Toxicological Profile for Nickel

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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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-duration 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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VERSION HISTORY

Date	Description
October 2024	Final toxicological profile released
August 2023	Draft for public comment toxicological profile 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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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 2024). 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.

Nickel is the 24th most abundant element in the Earth's crust (Iyaka 2011). It is ubiquitous in the environment and is released 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. Nickel has been detected at trace levels in air and water and in the parts per million (ppm) range in soil and sediments (EPA 2024; WQP 2024). While not considered an essential trace element in humans, it is essential for other animals, microorganisms, and especially plants. Because of this, there is evidence that nickel accumulates in plants (Correia et al. 2018; Li et al. 2020a; Peralta-Videa et al. 2002), but there is no evidence of nickel bioaccumulating or biomagnifying in the food chain (McGreer et al. 2003).

The general population is primarily exposed to nickel by food and water intake. The National Academy of Sciences (NAS) reported that there are insufficient data to determine a Recommended Dietary Allowance for nickel (Institute of Medicine 2001). The Tolerable Upper Intake Levels for nickel reported by the National Academies of Sciences, Engineering, and Medicine (NASEM) are 1.0 mg/day as soluble salts for adults ≥14 years, and 0.6, 0.3, and 0.2 mg/day for children for 9–13, 4–8, and 1–3 years old, respectively (NASEM 2019). The European Food Safety Authority derived a tolerable daily intake of 13 μg/kg body weight/day (EFSA 2020). The Institute of Medicine (2001) estimates that the general population has a nickel intake of <0.5 mg/day. The nickel content of food has been well characterized by a recent Food and Drug Administration (FDA) Total Diet Study (FDA 2023c). Nickel has been detected at trace levels in drinking water (EFSA 2020; FDA 2023c). Small amounts of nickel may leach out of stainless-steel cookware during heating of acidic foods (Hedberg et al. 2014; Kamerud et al. 2013).

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). Consumers may be exposed to small amounts of nickel leaching from jewelry or other metal products after prolonged dermal contact (Hamann et al. 2015; Thyssen and Maibach 2008; Uter and Wolter 2018). Nickel has been qualitatively identified in some children's toys (Jensen et al. 2014).

Additionally, occupational exposures can occur following inhalation of dusts or powders containing elevated levels of nickel or nickel compounds. People who work in industries producing nickel or using nickel products may be exposed to nickel dermally or through inhalation (Hughson et al. 2010; Julander et al. 2010). Nickel has been measured in blood, breastmilk, exhaled breath condensate, feces, hair, nasal mucosa, saliva, serum, sweat, toenails, and urine (Berniyanti et al. 2020; Chen et al. 2017; Kettelarij et al. 2016; Vuskovic et al. 2013). 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 (Arain et al. 2015; Hess et al. 2017; Mohammad et al. 2019).

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 in workers and on the general population. Experimental studies in humans primarily test dermal reactions to nickel, particularly as a concern of allergic contact dermatitis. Inhalation studies in animals have examined the toxicity of several nickel compounds and evaluated a wide range of potential endpoints following acute-, intermediate-, or chronic-duration exposure. A limited number of studies in both humans and animals have examined nickel toxicity due to oral or dermal exposure.

As illustrated in Figures 1-1 and 1-2, the most sensitive effects appear to be lung inflammation, nasal olfactory lesions, and immunotoxicity following inhalation exposure and neurobehavioral effects, body weight, reproductive, and developmental effects. Allergic contact dermatitis has also been observed in sensitized humans exposed to relatively low doses of nickel compounds. The toxicity of metallic nickel and several nickel compounds have been evaluated in animal studies. The nickel compounds can be grouped according to their solubility in water: soluble compounds include nickel chloride, nickel sulfate, and nickel nitrate, and less-soluble compounds include nickel oxide and nickel subsulfide. Generally, the soluble compounds are considered more toxic due to higher bioavailability, although the less-soluble

compounds are more likely to be carcinogenic at the site of deposition. The effect levels shown in Figures 1-1 and 1-2 are specific to a nickel compound and not all compounds may cause these effects.

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

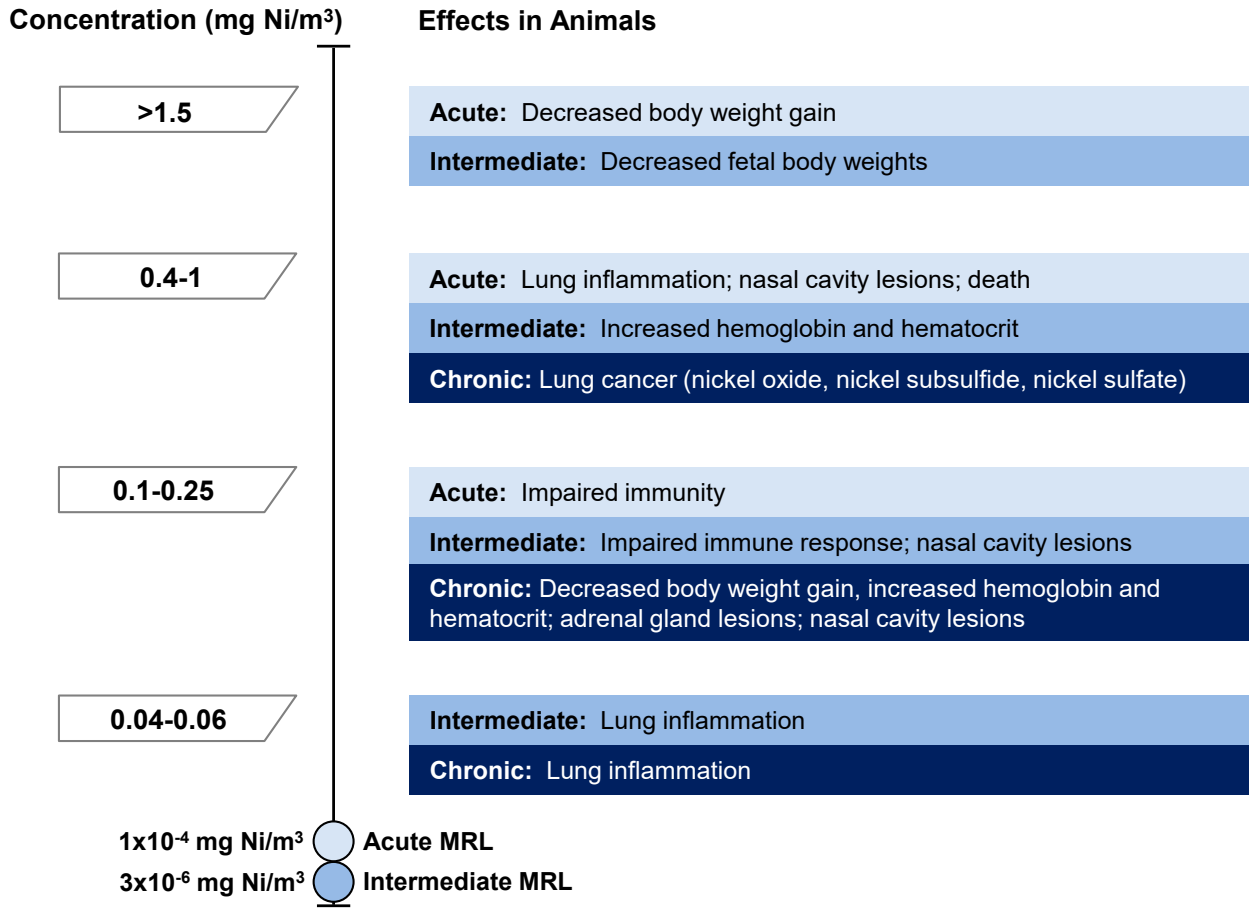
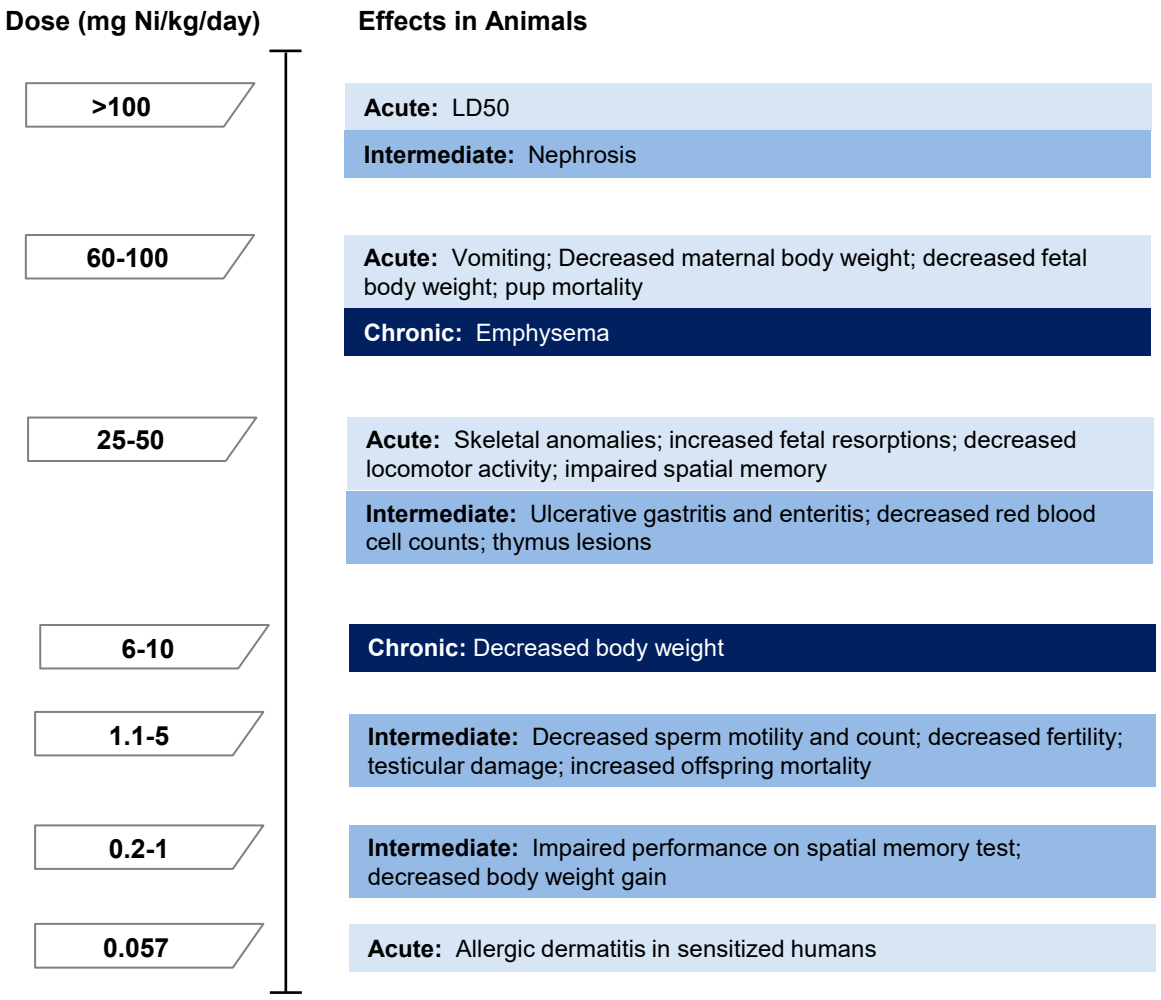


Figure 1-2. Health Effects Found in Humans* and Animals Following Oral Exposure to Nickel



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

A systematic review of the noncancer endpoints resulted in the following hazard identification conclusions:

- Respiratory effects are a presumed health effect of nickel exposure.
- Immunological effects are a presumed health effect of nickel exposure.
- Reproductive effects are not classifiable as to whether they are a health effect of nickel exposure.
- Developmental 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. Effects reported in nickel workers include symptoms of respiratory irritation, alterations in lung function tests, and increased risk of pulmonary fibrosis (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022). A large number of animal studies have examined the respiratory toxicity of nickel and nickel compounds following acute-, intermediate-, or chronic-duration inhalation exposures of rats and mice. The most commonly reported effect was chronic lung inflammation or other forms of inflammation such as alveolitis and peribronchiolar inflammation (Benson et al. 1995a, 1995b; NTP 1996a, 1996b, 1996c; Oller et al. 2008, 2023; see Section 2.4 for complete reference list) following inhalation exposure to nickel sulfate, nickel subsulfide, nickel oxide, and metallic nickel. Acute- and intermediate-duration studies suggest that nickel sulfate and nickel subsulfide are more toxic than nickel oxide. Other pulmonary effects include degeneration of bronchiolar epithelium, necrosis of alveolar and bronchiolar epithelium, alveolitis, pulmonary edema, and fibrosis (NTP 1996b, 1996c; Oller et al. 2023). In addition to the pulmonary effects, atrophy or degeneration of the olfactory epithelium has been observed in rats and mice exposed to nickel sulfate or nickel subsulfide (Benson et al. 1995b; Evans et al. 1995; NTP 1996b, 1996c). Oral exposure to nickel compounds has also resulted in respiratory effects including pneumonitis in rats exposed to nickel chloride for 91 days (American Biogenics Corporation 1988) and cholesterol granulomas, emphysema, and bronchiolectasis in dogs exposed to nickel sulfate for 2 years (Ambrose et al. 1976).

Immunological Effects. Immunological effects following nickel exposure are evaluated in human and animal studies. Contact dermatitis resulting from an allergic response, or sensitivity, to nickel has been reported in 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 dermal contact. Survey studies of patients undergoing patch testing with nickel sulfate suggest that the prevalence ranges from 13 to 41% (see Table 2-6 for citations). Positive patch testing is more frequent in females than males, which is probably reflective of previous exposure (e.g., prolonged exposure to nickel releasing items such as jewelry) rather than sex-related difference in susceptibility.

In animals, nickel exposure results in histological alterations and impaired immune function. Lymphoid hyperplasia in the bronchial and mediastinal lymph nodes have been observed in rats and mice following inhalation exposure to nickel sulfate, nickel subsulfide, and nickel oxide (NTP 1996a, 1996b, 1996c) and histiocyte infiltrate has been observed in the bronchial lymph nodes of rats exposed to metallic nickel (Oller et al. 2008). Inhalation studies with nickel chloride have reported increased susceptibility to

bacteria (Adkins et al. 1979) and an impaired response to sheep red blood cells (sRBCs) (Graham et al. 1978; Spiegelberg et al. 1984). Impaired immune responses to sRBC or a virus were also observed in mice following oral exposure to nickel sulfate or nickel chloride (Dieter et al. 1988; Ilbäck et al. 1994); alterations in spleen and thymus T cell phenotypes have also been observed in rats exposed to nickel sulfate (Obone et al. 1999).

Reproductive. A limited number of epidemiological studies have evaluated the potential reproductive toxicity of nickel. Two studies of female nickel refinery workers have found conflicting results on the association between nickel exposure and the risk of spontaneous abortions (Chashschin et al. 1994; Vaktskjold et al. 2008b). A number of animal studies have also examined reproductive endpoints. Decreased sperm concentrations were observed in rats exposed via inhalation to nickel oxide for 13 weeks (NTP 1996a), but were not observed in rats or mice similarly exposed to nickel sulfate or nickel subsulfide (NTP 1996b, 1996c). The National Toxicology Program (NTP) studies did not find histological alterations in reproductive tissues following acute-, intermediate-, or chronic-duration inhalation exposure (NTP 1996a, 1996b, 1996c). Histological alterations in the epididymis and seminiferous tubules were found in mice orally exposed to nickel sulfate (Käkelä et al. 1999; Pandey et al. 1999; Toman et al. 2012); however, other studies have not found these effects in rats or dogs (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Springborn Laboratories 2000b). Decreases in sperm count and motility have also been observed in mice orally exposed to nickel sulfate (Pandey and Srivastava 2000; Pandey et al. 1999) but not in rats exposed to nickel sulfate (Springborn Laboratories 2000b). Conflicting findings have been reported in oral studies examining fertility in rats, with one study reporting decreased fertility following male-only or male and female exposures but not after female-only exposure (Käkelä et al. 1999) and other studies involving male and female exposure (EPA 1988a, 1988b; Springborn Laboratories 200b) not finding effects.

Developmental. The limited available epidemiological data on the potential of nickel to induce developmental effects have not found associations (Vaktskjold et al. 2006, 2007, 2008a). However, these studies only examined nickel refinery workers living in one region in Russia. No alterations in fetal body weights were observed in the offspring of rats exposed via inhalation to nickel oxide (Weischer et al. 1980). Oral exposure studies of metallic nickel or insoluble nickel compounds have also not found developmental effects. In contrast, oral exposure studies of soluble nickel compounds have reported developmental effects. Observed effects include fetal loss, decreased survival, decreased offspring body weight, and skeletal abnormalities (Ambrose et al. 1976; El-Sekily et al. 2020; EPA 1988a, 1988b; Käkelä et al. 1999; Saini et al. 2013, 2014a, 2014b; Springborn Laboratories 2000b).

Cancer. There is an extensive occupational exposure database on the carcinogenicity of nickel. As concluded by the International Agency for Research on Cancer (IARC), increased risks of lung and nasal cancers have been observed in nickel refinery workers and increased risks of lung cancer have been observed in nickel smelter workers (IARC 1990, 2012). Increases in lung tumors have also been observed in rats chronically exposed to airborne nickel oxide, nickel subsulfide, or nickel sulfide (NTP 1996a, 1996b; Ottolenghi et al. 1975). Lung tumors have not been observed in rats exposed to nickel sulfate (NTP 1996c) or metallic nickel (Oller et al. 2008). Increases in benign or malignant adrenal gland pheochromocytomas have also been observed in rats exposed via inhalation to nickel subsulfide, nickel oxide, or metallic nickel (NTP 1996a, 1996b; Oller et al. 2008). No tumors were observed in oral exposure studies (Heim et al. 2007; Schroeder et al. 1964, 1974).

The U.S. Department of Health and Human Services (NTP 2016) has determined that metallic nickel may reasonably be anticipated to be a human carcinogen and that nickel compounds are known to be human carcinogens. Similarly, IARC (1990, 2021) classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). The U.S. Environmental Protection Agency (EPA) has classified nickel refinery dust and nickel subsulfide in Group A (human carcinogen) (IRIS 1987a, 1987b); other nickel compounds have not been classified by EPA.

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 inhalation database was adequate for the derivation of acute- and intermediate-duration inhalation MRLs for nickel but was insufficient for derivation of a chronic-duration inhalation MRL. The immunological, reproductive, and developmental systems and body weight appear to be the most sensitive target of oral nickel toxicity (see Figure 1-4). The oral exposure database was insufficient for the derivation of oral MRLs for any exposure duration. The inhalation MRL derived for nickel is summarized in Table 1-1 and is discussed in greater detail in Appendix A.

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

Available data indicate that the immunological and respiratory systems are the most sensitive targets of nickel inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.

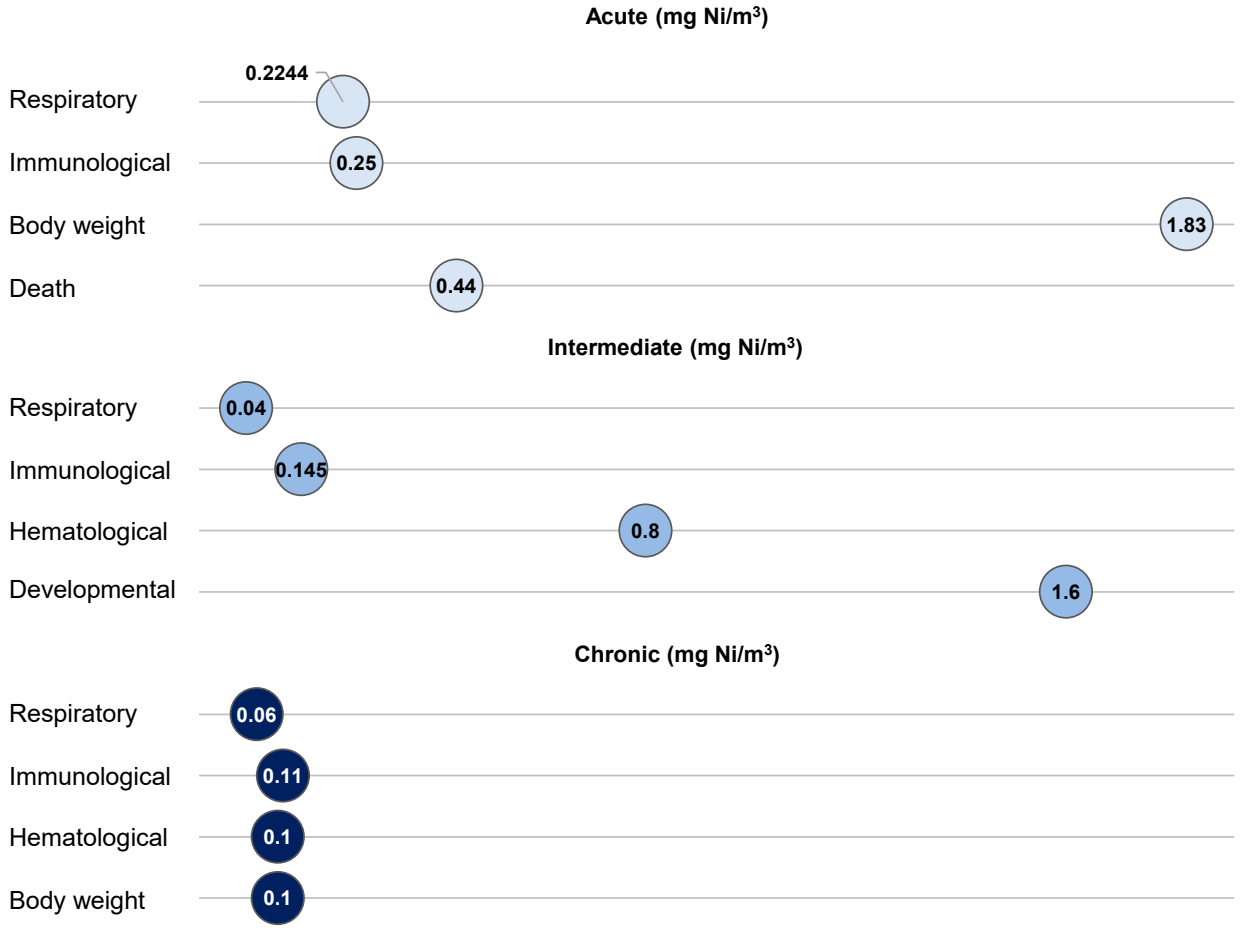


Figure 1-4. Summary of Sensitive Targets of Nickel – Oral

Available data indicate that the immunological, developmental, neurological, and gastrointestinal 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.

