the rat values. For nickel oxide, clearance rate coefficient constant *a* was estimated to be 0.13 times the rat value; constants *b* and *c* were assumed to be the same as rats. Since clearance for nickel subsulfide is due to both mechanical transport and dissolution; the clearance rate coefficient constant *a* was estimated to be the sum of the clearance rate coefficient constant *a* for insoluble nickel (nickel oxide) and the difference between the clearance rate coefficient constant *a* for nickel oxide and for nickel subsulfide. For the soluble nickel sulfate, clearance rate coefficient constants in humans were assumed to be the same as in rats. The human coefficient constants are presented in Table 3-2.

Hsieh et al. (1999c) also developed a similar model for mice. The retention half times for the less soluble particles in mice were less than the retention half times in rats. The retention half times for the more

soluble particles were the same between species. Mice also have different regional deposition fractions, have smaller deposition rates, and higher clearance rates than rats. These differences may lead to different estimates in lung burden when extrapolating to humans depending on which model is used (Hsieh et al. 1999c).

A further modification to the model was developed by Yu et al. (2001) by incorporating three additional factors: inhalability, mixed breathing mode, and clearance rate coefficient of a mixture of nickel compounds.

Both the original rat model and the Yu et al. (2001) modification were validated to some extent. To validate the Hsieh et al. (1999a) model, the model predictions were compared to measured lung burden data in the NTP studies. In general, there was good agreement between the predicted lung burdens and measured burdens. However, there was less agreement between the predicted and measured lung burden data for the shorter term NTP studies (16 days and 13 weeks). The authors suggest that the differences may be due to assumptions used in the model (e.g., average body weight, constant respiratory parameters), using lung geometry data for Long Evans rats rather than for the Fischer rats used by NTP, or other shortcomings in the experimental data. The Hsieh et al. (1999b) model modification was not validated. The Yu et al. (2001) modification of the model was used to predict lung burdens in nickel refinery workers and a comparison with measured lung burdens in deceased nickel refinery workers (Andersen and Svenes 1989) demonstrated good agreement between predicted and measured body burdens.

Table 3-2. Clearance Rate Coefficient Constants of Nickel Compounds

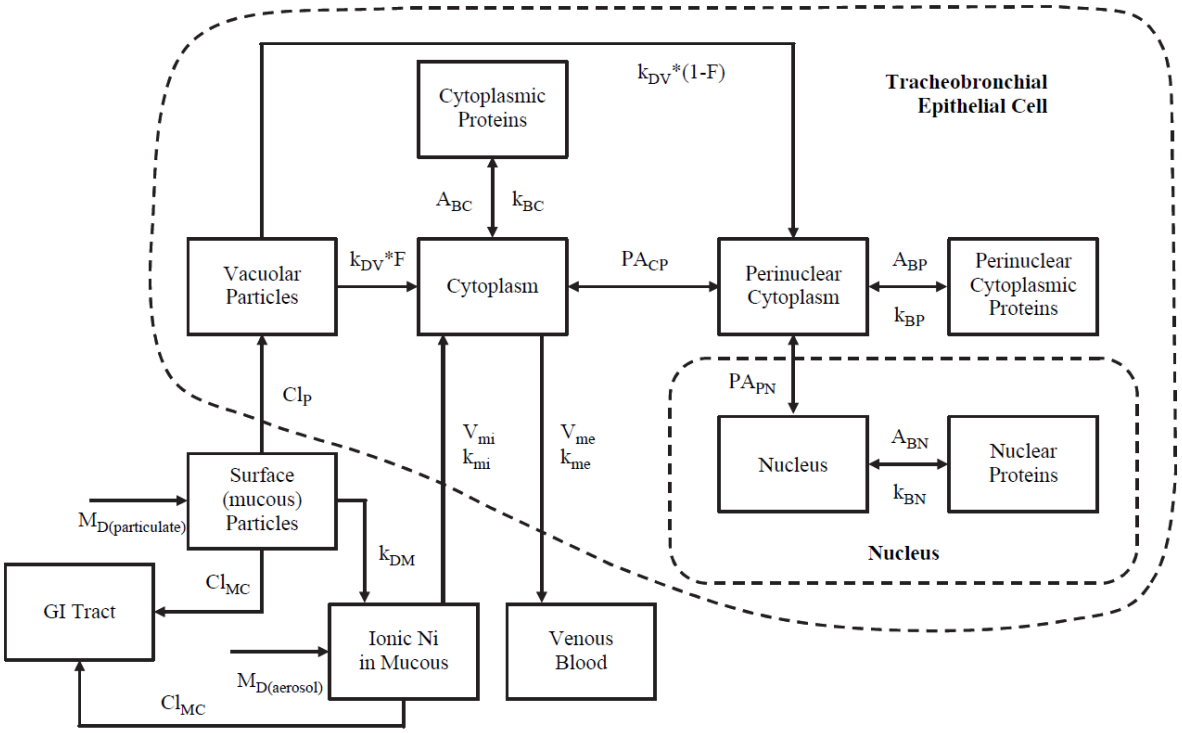
Species	Nickel compound	Clearance rate coefficient constant		
		a	*b*	*c*
Rat[a]	Nickel sulfate	10.285	17.16	0.105
	Nickel subsulfide	0.00768	-20.135	0.266
	Nickel oxide	0.0075	300	0.95
Human[b]	Nickel sulfate	10.285	17.16	0.105
	Nickel subsulfide	0.00117	-20.135	0.266
	Nickel oxide	0.00099	300	0.95

[a]Data from Hsieh et al. 1999a
[b]Data from Hsieh et al. 1999b

Hack et al. 2007 Model

Hack et al. (2007) describe a physiological model of the intracellular dosimetry of inhaled nickel using *in vitro* data that describe the uptake and delivery to tracheobronchial epithelial cells. The model also accounts for differences in uptake and delivery of different forms of nickel. The model includes seven intracellular compartments of the tracheobronchial epithelial cell and four extracellular compartments (Figure 3-3).

Figure 3-3. Hack et al. 2007 Intracellular Dosimetry Model for Nickel



M_D	= Deposited dose = f(MMAD,conc)	A_{B*},k_B	= Binding (BC: cytoplasm, BN: nucleus, BP: perinuclear)
Cl_{MC}	= Mucociliary clearance	Cl_P	= Phagocytosis
V_{mi},k_{mi}	= Influx	PA_*	= Diffusion into nucleus (PN: nucleus to perinuclear, CP: cytoplasm to perinuclear)
V_{me},k_{me}	= Efflux	K_{D*}	= Dissolution rate (DM: mucous; DV: vacuoles
F	= Fraction dissolved before migration of phagocytized particle to perinuclear cytoplasm		

Source: Adapted from Hack et al. 2007

Following inhalation of nickel particles or aerosols, nickel is deposited in the mucous layer where particulate nickel compounds are either cleared by mucociliary action, dissolved into nickel ions, or phagocytized and subsequently dissolved. Soluble nickel is dissolved, resulting in the release of nickel ions which are transported into cells by divalent transport systems. The model assumes that both influx and efflux of nickel ions are described by saturable Michaelis-Menten kinetics. Nickel ions may bind with cytosolic proteins or diffuse through the cytoplasm to the perinuclear cytoplasm where the ions can bind reversibly to perinuclear proteins, enter the nucleus, and bind to nuclear proteins. The model generally uses first order rate constants; however, Michaelis-Menten kinetics are used for influx and efflux of nickel from mucous to cytoplasm to venous blood. Hack et al. (2007) validated their model using outside data

for nickel chloride, nickel subsulfide, and crystalline nickel sulfide. The model predictions for uptake of nickel chloride were better for steady state concentrations than the rate of uptake within the first 30 minutes post-exposure where the model underpredicted intracellular levels. Good observed to predicted ratios for nickel subsulfide in the nucleus, for nickel chloride in the nucleus, whole cell, and cytoplasm were reported using one data set, but with another data set the ratios were more variable.

3.1.6 Animal-to-Human Extrapolations

The available data on the toxicity of inhaled nickel provide strong evidence that the respiratory tract, in particular the lung, is the most sensitive target of nickel toxicity in humans and animals. A PBPK model (Benson et al. 1995b; Benson et al. 1995a; NTP 1996a, 1996b, 1996c) of lung deposition and clearance of inhaled nickel found a higher deposition of nickel in the alveolar region of humans compared to rats; however, adjustment for differences in lung weights resulted in a lower alveolar deposition of nickel in humans than in rats. This model, as described in more detail in Section 3.1.5, allows for prediction of human lung burden. Hack et al. (2007) used *in vitro* data for the uptake and delivery of nickel to tracheobronchial epithelial cells. This model also accounts for differences in uptake and delivery of different forms of nickel and includes seven intracellular compartments of the tracheobronchial epithelial cell and four extracellular compartments (Hack et al. 2007). Oller et al. (2008) describes an approach to derive human equivalent concentrations from rat studies, accounting for differences in respiratory tract deposition and clearance. Deposition fractions in the respiratory tract of rats and human were calculated using the Multiple Path Particle Dosimetry (MPPD) model; this approach was similarly done in calculating human equivalent concentrations to derive inhalation MRL values (See APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS). A cancer bioassay in rats and mice conducted by NTP (1996c) did not find significant increases in the occurrence of lung tumors. However, several occupational exposure studies have reported increases in the occurrence of nasal and lung tumors in workers exposed to soluble nickel compounds (primarily nickel sulfate and nickel chloride) in combination with exposures to other nickel compounds and/or carcinogenic agents (Anttila et al. 1998; Grimsrud et al. 2002; Grimsrud et al. 2000; International Committee on Nickel Carcinogenesis in Man 1990). It is not known if the apparent species differences are due to differences in carcinogenic potential, co-exposure to other nickel compounds or other metals, or differences in exposure concentration. The available data on the oral toxicity of nickel are insufficient for comparing sensitive targets of toxicity and dose-response relationships between humans and laboratory animals. Except for dogs, the toxicokinetic properties of nickel did not differ between species. In dogs, serum albumin lacks the histidine residue at the third position from the amino terminus (Hendel and Sunderman 1972); thus, dogs would not be a

good model for the disposition of nickel in humans. In the absence of data to the contrary, it is assumed that most laboratory animals are a good model for humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to nickel are discussed in Section 5.7, Populations with Potentially High Exposures.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Based on the developmental stage, the vulnerability of a child may vary with critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function being most sensitive to disruption. There are often differences in pharmacokinetics and metabolism between children and adults. Even though infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993). There are limited data on the toxicity of nickel in children. Several surveys of nickel-induced dermatitis found higher incidences of nickel sensitivity among young girls (Uter et al. 2003; Wantke et al. 1996). This apparent age-related increase in nickel-induced dermatitis is likely the result of increased nickel exposure in this segment of the population rather than an increase in sensitivity. For most of the general population, the sensitizing exposure is through consumer products, particularly jewelry. The higher prevalence of ear piercing in young women probably results in a higher prevalence of nickel sensitivity (Akasya-Hillenbrand and Ozkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widström 1985; Meijer et al. 1995; Uter et al. 2003). With the exception of nickel

sensitization, there are limited toxicity data on age-related differences in toxicity in humans or animals. Zhang et al. (2000) found that older rats (aged 20 months) were more susceptible to the proinflammatory effects in the lungs of inhaled ultrafine nickel as compared to juvenile rats (aged 2 months). A study of 72 pregnant women measured higher nickel levels in umbilical cord blood among women with either gestational diabetes, hypertensive disorder complicating pregnancy, or both (Ding et al. 2021). Study authors suggest that the placental barrier against nickel in women with pregnancy complications may be weakened.

Several inhalation and oral exposure studies in rats and mice provide suggestive evidence that the fetus and neonate are targets of nickel toxicity. Increases in spontaneous abortions and stillbirths and decreases in neonatal survival have been observed in rats (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993) and mice (Berman and Rehnberg 1983) following oral exposure to nickel. Decreases in pup body weight have also been observed in rats following inhalation (Weischer et al. 1980) or oral (Ambrose et al. 197 6; RTI 1988a, 1988b) exposure. No human or animal data on the toxicokinetic properties of nickel in children or immature animals or studies examining possible age-related differences in the toxicokinetics of nickel were located. Parenteral administration studies in rats and mice demonstrate that water-soluble nickel compounds are transferred across the placenta (Olsen and Jonsen 1982) and via maternal milk (Dostal et al. 1989). The available information is from adults and mature animals; no child-specific information was identified.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for nickel from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to nickel are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by nickel are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Biological monitoring data are predominantly available from studies conducted in occupational settings. Determination of nickel in the urine, feces, serum, hair, and nasal mucosa has been used to demonstrate human exposure to nickel compounds (Angerer and Lehnert 1990; Bencko et al. 1986; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Based on an extensive review of biological monitoring data, Sunderman (1993) concluded that serum and urine nickel levels were the most useful biomarkers of nickel exposure. Levels of nickel in urine and serum provide the most information about levels of nickel exposure if the route, sources, and duration of exposure are known, if the chemical identities and physical-chemical properties of the nickel compounds are known, and if physiological information (e.g., renal function) of the exposed population is known (Sunderman 1993). In the general population, average nickel concentrations in serum and urine are 0.2 and 1–3 μg/L, respectively (Templeton et al. 1994). Based on the 2017-2018 cycle of the National Health and Nutrition Examination Survey (NHANES), the geometric mean concentration of urinary nickel is 1.11 μg/L.

Significant correlations have been found between occupational exposure to less-soluble nickel compounds (breathing zone samples) and the levels of nickel in the urine and serum in various groups of workers (Morgan and Rouge 1984). Nickel levels in urine and serum of workers inhaling nickel powder, alloys, or slightly soluble compounds reflect the combined influences of long-term accumulation and recent exposures (Sunderman et al. 1986). Correlations between exposure concentration and levels in the

urine and serum were found only in groups and not in individual workers. A relationship between exposure concentrations of soluble nickel compounds and levels of nickel in the urine and serum has also been reported (Bernacki et al. 1980). Urine and serum levels of nickel in workers inhaling soluble nickel compounds reflect the amount of nickel absorbed in the previous 1 or 2 days (Sunderman et al. 1986). With respect to monitoring nickel following exposure to soluble compounds, the best correlations between exposure concentration and urine levels were found with "end-of-shift" urine sampling (Bernacki et al. 1980) or "next morning" urine sampling (Tola et al. 1979). A correlation was found between urinary nickel and plasma nickel in workers, with nickel levels in urine being about 8-fold higher than plasma levels (Angerer and Lehnert 1990; Bernacki et al. 1978). Alternatively, Bavazzano et al. (1994) did not find any significant correlations between urinary nickel concentrations in nickel electroplating workers and air concentrations of soluble nickel compounds. Among nickel refinery workers, there was a significant correlation between urinary nickel levels (unadjusted or adjusted for creatinine levels) and soluble nickel concentrations in air; the correlation coefficients were approximately 0.35 and 0.55 for unadjusted and adjusted urine (Werner et al. 1999). Adding insoluble nickel air concentrations into the regression analysis as a predictor value resulted in a negligible change. Similarly, Oliveira et al. (2000) found significant correlations between post shift urinary nickel levels (adjusted for creatinine excretion) and nickel concentrations in the air among workers at a galvanizing facility exposed to soluble nickel compounds. A lower correlation coefficient was found for the relationship between pre-shift adjusted urinary levels and airborne nickel concentrations (Oliveira et al. 2000).

Workers exposed to high levels of nickel showed significantly lower levels of antioxidants (glutathione and catalase) than those with a lower exposure to nickel (Tsao et al. 2017). Higher concentrations of nickel in the urine and the plasma and lower concentrations of nickel in the nasal mucosa were observed in workers exposed to soluble nickel compounds when compared to workers exposed to less-soluble compounds (Bernacki et al. 1978; Torjussen and Andersen 1979). Less-soluble nickel compounds tended to remain in the nasal mucosa (half-life of ≈3.5 years); therefore, urinary and plasma levels were relatively low (Torjussen and Andersen 1979).

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

Exposure to nickel has also been monitored by assessing the content of nickel in the hair (Bencko et al. 1986; Michalak et al. 2012). Analysis of the nickel content of hair provides evidence of past exposure and

not changes in recent exposure to nickel. Correlations between exposure concentration and the level of nickel in hair were not reported. Like hair, toenails may also provide evidence of past exposure. Exposure to nickel has been monitored by assessing the content of nickel in toenails, and a systematic review found that nickel levels in toenails may indicate exposure occurring 7-12 months before measurement (Salcedo-Bellido et al. 2021). In a study of 47 welders in Massachusetts, nickel levels in toenails and welding hours were not significantly associated (Grashow et al. 2015). However, study authors reported that nickel levels and welding hours 7 to 9 months prior to measurement approached statistical significance.

Sensitization to nickel produces changes in serum antibodies (an increase in IgG, IgA, and IgM and a decrease in IgE) that may be monitored to determine if exposure to nickel has occurred (Bencko et al. 1983; Bencko et al. 1986; Novey et al. 1983). These changes were found in both sensitized (Novey et al. 1983) and non-sensitized (Bencko et al. 1983; Bencko et al. 1986) individuals. Information regarding the exposure concentration of nickel needed to produce serum antibody changes was not reported. A recent study shows that exposure to nickel induced epithelial-mesenchymal transition (EMT) as a crucial step in the pathogenesis of several lung diseases. This leads to a persistent downregulation of E-cadherin expression in human lung epithelial cells and the EMT remained irreversible postexposure (Zhang et al. 2022). This is not a biomarker of exposure unique to nickel and therefore cannot be used alone as a biomarker of nickel exposure.

3.3.2 Biomarkers of Effect

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

3.4 INTERACTIONS WITH OTHER CHEMICALS

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

tetraazacyclotetradecane), were more effective than hydrophilic chelating agents such as EDTA, cyclohexanediamine tetraacetic acid (CDTA), diethylenetriamine pentaacetic acid (DTPA), and hydroxyethylenediamine triacetic acid (HEDTA) (Misra et al. 1988). The higher efficacy of the lipophilic agents may be due to their ability to bind to nickel both intracellularly and extracellularly, while the hydrophilic agents can only bind extracellularly. A cross-reactivity between nickel and cobalt in sensitive individuals has been noted. For example, eight patients with asthma resulting from cobalt exposure also developed asthma when challenged with nickel sulfate (Shirakawa et al. 1990). Cobalt and nickel sensitization has been reported in individuals exposed to the two metals in numerous studies. Exposure to both metals increases the dermatological impact and causes more intense reactions in individuals (Veien et al. 1987 ; Fischer and Rystedt 1983). One animal study using guinea pigs showed some interaction between nickel and cobalt (Wahlberg and Lidén 2000). Co-exposure to cobalt and nickel chlorides in studies using cultured alveolar type II cells showed a synergistic (greater than additive) response (Cross et al. 2001). Dermal exposure in mice to a mixture of nickel and cobalt increased immune response to both metals in combination than to either metal alone.

Nickel has also been found to interact with other metals such as iron, chromium, magnesium, manganese, zinc, and cadmium. The toxicity of nickel was mitigated by treatment with zinc (Waalkes et al. 1985) and magnesium (Kasprzak et al. 1986). The data suggest that magnesium, but not zinc, acted by altering the pharmacokinetics of nickel. The mechanism of action for zinc could not be determined from the study (Waalkes et al. 1985). Nickel absorption is increased during iron deficiency (Müller-Fassbender et al. 2003; Tallkvist and Tjälve 1994), suggesting that iron deficiency may result in increased nickel toxicity. Coadministration of magnesium and nickel resulted in increased urinary excretion of nickel and decreased deposition of nickel in the lung, liver, and kidneys (Kasprzak et al. 1986). Manganese dust inhibited nickel subsulfide-induced carcinogenesis following simultaneous intramuscular injection of the two compounds (Sunderman and McCully 1983). The inhibition by manganese was a local and not a systemic effect.

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

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

In iron-deficient rats, nickel enhanced the absorption of iron (Nielsen 1980; Nielsen et al. 1980; Nielsen and Flyvholm 1984). This effect of nickel was only observed when ferric sulfate was given. No interaction was observed when iron was given as a 60% ferric/40% ferrous sulfate mixture. It has been proposed that nickel facilitates the passive diffusion of ferric ions by stabilizing the transport ligand (Nielsen 1980). In a study by Salnikow (2004) exposure to nickel sulfate caused hypoxia-like conditions in the human airway epithelial cells which was mitigated by the addition of iron in either ferric or ferrous form.

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

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Nickel is a transition metal in group 10 of the periodic table following iron and cobalt (Cotton and Wilkinson 1980). Its outer shell of electrons has a $3d^8 4s^2$ configuration (Haynes et al. 2015). Nickel occurs naturally in the earth's crust. In the United States, nickel is primarily used for stainless and alloy steels, nonferrous alloys and superalloys, and electroplating (USGS 2021). While nickel can exist in oxidation states -1, 0, +2, +3, and +4, its only important oxidation state is nickel (+2) under normal environmental conditions. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for nickel and nickel compounds.

Table 4-1. Chemical Identity of Nickel and Selected Nickel Compounds

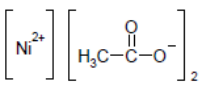
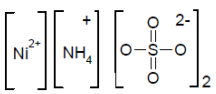
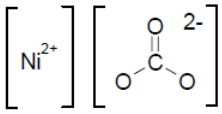
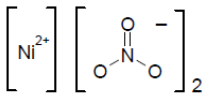
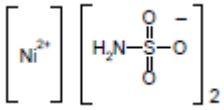
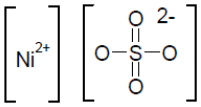
Characteristic	Nickel	Nickel acetate	Nickel ammonium sulfate	Nickel carbonate
Synonym(s) and Registered trade name(s)	CI 77775; NI 0901-S; NI 270; NI 4303T; Nickel 200; Nickel 201; Nickel 205; Nickel 207; Nickel 270; Nickel sponge; NI 0901-S (Harshaw); NP-2; Raney alloy; Raney nickel; RCH 55/5[b]	Nickel (II) acetate; nickelous acetate; nickel diacetate; acetic acid, nickel(2+) salt; AI3-26110; nickel(2+) acetate[c]	Nickel (II) ammonium sulfate; Diammonium nickel bis(sulphate); Ammonium disulfatonickelate(II); Sulfuric acid, ammonium nickel(2+) salt (2:2:1); diazanium;nickel(2+);disulfate; ammonium nickel sulfate (anhydrous); ammonium nickel(2+) sulfate (2/1/2)[d]	CI 7779; Carbonic acid, nickel (2+) salt; nickel (II) carbonate; nickelous carbonate[e]
Chemical formula	Ni[a]	$C_4H_6NiO_4$[a]	$Ni(NH_4)_2(SO_4)_2$[a]	$NiCO_3$[a]
Chemical structure	Ni			
CAS registry number	7440-02-0[a]	373-02-4[a]	15699-18-0[a]	3333-67-3[a]

Table 4-1. Chemical Identity of Nickel and Selected Nickel Compounds

Characteristic	Nickel chloride	Nickel cyanide	Nickel oxide	Nickel nitrate
Synonym(s) and Registered trade name(s)	Nickel (2+) chloride; nickel dichloride; nickel(II) chloride; nickelous chloride[f]	Dicyanonickel; Nickel dicyanide; Nickel (II) cyanide[g]	Bunsenite; CI 77777; Green nickel oxide; mononickel oxide; nickel (II) oxide; nickel(2+) oxide; nickel protoxide[h]	Nickel dinitrate; nickel (II) nitrate; nickel(2+) nitrate; nickelous nitrate; nitric acid, nickel(II) salt; nitric acid, nickel(2+) salt[i]
Chemical formula	$NiCl_2$[a]	C_2N_2Ni[g]	NiO[a]	$Ni(NO_3)_2$[a]
Chemical structure[m]	Cl – Ni – Cl	CN – Ni – CN	Ni – O	
CAS registry number	7718-54-9[a]	557-19-7[g]	1313-99-1[a]	13138-45-9[a]

Characteristic	Nickel subsulfide	Nickel sulfamate	Nickel sulfate
Synonym(s) and Registered trade name(s)	Trinickel disulfide; Heazlewoodite; nickel subsulphide; nickel sulfide; alpha-nickel sulfide (3:2) crystalline; nickel sulphide; nickel tritadisulphide[j]	Nickel bis(sulphamidate); nickel (II) sulfamate; Aeronikl 250; Aeronikl 400; Aeronikl 575; sulfamic acid, nickel(2+) salt (2:1); Nickel aminosulfonate[k]	NCI-C60344; Nickel (II) sulfate; nickelous sulfate; nickel(2+) sulfate; nickel sulphate; sulfuric acid, nickel(2+) salt; sulphuric acid, nickel (II) salt[l]
Chemical formula	Ni_3S_2[a]	$Ni(SO_3NH_2)_2$[k]	$NiSO_4$[a]
Chemical structure	No data		
CAS registry number	12035-72-2[a]	13770-89-3[k]	7786-81-4[a]

CAS = Chemical Abstract Service

[a]Haynes et al. 2015
[b]HSDB 2000f
[c]HSDB 2000e
[d]PubChem 2021e
[e]HSDB 2000d
[f]HSDB 2000c
[g]HSDB 2000b
[h]HSDB 2000a
[i]HSDB 2000i
[j]HSDB 2000g
[k]PubChem 2021a
[l]HSDB 2000h
[m]Chemical structures are from the HSDB page for each compound, except nickel sulfamate and nickel ammonium sulfate which are from PubChem.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Nickle exists in the solid state and is a hard, lustrous, silvery white metal that takes on a high polish (Haynes et al. 2015). Nickel has typical metallic properties; it is malleable, ductile, ferromagnetic and a good conductor of both heat and electricity (Haynes et al. 2015). Nickel forms useful alloys with many metals. It is added to metals to increase their hardness, strength, and corrosion resistance. The most familiar are nickeliferous alloys used in stainless steel and copper nickel alloys used in coinage metal.

Nickel ammonium sulfate, nickel sulfate, nickel chloride, and nickel nitrate usually exist as hexahydrates, while nickel acetate, nickel cyanide, and nickel sulfamate are in the form of a tetrahydrate. Nickel compounds are also solid, and colors include a yellow-brown or a blue-green color.

Metallic nickel is insoluble in water and slightly soluble in dilute acid. Nickel and its compounds are nonvolatile and exist in the atmosphere in particulate form. Table 4-2 lists important physical and chemical properties of nickel and nickel compounds.

Table 4-2. Physical and Chemical Properties of Nickel and Selected Nickel Compounds

Property	Nickel	Nickel acetate	Nickel ammonium sulfate	Nickel carbonate
Molecular weight	58.7[a]	176.78[a]	286.9[a]	118.70[a]
Color	Silvery white[a]	Green[a,c]	Blue-green[a]	Green[a]
Physical state	Solid[a]	Solid[a,c]	Solid[a]	Solid[a]
Melting point	1,455 °C[a]	Decomposes at 250 250 °C[a,c]	No data	Decomposes at 250°C[a]
Boiling point	2,913 °C[a]	16 °C[a,c]	No data	No data
Density:	8.9[a]	1.74 g/cm^3[a,c]	1.92 g/cm^3[a,e]	4.39 g/cm^3[a]
Odor	Odorless[b]	Acetic acid odor[d]	Odorless[f]	No data
Odor threshold: Water Air	 No data No data	 No data No data	 No data No data	 No data No data
Taste threshold	No data	No data	No data	No data
Solubility: Water Organic solvent(s)	 Insoluble in H_2O[a] slightly soluble in dilute acid[a]	 Very soluble in H_2O[a]; 17lb/100 lb water at 68 °F[d] Soluble in ethanol[a]	 Slightly soluble in H_2O[a]; 6.5 g/100g H_2O[a,e]	 0.043 g/100 g H_2O[a] Soluble in dilute acid[a]
Partition coefficient s: Log K_{OW} Log K_{OC}	 No data No data	 No data No data	 No data No data	 No data No data
Vapor pressure	0 mmHg (approximate)[b]	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	Nonflammable[d]	No data	No data
Flashpoint	No data	Nonflammable[d]	No data	No data
Flammability limits	No data	Nonflammable[d]	Nonflammable[f]	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data
Property	Nickel chloride	Nickel cyanide	Nickel oxide	Nickel nitrate
Molecular weight	129.60[a]	110.73[e]	74.69[a]	182.7[a]
Color	Yellow[a]	Yellow-brown[h]	Green[a]	Green[a]
Physical state	Solid[a]	Solid[h]	Solid[a]	Solid[a]
Melting point	1,031 °C[a]	>200 °C[h]	1,957 °C[a]	Decomposes at 56 °C[a,e]
Boiling point	Sublimation point 985 °C[a]	No data	No data	No data
Density	3.51 g/cm^3[a]	2.393 g/cm^3[h]	6.72 g/cm^3[a]	2.05 g/cm^3[a,e]
Odor	Odorless[g]	Weak almond odor[h]	Odorless[i]	No data
Odor threshold:				

Table 4-2. Physical and Chemical Properties of Nickel and Selected Nickel Compounds

Water Air	No data No data	No data No data	No data No data	No data No data
Taste threshold	No data	No data	No data	No data
Solubility: Water Organic solvent(s)	67.5 g/100 g H_2O[a] Soluble in ethanol[a]	Insoluble in H_2O[h] Soluble in aqueous alkali cyanides and other bases[h]	Insoluble in H_2O[a] Soluble in acid[a]	99.2 g/100 g H_2O[a] Soluble in ethanol[a]
Partition coefficient s: Log K_{OW} Log K_{OC}	 No data No data	 No data No data	 No data No data	 No data No data
Vapor Pressure	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	Nonflammable[g]	Nonflammable[h]	No data	No data
Flashpoint	Nonflammable[g]	Nonflammable[h]	No data	No data
Flammability limits	Nonflammable[g]	Nonflammable[h]	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	Mixture of potassium and $NiCl_2$ produces strong explosion on impact[g]	No data	No data	May explode after prolonged exposure to fire or heat[j]
Property	Nickel subsulfide	Nickel sulfamate	Nickel sulfate	
Molecular weight	240.21[a]	250.87[l]	154.76[a]	
Color	Yellow [a]	No data	Greenish-yellow[a]	
Physical state	Solid [a]	Liquid[l]	Solid[a]	
Melting point	789 °C[a]	No data	Decomposes at 840 °C[a]	
Boiling point	No data	No data	No data	
Density	5.87 g/cm^{3}[a]	No data	4.01 g/cm^{3}[a]	
Odor	No data	No data	Odorless	
Odor threshold: Water Air	 No data No data	 No data No data	 No data No data	
Taste threshold	No data	No data	Sweet astringent taste[m]	
Solubility: Water Organic solvent(s)	Insoluble in cold water[k] Soluble in nitric acid[k]	No data	40.4 g/100 g H_2O[a]	
Partition coefficient s: Log K_{OW} Log K_{OC}	 No data No data	 No data No data	 No data No data	

Table 4-2. Physical and Chemical Properties of Nickel and Selected Nickel Compounds

Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	Nonflammable[m]
Flashpoint	No data	No data	Nonflammable[m]
Flammability limits	No data	No data	Nonflammable[m]
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

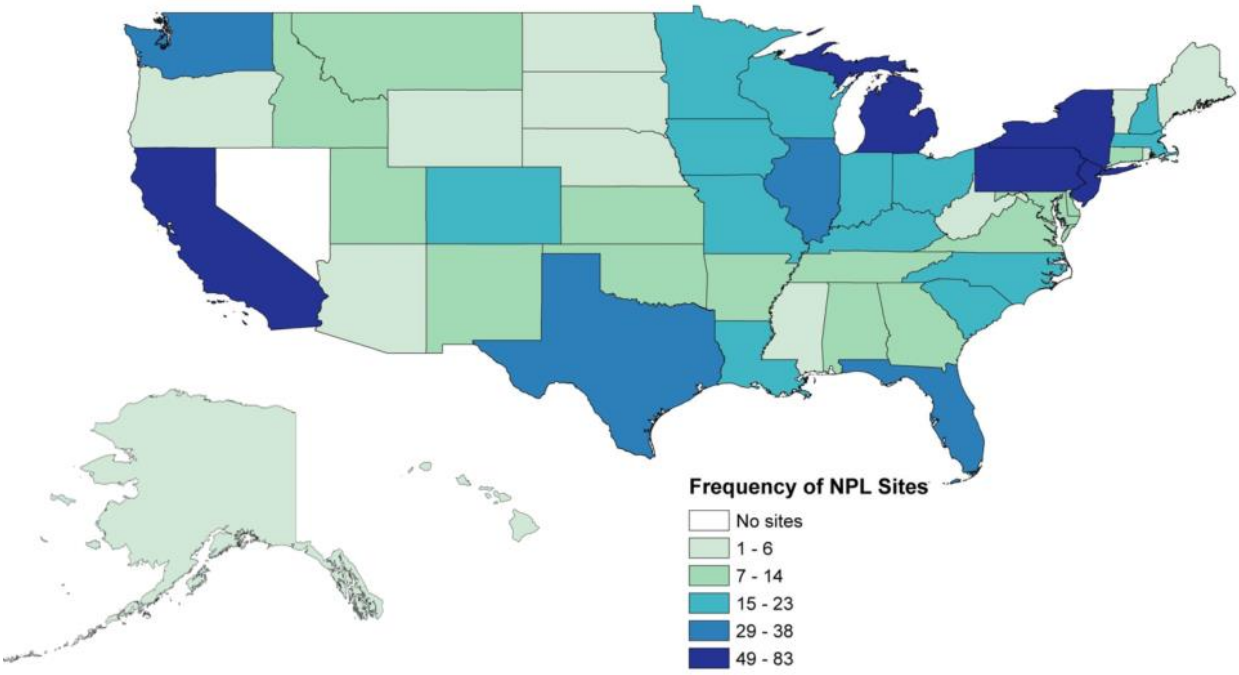
[a]Haynes et al. 2015
[b]NIOSH 2019b
[c]Data are for the tetrahydrate.
[d]PubChem 2021b
[e]Data are for the hexahydrate.
[f]PubChem 2021e
[g]PubChem 2021f
[h]PubChem 2021c
[i]PubChem 2021i
[j]PubChem 2021h
[k]PubChem 2021g
[l]PubChem 2021a
[m]PubChem 2021d

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Nickel and nickel compounds have been identified in at least 867 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites evaluated for nickel and nickel compounds is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 862 are located within the United States, none are in the Virgin Islands, 4 are located in Puerto Rico, and 1 is located in Guam (not shown).

Figure 5-1. Number of NPL Sites with Nickel and Nickel Compound Contamination



Source: ATSDR 2022

- Nickel is primarily used for stainless and alloy steels, nonferrous alloys, superalloys, and electroplating.
- Nickel is released to the atmosphere from natural sources such as windblown soil particles and anthropogenic sources such as oil combustion.
- Nickel is released to the atmosphere as particulate matter or adsorbed to particulate matter. It is dispersed by wind and removed by various processes. Nickel typically accumulates at the surface

of soils due to deposition and is strongly adsorbed by soil. Nickel does not bio-magnify in the food chain. It does accumulate in plants.

- Nickel levels monitored in ambient air are generally less than 0.003 μg/m^3. Nickel naturally occurs in the earth's crust and is present in the soil. Concentrations of nickel in surface water and groundwater in the United States are generally low.
- The general population may be exposed to nickel through inhalation of ambient air and ingestion of food and drinking water. Exposure may also occur from consumer goods, like toys and jewelry.
- Occupational exposure via inhalation and dermal routes occurs in industries that work with nickel and its compounds such as electroplating. Dental technicians may be exposed to nickel in alloys used in the industry, and people who smoke may also be exposed to higher levels of nickel in tobacco products and e-cigarettes.

Nickel and its compounds are naturally present in the Earth's crust and can be found in many minerals. In 2020, nickel in the United States was produced from one mine in Michigan (USGS 2021). The United States imports more nickel than it produces or exports. Nickel is primarily used for stainless and alloy steels, nonferrous alloys and superalloys, and electroplating (USGS 2021). Nickel is also used as an alloy in medical and dental appliances and tools, and for cast iron, chemical uses, and to make U.S. coins.

Since nickel and its compounds are naturally occurring, they are released from natural sources such as windblown dust, volcanic ash, forest fires, meteoric dust, and sea salt spray. Anthropogenic sources of nickel include coal and oil combustion, and waste and sewage incineration (Cempel and Nikel 2006; Pacyna and Pacyna 2001). Most nickel from facilities required to report to the EPA's Toxics Release Inventory (TRI) is released to the soil. Natural sources will also release nickel to the soil, such as weathering of ultramafic rocks (Li et al. 2020b).