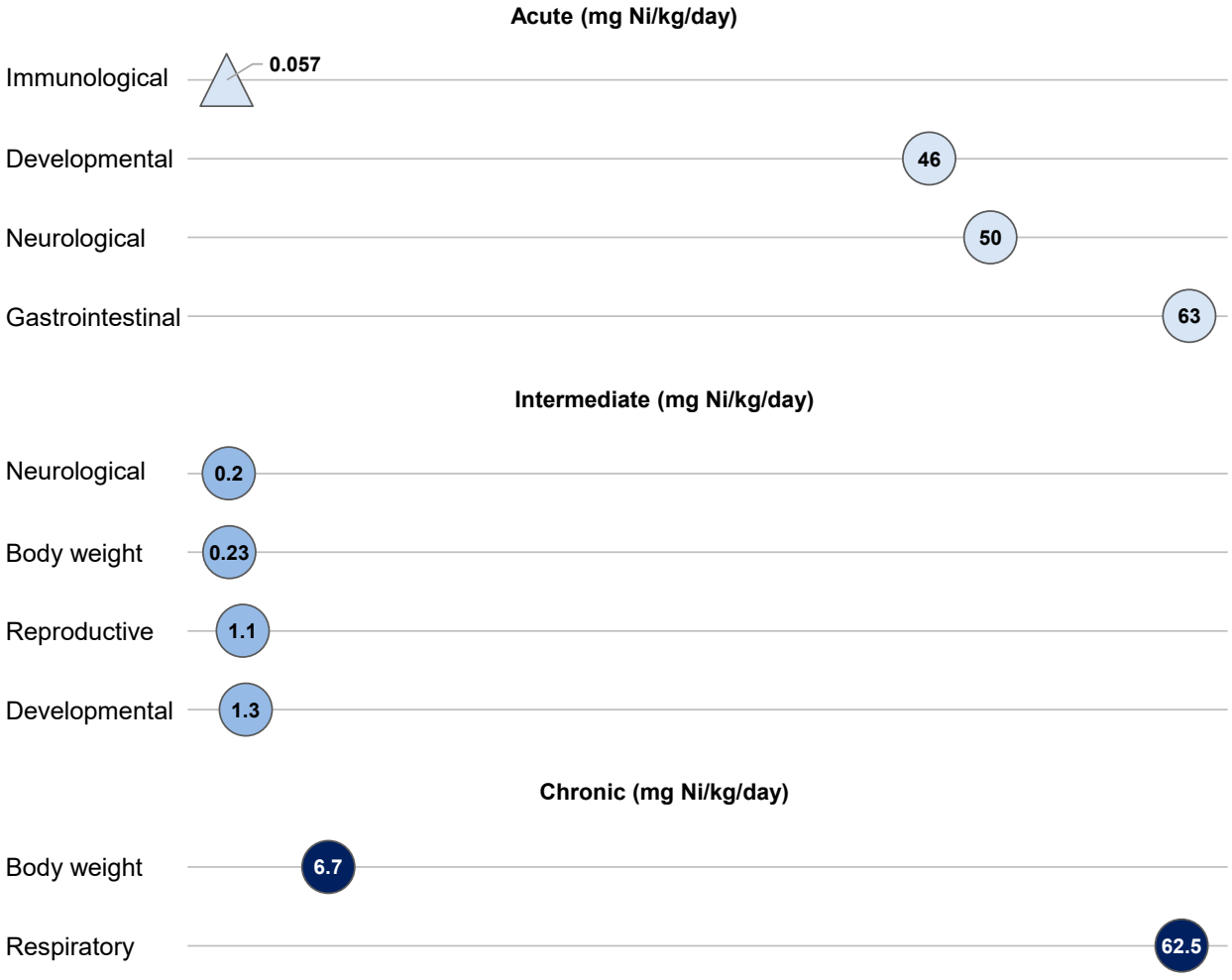


Table 1-1. Minimal Risk Levels (MRLs) for Nickel[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**$1x10^{-4}$ mg Ni/m^3**	Bronchiole epithelial degeneration/hyperplasia	$LOAEL_{HEC}$	0.0403 mg Ni/m^3	UF: 300	Efremenko et al. 2017a, 2017b
	Intermediate	**$3x10^{-6}$ mg Ni/m^3**	Alveolitis and perivascular/ peribronchiolar inflammation	$BMCL_{HEC}$	$9.82x10^{-5}$ mg Ni/m^3	UF: 30	Oller et al. 2023
	Chronic	None					
Oral	**No oral MRLs were derived for any duration.**						

[a]See Appendix A for additional information.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of nickel. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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

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

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

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

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

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

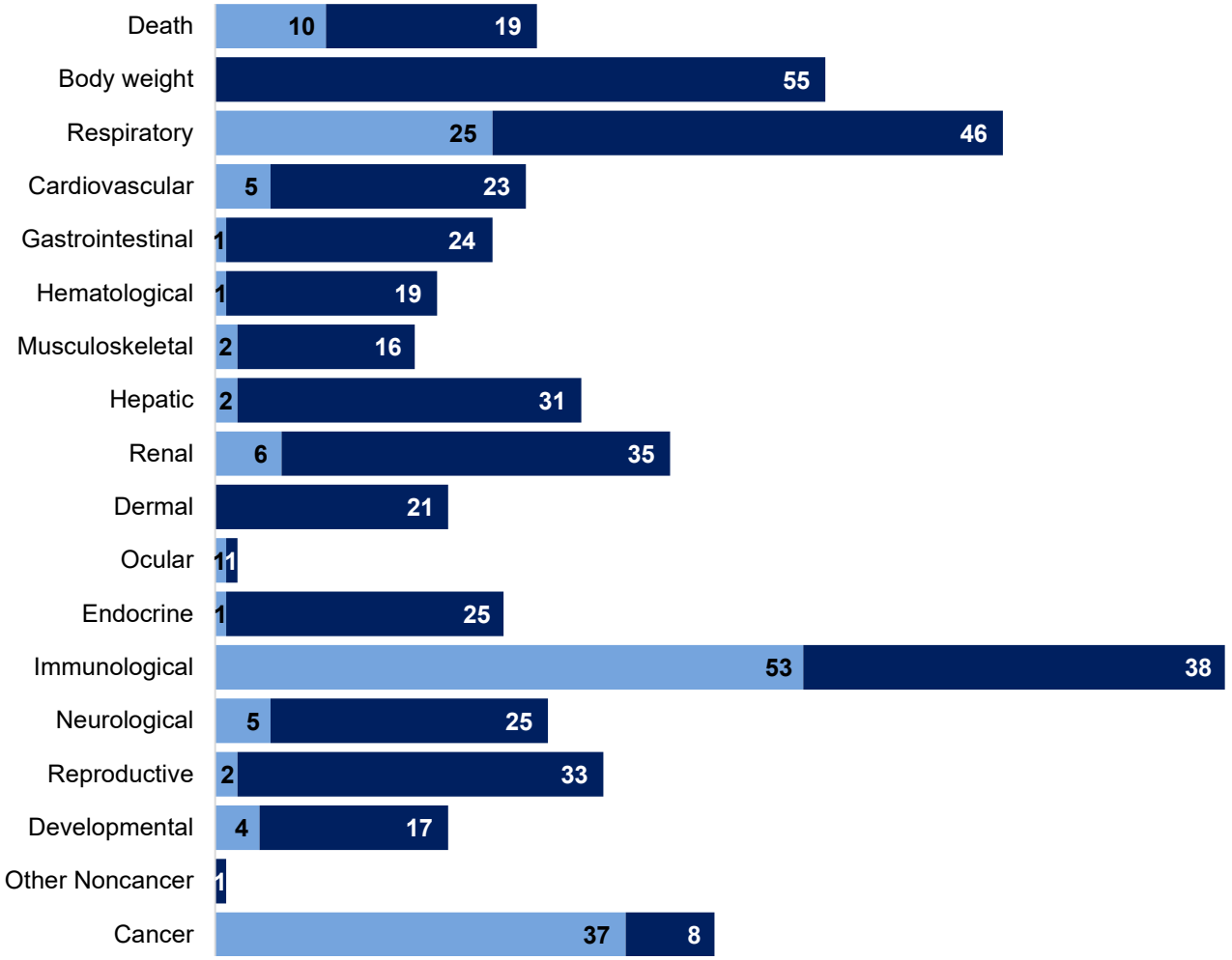
The health effects of nickel and compounds have been evaluated in epidemiological and laboratory animal studies. A large number of epidemiological studies have evaluated the toxicity of nickel; study types include case reports/case series, controlled oral exposure, and occupational exposure. In addition,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

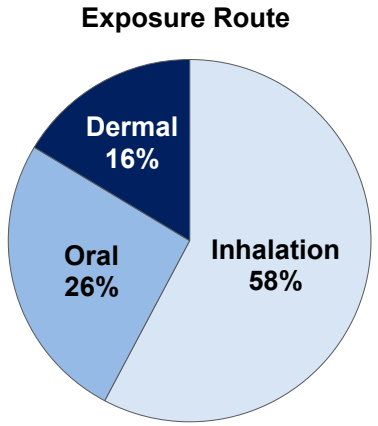
The human and animal studies suggest several sensitive targets of nickel toxicity (see Appendix C for details on the systematic review):

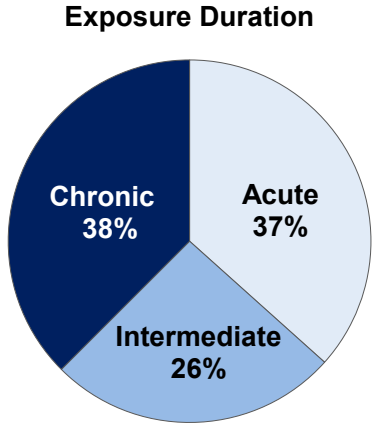
- **Respiratory Endpoints:** Respiratory effects are a presumed health effect for humans based on low-level evidence in occupational exposure studies and high level of evidence of lung inflammation and nasal lesions in animals following acute-, intermediate-, or chronic-duration exposure to several nickel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

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

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







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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

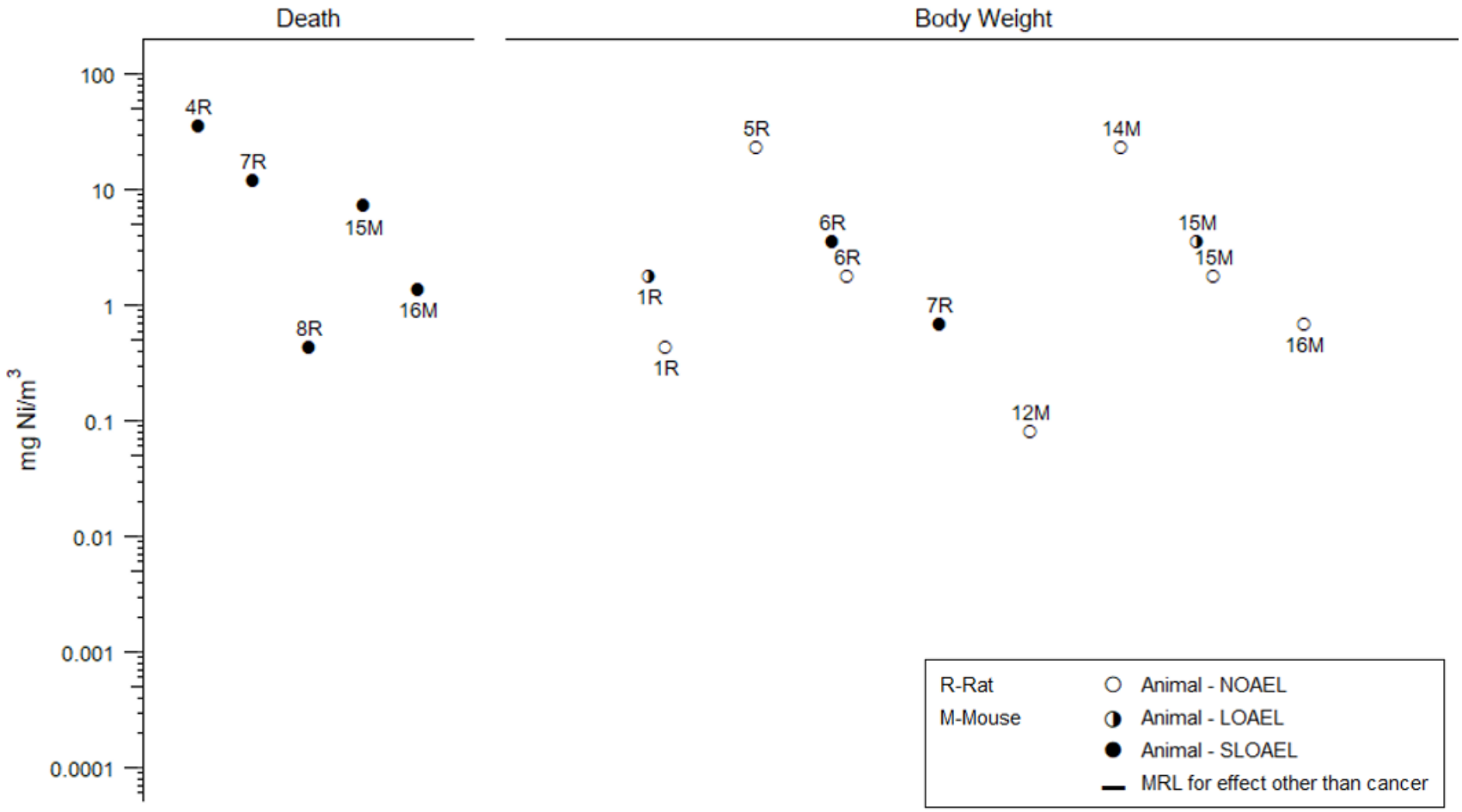


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

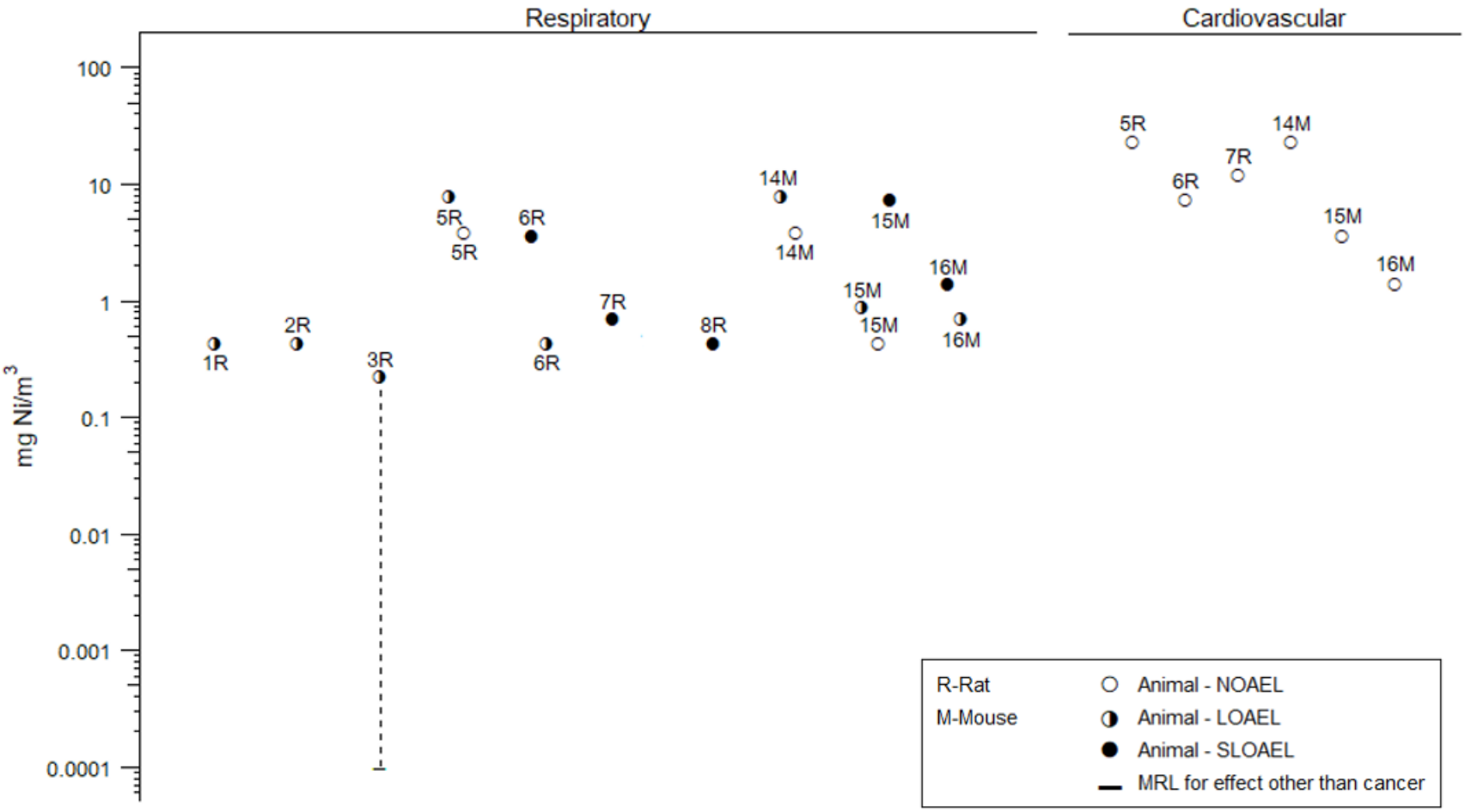


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

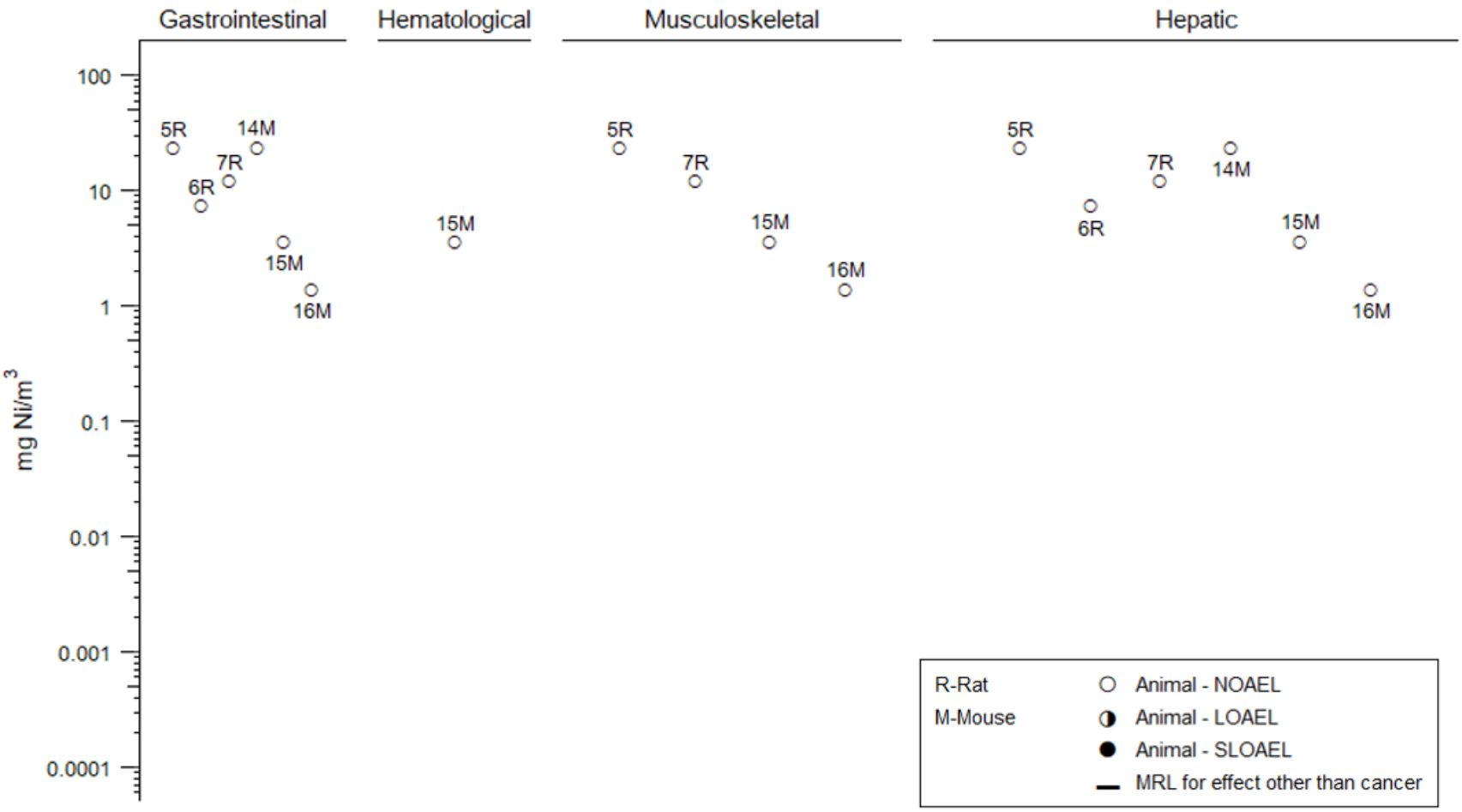


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

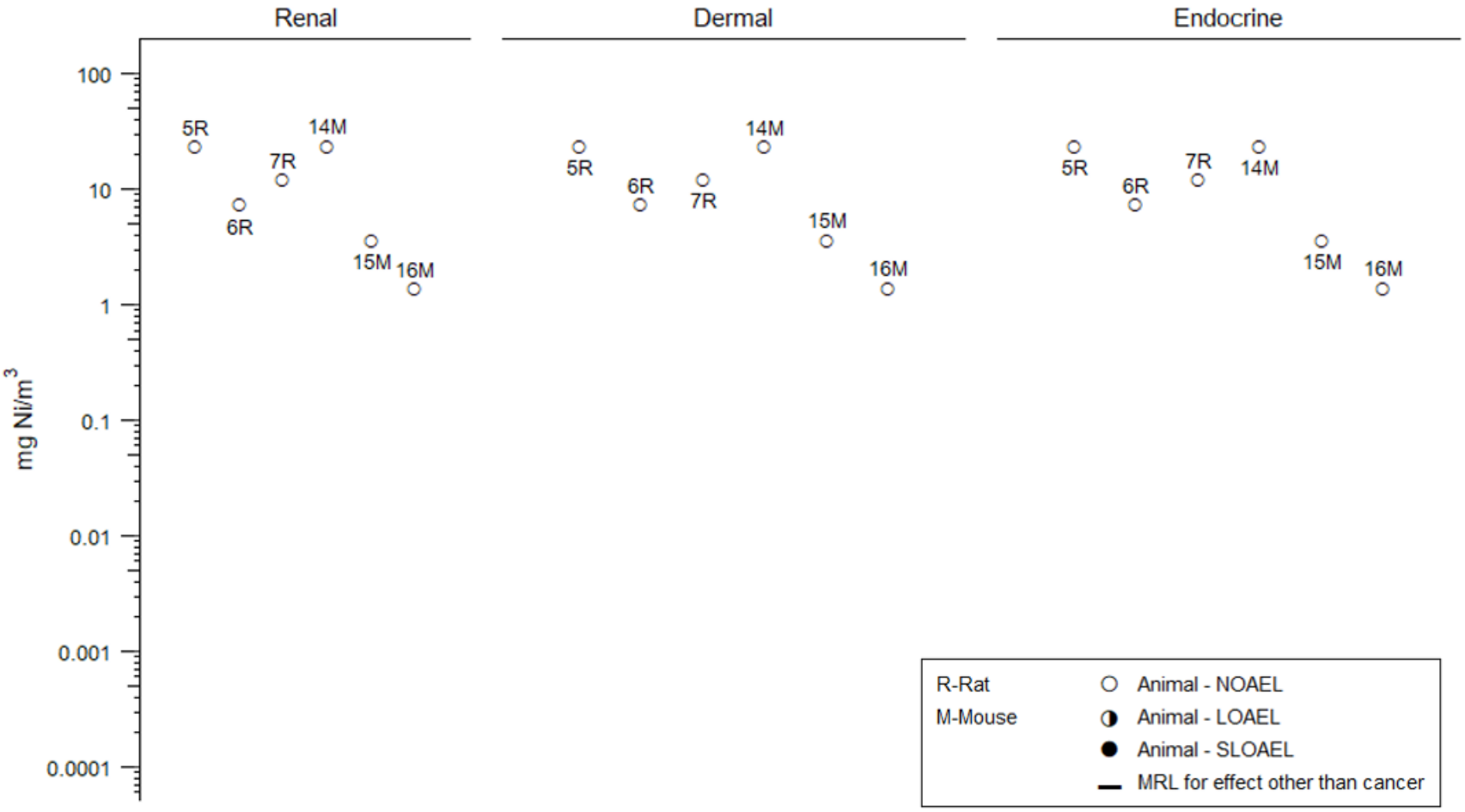


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Acute (≤14 days)

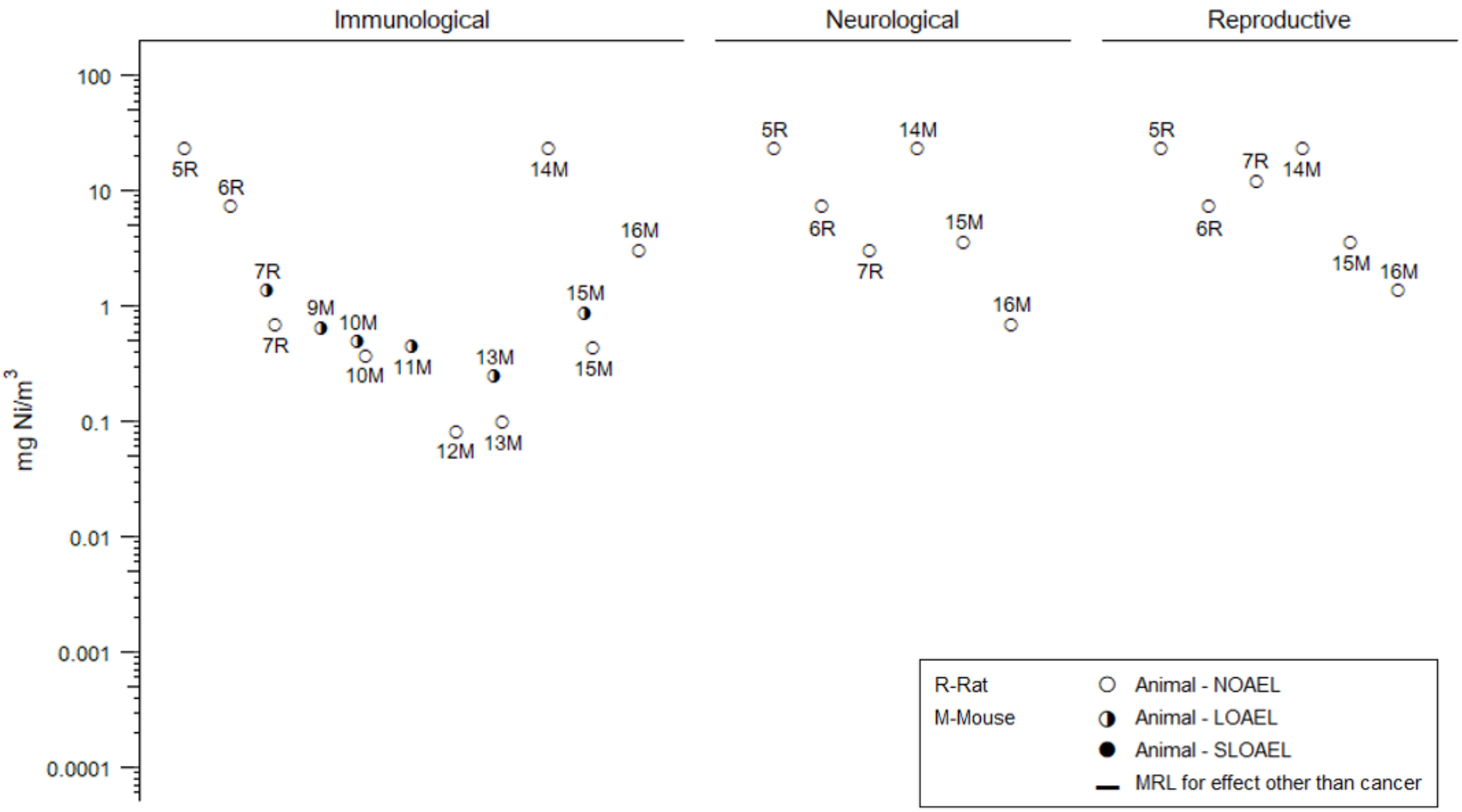


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

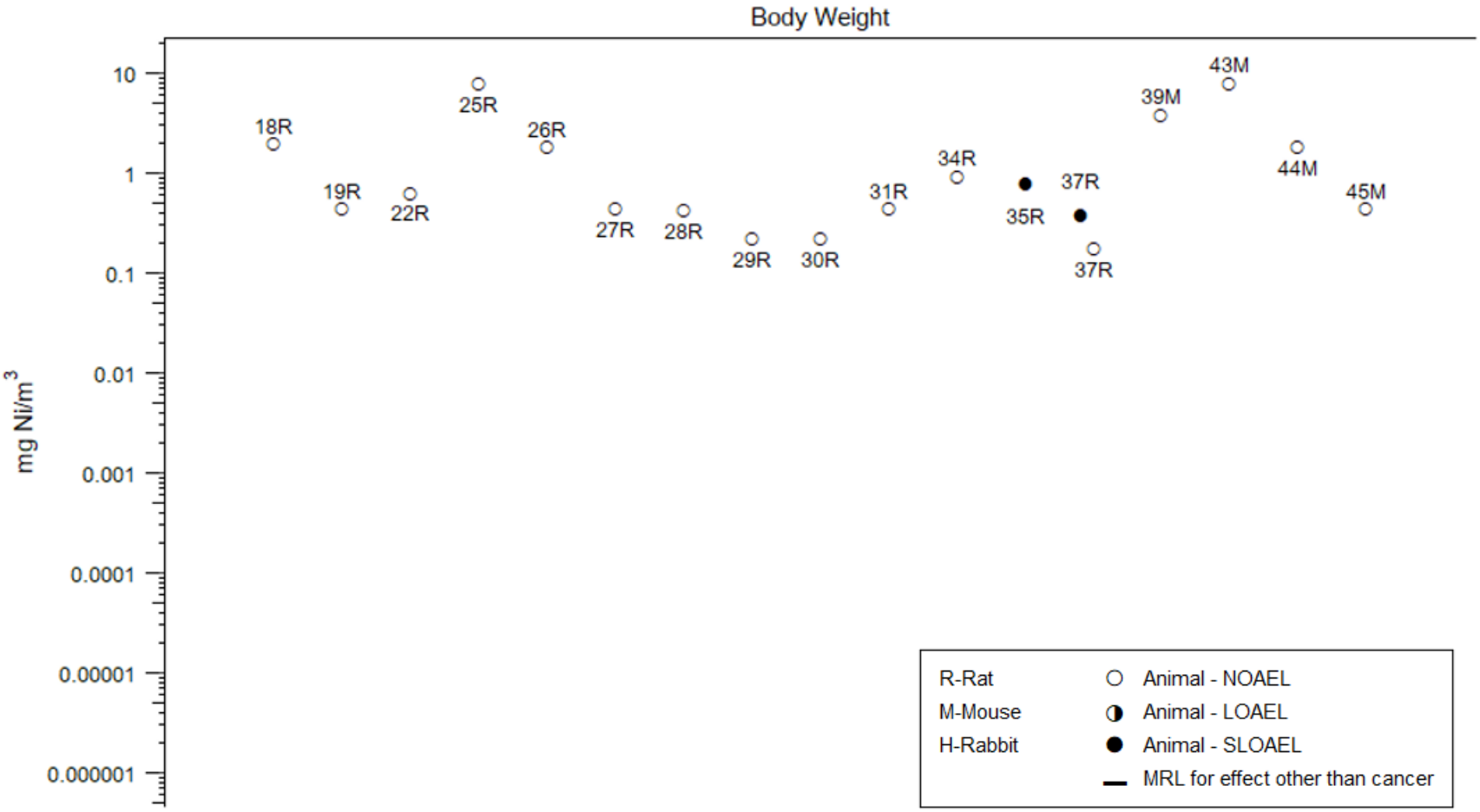


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

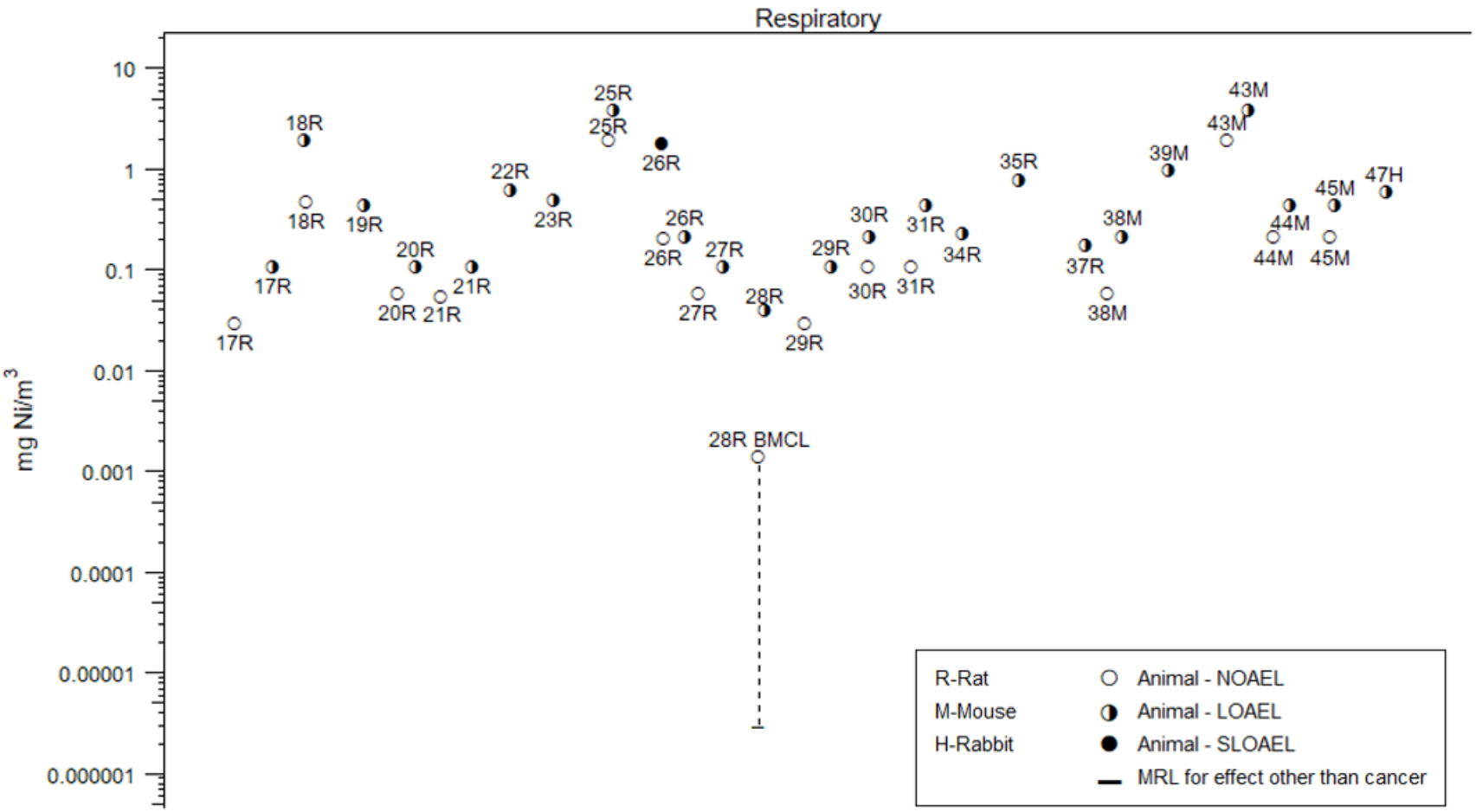


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

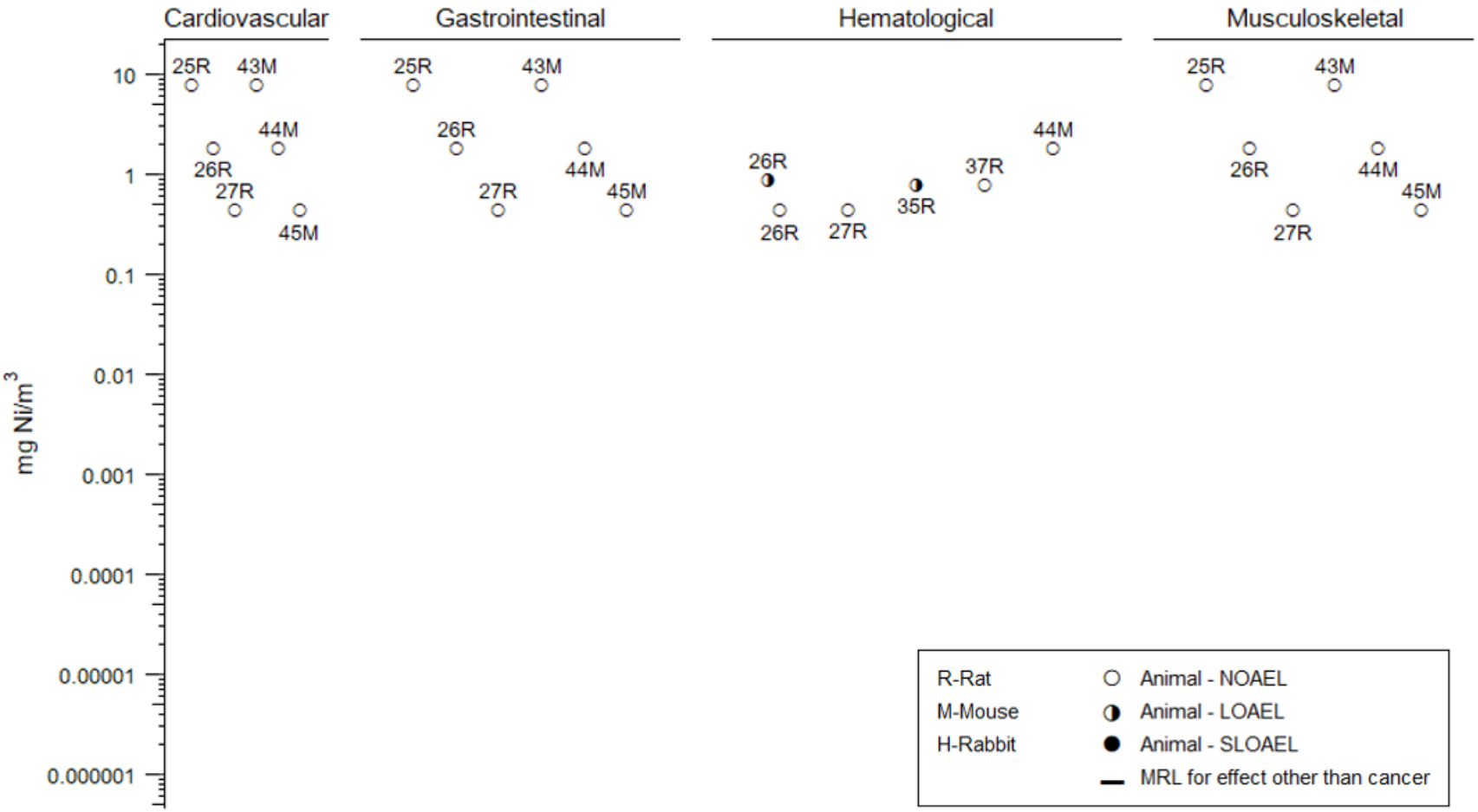


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

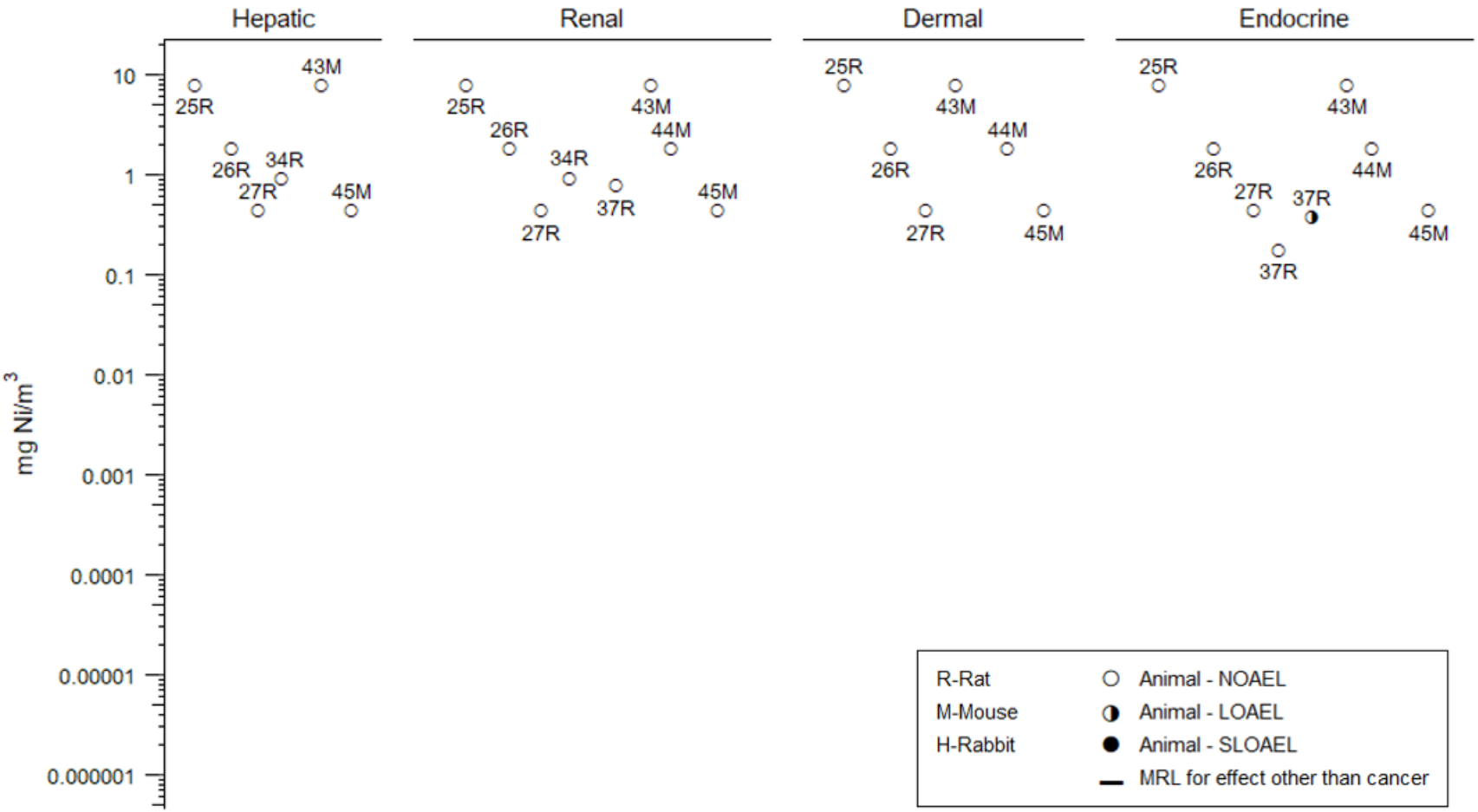


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

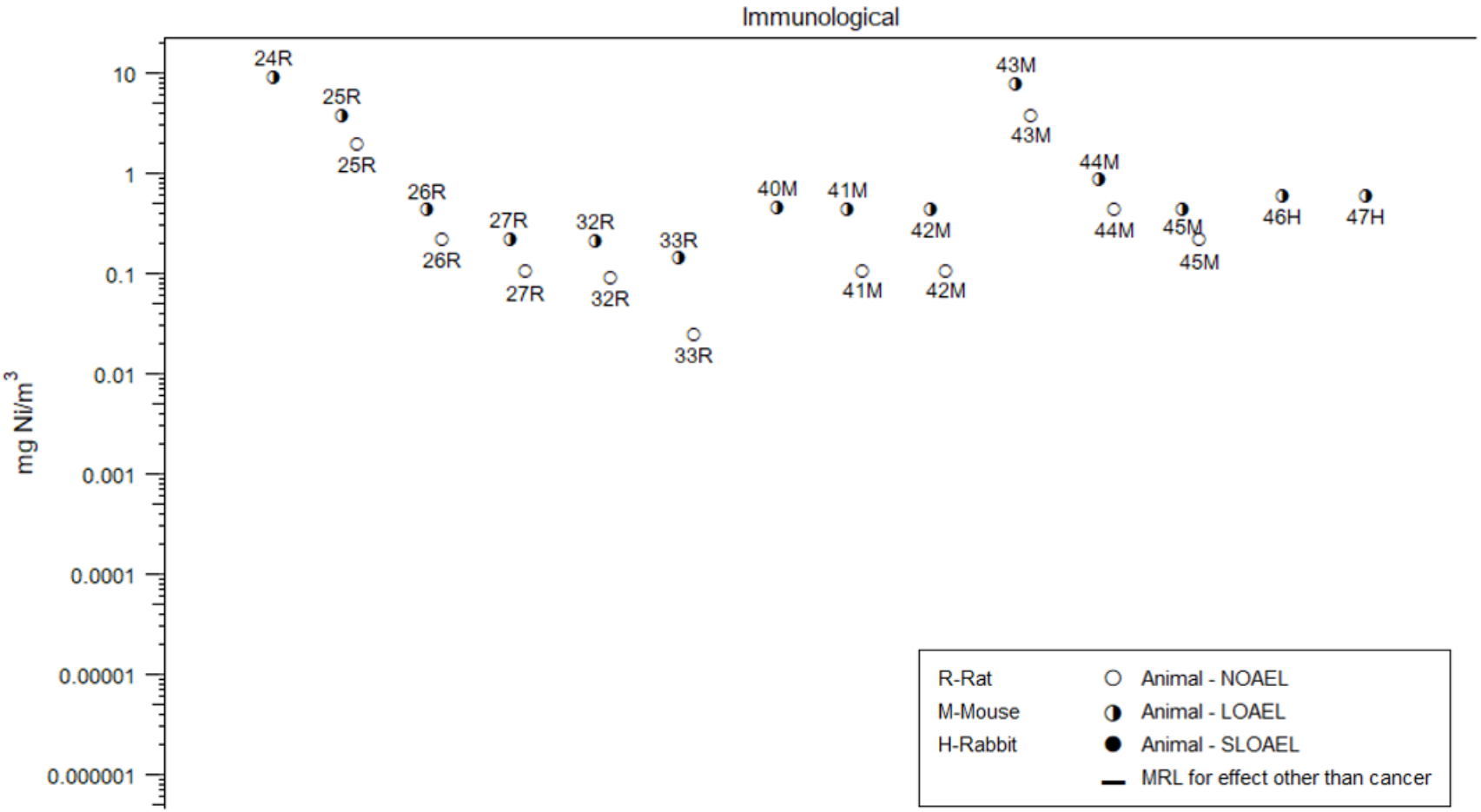


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Intermediate (15–364 days)