Nickel is released to the atmosphere as particulate matter or adsorbed to particulate matter. It is dispersed by wind and removed by gravitational settling, dry deposition, washout by rain, and rainout (Schroeder et al. 1987). Adsorption of nickel onto suspended particles in water is one of the main removal mechanisms of nickel from the water column. Nickel typically accumulates at the surface of soils due to deposition and is strongly adsorbed by soil and accumulates and concentrates in various plant species. Tomatoes are moderate accumulators of nickel (Correia et al. 2018). Nickel does not appear to accumulate in aquatic organisms or bio-magnify in aquatic food webs. Studies on voles and rabbits also do not indicate that nickel is biomagnified in the food chain (Alberici et al. 1989; Dressler et al. 1986).

Nickel is present in the air at concentrations typically below 3 ng/m^3 (EPA 2020a). Nickel concentrations may be higher in urban air and in air near industrial facilities. In New York City, concentrations are known to vary by season, likely due to increased fuel oil burning in the winter for space heating (Hsu et al. 2012a; Peltier and Lippmann 2010b; Rohr et al. 2014b). Indoor air concentrations are lower than outdoor air concentrations but are affected by outdoor sources and may also vary seasonally (Habre et al. 2014; Peltier and Lippmann 2010a; Schachter et al. 2020). Nickel is naturally present in soil and sediment, and in food. According to the FDA's Total Diet Study, the average concentration of nickel in various U.S. foods ranges from 0.0004 to 3.2 mg/kg (FDA 2017a). As shown in Table 5-13, nickel is also present in cigarettes and smokeless tobacco products at concentrations ranging from 1.19 to 16.8 µg/g, and in e-cigarette liquid at concentrations up to 22,600 µg/L.

The general population is primarily exposed to nickel in food and exposed to low levels in ambient air and water. The average daily dietary nickel intake for U.S. diets is 69–162 µg (Institute of Medicine 2001; O'Rourke et al. 1999; Pennington and Jones 1987; Thomas et al. 1999). The general population may also be exposed to nickel present in stainless steel cookware, jewelry, clothing buckles and fasteners, technology, and toys.

Individuals who work in the mining of or the production of nickel and nickel products may be exposed to higher levels of nickel than the general population. Workers in primary nickel production, primary nickel user industries, manufacturing, nickel refining, and electroplating may be exposed to nickel via inhalation or dermal routes. Populations living near these industry sites or near disposal sites may also have high exposures to nickel. Dental technicians are also likely to be exposed to higher levels of nickel than the general population, as are people who smoke cigarettes.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Nickel is the 5th most common element on earth and 24th most abundant element in the earth's crust, accounting for about 3% of the earth's composition (Harasim and Filipek 2015; Iyaka 2011). Nickel is found in the minerals pentlandite, garnierite, millerite, niccolite, and ullmannite and in the ore types sulphide and laterite (Harasim and Filipek 2015). Nickel ores are of two general types: magmatic sulfide ores, which are mined underground, and lateritic hydrous nickel silicates or garnierites, which are surface mined (Duke 1980a; Warner 1984).

The most important nickel sulfide-arsenide deposits are in hydrothermal veins associated with mafic (i.e., rich in magnesium and iron) and ultramafic igneous rock. These ores typically contain 1–3% nickel;

pentlandite $(Ni,Fe)_9S_8$ is the principal ore. Pentlandite often occurs along with the iron mineral pyrrhotite and the copper mineral chalcopyrite, and part of the smelting and refining process separates the copper and iron from the nickel. The ore is concentrated by physical means (i.e., flotation and magnetic separation) after crushing.

The lateritic hydrous nickel silicate ores are formed by the weathering of rocks rich in iron and magnesium in humid tropical areas. The repeated processes of dissolution and precipitation lead to a uniform dispersal of the nickel that is not amenable to concentration by physical means; therefore, these ores are concentrated by chemical means such as leaching. Lateritic ores are less well defined than sulfide ores. The nickel content of lateritic ores is like that of sulfide ore and typically ranges from 1–3% nickel.

Sulfide ores are processed by several pyrometallurgical processes: roasting, smelting, and converting. During these processes, sulfur and iron are removed to yield a sulfur-deficient copper-nickel matte. Especially after roasting and converting, the nickel in the matte may consist primarily of nickel subsulfide. After physical separation of the copper and nickel sulfides, the nickel is refined electrochemically or by carbonyl process. The treatment of the matte depends on the end use of the nickel. Alternatively, the sulfide can be roasted to form a nickel oxide sinter that is used directly in steel production.

Lateritic ore is processed by pyrometallurgical or hydrometallurgical processes. In the pyrometallurgical process, sulfur is generally added to the oxide ore during smelting, usually as gypsum or elemental sulfur, and an iron-nickel matte is produced. The smelting process that does not include adding sulfur produces a ferronickel alloy, containing ≤50% nickel, which can be used directly in steel production. Hydro-metallurgical techniques involve leaching with ammonia or sulfuric acid, after which the nickel is selectively precipitated (Duke 1980b; IARC 1990a; Tien and Howson 1981; Warner 1984). Alloys, such as stainless steels, are produced by melting primary metals and scrap in large arc furnaces and adjusting the carbon content and concentration of alloying metals to the desired levels.

There is an estimated 300 million tons of nickel available in identified land-based resources with at least 0.5% nickel (USGS 2021). Approximately 60% of these resources is in laterites and 40% is in sulfide deposits, but nickel can also be found in manganese crusts and nodules on the ocean floor (USGS 2021). Nickel has also been found in meteorites, with the content ranging from 5 to 50% (Duke 1980a; Mastromatteo 1986). In 2020, all of the 16,000 tons of nickel produced in the United States occurred at the underground Eagle Mine in Michigan (USGS 2021). One company in Missouri recovered nickel from mine tailings, and nickel was also produced as a byproduct of smelting and refining ore in Montana (USGS 2021).

Table 5-1 lists facilities in each state that manufacture, process, or use nickel or nickel compounds, the intended use reported by the facility, and the range of maximum amounts of these substances that are stored on site. In 2019, there were 2,495 reporting facilities that produced, processed, or used nickel and 1,109 that produced, processed, or used nickel compounds in the United States. The data listed in Table 5-1 are derived from the Toxics Chemicals Release Inventory (TRI) (TRI19 2020). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Nickel and Nickel Compounds

State[a]	Number of facilities	Minimum on site in pounds[b]	Maximum on site in pounds[b]	Activities and uses[c]
AK	4	1000	9999999	1, 5, 8, 12, 13, 14
AL	106	0	10000000000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	55	1000	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	35	0	9999999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
CA	142	0	999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	30	0	999999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
CT	62	100	9999999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 14
DC	1	1000	9999	1, 3, 11
DE	7	1000	99999	1, 2, 3, 8, 10, 13, 14
FL	44	100	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
GA	63	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
HI	2	0	99	1, 5
IA	83	100	9999999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	11	1000	999999	1, 5, 7, 8, 11, 12, 13, 14
IL	201	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	217	0	49999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	53	0	9999999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
KY	101	0	49999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	72	0	49999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	42	1000	999999	1, 2, 3, 6, 7, 8, 9, 11, 12, 14
MD	21	100	999999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
ME	11	0	999999	1, 2, 3, 5, 7, 8, 9, 11, 12
MI	177	0	49999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	72	0	9999999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
MO	73	0	9999999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MS	46	1000	9999999	1, 2, 3, 4, 5, 7, 8, 10, 11, 12, 13, 14
MT	10	1000	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NC	87	100	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	10	1000	999999	1, 5, 8, 9, 10, 12, 13, 14
NE	36	0	999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NH	18	100	9999999	2, 3, 4, 7, 8, 9, 11, 14

Table 5-1. Facilities that Produce, Process, or Use Nickel and Nickel Compounds

State[a]	Number of facilities	Minimum on site in pounds[b]	Maximum on site in pounds[b]	Activities and uses[c]
NJ	33	1000	9999999	2, 3, 4, 7, 8, 9, 10, 11, 12, 14
NM	7	100	999999	1, 2, 3, 4, 5, 9, 10, 11, 12, 13, 14
NV	21	0	9999999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
NY	62	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
OH	298	0	49999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	104	0	99999999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
OR	24	1000	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
PA	294	0	499999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	6	1000	999999	1, 3, 5, 6, 7, 8, 11, 12, 14
RI	12	100	9999999	7, 8, 10, 12, 14
SC	81	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	11	1000	99999	8, 14
TN	110	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	289	0	999999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	30	1000	49999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	35	1000	999999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13, 14
VT	4	100	99999	2, 3, 7, 8, 11, 14
WA	36	0	9999999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
WI	220	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	18	100	9999999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
WY	8	1000	9999999	1, 2, 3, 4, 5, 9, 10, 12, 13, 14

[a]Post office state abbreviation used.
[b]Amounts on site reported by facilities in each state,
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI19 2020; Data are from 2019

5.2.2 Import/Export

According to USGS (2021), an estimated 120 metric tons of nickel ore and concentrates, 110,000 metric tons of primary nickel, and 32,000 metric tons of secondary nickel were imported into the United States in 2020. Between 2016 and 2019, annual imports ranged from 3 to 64 metric tons of ores and concentrates, 111,000 to 150,000 metric tons of primary nickel, and 32,300 to 45,100 of secondary nickel (USGS 2021). Between 2016 and 2019, Canada, Norway, Finland, and Russia supplied 42, 10, 9, and 8% of nickel, respectively (USGS 2021). Canada, Mexico, and the United Kingdom supplied 38, 27, and 9%

of nickel-containing scrap, respectively (USGS 2021). The product class with the highest quantity of imports in 2016 was unwrought cathodes, pellets, briquets, and shot at 95,100 metric tons of contained nickel, followed by stainless steel scrap at 19,700 metric tons of contained nickel (McRae 2020).

Nickel exports of ores and concentrates in the United States ranged from 14,700 to 22,400 metric tons between 2016 and 2019; primary nickel exports ranged from 9,780 to 12,800 and secondary nickel exports ranged from 51,100 to 63,700 (USGS 2021). Exports in 2020 are estimated to be 13,000 metric tons of ores and concentrates, 11,00 metric tons of primary nickel, and 34,000 metric tons of secondary nickel (USGS 2021). In 2016, stainless steel scrap was the product class with the most exports at 49,000 metric tons of contained nickel (McRae 2020). Most exports of nickel in 2016 were to Canada (26,300 metric tons) followed by China (11,700 metric tons) and Taiwan (9,630 metric tons) (McRae 2020).

5.2.3 Use

Nickel is useful in many applications due to its resistance to corrosion, strength, and ability to withstand extreme temperatures. In 2016, 126,000 of the 188,000 metric tons of nickel consumed in the United States was for stainless and heat resistant steel (McRae 2020). In 2020 the estimated total apparent consumption of nickel in the U.S. was 200,000 metric tons (USGS 2021). Total apparent consumption ranged from 217,000 to 273,000 between 2016 and 2019 (USGS 2021). The primary uses of nickel in the United States are for stainless and alloy steels, nonferrous alloys and superalloys, and electroplating (USGS 2021). More than 85% of consumption in the U.S. is typically accounted for by stainless and alloy steel and nickel-containing alloys (USGS 2021). Nickel-containing alloys are often used in equipment and parts in chemical plants, petroleum refineries, jet engines, power generation facilities, and offshore installations due to nickel’s ability to withstand corrosion and high temperatures (USGS 2012). Nickel alloys are used in dental appliances and tools (Berniyanti et al. 2020; Hariyani et al. 2015; Kulkami et al. 2016). Nickel alloys are commonly used in medical devices and implants including orthopedic implants and cardiovascular prosthesis (i.e., stents, pacemakers), and in permanent birth control implants (FDA 2020a; Saylor et al. 2018; Tramontana et al. 2020). Some batteries contain nickel, such as nickel-cadmium, nickel-metal hydride, and sodium nickel-chloride batteries which are used in satellites, portable electronic equipment, and electric vehicles (Bukhari et al. 2015; Matheys et al. 2006). Nickel is also used in cast irons, for chemical uses, and as a catalyst (McRae 2020; USGS 2021). Nickel is used in all U.S. coins but the penny (USDT 2018).

5.2.4 Disposal

Little information concerning the disposal of nickel and its compounds is found in the literature. Much of the nickel used in metal products (e.g., stainless steel, nickel plate, various alloys) is recycled, which is

evident from the fact that 50% of nickel consumption in 2020 was derived from secondary, purchased scrap (McRae 2020). According to TRI, 78% of the 7,739,516 pounds of nickel and 89% of the 28,733,807 pounds of nickel compounds disposed of or otherwise released is released to land (TRI19 2020). TRI reported that 180,953,052 pounds of nickel were transferred off-site for waste management and 175,387,142 pounds of nickel compounds were transferred to recycling. Additionally, 44,331,567 pounds of nickel compounds were transferred off-site for waste management and 35,736,253 pounds of nickel compounds were transferred to recycling (TRI19 2020). Steel and other nickel-containing items discarded by households and commercial establishments are generally recycled, landfilled, or incinerated along with normal commercial and municipal trash.

Nickel is removed from electroplating wastes by treatment with hydroxide, lime, and/or sulfide to precipitate the metal (HSDB 2000f). Adsorption with activated carbon, activated alumina, and iron filings is also used for treating nickel-containing waste water (HSDB 2000f).

Nickel and its compounds have been designated as toxic pollutants by EPA pursuant to Section 307(a)(1) of the Federal Water Pollution Control Act (EPA 2003). As such, permits are issued by the states under the National Pollutant Discharge Elimination System (NPDES) for discharges of nickel that meet the applicable requirements (EPA 2010).

5.3 RELEASES TO THE ENVIRONMENT

Table 5-2 and Table 5-3 show the releases of nickel and nickel compounds, respectively, to the air, water, and soil from facilities required to report to the Toxics Release Inventory (TRI). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5. POTENTIAL FOR HUMAN EXPOSURE

Most analytical methods for nickel in environmental samples do not distinguish between compounds of nickel or the nature of its binding to soil and particulate matter. It is generally difficult to determine with certainty what forms of nickel are released from natural and anthropogenic sources, what forms are deposited or occur in environmental samples, and to what forms of nickel people are exposed. The form of nickel has important consequences as far as its transport, transformations, and bioavailability are concerned.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Nickel

	Reported amounts released in pounds per year[b]								
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
IL	160	10,834	28,438	80	1,978,853	5,325	11,613	2,011,918	2,023,530
NE	12	487	22	0	847,229	0	847,608	130	847,738
KS	65	8,422	153	0	639,584	1,383	8,446	641,095	649,541
AZ	22	468	61	0	648,040	164	647,858	875	648,734
WA	24	1,256	831	0	27,975	411,589	1,257	440,395	441,652
ND	218	13,176	3,125	0	113,663	250,994	15,333	365,627	380,960
NH	22	1,069	65	0	235,499	334	1,084	235,883	236,967
AL	67	4,259	9,552	0	38,477	141,650	4,609	189,329	193,938
IN	72	3,229	1,084	0	108,288	65,613	5,375	172,840	178,215
TN	66	6,566	2,689	121	92,045	75,341	10,901	165,861	176,762
CA	101	2,046	7,002	0	149,154	9,567	77,564	90,204	167,768
TX	186	13,366	1,935	69,229	68,184	8,389	103,178	57,927	161,104
CO	17	43	20	0	133,029	0	133,049	42	133,092
MI	51	2,460	74	0	124,700	335	74,988	52,581	127,569
WI	188	6,012	30,177	0	75,142	12,730	6,741	117,320	124,061
OR	211	10,337	2,647	3	74,882	28,244	10,810	105,303	116,113
MT	25	654	2,847	0	108,928	2,847	19,859	95,416	115,275
RI	55	1,258	593	0	55,354	55,998	2,454	110,749	113,203
OK	19	955	380	0	70,627	21,703	53,208	40,458	93,666
ID	140	3,413	2,955	0	73,149	10,249	21,986	67,779	89,766
NM	50	2,910	2,062	0	52,135	14,645	3,278	68,475	71,752
NV	14	48	65	0	10,865	52,867	59	63,786	63,845
UT	14	321	19	0	538	58,136	321	58,693	59,014
HI	7	23	0	0	48,770	3,170	48,757	3,206	51,963
VT	3	0	10	0	1,057	49,381	0	50,448	50,448

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Nickel

	Reported amounts released in pounds per year[b]								
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
MA	114	2,748	2,429	0	22,948	17,922	2,904	43,144	46,048
FL	26	1,468	111	5,464	14,191	22,301	6,942	36,593	43,534
VA	27	568	285	1	41,578	476	2,430	40,478	42,909
NJ	2	44	0	0	39,000	0	39,044	0	39,044
WY	2	26	11	0	31,249	0	31,286	0	31,286
MS	59	25,812	842	0	3,714	36	25,839	4,566	30,405
GA	42	3,255	79	0	25,573	67	24,028	4,945	28,973
KY	32	1,050	3,793	3,559	18,639	1	8,451	18,591	27,042
CT	48	1,817	7,890	0	6,781	9,512	1,861	24,140	26,000
MD	35	513	529	0	12,777	11,673	824	24,668	25,493
MN	28	3,350	2,561	0	12,370	295	5,888	12,689	18,577
AR	36	3,827	605	0	6,482	1,982	3,919	8,976	12,895
WV	5	11,701	536	0	0	427	11,776	887	12,663
OH	76	7,028	44	0	4,875	0	7,049	4,898	11,947
NY	64	3,397	105	0	6,353	1,366	4,800	6,422	11,222
LA	8	274	33	0	1,278	2,760	290	4,055	4,345
AK	1	0	0	0	4,200	0	4,200	0	4,200
IA	42	2,129	42	0	679	238	2,151	937	3,088
PA	6	1	1,671	0	0	61	1	1,733	1,734
DE	3	1	0	0	614	84	1	698	699
ME	9	21	12	0	66	369	21	447	469
NC	5	164	7	0	7	0	164	14	178
MO	1	44	5	0	10	0	54	5	59
SC	11	30	1	0	0	2	30	3	33
PR	4	0	0	0	0	0	0	0	0

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Nickel

	Reported amounts released in pounds per year[b]								
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
Total	2,495	162,882	118,398	78,457	6,029,552	1,350,227	2,294,288	5,445,228	7,739,516

The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI19 2020; Data are from 2019

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Nickel Compounds

		Reported amounts released in pounds per year[b]							
								Total Release	
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
MI	63	8,841	8,104	0	6,236,671	78,729	5,950,271	382,075	6,332,346
UT	16	1,694	616	0	2,734,146	45	2,675,891	60,611	2,736,502
NV	10	18,360	19	0	2,303,896	0	2,284,107	38,168	2,322,275
AK	3	66	8	0	2,000,422	0	2,000,496	0	2,000,496
KY	36	4,445	7,913	0	1,184,746	358,501	377,978	1,177,626	1,555,605
IL	61	19,820	13,003	0	1,118,669	118,575	746,187	523,880	1,270,067
TX	105	21,117	12,526	121,236	914,001	167,073	553,824	682,129	1,235,953
OH	81	20,143	15,207	90,475	956,937	104,377	465,406	721,733	1,187,139
IN	58	8,022	37,849	1,187	967,127	62,805	720,197	356,794	1,076,990
CA	42	3,222	4,141	0	939,371	22,828	823,196	146,366	969,563
AL	39	4,692	3,914	0	847,138	67,638	491,495	431,887	923,382
PA	84	17,742	4,159	24	702,675	66,141	329,517	461,225	790,741
MT	9	1,191	51	0	744,763	94	553,635	192,463	746,098
GA	21	1,367	5,106	0	96,781	545,322	84,186	564,390	648,576
AR	19	785	1,049	0	569,687	5,037	551,056	25,502	576,558
NC	23	3,666	602	0	530,737	877	479,486	56,396	535,882
WV	14	4,285	1,675	0	504,405	10,268	390,995	129,638	520,634
LA	40	19,461	6,141	10,645	341,751	14,422	286,013	106,406	392,419
FL	18	1,925	4,638	46	310,665	27,638	213,469	131,443	344,912
OK	28	1,408	390	5	338,150	11	287,886	52,077	339,963
TN	45	2,414	9,001	0	308,580	14,164	170,979	163,181	334,160
MS	18	6,609	2,687	127,221	54,217	8,981	140,672	59,044	199,715
ID	4	490	52	0	190,149	0	190,395	296	190,691
NJ	11	432	150,615	0	10,874	16,593	626	177,888	178,514
SC	26	2,109	3,354	0	71,913	96,305	12,374	161,307	173,681

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Nickel Compounds

		Reported amounts released in pounds per year[b]							
								Total Release	
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
AZ	13	1,002	10	0	120,131	1,314	118,607	3,851	122,457
WY	6	751	0	0	115,608	3,300	116,359	3,300	119,659
WI	32	733	1,008	2,634	75,048	27,867	2,607	104,683	107,290
CO	13	5,287	208	0	97,154	0	79,508	23,141	102,649
ND	5	1,933	5	20	75,876	5,202	50,038	32,998	83,036
KS	11	821	69	115	31,205	45,490	29,497	48,203	77,700
MN	21	1,379	709	0	41,594	23,603	35,904	31,380	67,284
NE	11	665	306	0	34,581	29,986	18,960	46,578	65,538
NM	5	226	11	7	46,196	15,918	46,439	15,919	62,358
IA	11	966	299	18,000	37,737	0	41,344	15,658	57,002
MO	14	714	162	245	40,507	195	39,759	2,064	41,824
PR	2	119	3	0	34,630	0	119	34,633	34,752
HI	2	14,000	2	0	20,000	0	14,002	20,000	34,002
VA	8	364	9,084	0	20,189	3,123	20,477	12,283	32,760
MA	7	2,029	6,368	0	5,235	17,663	2,029	29,266	31,295
MD	12	736	296	0	26,168	0	1,282	25,918	27,200
NY	12	675	375	0	4,816	20,491	1,664	24,694	26,358
CT	14	3,042	659	0	2,935	19,382	3,271	22,747	26,019
WA	12	2,498	1,308	0	17,141	1,033	4,699	17,281	21,980
OR	5	68	17	0	2,984	0	86	2,983	3,069
DE	4	1,781	396	0	0	573	2,177	573	2,750
ME	3	189	240	0	1,700	3	2,129	3	2,132
RI	6	88	216	0	0	755	88	972	1,060
VT	1	0	0	0	612	0	0	612	612
DC	1	0	12	0	147	0	0	160	160

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Nickel Compounds

		Reported amounts released in pounds per year[b]							
								Total Release	
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
NH	4	0	0	0	0	0	0	0	0
Total	1,109	214,373	314,585	371,861	25,830,665	2,002,324	21,411,382	7,322,425	28,733,807

The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI19 2020; Data are from 2019

5.3.1 Air

Nickel is released to the air from both anthropogenic and geogenic sources. Natural sources of nickel include windblown dust, volcanic ash, forest fires, meteoric dust, and sea salt spray. It is estimated that 30 million kilograms of nickel are emitted to the atmosphere annually from natural sources (Duce et al. 1991; Giusti et al. 1993). Between 30 and 50% of natural emissions are from windblown soil particles from eroded areas (Nieminen et al. 2007). Pacyna and Pacyna (2001) estimate that oil combustion accounts for 90% of anthropogenic emissions. Other anthropogenic sources include the combustion of coal and the incineration of waste and sewage (Cempel and Nikel 2006). Nickel has been measured in the vapor of e-cigarettes (Goniewicz et al. 2014a; Pappas et al. 2020), and this may also contribute to releases to indoor air.

Emissions also occur from industries that produce, process, and use nickel and its compounds. Estimated releases of 162,882 pounds (~74 metric tons) of nickel to the atmosphere from 2,495 domestic manufacturing and processing facilities in 2019 accounted for about 2.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). These releases are summarized in Table 5-2.

Estimated releases of 214,373 pounds (~97 metric tons) of nickel compounds to the atmosphere from 1,109 domestic manufacturing and processing facilities in 2019 accounted for about 0.7% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). These releases are summarized in Table 5-3.

Emissions factors (i.e., kg of nickel emissions per unit consumption or production) have been estimated for various source categories, and these are used by EPA to estimate emissions. Emissions factors from some of these source categories are shown in Table 5-4.

Table 5-4. Nickel Emission Factors from AP-42

Source category	Emission Factor	Reference
Fuel oil combustion	0.0845 lb/10^3 gal	EPA 2010
Anthracite coal combustion	0.026 lb/ton	EPA 1996
Bituminous and subbituminous coal combustion	0.00028 lb/ton	EPA 1998
Natural gas combustion	0.0021 lb/10^6 scf	EPA 1998
Wood residue combustion in boilers	0.000033 lb/MMBtu	EPA 2003
Residential wood stoves		EPA 1996
Conventional	0.000014 lb/ton	
Noncatalytic	0.00002 lb/ton	
Catalytic	0.0000022 lb/ton	
Waste oil combustion		EPA 1996
Small boilers	0.011 lb/10^3 gal	
Space heaters: vaporizing burner	0.05 lb/10^3 gal	

Table 5-4. Nickel Emission Factors from AP-42

Source category	Emission Factor	Reference
Space heaters: atomizing burner	0.16 lb/10^3 gal	
Steel mini-mills	0.0000055 lb/ton	EPA 2009
Electroplating		EPA 1996
Nickel electroplating tank	0.63 grains/ampere-hr	
With wet scrubber	0.0000067 grains/dscf	
Coke production		EPA 2008
Coke oven pushing		
Uncontrolled	0.0000399 lb/ton	
Controlled	0.0000112 lb/ton	
Combustion stacks	0.00000187 lb/ton	
Nonrecovery combustion stacks	0.00058 lb/ton	
Nonrecovery charging		
Uncontrolled	0.0000005 lb/ton	
Controlled	0.00000015 lb/ton	
Sewage sludge incineration		EPA 1995
Uncontrolled	0.016 lb/ton	
Controlled	0.000006 – 0.009 lb/ton	
Refuse combustion[a]		EPA 1996
Modular excess air combustors		
Uncontrolled	0.00393 lb/ton	
Controlled	0.0000258 – 0.00161 lb/ton	
Mass burn and modular excess air combustors		
Uncontrolled	0.00785 lb/ton	
Controlled	0.0000322-0.00027 lb/ton	
Refuse-derived fuel-fired combustors		
Uncontrolled	0.00436 lb/ton	
Controlled	0.0000630 – 0.0181 lb/ton	
Modular starved-air combustors		
Uncontrolled	0.00552 lb/ton	
Controlled	0.00101 lb/ton	

[a]Involves burning of garbage and other nonhazardous solids, also known as municipal solid waste

Residual fuel oil combustion for residential space and water heating is a potential source of nickel releases to air, including indoor air (Habre et al. 2014; Hsu et al. 2012b; Schachter et al. 2020). Huggins et al. (2011) studied emissions from the stacks of eight residual fuel oil burning electric utility steam-generating units in New York, Hawaii, and Florida to determine the nickel species present in particulate matter. Nickel was present predominantly in the form of $NiSO_4 \cdot 6H_2O$, with lesser amounts of nickel oxides (Huggins et al. 2011). Nickel sulfide and nickel subsulfide were present at or below 3% total nickel in the particulate matter samples (Huggins et al. 2011). Nickel concentrations tend to increase with decreasing particle size (Galbreath and Zygarlicke 2004). Other studies found that only 17–22% of nickel emissions from coal-fired power plants were associated with particles of >2 μm, and that the mass medium diameter (MMD) of nickel-containing particles from a plant with pollution control devices was 5.4 μm (Gladney et al. 1978; Lee et al. 1975). In one study, 40% of the nickel in coal fly ash was

adsorbed on the surface of the particles rather than being embedded in the aluminosilicate matrix (Hansen and Fisher 1980). Surface-adsorbed nickel would be more available than embedded nickel.

Nickel emissions from municipal incinerators depend on the nickel content of the refuse and the design and operation of the incinerator. By comparing the nickel content of particles emitted from two municipal incinerators in Washington, DC, with that of atmospheric particulate matter, Greenberg et al. (1978) concluded that refuse incineration is not a major source of nickel in the Washington area. The average nickel concentrations in suspended particles from these incinerators ranged from 170 to 200 ppm. Nickel is not primarily associated with very fine or coarse particles. From 2003 to 2010, the concentration of nickel in stack emissions from 10 municipal waste incinerators in the United Kingdom ranged from 0 to 177.50 µg/m^3 with a median of 6.80 µg/m^3 (Font et al. 2015).

de Foy et al. (2012) performed a detailed study of potential sources of nickel releases to the air in Milwaukee, Wisconsin in 2010. Most estimated emissions of nickel in Milwaukee were from point sources; point sources in Milwaukee and Waukesha counties contributed 2,184 lb/year and regional point sources contributed 105,660 lb/year of the total nickel emissions (117,195 lb/year) in Milwaukee (de Foy et al. 2012). Emissions from Milwaukee ships accounted for 145 lb/year of nickel emissions (de Foy et al. 2012). Local point sources that contributed to nickel emissions in Milwaukee and Waukesha included secondary metal production, primary metal production, fabricated metal products, organic solvent evaporation, electric generation, and metal production contributed the most to nickel emissions (de Foy et al. 2012). Local area sources included commercial marine vessels, industrial area sources, and gasoline highway vehicles (de Foy et al. 2012). The authors of a long-term study of nickel in seven Korean cities between 1998 and 2010 concluded the sources of nickel in urban environments could include non-road sources such as aircraft and maritime shipping ports, but these sources are more likely to affect local concentrations rather than long-term urban concentrations (Kim et al. 2014).

5.3.2 Water

Nickel is a natural constituent of soil and is transported into streams and waterways in runoff either from natural weathering or from disturbed soil. Much of this nickel is associated with particulate matter. Nickel also enters bodies of water through atmospheric deposition.

Emission factors have been estimated for the release of trace metals to water from various source categories and these have been used to estimate inputs of these metals into the aquatic ecosystem. The global anthropogenic input of nickel into the aquatic ecosystem for 1983 is estimated to be between 33 and 194 million kg/year with a median value of 113 million kg/year (Nriagu and Pacyna 1988).

A survey of raw and treated waste water from 20 industrial categories indicated that nickel is commonly found in some waste waters (EPA 1981b). Those industries with mean effluent levels of >1,000 µg/L in raw waste water were inorganic chemicals manufacturing (20,000 µg/L), iron and steel manufacturing (1,700 µg/L), battery manufacturing (6,700 µg/L), coil coating (1,400 µg/L), metal finishing (26,000 µg/L), porcelain enameling (19,000 µg/L), nonferrous metal manufacturing (<91,000 µg/L), and steam electric power plants (95,000 µg/L) (EPA 1981b). Those industries with mean effluent levels >1,000 µg/L in treated waste water were porcelain enameling (14,000 µg/L) and nonferrous metal manufacturing (14,000 µg/L) (EPA 1981b). The maximum levels in treated discharges from these industries were 67,000 and 310,000 µg/L, respectively. In addition, four other industrial categories had maximum concentrations in treated discharges >1,000 µg/L. These were inorganic chemicals manufacturing (1,400 µg/L), iron and steel manufacturing (7,800 µg/L), aluminum forming (20,000 µg/L), and paint and ink formulation (80,000 µg/L).

Domestic waste water is the major anthropogenic source of nickel in waterways (Nriagu and Pacyna 1988). Concentrations of nickel in influents to 203 municipal waste water treatment plants (9,461 observations) ranged from 2 to 111,400 µg/L; the median value was ≈300 µg/L (EPA 1981a). From a study of influent streams of a waste water treatment plant in Stockholm, Sweden, it was determined that the waste streams from households (e.g., drinking water) and businesses (e.g., drinking water, car washes, chemical uses) account for 29% of nickel in influent streams (Sörme and Lagerkvist 2002), which is likely to be comparable to what occurs in the United States. Another 31% of the nickel in influent streams is added at the wastewater treatment plant through the addition of water treatment chemicals. Storm water accounts for between 1 and 5% of the nickel in influent streams. Concentrations in treated effluents were not reported. However, nickel may be removed by chemical precipitation or coagulation treatment in publicly owned treatment works, which reduces nickel releases (EPA 1981a). For example, improvements in sewage treatment facilities have attributed to a reduction in the flux of nickel in waste water effluents into the Hudson River estuary, decreasing from 518 kg/day in 1974 to 43 kg/day in 1997 (Sañudo-Wilhelmy and Gill 1999).

Effluent water generated from mining and smelting operations comes from seepage, runoff from tailing piles, or from utility water used for mine operations. These discharges consist mostly of less-soluble silicates and sulfides and readily settle out. Tailing effluents from sulfidic ores are acidic due to the bacterial generation of sulfuric acid from the sulfidic minerals in the tailings, and very high concentrations of soluble nickel sulfate may be released. Tailing waters from the Onaping and Sudbury areas of Ontario, Canada, have an average nickel content of 42,500 µg/L, a factor of 8,300 greater than that found in river water (Mann et al. 1989). Since there is presently no nickel mining of sulfidic ore in

the United States, nickel-containing wastewater is not generated by this activity. However, past nickel mining may have contributed to nickel entering our waterways and accumulating in sediment. Old tailing piles may contribute to runoff for decades.

In the EPA-sponsored National Urban Runoff Program, in which 86 samples of runoff from 15 cities throughout the United States were analyzed, nickel was found in 48% of runoff samples, at concentrations of 1–182 µg/L (Cole et al. 1984). The geometric mean nickel concentration in runoff water from the cities studied was between 5.8 and 19.1 µg/L. In a more recent study of nickel concentrations in storm runoff water samples taken from different urban source areas, the arithmetic means of the concentrations for dissolved nickel ranged from <1 to 87 µg/L, and from 17 to 55 µg/L for nickel that also included the metal associated with particulates (Pitt et al. 1995).

One potential source of chemical release at waste sites is landfill leachate. In a study that looked at leachate from three municipal landfills in New Brunswick, Canada, the results were conflicting (Cyr et al. 1987). Average nickel concentrations in the three leachates (control) were 28 (45) µg/L, 33 (not detectable) µg/L, and 41 (23) µg/L. Sediment at three sites below the leachate outfalls contained 11.9, 37.4, and 71.2 ppm of nickel (dry weight).

Estimated releases of 118,398 pounds (~54 metric tons) of nickel to surface water from 2,495 domestic manufacturing and processing facilities in 2019 accounted for about 1.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An estimated 40,633 pounds (~18 metric tons) were released to publicly owned treatment works (POTWs) (TRI19 2020). These releases are summarized in Table 5-2.

Estimated releases of 314,585 pounds (~143 metric tons) of nickel compounds to surface water from 1,109 domestic manufacturing and processing facilities in 2019 accounted for about 1.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An estimated 41,382 pounds (~19 metric tons) were released to publicly owned treatment works (POTWs) (TRI19 2020). These releases are summarized in Table 5-3.

5.3.3 Soil

Nickel is naturally present in the earth’s crust, and natural sources/processes will also release nickel to the soil. Ultramafic rocks contain high concentrations of nickel, and weathering results in geogenic releases of nickel to the soil (Li et al. 2020b). The major sources of anthropogenic nickel release to soil are industrial waste materials, lime, fertilizer, and sewage sludge (McIlveen and Negusanti 1994).

Estimated releases of 6.03 million pounds (~2,735 metric tons) of nickel to soils from 2,495 domestic manufacturing and processing facilities in 2019, accounted for about 78% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An additional 78,457 pounds (~36 metric tons), constituting about 1% of the total environmental emissions, were released via underground injection (TRI19 2020). These releases are summarized in Table 5-2.

Estimated releases of 25.8 million pounds (~11,703 metric tons) of nickel compounds to soils from 1,109 domestic manufacturing and processing facilities in 2019, accounted for about 89% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An additional 371,861 pounds (~169 metric tons), constituting about 1.3% of the total environmental emissions, were released via underground injection (TRI19 2020). These releases are summarized in Table 5-3.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Nickel is released into the atmosphere in the form of particulate matter or adsorbed to particulate matter. It is dispersed by wind and removed by gravitational settling (sedimentation), dry deposition (inertial impaction characterized by a deposition velocity), washout by rain (attachment to droplets within clouds), and rainout (scrubbing action below clouds) (Schroeder et al. 1987). The removal rate and distance traveled from the source depends on source characteristics (e.g., stack height), particle size and density, and meteorological conditions.

Gravitational settling governs the removal of large particles (>5 μm), whereas smaller particles are removed by other forms of dry and wet deposition. The partitioning between dry and wet deposition depends on the intensity and duration of precipitation and particle size. The importance of wet deposition relative to dry deposition generally increases with decreasing particle size. Removal of coarse particles may occur in a matter of hours. Small particles within the size range of 0.3–0.5 μm may have an atmospheric half-life as long as 30 days and, therefore, have the potential to be transported over long distances (Schroeder et al. 1987). Evidence for the long-range transport of nickel is provided by the fact that emission sources in North America, Greenland, and Europe are responsible for elevated atmospheric nickel concentrations in the Norwegian Arctic during both the summer and winter (Pacyna and Ottar 1985).