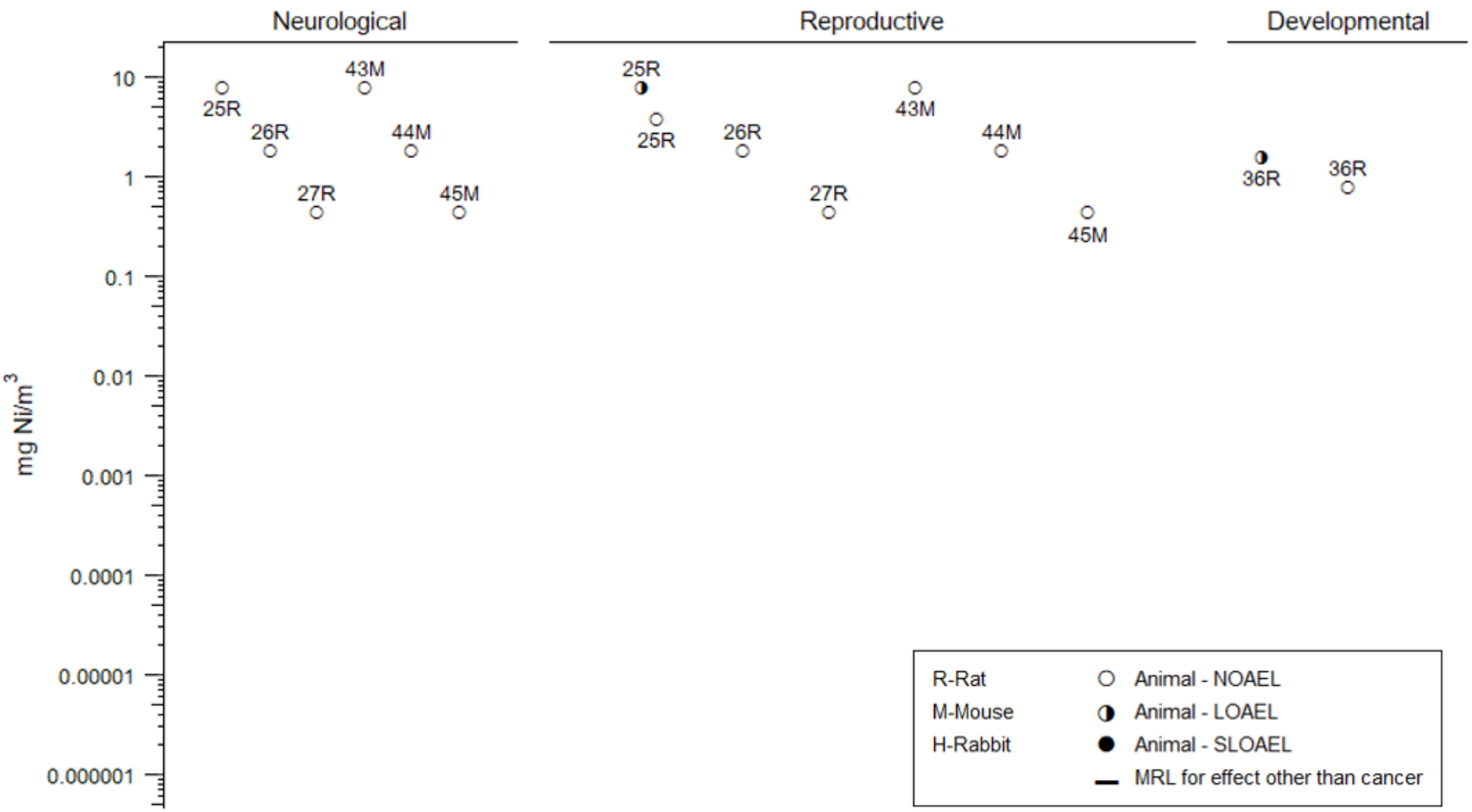


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

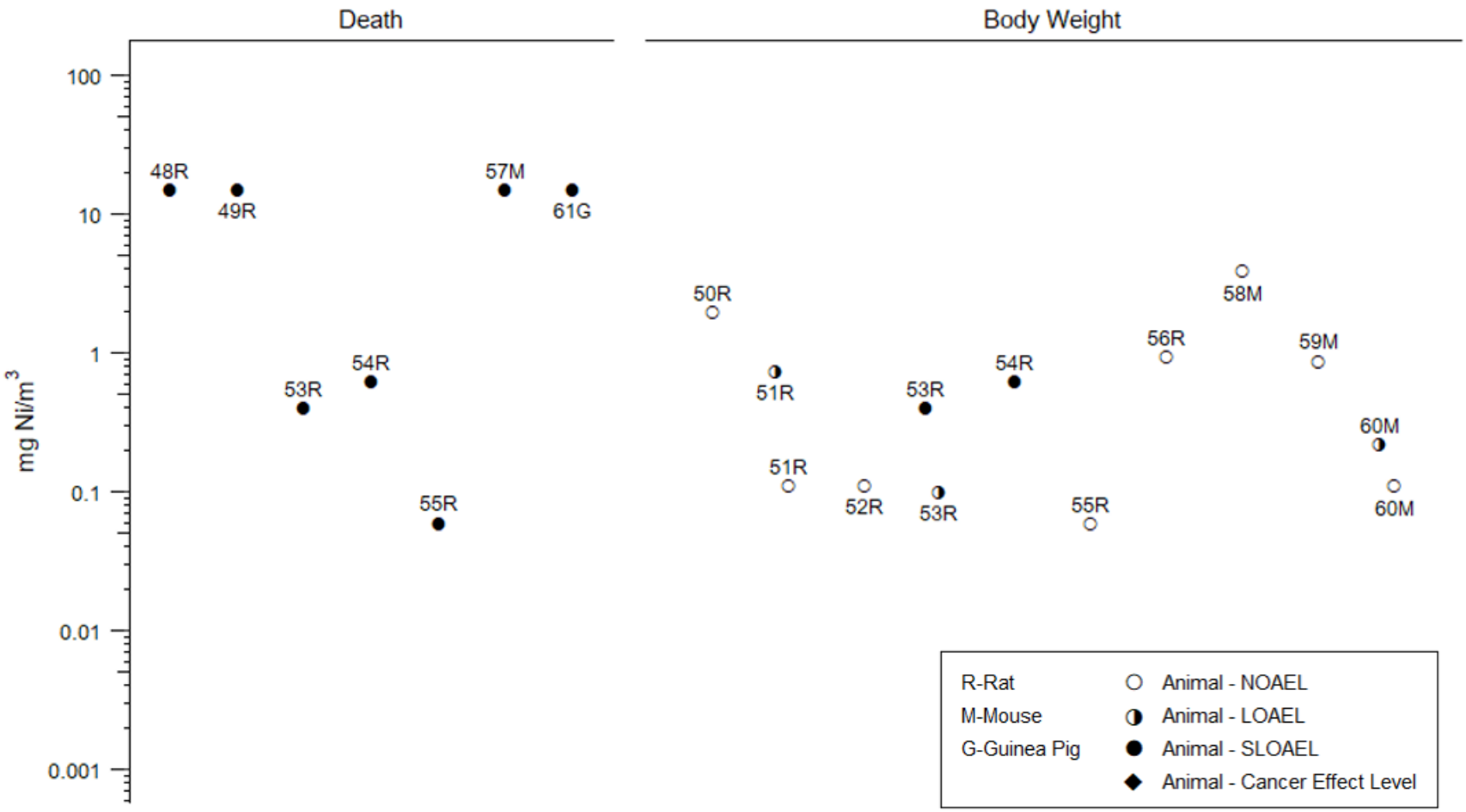


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

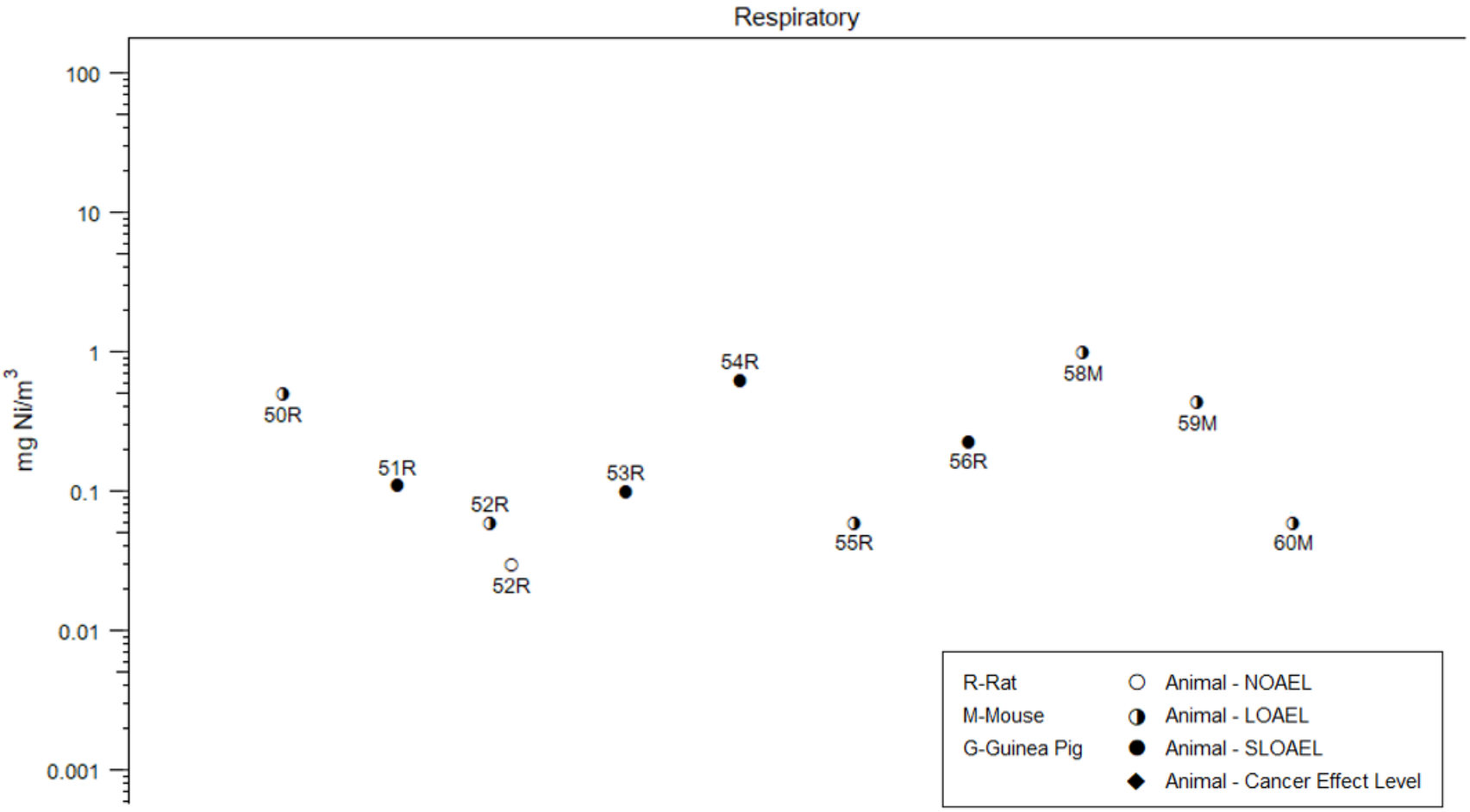


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

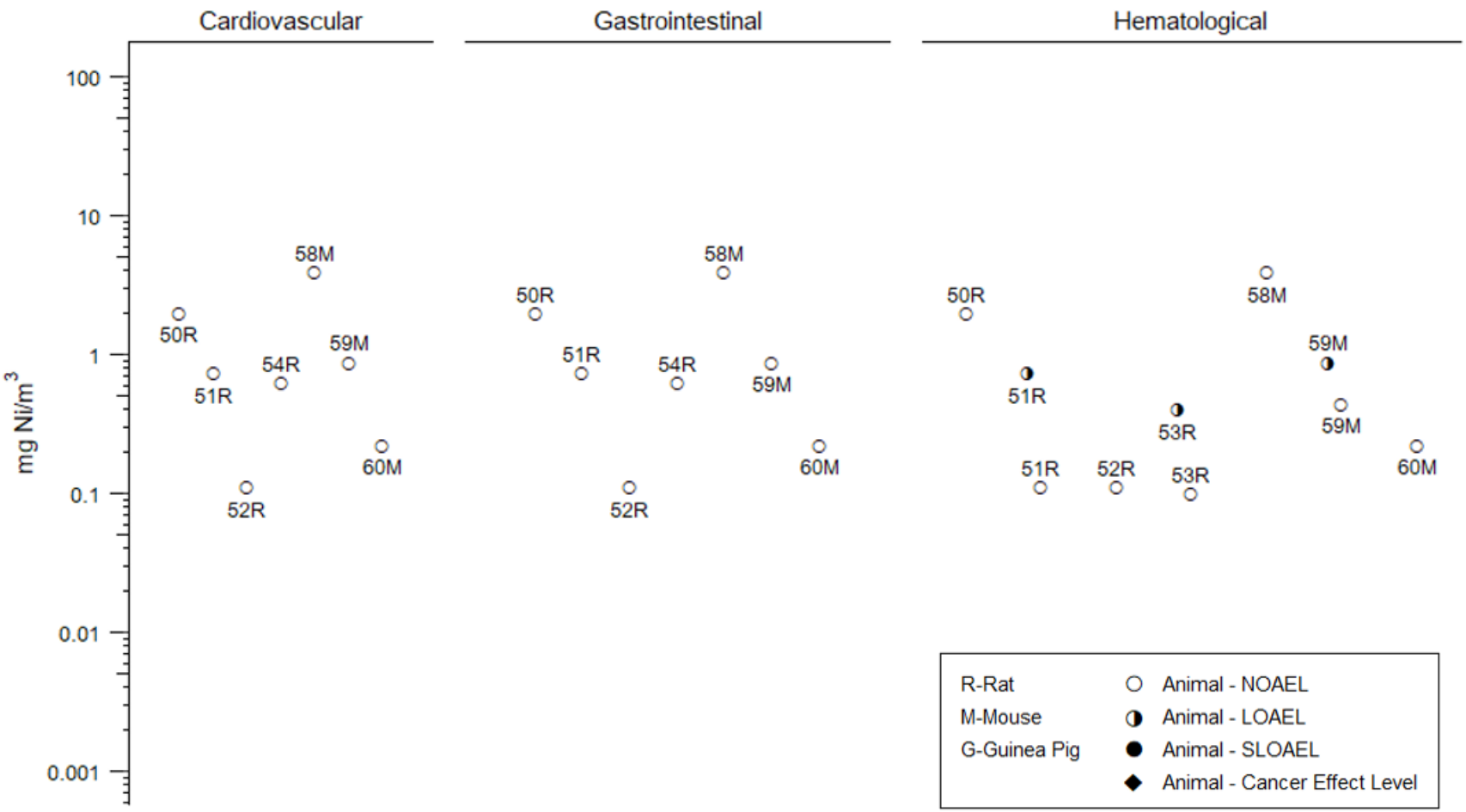


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

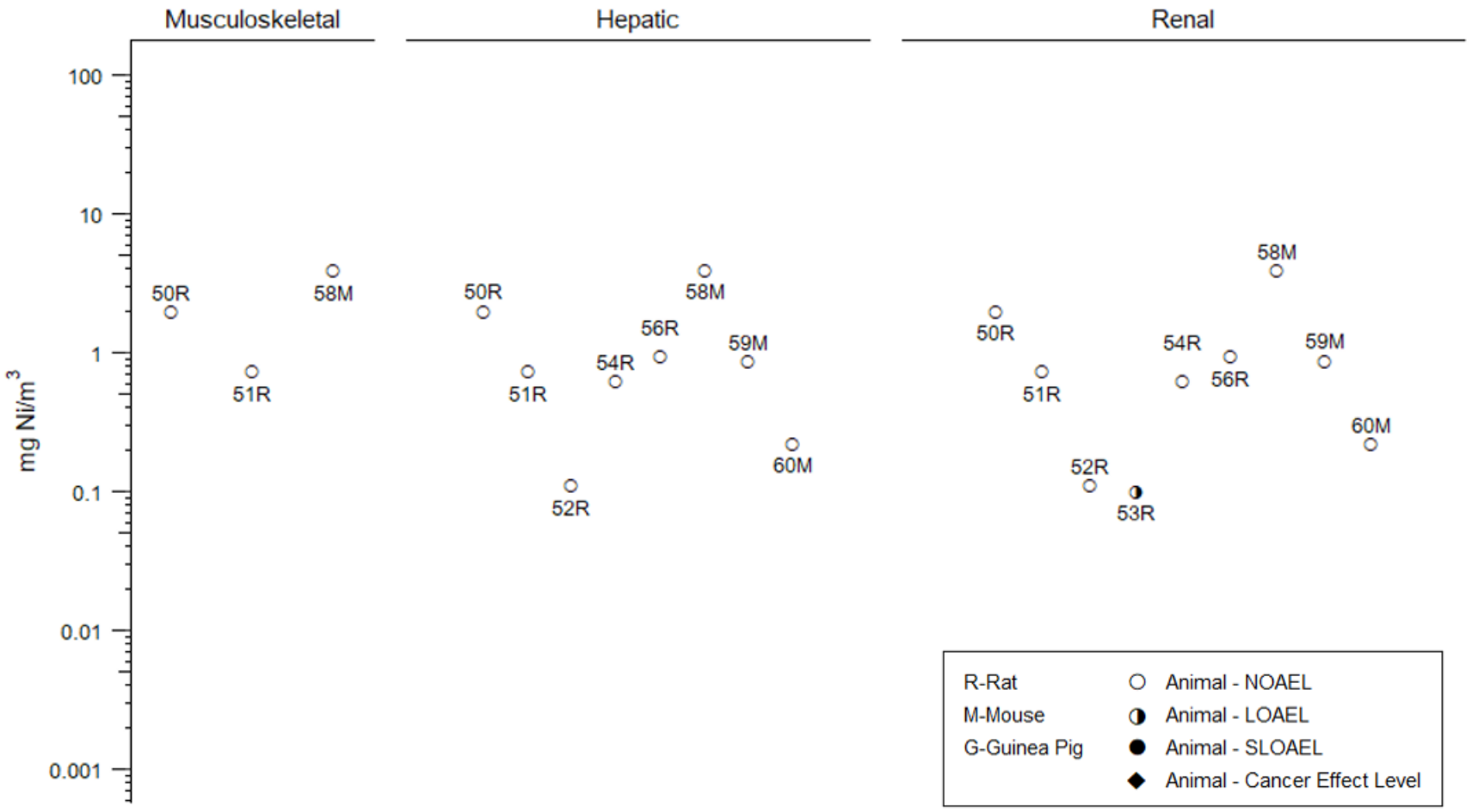


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

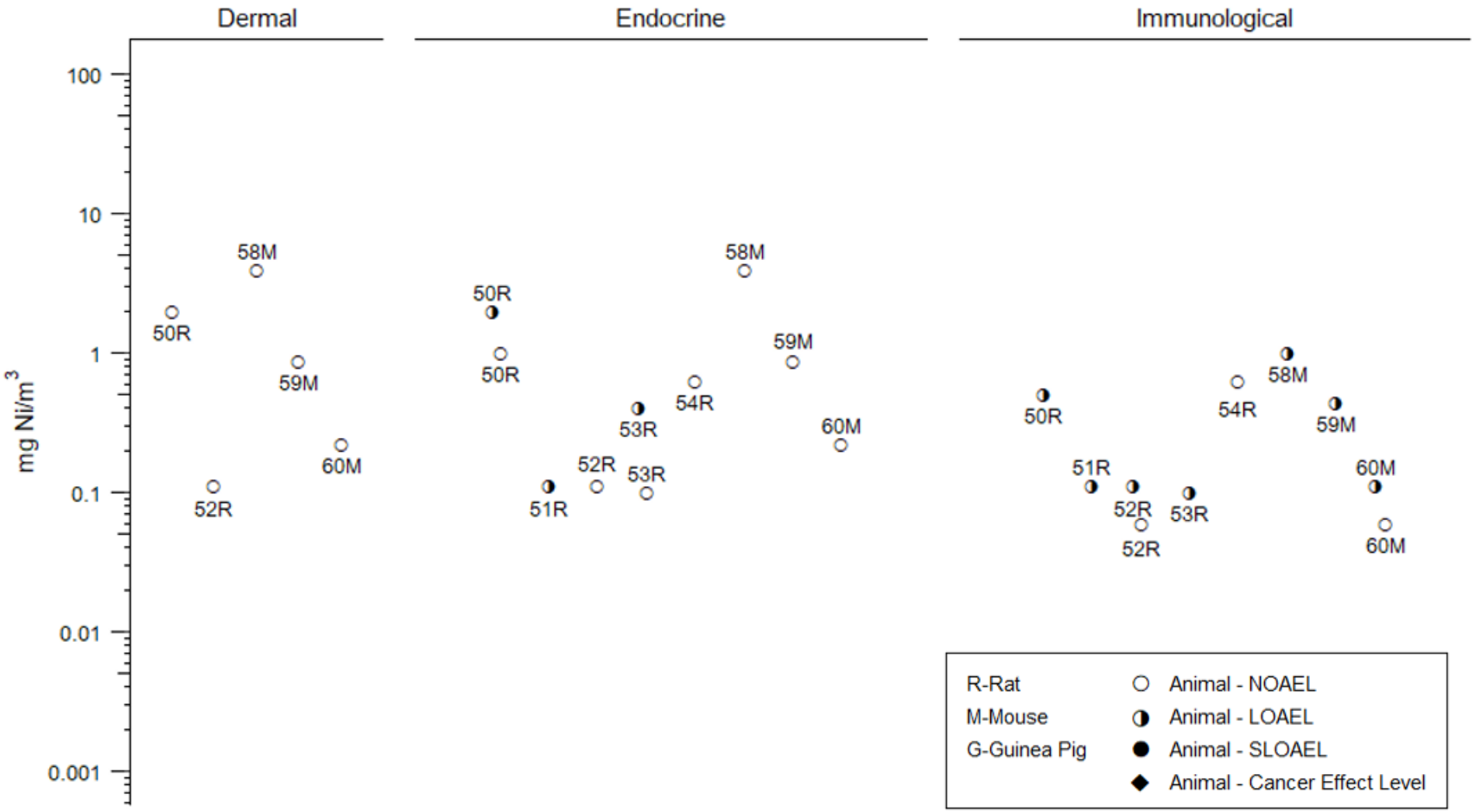


Figure 2-2. Levels of Significant Exposure to Nickel – Inhalation
Chronic (≥365 days)