Available studies indicate that nickel is broadly distributed among aerosol size groups. It has been concluded, based on the chemical and physical properties of atmospheric particles, that the concentrations of nickel in large particles (>1 μm diameter) that are commonly associated with particulates derived from

natural sources are less than concentrations in smaller particles (<1 μm diameter) that are typically derived from anthropogenic sources (Giusti et al. 1993; Scudlark et al. 1994; Stoessel and Michaelis 1986). However, experiments in Ontario showed that nickel is associated with relatively large particles, 5.6±2.4 μm (Chan et al. 1986). A 1970 National Air Surveillance Network study of the average nickel size distribution in six American cities indicated that the mass median diameter (MMD) is ≈1.0 μm in all six cities (Lee et al. 1972). Although the sampling procedure used in this study may have underestimated large particles (Davidson 1980), it represents one of the few studies involving the size distribution of nickel aerosols in U.S. cities.

Metal deposition is characterized by large temporal and spatial variability. Estimated nickel deposition rates range from 0.01 to 0.5 kg/hectare/year (1–50 mg/m^2/year) and from 0.1 to 5.95 kg/hectare/year (10–595 mg/m^2/year) in rural and urban areas, respectively (Schroeder et al. 1987). In the Florida Atmospheric Mercury Study (FAMS) conducted during 1993– 1994, bulk deposition rates for nickel varied between 1.700 and 4.130 mg/ m^2/year, depending on local/regional anthropogenic activity (Landing et al. 1995). Wet and dry deposition of particulates emitted from the Claremont Incinerator in Claremont, New Hampshire, were measured within an area between 2 and 15 km from the incinerator. Wet deposition rates varied between 0.50 and 8.87 μg/m^2/day with a mean value of 3.0 μg/ m^2/day and depended on distance from the incinerator and frequency that the wind blew. The mean wet deposition rate of 3.0 μg/ m^2/day was a factor of approximately 19 greater than the mean dry deposition rate of 0.16 μg/ m^2/day, which had been calculated from values ranging from 0.067 to 0.29 μg/ m^2/day (Feng et al. 2000).

Atmospheric deposition of nickel in coastal waters has been reported. Bulk and wet deposition of nickel into Massachusetts Bay was determined to be 7,200 and 3,000 μg/m^2/year (Golomb et al. 1997), respectively, whereas a lower wet deposition rate of 257 μg/ m^2/year was measured for nickel in Chesapeake Bay (Scudlark et al. 1994). Atmospheric input of nickel into the Great Lakes has been estimated to average 160–590 ng/m^2/year (Nriagu et al. 1996). Wet and dry deposition of nickel into the world's oceans is estimated to be 8–11 and 14–17 gigagrams (10^9 grams) per year, respectively (Duce et al. 1991). However, atmospheric deposition is only a minor contributor to the flow of nickel into the oceans and coastal waterways as compared to riverine and fluvial input of nickel. The nickel that is carried into oceans in both dissolved and particulate forms through riverine input is rated at 1,411 gigagrams per year, which is a factor of approximately 50 greater than the sum of the wet and dry deposition of nickel of 22–28 gigagrams per year (Duce et al. 1991). In an example of nickel input into Chesapeake Bay, the fluvial input of nickel of 98,700 kg/year (0.0987 gigagrams/year) is 25 times greater than bulk deposition of nickel from the atmosphere (Scudlark et al. 1994). However, for the Great Lakes

the atmospheric input of nickel accounts for 60–80% of the total anthropogenic input of nickel into Lake Superior, and 20–70% of the total inputs into Lakes Erie and Ontario (Nriagu et al. 1996).

Water. The fate of heavy metals in aquatic systems depends on partitioning between soluble and particulate solid phases. Adsorption, precipitation, coprecipitation, and complexation are processes that affect partitioning. These same processes, which are influenced by pH, redox potential, the ionic strength of the water, the concentration of complexing ions, and the species and concentration of the metal, affect the adsorption of heavy metals to soil (Richter and Theis 1980).

Adsorption of nickel onto suspended particles in water is one of the main removal mechanisms of nickel from the water column. The adsorption of nickel on water-borne particulate matter is in competition with adsorption onto dissolved organic matter, which limits the amount of nickel that can be removed from the water column through the settling of suspended particles (Martino et al. 2003). Much of the nickel released into waterways as runoff is associated with particulate matter; it is transported and settles out in areas of active sedimentation such as the mouth of a river. Additionally, when a river feeds into an estuary, the salinity changes may affect absorptivity due to complexation and competition for binding sites (Bowman et al. 1981). During a 4-month study of Lake Onondaga in Syracuse, New York, 36% of the nickel in the lake was lost to sediment (Young et al. 1982). Seventy-five percent of the nickel load into the lake was soluble and remained in the lake. The soluble nickel is not likely to be as the Ni(II) ion but is expected to exist as a complex. For example, in an analysis of the speciation of nickel in waste water effluents and runoff discharging into San Francisco Bay, it was found that approximately 20% of soluble nickel was complexed to moderately strong complexing agents, such as humic acid and biopolymers from activated sludges (Sedlak et al. 1997). However, a larger proportion of the nickel, 75% in wastewater effluent and 25% in runoff, is found strongly complexed, with stability constants that are similar to those found for synthetic chelating agents such as EDTA, DTPA, and phosphonates. Nickel is strongly adsorbed at mineral surfaces such as oxides and hydrous oxides of iron, manganese, and aluminum (Evans et al. 1995; Rai and Zachara 1984). Such adsorption plays an important role in controlling the concentration of nickel in natural waters.

Sediment and Soil. Nickel typically accumulates at the surface of soils due to deposition (Nriagu et al. 1996). Nickel is strongly adsorbed by soil, although to a lesser degree than other metals such as lead, copper, and zinc (Rai and Zachara 1984). There are many adsorbing species in soil, and many factors affect the extent to which nickel is adsorbed, so the adsorption of nickel by soil is site specific. Soil properties such as texture, bulk density, pH, organic matter, the type and amount of clay minerals, and certain hydroxides, as well as the extent of groundwater flow, influence the retention and release of

metals by soil (Richter and Theis 1980). Hsieh et al. (2019) concluded that nickel favored binding with high molecular weight soil humic substances extracted from agricultural soils.

Amorphous oxides of iron and manganese, and to a lesser extent clay minerals, are the most important adsorbents in soil. In alkaline soils, adsorption may be irreversible (Rai and Zachara 1984), which limits nickel's availability and mobility in these soils. For example, studies of nickel speciation in ferromanganese nodules from loess soils of the Mississippi Basin found higher partitioning of nickel in the soil nodules than in soil clay matrices (Manceau et al. 2003). This is due to the selective sequestration of nickel by finely divided iron and manganese oxides in goethite and lithiophorite minerals present in the soils. Cations such as Ca^{2+} and Mg^{2+} have been reported to reduce adsorption due to competition for binding sites, whereas anions like sulfate reduce adsorption because of complexation. Nickel adsorption depends strongly on metal concentration and pH (Giusti et al. 1993).

Batch equilibrium studies were performed using seven soils and sediments spiked with varying concentrations of nickel to assess the potential mobility of nickel in contaminated subsoil (LaBauve et al. 1988). Nickel was more mobile in soils than lead, cadmium, and zinc. The retention of nickel to two of the test subsoils diminished in the presence of synthetic landfill leachate, possibly because of complex formation. In another study in which batch adsorption experiments were conducted with a mixture of cadmium, cobalt, nickel, and zinc, and 38 different agricultural soils, taken from three depths at 13 sites, the adsorption constants ranged from 10 to 1,000 L/kg (Anderson and Christensen 1988). Soil pH, and to a lesser extent clay content and the amount of hydrous iron and manganese oxides, most influenced nickel sorption.

In 12 New Mexican soils from agricultural areas and potential chemical waste disposal sites, most soils had an extremely high affinity for nickel and once sorbed, nickel was difficult to desorb (Bowman et al. 1981). Sadiq and Enfield (1984b) observed nickel ferrite formation following adsorption. Bowman et al. (1981) found that when nickel levels were >10 ppm, adsorption decreased. High concentrations of chloride decreased adsorption, but not as much as did calcium ions, which indicates that calcium competition for sorbing sites is more important than chloride complexation for reducing adsorption.

The capacity of soil to remove nickel and the nature of the bound nickel were evaluated for 10 mineral and 3 organic soils from the southeastern United States (King 1988). Some soil samples were taken from the subsoil as well as the surface. The amount of sorbed nickel removed from solution ranged from 13 to 95%; the low value was found in subsoil, and the high value was found in soil high in organic matter. When extracted with potassium chloride, 5–87% of the nickel was nonexchangeable. Soil pH was the most important factor affecting sorbed and nonexchangeable nickel in all soil horizons. Both King (1988)

and Tyler and McBride (1982) found much stronger nickel absorptivity in organic soil than in mineral soils. Adsorption was improved by the quality and quantity of humus in the soil (Hargitai 1989). Nickel was enriched in humic and fulvic acids from Lake Ontario sediment (Nriagu and Coker 1980). It was estimated that 5– 10% of the nickel in this sediment was bound to organic matter.

The leachability of nickel from some soils does not necessarily correlate with the total concentration of nickel in the soil. In an extraction study of soils sampled from the mining and smelting regions of Sudbury, Ontario, the percentage of nickel that is most easily extractable (in acetic acid) varied between 12 and 31% of the total nickel content (220–455 mg/kg) among the different sampling sites (Adamo et al. 1996). The remaining nickel was found in less extractable forms: 6–11% was found to be associated with manganese oxides and easily reducible iron oxides, 6–20% either bound to readily oxidizable organics or sulfides, and the remainder (55–73%) was associated with sulfides as separate grains or inclusions, iron oxide phases, carbon particles, and silicate spheroids. Similarly, in soils that are naturally enriched in heavy metals sampled from the Port MacQuaire region in Australia, the amount of nickel that can be easily extracted from soil samples is only a small fraction of the total nickel content (Lottermoser 2002). Extraction of these soils with EDTA or acetic acid yielded leachable nickel which amounted to between <0.1–4.1 and <0.01%, respectively, of the total nickel concentrations in the soil samples. Use of stronger extraction methods, for example hydrochloric acid, yielded only leachable nickel in percentages (0.1–2.4%) equivalent to those found for EDTA. The low amount of acetic acid extractable nickel indicates negligible leaching of this metal from these soils into groundwater and surface waters (Lottermoser 2002).

Amendment of soils with exogenous humic acid reduces mobility of dissolved nickel in soil and also increases the bioavailability of this nickel to plants. Halim et al. (2003) showed that humic acid in soils from nickel-humic acid complexes results in the removal of dissolved and exchangeable nickel from soil water. The extractability of nickel increased with the aging time of the organic material. The increased bioavailability of nickel bound to humic acid is temporary and is thought to occur mainly as the result of preventing nickel from undergoing a transformation into insoluble species in soil.

Nickel (II) is poorly removed from waste water in the activated sludge process because of its high solubility (Stephenson et al. 1987). Only 30–40% of nickel was removed in a pilot activated sludge plant. Nickel removal in activated sludge plants is best correlated with effluent suspended solids (Kempton et al. 1987). Nickel is predominantly soluble in the effluent and is found complexed to humic acid, biopolymers, and other chelating agents (Sedlak et al. 1997).

In order to evaluate the potential of elements to leach from land-spread sewage sludge, Gerritse et al. (1982) studied the adsorption of elements to sandy and sandy loam topsoils from water, salt solutions, and sludge solutions. They used metal levels that occurred in the solution phase of sewage sludge, 100– 1,000 ppb in the case of nickel. The results indicated that nickel is fairly mobile in these soils; the adsorption constants were ≈10–100 in the sandy soil and a factor of ≈10 higher in the sandy loam soil. The presence of sludge increases the mobility of nickel, particularly in sandy and sandy loam soils, which may be because of complexation with dissolved organic compounds (Kaschl et al. 2002) or increased ionic strength (Gerritse et al. 1982). However, land application of nickel-contaminated sludge did not give rise to increased levels of nickel in groundwater (Demirjian et al. 1984). Higher doses and repeated application of nickel-containing sewage sludge did not result in a proportional increase in nickel mobility (Hargitai 1989).

As part of EPA's Nationwide Urban Runoff Program in Fresno, California, the soil water and groundwater at depths ≤26 m beneath five urban runoff retention/recharge basins were monitored during a 2-year study (Nightingale 1987). The results indicated that there were no significant downward movements of nickel with the recharge water.

The presence of iron-(di)sulfides in wetland sediments has been associated with increased mobilization of nickel into groundwater during periods of drought in Holland (Lucassen et al. 2002). Desiccation of sediments leads to oxidation of iron-(di)sulfides and subsequent acidification of the sediments. When the S/(Ca + Mg) ratios in these sediments rise above 2/3, mobilization of heavy metals like nickel occurs, leading to groundwater concentrations of nickel that exceeded the Dutch signal level of 50 ppb for nickel in 50% of the monitoring locations.

Other Media. It has been reported that nickel is not accumulated in significant amounts by aquatic organisms (Birge and Black 1980; Zaroogian and Johnson 1984). The EPA considers bioconcentration factors (BCF) greater than 1,000 to be of concern for bioaccumulation in fish (EPA 2020b). BCF values for nickel calculated in fish and other aquatic organisms are reported to be well below 1,000. The mean bioconcentration factor (BCF) for three carnivorous fish was 36. The concentration of nickel in mussels and oysters treated with 5 μg nickel/kg of seawater for 12 weeks averaged 9.62 and 12.96 μg nickel/g, respectively, on a dry weight basis (Zaroogian and Johnson 1984). When these data are adjusted for controls and the nickel concentration in tissue is expressed on a wet weight basis, the BCF for the mussels and oysters is ≈100. After 2 weeks in flowing seawater, 58 and 38% of the tissue nickel was lost from the mussel and oyster, respectively. No significant loss of nickel occurred during the remainder of the 28-week depuration period. In the work of McGeer et al. (2003), BCFs for nickel in various aquatic

organisms (e.g., algae, arthropods, mollusks, and fish) was assessed based on whole-body metal concentrations and exposure concentrations that were obtained from the literature. For exposure concentrations within the range of 5– 50 μg/L nickel in water, mean BCF values of 106±53 (1 standard deviation) was obtained for all organisms. When the authors also included data for exposure concentrations outside the range of 5–50 μg/L, a BCF value of 157±135 was obtained. The authors noted that the BCF values were inversely correlated with the exposure concentrations, where the highest BCF values were obtained at the lowest exposure concentrations.

There was no evidence that nickel biomagnifies in aquatic food webs, while there is evidence to indicate that the nickel concentrations in organisms decrease with increasing trophic level (McGeer et al. 2003; Suedel et al. 1994). As part of the U.S. Geological Survey National Water-Quality Assessment (NAWQA) Program, there was no statistically significant correlation between nickel concentrations in bed-sediments collected from streams and rivers in both the Northern Rockies Intermontane Basin study area and the New Jersey study area, and nickel concentrations measured in liver and fillet samples taken from fish collected in the same study areas (Long et al. 2000; Maret and Skinner 2000).

Uptake and accumulation of nickel into various plant species is known to occur. For example, Peralta-Videa et al. (2002) report the accumulation of nickel in alfalfa grown from soils contaminated with a mixture of four metals (e.g., Cd(II), Cu(II), Ni(II), and Zn(II)) at a loading of 50 mg/kg for each metal. Concentration ratios of nickel in plant versus soil (based on dry weights) ranged between 22 and 26 over a pH range of 4.5–7.1. As with most plant species that hyperaccumulate metals, the alfalfa actively removes and translocates heavy metals, like nickel, from the roots to the shoots. To assess the accumulation and bioavailability of nickel in rice, wheat, and soil, Li et al. (2020a) analyzed soil samples with elevated nickel concentrations due to natural sources. Li et al. (2020a) found that the mean nickel concentration in soils with naturally elevated levels in China was 85.2±24.2 mg/kg in wheat-growing soil and 75.9±21.1 mg/kg in rice-growing soil. In the crops, the mean nickel concentration was 2.66±1.46 mg/kg in rice and 1.32±0.78 mg/kg in wheat, indicating that nickel bioavailability is higher in rice than in wheat (Li et al. 2020a).

The uptake of nickel into plants is modulated by the acidity (pH) of the soil. Smith (1994) showed that nickel concentrations in rye grass were reduced by a factor of three as the soil pH was raised from 4 to 7. This is thought to be due to a decrease in bioavailability of nickel with increasing pH. The bioavailability of nickel to plants is also affected by soil type. Weng et al. (2004) found that the bioavailability of nickel to oat plants grown in soil rich in organic matter is half that of sandy or clay soils in the pH range of 4.4–7.0. These differences in bioavailability are attributed to a stronger binding of nickel to organic matter than to the silicates and iron hydroxides/oxides in clay and sand under the acidic conditions of the

experiment. Tomato plants appear to take up nickel from soil and store it in its fruit (Roccotiello et al. 2022). Nickel concentrations in the tomato plant increased with nickel soil concentration and levels reach toxicity to the plant, with highest nickel concentrations in the root (Correia et al. 2018). The ratio between the concentration of nickel in the whole tomato plant and nickel in soil was between 0.26 and 0.56, indicating that tomatoes are moderate accumulators of nickel (Correia et al. 2018). BCF values also indicate that nickel does not tend to accumulate in the roots of tomatoes (Correia et al. 2018).

Two studies concerning levels in voles and rabbits living on sludge-amended land did not indicate any accumulation of nickel in these herbivores or in the plants they fed upon (Alberici et al. 1989; Dressler et al. 1986). The lack of significant bioaccumulation of nickel in aquatic organisms, voles, and rabbits indicates that nickel is not biomagnified in the food chain.

5.4.2 Transformation and Degradation

Air. Little is known about the chemical forms and physical and chemical transformations of trace elements in the atmosphere primarily because analytical methods provide information concerning the metal content rather than the specific compounds or species. In the absence of specific information, it is generally assumed that elements of anthropogenic origin, especially those emanating from combustion sources are present as the oxide, and nickel oxide has been identified in industrial emissions (Schroeder et al. 1987). Windblown dust particles may contain nickel in mineral species, which often contain nickel as the sulfide. Increases in the concentration of nickel in Sequoia National Park in California during rain coming from the south correlated with a sharp (7–13 times greater concentration) increase in sulfate (Cahill 1989). Nickel sulfate is a probable atmospheric species resulting from the oxidation of nickel in the presence of sulfur dioxide (Schmidt and Andren 1980).

Water. In natural waters, nickel primarily exists as the hexahydrate. While nickel forms strong, soluble complexes with OH^-, SO_4^{2-}, and HCO_3^-, these species are minor compared with hydrated Ni^{2+} in surface water and groundwater with pH <9 (Rai and Zachara 1984). Under anaerobic conditions, such as may exist in deep groundwater, nickel sulfide would reduce free aqueous nickel concentrations to low levels.

Precipitation can remove soluble nickel from water. In aerobic waters, nickel ferrite is the most stable compound (Rai and Zachara 1984). Nickel may also be removed by coprecipitation with hydrous iron and manganese oxides. Nickel removed by precipitation and coprecipitation settles into the sediment.

Nickel in sediment may be strongly bound or present in a removable form. A metal's form in soil or sediment and its availability are determined by measuring the extractability of the metal with different solvents. Sediment samples from western Lake Ontario were analyzed in regard to the compositional

associations of nickel by a series of sequential extractions (Poulton et al. 1988). The mean nickel percentages in the various fractions were as follows: exchangeable, 0.7±1.4; carbonate, 0.0; iron or manganese oxide-bound, 0.0; organic-bound, 7.4±4.1; and residual, 91.9±4.5. The nickel concentration in 450 uncontaminated estuarine and coastal marine sites in the southeastern United States covaried significantly with the aluminum concentration, suggesting that natural aluminosilicates are the dominant natural metal-bearing phase in some aquatic systems (Windom et al. 1989). In 13 random samples of bottom sediment from the highly industrialized Meuse River in The Netherlands, between 0 and 88% (median 33%) of the nickel was removable at low pH, showing the great variability of nickel to adsorb to sediments (Mouvet and Bourg 1983).

Nickel removed by coprecipitation can be remobilized by microbial action under anaerobic conditions (Francis and Dodge 1990). Remobilization results from enzymatic reductive dissolution of iron with subsequent release of coprecipitated metals. A lowering of pH as a result of enzymatic reactions may indirectly enhance the dissolution of nickel. Experiments using mixed precipitates with goethite (α-FeOOH) indicated that a *Clostridium* species released 55% of the coprecipitated nickel after 40 hours. Similarly, precipitated nickel sulfides in sediment can be mobilized through sulfur oxidation by *Thiobacilli* (Wood 1987). In this case, the oxidized sulfur may produce H_2SO_4 and decrease the pH.

Sediment and Soil. An analysis of the thermodynamic stability models of various nickel minerals and solution species indicates that nickel ferrite is the solid species that will most likely precipitate in soils (Sadiq and Enfield 1984a). Experiments on 21 mineral soils supported its formation in soil suspensions following nickel adsorption (Sadiq and Enfield 1984b). The formation of nickel aluminate, phosphate, or silicate was not significant. Ni^{2+} and $Ni(OH)^{+}$ are major components of the soil solution in alkaline soils. In acid soils, the predominant solution species will probably be Ni^{2+}, $NiSO_4$, and $NiHPO_4$ (Sadiq and Enfield 1984a).

A large percentage of nickel in sewage sludges exists in a form that is easily released from the solid matrix (Rudd et al. 1988). Although the availability of nickel to plants grown in sludge-amended soil is correlated with soil-solution nickel, it is only significantly correlated with diethylenetriaminepentaacetic acid-extractable nickel (Adams and Kissel 1989).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to nickel depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of nickel in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on nickel levels monitored or estimated in the environment,

it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-5 shows the limit of detections typically achieved by analytical analysis in environmental media. Presented in Table 5-6 is a summary of the range of concentrations detected in environmental media at NPL sites.

Table 5-5. Lowest Limit of Detection for Nickel Based on Standards[a]

Media	Detection limit	Reference
Animal tissue	0.05 µg/L	USGS 2006
Water	0.3 µg/L	USGS 1998
Air	0.6 ng/cm^2	EPA 1999
Soil and sediment	0.05 µg/L	USGS 2006
Urine	0.31 µg/L	CDC 2020
Food	6.38 µg/kg	FDA 2020b

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-6. Nickel Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium (units)	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (mg/L)	0.188	0.3	12.4	426	242
Soil (mg/kg)	71.7	90.1	10.2	414	224
Air (mg/m^3)	2.0x10^{-4}	3.52x10^{-3}	156.42	13	10

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Table 5-7 shows the mean ambient air nickel concentrations measured by EPA, state, local, and tribal air pollution control agencies for the Air Quality System (AQS). Mean ambient air concentrations are typically below 0.003 µg/m^3 (3 ng/m^3), with a maximum mean concentration of 0.18 µg/m^3 (180 ng/m^3) in the last 5 years according to this data. Recent studies with data on outdoor air concentrations are presented in Table 5-8. These studies focused on urban areas and major cities. Outdoor air concentrations in urban areas are typically higher than most of the mean concentrations of nickel in ambient air measured for AQS, but below the maximum from the last five years. Very high nickel concentrations may be found near industrial facilities; mean concentrations at the fence lines of four metal recycling facilities in

Houston, Texas were as high as 769.8 ng/m^3, but decreased to levels similar to background concentrations at 600 meters (Han et al. 2020).

Many recent studies of outdoor air focus on New York City. Outdoor air concentrations in New York City range from 3.0 to 24.6 ng/m^3 (Habre et al. 2014; Peltier and Lippmann 2010a; Rohr et al. 2014a; Sax et al. 2006). Nickel concentrations in outdoor air in New York City are higher than in outdoor air in Los Angeles and Seattle (Hsu et al. 2012b; Sax et al. 2006). The source of nickel in outdoor air in New York City is primarily residual fuel oil combustion, which is used for space and water heating (Hsu et al. 2012b; Peltier and Lippmann 2010a; Rohr et al. 2014a). Peliter and Lippman (2010) also attributed nickel air concentrations to shipping ports. Shipping ports and space heating also affect spatial and temporal differences in nickel air concentrations within New York City. Mean nickel concentrations in New York City were 5.5 to 24.6 ng/m^3 in winter samples and 3.0 to 15.1 ng/m^3 in summer samples (Peltier and Lippmann 2010a). In the winter, fuel oil combustion typically increases for heating residential buildings (Schachter et al. 2020).

Table 5-7. Percentile Distribution of Mean Nickel (TSP) Concentrations (µg/m^3) Measured in Ambient Air at Locations Across the United States

		Percentile				
Year	Number of U.S. locations	25th	50th	75th	95th	Maximum
2016	96	0.00081	0.0012	0.0023	0.0099	0.048
2017	88	0.00073	0.0013	0.0029	0.011	0.18
2018	81	0.00097	0.0014	0.0029	0.0096	0.13
2019	74	0.00092	0.0012	0.0027	0.0059	0.077
2020	22	0.00078	0.0014	0.0049	0.13	0.16

TSP = total suspended particles

Source: EPA 2020a (Data current as of 11/24/2020)

Table 5-8. Outdoor Air Monitoring Data for Nickel

Location	Geographic type	Date(s)	Mean concentration	Notes	Reference
Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan, Korea	Urban	1998-2010	3.71-12.6 ng/m^3	Results from 42 monitoring stations. Mean concentration is reported as a range of the lowest mean in Gwangju to the highest mean in Daegu	Kim et al. 2014

Table 5-8. Outdoor Air Monitoring Data for Nickel

Location	Geographic type	Date(s)	Mean concentration	Notes	Reference
Houston, Texas	Urban	September 2015-May 2017	14.24±7.98-769.8±668.6 ng/m^3	63 samples total from four metal recycling facilities. Mean concentration is reported as a range of the concentrations at the facilities.	Han et al. 2020
New York City, New York	Urban	May-February and June-September 2008; November 2008-April 2009; June-October 2009	8.8±7.4 ng/m^3	360 samples	Rohr et al. 2014a
New York, Kings, Queens, and Bronx Counties, New York	Urban	Winter 2007-2008; Summer 2008	3.0±0.6-24.6±21.2 ng/m^3	13 locations were monitored; 157 filters were collected during the winter period and 129 were collected during the summer period.	Peltier and Lippmann 2010a
New York City, New York	Urban	February–May 2008; November 2008–April 2009; June–September 2008; June–October 2009	8.7±6.0 ng/m^3	121 samples	Habre et al. 2014
New York City, New York	Urban	February-April 1999; June-August 1999	21.3 ng/m^3	30% of samples were above the LOD. Median concentration = 19.2 ng/m^3. Maximum concentration = 94.3 ng/m^3.	Sax et al. 2006
Los Angeles, California	Urban	February-March 2000; September-October 2000	6.71 ng/m^3	All samples were above the LOD. Median concentration = 4.78 ng/m^3. Maximum concentration 29.7 ng/m^3.	Sax et al. 2006

Table 5-8. Outdoor Air Monitoring Data for Nickel

Location	Geographic type	Date(s)	Mean concentration	Notes	Reference
United Kingdom	Rural	2010	NR	Median concentration = 0.52 ng/m^3. Minimum = 0.06 ng/m^3. Maximum = 11.2 ng/m^3. 579 samples.	Font et al. 2015

LOD = limit of detection; NR = not reported; SD = standard deviation

The results of studies which monitored indoor air concentrations of nickel are presented in Table 5-9. Many studies have collected data on indoor air pollution to study its effect on children with asthma, especially in New York City. Many studies find that concentrations are higher in winter than in summer (Habre et al. 2014; Peltier and Lippmann 2010a; Schachter et al. 2020). Schachter et al. (2020) found that weekly concentrations of nickel in the summer and winter were 2.79 and 11.72 ng/m^3, respectively. Mean nickel concentrations in New York City were 5.5 to 24.6 ng/m^3 in winter samples and 3.0 to 15.1 ng/m^3 in summer samples (Peltier and Lippmann 2010a). Seasonal differences in indoor air concentrations are likely due to reduced ventilation in the winter and increased fuel oil combustion for residential heating (Hsu et al. 2012b; Schachter et al. 2020). Schachter et al. (2020) concluded that shipping ports were also a source of nickel in indoor air. Habre et al. (2014) concluded that the source of nickel in indoor air was of outdoor origin.

Table 5-9. Indoor Air Monitoring Data for Nickel

Location	Geographic type	Date(s)	Mean concentration	Notes	Reference
New York, New York	Urban	February-May 2008; November 2008-April 2009; June-September 2008; June-October 2009	7.2±10.1 ng/m^3	121 samples	Habre et al. 2014
New York, New York	Urban	February-April 1999; June-August 1999	23.7 ng/m^3	48% of samples were above the LOD. Median concentration = 15.7 ng/m^3. Maximum concentration = 348 ng/m^3.	Sax et al. 2006
Los Angeles, California	Urban	February-March 2000; September-October 2000	6.56 ng/m^3	All samples were above the LOD. Median concentration =	Sax et al. 2006

Table 5-9. Indoor Air Monitoring Data for Nickel

Location	Geographic type	Date(s)	Mean concentration	Notes	Reference
				4.17 ng/m^3. Maximum concentration = 42.5 ng/m^3.	
New York City, New York	Urban	Summers and winters of 2008 and 2009	2.79±1.66-11.72±13.3 ng/m^3	57 samples in summer and 56 samples in winter.	Schachter et al. 2020

LOD = limit of detection

Sax et al. (2006) also measured the mean nickel concentration of personal air of teenagers using a sampler in a backpack. The mean concentration was 28.7±52.8 ng/m^3 for New York City teenagers (Sax et al. 2006). In south central Los Angeles, mean nickel concentrations in personal air (28.7±52.8 ng/m^3) were similar to samples in New York City, even though mean concentrations were lower in indoor and outdoor air samples in Los Angeles (Sax et al. 2006).

5.5.2 Water

Uncontaminated freshwater and seawater typically contain about 300 ng/L of nickel (Barceloux 1999). The concentration in seawater ranges from 100 to 3,000 ng nickel/L. Higher levels of nickel are found in deeper waters than in surface water (Mart et al. 1984; van Geen et al. 1988; Yeats 1988). Water from the surface of the Atlantic Ocean, deep within the Atlantic Ocean (400 m), and the Atlantic shelf contained 1.8 nM (106 ng/L), 2.7 nM (158 ng/L), and 3.5 nM (205 ng/L) nickel, respectively (van Geen et al. 1988). Nickel concentration in surface water was found to decrease by a factor of approximately 2 with increases in percent salinity from approximately 30 to 36% and increased with increasing phosphorus concentration (Yeats 1988). Nickel concentrations in South San Francisco Bay were about 3,000 ng/L, with one-third to one-half of the nickel complexed to a class of strong organic ligands (Donat et al. 1994).

The concentration of nickel in samples reported to the Water Quality Portal (WQP) in which nickel was detected ranged from 0 to 18,200 µg/L in groundwater and 0 to 6,390 µg/L in surface water (WQP 2021). The nickel content of fresh surface water has been reported to average between 15 and 20 µg nickel/L (Grandjean 1984; NAS 1975). The concentration of dissolved nickel in the lower Mississippi River ranged from 1.2 to 1.5 µg/L in seven samples taken at different flow conditions (Shiller and Boyle 1987). In a 1977–1979 study of representative groundwaters and surface waters throughout New Jersey, in which >1,000 wells and 600 surface waters were sampled, the median nickel levels in groundwater and surface water were both 3.0 µg/L. The respective 90 percentile and maximum levels were 11 and 600 µg/L for

groundwater and 10 and 45 µg/L for surface water. The nature of the sites with elevated nickel levels was not indicated. However, groundwater polluted with nickel compounds from a nickel-plating facility contained as high as 2,500 µg/L (IARC 1990b). Nickel concentrations were measured in 30 groundwater samples taken from the South Platte River alluvial aquifer underlying Denver, Colorado (Bruce and McMahon 1996). The samples represented a variety of land-use activities, including commercial, industrial, residential, and agricultural. A median nickel concentration of 3 µg/L was determined, with maximum and minimum concentrations values of 20 and 1 µg/L, respectively.

Nickel concentrations from five stations in Lake Huron in 1980 had median and maximum nickel concentrations of 0.54 and 3.8 µg/L, respectively (Dolan et al. 1986). In a 1982 survey, nickel concentrations in Hamilton Harbor, Lake Ontario, ranged from <1 to 17 µg/L, with a median of 6 µg/L (Poulton 1987). The median nickel concentration from an analogous 1980 survey was 4 µg/L. Suspended sediment in surface samples (0.2 m) at Hamilton Harbor, Lake Ontario, contained 17–23 ppm nickel; samples from a depth of 20 m contained 67–87 ppm, similar to the 66 ppm of nickel found in bottom sediment samples (Poulton 1987). These findings suggest that resuspension of bottom sediment is a major contributor to the suspended sediment at a 20 meter depth. In a 1993 survey of heavy metal concentrations in the Great Lakes, average nickel concentrations of 872 and 752 ng/L were measured in Lakes Erie and Ontario, respectively (Nriagu et al. 1996). Concentrations were highest in near-shore waters due to their proximity to urban centers and polluted river mouths. A decrease in the average concentration of nickel measured in Lake Ontario, from 838 ng/L measured in May/June to a value of 751 ng/L obtained in October, indicates that sedimentation of suspended particles results in a fast depletion of nickel during the summer stratification (Nriagu et al. 1996).

Nickel was not detected in bottled drinking water collected for the FDA’s Total Diet Study between 2006 and 2013 (FDA 2017a). Limited drinking water data is available through the WQP; 28 samples of drinking water analyzed for nickel contained concentrations less than 15 µg/L (WQP 2021). Tap water that is used for drinking purposes generally contains nickel at concentrations ranging from 0.55 to 25 µg/L in the United States (O'Rourke et al. 1999; Thomas et al. 1999). Analysis of data obtained during 1995–1997 from the National Human Exposure Assessment Study (NHEXAS) yielded median concentrations of nickel in tap water (used as drinking water) of 4.3 µg/L (10.6 µg/L, 90% percentile) in the Arizona study and 4.0 µg/L (11 µg/L, 90% percentile) in the EPA Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) study (O'Rourke et al. 1999; Thomas et al. 1999).

In a national survey of raw, treated, and distributed water from 71 municipalities across Canada, the median nickel concentration in both treated and distributed provincial drinking water were ≤0.6–1.3 µg/L for treated water and 1.8 µg/L for distributed water (Méranger et al. 1981). The maximum value was 72.4

µg/L from Sudbury, Ontario. The similarity between median and maximum values for treated and distributed water suggests that nickel is not generally picked up in the distribution system. An exception is Quebec where the maximum nickel concentration increased from 8.3 to 22.0 µg/L between the treated and distributed water. The median nickel levels in the provincial raw water ranged from ≤0.6 to 2.3 µg/L. The maximum levels in tap waters from British Columbia, Prince Edward Island, the Yukon, and Northwest Territories were below the detection limit. The similarity in values between raw and treated water indicates that treatment methods (mainly treatment with lime, alum, or soda ash) did not remove nickel effectively.

Elevated nickel levels may exist in drinking water because of the corrosion of nickel-containing alloys used as valves and other components in the water distribution system as well as from nickel-plated or chromium-nickel-plated faucets. In a Seattle study, mean and maximum nickel levels in standing water were 7.0 and 43 µg/L, respectively, compared with 2.0 and 28 µg/L in running water (Ohanian 1986). A similar result was observed in a comparison of the mean (±1 standard deviation) and 90th percentile concentrations of nickel measured during the NHEXAS EPA Region 5 study in standing tap water (9.2 [±21] and 16 µg/L) and in tap water sampled after the water line had been flushed for 3 minutes (5.3 [±4.4] and 11 µg/L) (Thomas et al. 1999). Even if an individual was to consume only first draw water (containing nickel at the maximum concentration [48 µg/L] obtained from the Seattle study) as their sole source of drinking water, their daily intake of 96 µg/day is still less than the lifetime daily limit of 1,400 µg/day set by EPA, assuming a drinking water equivalent level (DWEL) of 700 µg/L and a consumption of 2 L/day (EPA 2000). Although leaching of metals from pipes generally increases with decreasing pH, none of the nickel studies reported the pH of the tap water. First water drawn from hot water taps plated with nickel may contain concentrations as high as 1–1.3 mg/L (Barceloux 1999).