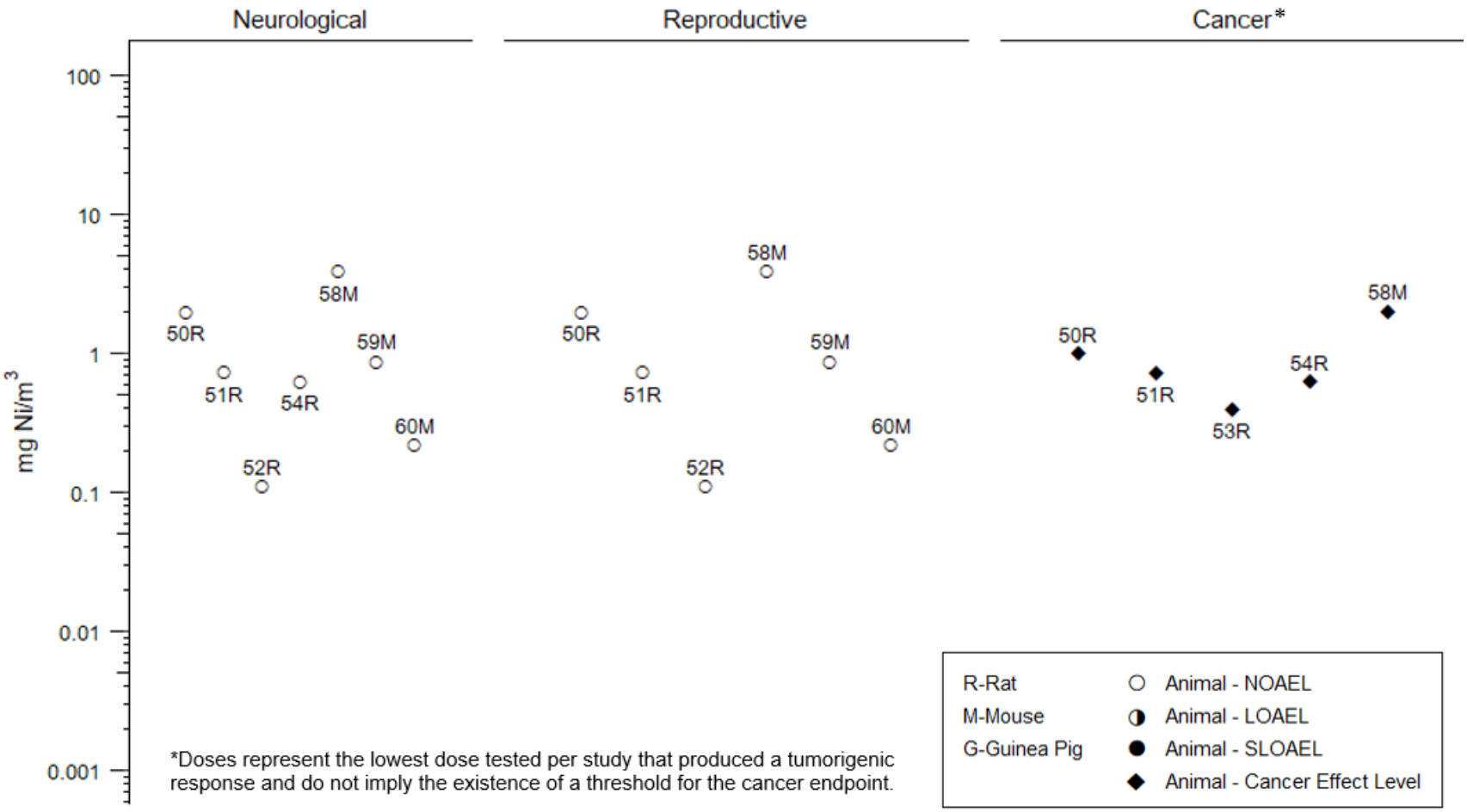


Table 2-2. Levels of Significant Exposure to Nickel – Oral (mg/kg/day)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

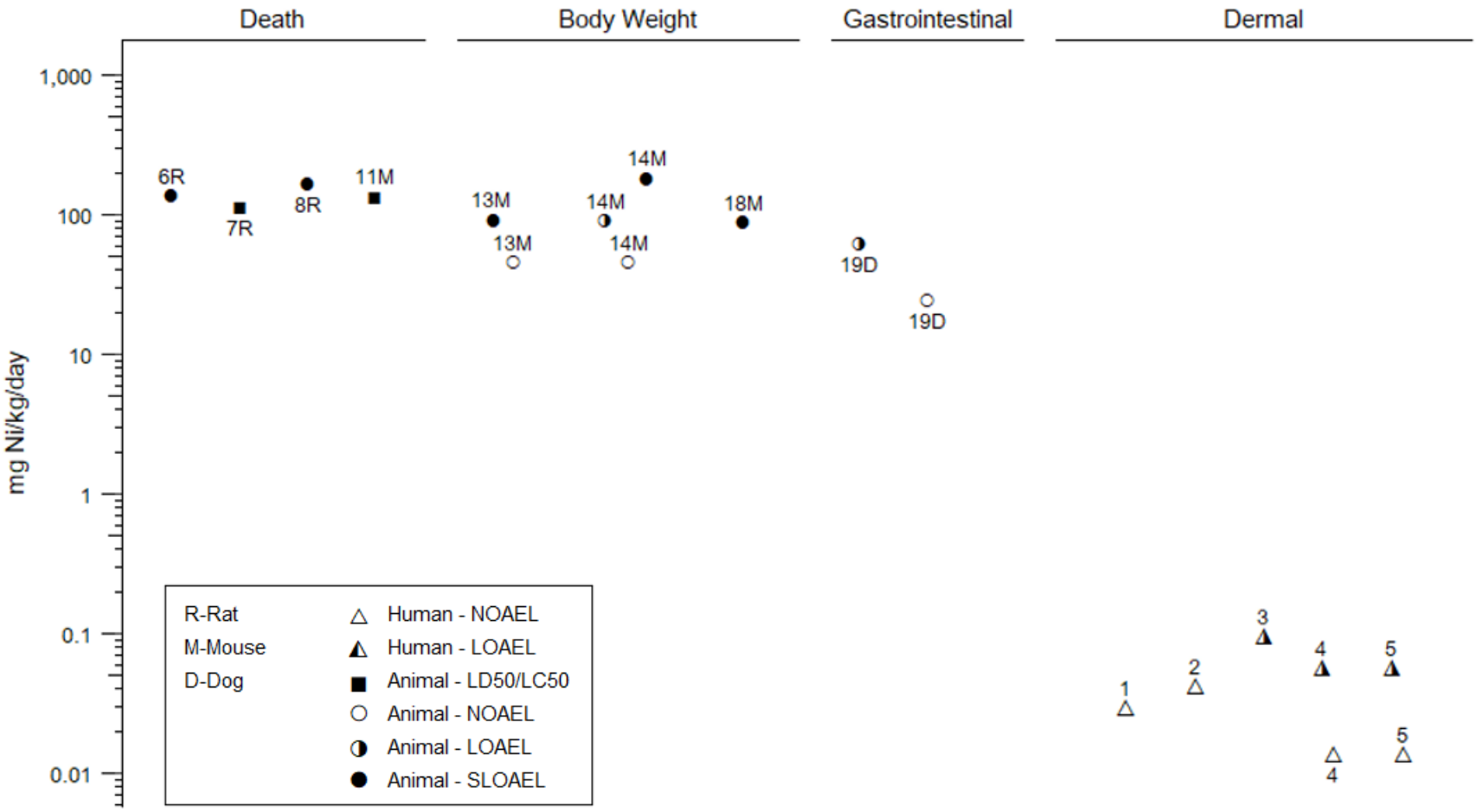


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Acute (≤14 days)