Nickel concentrations were measured as part of a study of heavy metal content in streams and creeks, located in the Black Hills of South Dakota that are impacted by abandoned or active mining operations (May et al. 2001). The concentrations of nickel in these surface waters generally ranged between 1.3 and 7.6 µg/L and were typically highest near where they received drainage water from abandoned or active mining operations. At one location, nickel concentrations as high as 20 µg/L were determined and were attributed to effluent and entrained streambed tailings from previous mining activities. The concentrations of nickel in water did not correlate with the concentrations of nickel in the underlying sediments.

Several investigators reported the presence of nickel concentrations in rain. The annual mean nickel concentration in precipitation at Lewes, Delaware, was 0.79 µg/L (Barrie et al. 1987). The mean concentration (± standard deviation) of nickel collected from rain showers in southern Ontario, Canada, in 1982 was 0.56±0.07 µg/L (Chan et al. 1986). The mean concentrations in northern and central Ontario

were both 0.61 μg/L, indicating a lack of spatial variability. Sudbury, the site of a large nickel smelter, is in central Ontario. The nickel concentration in rainwater collected near a large municipal incinerator in Claremont, New Hampshire, was measured at a mean value of 0.69 μg/L (Feng et al. 2000). Nickel concentrations in rain collected between 1985 and 1990 from remote regions of the Atlantic Ocean ranged from 0.63 to 1.42 μg/L (Helmers and Schrems 1995). The concentration of nickel in cloud water sampled on the Olympic Peninsula of Washington State in May 1993 was measured at 0.5±0.4 μg/L; the air-equivalent concentration is 0.2 ng/m^3 (Vong et al. 1997).

Nickel in snow from Montreal, Canada, was highly enriched compared with ambient air, ranging from 2 to 300 ppb (Landsberger et al. 1983). The nickel content of snow particulate matter was 100–500 ppb. Nickel concentrations were highly correlated with those of vanadium, suggesting that oil combustion was a source. The nickel concentration in snow collected near a large municipal incinerator in Claremont, New Hampshire, was measured at a mean value of 0.62 μg/L (Feng et al. 2000). Snow samples were collected several hundred kilometers from the nearest known nickel emission sources (e.g., smelters and ore processing facilities) in northwestern Russia, near the Finish and Norwegian borders. Mean nickel concentrations of 0.0019 mg/L (1.9 μg/L) were measured in the snow melt or, based on the volume of accumulated snow, 0.26 mg/m^3 (Kashulin et al. 2001).

5.5.3 Sediment and Soil

Nickel is the 24th most abundant element in the earth's crust, accounting for about 3% of the earth's composition (Iyaka 2011). The level of nickel in soil may vary widely and is dependent on the concentration in parent rocks, soil-forming process, and pollution (Iyaka 2011).

Sediment is an important sink for nickel in water. Nickel content in sediments is expected to be high near sources of nickel emissions. For example, nickel carried into creeks and streams from drainage and runoff originating from active or abandoned mining operations in the Black Hills of South Dakota can lead to increased concentrations of this metal in sediments (May et al. 2001). Soil concentrations are also expected to be higher near emission sources and to decrease further from sources (Koptsik et al. 2003; Rope et al. 1988; Suh et al. 2019; Webber and Shamess 1987). Table 5-10 shows the results of several studies measuring concentrations of nickel in soil and sediment.

Table 5-10. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
Jiangsu Province, China			Li et al. 2020a
Soil		Nickel is naturally elevated in this area	
Wheat-growing		29 samples	

Table 5-10. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
Range	53.3-131 mg/kg		
Mean	85.2±24.2 mg/kg		
Rice-growing		29 samples	
Range	42.6-118 mg/kg		
Mean	75.9±21.1 mg/kg		
U.S. neighborhood near a metal forge			Suh et al. 2019
Baghouse dust		2 samples; source material from alloy grinding operations	
Concentration	45,000 mg/kg		
Surface dust		6 samples from immediately outside of the facility	
Range	299-24,258 mg/kg		
Soil		8 samples from adjacent to and across the street from facility	
Range	32.1-185 mg/kg		
Background soil		5 samples from 1 mile from facility	
Range	19.8-63.8 mg/kg		
Idaho National Engineering Laboratory			Rope et al. 1988
Soil			
Geometric mean	23.4 ppm		
Twin Falls County, Idaho		Represents background concentration for Rope et al. 1988	Rope et al. 1988
Soil			
Geometric mean	18.0 ppm		
Lemhi County, Idaho		Represents background concentration for Rope et al. 1988	Rope et al. 1988
Soil			
Geometric mean	11.8 ppm		
Kola Peninsula, Russia		Samples were taken near a nickel-copper smelter	Koptsik et al. 2003
Soil			
Mean 1 km from facility	30 mmoles/kg (1,760 mg/kg)		
Mean 8 km from facility	9.6 mmoles/kg (560 mg/kg)		
Mean 16 km from facility	6.5 mmoles/kg (380 mg/kg)		
Range 41 km from facility	1.0–1.2 mmoles/kg (59–7 mg/kg)		
Copper Cliff, Sudbury, Ontario		Within 5 km of smelting operations	Adamo et al. 1996
Soil			
Mean	580 mg/kg		
Range	80-2,149 mg/kg		
Falconbridge, Sudbury, Ontario		Within 5 km of smelting operations	Adamo et al. 1996

Table 5-10. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
Soil			
Mean	210 mg/kg		
Range	23-475 mg/kg		
Coniston, Sudbury, Ontario		Within 5 km of smelting operations	Adamo et al. 1996
Soil			
Mean	286 mg/kg		
Range	156-628 mg/kg		
Copper Cliff smelter, Sudbury, Ontario			Taylor and Crowder 1983
Wetland soil/sediment			
Minimum	38 µg/g		
Median	481 µg/g		
Maximum	9,372 µg/g		
Ontario, Canada			Webber and Shamess 1987
Sludge-treated soil		57 samples	
Mean	20 ppm		
Range	6.2 to 34 ppm		
Untreated soil		252 samples	
Mean	16.2 ppm		
Range	4.0–48 ppm		
New Jersey			USGS 2000b
Stream and riverbed-sediment			
Range	18-43 µg/g		
Northern Rockies Intermontane Basin			USGS 2000a
Stream and riverbed-sediment			
Median	18 µg/g		
Range	12-24 µg/g		
United States		541 samples from 20 study areas of the National Water-Quality Assessment Program	Rice 1999
Streambed sediment			
Minimum	6 µg/g		
25th percentile	20 µg/g		
50th percentile	27 µg/g		
75th percentile	36 µg/g		
Maximum	530 µg/g		
Black Hills, South Dakota		Sampling locations were near mining operations	May et al. 2001
Sediment			
Range	10-64 µg/g		
Beaufort Sea, Northern Arctic Alaska			Sweeney and Naidu 1989
Sediment			
Harrison Bay		21 samples	
Range	15-49 µg/g		
Mean	31 µg/g		

Table 5-10. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
Simpson Lagoon-Gwydyr Bay		53 samples	
Range	8.4-59 µg/g		
Mean	25 µg/g		
Stefansson Sound-Prudhoe Bay		27 samples	
Range	15-43 µg/g		
Mean	29 µg/g		
Beaufort Lagoon		17 samples	
Range	11-35 µg/g		
Mean	25 µg/g		
Open Shelf		19 samples	
Range	7.0-49 µg/g		
Mean	25 µg/g		
Lake St. Clair			Rossman 1988
Open water sediment			
Range	8.5-21.1 ppm		
Sand sediment			
Mean	13.6 ppm		
Silty clay sediment			
Mean	17.6 ppm		
Clark Fork-Pend Oreille and Spokane River Basins			USGS 2000a
Sediment			
Range	12-27 ppm		
Casco Bay, Gulf of Maine			Larsen et al. 1983
Sediment			
Mean	17.6 ppm		
Eastern Long Island			Larsen et al. 1983
Sediment			
Mean	7.6 ppm		

5.5.4 Other Media

Table 5-11 and Table 5-12 present the results of the FDA's Total Diet Study from 2006 through 2013 (FDA 2017a) for general food items and for baby food items. For the Total Diet Study, Market Based Surveys were carried out in each of four geographic regions of the United States (north central, west, south, and northeast) by testing foods purchased in each region for different elements, pesticides, and radionuclides. Foods with at least one positive detection of nickel are reported in Table 5-11 and Table 5-12. Products with the highest nickel concentrations are legumes and nuts; cereals containing largely whole wheat, corn, oats, or rice; and chocolate products.

Table 5-11. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Sunflower seeds (shelled), roasted, salted	32	32	3.200	0.996
Oat ring cereal	32	32	2.100	0.573
Granola with raisins	32	32	0.947	0.220
Candy bar, milk chocolate, plain	32	32	0.947	0.244
Syrup, chocolate	32	32	0.927	0.168
Brownie	32	32	0.641	0.191
Chocolate chip cookies	32	31	0.610	0.153
Pinto beans, dry, boiled	32	32	0.600	0.149
Granola bar, with raisins	32	32	0.598	0.125
Lima beans, immature, frozen, boiled	32	32	0.577	0.285
Cake, chocolate with icing	32	32	0.554	0.145
Refried beans, canned	32	32	0.526	0.141
Peanuts, dry roasted, salted	32	32	0.489	0.117
Peanut butter, smooth/creamy	32	31	0.472	0.142
Sandwich cookies w/ crème filling	32	32	0.467	0.184
Pork and beans, canned	32	32	0.423	0.167
Fruit-flavored cereal, presweetened	32	32	0.385	0.148
Candy bar, chocolate, nougat, and nuts	32	32	0.380	0.095
Oatmeal, plain, cooked	32	32	0.355	0.108
Avocado, raw	32	32	0.340	0.393
White beans, dry, boiled	32	32	0.316	0.146
Popcorn, microwave, butter-flavored	32	31	0.293	0.092
Chili con carne with beans, canned	32	31	0.264	0.111
Doughnut, cake-type, any flavor, from donut store	32	31	0.237	0.090
Burrito with beef, beans and cheese, from Mexican carry-out	32	32	0.236	0.063
Peas, green, fresh/frozen, boiled	32	32	0.207	0.089
Corn/tortilla chips	32	32	0.205	0.053
Bread, multigrain (formerly cracked wheat)	32	32	0.204	0.052
Bread, whole wheat	32	32	0.202	0.034
Raisin bran cereal	32	32	0.193	0.071
French fries, fast-food	32	32	0.188	0.062
Soup, bean with bacon/pork, canned, condensed, prepared with water	32	31	0.172	0.099
Crisped rice cereal	32	32	0.166	0.059
Milk shake, chocolate, fast-food	32	32	0.158	0.071
Prune juice, bottled	32	32	0.143	0.042

Table 5-11. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Catfish, pan-cooked with oil	32	10	0.143	0.341
Shredded wheat cereal	32	32	0.139	0.119
Potato chips	32	32	0.134	0.075
Beef, ground, regular, pan-cooked	32	10	0.130	0.310
Chicken nuggets, fast-food	32	31	0.130	0.063
Taco/tostada with beef and cheese, from Mexican carry-out	32	31	0.129	0.059
Tomato salsa, bottled	32	31	0.129	0.050
Lasagna with meat, frozen, heated	32	31	0.129	0.043
Pineapple juice, frozen concentrate, reconstituted	32	32	0.128	0.040
Bread, rye	32	32	0.126	0.031
Green beans, fresh/frozen, boiled	32	32	0.124	0.076
Lettuce, iceberg, raw	32	32	0.120	0.080
Mixed vegetables, frozen, boiled	32	32	0.120	0.073
Asparagus, fresh/frozen, boiled	32	31	0.119	0.080
Biscuits, refrigerated-type, baked	32	32	0.118	0.040
Sweet roll/Danish pastry	32	32	0.113	0.037
Brown gravy, canned or bottled	32	25	0.108	0.097
Tomato sauce, plain, bottled	32	32	0.098	0.033
Pie, pumpkin, fresh/frozen	32	31	0.098	0.06
Pork sausage (link/patty), oven-cooked	32	20	0.097	0.152
Pancakes, frozen, heated	32	32	0.097	0.061
Apricots, canned in heavy/light syrup	32	32	0.097	0.036
Pudding, ready-to-eat, flavor other than chocolate	32	30	0.097	0.081
Corn flakes cereal	32	32	0.096	0.030
Crackers, graham	32	32	0.096	0.024
Tortilla, flour	32	32	0.093	0.023
Mustard, yellow, plain	32	31	0.093	0.026
Squash, winter (Hubbard/acorn), fresh/frozen, boiled	31	30	0.092	0.066
Sweet & sour sauce	32	32	0.090	0.052
Bread, white, enriched	32	32	0.089	0.028
Spaghetti with meat sauce, homemade	32	32	0.087	0.062
Pineapple, canned in juice	32	32	0.086	0.038
Green beans, canned	32	32	0.086	0.054
Pepper, sweet, green, raw	32	26	0.086	0.096

Table 5-11. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Sweet potatoes, canned	32	31	0.086	0.045
Cornbread, homemade	32	31	0.085	0.043
Soup, tomato, canned, condensed, prepared with water	32	31	0.084	0.048
Pizza, cheese and pepperoni, regular crust, from pizza carry-out	32	31	0.084	0.026
English muffin, plain, toasted	32	32	0.082	0.018
Clam chowder, New England, canned, condensed, prepared with whole milk	32	31	0.081	0.066
Breakfast tart/toaster pastry	32	32	0.081	0.051
Milk, chocolate, lowfat, fluid	32	32	0.080	0.023
Crackers, saltine	32	32	0.079	0.017
Black olives	32	31	0.078	0.031
Peach, raw/frozen	32	32	0.077	0.051
Bagel, plain, toasted	32	32	0.076	0.014
Tomato juice, bottled	32	32	0.075	0.038
Fish sticks or patty, frozen, oven-cooked	32	31	0.073	0.025
Cantaloupe, raw/frozen	32	32	0.072	0.043
Liver (beef/calf), pan-cooked with oil	32	9	0.071	0.189
Tomato catsup	32	31	0.071	0.023
Raisins	32	30	0.070	0.035
Pretzels, hard, salted	32	30	0.070	0.030
Crackers, butter-type	32	32	0.069	0.023
Fish sandwich on bun, fast-food	32	32	0.069	0.026
Beef with vegetables in sauce, from Chinese carry-out	32	32	0.068	0.024
Peach, canned in light syrup	32	32	0.067	0.021
Chicken with vegetables in sauce, from Chinese carry-out	32	32	0.067	0.042
Fruit cocktail, canned in light syrup	32	32	0.066	0.013
Fried rice, meatless, from Chinese carry-out	32	32	0.064	0.017
Cake, white with icing (formerly yellow cake)	32	32	0.064	0.048
Lettuce, leaf, raw	32	30	0.062	0.038
Chicken filet (broiled) sandwich on bun, fast-food	32	30	0.061	0.027
Sugar cookies	32	31	0.060	0.034
Watermelon, raw/frozen	32	32	0.059	0.048
Broccoli, fresh/frozen, boiled	32	29	0.059	0.041

Table 5-11. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Potato, baked (with peel)	32	29	0.059	0.040
Soup, chicken noodle, canned, condensed, prepared with water	32	14	0.058	0.100
Stew, beef and vegetable, canned	23	23	0.058	0.033
Meal replacement, liquid RTD, any flavor	32	32	0.055	0.034
Quarter-pound hamburger on bun, fast-food	32	30	0.054	0.024
Quarter-pound cheeseburger on bun, fast-food	32	31	0.054	0.033
Cauliflower, fresh/frozen, boiled	32	29	0.053	0.036
Soup, vegetable beef, canned, condensed, prepared with water	32	32	0.053	0.030
Pear, raw (with peel)	32	28	0.051	0.031
Margarine, regular (not lowfat), salted	32	18	0.050	0.054
Egg, cheese, and ham on English muffin, fast-food	32	30	0.050	0.019
Pork bacon, oven-cooked	32	22	0.049	0.063
Spinach, fresh/frozen, boiled	32	32	0.049	0.031
Potato salad, mayonnaise-type, from grocery/deli	32	25	0.048	0.038
Carrot, fresh, peeled, boiled	32	31	0.047	0.023
Tuna noodle casserole, homemade	32	25	0.046	0.035
Chicken potpie, frozen, heated	32	28	0.045	0.021
Cheese, American, processed	32	23	0.044	0.039
Muffin, blueberry	32	29	0.044	0.018
Okra, fresh/frozen, boiled	32	28	0.044	0.028
Strawberries, raw/frozen	32	31	0.043	0.023
Beef stroganoff with noodles, homemade	32	22	0.043	0.062
Carrot, baby, raw	32	31	0.043	0.019
Rice, white, enriched, cooked	32	31	0.042	0.020
Summer squash, fresh/frozen, boiled	32	25	0.042	0.035
Corn/hominy grits, enriched, cooked	32	30	0.040	0.017
Banana, raw	32	25	0.040	0.033
Collards, fresh/frozen, boiled	32	26	0.040	0.024
Brussels sprouts, fresh/frozen, boiled	32	29	0.039	0.024
Salami, luncheon-meat type (not hard)	32	18	0.036	0.041
Pear, canned in light syrup	32	28	0.036	0.021
Orange (navel/Valencia), raw	32	26	0.035	0.026
Potato, boiled (without peel)	32	26	0.034	0.030

Table 5-11. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Pie, apple, fresh/frozen	32	21	0.034	0.028
Bologna (beef/pork)	32	20	0.033	0.03
Corn, canned	32	27	0.033	0.024
Onion, mature, raw	32	24	0.033	0.026
Wine, dry table, red/white	32	32	0.032	0.009
Tea, decaffeinated, from tea bag	32	30	0.032	0.019
Corn, fresh/frozen, boiled	32	27	0.031	0.020
Beets, canned	32	24	0.031	0.025
Potatoes, mashed, prepared from fresh	32	25	0.029	0.021
Celery, raw	32	29	0.028	0.018
Salmon, steaks/fillets, baked	32	7	0.028	0.067
Noodles, egg, enriched, boiled	32	26	0.027	0.020
Jelly, any flavor	32	23	0.027	0.022
Sour cream dip, any flavor	32	11	0.027	0.067
Lamb chop, pan-cooked with oil	32	11	0.026	0.045
Grapefruit, raw	32	27	0.026	0.027
Spaghetti, enriched, boiled	32	26	0.026	0.016
Coleslaw, mayonnaise-type, from grocery/deli	32	17	0.026	0.028
Soup, Oriental noodles (ramen noodles), prepared with water	32	22	0.025	0.018
Frankfurter (beef/pork), boiled	32	16	0.024	0.028
Tea, from tea bag	32	28	0.023	0.013
Chicken leg, fried, fast-food (with skin)	32	13	0.023	0.034
Turkey breast, oven-roasted	32	15	0.021	0.030
Cucumber, peeled, raw	32	31	0.021	0.010
Salad dressing, Italian, regular	32	9	0.020	0.036
Orange juice, frozen concentrate, reconstituted	32	30	0.019	0.008
Grapefruit juice, bottled	31	26	0.019	0.025
Macaroni and cheese, prepared from box mix	32	17	0.019	0.019
Dill cucumber pickles	32	14	0.019	0.024
Yogurt, lowfat, fruit-flavored	32	18	0.019	0.022
Ham, cured (not canned), baked	32	12	0.018	0.026
Cream of wheat (farina), enriched, cooked	32	18	0.018	0.018
Fruit juice blend (100% juice), canned/bottled	32	28	0.018	0.010
Meatloaf, beef, homemade	32	8	0.017	0.036

Table 5-11. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Grape juice, frozen concentration, reconstituted	32	26	0.017	0.011
Chicken breast, fried, fast-food (with skin)	32	11	0.017	0.031
Chicken thigh, oven-roasted (skin removed)	32	13	0.017	0.023
Salad dressing, creamy/buttermilk type, low-calorie	32	15	0.017	0.019
Cabbage, fresh, boiled	32	24	0.016	0.012
Tomato, raw	32	22	0.016	0.014
Chicken breast, oven-roasted (skin removed)	32	4	0.016	0.054
Mushrooms, raw	32	5	0.016	0.067
Turnip, fresh/frozen, boiled	32	13	0.016	0.022
Cream substitute, non-dairy, liquid/frozen	32	8	0.015	0.036
Pork chop, pan-cooked with oil	32	6	0.014	0.033
Cranberry juice cocktail, canned/bottled	32	23	0.014	0.012
Orange juice, bottled/carton	32	25	0.014	0.008
Grapes (red/green), raw	32	9	0.013	0.038
Syrup, pancake	32	4	0.013	0.052
Candy, hard, any flavor	32	10	0.013	0.021
Butter, regular (not lowfat), salted	32	6	0.012	0.027
Honey	32	10	0.011	0.018
Sherbet, fruit-flavored	32	18	0.010	0.010
Macaroni salad, from grocery/deli	32	7	0.009	0.018
Beef roast, chuck, oven-roasted	32	5	0.008	0.021
Pork roast, loin, oven-roasted	32	5	0.008	0.019
Applesauce, bottled	32	8	0.008	0.015
Apple juice, bottled	32	18	0.008	0.007
Luncheon meat (chicken/turkey)	32	9	0.008	0.013
Coffee, decaffeinated, from ground	32	14	0.008	0.011
Eggs, boiled	32	2	0.006	0.024
Shrimp, boiled	32	4	0.006	0.016
Eggplant, fresh, peeled, boiled	32	7	0.006	0.012
Apple (red), raw (with peel)	32	2	0.005	0.022
Salad dressing, creamy/buttermilk type, regular	32	1	0.005	0.027
Coffee, from ground	32	10	0.004	0.008
Beef steak, loin/sirloin, broiled	32	3	0.004	0.014
Cream, half & half	32	1	0.003	0.017

Table 5-11. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Ice cream, regular (not lowfat), vanilla	32	2	0.003	0.013
Popsicle, fruit-flavored	32	2	0.003	0.012
Cottage cheese, creamed, lowfat (2% milk fat)	32	3	0.003	0.010
Tuna, canned in water, drained	32	2	0.003	0.011
Lemonade, frozen concentrate, reconstituted	32	5	0.002	0.005
Ice cream, light, vanilla	32	3	0.002	0.007
Cheese, Swiss, natural	32	1	0.002	0.011
Cream cheese	32	1	0.002	0.010
Luncheon meat, ham	32	2	0.002	0.009
Cheese, cheddar, natural (sharp/mild)	32	1	0.001	0.006
Eggs, scrambled with oil	32	1	0.001	0.006
Gelatin dessert, any flavor	32	1	0.001	0.004
Carbonated beverage, cola, regular	32	3	0.001	0.004
Fruit drink, from powder	32	1	0.001	0.008
Beer	32	2	0.001	0.003
Sour cream	32	1	0.001	0.007
Fruit drink (10% juice), canned or bottled	32	3	0.001	0.004
Olive oil	32	1	0.001	0.008
Vegetable oil	32	1	0.001	0.007
Milk, skim, fluid	32	1	0.0004	0.002

RTD = ready-to-drink; TDS = Total Diet Study
Source: FDA 2017a

Table 5-12. Nickel Detections in Baby Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Cereal, oatmeal, dry, prepared with water	32	32	0.419	0.089
Teething biscuits	31	31	0.178	0.119
Peaches	32	32	0.159	0.074
Squash	32	32	0.151	0.067
Green beans	32	32	0.138	0.050
Peas	32	32	0.136	0.071
Vegetables and beef	32	31	0.135	0.048

Table 5-12. Nickel Detections in Baby Food from the U.S. Food and Drug Administration (FDA) Total Diet Study, 2006-2013

TDS Food Name	Number of analyses	Number of detects	Mean (mg/kg)	Standard deviation (mg/kg)
Chicken noodle dinner	32	32	0.131	0.051
Chicken and broth/gravy	32	30	0.124	0.154
Pears	32	32	0.119	0.032
Vegetables and chicken	32	31	0.118	0.056
Sweet potatoes	32	31	0.117	0.064
Cereal, rice with apples, dry, prepared with water	13	13	0.094	0.029
Mixed vegetables	32	32	0.086	0.037
Turkey and rice	32	30	0.081	0.053
Carrots	32	30	0.078	0.063
Macaroni, tomato, and beef	32	32	0.069	0.027
Vegetables and ham	4	4	0.068	0.017
Fruit dessert/pudding	22	22	0.061	0.024
Bananas	32	32	0.056	0.018
Cereal, rice, dry, prepared with water	32	27	0.053	0.036
Infant formula, soy-based, RTF	32	32	0.027	0.004
Custard/pudding	23	15	0.025	0.025
Turkey and broth/gravy	32	19	0.024	0.029
Beef and broth/gravy	32	15	0.023	0.046
Lamb and broth/gravy	17	6	0.019	0.033
Applesauce	32	9	0.015	0.037
Veal and broth/gravy	17	5	0.010	0.017
Juice, apple	32	15	0.008	0.009
Infant formula, milk-based, low iron, RTF	10	2	0.004	0.008
Infant formula, milk-based, iron fortified RTF (formerly high iron)	32	6	0.002	0.005

RTF = ready-to-feed; TDS = Total Diet Study
Source: FDA 2017a

Cabrera-Vique et al. (2011) analyzed 170 samples of food from 43 convenience stores and fast food restaurants in Spain. Nickel concentrations ranged from 18.5 to 95.0 ng/g, and the highest concentrations were in egg-based food, pork-based foods, and sauces (Cabrera-Vique et al. 2011). Foods that contained spices and herbs, whole cereals, dry fruits, cheese, and mushrooms tended to have higher nickel concentrations (Cabrera-Vique et al. 2011).

Many studies have measured nickel levels in cigarettes, smokeless tobacco products, and e-cigarettes. These studies are shown in Table 5-13. According to these studies, the mean concentration of nickel ranges from 2.1 to 3.9 µg/g in traditional cigarettes, 1.19 to 16.8 µg/g in smokeless tobacco products, and below detection to 22,600 µg/L in e-cigarette liquid. The age of e-cigarette devices may affect the metal concentrations in the liquid (Gray et al. 2019).

Table 5-13. Concentrations of Nickel in Cigarettes, Electronic Cigarettes, and Smokeless Tobacco Products

Product	Concentration	Notes	Source
Cigarettes			
	2.1±0.1 to 3.9±0.5 µg/g	Range of means of 50 cigarette brands purchased in Atlanta, GA in 2011.	Fresquez et al. 2013
	2.21±0.54 µg/g	Mean of cigarettes supplied by participants in the International Tobacco Control United States Survey. Range of samples was 0.60-4.40 ug/g.	Caruso et al. 2013
Smokeless tobacco			
Moist snuff	2.28±0.36 µg/g	Mean 17 brands purchased in Atlanta, Georgia. Means of each brand ranged from 1.39±0.11-2.73±0.06 µg/g.	Pappas et al. 2008
Moist snuff	8.03±0.38 to 13.5±0.61 µg/g	Range of means of 23 brands purchased in Pakistan.	Arain et al. 2015
Iqmik tobacco[a]	2.32±1.63 µg/g	Mean of 17 samples.	Pappas et al. 2008
Dokha	25.58±2.50 µg/g	Mean of 13 products from stores in the UAE. Mean of each product ranged from 17.5±2.5-35±2.5 µg/g.	Mohammad et al. 2019
Shisha	27.67±5.31 µg/g	Mean of 3 products from stores in the UAE. Mean of each product ranged 20±3.33-36.6±7.4 µg/g.	Mohammad et al. 2019
Mainpuri	10.6±0.34 to 16.8±0.46 µg/g	Range of means of 12 brands purchased in Pakistan.	Arain et al. 2013; Arain et al. 2015
Gutkha	1.19±0.13 to 2.43±0.17 µg/g	Range of means 11 brands purchased in Pakistan.	Arain et al. 2015
Electronic cigarettes			
Liquid	<LRL[b]-4.04 µg/g	Range of means of liquids from refill bottles, pods, cartridges, and single-use devices from vendors in Atlanta, Georgia or online.	Gray et al. 2019
Liquid	58.7±22.4 to 22,600±24,400 µg/L	Range of means of 5 commercial brands in the U.S. Range across the 48 samples was 13.7-72,700 µg/L. Medians for each brand ranged from 58.1-15,400 µg/L.	Hess et al. 2017

Table 5-13. Concentrations of Nickel in Cigarettes, Electronic Cigarettes, and Smokeless Tobacco Products

Product	Concentration	Notes	Source
Aerosols	490–190,000 nickel-containing particles per 10 puffs	5 brands were studied. 2 brands were not able to give accurate particle counts. Mean particle size ranged from 55±17-138±23.	Pappas et al. 2021
Vapor	0.11±0.06 to 0.29±0.08 µg per cigarette (150 puffs)	Range of means of 11 popular brands in Poland and 1 in Great Britain purchased online.	Goniewicz et al. 2014b

[a]*Iqmik* is a smokeless tobacco product that is popular among Alaska Natives.
[b]LRL = 0.032 µg/g
LRL = lowest reportable level; UAE = United Arab Emirates

In a comprehensive survey of heavy metals in sewage sludge, 31 sludges from 23 American cities were analyzed by electrothermal atomic absorption spectroscopy (AAS) (Mumma et al. 1984). The nickel concentration in the sludges ranged from 29.0 to 800 ppm (dry weight) and had a median value of 195 ppm. The highest concentration of nickel in sludge was in Detroit, Michigan. For comparison, the concentration of nickel in cow manure was 28.0 ppm. In another study of heavy metal in sludges generated at waste water treatment plants in 16 large U.S. cities, nickel concentrations (dry weight) were found to range from 18 to 186 ppm, with a median value of 66.8 ppm (Gutenmann et al. 1994).

Nickel in fish and shellfish caught in Alaska ranged from non-detects to 0.85 mg/kg wet weight (Alaska Department of Environmental Conservation 2021). Mean concentrations were up to 0.71 mg/kg wet weight in marine fish, 0.64 mg/kg wet weight in salmonids, 0.69 mg/kg wet weight in marine forage fish, 0.494 mg/kg wet weight in marine invertebrates, and 0.85 mg/kg wet weight in freshwater fish (Alaska Department of Environmental Conservation 2021).

Nickel was measured in cement dust from the United States at an average concentration of 47.45 ± 3.21 µg/g (Ogunbileje et al. 2013).

5.6 GENERAL POPULATION EXPOSURE

Nickel occurs naturally in the Earth’s crust, and the general population will be exposed to low levels of nickel in ambient air and water.

Table 5-14 presents the geometric mean and selected percentiles of urinary nickel in the United States population from the 2017-2018 cycle of the NHANES. In the total population, the geometric mean concentration of urinary nickel is 1.11 µg/L.

Table 5-14. Geometric Mean and Selected Percentiles of Urinary Nickel (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2020)

			Selected percentiles				
	Survey years	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total	2017-2018	1.11 (1.03−1.20)	1.16	1.95	3.03	4.23	2791
Age group							
12-19 years	2017-2018	1.30 (1.20−1.40)	1.30	2.30	3.57	4.17	362
20-59 years	2017-2018	0.99 (0.90−1.10)	1.03	1.69	2.67	3.88	1037
60 years and older	2017-2018	1.18 (1.05−1.31)	1.22	2.00	2.98	4.34	665
Sex							
Females	2017-2018	1.14 (1.04−1.25)	1.19	1.89	3.00	4.31	1376
Males	2017-2018	1.09 (0.97−1.22)	1.12	2.00	3.08	4.15	1415
Race/ethnicity							
Mexican American	2017-2018	1.15 (1.05−1.26)	1.17	2.08	3.06	3.85	434
Other Hispanic	2017-2018	1.09 (0.97−1.22)	1.10	1.92	2.84	3.98	241
Non-Hispanic White	2017-2018	1.07 (0.95−1.20)	1.09	1.76	2.98	4.18	908
Non-Hispanic Black	2017-2018	1.34 (1.26−1.43)	1.37	2.22	3.44	4.64	637
Other race	2017-2018	1.12 (1.00−1.26)	1.21	2.16	3.30	4.12	571

Since nickel is present in many foods, the general population is expected to be exposed to nickel via consumption of common food products; measurements of nickel in U.S. foods are available (see Table 5-11). The Tolerable Upper Intake Level for nickel by life stage group is shown in Table 5-15.

Table 5-15. Tolerable Upper Intake Levels for Nickel

Life Stage Group	UL (mg/day)
0 – 12 months	ND[a]
1 – 3 years	0.2
4 – 8 years	0.3
9 – 13 years	0.6
14 – 18 years	1.0
19 years and older	1.0
Pregnant females, 14 – 18 years	1.0
Pregnant females, 19-50 years	1.0
Lactating females, 14 – 18 years	1.0
Lactating females, 19-50 years	1.0

[a]Data are insufficient to determine a UL.
ND = not determined; UL = Tolerable Upper Intake Level
Source: Institute of Medicine 2001

Using data for the 1991 to 1997 Total Diet Study and the 1988 to 1994 NHANES, the Institute of Medicine (2001) estimates that the nickel intake from food for the general population is less than 0.5 mg/day and supplements provide 9.6 to 15 µg/day. Based on several older dietary studies, the average daily dietary intake of nickel in food ranges between 69 and 162 µg/day (Institute of Medicine 2001; O'Rourke et al. 1999; Pennington and Jones 1987; Thomas et al. 1999). In one total dietary study (Institute of Medicine 2001), the mean daily dietary intake of nickel ranged from 101 to 162 µg/day for individuals >18 years of age with males ranging from 136 to 140 µg/day and females ranging from 107 to 109 µg/day. Pregnant females averaged a daily dietary intake of 121 µg/day, whereas lactating females averaged 162 µg/day. However, recent studies quantifying the daily intake of nickel in the U.S. from food are lacking.

Some studies have assessed the dietary intake of nickel outside of the U.S. The mean concentration of nickel measured in cucumbers and bell peppers in Iran was 0.18 and 0.08 µg/g, respectively (Khoshgoftarmanesh et al. 2009). The estimated total dietary intake from these two foods is 0.06 to 0.17 ug/kg for children, 0.07-0.24 on average, and 0.03 to 0.19 for adults over 55 years of age (Khoshgoftarmanesh et al. 2009). The nickel concentrations in these foods from Iran are similar to those for cucumbers (0.21 mg/kg) and raw sweet green peppers (0.086 mg/kg) in the U.S. Total Diet Study (FDA 2017a). Thus, the daily nickel intake in the U.S. from cucumbers and bell peppers may be comparable. The concentration of nickel in drinks (48.4 to 319 µg/kg), legumes (149 to 744 µg/kg), breakfast cereals (413 to 485 µg/kg), soy based foods (281 to 2,389 µg/kg), dried fruits (184 to 1,085 µg/kg), nuts (1,061 to 2,649 µg/kg), and chocolate (4,114 to 4,785 µg/kg) was measured in Belgium (Babaahmadifooladi et al. 2021). Based on these concentrations, the mean daily exposure to nickel through the consumption of different foods ranges from 0.31 to 4.70 µg/kg bw/day in individuals aged 3 to 9 years, 0.13 to 2.00 in individuals aged 10 to 17 years µg/kg bw/day, and 0.09 to 1.20 µg/kg bw/day in individuals aged 18 to 64 years (Babaahmadifooladi et al. 2021). The exposure decreases when considering the bioaccessible fraction and dialyzable fraction (Babaahmadifooladi et al. 2021). Li et al. (2020a) estimated that the daily intake of nickel from wheat and soil grown in soils with naturally elevated nickel concentrations in China was 12.2±8.41 µg/kg bw/day for rice and 0.84±0.40 µg/kg bw/day for wheat. A study of exposure to nickel via food consumption in Greece found that median hair nickel concentrations were significantly higher in females (0.08 µg/g) than in males (less than 0.05 µg/g) (Sazakli and Leotsinidis 2017). Foods that affected hair nickel levels were meat, yogurt, fast food, rice and pasta, coffee, and pre-treated meat (Sazakli and Leotsinidis 2017).

There is limited evidence that stainless steel pots and utensils may release nickel into acid solution (IARC 1990b). Six stainless steel pots of different origins were tested to see whether they would release nickel

by boiling 350 mL of 5% acetic acid in them for 5 minutes (Kuligowski and Halperin 1992). The resulting concentrations of nickel ranged from 0.01 to 0.21 ppm. Cooking acidic fruits in new stainless steel pans resulted in an increase of nickel that was about one-fifth the average daily nickel intake (Flint and Packirisamy 1995). Further use of the pans did not result in any release of nickel into the food. The use of nickel-containing catalysts in the hydrogenation of food fats may contribute to elevated nickel levels in food (Mastromatteo 1986). Grain milling may also lead to higher nickel levels (IARC 1990b). The results from a study that attempted to identify the influence of the container on the trace metal content of preserved pork products showed no clear evidence that the metal container contributed to the metal content of the food (Brito et al. 1990). The nickel concentration was highest in products in China and glass containers, rather than those in metal and plastic containers. One study found that nickel was released into food from 18/10 (grade 316) stainless steel pots while cooking (Guarneri et al. 2017). The amount of nickel released was higher in unused pots than used pots, increased with cooking time, and varied by manufacturer (Guarneri et al. 2017). This indicates that while the general population is expected to be exposed to nickel in food, exposure may increase if an individual uses stainless steel cookware.

People may also be exposed to nickel in jewelry. In a study of earrings in Germany, 16% of piercing posts released nickel at a rate exceeding 0.35 μg/cm^2/week, while 5.9% of clasp parts and 4% of decorative parts released at least 0.88 μg/cm^2/week (Uter and Wolter 2018). Thyssen and Maibach (2008) tested 277 earrings bought from local artists, tourist stores, and chain stores in San Francisco. Eighty-five earrings had a positive dimethylglyoxime spot test, which indicates nickel release (Thyssen and Maibach 2008). Positive reactions were identified in 69% of earrings from local artists, 42.9% of earrings from tourist stores, 24.1% of earrings from chain stores targeting girls and young women, and 1.7% of chain stores targeting adult women (Thyssen and Maibach 2008). Hamann et al. (2015) further analyzed the samples from the Thyssen and Maibach (2008) study. The concentration of nickel in inexpensive earrings and fashion jewelry in the U.S. was less than 0.5 to 65%, with a median of 18%. After being immersed in artificial sweat for a week, nickel release was detected in 79 of the 96 samples at a rate ranging from 0.01 to 598 μg/cm^2/week (Hamann et al. 2015).

Nickel is a common allergen for children in the U.S., who may be exposed to nickel in jewelry, clothing buckles and fasteners, and technology (Tuchman et al. 2015). Jensen et al. (2014) describes children's toys as another potential source of nickel exposure. To evaluate nickel release from children's toys, Jensen et al. (2014) purchased 63 toys from toy and thrift shops in the U.S. and an online retailer and 149 toys from 8 toy stores in Denmark. Of the toys in the U.S., 50.8% tested positive for nickel release with a DMG test compared to 27.5% of the toys from Denmark (Jensen et al. 2014). Other sources of nickel exposure in children are food consumption and accidental ingestion of soil containing nickel. Nickel

concentrations in baby food in the U.S. range from 0.002 to 0.149 mg/kg (FDA 2017a). In Portugal, where samples of commercial premade baby foods contained nickel at concentrations up to 225.7 µg/kg, the average estimated daily intake of nickel in these foods is 1.12 µg/kg bw for 6 month old children, 2.76 µg/kg bw for 1 year old children, and 3.13 µg/kg bw for 2 year old children (Pereira et al. 2020). Wittsiepe et al. (2009) estimated that the daily dietary intake rate for 4 to 7-year old children in Germany was 12 to 560 µg/day based on concentrations in food samples, or 35 to 1050 µg/day based on dietary records; both estimates were higher than recommendations. Children living in urban areas who consumed food from family gardens or local food and local animal products were exposed to higher nickel levels in food than children who ate food primarily from supermarkets (Wittsiepe et al. 2009). It is possible that children who play outside may be exposed to nickel through incidental soil ingestion. Li et al. (2020a) found that nickel intake from soil ingestion from soils with elevated nickel concentrations is negligible. Through this pathway, intake was estimated to be 0.02±0.01 µg/kg bw/day (Li et al. 2020a).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals who work in the mining of nickel or the production of nickel and nickel products may be exposed to higher levels of nickel than the general population. Several studies have assessed exposures in industries by measuring dermal exposures, occupational air concentrations, and serum or blood concentrations in exposed groups. Hughson et al. (2010) measured dermal and inhalable nickel exposure in workers in primary nickel production and primary nickel user industries, including workers involved in front-end refinery processes, electrowinning/electrolysis, packing solid nickel metal products, packing nickel compounds, packing nickel metal powders, powder metallurgy, and stainless-steel production; these workers had inconsistent use of personal protective equipment. The highest mean total dermal exposures were found on the face of individuals packing nickel powder (15.16 µg/cm^2) (Hughson et al. 2010). Those packing nickel powder also had the highest exposures on the hands and forearms at a mean total nickel exposure of 6.20 µg/cm^2. Mean inhalable total nickel exposures were: 0.13 mg/m^3 (front-end refinery), 0.04 mg/m^3 (electro-winning/electrolysis), 0.08 mg/m^3 (packing nickel metal products), 0.02 mg/m^3 (packing nickel compounds), 0.77 mg/m^3 (packing nickel powders), 0.05 mg/m^3 (powder metallurgy), and 0.03 mg/m^3 (stainless steel production) (Hughson et al. 2010). Julander et al. (2010) studied skin deposition in 24 workers who worked in the development and manufacturing of gas turbines and space propulsion structures; study participants were tasked with sharpening tools, producing combustion structures, and the thermal application of metal-containing powders. Nickel could be found on all skin surfaces of the forehead and hands. The department with the highest nickel exposure was the thermal applications department, in which the highest level detected was 15 µg/cm^2/hour on the index and

middle fingers (Julander et al. 2010). The authors concluded that the exposures to nickel likely resulted from direct skin contact with items rather than from airborne dust deposition.

Vuskovic et al. (2013) assessed nickel exposure in nickel refinery workers in Jinchang, residents of Jinchang, and residents of Zhangye. Urinary nickel levels were significantly higher in refinery works (8.43±3.22 µg/L) than in Jinchang residents (6.55±3.51 µg/L) or Zhangye residents (6.83±3.53 µg/L) (Vuskovic et al. 2013). A study of electroplating workers in Egypt showed that serum nickel concentrations in exposed workers were 12.30 µg/L and significantly higher than the serum concentration of 0.40 µg/L in non-occupationally exposed controls (El Safty et al. 2018).

Since nickel is used in dental applications, dental technicians are expected to have higher nickel exposures than the general population. In a study of metal release from dental tools and alloys immersed in artificial sweat for a week, nickel was released from dental tools in the range of 0.0051 to 10 µg/cm^2/week and from dental alloys in the range of 0.0046 to 0.024 µg/cm^2/week (Kettelarij et al. 2014). A study of dental technicians in Sweden compared dental technicians exposed to cobalt-chrome via work tasks, such as preparing prostheses and metal constructions for dental crowns, to non-exposed technicians aiming to quantify exposure to nickel, cobalt, and chromium (Kettelarij et al. 2016). The study authors reported that nickel was found on all participants both after 2 hours of exposure with no handwashing and at the end of the workday indicating exposure might be attributed to use of tools and materials that release nickel. Before work, the median concentrations of nickel on the skin were 0.014 µg/cm^3 in exposed technicians and 0.026 µg/cm^3 in non-exposed technicians, then increased to 0.0.57 µg/cm^3 in exposed technicians and 0.012 µg/cm^3 for non-exposed technicians after 2 hours of work with no hand washing (Kettelarij et al. 2016). At the end of the day, the median concentrations were 0.018 µg/cm^3 in exposed technicians and 0.014 µg/cm^3 in non-exposed technicians (Kettelarij et al. 2016). Nickel was found in 4 of 10 air samples taken during this study at concentrations ranging from 0.48 to 3.7 µg/m^3 and metal urine concentrations were normal (Kettelarij et al. 2016). Berniyanti et al. (2020) measured blood concentrations of nickel in exposed dental technicians and controls. The mean concentration of nickel in blood was 36.76 µg/L in exposed individuals and 3.35 µg/L in controls (Berniyanti et al. 2020). Hariyani et al. (2015) found similar results, calculating mean blood nickel concentrations of 36.76 µg/L and 3.19 µg/L in dental technicians and controls, respectively. Lower mean blood nickel levels were observed in groups who used gloves, protective clothing, and masks, although these results were not statistically significant (Hariyani et al. 2015). While dental technicians are likely to have higher exposures to nickel, Kulkarni et al. (2016) concluded that nickel releases from stainless steel crowns and space maintainers are unlikely to release high enough concentrations of nickel to produce toxicity.

Populations living near other industries known to emit nickel may be at risk of high exposure to nickel. Populations near oil refineries and coal-fired power plants, including children, have increased urinary nickel concentrations (Chen et al. 2017). Mean urinary nickel in the elderly living near these facilities was 11.28±15.34 µg/g-creatinine compared to 8.33±29.64 µg/g-creatinine in elderly living further from the facilities (Chen et al. 2017). In children, mean urinary nickel was 10.41±16.62 µg/g-creatinine in subjects living close to the facilities and 3.70±2.89 µg/g-creatinine in those living further from the facilities (Chen et al. 2017). A study of metal concentrations in air was conducted in four communities near metal recyclers in Houston, Texas (Han et al. 2020). Mean concentrations at the fence lines of the four facilities ranged from 14.24-769.8 ng/m^3 and decreased to levels like background concentrations at 600 meters away (Han et al. 2020). Han et al. (2020) estimated that the cancer risk due to inhalation of nickel was 0.21 to 14 cases per million at the fence line, 0.03 to 1.1 cases per million in near neighborhoods, and 0.21 to 0.47 cases per million in far neighborhoods.

Many studies have measured nickel in tobacco products and e-cigarettes indicating that people who smoke cigarettes or e-cigarettes, or who use smokeless tobacco products may have higher exposures than the general population. Smoking is associated with nickel sensitization (Thyssen et al. 2010). Pappas et al. (2008) found that in smokeless tobacco products including snuff products and iqmik (tobacco mixture), the average nickel concentration among 17 commercially available brands is 2.28 µg/g. Using artificial saliva, study authors found that 20 to 46% of nickel contained in the products is extractable (Pappas et al. 2008). In a study analyzing smokeless tobacco products in Pakistan, Arain et al. (2015) found that nickel intake was 10.6 to 25.9 µg/10 g of gutkha (chewing tobacco mixture), 75.6 to 141 µg/10 g of moist snuff (finely ground or pulverized tobacco leaves), and 103 to 173 µg/10 g of mainpuri (chewing tobacco mixture). Whole blood and scalp hair nickel concentrations of people who do not consume smokeless tobacco products are two to three times lower than those of people who do consume these products (Arain et al. 2015). In a separate study, Arain et al. (2013) estimated that people who consume 10 g of mainpuri product have a mean daily nickel intake of 135 µg. The levels of nickel in blood and scalp hair of oral cancer patients who used these smokeless tobacco products were 5 to 6 times higher than levels in controls (Arain et al. 2015). Other studies have measured nickel in the serum (7.0 µg/L), urine (0.9 µg/L), saliva (2.3 µg/L), and exhaled breath condensate (1.3 µg/L) of cigarette and e-cigarette users (Aherrera et al. 2017; Badea et al. 2018).

CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

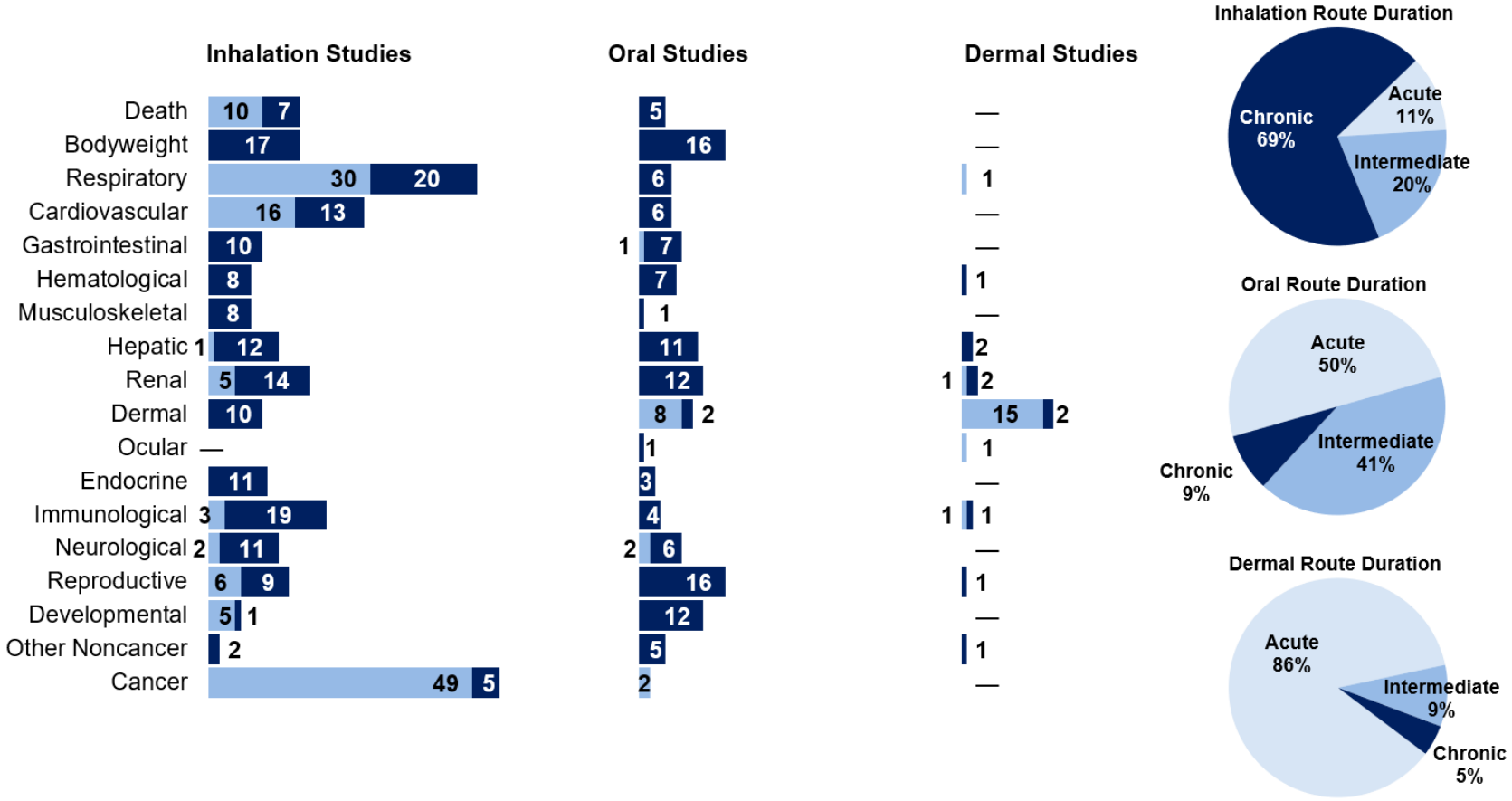
6.1 EXISTING INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to nickel that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of nickel. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As shown in Figure 6-1, information on the health effects in humans exposed to nickel primarily examines inhalation exposure. Most of these studies are epidemiological investigations of occupationally exposed workers followed by population level studies of exposure to nickel in ambient air.

Figure 6-1. Summary of Existing Health Effects Studies on Nickel by Route and Endpoint*

Potential respiratory, dermal, and cancer effects were the most studies endpoints.
The majority of the studies examined inhalation exposure in **animals** (versus **humans**).



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect and most studies examined multiple endpoints.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The acute-duration inhalation animal database was not adequate for the derivation of an acute-inhalation MRL. No human studies evaluated acute-duration inhalation exposure. Several studies in animals evaluated the respiratory system, identifying it as the most sensitive endpoint to nickel toxicity. Multiple rat studies identified 0.43 to 0.44 mg Ni/m^3 as the LOAEL for respiratory toxicity as lung lesions, including alveolitis and lung inflammation, were seen following 5-12 days of exposure (Benson et al. 1995b; Efremenko et al. 2014; NTP 1996c). The lungs were not evaluated in studies where lower concentrations were tested on animals; therefore, a concentration-response cannot be established. While immune function was evaluated at lower concentrations of 0.08 and 0.369 mg Ni/m^3 (Adkins et al. 1979a, 1979b, 1979c; Buxton et al. 2021; Graham et al. 1978), these studies did not evaluate respiratory function. Studies evaluating the lung following exposure to lower concentrations of nickel in rats would be useful to establish a concentration-response relationship, especially given acute-duration exposure to high levels of nickel in air is of concern in occupational studies, as evidenced by several case studies documenting acute toxicity. Few studies in humans examining oral exposure to nickel have reported allergic dermatitis, however these studies examine nickel-sensitized individuals and the small sample sizes do not allow for statistically correct extrapolation to a larger population (Gawkrodger et al. 1986; Hindsén et al. 2001; Jensen et al. 2003). Oral exposure studies examining allergic dermatitis using larger sample groups would elucidate whether incidence is significant among a larger population. Several experimental studies in animals suggest reproductive and developmental toxicity following oral exposure, however these data indicate toxicity at doses lower than those tested (El Sekily et al. 2020; Saini et al. 2014b; Sobti and Gill 1989). Studies examining reproductive and developmental outcomes from oral exposure to nickel are needed to establish a NOAEL for these endpoints.

Intermediate-Duration MRLs. The intermediate-duration inhalation database was adequate for the derivation of an intermediate inhalation MRL. Multiple occupational cohort studies and case studies demonstrate that the respiratory system is the target of nickel toxicity following varying durations of exposure to elevated nickel concentrations in air. Multiple experimental animal studies demonstrate a concentration-response relationship between nickel exposure and respiratory toxicity including lung inflammation and alveolitis (Benson et al. 1995b; Efremenko et al. 2014; NTP 1996c; Oller et al. 2022).

The intermediate-duration oral database was not adequate for the derivation of an oral MRL. Several studies report developmental and reproductive effects in rats and mice (Berman and Rehnberg 1983; Kakela et al. 1999; Pandey et al. 1999; Pandey and Srivastava 2000; RTI 1988a, 1988b; Smith et al. 1993; Springborn Laboratories 2000b; Toman et al. 2012). The available studies did not provide sufficient evidence of a reproductive or developmental NOAEL. Additional intermediate-duration studies may be useful to understand if developmental and reproductive toxicity following intermediate-duration exposure may be of concern to humans exposed to elevated levels of nickel in food or water.

Chronic-Duration MRLs. The chronic-duration inhalation database was adequate for the derivation of a chronic inhalation MRL. Several chronic-duration exposures studies in workers indicate that the respiratory system is a sensitive target of nickel toxicity (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990). A concentration-response between nickel and lung toxicity is established by NTP (1996c) with a LOAEL of 0.06 mg Ni/m^3. Takenaka et al. (1995) supports this LOAEL where rats showed lung congestion, increased lung weight, and alveolar proteinosis following exposure to the same concentration. The chronic-duration oral database was not adequate for the derivation of an oral MRL. No studies in humans examine chronic-duration oral exposure to nickel. A limited number of studies in animals only suggest that chronic-duration exposure results in body weight changes in rats (Ambrose et al. 1976; Heim et al. 2007). There does not appear to be a need for chronic-duration oral exposure studies given the lack of toxicity demonstrated in published studies.

Health Effects.

Immunological. Human exposure to a large dose of nickel can result in sensitization manifested as contact dermatitis. Although the data are limited for the inhalation route, there are extensive data for the oral and dermal routes. Three studies examined immunological endpoints following inhalation exposure; two of these studies (Bencko et al. 1983, 1986) measured immunoglobulin levels in nickel workers and found significant alterations. The third study (Shirakawa et al. 1990) found positive results in patch tests of workers with hard metal lung disease. In nickel-sensitized individuals, oral exposure to fairly low doses of nickel can result in contact dermatitis (Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Hindsén et al. 2001; Jensen et al. 2003; Veien et a l. 1987). There is extensive information on the immunotoxicity of nickel in humans following dermal exposure, generally tested either by patch testing in individuals with contact dermatitis or studies designed to assess the occurrence of nickel sensitivity in the general population. Animal studies demonstrate that nickel can induce immunological effects in nonsensitized individuals. Alterations in nonspecific immunity (e.g., macrophage activity) (Adkins et al. 1979a; Haley et al. 1990; Johansson et al. 1980) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) (Adkins et al.

1979b, 1979c; Graham et al. 1978; Morimoto et al. 1995; Spiegelberg et al. 1984) has been observed in animals following inhalation exposure. Similarly, oral exposure to nickel has resulted in alterations in natural killer cells (Ilback et al. 1994) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) (Dieter et al. 1988; Ilback et al. 1994). One dermal exposure study in mice examined the exposure-response relationship for nickel sensitization in mice (Siller and Seymour 1994). Studies designed to assess the dose-response relationship for contact dermatitis and oral dose are needed. Additionally, studies that examined whether tolerance to nickel can develop and that assess cross sensitization of nickel with other metals would also be useful.

Neurological. A case-study reported seizures in an individual suspected of occupational nickel exposure indicated by elevated levels of nickel in urine (Denays et al. 2005). One retrospective case-control study suggests a potential association between autism and increased concentration of nickel in air (Windham et al. 2006). No studies on the neurotoxicity of nickel in humans following dermal exposure were located. Neurological effects (giddiness, weariness) were reported in individuals accidentally exposed to nickel sulfate, nickel chloride and boric acid in drinking water (Sunderman et al. 1988). Temporary blindness, manifesting as loss of sight in the same corresponding two left halves of the visual fields of both eyes, occurred shortly after one person took a 0.05-mg/kg dose of nickel as nickel sulfate in drinking water (Sunderman et al. 1989b). There is limited information on the neurotoxicity of nickel in laboratory animals. No histological alterations were observed in the central nervous system following inhalation (NTP 1996a, 1996b, 1996c) or oral exposure (Ambrose et al. 1976; Obone et al. 1999). Although histological damage to the nasal olfactory epithelium was observed in animals following inhalation exposure to nickel sulfate or nickel subsulfide (Evans et al. 1995; NTP 1996b, 1996c), functional changes were not noted (Evans et al. 1995). Neurological signs (lethargy, ataxia, prostration) were observed in dying rats treated with nickel for 3 months; however, these effects were probably associated with overall toxicity (American Biogenics Corporation 1988). Clinical neurological signs of toxicity, including increased salivation and hypoactivity were seen in rats exposed orally for 3 days (Oller and Erexson 2007). No animal dermal exposure studies examined neurological endpoints. The human data provide suggestive evidence that exposure to nickel may result in neurological effects and a recent systematic review by Anyachor et al. (2022) suggests that environmental exposures to nickel may be involved in the development of neurodegenerative diseases. Additional animal studies examining neurobehavioral performance and neurodevelopment would provide valuable information on the neurotoxic potential of nickel and its potential role in neurodegenerative disorders.

Reproductive. Data on the reproductive toxicity of nickel in humans is limited to a study of women working at a nickel hydrometallurgy refining plant (Chashschin et al. 1994). However, interpretation of

these study results is limited by the lack of information on the control of potential confounding variables, heavy lifting, and possible heat stress. Large epidemiological studies of the population from this area (Kola Peninsula) suggest that exposure of female refinery workers to soluble nickel did not result in adverse outcomes such as male newborns with genital malformations (Vaktskjold et al. 2006), spontaneous abortions (Vaktskjold et al. 2008b), small-for-gestational-age newborns (Vaktskjold et al. 2007), or congenital musculoskeletal effects (Vaktskjold et al. 2008a). Several oral exposure studies in animals suggest that nickel can result in testicular and epididymal damage (Käkelä et al. 1999; Pandey et al. 1999), decreases in sperm motility, count, and sperm abnormalities (Pandy and Srivastava 2000; Pandey et al. 1999; Sobti and Gill 1999; Toman et al. 2012), or alterations in fertility (Käkelä et al. 1999; Pandey et al. 1999). Other oral studies have not found histological alterations in male or female reproductive tissues or impaired fertility following intermediate- or chronic- duration exposure to nickel (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; RTI 1988a, 1988b; Springborn Laboratories 2000a). Although testicular effects were also observed following inhalation exposure, the investigators (NTP 1996b, 1996c) considered the testicular effects to be secondary to emaciation. Fertility was not adversely affected in two multigeneration studies (RTI 1988a, 1988b; Springborn Laboratories 2000a). However, the single generation study (Springborn Laboratories 2000b) did observe significant post-implantation loss, and individual level data per dam indicates a dose-response relationship. The poor reporting of the study results, particularly incidence data and statistical analysis, limits the interpretation of the Käkelä et al. (1999), Pandey et al. (1999), and Pandey and Srivastava (2000) studies. An expert evaluation of the unpublished results of these studies, along with the other available reproductive toxicity studies (RTI 1988a, 1988b; Springborn Laboratories 2000a, 2000b), may provide insight on the apparent differences between the studies. Nickel treatment of rats during lactation has also been shown to change the quality of the milk (Dostal et al. 1989). Further studies concerning the role of physiological levels, as well as toxic levels, of nickel in the release of prolactin from the pituitary could provide useful information on potential reproductive and developmental effects of nickel.

Developmental. There are limited data on the potential developmental toxicity of nickel in humans. An increase in structural malformations was observed in infants of women who worked in a nickel hydrometallurgy refining plant (Chashschin et al. 1994); however, the lack of information on control of potential confounding variables such as smoking and alcohol use and heavy lifting, and possible heat stress limits the interpretation of these results. In a separate study, among female refinery workers with exposure to nickel there was a non-significant association between maternal exposure and musculoskeletal defects in offspring (Arild et al. 2008). Additionally, several population studies suggest that increased levels of nickel in air are associated with decreased birthweight (Bell et al. 2010; Ebisu and Bell 2012; Pedersen et al. 2016); however these studies are limited based on the design and the possible

influence of other factors and pollutants. Decreased fetal body weight was observed in offspring of rats exposed to high levels of nickel via inhalation during gestation (Weischer et al. 1980). Developmental effects such as increased pup mortality at birth, decreased litter size to post-natal day 21, and decreased pup body weight were observed in oral exposure single-generation studies involving male-only, female-only, or male and female exposure to nickel (Käkelä et al. 1999), multigeneration studies in rats (Ambrose et al. 1976; RTI 1988a, 1988b; Springborn Laboratories 2000b), and multi-litter studies in rats (Smith et al. 1993). The available studies have consistently found decreases in pup survival, decreases in maternal body weight, food consumption, and water consumption often occur at the same dose levels. Thus, it is not known if the effects are due to nickel-induced damage to the offspring or are secondary to the maternal toxicity. Studies that control for maternal food intake and water consumption would be useful in understanding the mechanism of nickel toxicity. Developmental toxicity studies utilizing several dose levels would provide useful information in establishing the dose-response relationships for nickel, especially testing lower doses than in the current database.

Epidemiology and Human Dosimetry Studies. Several epidemiology studies regarding nickel toxicity are available in the literature. Most of these studies have focused on the carcinogenicity of inhaled nickel exposure (Anttila et al. 1998; Chovil et al. 1981; Coyle et al. 2005; Doll et al. 1977; Enterline and Marsh 1982; Grimsrund et al. 2003; Heck et al. 2015; Kresovich et al. 2019; Luo et al. 2011; Magnus et al. 1982; Pedersen et al. 1973; Raaschou-Nielsen et al. 2016; Sunderman et al. 1989a; White et al. 2019), nickel sensitivity following oral exposure (Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Jensen et al. 2003; Jordan and King 1979; Sjovall et al. 1987; Veien et al. 1987), or dermal exposure (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Alinaghi et al. 2019; Cavelier et al. 1988; Dotterud and Falk 1994; Emmett et al. 1988; Eun and Marks 1990; Keczkes et al. 1982; Larsson-Stymme and Widstrom 1985; Meijer et al. 1995; Menne and Holm 1983; Menne et al. 1987; Nielsen et al. 2002; Simonetti et al. 1998; Uter et al. 2003; Wantke et al. 1996). As nickel exposure levels in the occupational environments have been reduced, continued health monitoring of populations occupationally exposed to nickel would be useful to determine if more subtle adverse health effects occur in humans at lower concentrations. Continued monitoring of nickel sensitization in the general population to identify trends and differences in exposure risk behaviors (such as increased popularity of body piercing) would inform future prevention efforts. Additional studies on the dose-response relationship of ingested nickel dose and contact dermatitis would be useful. Few epidemiological studies (Arild et al. 2008; Bell et al. 2010; Ebisu and Bell 2012; Pedersen et al. 2016) and some animal data provide some suggestive evidence that nickel may be a reproductive toxicant and maternal exposure may result in increases in neonatal mortality. Inclusion of these endpoints in occupational exposure studies may provide valuable information on whether these endpoints are of concern for humans. As noted in Section 3.4,

there are many reported interactions with nickel including interactions that may occur in occupational settings with nickel exposure, including those that may elevate toxicity. Literature on the impact of co-exposures that are likely to occur in occupational settings would be useful.

Biomarkers of Exposure and Effect.

Exposure. Nickel is a naturally occurring component of the diet and can be detected in hair, blood, urine, and feces (Angerer and Lehnert 1990; Bencko et al. 1986; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Positive qualitative correlations have been found between air concentrations of nickel and nickel levels in the feces (Hassler et al. 1983) and urine (Angerer and Lehnert 1990; Bavazzano et al. 1994; Bernacki et al. 1978, 1980; Morgan and Rouge 1984; Oliveira et al. 2000; Sunderman et al. 19 86; Tola et al. 1979; Torjussen and Andersen 1979; Werner et al. 1999) due to excessive exposure to nickel. Additional studies examining the relationship between levels of nickel in the urine and body burden levels and studies associating urinary nickel levels and the manifestation of adverse health effects would be useful in establishing biological exposure indices for nickel.

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

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetic studies in humans indicate that nickel is absorbed through the lungs (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991), gastrointestinal tract (Nielsen et al. 1999; Patriarca et al. 1997; Sunderman et al. 1989b), and skin (Fullerton et al. 1986; Norgaard 1955). Food greatly decreases the absorption of nickel from the gastrointestinal tract (Sunderman et al. 1989b). Dede et al. (2018) modified the Sunderman et al. (1989b) model to evaluate nickel exposures from food and accounted for the unabsorbed nickel by adding a feces compartment. Following absorption from the lungs and the gastrointestinal tract, nickel is excreted

in the urine (Angerer and Lehnert 1990; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Sunderman et al. 1989b; Torjussen and Andersen 1979). Increased levels of nickel were found in the lungs, nasal septum, liver, and kidneys of workers inhaling nickel (Andersen and Svenes 1989; Kollmeier et al. 1987; Raithel et al. 1988; Rezuke et al. 1987; Sumino et al. 1975; Svenes and Andersen 1998; Torjussen and Andersen 1979). Animal data indicate that after inhalation, nickel particles can remain in the lungs (nickel oxide) or be absorbed and then excreted in the urine (nickel sulfate). High levels of nickel have been found in the liver, kidneys, and spleen of animals after inhaling high levels of nickel (Benson et al. 1987, 1988, 1994, 1995a; NTP 1996a, 1996b, 1996c; Tanaka et al. 1985). Nickel absorbed after oral exposure is primarily distributed to the kidneys before being excreted in the urine. High levels of nickel were also found in the liver, heart, lungs, fat, peripheral nervous tissue, and brain (Ambrose et al. 1976; Borg and Tjalve 1989; Dieter et al. 1988; Jasim and Tjalve 1986a, 1986b; Oskarsson and Tjalve 1979; Whanger 1973). Overall, studies examining the bioavailability of nickel from soil following oral exposure would be useful for determining the absorbed dose from nickel-contaminated soil at a hazardous waste site.

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

Children's Susceptibility.

Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are limited data on the toxicity of nickel in children. Several patch testing studies have included children (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995; Uter et al. 2003; Wantke et al. 1996), the results of which suggest that children may be more susceptible than adults. However, the increased susceptibility observed in children

may be due to prolonged exposure to nickel-containing products such as earrings, rather than increased sensitivity; additional studies are needed to verify this assumption. Studies in laboratory animals provide evidence that the fetus and neonates are sensitive targets of nickel toxicity following inhalation or oral exposure (Ambrose et al. 1976; Berman and Rehnberg 1993; Käkelä et al. 199 9; RTI 1988a, 1988b; Smith et al. 1993; Weischer et al. 1980). As noted in the Developmental Toxicity section, additional studies are needed to verify the apparent sensitivity to nickel. Additional studies examining potential age-related differences in nickel would provide valuable information on the susceptibility of children to nickel toxicity. This information is necessary for assessing the need to conduct health studies on children. Some data on daily intake of nickel is available for children under the age of 18 years (Thomas et al. 1999), including data for various age ranges of children (Moschandreas et al. 2002; NAS 2002; O'Rourke et al. 1999). The nickel levels in urine are available (Baranowska-Dutkiewicz et al. 1992), but information on levels in other body fluids, tissue, hair, and nails are not available. These data do not refer to populations living around the hazardous waste sites that contain elevated levels of nickel. Additional studies that examine nickel levels in body fluids and tissues from children living near hazardous waste sites that contain elevated levels of nickel would be useful. No human or animal data on the toxicokinetic properties of nickel in children or immature animals or studies examining possible age-related differences in the toxicokinetics of nickel were located.

Physical and Chemical Properties. The physical and chemical properties of nickel and its compounds are well documented and have been adequately characterized.

Production, Import/Export, Use, Release, and Disposal. Information on the production, import, export, and use of nickel and its alloys and compounds is readily available. Except for recycling of metal scrap, little information is available regarding the disposal of nickel and its compounds. More detailed information regarding disposal methods, disposal quantities, and the form of nickel disposed of is necessary to assess potential nickel exposure. Releases to the air, soil, and water in the U.S. are reported to the Toxics Release Inventory (TRI). However, only certain facilities are required to report, and this is not an exhaustive list.

Environmental Fate. Nickel is an element and therefore, is not destroyed in the environment. In assessing human exposure, one must consider the form of nickel and its bioavailability. This information is site specific. Data regarding the forms of nickel in air, soil, and sediment are fragmentary and inadequate (Galbreath et al. 2003; Sadiq and Enfield 1984a; Schroeder et al. 1987). Also lacking is adequate information on the transformations that may occur, the transformation rates, and the conditions that facilitate these transformations. Information relating to the adsorption of nickel by soil and sediment

is not adequate. In some situations, adsorption appears to be irreversible. In other situations, however, adsorption is reversible. More data would be helpful in detailing those situations where adsorbed nickel may be released and those where release is unlikely.

Bioavailability from Environmental Media. The absorption and distribution of nickel as a result of inhalation, ingestion, and dermal exposure are discussed in Chapter 3. Quantitative data relating the physical/chemical properties of nickel (e.g., particle size, chemical forms of nickel) with its bioavailability are available for inhaled nickel. In aqueous media, nickel is in the form of the hexahydrate ion, which is poorly absorbed by most living organisms (Sunderman and Oskarsson 1991), although uptake of nickel into rye and oats has been reported. One study assessed the bioavailability from soil affected by metal forge operations (Li et al. 2020). Additional studies that examine the absorption of nickel from soil would be useful.

Food Chain Bioaccumulation. The uptake and accumulation of nickel in various plant species has been reported. Data are available on the bioconcentration of nickel in fish and aquatic organisms (Birge and Black 1980; EPA 1979; McGeer et al. 2003; Suedel et al. 1994; Zaroogian and Johnson 1984). Higher levels of nickel have been found in gar compared with catfish from the same environment (Winger et al. 1990). More data on different species of fish at different sites would be useful in explaining these results. Data are limited on nickel levels in wild birds and mammals (Alberici et al. 1989; Dressler et al. 1986; Jenkins 1980). Nickel does not appear to bio-magnify in food webs, but quantitative data is needed to fully assess this. A larger database including information on both herbivorous and carnivorous species living in both polluted and unpolluted environments is desirable in establishing whether nickel biomagnification in the food chain occurs under some circumstances.

Exposure Levels in Environmental Media. Adequate information exists on the concentrations of nickel in air, water, and soil. Nickel levels in food in the U.S. are monitored by the FDA (FDA 2017), and nickel levels in air and water are monitored by EPA (EPA 2020a; WQP 2021). Reliable monitoring data for the levels of nickel in contaminated media at hazardous waste sites are needed so that the information obtained on levels of nickel in the environment can be used in combination with the known body burden of nickel to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Also, few data are available regarding nickel levels at contaminated or hazardous waste sites (Agency for Toxic Substances and Disease Registry 2003; Bradley and Morris 1986; Duke 1980b; Taylor and Crowder 1983). This information is necessary for exposure assessment analysis at these sites. This should include monitoring of air and drinking water concentrations of nickel surrounding

these sites. Since nickel is found in all soil, studies should focus on waste sites where nickel levels are substantially higher than background levels.

Exposure Levels in Humans. Nickel levels in body fluids, tissue, hair, nails, and breast milk are available. Serum, urine, and skin levels in some exposed workers have been reported. It is recommended that additional studies be conducted that examine biomarkers of exposure or markers of early biological effects, such as changes in gene expression measured by microarrays. These studies could be piloted with *in vitro* cell lines to determine nickel-specific markers, followed by *in vivo* screening of people living in or near sites that contain levels of nickel that are elevated above background concentrations or who have occupational exposures to nickel. This information is necessary for assessing the need to conduct health studies on these populations. While levels in food are known, most recent studies assessing dietary intake of nickel are from outside of the U.S. More recent information on dietary intake in the U.S. would be useful for assessing this route of exposure.