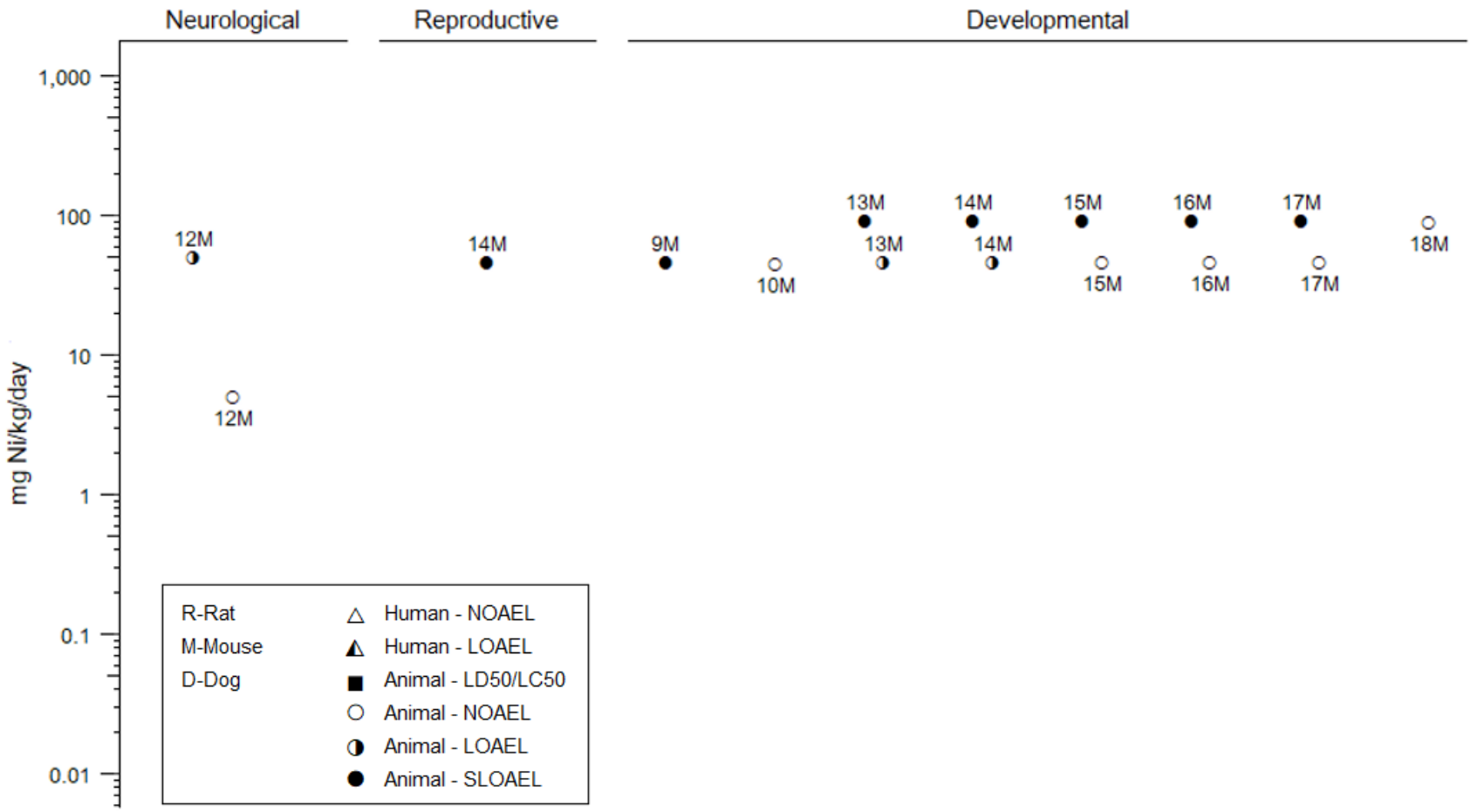


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

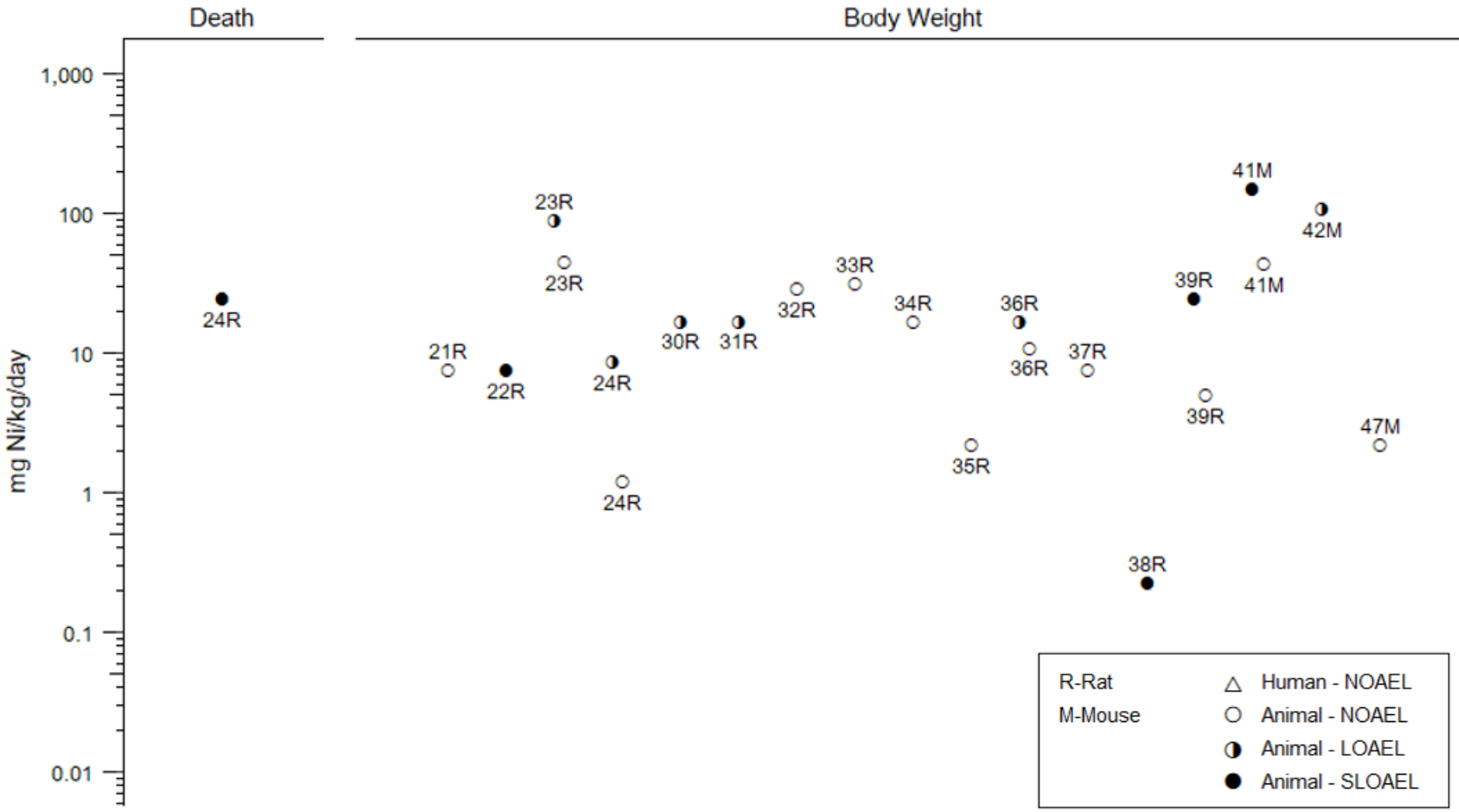


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

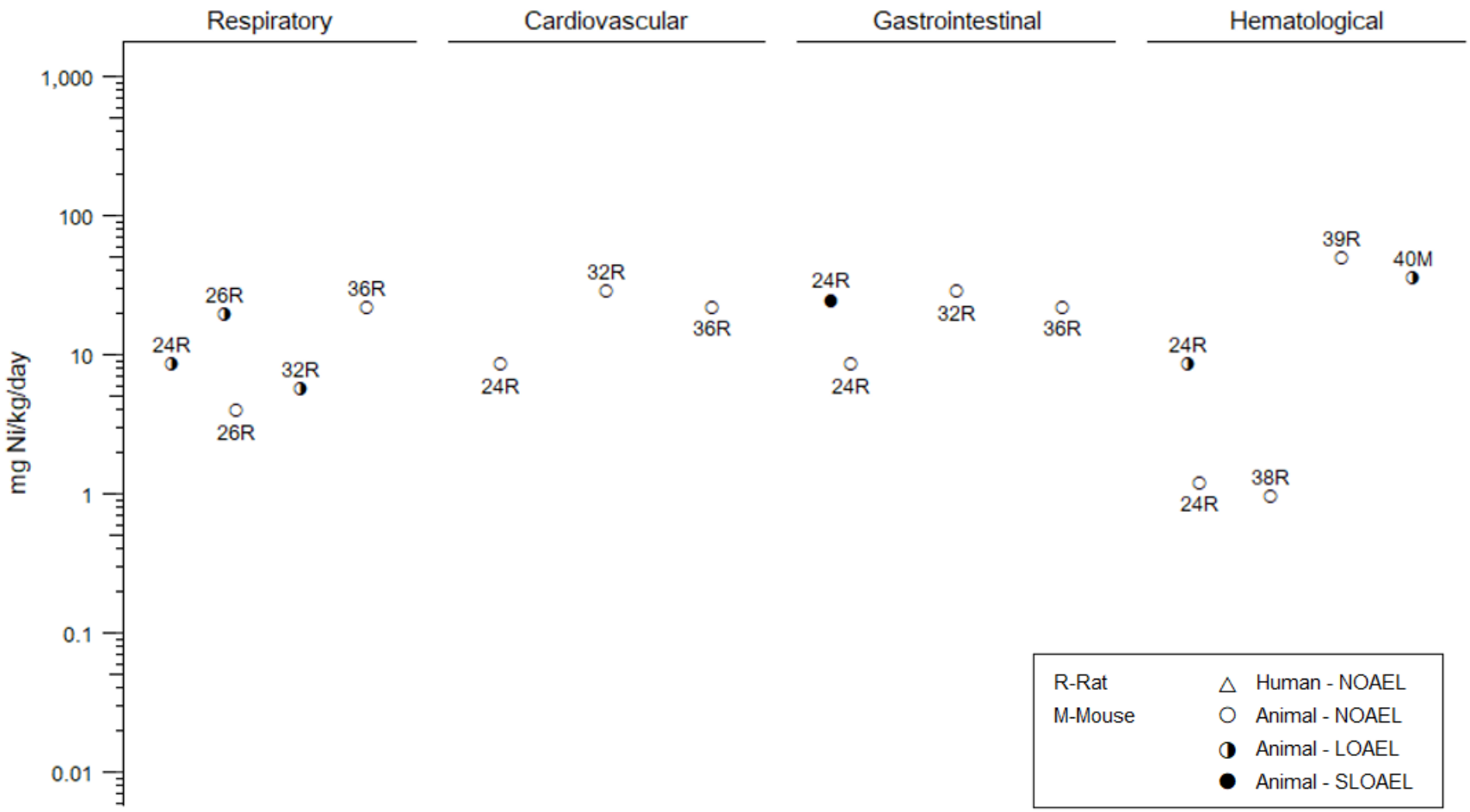


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

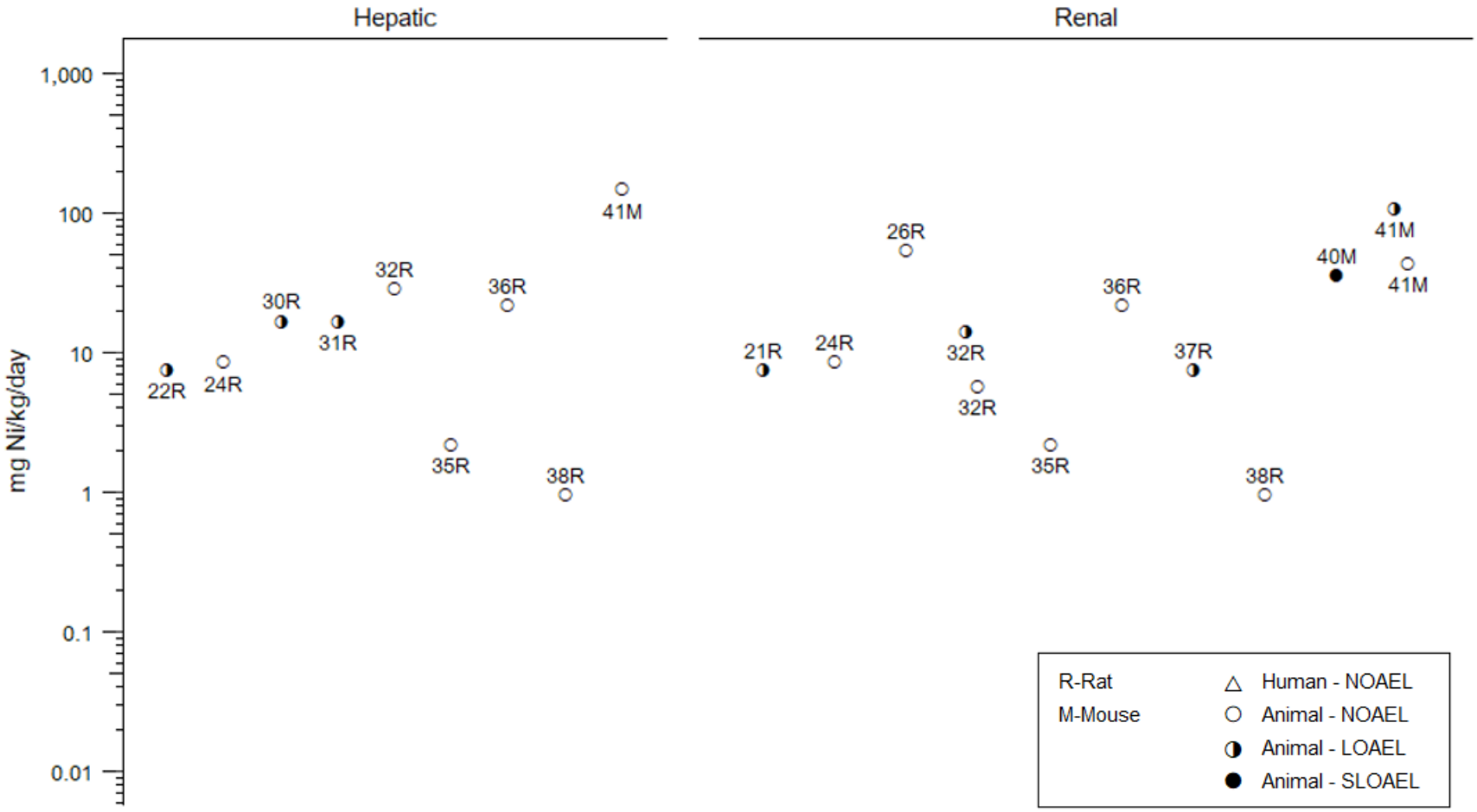


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

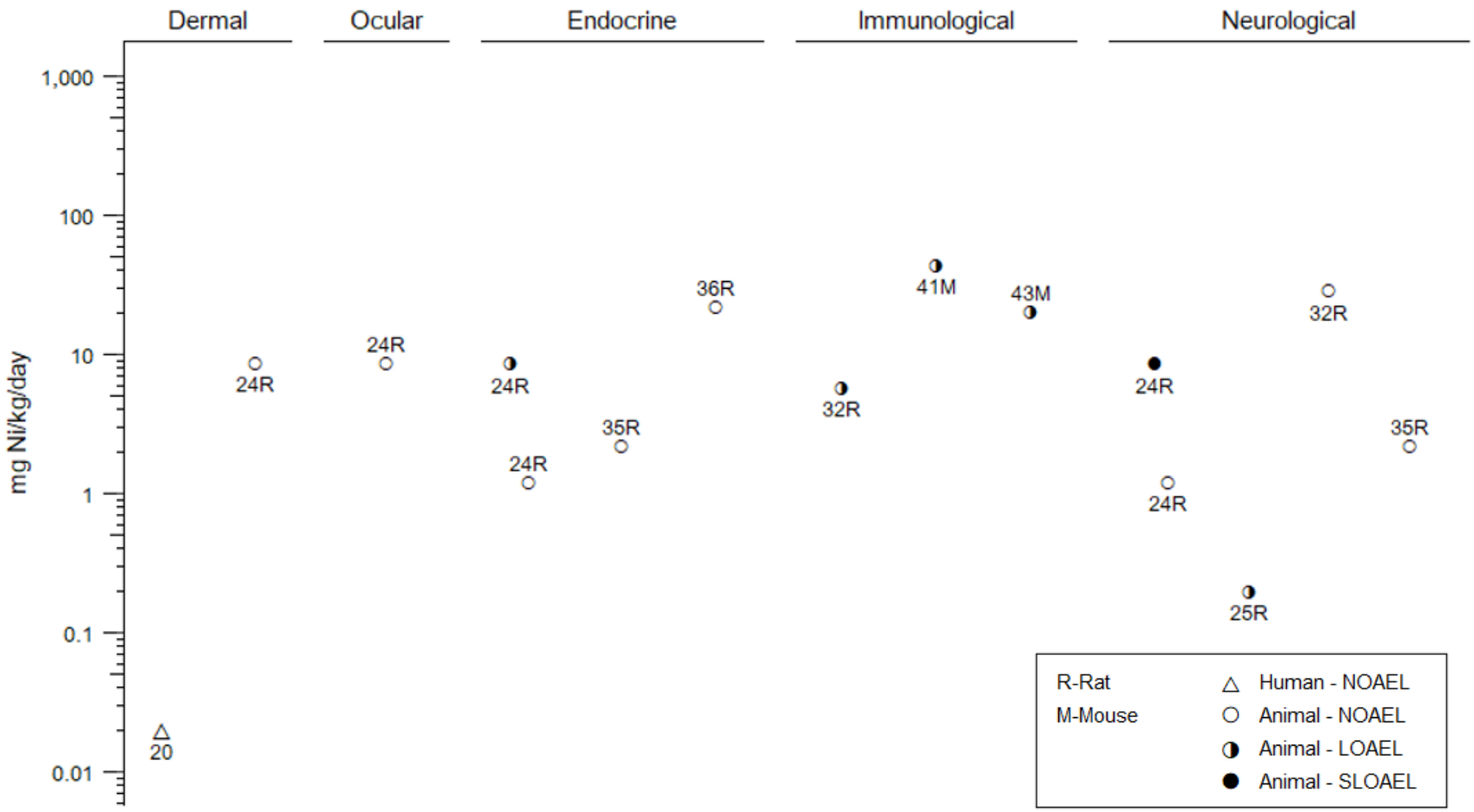


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

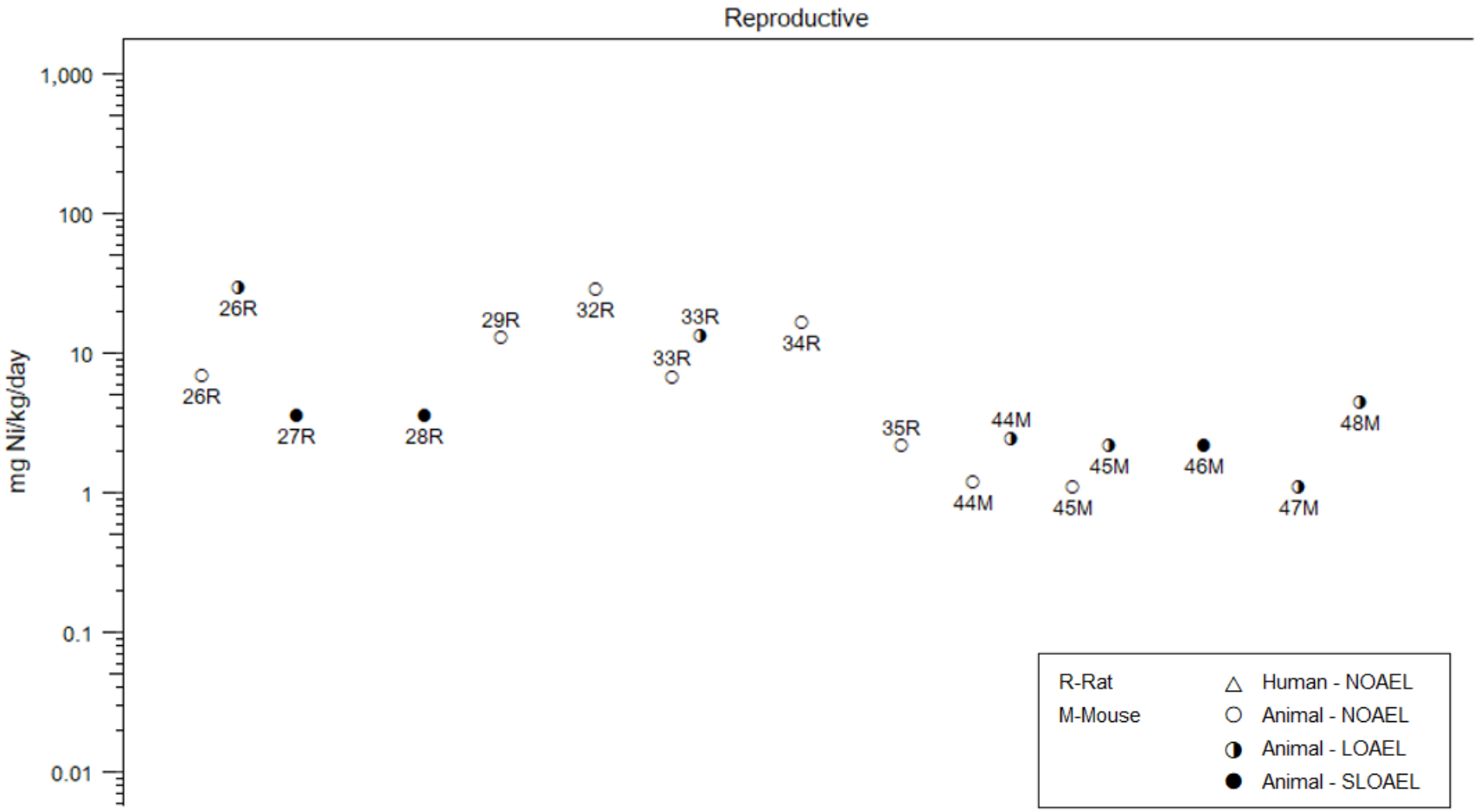


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Intermediate (15–364 days)

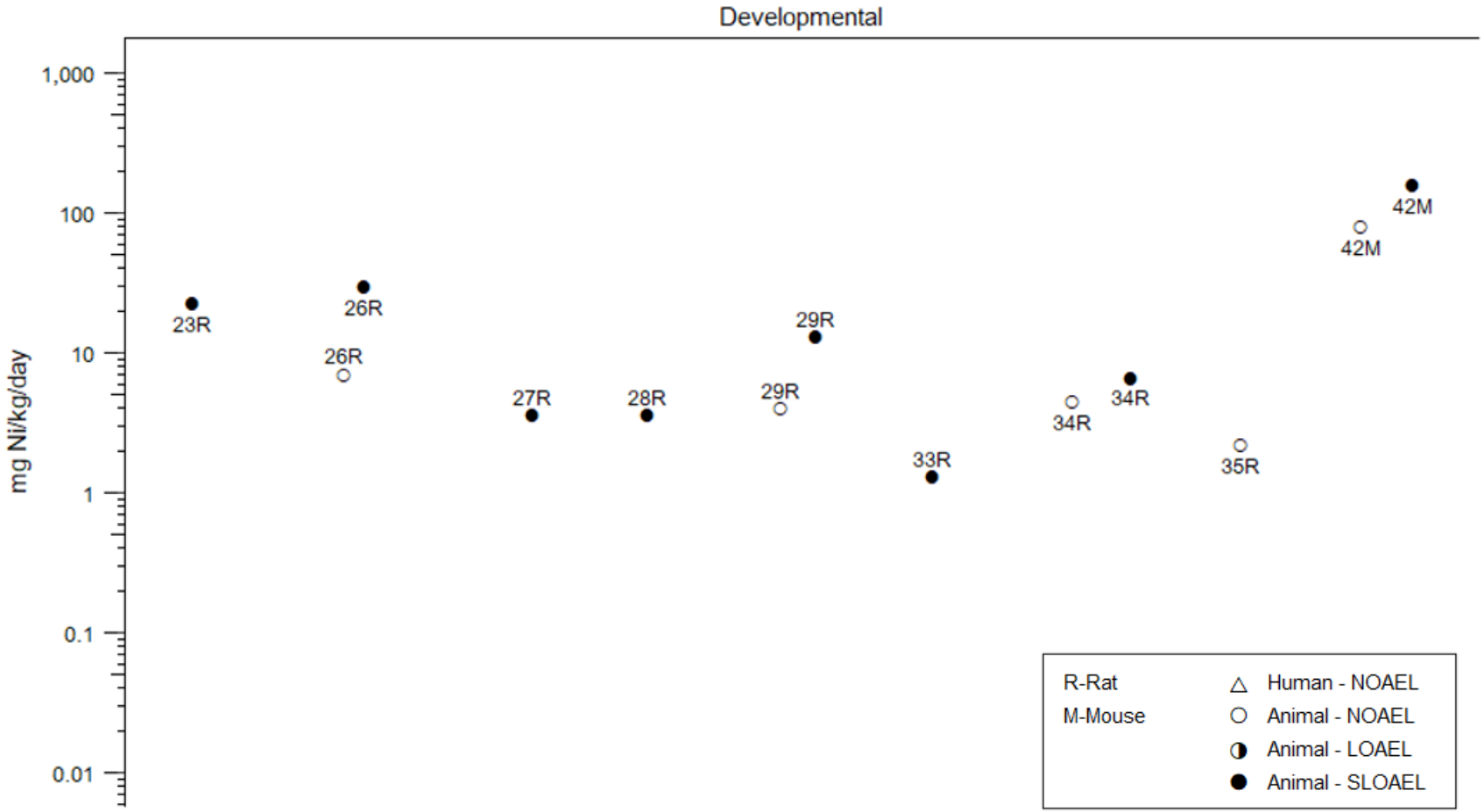


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

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

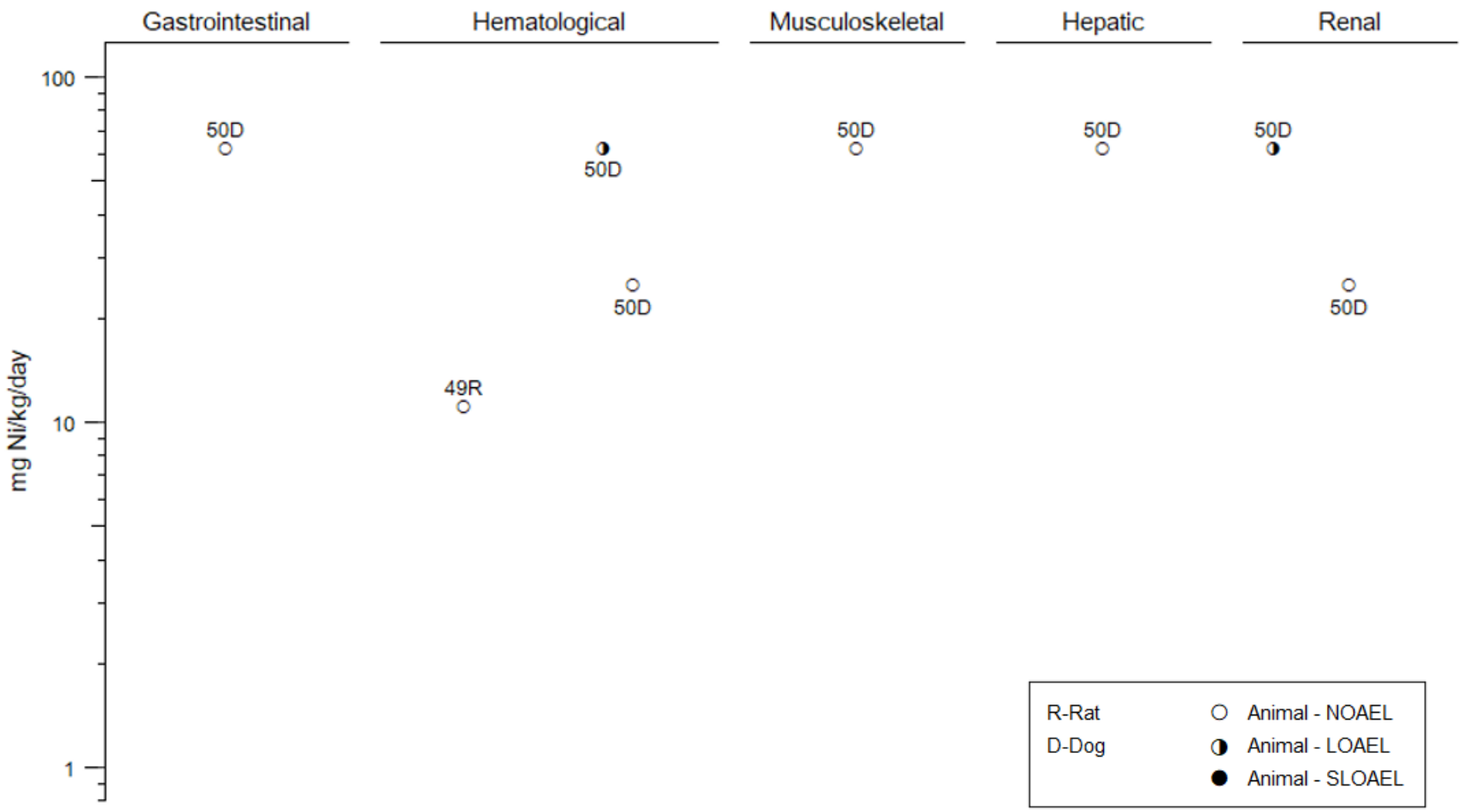


Figure 2-3. Levels of Significant Exposure to Nickel – Oral
Chronic (≥365 days)

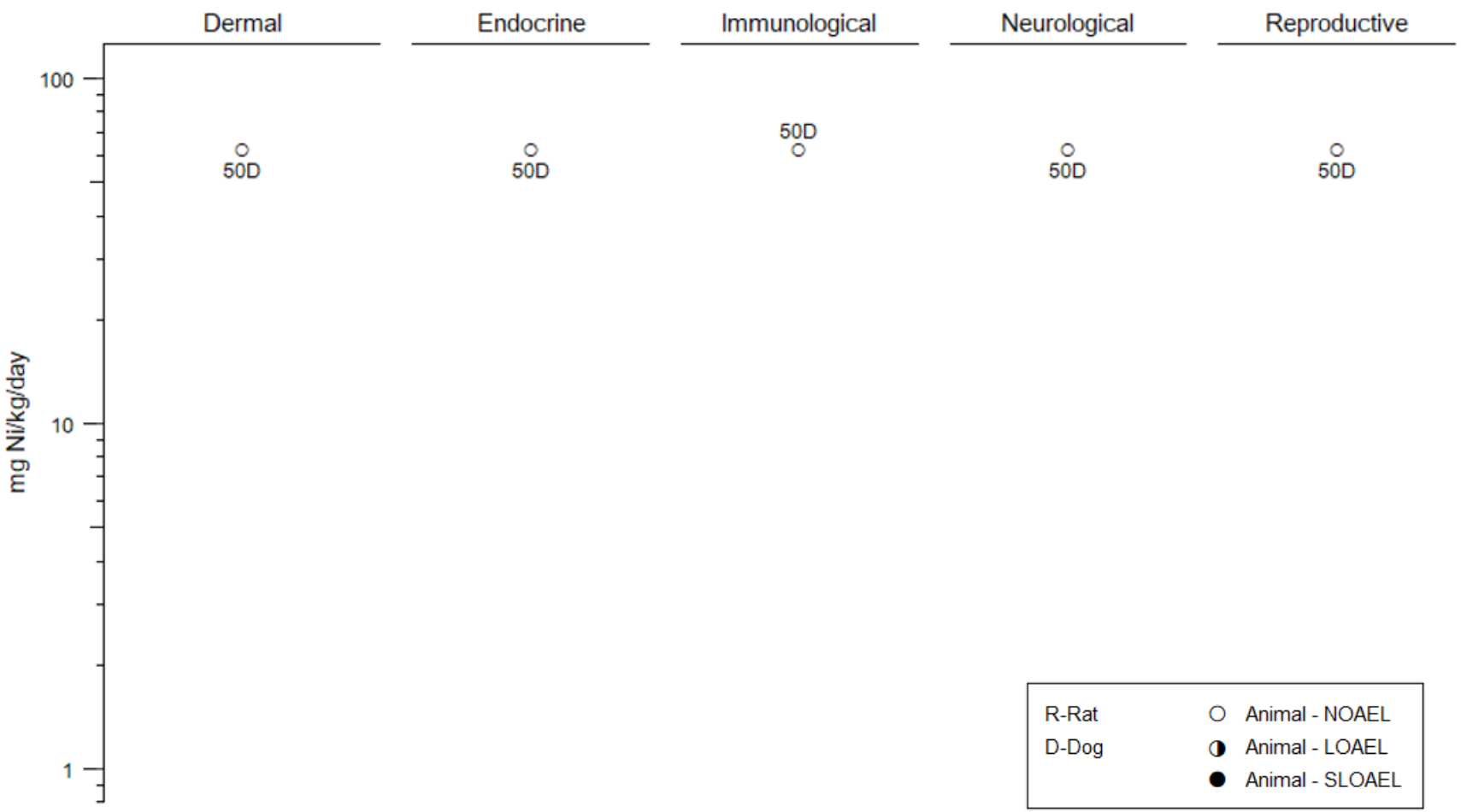


Table 2-3. Levels of Significant Exposure to Nickel – Dermal

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

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

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

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

2.2 DEATH

Death from adult respiratory distress syndrome (ARDS) was reported in one person who sprayed nickel with a metal arc process without wearing personal protective equipment (Rendall et al. 1994). Death occurred 13 days after a 90-minute exposure to an estimated concentration of 382 mg Ni/m^3 of principally metallic nickel with the majority of particle sizes of <1.4 µm (Sunderman 1993). Histological examination of the lungs revealed alveolar wall damage and edema in alveolar spaces, and marked tubular necrosis was noted in the kidneys.

Human data regarding chronic-duration inhalation exposure to nickel are limited to occupational exposure studies. Most of these studies analyzed the toxicity of nickel, usually in the form of nickel oxide, metallic nickel, or nickel refinery dust, by calculating standardized mortality ratios (SMRs) for all causes of death. Generally, the studies reported a higher incidence of cancer deaths from lung and nasal cancers in the exposed workers (see Section 2.19 Cancer). Two studies also reported a higher incidence of deaths resulting from nonmalignant respiratory disease (Cornell and Landis 1984; Polednak 1981). However, all of the workers were exposed to other metals (arsenic, uranium, iron, lead, chromium) and non-metallic substances, so it cannot be concluded that nickel was the sole causative agent. Other studies of humans occupationally exposed to nickel compounds have not reported increased mortality resulting from respiratory diseases (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh 1982; Redmond 1984; Shannon et al. 1984a, 1984b, 1991).

During the first 2 days after a single 2-hour exposure, 4 out of 28 Fischer-344 rats died after exposure to nickel sulfate at 36.5 mg Ni/m^3 (Hirano et al. 1994). Severe hemorrhage of the lungs was observed in the lungs of the rats that died. No deaths were observed in rats exposed to 0.00672 mg Ni/m^3 as nickel oxide for 4 hours followed by a 14-day observation period (Lyons-Darden et al. 2023). Significant mortality was observed during the last 26 weeks of a 31-month inhalation study of Fischer-344 rats exposed to 0.63 mg Ni/m^3 as nickel sulfide (Ottolenghi et al. 1975). Less than 5% of the treated rats survived the study (78 weeks of exposure plus 30 weeks of observation) compared to 31% of the controls (Ottolenghi et al. 1975). A significant decrease in mean survival time was observed in Wistar rats exposed 23 hours/day for life to 0.06 mg Ni/m^3 as nickel oxide (Takenaka et al. 1985); the average survival times for rats exposed to 0 or 0.06 mg Ni/m^3 were 125.2 and 87.7 weeks, respectively. Male and female Wistar rats showed reduced survival by 72 and 48%, respectively, by 103 weeks of continuous exposure 0.11 mg Ni/m^3 as metallic nickel (5 days/week, 6 hours/day) (Oller et al. 2008).