Exposures of Children. Sources of exposures of children are known (Jensen et al. 2014; Tuchman et al. 2015). Some data on daily intake of nickel is available for children under the age of 18 years (Thomas et a l. 1999), including data for various age ranges of children (Moschandreas et al. 2002; NAS 2002; O'Rourke et al. 1999; Periera et al. 2020). The nickel levels in urine are available (Baranowska-Dutkiewicz et al. 1992), but information on levels in other body fluids, tissue, hair, and nails is not available for children. Available data do not refer to populations living around the hazardous waste sites that contain elevated levels of nickel. Additional studies that examine nickel levels in body fluids and tissues from children living near hazardous waste sites that contain elevated levels of nickel would be useful.

6.3 ONGOING STUDIES

There is no information on any ongoing studies for nickel.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding nickel in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for nickel.

Table 7-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
	Air		
EPA	RfC		
	Nickel, soluble salts	Not evaluated	IRIS 1994
	Nickel refinery dust	Not evaluated	IRIS 1987a
	Nickel carbonyl	Not evaluated	IRIS 1987c
	Nickel subsulfide	Not evaluated	IRIS 1987b
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards		EPA 2018
	1-day health advisory for a 10-kg child	1 mg/L	
	10-day health advisory for a 10-kg child	1 mg/L	
	DWEL	0. 7 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL	No data	
	Public health goal	No data	
	RfD		
	Nickel, soluble salts	0.02 mg/kg/day[a]	IRIS 1994
	Nickel refinery dust	Not evaluated	IRIS 1987a
	Nickel carbonyl	Not evaluated	IRIS 1987c
	Nickel subsulfide	Not evaluated	IRIS 1987b
WHO	Guideline value for chemicals that are of health significance in drinking water	0.07 mg/L (70 µg/L)	WHO 2017
FDA	Substances Added to Food (EAFUS)	21 CFR 176.180 for use as indirect food additive in paper and paper cardboard components	FDA 2021b
		21 CFR 184.1537 GRAS Status	FDA 2021a

Table 7-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
	Cancer		
HHS	Carcinogenicity classification		NTP 2016
	Nickel compounds	Known to be human carcinogens	
	Nickel metallic	Reasonably anticipated to be a human carcinogen	
EPA	Carcinogenicity classification		
	Nickel, soluble salts	Not evaluated	IRIS 1994
	Nickel refinery dust	A[b]	IRIS 1987a
	Nickel carbonyl	B2[c]	IRIS 1987c
	Nickel subsulfide	A[b]	IRIS 1987b
IARC	Carcinogenicity classification		IARC 2021
	Nickel compounds	Group 1[d]	
	Nickel, metallic	Group 2B[e]	
	Occupational		
OSHA	PEL (8-hour TWA) for general industry		OSHA 2020a
	Nickel, metal, and insoluble compounds	1 mg/m^3	29CFR1910.1000
	Nickel, soluble compounds	1 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2020b
	Nickel, metal, and insoluble compounds	1 mg/m^3	29CFR1926.55
	Nickel, soluble compounds	1 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2020c
	Nickel, metal, and insoluble compounds	1 mg/m^3	29CFR1915.1000
	Nickel, soluble compounds	1 mg/m^3	
NIOSH	REL (up to 10-hour TWA)	0.015 mg/m^3	NIOSH 2019a
	Emergency Criteria		
AIHA	ERPGs	No data	AIHA 2016
EPA	AEGLS-air	No data	AEGLs 2018
	Nickel carbonyl		
	AEGL 1		
	10 min	NR	
	30 min	NR	
	60 min	NR	
	4 hr	NR	
	8 hr	NR	
	AEGL 2		
	10 min	0.10 ppm	
	30 min	0.072 ppm	
	60 min	0.036 ppm	
	4 hr	0.0090 ppm	
	8 hr	0.0045 ppm	
	AEGL 3		
	10 min	0.46 ppm	
	30 min	0.32 ppm	
	60 min	0.16 ppm	
	4 hr	0.040 ppm	
	8 hr	0.020 ppm	

Table 7-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
DOE	PACs-air[f]		DOE 2018
	Nickel		
	PAC-1	4.5 mg/m^3	
	PAC-2	50 mg/m^3	
	PAC-3	99 mg/m^3	
	Nickel acetate tetrahydrate		
	PAC-1	13 mg/m^3	
	PAC-2	140 mg/m^3	
	PAC-3	830 mg/m^3	
	Nickel(II) carbonate		
	PAC-1	0.61 mg/m^3	
	PAC-2	6.6 mg/m^3	
	PAC-3	40 mg/m^3	
	Nickel chloride		
	PAC-1	0.66 mg/m^3	
	PAC-2	22 mg/m^3	
	PAC-3	130 mg/m^3	
	Nickel cyanide		
	PAC-1	1.1 mg/m^3	
	PAC-2	13 mg/m^3	
	PAC-3	75 mg/m^3	
	Nickel(II) nitrate		
	PAC-1	0.93 mg/m^3	
	PAC-2	10 mg/m^3	
	PAC-3	61 mg/m^3	
	Nickel oxide		
	PAC-1	0.76 mg/m^3	
	PAC-2	220 mg/m^3	
	PAC-3	1,300 mg/m^3	
	Nickel sulfamate		
	PAC-1	1.3 mg/m^3	
	PAC-2	12 mg/m^3	
	PAC-3	71 mg/m^3	
	Nickel sulfate		
	PAC-1	0.79 mg/m^3	
	PAC-2	8.6 mg/m^3	
	PAC-3	51 mg/m^3	

[a]RfD: The RfD is based on a LOAEL of 50 mg/kg/day for decreased body and organ weights in chronic-duration exposures in rats (Ambrose et al. 1976).
[b]A: human carcinogen
[c]B2: probable human carcinogen
[d]Group 1: carcinogenic to humans
[e]Group 2B: Possibly carcinogenic to humans
[f]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2016).

AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; HHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration;

Table 7-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference

GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide

MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MRL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL. The acute-duration inhalation database indicates respiratory toxicity as a sensitive endpoint to nickel however the lowest LOAEL for this endpoint is for serious effects. The immune endpoint was also considered however given the lack of information on the respiratory effects below the SLOAEL for forms of nickel that may be more potent, it is not known if the NOAEL value for immunotoxicity would be protective of respiratory effects.

Rationale for Not Deriving an MRL: Several case studies in workers who inhaled large amounts of nickel dust or fumes indicate the respiratory system is the most sensitive endpoint for nickel toxicity (Bowman et al. 2018; Kunimasa et al. 2011). A single case of death from adult respiratory distress syndrome (ARDS) has been reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994).

While numerous animal studies have identified the respiratory system as a sensitive endpoint of nickel, a study NOAEL to serve as a basis for MRL derivation has not been identified (Bai et al. 2013; Benson et al. 1995b; Efremenko et al. 2014; NTP 1996a, 1996b, 1996c). Several studies examining the respiratory system identified 0.4 mg Ni/m^3 as a LOAEL including endpoints considered serious effects, precluding derivation from this LOAEL value. At 0.43 mg Ni/m^3 as nickel subsulfide, Efremenko et al. (2014) reported peribronchiolar and perivascular inflammation in 5/5 rats after histological examination. The same concentration in rats resulted in elevated lactate dehydrogenase (LDH) in bronchoalveolar lavage fluid (BALF) (250%) compared to controls (Efremenko et al. 2014). Additionally, Efremenko et al. (2014) identified the lowest acute-duration respiratory NOAEL of 0.11 mg Ni/m^3 as nickel subsulfide for BALF evaluation. In Benson et al. (1995b), 0.44 mg Ni/m^3 as nickel subsulfide resulted in lung alveolitis in 6/6 rats exposed for 7 days. Similarly, NTP (1996b) identified a LOAEL of 0.44 mg Ni/m^3 for chronic lung inflammation in 10/10 rats and atrophy of the olfactory epithelium in 6/10 rats. The experiments conducted by the National Toxicology Program (NTP) observed respiratory toxicity following inhalation of nickel oxide (NTP 1996a), nickel subsulfide (NTP 1996b), and nickel sulfate hexahydrate (NTP 1996c) for 12 days, six hours per day, in both rats and mice. In mice 0.44 mg Ni/m^3 was identified as a NOAEL as neither histological changes nor clinical signs of respiratory toxicity were observed (NTP 1996b). Mice of both sexes also showed respiratory toxicity at doses ≥0.88 mg Ni/m^3 including chronic long inflammation, atrophy of the olfactory epithelium, necrotizing inflammatory lesions, edema, and vascular congestion in the lung (NTP 1996b, 1996c). Several of these studies identified lung lesions at 0.4 mg Ni/m^3 however, NTP (1996a) identified respiratory NOAELs of 3.9 mg Ni/m^3. Acute lung inflammation was observed in rats only at exposures ≥7.9 mg Ni/m^3 (NTP 1996a). Studies are summarized in Table A-1.

Two studies examined immunotoxicity in mice to nickel chloride at lower concentrations than in rat respiratory studies (Buxton et al. 2021; Graham et al. 1978) and identified a NOAEL similar to Efremenko et al. (2014). Graham et al. (1978) identified an immunological LOAEL of 0.25 mg Ni/m^3 as nickel subsulfide for impaired humoral immunity in female mice and a NOAEL of 0.1 mg Ni/m^3 in Swiss mice. Buxton et al (2021) tested lower concentrations and identified a NOAEL of 0.08 mg Ni/m^3 based

on immune response in ICR mice. Deriving a MRL based on immune effects in mice would not be protective as rats appear more sensitive to the effects of nickel, and data on immunotoxicity in rats are insufficient. Additionally, data on respiratory toxicity in mice are limited; respiratory effects are not reported in a different mouse strain (B6C3F1) exposed to 0.44 mg Ni/m^3 (NTP 1996b). Graham et al. (1978) compared immunotoxicity and showed that nickel sulfate hexahydrate is immunosuppressive at lower concentrations compared to nickel chloride. This suggests further evidence is needed on immune effects in rats at lower concentrations and in other nickel forms.

Immunotoxicity at higher concentrations has been evaluated in several other acute-duration inhalation studies. Adkins et al. (1979c) observed a concentration-related increase in susceptibility to infection resulting in increased mortality and reduced survival time in female mice exposed to concentrations up to 0.5 mg Ni/m^3 for 2 hours as nickel chloride and then exposed to Streptococcal bacteria. Mortality among mice at the highest concentration was 26% higher than controls ($p<0.05$). Mice exposed to 0.66 mg Ni/m^3 for 2 hours as nickel chloride showed a reduced ability to clear inhaled bacteria 96 hours after exposure and the incidence of mortality and sepsis was higher than controls(Adkins et al. 1979a). Exposure to a single concentration of 0.46 mg Ni/m^3 as nickel sulfate for 2 hours showed similar results indicating increased susceptibility to infection (Adkins et al. 1979b). Immune histopathological findings have also been reported. NTP (1996b) observed lymphoid hyperplasia in bronchial lymph nodes in mice of both sexes following exposure to 0.88 mg Ni/m^3 as nickel subsulfide. Likewise, female rats had hyperplasia in bronchial and mediastinal lymph nodes following exposure to 1.4 mg Ni/m^3 as nickel sulfate hexahydrate NTP (1996c).

Experimental animal studies have evaluated and observed body weight effects from acute-duration nickel inhalation exposure. Reduced body weight has been reported in rats of both sexes exposed to concentrations of 0.7 to 3.65 mg Ni/m^3 for 7 or 12 days (Benson et al. 1995b; NTP 1996b, 1996c). Weight loss or emaciation was also observed in male mice exposed 3.65 mg Ni/m^3 for 6 hours/day for 12 days (NTP 1996b). However, no exposure-related body weight changes were reported in males exposed to ≤1.83 mg Ni/m^3 and to 23.6 mg Ni/m^3 and in females exposed to 0.7 to 3.65 mg Ni/m^3 for 6 hours/day for 12 days (NTP 1996a, 1996b, 1996c).

Death occurred in rats and mice exposed to nickel via inhalation for 2 hours or 12 days. Following exposure to 1.4 or 7.3 mg Ni/m^3 for 12 days, all mice died (NTP 1996b, 1996c). All rats (5/5) exposed to 12.2 mg Ni/m^3 as nickel sulfate hexahydrate for 12 days died (NTP 1996c). Death was also reported in rats exposed for 2 hours at 36.6 mg Ni/m^3 as nickel sulfate (Hirano et al. 1994)

Multiple studies have assessed cardiovascular toxicity of acute-duration inhalation exposure to nickel oxide, nickel sulfate hexahydrate, nickel subsulfide, and nickel sulfate heptahydrate in rodents (NTP 1996a, 1996b, 1996c) and dogs (Muggenberg et al. 2003). None of these studies observed adverse cardiovascular effects, with the highest NOAEL at 23.6 mg Ni/m^3 as nickel oxide in rats and mice of both sexes (NTP 1996a). NTP studies observed no adverse dermal, endocrine, gastrointestinal, hepatic, musculoskeletal, neurological, renal, or reproductive effects following acute-duration inhalation of nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate in rats and mice (NTP 1996a, 1996b, 1996c). No hematological effects were observed for acute-duration nickel inhalation at a concentration up to 3.65 mg Ni/m^3 as nickel subsulfide in mice of both sexes (NTP 1996b). While this study did also test a concentration of 7.33 mg Ni/m^3, all animals died before hematological parameters and other examinations could be performed.

The relevant NOAEL and LOAEL values are presented in Table A-1.

Table A-1. Summary of Relevant Acute-Duration Inhalation NOAEL and LOAEL Values

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference
Respiratory					
Rat (M)	5 days 6 hours/day	0.11	0.43	Over 250% increase of LDH in BALF	Efremenko et al. 2014 (Nickel subsulfide)
Mouse (B)	12 days in 16 day period 6 hours/day	0.44	0.88	Atrophy of olfactory epithelium	NTP 1996b (Nickel subsulfide)
Rat (M)	5 days 6 hours/day		0.43	Peribronchiolar/ perivascular inflammation	Efremenko et al. 2014 (Nickel subsulfide)
Rat (B)	12 days in 16 day period 6 hours/day		0.44	Chronic lung inflammation and olfactory epithelium atrophy	NTP 1996b (Nickel subsulfide)
Rat (B)	7 days 6 hours/day		0.44*	Alveolitis in 6/6 rats	Benson et al. 1995b (Nickel subsulfide)
Rat (B)	12 days in 16 day period 6 hours/day		0.7	Increased respiration rate, chronic lung inflammation; olfactory epithelium atrophy	NTP 1996c (Nickel sulfate hexahydrate)
Mouse (B)	12 days in 16 day period 6 hours/day		0.7	Chronic lung inflammation and olfactory epithelium atrophy	NTP 1996c (Nickel sulfate hexahydrate)
Rat (B)	12 days in 16 day period 6 hours/day	3.9	7.9	Lung inflammation	NTP 1996a (Nickel oxide)
Mouse (B)	12 days in 16 day period 6 hours/day	3.9	7.9	Elevated incidence of alveolar macrophage hyperplasia	NTP 1996a (Nickel oxide)
Immunological					
Mouse (F)	24 hours	0.08		Immunosuppressive effects	Buxton et al. 2021 (Nickel chloride)
Mouse (F)	2 hours	0.1	0.25	Impaired humoral immunity	Graham et al. 1978 (Nickel chloride)
Mouse (B)	12 days in 16 day period 6 hours/day	0.44	0.88	Lymphoid hyperplasia in bronchial lymph nodes	NTP 1996b (Nickel subsulfide)

B=both; BALF=bronchoalveolar lavage fluid; HEC=human equivalent concentration; LDH=lactate dehydrogenase; M=males; NS=Not Specified
* = Serious lowest observed adverse effect level (SLOAEL)

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
MRL: 0.00003 mg Nickel/m^3 (provisional)
Critical Effect: Chronic lung inflammation
Reference: NTP 1996c
Point of Departure: NOAEL of 0.06 mg Ni/m^3 ($NOAEL_{HEC,ADJ}$ of 0.001 mg Ni/m^3)
Uncertainty Factor: 30
LSE Graph Key: 30R
Species: Rats

MRL Summary: A provisional intermediate-duration inhalation MRL of 0.00003 mg Ni/m^3 was derived for nickel based on a NOAEL of 0.06 mg Ni/m^3 accompanied by a LOAEL of 0.11 mg Ni/m^3 for chronic lung inflammation observed in female rats exposed for 6 hours per day, 5 days/week for 13 weeks (NTP 1996c). The NOAEL of 0.06 mg Ni/m^3 was adjusted for intermittent exposure and converted to a human equivalent concentration of 0.001 mg Ni/m^3. The $NOAEL_{HEC,ADJ}$ of 0.001 mg Ni/m^3 was divided by a total uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: The intermediate-duration toxicity of nickel has been assessed in several animal studies involving exposure to metallic nickel, nickel sulfate, nickel sulfate hexahydrate, nickel chloride, nickel subsulfide, and nickel oxide. Nickel is known to cause effects in the respiratory system, and these were observed at concentrations $\geq$ 0.1 mg/m^3. Researchers recorded inflammatory changes in the lungs (Benson et al. 1995a, 1995b; Horie et al. 1985; NTP 1996a, 1996b, 1996c), alveolar macrophage hyperplasia (Benson et al. 1995b; Johansson and Camner 1986; NTP 1996a, 1996b, 1996c), and atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c). Further respiratory effects were hyperplasia in the bronchial and mediastinal lymph nodes (Bingham et al. 1972, NTP 1996b, 1996c) and altered enzyme levels in bronchoalveolar lavage fluid (BALF) (Efremenko et al. 2014).

Impaired immune function was consistently observed (Section 2.14) at levels $\leq$9.2 mg Ni/m^3. Other observed effects that occurred with less dose consistency included decreased body weight gain (Benson et al. 1995b; Weischer et al. 1980), decreased sperm concentration (NTP 1996a), vascular endothelial and microcirculatory dysfunction (Xu et al. 2012; Ying et al. 2013), changes in hematological parameters (NTP 1996b; Weischer et al. 1980), urea changes (Weischer et al. 1980), and developmental toxicity (Weischer et al. 1980). A cancer effect level of 0.5 mg Ni/m^3 as nickel oxide was reported in Horie et al. (1985) for adenocarcinoma in 1 of 6 male rats.

Intermediate-duration inhalation studies conducted by the National Toxicology Program in rats and mice indicate that the most sensitive target of nickel toxicity is the respiratory system (NTP 1996a, 1996b, 1996c). In these studies, chronic lung inflammation was observed following 13-week (6 hours/day, 5 days/week) exposures to nickel oxide (NTP 1996a), nickel subsulfide (NTP 1996b), and nickel sulfate hexahydrate (NTP 1996c). The intermediate-duration studies by NTP indicate that nickel sulfate hexahydrate is more toxic than nickel subsulfide and nickel oxide (NTP 1996a, 1996b, 1996c). In rats, the respective NOAEL and LOAEL values for chronic lung inflammation were 0.06 and 0.11 mg Ni/m^3 for

nickel sulfate (NTP 1996c), 0.11 and 0.22 mg Ni/m^3 for nickel subsulfide (NTP 1996b), and 2.0 and 3.9 mg Ni/m^3 for nickel oxide, respectively (NTP 1996a). Atrophy of the nasal olfactory epithelium was observed at 0.22 mg Ni/m^3 in males rats exposed to nickel sulfate hexahydrate (NTP 1996c). Labored breathing was observed in rats exposed to 1.83 mg Ni/m^3 as nickel subsulfide. Respiratory toxicity findings from the NTP studies are supported by findings from Efremenko et al. (2014) and Oller et al. (2022) which reported histological changes at a LOAEL of 0.11 mg Ni/m^3. Efremenko et al. (2014) observed minimal to mild alveolus inflammation characterized by prominent macrophages in alveoli with distended cytoplasm. In rats exposed to ≥0.11 mg Ni/m^3 as nickel sulfate hexahydrate, Oller et al. (2022) reported the incidence and severity of pulmonary lesions increased with increasing nickel concentration. Pulmonary lesions include perivascular and peribronchiolar lesions, and alveolitis. At 0.03 mg Ni/m^3, the incidence of lesions, inflammation, and lung weights were similar to controls. Oller et al. (2022) reported similar findings for a 13-week exposure to nickel subsulfide.

The NTP studies reported similar differential effects in mice. For nickel sulfate hexahydrate and nickel subsulfide, the LOAEL values for mice were higher than the LOAELs in rats; the LOAEL for respiratory effects following exposure to nickel oxide was the same in rats and mice for chronic inflammation and perivascular lymphocytic infiltrates, respectively.

Xu et al. (2012) only tested one concentration of 0.00017 mg Ni/m^3 as nickel sulfate and observed microcirculatory dysfunction and increased macrophages in lung and epididymal white adipose tissues (eWAT) of male apolipoprotein E deficient mice. Similarly, Ying et al. (2013) only tested 0.0004 mg Ni/m^3 metallic nickel in the same mouse strain and observed vascular endothelial dysfunction. The cardiovascular effects noted in these two studies are not corroborated by other findings in rats and mice studies. All the NTP studies examined the cardiovascular system for histological and organ weight changes and no exposure-related changes were noted (NTP 1996a, 1996b, 1996c). Additionally, no cardiovascular clinical signs were noted in any of the animals. The NOAEL and LOAEL values considered for MRL derivation are presented in Table A-2.

Table A-2. Summary of NOAEL and LOAEL Values for Considered for Derivation of an Intermediate-Duration Inhalation MRL

Species (sex)	Frequency/ Duration	NOAEL ($NOAEL_{HEC,ADJ}$) (mg Ni/m^3)	LOAEL ($LOAEL_{HEC,ADJ}$) (mg Ni/m^3)	Effect	Reference (Chemical Form)
Respiratory					
Rat (M)	13 weeks, 5 days/week, 6 hours/day	0.03 (0.0005)	0.11 (0.002)	Increased incidence and severity of lung lesions	Oller et al. 2022 (Nickel sulfate hexahydrate)
Rat (M)	2-6 months, 5 days/week 6 hours/day	0.03 (0.0005)	0.11 (0.002)	Alveolitis that persisted for 4 months after the exposure	Benson et al. 1995a (Nickel sulfate)
Rat (F)	13 weeks, 5 days/week, 6 hours/day	0.06 (0.001)	0.11 (0.003)	Chronic lung inflammation, interstitial infiltrates	NTP 1996c (Nickel sulfate hexahydrate)
Rat (M)	4 weeks, 5 days/week 6 hours/day	0.06 (0.001)	0.11 (0.002)	Minimal to mild alveolus inflammation in 5/5 rats	Efremenko et al. 2014 (Nickel subsulfide)

F=females; HEC=human equivalent concentration; M=males
Indicates study selected as the principal study

Selection of the Principal Study: NTP (1996c) was selected as the principal study. NTP (1996c) and Oller et al. (2022) both identified a respiratory LOAEL of 0.11 mg Ni/m^3 for similar histological effects. The NTP study identified a higher respiratory NOAEL value that was not examined in the Oller et al. (2022) study. Additionally, NTP (1996c) exposed rats to nickel sulfate hexahydrate, therefore, using this study would also be protective against the toxicity of other nickel compounds. The observed respiratory effects are supported by a large body of evidence indicating the lungs are a primary target of intermediate-duration exposure to inhaled nickel.

Summary of the Principal Study:
NTP 1996c. Toxicology and carcinogenesis of nickel sulfate hexahydrate (CAS No. 10101 97-0) in F344/N rats and B6C3F1 mice (inhalation studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

Groups of 10 male and 10 female F344/N rats were exposed to 0.12, 0.25, 0.5, 1.0, or 2.0 mg/m^3 nickel sulfate hexahydrate, corresponding to nickel concentrations of 0.03, 0.06, 0.11, 0.22, or 0.44 mg Ni/m^3, (as calculated by study authors). Rats were exposed for 13 weeks, 6 hours/day, 5 days/week. The mass median aerodynamic diameter (MMAD) (and sigma g) values reported in Table K1 of the paper were 2.31 (2.1), 2.11 (2.7), 3.08 (2.9), 1.81 (2.2), and 2.01 (2.0) for the 0.03, 0.06, 0.11, 0.22, and 0.44 mg Ni/m^3 concentrations, respectively. Endpoints examined included body weight gain, clinical signs, hematology, and organ weight. Furthermore, microscopic examinations of the following organs were completed: adrenal gland, bone, brain, clitoral gland, epididymis, oviduct, esophagus, heart, large intestine, small intestine, kidneys, larynx, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary, preputial gland, prostate, salivary gland, seminal vesicle, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, bladder, and uterus.

No exposure related deaths, alterations in body weight gain, or clinical signs were observed in rats. Several hematological parameters were measured in female rats. Increases in hematocrit, hemoglobin, and erythrocyte concentrations were described as minimal and appeared consistent with mild dehydration. Increased lymphocytes and segmented neutrophils could not be linked to nickel exposure and likely resulted in elevated leukocyte numbers.

Significant alterations in absolute lung weights were observed at concentrations ≥0.11 mg Ni/m^3. Lung lesions consisted of minimal alveolar macrophage hyperplasia at 0.03–0.11 mg Ni/m^3, mild to moderate macrophage hyperplasia at 0.22 and 0.44 mg Ni/m^3, interstitial infiltrates at 0.22 mg Ni/m^3 and higher in males and at 0.11 mg Ni/m^3 and higher in females. Additionally chronic active inflammation characterized by slight thickening of alveolar septa due to an increase in mononuclear inflammatory cells, and few neutrophils and fibroblasts in the interstitium was reported at 0.11 and 0.22 mg Ni/m^3 in females and males, respectively. Hyperplasia of bronchial and mediastinal lymph nodes was observed at 0.22 mg Ni/m^3 and higher. Atrophy of the olfactory epithelium was seen at 0.22 and 0.44 mg Ni/m^3. The minimal alveolar macrophage hyperplasia observed at 0.03 to 0.11 mg Ni/m^3 was not considered an adverse health effect. This is because the slight changes in the number of macrophages were part of the normal physiologic response to inhaled particles and it is not believed to compromise the lung's ability to clear foreign matter. Table A-3 presents the incidence data for chronic active lung inflammation and lung interstitial infiltrates in both sexes.

Table A-3. Incidence of Select Nonneoplastic Lung Lesions in Rats Exposed to Nickel Sulfate Hexahydrate for 13 Weeks via Inhalation (NTP 1996c)

Concentration (mg Ni/m^3)	Chronic Active Inflammation n=10/sex Incidence (Severity)[a]		Interstitial Infiltrate n=10/sex Incidence (Severity)	
	Females	Males	Females	Males
0	0	0	0	1
0.03	0	0	0	0
0.06	0	0	0	1
0.11	4* (1.0)	2 (1.0)	6* (1.0)	5 (1.0)
0.22	10* (1.3)	10* (1.5)	10* (1.0)	10* (1.0)
0.44	10* (1.0)	8* (1.3)	10* (1.0)	9* (1.1)

*Statistically significant from control group
[a]Severity stated where applicable; represents average severity of lesions in affected animals. 1=minimal, 2=mild, 3=moderate, 4=marked

Selection of the Point of Departure for the Provisional MRL:
The NOAEL of 0.06 mg/m^3 for chronic active inflammation in rats is the basis of the intermediate-duration inhalation MRL for nickel. Minimal alveolar macrophage hyperplasia was observed in rats exposed at the two lowest concentrations (0.03 and 0.06 mg Ni/m^3), however NTP noted that when lung effects only consisted of alveolar macrophage hyperplasia, there was only a slight increase in the number of alveolar macrophages and the differences between controls and nickel-exposed animals were subtle. Therefore, the effect was not considered adverse because it is 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 the Benson et al. (1995a) study, which found no effect on the clearance of a nickel sulfate tracer in animals exposed to 0.03 or 0.11 mg Ni/m^3 as nickel sulfate for 6 months. Thus, the 0.06 mg Ni/m^3 concentration was identified as a NOAEL and adjusted for intermittent exposure ($NOAEL_{ADJ}$).

Incidence data for chronic active inflammation in female rats (Table A-3) were fit to all dichotomous models in EPA's BMDS (version 3.2) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. One model was determined to have an adequate model fit and a BMDL value of 0.065 mg Ni/m^3 which is slightly higher than the study NOAEL. Therefore, the POD was defined as the NOAEL of 0.06 mg Ni/m^3 and supported by the BMD modeling.

Adjustment for Intermittent Exposure: The NOAEL of 0.06 mg Ni/m^3 was adjusted from intermittent exposure to continuous exposure using the following equation:

$$NOAEL_{ADJ} = 0.06\ mg\ Ni/m^3 \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.011\ mg\ Ni/m^3$$

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated using the following equation from Lee et al. (2019), adopted from NIOSH (2013):

$$NOAEL_{HEC,ADJ} = NOAEL_{ADJ} \times \frac{VR_R}{VR_H} \times \frac{DF_R}{DF_H} \times \frac{\frac{1-k_R^n}{1-k_R}}{\frac{1-k_H^n}{1-k_H}} \times \frac{RH_R}{RH_H} \times \frac{SA_H}{SA_R}$$

Where VR= ventilation rate, DF = deposition fraction, k = 1-clearance rate, RH=particle retention half time, SA = alveolar surface area, n = exposure days, R = rat, and H = human. For this equation, deposition fractions and ventilation rates for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the pulmonary region is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD V 3.04) developed by Applied Research Associates, Inc. (ARA) to first calculate the deposition fraction (DF) for rats and humans. The MPPD model parameters and results for the rat and human deposition fractions are presented in Table A-4.

Table A-4. MPPD model (v 3.04) Inputs and Results for Rat and Human Models

Parameters	Rats	Humans
Airway morphometry		
Model	Asymmetric Multiple Path	Yem/Schum 5-Lobe
Functional residual capacity (FRC)	4 ml (default)	3300 ml (default)
Upper respiratory tract (URT)	0.42 ml (default)	50 ml (default)
Inhalant properties		
Density[1]	2.07	2.07
Diameter, MMAD[2]	2.11 µm	2.11 µm
GSD[2]	2.7	2.7
Exposure condition		
Aerosol concentration ($NOAEL_{ADJ}$)	0.011 mg/m^3	0.011 mg/m^3
Breathing frequency	102 breaths/min (default)	12 breaths/min (resting default)
Tidal volume	2.1 ml (default)	625 ml (resting default)
Breathing scenario	Nose only	Nasal
Results		
Alveolar region deposition fraction (Total pulmonary deposition fraction)	0.0361	0.1199

[1]PubChem, Ni Sulfate Hexahydrate
[2]From NTP (1996c), Table K1

The daily ventilation rate for rats (VR_R) was calculated using the breathing frequency and tidal volume presented in Table A-4 as follows:

$$102\ \text{min} \times 2.1\ ml = 214.2\ ml/min$$

$$214.2\frac{ml}{min} = 0.0002142\frac{m^3}{min}$$

$$\frac{0.0002142\ m^3}{1\ min} = \frac{X}{1440\ \text{min}\ \ (full\ day)}$$

$$VR_R = 0.31\ \frac{m^3}{day}$$

The daily ventilation rate for humans (VR_H) of 15.3 m^3/day is provided in ATSDR's Guidance for Inhalation Exposures (ATSDR 2021; Table A-1). The ventilation rate was calculated by applying a weighted average of adult age ranges to EPA's inhalation rates for male and female adults >21 years of age, as reported in the Exposure Factors Handbook (EPA 2011; Table 6-1).

The depositions fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $NOAEL_{HEC,ADJ}$. Table A-5 lists the values used within the equation and the source of these values. The exposure days (n) are 91 days to represent 13 weeks of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure.

$$NOAEL_{HEC,ADJ} = 0.011\ \frac{mg^3}{m} \times \frac{0.31\frac{m^3}{day}}{15.3\frac{m^3}{day}} \times \frac{0.0361}{0.1199} \times \frac{\frac{1-(1-0.00105652)^{91}}{1-(1-0.00105652)}}{\frac{1-(1-0.00002)^{91}}{1-(1-0.00002)}} \times \frac{1}{10} \times \frac{54\ m^2}{0.34\ m^2}$$

$$NOAEL_{HEC,ADJ} = 0.001\ mg/m^3$$

Table A-5. Values Used to Calculate Human Equivalent Concentration (HEC) NOAEL for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.31 m^3/day	15.3 m^3/day	Calculated daily ventilation rate
Deposition fraction (DF)	0.0361	0.1199	Calculated using MPPD software
1-clearance rate (k)	0.9989	0.99998	MPPD
Clearance rate	0.00105652	0.00002	MPPD
Ratio of retention half-time (RH)	1	10	NIOSH (2013) per Lee et al. (2019) and Oller et al. (2014)
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA (1994), Table 4-4
Exposure days (n)	91 days	91 days	NTP (1996c)

Uncertainty Factor: The $NOAEL_{HEC,ADJ}$ is divided by a total uncertainty factor of 30:

- 3 for species-to-species extrapolation with dosimetric adjustments
- 10 for human variability

$$Provisional\ MRL = \frac{NOAEL_{HEC,ADJ}}{UFs} = \frac{0.001\ mg\ Ni/m^3}{30}$$

$$= 0.00003\ mg\ Ni/m^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The proposed intermediate-duration inhalation MRL is supported by the LOAEL reported in Xu et al. (2012). In this study, only a single concentration of 0.00017 mg Ni/m^3 as nickel sulfate was tested in mice, which resulted in microcirculatory dysfunction, and increased macrophages in lung and eWAT tissues. Further, the critical effect is supported by Benson et al. (1995a), Efremenko et al. (2014), and Oller et al. (2022) which also identified LOAELs of 0.11 mg Ni/m^3 for lung lesions.

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic
MRL: 0.00001 mg Nickel/m^3 (provisional)
Critical Effect: Chronic lung inflammation, fibrosis, alveolar proteinosis
Reference: NTP 1996c
Point of Departure: NOAEL of 0.03 mg Ni/m^3 ($NOAEL_{HEC,ADJ}$ of 0.00036 mg Ni/m^3)
Uncertainty Factor: 30
LSE Graph Key: 58R
Species: Rats

MRL Summary: A provisional chronic-duration inhalation MRL of 0.00001 mg Ni/m^3 was derived for nickel based on a NOAEL of 0.03 mg Ni/m^3 accompanied with a LOAEL of 0.06 mg Ni/m^3 as nickel sulfate hexahydrate for chronic lung inflammation, fibrosis, and alveolar proteinosis observed in male and female rats exposed for 6 hours per day, 5 days/week for 2 years (NTP 1996c). The NOAEL of 0.03 mg Ni/m^3 was adjusted for intermittent exposure and converted to a human equivalent concentration of 0.00036 mg Ni/m^3. The $NOAEL_{HEC,ADJ}$ of 0.00036 mg Ni/m^3 was divided by a total uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Numerous studies in workers have examined respiratory toxicity following chronic-duration exposure to nickel. Several studies have found no increased risk in death (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. 1984b; Shannon et al. 1991). However respiratory effects have been reported in workers such as welders and nickel refinery workers, these effects include reduced vital capacity, respiratory symptoms, chronic bronchitis, pulmonary fibrosis, and asthma (Berge and Skyberg 2003; Dolovich et al. 1984; Fishwick et al. 2004; Kilburn et al. 1990; Novey et al. 1983; Shirakawa et al. 1990). Two case studies of metalworkers exposed to nickel in indoor air for 5 to 6 years reported nasal septal perforation, nasal obstruction, and mild right-sided epistaxis (Bolek et al. 2017; Peric and Durdevic 2020).

Several animal studies (NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974; Takenaka et al. 1985; Tananka et al. 1988) assessed the noncarcinogenic toxicity of nickel sulfate, nickel chloride, nickel subsulfide, and nickel oxide. The respiratory system is a sensitive target of chronic-duration exposure with LOAELs ranging from 0.06 mg Ni/m^3 to 1 mg Ni/m^3. Respiratory effects observed include inflammatory changes in the lungs (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1974; Tanaka et al. 1988), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), congestion, and increased lung weight (Takenaka et al. 1985). Rats exposed to ≥0.06 to 0.2 mg Ni/m^3 as nickel oxide had decreased survival time compared to controls (Takenaka et al. 1985). Other non-cancerous health effects due to nickel exposure include evidence of renal damage (Oller et al. 2008), changes in hematological parameters (NTP 1996b; Oller et al. 2008), damage to the bronchial lymph nodes (NTP 1996a, 1996b, 1996c; Oller et al. 2008), and decreased body weight gain likely associated with impaired lung function (NTP 1996b, 1996c). Cancer effect levels of 0.4 to 2 mg Ni/m^3 were identified for pheochromocytoma, adenomas and carcinomas in the adrenal cortex and lung (NTP 1996a, 1996b; Oller et al. 2008; Ottolenghi et al. 1974).