NTP studies observed that B6C3F1 mice were more sensitive to lethality from nickel exposure than Fischer-344 rats. At 1.4 mg Ni/m^3 as nickel sulfate hexahydrate, all mice and no rats died, and at 7.33 mg Ni/m^3 as nickel subsulfide, all mice and only 2 of 10 rats died following exposure for 6 hours/day, 5 days/week, for up to 12 exposures (NTP 1996b, 1996c). No rats or mice died following exposure to 23.6 mg Ni/m^3 as nickel oxide (NTP 1996a). No deaths were reported in rats or mice following 13 weeks of exposure (6 hours/day, 5 days/week) to nickel at 7.9, 1.83, or 0.44 mg Ni/m^3 as nickel oxide, nickel subsulfide, or nickel sulfate, respectively (NTP 1996a, 1996b, 1996c). Survival was not affected in rats exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c) or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c).

All rats (Bethesda Black), guinea pigs (Strain 13), and mice (C57) exposed to 15 mg Ni/m^3 as metallic nickel for 21 months died before the end of the study, with most of the guinea pigs and mice dying by 15 months (Hueper 1958). Lung lesions, including edema, hyperemia, and hemorrhage, were the principal causes noted. A major study deficiency was the lack of control animals, the study instead compared exposure groups to data of same-species controls from previous carcinogenic studies (Hueper 1958).

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

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

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

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

[a]95% CI was not calculated.

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

Source: Henderson et al. 2012

Increases in mortality were observed in Sprague-Dawley rats administered via gavage 25 mg Ni/kg/day as nickel chloride hexahydrate for 91 days (American Biogenics Corporation 1988). Clinical signs observed included lethargy, ataxia, irregular breathing, hypothermia, salivation, squinting, and loose stools. As part of a longer-term study, increases in mortality in Sprague-Dawley rats were observed within 2 weeks of exposure to 140 mg Ni/kg/day as nickel chloride (EPA 1988a). Over a 2-year study, increases in mortality were observed in female Fischer-344 rats exposed to 6.7 mg Ni/m^3 as nickel sulfate hexahydrate (Heim et al. 2007). No exposure-related response was seen in male rats exposed during the same period. In other studies, no deaths were observed in Sprague-Dawley rats given 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999), Fischer-344 rats administered 22 mg Ni/kg/day (males) or 33 mg Ni/kg/day (females) as nickel sulfate hexahydrate for 90 days (Springborn Laboratories 2002), or B6C3F1 mice exposed with nickel sulfate in the drinking water at doses up to 150 mg Ni/kg/day for 180 days (Dieter et al. 1988).

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

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

An increase in mortality was not observed in chronic-duration studies in Wistar rats or Beagle dogs fed nickel sulfate in the diet at doses up to 188 mg/kg/day for rats and 62.5 mg/kg/day for dogs (Ambrose et al. 1976).

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

2.3 BODY WEIGHT

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

Decreases in body weight gain have been observed in rats and mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide for acute, intermediate, and chronic exposures. In many of the studies, the decreases in body weight gain were associated with lung inflammation, impaired lung function (as evidenced by labored breathing), and lethality. Exposure to nickel sulfate resulted in serious decreases in body weight gain (terminal body weights >25% lower than controls) in rats exposed to ≥0.7 mg Ni/m^3 and in mice exposed to 1.4 mg Ni/m^3 6 hours/day for 12 days in a 16-day period (NTP 1996c); no alterations in body weight gain were observed in mice exposed to 0.7 mg Ni/m^3. No significant alterations in body weight gain were observed in rats or mice exposed to ≤0.44 mg Ni/m^3 for 13 weeks (NTP 1996c; Oller et al. 2023), rats exposed to 0.11 mg Ni/m^3 for 2 years (NTP 1996c), or mice exposed to 0.22 mg Ni/m^3 for 2 years (NTP 1996c).

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

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

Most studies did not find significant body weight alterations in rats and mice exposed to inhaled nickel oxide. A NOAEL of 23.6 mg Ni/m^3 was identified in rats and mice exposed 6 hours/day for 12 days in a 16-day period (NTP 1996a). For intermediate-duration exposure, NOAELs of 1.9–7.9 mg Ni/m^3 were identified in rats and mice (Benson et al. 1995a; NTP 1996a). However, Weischer et al. (1980) reported 30–36% decreases in body weight gain in male and female rats exposed to 0.385 or 0.8 mg Ni/m^3, respectively, continuously for 21–28 days. In pregnant rats, an 11% decrease in body weight gain was observed at 0.8 mg Ni/m^3 compared to the 36% decrease observed in similarly exposed nonpregnant rats. NTP (1996a) did not find alterations in body weight gain in rats or mice exposed to 2 or 3.9 mg Ni/m^3, respectively, 6 hours/day, 5 days/week for 2 years; a NOAEL of 0.9 mg Ni/m^3 was also identified in rats exposed 7 hours/day, 5 days/week for 12 months (Tanaka et al. 1988). In contrast, Takenaka et al. (1985) reported weight loss in rats continuously exposed to 0.06 mg Ni/m^3 for 31 months; the weight loss began after 13 months of exposure. These data suggest that continuous exposure is more toxic than intermittent exposure (the duration-adjusted NOAEL for the rat NTP [1996a] study is 0.36 mg Ni/m^3). Continuous exposure resulted in higher lung burdens than intermittent exposure, which would lead to increased lung damage.

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

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

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

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

2.4 RESPIRATORY

Human studies have examined the potential of nickel and nickel compounds to induce respiratory effects. Epidemiological studies of respiratory effects are summarized in Table 2-5. Most of these studies were cohort mortality studies in nickel-exposed workers. A significant excess of deaths from nonmalignant respiratory system disease was found among foundry workers; the excess was associated with the duration of foundry employment, regardless of exposure to nickel (Cornell and Landis 1984). Other studies of workers exposed to nickel have not found increases in deaths from respiratory disease (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Moulin et al. 2000; Polednak 1981; Redmond 1984; Roberts et al. 1989a; Shannon et al. 1984a, 1984b, 1991). A common limitation of the cohort mortality studies is that the numbers of observed deaths from all causes were lower (significantly lower in many cases) than the numbers of expected deaths, suggesting a healthy worker effect. Additionally, the workers were exposed to other respiratory toxicants; this is particularly

true for welders exposed to elevated levels of chromium. A single case of death from ARDS was reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994). Histological changes noted in the lungs of this case included alveolar wall damage with fibrotic changes, and edema in the alveolar space.

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

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

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

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

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

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

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

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

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

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

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

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

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

Studies in rats and mice demonstrate that chronic active inflammation in the lungs is the most prominent effect following inhalation exposure to nickel sulfate, nickel subsulfide, or nickel oxide. In acutely exposed Fischer-344 rats, chronic lung inflammation was observed at the lowest nickel sulfate (0.7 mg Ni/m^3) and nickel subsulfide (0.44 mg Ni/m^3) concentrations tested in 12-day exposure studies (6 hours/day, 12 days in a 16-day period) (NTP 1996b, 1996c); the results of the NTP (1996a, 1996b, 1996c) studies are also presented in Dunnick et al. (1988). At higher concentrations of nickel sulfate and nickel subsulfide (1.4 and 3.65 mg Ni/m^3, respectively), the inflammation was accompanied by labored breathing. The chronic active lung inflammation was characterized by focal accumulation of alveolar macrophages and interstitial (nickel subsulfide) or inflammatory cell (nickel sulfate) infiltrates. At the higher concentrations, necrotic cellular debris were also present. Peribronchiolar/perivascular

inflammation was also observed in rats exposed to 0.44 mg Ni/m^3 as nickel subsulfide for 5 days (6 hours/day) (Efremenko et al. 2014). Exposure to ≥0.7 mg Ni/m^3 as nickel sulfate also resulted in bronchiolar epithelium degeneration in rats (Efremenko et al. 2017a, 2017b; NTP 1996c). Consistent with these findings is the observation of alveolitis in Fischer-344 rats exposed to 0.44 mg Ni/m^3 as nickel subsulfide 6 hours/day for 7 days (Benson et al. 1995b). Additionally, exposure to 1.83 mg Ni/m^3 as nickel subsulfide resulted in alveolitis and alveolar proteinosis after 4 days of exposure (Benson et al. 1995b). In contrast, acute lung inflammation, consisting of neutrophilic infiltrates, was first observed in rats exposed to nickel oxide at 7.9 mg Ni/m^3 (NTP 1996a); chronic lung inflammation was not observed at doses as high as 23.6 mg Ni/m^3. Mice appear to be less sensitive than rats to the acute toxicity of nickel, with LOAELs for chronic inflammation of 0.7, 1.83, and >23.6 mg Ni/m^3 as nickel sulfate, nickel subsulfide, and nickel oxide, respectively (NTP 1996a, 1996b, 1996c).

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

As with acute-duration exposure, chronic lung inflammation was typically observed at the lowest-adverse-effect level following intermediate-duration exposure. Thirteen-week (6 hours/day, 5 days/week) NTP studies of rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide (NTP 1996a, 1996b, 1996c) identified LOAELs for chronic active lung inflammation of 0.11, 0.22, and 3.9 mg Ni/m^3, respectively; NOAEL values of 0.06, 0.11, and 2 mg Ni/m^3, respectively, were also identified for chronic inflammation. Similar lung effects (alveolitis, perivascular/peribronchiolar inflammation, and bronchiolar epithelial degeneration) were observed in rats exposed to 0.04 mg Ni/m^3 as nickel subsulfide or 0.11 mg Ni/m^3 as nickel sulfate 6 hours/day, 5 days/week for 4 or 13 weeks (Efremenko et al. 2017a, 2017b; Oller et al. 2023). Comparison of lesions showed that the incidence and severity of perivascular/peribronchiolar lesions and alveolar type II cell hyperplasia was higher in rats exposed to nickel subsulfide (Oller et al. 2023). Alveolitis was reported in rats exposed to 0.11 mg Ni/m^3 as nickel sulfate and 1.96 mg Ni/m^3 as nickel oxide for 6 months (6 hours/day, 5 days/week) (Benson et al. 1995a). Similarly, localized interstitial pneumonia, represented by lymphoid infiltration and fibrosis of alveolar septa, emphysema, and atelectasis of varying degrees, was seen in rats exposed to 0.5 mg Ni/m^3 as nickel oxide for 1 month (Horie et al. 1985).

Several other lung effects have also been observed in rats exposed to nickel for intermediate durations. Minimal alveolar macrophage hyperplasia was observed at the lowest nickel sulfate, nickel subsulfide,

and nickel oxide concentrations evaluated (0.03, 0.11, and 0.4 mg Ni/m^3, respectively) (NTP 1996a, 1996b, 1996c). These slight changes in the number of macrophages were not considered adverse because it is considered part of the normal physiologic response to inhaled particles, and it is not believed to compromise the lung's ability to clear foreign matter. This is supported by results from Oller et al. (2023) where the incidence of alveolar macrophage hyperplasia was similar between controls and groups of rats exposed to concentrations of nickel sulfate or nickel subsulfide up to 0.22 and 0.44 mg Ni/m^3, respectively. However, the increased severity of this lesion appears to be concentration related (Oller et al. 2023). At higher nickel concentrations, mild to moderate changes in alveolar macrophage hyperplasia were found. Interstitial infiltrates were observed in rats exposed to ≥0.11 or 0.22 mg Ni/m^3 as nickel sulfate or nickel subsulfide (NTP 1996b, 1996c), granulomatous inflammation was observed in rats exposed to 3.9 mg Ni/m^3 as nickel oxide (NTP 1996a), and alveolar wall thickening was observed in rats exposed to 0.12 mg Ni/m^3 as nickel oxide (Bingham et al. 1972). The highest NOAEL values for respiratory effects in rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for intermediate durations were 0.03 mg Ni/m^3 (NTP 1996c), 0.11 mg Ni/m^3 (NTP 1996b), and 0.49 mg Ni/m^3, respectively (Benson et al. 1995a).

Similar effects have been observed in mice exposed to nickel for intermediate durations, although the LOAELs for the lung effects tend to be higher, suggesting a lower sensitivity compared to rats. Chronic active lung inflammation was observed in mice exposed to ≥0.44 and 0.88 mg Ni/m^3 as nickel sulfate or nickel subsulfide, respectively (NTP 1996b, 1996c). Lung inflammation was not found in mice exposed to nickel oxide at concentrations as high as 7.9 mg Ni/m^3 (NTP 1996a); however, perivascular lymphocyte infiltrates were observed at 3.9 and 7.9 mg Ni/m^3 (NTP 1996a). Interstitial pneumonia has also been observed in mice exposed to 0.22 or 0.98 mg Ni/m^3 as nickel sulfate or nickel oxide (Benson et al. 1995a). Other lung effects in mice include minimal alveolar macrophage hyperplasia at 0.11, 0.22, or 0.4 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c), interstitial infiltrates at ≥0.44 or 0.44 mg Ni/m^3 as nickel subsulfide or nickel sulfate, respectively (NTP 1996b, 1996c), and fibrosis at 0.44 and 0.88 mg Ni/m^3 as nickel sulfate or nickel subsulfide, respectively (NTP 1996b, 1996c). As with rats, minimal alveolar macrophage hyperplasia was not considered adverse. The highest NOAEL values for respiratory effects in mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide for intermediate durations were 0.22, 0.22, and 3.9 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c).

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

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

The NTP (1996a, 1996b, 1996c) studies allow for the comparison of the toxicity of nickel sulfate, nickel subsulfide, and nickel oxide in rats and mice. Following acute- or intermediate-duration exposure, the toxicity of the different nickel compounds is related to its solubility, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The difference in the toxicity across compounds is probably due to the ability of water-soluble nickel compounds to cross the cell membrane and interact with cytoplasmic proteins. In contrast, the severity of inflammatory and proliferative lesions following chronic-duration exposure was greater in rats exposed to nickel subsulfide or nickel oxide, as compared to nickel sulfate. Additionally, parenchymal damage secondary to inflammation was evident in the rats exposed to nickel subsulfide and nickel oxide, but not nickel sulfate. For all durations and nickel compounds evaluated, rats appear to be more sensitive to the lung effects than mice; significant increases in the incidence of chronic lung inflammation were observed at lower concentrations in the rats than mice. Intermediate-duration studies (Benson et al. 1995a; Horie et al. 1985) that monitored animals for months after exposure termination suggest that nickel-induced lung damage is not readily reversible after exposure termination. In the Benson et al. (1995a) studies, alveolitis was observed in rats exposed to 0.11 mg Ni/m^3 as nickel sulfate and 1.96 mg Ni/m^3 as nickel oxide at the end of the 6-month exposure period and 4 months after exposure termination. Horie et al. (1985) reported localized interstitial pneumonia in rats exposed 6 hours/day, 5 days/week to 0.5 mg Ni/m^3 as nickel oxide for 1 month. At 12 and 20 months after termination of exposure to 6.3 mg Ni/m^3, squamous metaplasia of the bronchial epithelium, hyperplasia of the bronchial gland, and chronic bronchitis were observed.

In addition to the lung effects, several studies have demonstrated that exposure to nickel sulfate or nickel subsulfide can induce atrophy of the nasal olfactory epithelium (Evans et al. 1995; NTP 1996b, 1996c). In studies examining the lungs and nasal cavity, the nasal lesions were typically observed at higher concentrations than the lung effects. In a study designed specifically to examine the effects of nickel on

the olfactory system, rats were exposed to nickel sulfate at 0 or 0.635 mg Ni/m^3 6 hours/day for 16 days (Evans et al. 1995). Histological changes in the olfactory epithelium of exposed rats included a slight reduction in the number of bipolar sensory receptor cells, a decrease in the thickness of the olfactory epithelium resulting from a loss of sustentacular cells, a thinning of apical cytoplasm, and a reduction in the number of sensory cilia on the surface of the cells. After a recovery period of 22 days, the only change that remained was fewer sensory cilia, indicating that the effects of an intermediate-duration exposure to nickel were reversible.

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

Respiratory effects have also been observed in animals following oral exposure to nickel. Irregular respiration was one of several clinical signs of nickel toxicity observed in rats administered doses of nickel sulfate ≥111.6 mg Ni/kg/day for 3 days (Oller and Erexson 2007). Pneumonitis was observed in rats treated for 91 days by gavage with 8.6 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988). Significant increases in absolute and relative lung weights were observed in rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999). This study also found alterations in enzyme activity in bronchoalveolar lavage fluid (BALF) and lung tissues, including increases in protein levels in BALF at ≥14.4 mg Ni/kg/day, decreases in alkaline phosphatase (ALP) activity in BALF at ≥5.75 mg Ni/kg/day, and decreases in ALP activity in lung tissue at 28.8 mg Ni/kg/day. No histological alterations were observed in the lungs. The study authors suggested that the decrease in ALP activity was indicative of decreased activity of type II alveolar cells and that the increased total protein was indicative of increased air-blood barrier permeability. In a multigeneration study (EPA 1988a, 1988b), increased relative lung weights were observed in rats provided with nickel chloride in the drinking water at 55 mg Ni/kg/day, and an increase in cellular infiltration of the lungs was observed at 20 mg Ni/kg/day. Emphysema, bronchiectasis, and cholesterol granulomas were also observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years, but not in rats exposed at up to 187.5 mg/kg/day for 2 years (Ambrose et al. 1976).

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

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

2.5 CARDIOVASCULAR

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

Nickel sulfate crystals (rough estimate of 570 mg Ni/kg) were accidentally ingested by a 2-year-old child (Daldrup et al. 1983). Four hours after ingestion, cardiac arrest occurred, and the child died 8 hours after exposure. No studies were identified that examined cardiovascular effects in humans after dermal exposure to nickel.

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

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

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

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

2.6 GASTROINTESTINAL

No studies were identified that examined gastrointestinal effects in humans after inhalation or dermal exposure to nickel. Symptoms of gastrointestinal distress were most frequently reported by workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. Of the 32 workers exposed, 20 reported symptoms including nausea (15 workers), abdominal cramps (14 workers), diarrhea (4 workers), and vomiting (3 workers).

The gastrointestinal symptoms persisted 1–2 days in 10 workers who were then hospitalized. Although the actual contribution of boric acid to these effects is not known, the study authors indicated that the intake of 20–200 mg boric acid probably did not contribute to the observed effects because the effects of boric acid are generally observed only following ingestion of ≥4 g by adults (Sunderman et al. 1988).

Histopathological examinations of the gastrointestinal tract of mice and rats exposed to airborne nickel sulfate, nickel subsulfide, or nickel oxide for 6-hour exposures over 12 days did not reveal any changes at concentrations as high as 12.2, 7.33, or 23.6 mg Ni/m^3, respectively, in rats and 1.4, 3.65, or 23.6 mg Ni/m^3, respectively, in mice (NTP 1996a, 1996b, 1996c). Likewise, no histological alterations were observed in the gastrointestinal tracts of rats and mice exposed to 0.44, 1.83, or 7.9 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic-duration exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice to 0.22, 0.88, or 3.9 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, did not result in microscopic changes in the gastrointestinal tract (NTP 1996a, 1996b, 1996c). Continuous chronic-duration exposure (6 hours/day, 5 days/week) of rats to 0.63 mg Ni/m^3 as nickel sulfide for 78 weeks also did not affect the microscopic appearance of the intestines (Ottolenghi et al. 1975).

Discolored gastrointestinal contents, ulcerative gastritis, and enteritis were observed in rats that died following treatment by gavage with 25 mg Ni/kg/day as nickel chloride hexahydrate for up to 91 days (American Biogenics Corporation 1988). Discolored (green) gastrointestinal contents were also observed at 1.2 and 8.6 mg/kg/day. The discoloration may have been due to the presence of nickel chloride in the gastrointestinal tract and is not considered an adverse effect. Adverse gastrointestinal effects were not observed in rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999), rats treated with nickel sulfate in the diet at 187.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976), or rats receiving gavage doses of 22 (males) or 33 (females) mg Ni/kg/day as nickel sulfate (Springborn Laboratories 2002). During the first 3 days of a 2-year study, dogs vomited following treatment with nickel sulfate in the diet at 62.5 mg Ni/kg/day (Ambrose et al. 1976). The dose was lowered to 37.5 mg Ni/kg/day for 2 weeks, and then incrementally raised at 2-week intervals back to 62.5 mg/kg/day, at which time, no further gastrointestinal distress was noted. These studies indicate that high doses of nickel can be irritating to the gastrointestinal tract, although acclimation to high levels of dietary nickel can occur. The toxicological significance of the results of the American Biogenics Corporation (1988) is not known, particularly since studies in rats (Ambrose et al. 1976; Obone et al. 1999; Springborn Laboratories 2000a, 2002) have not reported gastrointestinal effects.

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

2.7 HEMATOLOGICAL

No studies were identified that examined hematological effects in humans after inhalation or dermal exposure to nickel. A transient increase in blood reticulocytes was observed in 10 workers who were hospitalized for gastrointestinal symptoms after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). These workers were among 20 workers who reported symptoms following exposure and were hospitalized due to the 1–2-day persistence of clinical gastrointestinal symptoms. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Several hematological alterations were observed in studies by Weischer et al. (1980) and NTP (1996a, 1996b, 1996c). A decrease in hematocrit level was observed in male rats continuously exposed to 0.178 or 0.385 mg Ni/m^3 as nickel oxide for 28 days (Weischer et al. 1980); no significant alterations were observed at 0.785 mg Ni/m^3. The biological significance of a decrease in hematocrit level in the absence of hemoglobin or erythrocyte alterations is not known and lacks a clear dose-response. In nonpregnant females continuously exposed to nickel oxide for 21 days, increases in hematocrit and hemoglobin levels were observed at ≥0.8 mg Ni/m^3; an increase in mean cell volume and a decrease in erythrocyte levels were observed at ≥1.6 mg Ni/m^3 (Weischer et al. 1980). Similarly, increases in hematocrit, hemoglobin, and erythrocyte levels were observed in rats exposed to nickel subsulfide at 0.73 mg Ni/m^3 6 hours/day, 5 days/week for 2 years (NTP 1996b). Chronic-duration exposure of rats to nickel oxide or nickel sulfate at concentrations up to 2 or 0.11 mg Ni/m^3, respectively, and chronic-duration exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in significant hematological effects (NTP 1996a, 1996b, 1996c). Oller et al. (2008) observed increases in hemoglobin and hematocrit levels in rats after 78 weeks of exposure to concentrations ≥0.1 mg Ni/m^3 as metallic nickel. These same rats showed labored breathing and chronic lung inflammation. As noted by NTP (1996b), increases in hematocrit, hemoglobin, and erythrocytes are consistent with erythropoietin production in response to tissue hypoxia, possibly because of the nickel-induced lung damage.