Chronic-duration exposure to nickel sulfate, nickel subsulfide, or nickel oxide resulted in chronic active lung inflammation. A 2-year exposure (6 hours/day, 5 days/week) to nickel sulfate resulted in chronic lung inflammation, fibrosis, bronchiolization, and alveolar proteinosis at 0.06 mg Ni/m^3 and atrophy of the olfactory epithelium at 0.11 mg Ni/m^3 (NTP 1996c); no adverse respiratory effects were observed at 0.03 mg Ni/m^3. A similar exposure to nickel subsulfide (NTP 1996b) resulted in chronic inflammation, alveolar epithelium hyperplasia, fibrosis, and rapid and shallow breathing at 0.11 mg Ni/m^3, and atrophy of the nasal olfactory epithelium at 0.73 mg Ni/m^3. Chronic lung inflammation and alveolar epithelial hyperplasia were observed at the lowest nickel oxide concentration tested (0.5 mg Ni/m^3) (NTP 1996a). Similar effects were observed in mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 2 years; however, at LOAEL values similar to or higher than to those in rats. The respiratory NOAEL and LOAEL values considered for MRL derivation are presented in Table A-6.

Table A-6. Respiratory NOAEL and LOAEL Values Relevant to Derivation of a Chronic-Duration Inhalation MRL

Species (sex)	Frequency/ Duration	NOAEL ($NOAEL_{HEC,ADJ}$) (mg Ni/m^3)	LOAEL ($LOAEL_{HEC,ADJ}$) (mg Ni/m^3)	Effect	Reference
Rat (B)	2 years, 5 days/week, 6 hours/day	0.03 (0.00036)	0.06 (0.0009)	Chronic lung inflammation, lung fibrosis	NTP 1996c (Nickel sulfate hexahydrate)
Rat (M)	31 months, 7 days/week, 23 hours/day		0.06 (N/A)[a]	Congestion, increased lung weight, alveolar proteinosis	Takenaka et al. 1985 (Nickel oxide)

B=Both; F=females; M=males; HEC=human equivalent concentration
[a]No information on particle size was provided by the study authors; the HEC could not be modeled.
Indicates study selected as the principal study.

Selection of the Principal Study: NTP (1996c) was selected as the principal study for derivation, as it identified the highest NOAEL in the chronic-duration inhalation database below the lowest LOAEL which was identified for lung lesions in rats. Use of this study would be protective against the toxicity of other nickel compounds, and as similarly observed in the intermediate-duration database, there is substantial evidence indicating the lungs are a primary target of chronic-duration exposure to inhaled nickel. The same study tested concentrations in mice, however the lowest concentration tested was also the LOAEL (0.06 mg Ni/m^3) in the rat studies. Therefore, the rat studies are specifically selected for derivation of this MRL.

Summary of the Principal Study:
NTP 1996c. Toxicology and carcinogenesis of nickel sulfate hexahydrate (CAS No. 10101 97-0) in F344/N rats and B6C3F1 mice (inhalation studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

Groups of 10 male and 10 female F344/N rats were exposed to 0.12, 0.25, or 0.5 mg/m^3 nickel sulfate hexahydrate (0, 0.03, 0.06, or 0.11 mg Ni/m^3 as calculated by study authors) for 6 hours/day, 5 days/week for 2 years. The mean mass median aerodynamic diameter (MMAD) and sigma g values (reported in Table K2 of the paper) were 2.50 (sigma g of 2.38), 2.24 (2.21), and 2.25 (2.08) for the 0.03, 0.06, and 0.11 mg Ni/m^3 concentrations, respectively. Endpoints examined included body weight gain, clinical observations, hematology, and organ weights. Microscopic examinations of the following organs were completed: adrenal gland, bone, brain, clitoral gland, epididymis, oviduct, esophagus, heart, large

intestine, small intestine, kidneys, larynx, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary, preputial gland, prostate, salivary gland, seminal vesicle, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, bladder, and uterus.

No significant alterations in survival, body weight, or the occurrence of clinical signs were observed. The only treatment-related changes noted were in the respiratory tract. Lung lesions consisted of chronic active inflammation, hyperplasia of alveolar macrophages, alveolar proteinosis, and fibrosis at 0.06 and 0.11 mg Ni/m^3. The combined incidences of chronic active inflammation in the male and female rats were 28/106, 24/106, 91/106, and 98/107 in the 0, 0.03, 0.06, and 0.11 mg Ni/m^3 groups, respectively. The chronic inflammation consisted of multifocal, minimal to mild accumulation of macrophages, neutrophils, and cellular debris within the alveolar spaces. No significant alterations in malignant tumors were observed in the lungs. Significant increases in the incidence of lymphoid hyperplasia of the bronchial lymph nodes and atrophy of the olfactory epithelium were observed at 0.11 mg Ni/m^3. Table A-7 presents the incidence data for chronic active lung inflammation and lung interstitial infiltrates in both sexes.

Table A-7. Incidence of Select Nonneoplastic Lung Lesions in Rats Exposed to Nickel Sulfate Hexahydrate for 2 Years via Inhalation (NTP 1996c)

Concentration (mg Ni/m^3)	Chronic Active Inflammation n=53/sex Incidence (Severity)[a]		Lung Fibrosis n=53/sex Incidence (Severity)[a]	
	Females[1]	Males[2]	Females[1]	Males[2]
0	14 (1.4)	14 (1.1)	8 (1.4)	3 (1.0)
0.03	13 (1.2)	11 (1.2)	7 (1.3)	6 (1.2)
0.06	49* (2.1)	42* (1.9)	45* (1.7)	35* (1.7)
0.11	52* (2.3)	46* (2.2)	49* (1.9)	43* (1.8)

*Statistically significant from control group (p≤0.01)
[a]Severity stated where applicable; represents average severity of lesions in affected animals. 1=minimal, 2=mild, 3=moderate, 4=marked

[1]For control group, n=52; For 0.11 mg Ni/m^3 group, n=54
[2]For control group, n=54

Selection of the Point of Departure for the Provisional MRL:
The NOAEL of 0.03 mg Ni/m^3 for chronic active inflammation in rats is the basis of the chronic-duration inhalation MRL for nickel. The NOAEL from NTP (1996c) is the highest NOAEL below the lowest LOAEL in the chronic-duration inhalation database. The LOAEL of 0.06 mg Ni/m^3 is for significantly increased incidence of chronic lung inflammation and lung fibrosis in male and female rats. The concentration of 0.03 mg Ni/m^3 was selected as the POD and adjusted for intermittent exposure ($NOAEL_{ADJ}$).

Incidence data for chronic active inflammation in female rats (Table A-6) were fit to all dichotomous models in EPA's BMDS (version 3.2) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-value (p≥0.1), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. For all model tests, the BMDS recommendation was "Questionable" as none of the models provided an adequate fit for the data. Therefore, the POD was defined as the NOAEL of 0.03 mg/m^3.

Adjustment for Intermittent Exposure: The NOAEL of 0.03 mg Ni/m^3 was adjusted from intermittent exposure to a continuous exposure scenario using the following equation:

$$NOAEL_{ADJ} = 0.03\ mg\ Ni/m^3 \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.0054\ mg\ Ni/m^3$$

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated using the following equation from Lee et al. (2019), adopted from NIOSH (2013):

$$NOAEL_{HEC,ADJ} = NOAEL_{ADJ} \times \frac{VR_R}{VR_H} \times \frac{DF_R}{DF_H} \times \frac{\frac{1-k_R^n}{1-k_R}}{\frac{1-k_H^n}{1-k_H}} \times \frac{RH_R}{RH_H} \times \frac{SA_H}{SA_R}$$

Where VR= ventilation rate, DF = deposition fraction, k = 1-clearance rate, RH=particle retention half time, SA = alveolar surface area, n = exposure days, R = rat, and H = human. For this equation, deposition fractions and ventilation rates for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the pulmonary region is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD V 3.04) developed by Applied Research Associates, Inc. (ARA) to first calculate the deposition fraction (DF) for rats and humans. The MPPD model parameters and results for the rat and human deposition fractions are presented in Table A-8.

Table A-8. MPPD model (v 3.04) Inputs and Results for Rat and Human Models

Parameters	Rats	Humans
Airway morphometry		
Model	Asymmetric Multiple Path	Yem/Schum 5-Lobe
Functional residual capacity (FRC)	4 ml (default)	3300 ml (default)
Upper respiratory tract (URT)	0.42 ml (default)	50 ml (default)
Inhalant properties		
Density[1]	2.07	2.07
Diameter, MMAD[2]	2.5 µm	2.5 µm
GSD[2]	2.38	2.38
Exposure condition		
Aerosol concentration ($NOAEL_{ADJ}$)	0.0054 mg/m^3	0.0054 mg/m^3
Breathing frequency	102 breaths/min (default)	12 breaths/min (resting default)
Tidal volume	2.1 ml (default)	625 ml (resting default)
Breathing scenario	Nose only	Nasal
Results		
Alveolar region deposition fraction (Total pulmonary deposition fraction)	0.0362	0.1224

[1]PubChem, Ni Sulfate Hexahydrate
[2]From NTP (1996c), Table K1

The daily ventilation rate for rats (VR_R) was calculated using the breathing frequency and tidal volume presented in Table A-7 as follows:

$$102\ \text{min} \times 2.1\ ml = 214.2\ ml/min$$

$$214.2\frac{ml}{min} = 0.0002142\frac{m^3}{min}$$

$$\frac{0.0002142\ m^3}{1\ min} = \frac{X}{1440\ \text{min}\ \ (full\ day)}$$

$$VR_R = 0.31\ \frac{m^3}{day}$$

The daily ventilation rate for humans (VR_H) of 15.3 m^3/day is provided in ATSDR's Guidance for Inhalation Exposures (ATSDR 2021; Table A-1). The ventilation rate was calculated by applying a weighted average of adult age ranges to EPA's inhalation rates for male and female adults >21 years of age, as reported in the Exposure Factors Handbook (EPA 2011; Table 6-1).

The deposition fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $NOAEL_{HEC,ADJ}$. Table A-9 lists the values used within the equation and the source of these values. The exposure days (n) are 91 days to represent 13 weeks of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure.

$$NOAEL_{HEC,ADJ} = 0.0054\ \frac{mg^3}{m} \times \frac{0.31\frac{m^3}{day}}{15.3\frac{m^3}{day}} \times \frac{0.0362}{0.1224} \times \frac{\frac{1-(1-0.00105652)^{730}}{1-(1-0.00105652)}}{\frac{1-(1-0.00002)^{730}}{1-(1-0.00002)}} \times \frac{1}{10} \times \frac{54\ m^2}{0.34\ m^2}$$

$$NOAEL_{HEC,ADJ} = 0.00036\ mg/m^3$$

Table A-9. Values Used to Calculate Human Equivalent Concentration (HEC) NOAEL for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.31 m^3/day	15.3 m^3/day	Calculated daily ventilation rate
Deposition fraction (DF); calculated using MPPD software	0.0362	0.1224	Calculated using MPPD software
1-clearance rate (k)	0.9989	0.99998	MPPD
Clearance rate	0.00105652	0.00002	MPPD
Ratio of retention half-time (RH)	1	10	NIOSH 2013 per Lee et al. 2019 and Oller et al. 2014
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA 1994, Table 4-4
Exposure days (n)	730 days	730 days	NTP (1996c)

Uncertainty Factor: The $NOAEL_{HEC,ADJ}$ is divided by a total uncertainty factor of 30:

- 3 for interspecies extrapolation with dosimetric adjustments
- 10 for human variability

$$Provisional\ MRL = \frac{NOAEL_{HEC,ADJ}}{UFs} = \frac{0.00036\ mg\ Ni/m^3}{30}$$

$$= 0.000012\ mg\ Ni/m^3\ (Rounded\ to\ 0.00001\ mg\ Ni/m^3)$$

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL. Data in humans are limited by small sample sizes and not appropriate for extrapolation to a large population. Data from animals in the acute-duration oral database does not provide sufficient information to derive an MRL because serious health effects are seen at the lowest doses tested for critical endpoints in animals.

Rationale for Not Deriving an MRL: Several studies in humans (Gawkrodger et al. 1986; Hindsén et al. 2001; Jensen et al. 2003) examined allergic dermatitis at various challenge doses. These studies were not considered for MRL development as sample sizes for doses tested were no more than 10 individuals in any study, and Jensen et al. (2003) noted that extrapolation of these results to larger populations would not be statistically correct. Jensen et al. (2003) calculated that a sample size of 36 individuals per dose would be required to reach statistical significance. In nickel-sensitized individuals, allergic dermatitis occurred from ingesting a single challenge dose ≥0.058 mg Ni/kg as nickel sulfate (Gawkrodger et al. 1986; Hindsén et al. 2001; Jensen et al. 2003). Sunderman et al. (1988) was the only human study to observe non-dermal effects. However, this resulted from worker exposure to a solution containing nickel sulfate and nickel chloride and exposure could only be estimated.

Several animal studies report serious development and reproductive toxicity at the lowest doses tested thus precluding MRL derivation from these end points due to the ATSDR policy of not deriving MRLs from serious LOAELs. As Table A-10 shows, the severity of development and reproductive effects at 10.3 mg Ni/kg/day varies, including no developmental effects reported (Saini et al. 2014b). Since the database is inconclusive on the potential toxicity at 10.3 mg Ni/kg/day, deriving an MRL based on this value would not be protective, and further data on toxicity at lower doses is needed. At 10.29 mg Ni/kg, pregnant mice showed reduced gestation index (percent of pregnancies resulting in live litter) (Saini et al. 2014b). In the same study, the offspring of exposed dams showed a bodyweight reduction of 14% compared to controls when observed on gestation days 6 through 13 (Saini et al. 2014b). While Saini et al. (2014b) observed no effects for developmental effects at 10.29 mg Ni/kg, this was due to no abnormalities observed in offspring on gestation days 0 through 5 and days 14 through 18. At higher doses, pregnant dams showed reduced litter size, greater offspring body weight loss, and offspring mortality (Saini et al. 2014b). In a separate study, the offspring of dams exposed to 10.29 mg Ni/kg showed skeletal abnormalities including delayed ossification of skull bone, vertebrate, and sternum (El Sekily et al. 2020). The incidence of these abnormalities increased with dose. High fetal resorption and a significantly decreased number of live-birth offspring was reported at all doses (El Sekily et al. 2020). Two studies in mice report serious skeletal anomalies and post-implantation loss at 11.4 mg Ni/kg (Saini et al. 2013, 2014a), and sperm abnormalities in exposed males at 23 to 43 mg Ni/kg (Sobti and Gill 1989).

Only two studies examined neurotoxicity and due to limited evidence, the end point cannot be identified as a critical effect. Mice exposed to a single dose of 12.34 mg Ni/kg showed disturbances to aerobic metabolism, reduced spatial memory performance, and reduced locomotor activity. No effects were seen in mice exposed to 1.2 mg Ni/kg (He et al. 2013). Oller and Erexson (2008) reported neurological effects, as hypoactivity and increased salivation in rats exposed to 27.91 mg Ni/kg/day.

Other adverse effects have been observed in rats, mice, and dogs at doses ranging from 11.35 to 111.6 mg Ni/kg (Ambrose et al. 1976; Haro et al. 1968; He et al. 2013; Oller and Erexson 2007; RTI 1988a, 1988b; Saini et al. 2013, 2014a; Seidenberg et al. 1986; Singla et al. 2006, Sobti and Gill 1989). Haro et al. (1968) calculated LD_{50} values for rats and mice of both sexes following exposure to single doses of nickel acetate. Among rats the LD_{50} values were 116 and 120 mg/kg/day for females and males, respectively. Among mice the LD_{50} values were 139 and 136 mg/kg/day for females and males, respectively (Haro et al. 1968). Exposure-related death was observed at doses ≥140 mg/kg/day in rats (Oller and Erexson 2007; RTI 1988a, 1988b). The relevant NOAEL and LOAEL values are presented in Table A-10.

Table A-10. Effect levels for Select Acute-Duration Oral Exposure to Nickel Studies

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Developmental					
Mouse (NS)	8 days Daily		10.29*	Significant increase in fetal resorption and skeletal anomalies	El Sekily et al. 2020 (Nickel chloride hexahydrate)
Mouse (F)	GD 0-5 Daily	10.29	41.19*	11.75% offspring mortality	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (F)	GD 14-18 Daily	10.29	20.59*	11.11% offspring mortality	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (F)	GD 6-13 Daily		10.29	14% less offspring bodyweight at birth	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (B)	GD 0-5 Daily		11.35	12% fetuses with skeletal defect	Saini et al. 2014a (Nickel chloride hexahydrate)
Reproductive					
Mouse (F)	GD 0-5 Daily		10.29	Reduced gestation index (75%)	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (F)	GD 0-5 Daily		11.35*	Decreased implantation sites/dam and number of live fetuses/dams	Saini et al. 2014a (Nickel chloride hexahydrate)
Mouse (F)	GD 6-13 Daily		11.38*	4.16% embryos resorbed/post-implantation death	Saini et al. 2013 (Nickel chloride hexahydrate)
Dermal					
Human (F)	Once	0.014	0.057	Dermatitis in nickel sensitive subjects	Hindsen et al. 2001 (Nickel sulfate)
Human (F)	Once	0.014	0.057	Dermatitis in nickel sensitive subjects	Jensen et al. 2003 (Nickel sulfate)
Human (NS)	2 days 2 times/day	0.03			Burrows et al. 1981 (Nickel sulfate)
Human (F)	2 days Once/day	0.043	0.097	Allergic dermatitis in sensitized individuals	Gawkrodger et al. 1986 (Nickel sulfate)

B=Both; F=females; GD=gestation day; M=males; NS=Not Specified
* = Serious lowest observed adverse effect level (SLOAEL)

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL as a NOAEL has not been identified in the database and the lowest LOAEL is associated with serious effects, precluding MRL derivation.

Rationale for Not Deriving an MRL: An MRL cannot be derived from human studies as only one study examined effects of intermediate-duration oral nickel exposure. No dermal reactions were reported among 8 women exposed to oral doses of 0.02 mg/kg/day (Santucci et al. 1994).

Among experimental animal studies, Dahdouh et al. (2016) observed serious renal effects at the lowest LOAEL in the intermediate-duration oral database precluding derivation of an intermediate-duration oral MRL that is health protective. Dahdouh et al. (2016) tested the lowest dose in the intermediate-duration oral database for animals, observing adverse hematological and renal effects in male mice exposed to 0.036 mg Ni/kg/day as nickel sulfate. Hematological effects included reduced red blood cells and hemoglobin, and elevated white blood cells; renal effects included proximal tubule degeneration with tubular necrosis and inflammation (Dahdouh et al. 2016). The relevant exposure doses are summarized in Table A-11.

Developmental toxicity data from a two-generation (Springborn Labs 2000a) and a one-generation (Springborn Labs 2000b) rat study were considered for MRL derivation, but a resulting MRL would not be health protective. Springborn Laboratories (2000b) observed significantly increased incidence of stillborn offspring in rats exposed to ≥6.7 mg Ni/kg/day as nickel sulfate hexahydrate starting on postnatal day 22 for 1, 2, or 3 weeks, and in utero. Developmental effects did not appear significant at doses ≤4.5 mg Ni/kg/day (Springborn Laboratories 2000b). At 6.7 mg Ni/kg/day, there was also significant post-implantation loss indicative of reproductive toxicity (Springborn Laboratories 2000b). Both studies provided data on post-implantation loss incidence for each exposed dam and controls. While neither study identified a LOAEL for developmental effects, the data were amenable to benchmark dose modeling. Multiple other studies also report serious developmental effects in rats and mice at doses ranging from 1.3 to 160 mg Ni/kg/day including decreased pup survival, structural abnormalities, and spontaneous abortion (Berman and Rehnberg 1983; Kakela et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). In mice, post-implantation loss is reported at 2.2 mg Ni/kg/day (Pandey et al. 1999). Male reproductive toxicity is observed in several mouse studies at doses of 1.1 to 4.53 mg Ni/kg/day and included sperm abnormalities, changes in sperm motility, concentration, and count, and histological changes (Pandey et al. 1999; Pandey and Srivastava 2000; Toman et al. 2012).

The BMDL values from Springborn Laboratories (2000a, 2000b) are higher than the serious LOAEL identified by Dahdouh et al. (2016), thus these values would not be health protective nor suitable for MRL derivation. BMD modeling was conducted to identify a potential POD for incidence of litter-specific post-implantation loss. The data were fitted to all available dichotomous nested models in EPA's Benchmark Software (BMDS version 3.2). A BMR of 10% was selected in the absence of data that would support a lower BMR. Adequate model fit is judged by four criteria: chi squared goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, BMDLs <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among all of

the models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) is selected as the POD when the difference between the BMDLs estimated from these models was <3-fold; otherwise, the lowest BMDL was chosen. The recommended BMDLs were 3.34 mg Ni/kg/day from the Springborn Laboratories (2000b) data, and 2.01 mg Ni/kg/day from the Springborn Laboratories (2000a) data. Use of the lower BMDL from Springborn Laboratories (2000a) would not be protective since it is higher than the lowest LOAEL in the database where a SLOAEL of 0.036 mg/kg/day for renal effects in mice is identified. Additionally, Smith et al. (1993) identified a developmental SLOAEL of 1.3 mg/kg/day.

Table A-11. Summary of NOAEL, LOAEL, and SLOAEL Values for Intermediate-Duration Oral Exposure to Nickel, Excluding Death Effects

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference
Hematological					
Mouse (M)	28 days Daily		0.036	Changes in blood chemistry (reduced RBCs and hemoglobin; increased WBCs)	Dahdouh et al. 2016 (Nickel sulfate)
Rat (M)	28 days Daily	0.23	0.49	Increased leukocytes (36%)	Weischer et al. 1980 (Nickel chloride)
Renal					
Mouse (M)	28 days Daily		0.036*	Proximal tubule degeneration with tubular necrosis and inflammation	Dahdouh et al. 2016 (Nickel sulfate)
Rat (M)	28 days Daily		0.23	Decreased urea (15%)	Weischer et al. 1980 (Nickel chloride)
Developmental					
Rat (F)	11 weeks (breeding-lactation) 2 litters		1.3*	Decreased pup survival	Smith et al. 1993 (Nickel chloride)
Rat (B)	18 weeks daily	2.2		Post-implantation loss	Springborn Laboratories 2000a (Nickel sulfate hexahydrate)
Rat (F)	F1 generation began on PND 22 for 1, 2, or 3 weeks	4.5	6.7	Significantly increased incidence of stillborn pup	Springborn Laboratories 2000b (Nickel sulfate hexahydrate)

B=Both; F=Female; M=Male; RBCs=red blood cells; WBCs=white blood cells
* = Serious lowest observed adverse effect level (SLOAEL)

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL as the database indicates that serious adverse health effects are associated with the lowest levels of exposure, and no critical effect can be identified as the basis of an MRL.

Rationale for Not Deriving an MRL: No studies were located that exposed humans to nickel for chronic durations. Animal toxicity data following chronic-duration oral exposure to nickel are limited to a few studies that report serious LOAELs at the lowest doses tested. Thus, no exposure levels can be used to derive an MRL value. At the lowest dose tested in animals, 2.2 mg Ni/kg/day, 33% mortality was seen in female rats (20/60 died) (Heim et al. 2007). Heim et al. (2007) also observed increased leukocytes in female rats exposed to 2.2 mg Ni/kg/day as nickel sulfate hexahydrate, and reduced bodyweight in male rats exposed to 6.7 mg Ni/kg/day as nickel sulfate hexahydrate. Kidney, lung, blood effects and exposure-related body weight changes were observed in dogs following exposure to 62.5 mg Ni/kg/day as nickel sulfate (Ambrose et al. 1976).

The EPA derived an oral reference dose of 0.02 mg Ni/kg/day for nickel based on a rat study by Ambrose et al. (1976). This study was not used to derive an oral chronic-duration MRL as authors noted high mortality among all groups especially controls of both sexes and males at the highest dose. In the chronic-duration rat study, groups of 25 males and 25 females were exposed to doses of 0, 7.5, 75, 187.5 mg Ni/kg/day as nickel sulfate in their diet for 2 years. The exposure-related body weight and organ weight changes were the basis of EPA's oral reference dose (Ambrose et al. 1976). Body weight reductions in male and female rats exposed to 187.5 and 75 mg Ni/kg/day, respectively were significant compared to controls. The EPA also reported increased relative heart weights and decreased relative liver weights as critical effects. In the rat study by Ambrose et al. (1976), through the 2-year study poor survival was observed among control groups for both sexes (44/50 controls died) and was significantly higher than for any of the exposure groups. The study quality was deemed insufficient for derivation of a MRL by ATSDR as the high mortality among controls does not allow for accurate interpretation of the results. The EPA's derivation of the oral reference dose similarly states concerns with interpreting results from this study due to the high mortality. The relevant NOAEL and LOAEL doses are summarized in Table A-12.

Table A-12. Summary of Relevant NOAEL and LOAEL Values for Chronic-Duration Oral Exposure to Nickel, Excluding Death Effects

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference
Hematological					
Rat (F)	2 years Daily	11.2			Heim et al. 2007 (Nickel sulfate hexahydrate)
Bodyweight					
Rat (F)	2 years Daily	7.5	75*	34% less body weight compared to controls through 104 weeks of exposure	Ambrose et al. 1976[1] (Nickel sulfate)
Rat (M)	2 years Daily	75	187.5*	up to 35% less body weight compared to controls through 78 weeks of exposure	Ambrose et al. 1976[1] (Nickel sulfate)
Rat (M)	2 years Daily	2.2	6.7	11% reduced bodyweight	Heim et al. 2007 (Nickel sulfate hexahydrate)
Dog (NS)	2 years Daily	25	62.5	10% decrease in body weight gain	Ambrose et al. 1976 (Nickel sulfate)

F=females; M=males; NS=Not Specified

*= Serious lowest observed adverse effect level (SLOAEL)

[1]The chronic-duration rat study by Ambrose et al. (1976) is not included in Table 2-2 or **Figure 2-22. Levels of Significant Exposure to Nickel – Oral**Figure 2-22, as it was excluded from the LSE database due to poor study quality.

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR NICKEL

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to nickel.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for nickel. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of nickel have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of nickel are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion

Table B-1. Inclusion Criteria for the Literature Search and Screen

PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for nickel (ATSDR 2005); thus, the literature search was restricted to studies published between 2003 to 2020. The following main databases were searched in October 2020:

- Science Direct
- PubMed
- Medline
- SCOPUS

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for nickel. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to nickel were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date search hits	Query string
PubMed	
10/2020	TI/AB((Nickel OR “CI 777775” OR Alnico) OR RN(7440-02-0))
8,752 hits	AND
	(MeSH Terms (“Death”[MeSH Terms] OR “Body Weight”[MeSH Terms] OR “respiratory system”[MeSH Terms] OR “cardiovascular diseases”[MeSH Terms] OR “gastrointestinal diseases” [MeSH Terms] OR “hematologic diseases” [MeSH Terms] OR “musculoskeletal diseases” [MeSH Terms] OR “hepatic infraction” [MeSH Terms] OR “renal insufficiency” [MeSH Terms] OR dermatology [MeSH Terms] OR “endocrine system” [MeSH Terms] OR neurology[MeSH Terms] OR “reproductive health” [MeSH Terms] OR “developmental disabilities” [MeSH Terms] OR “psychology, developmental” [MeSH Terms] OR Neoplasms[MeSH Terms] OR “DNA Damage” [MeSH Terms])
	OR
	TI/AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (tiab(“nickel acetate” OR “Acetic acid” OR “Nickel di(acetate)” OR “Nickel diacetate” OR “Nickel(2+) acetate” OR “Nickel(2+) diacetate” OR “Nickel(2+) salt” OR “Nickel(cento) acetate” OR “Nickel(II) acetate” OR “Nickelous acetate”) OR RN(“373-02-4”))
	AND
	(MeSH Terms (“Death”[MeSH Terms] OR “Body Weight”[MeSH Terms] OR “respiratory system”[MeSH Terms] OR “cardiovascular diseases”[MeSH Terms] OR “gastrointestinal diseases” [MeSH Terms] OR “hematologic diseases” [MeSH Terms] OR “musculoskeletal diseases” [MeSH Terms] OR “hepatic infraction” [MeSH Terms] OR “renal insufficiency” [MeSH Terms] OR dermatology [MeSH Terms] OR “endocrine system” [MeSH Terms] OR neurology[MeSH Terms] OR “reproductive health” [MeSH Terms] OR “developmental disabilities” [MeSH Terms] OR “psychology, developmental” [MeSH Terms] OR Neoplasms[MeSH Terms] OR “DNA Damage” [MeSH Terms])
	OR
	TI/AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (tiab(“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	"Nickel ammonium sulfate" OR "Nickel(II) ammonium sulfate" OR "Sulfuric acid") OR RN("7785-20-8"))
	AND
	(MeSH Terms ("Death"[MeSH Terms] OR "Body Weight"[MeSH Terms] OR "respiratory system"[MeSH Terms] OR "cardiovascular diseases"[MeSH Terms] OR "gastrointestinal diseases" [MeSH Terms] OR "hematologic diseases" [MeSH Terms] OR "musculoskeletal diseases" [MeSH Terms] OR "hepatic infraction" [MeSH Terms] OR "renal insufficiency" [MeSH Terms] OR dermatology [MeSH Terms] OR "endocrine system" [MeSH Terms] OR neurology[MeSH Terms] OR "reproductive health" [MeSH Terms] OR "developmental disabilities" [MeSH Terms] OR "psychology, developmental" [MeSH Terms] OR Neoplasms[MeSH Terms] OR "DNA Damage" [MeSH Terms])
	OR
	TI/AB (Death OR "Body weight" OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR "health effects"))
MEDLINE	
10/2020	(Nickel OR "CI 777775" OR Alnico) OR RN ("7440-02-0")
5,186 hits	AND
	((MH Death OR "Body Weight" OR "respiratory system" OR "cardiovascular diseases" OR "gastrointestinal diseases" OR "hematologic diseases" OR "musculoskeletal diseases" OR "hepatic infraction" OR "renal insufficiency" OR dermatology OR "endocrine system" OR neurology OR "reproductive health" OR "developmental disabilities" OR "psychology, developmental" OR Neoplasms OR "DNA Damage") OR AB (Death OR "Body weight" OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR "health effects")) ("nickel acetate" OR "Acetic acid" OR "Nickel di(acetate)" OR "Nickel diacetate" OR "Nickel(2+) acetate" OR "Nickel(2+) diacetate" OR "Nickel(2+) salt" OR "Nickel(cento) acetate" OR "Nickel(II) acetate" OR "Nickelous acetate") OR RN ("373-02-4")
	AND
	((MH Death OR "Body Weight" OR "respiratory system" OR "cardiovascular diseases" OR "gastrointestinal diseases" OR "hematologic diseases" OR "musculoskeletal diseases" OR "hepatic infraction" OR "renal insufficiency" OR dermatology OR "endocrine system" OR neurology OR "reproductive health" OR "developmental disabilities" OR "psychology, developmental" OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR “Nickel ammonium sulfate” OR “Nickel(II) ammonium sulfate” OR “Sulfuric acid”) OR RN(“7785-20-8”) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”))
Science Direct 10/2020 547 hits	(Nickel OR “CI 777775” OR Alnico OR “7440-02-0”) AND 547 ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel acetate” OR “Acetic acid” OR “Nickel di(acetate)” OR “Nickel diacetate” OR “Nickel(2+) acetate” OR “Nickel(2+) diacetate” OR “Nickel(2+) salt” OR “Nickel(cento) acetate” OR “Nickel(II) acetate” OR “Nickelous acetate” OR “373-02-4”) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR “Nickel ammonium sulfate” OR “Nickel(II) ammonium sulfate” OR “Sulfuric acid” OR “7785-20-8”) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”))
Scopus 10/2020 3,520 hits	Title Abstract(Nickel OR “CI 777775” OR Alnico OR 7440-02-0) AND Title Abstract ((Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel acetate” OR “Acetic acid” OR “Nickel di(acetate)” OR “Nickel diacetate” OR “Nickel(2+) acetate” OR “Nickel(2+) diacetate” OR “Nickel(2+) salt” OR “Nickel(cento) acetate” OR “Nickel(II) acetate” OR “Nickelous acetate” OR “373-02-4”) AND Title Abstract (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR “health effects”) (“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	"Nickel ammonium sulfate" OR "Nickel(II) ammonium sulfate" OR "Sulfuric acid" OR "7785-20-8") AND Title Abstract (Death OR "Body weight" OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR "health effects")

The October 2020 results were:

- Number of records identified from Science Direct, PubMed, Medline, and SCOPUS (after duplicate removal): 10,739
- Number of records identified from other strategies: 6
- Total number of records to undergo literature screening: 10,745

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on nickel:

- Title and abstract screen
- Full text screen

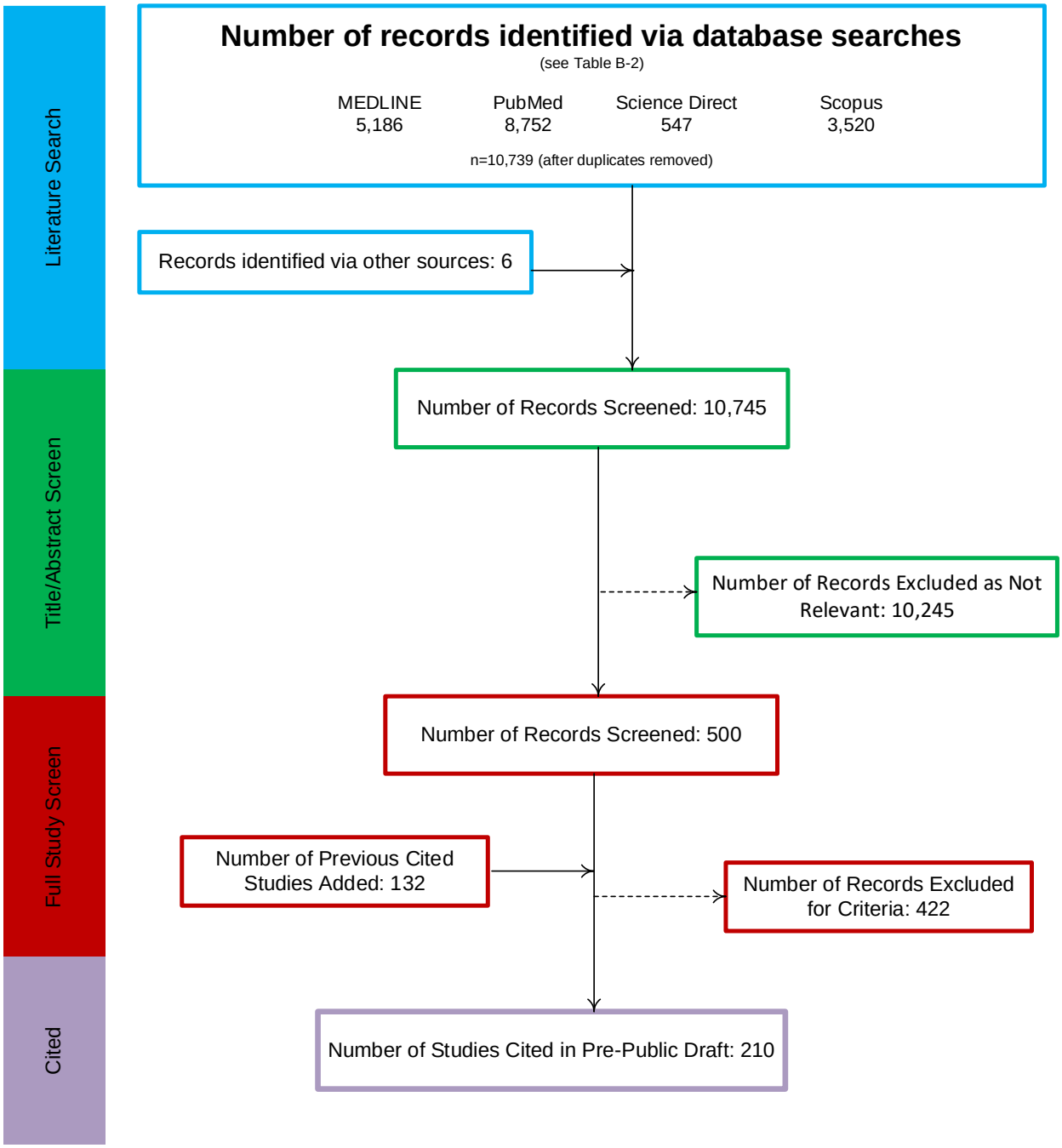
Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 10,745
- Number of studies considered relevant and moved to the next step: 500

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 500
- Number of studies cited in the pre-public draft of the toxicological profile: 78
- Total number of studies cited in the profile: 210

Figure B-1. October 2020 Literature Search Results and Screen for Nickel



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR NICKEL

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to nickel, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to nickel:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, and dermal exposure to nickel. The inclusion criteria used to identify relevant studies examining the health effects of nickel are presented in Table B-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of nickel. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the literature search to update the existing toxicological profile for nickel (ATSDR 2005) was restricted to studies published between 2003 and 2020. See Appendix B for the databases searched and the strategy.

A total of 10,739 records relevant to the health effects section of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR NICKEL, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of nickel.

Title and Abstract Screen. In the Title and Abstract Screen step, 10,745 records were reviewed; 500 studies were considered to meet the health effects inclusion criteria in Table B-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 500 health effects studies identified in the update literature was performed. Of these studies, 422 did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanism of action or were relevant to other sections of the toxicological profile. Additionally, 132 studies cited in the LSE tables for the existing profile were included in the full study screen bringing the total number of studies for the qualitative review to 210.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-1. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

A summary of the extracted data for each study is presented in the Supplemental Documents for nickel and overviews of the results of the inhalation, oral and dermal exposure studies are presented in Sections 2.2 - 2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Table 2-1, Table 2-2, and Table 2-3, respectively).

Table C-1. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for nickel identified in human and animal studies are presented in Tables C-2 and C-3, respectively.

Human studies evaluating noncancerous effects are primarily cohort studies of occupational exposure that examined respiratory effects. Several other studies were conducted at the population level to examine associations between exposure to nickel in air and respiratory and/or cardiovascular mortality. Most studies in humans analyzed the increased risk of various types of cancer both among general and occupational populations. Taken together, studies in humans indicate that the respiratory system is a target of nickel toxicity particularly through the inhalation route. Inhalation and oral animal studies have examined a wide range primarily focusing on the respiratory and immunological system and a majority of these studies indicated an adverse health effect. Dermal studies in humans focused on examining dermal effects while dermal studies in animals were limited to examining a few endpoints. The respiratory system is considered the target of nickel toxicity and given that effects were seen at low doses in animals, intermediate- and chronic-duration inhalation MRL were derived. Additionally, nickel allergy is commonly examined in humans through dermal patch testing, and many animal studies indicate nickel has some effect on immune function. Studies examining the respiratory and immune endpoints were carried through Steps 4–8 of the systematic review.

Table C-2. Overview of the Health Outcomes for Nickel Evaluated in Human Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Cohort	0	20	5	1	0	0	1	2	0	0	0	3	0	1	3	0	36
	0	7	0	0	0	0	1	2	0	0	0	3	0	1	3	0	20
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	5
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2
Population	0	5	11	0	0	0	0	0	0	0	0	0	1	5	1	0	9
	0	5	9	0	0	0	0	0	0	0	0	0	1	1	1	0	3
Case series	0	4	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
	0	4	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Oral Studies																	
Cohort	0	0	0	1	0	0	0	0	13	0	0	0	1	0	0	0	0
	0	0	0	1	0	0	0	0	9	0	0	0	1	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
Case series	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermal Studies																	
Cohort	0	1	0	0	0	0	0	1	15	0	0	1	0	0	0	0	0
	0	1	0	0	0	0	0	0	14	0	0	1	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

Table C-3. Overview of the Health Outcomes for Nickel Evaluated in Experimental Animal Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Acute-duration	5	6	4	3	1	3	3	3	3	0	3	6	3	3	0	0	0
	3	6	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0
Intermediate-duration	8	13	5	3	3	3	4	5	3	0	4	10	4	3	1	1	1
	2	13	2	0	2	0	0	1	0	0	0	10	1	1	1	1	1
Chronic-duration	6	7	4	4	4	2	5	6	4	0	4	5	4	3	0	1	4
	3	7	0	0	2	0	0	1	1	0	2	4	0	0	0	1	4
Oral Studies																	
Acute-duration	1	1	0	2	0	0	0	0	0	0	0	0	3	5	5	3	0
	1	1	0	2	0	0	0	0	0	0	0	0	2	4	4	3	0
Intermediate-duration	12	4	4	3	5	0	9	10	1	1	2	3	2	9	6	2	0
	7	3	1	1	5	0	4	7	0	0	1	3	1	5	6	2	0
Chronic-duration	2	1	1	1	2	1	1	1	1	0	1	1	1	1	0	0	0
	2	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
Dermal Studies																	
Acute-duration	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Intermediate-duration	0	0	0	0	1	0	2	2	1	0	0	0	0	1	0	1	0
	0	0	0	0	0	0	2	1	1	0	0	0	0	1	0	1	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies and animal experimental studies are presented in C-4, C-5, and C-6, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-4. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-5. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational epidemiological studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational epidemiological studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of nickel health effects studies (observational epidemiology and animal experimental studies) are presented in Table C-7 and C-8, respectively.

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables? *	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization? *	Detection bias — Is there confidence in the outcome assessment? *	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory							
Cohort Studies Inhalation							
Arena et al. 1998	++	+	++	-	-	++	Second
Bell et al. 2009	+	-	+	-	+	++	Second
Bell et al. 2014	-	-	+	-	+	++	Second
Berge and Skyberg 2003	+	+	-	-	-	++	Second
Cornell and Landis 1984	+	+	+	-	-	++	Second
Cox et al. 1981	+	-	+	-	-	+	Third
Cragle et al. 1984	+	-	+	-	-	+	Third
Dolovich et al.1984	-	+	+	-	+	+	Second

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables? ***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization? ***	Detection bias — **Is there confidence in the outcome assessment? ***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Egedahl et al. 2001	-	+	+	-	+	++	Second
Enterline and Marsh 1982	-	-	+	-	+	++	Second
Fishwick et al. 2004	++	+	+	-	-	++	Second
Gehring et al. 2015	+	+	+	--	-	+	Second
Kilburn et al. 1990	+	-	+	-	+	++	Second
Moulin et al. 2000	+	+	-	-	+	+	Second
Muir et al. 1993	+	+	-	-	+	+	Second
Patel et al. 2009	+	-	+	-	-	++	Third
Polednak 1981	-	-	+	+	+	+	Second
Redmond 1984	+	+	-	-	+	+	Second

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables? *	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization? *	Detection bias — Is there confidence in the outcome assessment? *	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Roberts et al. 1989a	+	-	+	-	+	+	Second
Rosa et al. 2016	+	+	+	-	-	+	Second
Schachter et al. 2020	-	+	+	-	+	+	Second
Shannon et al. 1984a	+	+	-	-	-	+	Second
Shannon et al. 1984b	+	-	-	--	-	+	Third
Shannon et al. 1991	+	-	+	+	-	+	Second
Shirakawa et al. 1990	-	+	+	-	+	+	Second
Outcome: Immunological							
Cohort Studies Inhalation							
Bencko et al. 1983	--	-	+	-	-	++	Third

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
Reference	Were the comparison groups appropriate?	**Did the study design or analysis account for important confounding and modifying variables? ***	Were outcome data complete without attrition or exclusion from analysis?	**Is there confidence in the exposure characterization? ***	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
Bencko et al. 1986	++	+	+	-	+	++	Second
Shirakawa et al. 1990	-	+	+	-	+	+	Second
Cohort Studies Dermal							
Mozzanica et al. 1990	+	-	+	+	-	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory									
Inhalation Acute Exposure									
Benson et al. 1995b (Rat)	-	-	+	-	+	++	+	+	First
Efremenko et al. 2014 (Rat)	++	-	+	-	+	+	++	+	First
Inhalation Intermediate Exposure									
Benson et al. 1995a (Rat)	-	-	+	-	+	++	+	+	First
Benson et al. 1995a (Rat)	-	-	+	-	+	++	+	+	First
Benson et al. 1995a (Mice)	-	-	+	-	+	++	+	+	First
Benson et al. 1995a (Mice)	-	-	+	-	+	++	+	+	First
Benson et al. 1995b (Rat)	-	-	+	-	+	++	+	+	First
Bingham et al. 1972 (Rat)	-	-	+	-	+	-	+	+	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
Bingham et al. 1972 (Rat)	-	-	+	-	+	-	+	+	Second
Efremenko et al. 2014 (Rat)	++	-	+	-	+	+	++	+	First
Evans et al. 1995 (Rat)	-	-	++	-	+	+	++	++	First
Horie et al. 1985 (Rat)	-	-	+	-	+	-	-	+	Second
Johansson and Camner 1986 (Rabbit)	-	-	-	-	+	-	-	+	Third
NTP 1996a (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 16 D	-	-	+	-	++	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
NTP 1996b (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
Oller et al. 2022 (Rat) 13 Wk	++	+	+	+	++	++	+	+	First
Oller et al. 2022 (Rat) 13 Wk	++	+	+	+	++	++	+	+	First
Weischer et al. 1980 (Rat)	-	-	+	-	+	-	+	+	Second
Inhalation Chronic Exposure									
NTP 1996a (Rat)	-	-	+	-	++	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
NTP 1996a (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice)	-	-	+	-	++	++	++	++	First
Oller et al. 2008 (Rat)	++	-	+	-	+	++	++	++	First
Ottolenghi et al. 1974 (Rat)	-	-	+	-	+	-	+	+	Second
Takenaka et al. 1985 (Rat)	-	-	++	-	+	-	+	+	Second
Oral Intermediate Exposure									
American Biogenics Corp 1988 (Rat)	++	-	+	-	+	++	+	+	First
Obone et al. 1999 (Rat)	-	-	+	-	++	+	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
RTI 1988a, 1988b (Rat)	+	-	+	-	+	-	+	+	First
Springborn Laboratories 2002 (Rat)	++	-	+	-	++	++	++	++	First
Oral Chronic Exposure									
Ambrose et al. 1976 (Rat)	-	-	+	-	+	-	+	+	Second
Ambrose et al. 1976 (Dog)	-	-	+	-	+	-	+	+	Second
Outcome: Immunological									
Inhalation Acute Exposure									
Adkins et al. 1979a (Mice)	-	-	+	-	+	-	+	+	Second
Adkins et al. 1979b (Mice)	-	-	+	-	+	-	+	+	Second
Adkins et al. 1979c (Mice)	-	-	+	-	+	-	+	+	Second
Buxton et al. 2021 (Mice)	++	-	++	-	+	+	+	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Graham et al. 1978 (Mice)	-	-	+	-	+	-	+	+	Second
Inhalation Intermediate Exposure									
Haley et al. 1990 (Mice)	+	-	+	-	+	++	++	++	First
Haley et al. 1990 (Mice)	+	-	+	-	+	++	++	++	First
Haley et al. 1990 (Mice)	+	-	+	-	+	++	++	++	First
Johansson et al. 1980 (Rabbit)	-	-	+	-	++	-	+	+	Second
Johansson et al. 1987 (Rabbit)	-	-	+	-	+	-	+	+	Second
Johansson et al. 1988 (Rabbit)	-	-	+	-	+	-	+	+	Second
Johansson et al. 1989 (Rabbit)	-	-	+	-	+	-	+	+	Second
Morimoto et al. 1995 (Rat)	-	-	+	-	+	+	+	+	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
NTP 1996a (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 13 Wk	-	-	+	-	++	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
NTP 1996c (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
Spiegelberg et al. 1984 (Rat)	-	-	+	-	+	-	+	+	Second
Xu et al. 2012 (Mice)	+	-	+	-	+	-	++	++	First
Inhalation Chronic Exposure									
NTP 1996a (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice)	-	-	+	-	++	++	++	++	First
Oller et al. 2008 (Rat)	++	-	+	-	+	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
Ottolenghi et al. 1974 (Rat)	-	-	+	-	+	-	+	+	Second
Oral Intermediate Exposure									
Dieter et al. 1988 (Mice)	-	-	+	-	+	-	+	+	Second
Ilback et al. 1994 (Mice)	+	-	+	-	+	-	+	+	First
Obone et al. 1999 (Rat)	-	-	+	-	++	+	++	++	First
Oral Chronic Exposure									
Ambrose et al. 1976 (Rat)	-	-	+	-	+	-	+	+	Second
Ambrose et al. 1976 (Dog)	-	-	+	-	+	-	+	+	Second
Dermal Acute Exposure									
Siller and Seymour 1994 (Mice)	-	-	+	-	+	-	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to nickel and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence**: the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence**: the true effect may be reflected in the apparent relationship
- **Low confidence**: the true effect may be different from the apparent relationship
- **Very low confidence**: the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study, observation epidemiology, human-controlled exposures, and experimental animals. Unless there was a clear need for delineation in the confidence for a particular outcome, confidence assessments were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to nickel and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key study design features was determined for individual studies using four "yes or no" questions which were customized for observational epidemiology, human-controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human-controlled exposure studies, and experimental animal studies are presented in C-9, C-10, and C-11, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence**: Studies in which the responses to the four questions were "yes."
- **Moderate Initial Confidence**: Studies in which the responses to only three of the questions were "yes."
- **Low Initial Confidence**: Studies in which the responses to only two of the questions were "yes."
- **Very Low Initial Confidence**: Studies in which the response to one or none of the questions was "yes."

Table C-9. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-10. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested (i.e., 10 or more subjects)
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-11. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested (i.e., 3 or more animals for acute exposure, 10-20 animals for intermediate exposure, 50 or more animals for chronic exposure)
Appropriate parameters used to assess a potential adverse effect (i.e., clinical, gross, and histopathological outcomes were assessed. If an endpoint was not amendable to a clinical assessment then we did not downgrade the confidence in a study for not including it)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis (i.e., the statistical procedures used were presented in the paper and they were appropriate for the data)

The presence or absence of the key features and the initial confidence levels for studies examining respiratory and immunological effects observed in observational epidemiology and animal experimental studies are presented in Tables C-12 and C-13, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-14.

Table C-12. Presence of Key Features of Study Design for Nickel—Observational Epidemiology Studies

Reference	Key features: Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	Initial study confidence
Outcome: Respiratory Effects					
Cohort Inhalation Studies					
Arena et al. 1998	No	Yes	No	Yes	Low
Bell et al. 2009	No	Yes	No	Yes	Low
Bell et al. 2014	No	Yes	No	Yes	Low
Berge and Skyberg 2003	No	No	Yes	Yes	Low
Cornell and Landis 1984	No	Yes	Yes	Yes	Moderate
Cox et al. 1981	No	Yes	Yes	Yes	Moderate
Cragle et al. 1984	No	Yes	Yes	Yes	Moderate
Dolovich et al.1984	No	Yes	Yes	Yes	Moderate
Egedahl et al. 2001	No	Yes	Yes	Yes	Moderate
Enterline and Marsh 1982	No	Yes	Yes	Yes	Moderate
Fishwick et al. 2004	No	Yes	Yes	Yes	Moderate
Gehring et al. 2015	No	No	Yes	Yes	Low
Kilburn et al. 1990	No	Yes	Yes	Yes	Moderate
Moulin et al. 2000	No	Yes	Yes	Yes	Moderate
Muir et al. 1993	No	Yes	Yes	Yes	Moderate
Patel et al. 2009	No	Yes	Yes	Yes	Moderate
Polednak 1981	No	Yes	Yes	Yes	Moderate
Redmond 1984	No	Yes	Yes	Yes	Moderate
Roberts et al. 1989a	No	Yes	Yes	Yes	Moderate
Rosa et al. 2016	No	Yes	Yes	Yes	Moderate
Schachter et al. 2020	No	Yes	Yes	No	Low
Shannon et al. 1984a	No	Yes	Yes	Yes	Moderate
Shannon et al. 1984b	No	Yes	Yes	No	Low
Shannon et al. 1991	No	Yes	Yes	Yes	Moderate
Shirakawa et al. 1990	No	Yes	Yes	Yes	Moderate
Outcome: Immunological Effects					
Cohort Inhalation Studies					
Bencko et al. 1983	No	Yes	Yes	Yes	Moderate

Table C-12. Presence of Key Features of Study Design for Nickel—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	
Bencko et al. 1986	No	Yes	Yes	Yes	Moderate
Shirakawa et al. 1990	No	Yes	Yes	Yes	Moderate
Cohort Dermal Studies					
Mozzanica et al. 1990	No	Yes	Yes	Yes	Moderate

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Respiratory Effects					
Inhalation Acute Exposure					
Benson et al. 1995b (Rat)	Yes	Yes	Yes	Yes	High
Efremenko et al. 2014 (Rat)	Yes	Yes	Yes	Yes	High
Inhalation Intermediate Exposure					
Benson et al. 1995a (Rat)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (Rat)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (Mice)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (Mice)	Yes	Yes	Yes	Yes	High
Benson et al. 1995b (Rat)	Yes	Yes	Yes	Yes	High
Bingham et al. 1972 (Rat)	Yes	Yes	Yes	No	Moderate
Bingham et al. 1972 (Rat)	Yes	Yes	Yes	No	Moderate
Efremenko et al. 2014 (Rat)	Yes	Yes	Yes	Yes	High

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Evans et al. 1995 (Rat)	Yes	Yes	Yes	Yes	High
Horie et al. 1985 (Rat)	Yes	No	Yes	No	Low
Johansson and Camner 1986 (Rabbit)	No	No	Yes	No	Very Low
NTP 1996a (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
Oller et al. 2022 (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
Weischer et al. 1980 (Rat)	Yes	Yes	Yes	Yes	High
Inhalation Chronic Exposure					
NTP 1996a (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (Rat)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (Rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1974 (Rat)	Yes	Yes	Yes	Yes	High
Takenaka et al. 1985 (Rat)	Yes	No	Yes	No	Low
Tanaka et al. 1988 (Rat)	Yes	No	Yes	No	Low
Oral Intermediate Exposure					

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features: Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
American Biogenics Corp 1988 (Rat)	Yes	Yes	Yes	Yes	High
Obone et al. 1999 (Rat)	Yes	No	Yes	Yes	Moderate
RTI 1988a, 1988b (Rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2002 (Rat)	Yes	Yes	Yes	Yes	High
Oral Chronic Exposure					
Ambrose et al. 1976 (Rats)	Yes	No	Yes	No	Low
Ambrose et al. 1976 (Dogs)	Yes	No	Yes	No	Low
Outcome: Immunological Effects					
Inhalation Acute Exposure					
Adkins et al. 1979a (Mice)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979b (Mice)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979c (Mice)	Yes	Yes	Yes	Yes	High
Buxton et al. 2021 (Mice)	Yes	Yes	Yes	Yes	High
Graham et al. 1978 (Mice)	Yes	Yes	Yes	Yes	High
Inhalation Intermediate Exposure					
Haley et al. 1990 (Mice)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (Mice)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (Mice)	Yes	Yes	Yes	Yes	High
Johansson et al. 1980 (Rabbit)	Yes	No	Yes	No	Low
Johansson et al. 1987 (Rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1988(Rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1989 (Rabbit)	Yes	No	Yes	Yes	Moderate
Morimoto et al. 1995 (Rat)	Yes	No	Yes	Yes	Moderate
NTP 1996a (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 13 Wk	Yes	Yes	Yes	Yes	High

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
NTP 1996b (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
Spiegelberg et al. 1984 (Rat)	Yes	Yes	Yes	Yes	High
Xu et al. 2012 (Mice)	Yes	No	Yes	Yes	Moderate
Inhalation Chronic Exposure					
NTP 1996a (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (Rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1974 (Rat)	Yes	Yes	Yes	Yes	High
Oral Intermediate Exposure					
Dieter et al. 1988 (Mice)	Yes	Yes	Yes	Yes	High
Ilback et al. 1994 (Mice)	Yes	No	Yes	Yes	Moderate
Obone et al. 1999 (Rat)	Yes	No	Yes	Yes	Moderate
Oral Chronic Exposure					
Ambrose et al. 1976 (Rats)	Yes	No	Yes	No	Low
Ambrose et al. 1976 (Dogs)	Yes	No	Yes	No	Low
Dermal Acute Exposure					
Siller and Seymour 1994 (Mice)	Yes	No	Yes	Yes	Moderate

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory Effects		
Inhalation Exposure		
Human Cohort Studies		
Arena et al. 1998	Low	Moderate
Bell et al. 2009	Low	
Bell et al. 2014	Low	
Berge and Skyberg 2003	Low	
Cornell and Landis 1984	Moderate	
Cox et al. 1981	Moderate	
Cragle et al. 1984	Moderate	
Dolovich et al.1984	Moderate	
Egedahl et al. 2001	Moderate	
Enterline and Marsh 1982	Moderate	
Fishwick et al. 2004	Moderate	
Gehring et al. 2015	Low	
Kilburn et al. 1990	Moderate	
Moulin et al. 2000	Moderate	
Muir et al. 1993	Moderate	
Patel et al. 2009	Moderate	
Polednak 1981	Moderate	
Redmond 1984	Moderate	
Roberts et al. 1989a	Moderate	
Rosa et al. 2016	Moderate	
Shachter et al. 2020	Low	
Shannon et al. 1984a	Moderate	
Shannon et al. 1984b	Low	
Shannon et al. 1991	Moderate	
Shirakawa et al. 1990	Moderate	
Animal Inhalation Acute Exposure		
Benson et al. 1995b (Rat)	High	High
Efremenko et al. 2014 (Rat)	High	
Animal Inhalation Intermediate Exposure		
Benson et al. 1995a (Rat)	High	High
Benson et al. 1995a (Rat)	High	
Benson et al. 1995a (Mice)	High	
Benson et al. 1995a (Mice)	High	
Benson et al. 1995b (Rat)	High	
Bingham et al. 1972 (Rat)	Moderate	
Bingham et al. 1972 (Rat)	Moderate	

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Efremenko et al. 2014 (Rat)	High	
Evans et al. 1995 (Rat)	High	
Horie et al. 1985 (Rat)	Low	
Johansson and Camner 1986 (Rabbit)	Very Low	
NTP 1996a (Rat) 16 D	High	
NTP 1996a (Mice) 16 D	High	
NTP 1996a (Rat) 13 Wk	High	
NTP 1996a (Mice) 13 Wk	High	
NTP 1996b (Rat) 16 D	High	
NTP 1996b (Mice) 16 D	High	
NTP 1996b (Rat) 13 Wk	High	
NTP 1996b (Mice) 13 Wk	High	
NTP 1996c (Rat) 16 D	High	
NTP 1996c (Mice) 16 D	High	
NTP 1996c (Rat) 13 Wk	High	
NTP 1996c (Mice) 13 Wk	High	
Oller et al. 2022 (Rat) 13 Wk	High	
Oller et al. 2022 (Rat) 13 Wk	High	
Weischer et al. 1980 (Rat)	High	
Animal Inhalation Chronic Exposure		
NTP 1996a (Rat)	High	High
NTP 1996a (Mice)	High	
NTP 1996b (Rat)	High	
NTP 1996b (Mice)	High	
NTP 1996c (Rat)	High	
NTP 1996c (Mice)	High	
Oller et al. 2008 (Rat)	High	
Ottolenghi et al. 1974 (Rat)	High	
Takenaka et al. 1985 (Rat)	Low	
Tanaka et al. 1988 (Rat)	Low	
Oral Exposure		
Animal Oral Intermediate Exposure		
American Biogenics Corp 1988 (Rat)	High	High
Obone et al. 1999 (Rat)	Moderate	
RTI 1988a, 1988b (Rat)	High	
Springborn Laboratories 2002 (Rat)	High	
Animal Oral Chronic Exposure		
Ambrose et al. 1976 (Rats)	Low	Low
Ambrose et al. 1976 (Dogs)	Low	

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Immunological Effects		
Inhalation Exposure		
Human Cohort Studies		
Bencko et al. 1983	Moderate	Moderate
Bencko et al. 1986	Moderate	
Shirakawa et al. 1990	Moderate	
Animal Inhalation Acute Exposure		
Adkins et al. 1979a (Mice)	High	High
Adkins et al. 1979b (Mice)	High	
Adkins et al. 1979c (Mice)	High	
Buxton et al. 2021 (Mice)	High	
Graham et al. 1978 (Mice)	High	
Animal Inhalation Intermediate Exposure		
Haley et al. 1990 (Mice)	High	High
Haley et al. 1990 (Mice)	High	
Haley et al. 1990 (Mice)	High	
Johansson et al. 1980 (Rabbit)	Low	
Johansson et al. 1987 (Rabbit)	Moderate	
Johansson et al. 1988(Rabbit)	Moderate	
Johansson et al. 1989 (Rabbit)	Moderate	
Morimoto et al. 1995 (Rat)	Moderate	
NTP 1996a (Rat) 16 D	High	
NTP 1996a (Mice) 16 D	High	
NTP 1996a (Rat) 13 Wk	High	
NTP 1996a (Mice) 13 Wk	High	
NTP 1996b (Rat) 16 D	High	
NTP 1996b (Mice) 16 D	High	
NTP 1996b (Rat) 13 Wk	High	
NTP 1996b (Mice) 13 Wk	High	
NTP 1996c (Rat) 16 D	High	
NTP 1996c (Mice) 16 D	High	
NTP 1996c (Rat) 13 Wk	High	
NTP 1996c (Mice) 13 Wk	High	
Spiegelberg et al. 1984 (Rat)	High	
Xu et al. 2012 (Mice)	Moderate	
Animal Inhalation Chronic Exposure		
NTP 1996a (Rat)	High	High
NTP 1996a (Mice)	High	
NTP 1996b (Rat)	High	

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1996b (Mice)	High	
NTP 1996c (Rat)	High	
NTP 1996c (Mice)	High	
Oller et al. 2008 (Rat)	High	
Ottolenghi et al. 1974 (Rat)	High	
Oral Exposure		
Animal Oral Intermediate Exposure		
Dieter et al. 1988 (Mice)	High	Moderate
Ilback et al. 1994 (Mice)	Moderate	
Obone et al. 1999 (Rat)	Moderate	
Animal Oral Chronic Exposure		
Ambrose et al. 1976 (Rats)	Low	Low
Ambrose et al. 1976 (Dogs)	Low	
Dermal Exposure		
Human Cohort Studies		
Mozzanica et al. 1990	Moderate	Moderate
Animal Dermal Acute Exposure		
Siller and Seymour 1994 (Mice)	Moderate	Moderate

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for neurological effects are presented in Table C-13. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with nickel exposure is presented in Table C-14.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-4, Table C-5, and Table C-6). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below

are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:

- No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
- Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
- Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% Cis for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.

- Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response, and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

The results of this assessment are presented in Table C-15, and the final confidence in the body of literature for the neurological endpoint is presented in Table C-16.

Table C-15. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Human studies	Moderate	-1 Risk of bias +1 Direction	Moderate
Animal studies	High	+1 Direction	High
Outcome: Immunological effects			
Human studies	Moderate	-1 Risk of bias	Low
Animal studies	High	None	High

Table C-16. Confidence in the Body of Evidence for Nickel

	Confidence in body of evidence	
Outcome	Human Studies	Animal Studies

Respiratory effects	Moderate	High
Immunological effects	Low	High

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for nickel, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence**: High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence**: Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence**: Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect**: High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence**: Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome or very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for nickel is presented in C-17.

Table C-17. Level of Evidence of Health Effects for Nickel

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human Studies			
Respiratory effects	Moderate	Health Effect	Moderate
Immunological effects	Low	Health Effect	Low
Animal Studies			
Respiratory effects	High	Health Effect	High
Immunological effects	High	Health Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

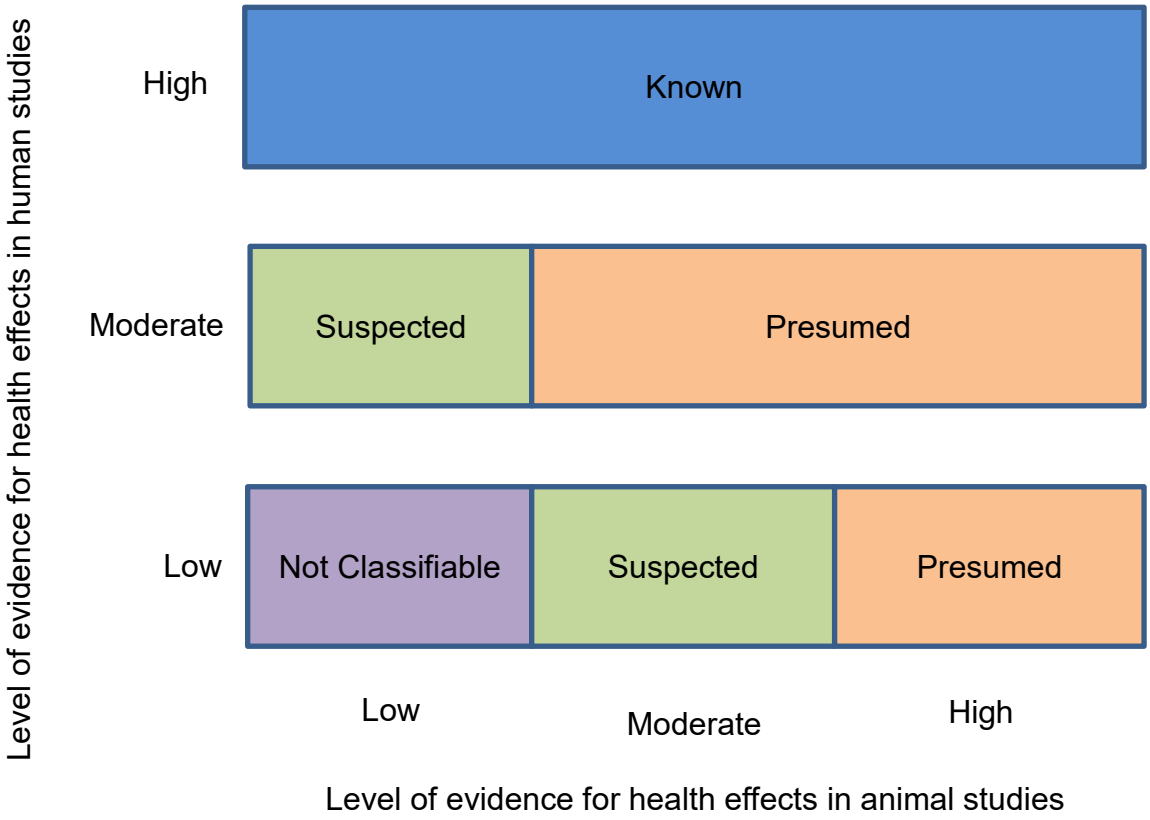
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known**: A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected**: A health effect in this category would have
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable**: A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used.

The hazard identification conclusions for nickel are listed below and summarized in C-18.

Presumed Health Effects

- Respiratory effects following inhalation and oral exposure.
  - Moderate level of evidence from human studies of occupational cohorts exposed via inhalation (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Redmond 1984; Roberts et al. 1989a; Shannon et al. 1984b; Shannon et al. 1991).

  - Moderate level of evidence from population level studies of exposure to nickel in air (Bell et al. 2009; Bell et al. 2014; Patel et al. 2009; Rosa et al. 2016; Schachter et al. 2020.
  - High level of evidence in rats and mice from acute-duration exposure to nickel (Bai et al. 2013; Benson et al. 1995b; Efremenko et al. 2014; Horie et al. 1985; NTP 1996b, 1996c), intermediate-duration exposure to nickel (Benson et al. 1995a; Bingham et al. 1972; NTP 1996a, 1996b, 1996c; Oller et al. 2022), and chronic-duration exposure to nickel (NTP 1996b, 1996c ; Ottolenghi et al. 1975; Takenaka et al. 1985).
  - High level of evidence in rats following acute-, intermediate-, and chronic-duration oral exposure (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Oller and Erexson 2007; RTI 1988a, 1988b).
- Immunological effects following inhalation, oral, and dermal exposure.
  - Low evidence from human inhalation studies due to the lack of controls and lack of confidence in the exposures (Bencko et al. 1983; Bencko et al. 1986; Shirakawa et al. 1990).
  - Low evidence from a limited number of dermal studies (Kapsenberg et al. 1988; Mozzanica et al. 1990).
  - High level of evidence in rats, mice, and rabbits from inhalation exposure to nickel (Adkins et al. 1979a, 1979b, 1979c; Bingham et al. 1972; Goutet et al. 2000; Haley et al. 1990; Johansson et al. 1980; Johansson et al. 1987; Johansson et al. 1988; Johansson et al. 1989; Morimoto et al. 1995; Oller et al. 2008; Xu et al. 2012).
  - High level of evidence in mice and rats from oral exposure to nickel (Dieter et al. 1988; Ilbäck et al. 1994; Obone et al. 1999), and in dogs (Ambrose et al. 1976).

Table C-18. Hazard Identification Conclusions for Nickel

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Immunological effects	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance

specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this

case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

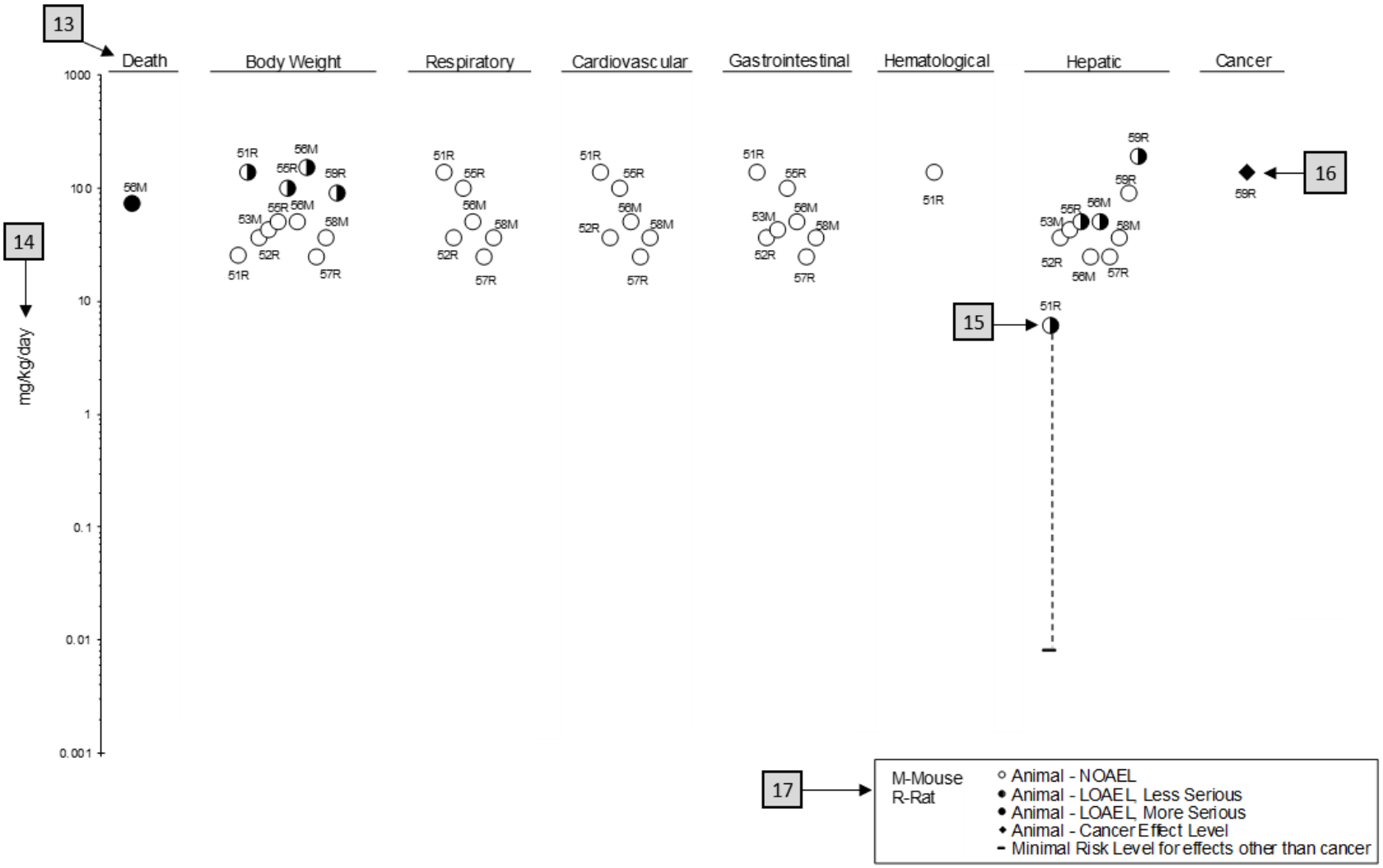
Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

(11)
[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc. gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with

realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_x	dose that produces a X% change in response rate of an adverse effect
$BMDL_x$	95% lower confidence limit on the BMD_x
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration

FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram

NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture

USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q1*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result