Hematological effects have also been reported in animals orally exposed to nickel. Rat studies have indicated that intermediate-duration exposure to ≥0.7 mg Ni/kg/day as various nickel salts produces hematological effects. Effects included a decreased hemoglobin level in rats exposed to 25 mg Ni/kg/day as nickel acetate in the diet for 6 weeks (Whanger 1973), decreased erythrocytes and platelet counts, and increased white blood cell (WBC) levels in mice exposed to 36 mg Ni/kg/day as nickel sulfate in the diet for 28 days (Dahdouh et al. 2016), increased leukocyte levels in rats exposed to 0.49 mg Ni/kg/day as nickel chloride in drinking water for 28 days, but not at 0.97 mg Ni/kg/day (Weischer et al. 1980), and increased platelet counts in rats administered via gavage 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988). Two years of daily exposure to doses of nickel sulfate hexahydrate up to 11.16 mg Ni/kg/day in rats did not result in significant exposure-related changes in hematological parameters including hemoglobin and hematocrit levels (Heim et al. 2007). No hematological effects were observed in rats administered via gavage 11.2 mg Ni/kg/day as nickel sulfate (Heim et al. 2007) or in rats exposed to 187.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976). Low hematocrit levels were observed in dogs after chronic-duration dietary exposure to 62.5 mg Ni/kg/day as nickel sulfate (Ambrose et al. 1976).

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

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

2.8 MUSCULOSKELETAL

Few studies were identified that examined musculoskeletal effects in humans after exposure to nickel. In a prospective cohort study of 1,424 male workers involved in pyrometallurgical nickel production, Syurin and Vinnikov (2022) observed no association between nickel exposure and workers' compensation claims for "musculoskeletal disorders of vertebral origin." The use of compensation claims to assess outcomes is a significant limitation of this study. Muscular pain was reported by one worker who drank water contaminated with nickel sulfate, nickel chloride, and boric acid during one work shift (Sunderman et al. 1988). This worker was among 20 workers who reported symptoms, primarily gastrointestinal, after 32 workers were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

No histological alterations were observed in the bone of rats and mice exposed to nickel sulfate 6 hours/day for 12 or 16 days (highest NOAEL is 12.2 mg Ni/m^3), 5 days/week for 13 weeks (0.44 mg Ni/m^3) or 5 days/week for 2 years (0.11 and 0.22 mg Ni/m^3 for rats and mice, respectively) (NTP 1996c); the muscles were not examined histologically in these studies. No alterations were observed in bone or muscle of rats and mice exposed to nickel oxide (6 hours/day, 5 days/week) at 23.6 mg Ni/m^3 for 16 days (12 or 16 days), 7.9 mg Ni/m^3 for 13 weeks, or 2 (rats) or 3.9 mg Ni/m^3 (mice) for 2 years (NTP 1996a). Similarly, exposure to nickel subsulfide 6 hours/day, 5 days/week did not result in alterations in bone or muscle in rats at 7.33 mg Ni/m^3 for 13 weeks or 0.73 mg Ni/m^3 for 2 years, or mice at 7.33 mg Ni/m^3 for 16 days, 1.83 mg Ni/m^3 for 13 weeks, or 0.88 mg Ni/m^3 for 2 years (NTP 1996b).

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

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

2.9 HEPATIC

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

A transient increase in serum bilirubin levels was observed in 3 of 10 workers who were hospitalized with primarily gastrointestinal symptoms after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). The workers who reported symptoms or who were hospitalized (20 of 32) were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

No histological alterations were observed in the livers of rats or mice exposed to nickel subsulfide, nickel sulfate, or nickel oxide at concentrations of 7.33, 12.2, or 23.6 mg Ni/m^3, respectively, in rats and 1.4, 12.2, or 23.6 mg Ni/m^3, respectively, in mice exposed 6 hours/day, 12 days in a 16-day period (NTP 1996a, 1996b, 1996c), or 1.83, 0.44, or 7.9 mg Ni/m^3 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Following chronic-duration exposure, no histological changes were observed in the livers of rats exposed to nickel sulfide at 0.63 mg Ni/m^3 (Ottolenghi et al. 1975) or 0.73 mg Ni/m^3 (NTP 1996b), to nickel oxide at 0.9 mg Ni/m^3 (Tanaka et al. 1988) or 2 mg Ni/m^3 (NTP 1996a), or to nickel sulfate at 0.11 mg Ni/m^3 (NTP 1996c). Chronic-duration exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the liver (NTP 1996a, 1996b, 1996c).

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

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

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

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

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

2.10 RENAL

Marked tubular necrosis was observed in the kidneys of a man who died of ARDS 13 days after a 90-minute exposure to a very high concentration, simulated by the study authors to be 382 mg/m^3 of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994). Several days after the exposure, urinary concentrations of nickel were 700 μg/L, in comparison to levels of <0.1–13.3 μg/L in persons not occupationally exposed to nickel (Sunderman 1993).

In nickel refinery workers, a significant association was found between increased levels of nickel in urine and increased urinary β2-microglobulin levels (Sunderman and Horak 1981). A significant increase in urinary β2-microglobulin levels was observed in a group of workers with urinary nickel levels >100 μg/L; urinary β2-microglobulin levels were not significantly altered in workers with urine nickel levels <100 μg/L. Urinary levels of total proteins, β2-microglobulin, retinol binding protein, and N-acetyl-β-D-glycosaminidase (NAG) were increased in 12 women, and urinary lysozyme and NAG were increased in 14 men occupationally exposed to soluble nickel (sulfate, chloride) compounds at an average concentration of 0.75 mg Ni/m^3 (Vyskocil et al. 1994a). Although the average exposure concentration was the same for women and men, women may have been more highly exposed as indicated by urine concentrations of 10.3 μg Ni/g creatinine in women compared to 5 μg Ni/g creatinine in men. The biomarkers of effect that were changed reflected tubular dysfunction. No effects on markers of glomerular function, urinary albumin levels, or transferrin levels were noted. Sanford and Nieboer (1992) did not find significant alterations in urinary β2-microglobulin levels in nickel refinery workers with urine nickel levels of <60 μg/L. Multiple 24-hour urine collections were collected from each participant. Sanford and Nieboer (1992) noted that elevated urinary β2-microglobulin levels were found in spot urine samples of three workers; however, when the levels were averaged over three or more voids (multiple samples from a participant), the average levels were within the normal range. Proteinuria was not observed in electroforming industry workers exposed to nickel. No information was provided on exposure level or nickel compound (Wall and Calnan 1980).

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

contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Among 32 exposed workers, 20 reported symptoms and 10 had to be hospitalized due to the persistence of gastrointestinal symptoms. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

No histological alterations were observed in the kidneys of rats or mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide 6 hours/day, 5 days/week, at concentrations of ≤12.2, 7.33, or 23.6 mg Ni/m^3, respectively, for 16 days (12 days in a 16-day period) (NTP 1996a, 1996b, 1996c), ≤0.44, 1.83, or 7.9 mg Ni/m^3, respectively, for 13 weeks (NTP 1996a, 1996b, 1996c), or 0.9 mg Ni/m^3 as nickel oxide for 12 months (Tanaka et al. 1988). Chronic-duration exposure of rats to nickel oxide (NTP 1996a; Tanaka et al. 1988), nickel subsulfide (NTP 1996b), nickel sulfate (NTP 1996c), or nickel sulfide at concentrations up to 2, 0.73, 0.11, or 0.63 mg Ni/m^3, respectively, did not result in histological alterations in the kidneys. Additionally, no alterations were observed in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c).

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

Renal effects have been reported in animals orally exposed to nickel. The effects included alterations in serum and urine parameters suggestive of impaired renal function and histological alterations. Renal tubular damage at the corticomedullary junction described as minor was observed in mice exposed to ≥108 mg Ni/kg/day as nickel sulfate in the drinking water for 180 days (Dieter et al. 1988). The renal effects included the loss of renal tubular epithelial cells and the presence of hyaline casts in the tubule (suggesting protein loss). No changes in markers of renal tubular function (urinary lactate dehydrogenase (LDH) and NAG levels and β2-microglobulin levels) were observed in male and female rats exposed to 6.9 and 7.6 mg Ni/kg/day, respectively, as nickel sulfate in the drinking water for 3–6 months (Vyskocil et al. 1994b). Urinary albumin levels, a marker of glomerular barrier dysfunction, were significantly increased in nickel-exposed female rats. Albumin excretion also tended to be higher in male rats but did not reach statistical significance because of two control rats with very high values. The study

investigators noted that male rats develop a spontaneous nephrosis as they age and that this may have obscured the effect of nickel. Significant decreases in urine volume and urine glucose levels and increases in relative kidney weight at 14.4 or 28.8 mg Ni/kg/day and increases in blood urea nitrogen (BUN) at 28.8 mg Ni/kg/day were observed in rats exposed to nickel sulfate in drinking water for 13 weeks (Obone et al. 1999); no changes in γ-glutamyl transpeptidase activity, NAG activities, or histological alterations were observed. A 28-day study in rats exposed to 36 mg Ni/kg/day as nickel sulfate in the diet reported proximal tubule degeneration with tubular necrosis and inflammation (Dahdouh et al. 2016). Renal dysfunction was further indicated by increases in serum urea, uric acid, and creatinine. Another intermediate-duration oral study reported increased plasma creatinine and urea levels in rats administered 7.6 mg Ni/kg/day as nickel sulfate for 21 days (Adeyemi and Elebiyo 2014). The study investigators also reported thickening of the glomerular wall, mild nephrosis, and necrosis; however, no incidence data were provided to assess whether the incidence was significantly different from controls. No histopathological lesions were observed in the kidneys of rats administered 2.2 mg/kg/day as nickel sulfate for 16 weeks (Springborn Laboratories 2000b), administered 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988), administered 22 mg Ni/kg/day as nickel sulfate for 90 days (Springborn Laboratories 2002), or exposed to 55 mg Ni/kg/day as nickel chloride in drinking water for 27–30 weeks (EPA 1988a, 1988b).

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

No gross or microscopic lesions were observed in the kidneys of rats treated dermally with ≤100 mg Ni/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977).

2.11 DERMAL

No studies were located regarding dermal effects in humans following inhalation exposure. However, contact dermatitis in persons exposed to nickel compounds is one of the most common effects of nickel exposure. Immunological studies indicate that dermatitis is an allergic response to nickel; therefore, studies of contact dermatitis in humans are discussed in Section 2.14.

There are limited data on the dermal effects in animals resulting from inhalation exposure. Microscopic changes in the skin were not observed in rats or mice exposed to nickel as nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 12.2, 7.33, or 23.6 mg Ni/m^3, respectively, for 6 hours/day for 12 days in a 16-day period (NTP 1996a, 1996b, 1996c) or 0.44, 1.83, or 7.9 mg Ni/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic-duration exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice at concentrations up to 0.22, 0.88, or 3.9 mg Ni/m^3, respectively, did not result in microscopic changes in the skin (NTP 1996a, 1996b, 1996c).

Histological changes in the skin have not been observed in rats treated by gavage with nickel chloride at a dose of 8.6 mg Ni/kg/day for 91 days (American Biogenics Corporation 1988) or in rats and dogs exposed to nickel sulfate in the diet for 2 years at doses of 187.5 and 62.5 mg Ni/kg/day, respectively (Ambrose et al. 1976). These studies suggest that the skin is not affected by orally administered nickel in animals that have not been previously sensitized to nickel.

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

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

2.12 OCULAR

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

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

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

2.13 ENDOCRINE

Only one study pertaining to endocrine effects in humans exposed to nickel was located. Lai et al. (2021) examined 49 welders and 20 office workers in a shipyard in Taiwan on two occasions 1 year apart and measured urinary nickel and cortisol concentrations. A significant association between higher urinary nickel concentration and decreased urinary cortisol (β = -0.161 for a 1-µg/g increase in creatinine-adjusted urinary nickel concentration) was observed (Lai et al. 2021). The study authors suggested that decreases in cortisol levels could be associated with adrenal gland dysfunction; however, no other studies were located regarding effects on cortisol, adrenal glands, or other endocrine effects in humans following exposure to nickel.

Histological examinations did not reveal any changes in the adrenal glands, pancreas, parathyroid, pituitary, or thyroid glands in rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 days (6-hour exposure) over 16 days or for 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). The NOAEL values for endocrine effects were 12.2, 23.6, and 7.33 mg Ni/m^3 in rats and mice exposed to nickel sulfate, nickel oxide, and nickel subsulfide, respectively, for the shorter duration study and 0.44, 7.9, and 1.83 mg Ni/m^3, respectively, for the 13-week study. Alterations in serum glucose levels were observed in rats exposed to airborne nickel oxide 23.6 hours/day for 21–28 days (Weischer et al. 1980). In female rats, decreased serum glucose levels were observed at 0.8 and 1.6 mg Ni/m^3 but not at 3.2 mg Ni/m^3, whereas increased serum glucose levels were observed in males exposed to 0.385 mg Ni/m^3.

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

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

No histological alterations were observed in the endocrine glands of rats administered 2.2 mg Ni/kg/day as nickel sulfate for 16 weeks (Springborn Laboratories 2000b) or 22 mg Ni/kg/day as nickel sulfate for 90 days (Springborn Laboratories 2002), or in rats and dogs exposed to nickel sulfate in the diet for 2 years at 187.5 mg Ni/kg/day for rats and 62.5 mg Ni/kg/day for dogs (Ambrose et al. 1976).

2.14 IMMUNOLOGICAL

Several immunological effects have been reported in humans exposed to nickel. In 38 production workers exposed to nickel (compound not specified), significant increases in levels of immunoglobulin G (IgG), IgA, and IgM and a significant decrease in IgE levels were observed (Bencko et al. 1983, 1986). Significant increases in other serum proteins, which may be involved in cell-mediated immunity (including α1-antitrypsin, α2-macroglobulin, ceruloplasmin), were also observed. The increase in immunoglobulins and serum proteins suggests that the immune system was stimulated by nickel exposure. Similar, but less-pronounced, effects were observed in eight workers with hard metal asthma attributed to cobalt exposure and who then underwent a bronchial provocation challenge to nickel sulfate

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

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

Nielsen et al. (1990) fed 12 women with hand eczema and known allergy to nickel a diet (oatmeal, soybeans, cocoa) with 5 times the normal level of nickel (about 0.007 mg/kg/day) for 4 days. An aggravation of hand eczema was found in 6 of 12 women by day 4 after the start of the challenge, and although excess nickel was excreted 2 days after the last treatment, further exacerbation of hand eczema was observed in 10 of 12 women by day 11. Diet was no longer tracked after day 4 of the challenge period; therefore, it is not known whether participant diet affected the reported outcomes. In a second study by this group (Nielsen et al. 1999), 20 nickel-sensitized women with hand eczema were given water containing 0.012 mg Ni/kg. A flare-up of hand eczema was observed in 9/20 nickel sensitized subjects which began within 12 hours of exposure. In the control group, there was no change in the hand eczema.

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

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

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

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

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

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

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

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

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

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

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

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

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

example, a large analysis of patch test results from 17,912 patients in North America reported that the prevalence of positive nickel patch test results was related to the number of piercings: 14.3% of patients with a single piercing tested positive while 34.0% of patients with five or more piercings tested positive (Warshaw et al. 2017). The prevalence of nickel allergy was 9% among girls (aged 8, 11, and 15 years; n=960) with pierced ears compared to 1% among girls without pierced ears. Girls with more than one hole in each ear were also more likely to be sensitive to nickel than girls with only one hole in each ear (19 versus 11%) (Larsson-Stymne and Widström 1985). In a study in school children aged 7–12 years, the frequency of nickel allergy was 30.8% among girls with pierced ears and 16.3% among girls who did not have pierced ears (Dotterud and Falk 1994). Similarly, 14% of females with pierced ears developed nickel allergy compared to 4% in females without pierced ears (Nielsen et al. 2002). Among a group of Swedish men (age 18–24 years) completing military service, 4.6% with pierced ears reacted to nickel, while 0.8% who did not have pierced ears had a positive reaction to nickel (Meijer et al. 1995). Keczkes et al. (1982) has shown that sensitivity to nickel remains for many years. Fourteen people who tested positively for nickel sensitivity using nickel sulfate also tested positive 10 years later. However, the time interval between exposures can influence the degree of reactivity (Hindsén et al. 1997). A stronger reaction was found in nickel sensitized women when there was a 1-month period between nickel sulfate exposures compared to a 4-month period. This study also found a stronger reaction when nickel sulfate was applied to an area with previous allergic contact dermatitis.

Patch test studies in sensitive individuals have shown a dose-response relationship between the amount of nickel and the prevalence and/or severity of the test response (Emmett et al. 1988; Eun and Marks 1990; Fischer et al. 2005, 2007). Fischer et al. (2005) synthesized the findings of eight dose-response studies of single occluded nickel patch tests and reported that 5 and 10% of sensitized individuals responded positively to concentrations of 0.44 and 1.04 µg Ni/cm^2, respectively. Menné and Calvin (1993) examined skin reactions to various concentrations of nickel chloride in 51 sensitive and 16 nonsensitive individuals. Although inflammatory reactions in the sweat ducts and hair follicles were observed at ≤0.01%, positive reactions to nickel were not observed. At 0.1%, 4/51 and 1/51 tested positive with and without 4% sodium lauryl sulfate, respectively. Menné et al. (1987) examined the nickel release into synthetic sweat from 111 different nickel alloys and the reactivity to these alloys in 173 nickel-sensitive individuals. With one exception (Inconel 600), alloys that released nickel into synthetic sweat at a rate of at least 1 µg/cm^2/week produced "strong" reactions. For those alloys releasing at least 1 µg/cm^2/week, the prevalence of positive patch test results (any reaction) ranged from 30 to 55% in this study (Menné et al. 1987).

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

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

Animal studies have evaluated several aspects of immune function following inhalation, oral, or dermal exposure to nickel. Alveolar macrophage function was evaluated in several inhalation studies. A significant reduction in pulmonary alveolar macrophage phagocytic activity was observed in mice exposed to 0.5–0.66 mg Ni/m^3 as nickel chloride for 2 hours (Adkins et al. 1979) or exposed to 0.47 mg Ni/m^3 as nickel oxide or 0.45 mg Ni/m^3 as nickel subsulfide 6 hours/day, 5 days/week for 65 days (Haley et al. 1990). Other alveolar macrophage alterations include decreased lysozyme activity in rabbits exposed to 0.6 mg Ni/m^3 as nickel chloride 6 hours/day, 5 days/week for 4– 6 weeks (Bingham et al.

1972; Johansson et al. 1987, 1988a, 1989), alterations in macrophage production of tumor necrosis factor (Goutet et al. 2000; Morimoto et al. 1995), and morphological alterations. Morimoto et al. (1995) found increased production of tumor necrosis factor in rats exposed to 9.2 mg Ni/m^3 as nickel oxide 8 hours/day, 5 days/week for 4 weeks. In contrast, Goutet et al. (2000) found a decrease in tumor necrosis factor production in rats following a single intratracheal instillation of nickel sulfate. The conflicting results may be due to exposure route, duration, or concentration differences between the studies. Alveolar macrophages from rabbits exposed to 1 mg Ni/m^3 as metallic nickel 6 hours/day, 5 days/week for 3–6 months (Johansson et al. 1980) or 0.6 mg Ni/m^3 as nickel chloride 6 hours/days, 5 days/week for 4–6 weeks (Johansson et al. 1987) or 4 months (Johansson et al. 1988a, 1989) had increases in membrane-bound lamellar bodies. Exposure to metallic nickel also resulted in macrophages with smooth surfaces; the frequency of occurrence was duration-related (Johansson et al. 1980).

A significant portion of nickel that is removed from the lung enters the lymphatic system, often inducing damage to the lymph nodes. Lymphoid hyperplasia in the bronchial and mediastinal lymph nodes was observed in rats exposed to 1.4 mg Ni/m^3 as nickel sulfate (NTP 1996c) and mice exposed to 0.88 mg Ni/m^3 as nickel subsulfide (NTP 1996b) 6 hours/day for 12 days in a 16-day period; no effects were observed in rats exposed to 7.33 mg Ni/m^3 as nickel subsulfide (NTP 1996b), rats or mice exposed to 23.5 mg Ni/m^3 as nickel oxide (NTP 1996a), or mice exposed to 3.1 mg Ni/m^3 as nickel sulfate (NTP 1996c). In intermediate-duration studies, exposure for 6 hours/day, 5 days/week resulted in lymphoid hyperplasia in bronchial lymph nodes of rats exposed to 0.22, 0.22, or 2 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.44, 0.88, or 2 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c). Similarly, lymphoid hyperplasia was observed in the bronchial lymph nodes of rats exposed to 0.11, 0.11, or 0.5 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.22, 0.44, or 1 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c). Exposure of rats to 0.1 mg Ni/m^3 as metallic nickel for 104 weeks resulted in increased incidence of minimal-to-severe histiocyte infiltrate in bronchial lymph nodes (Oller et al. 2008).

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

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

Oral exposure studies have evaluated histological alterations in immune tissues, alterations in lymphocytes, and immune function. Effects on the immunological system following exposure to ≥44 mg Ni/kg/day as nickel sulfate in the drinking water for 180 days were assessed in mice (Dieter et al. 1988). Mild thymic atrophy was observed at ≥44 mg Ni/kg/day and mild splenic atrophy was observed at ≥108 mg Ni/kg/day. Although several tests of immune function were performed, only two alterations were found (decreased spleen cellularity at 150 mg Ni/kg/day and impaired lymphoproliferative response to the B-cell mitogen, *Escherichia coli* lipopolysaccharide) at ≥44 mg Ni/kg/day; a marginal response to sRBCs was also observed at 150 mg Ni/kg/day. No response to concanavalin A (con A), natural killer cell activity, or resistance to *Listeria monocytogenes* challenge were observed. In addition to the immune function responses, exposure to nickel sulfate resulted in alterations in bone marrow, decreases in bone marrow cellularity at ≥108 mg Ni/k g/day, decreases in granulocyte macrophage progenitor cells (CFU-GM) at ≥44 mg Ni/kg/day, and multipotential stem cells (CFU-S) at ≥108 mg Ni/kg/day. The stem cell alterations were associated with alterations in glucose-6-phosphate dehydrogenase activity: increased at 44 mg Ni/kg/day and decreased at 108 and 150 mg Ni/kg/day. Obone et al. (1999) reported alterations in T- and B-cell subpopulations in the thymus and splenic lymphocytes in rats exposed to nickel sulfate in drinking water for 13 weeks. In the spleen, the changes consisted of an increase in the total number of cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; an increase in CD^{4+} T cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; increases in CD^{8+} T cells at 14.4 and 28.8 mg Ni/kg/day; an increase in the number of B cells at 14.4 mg Ni/kg/day; and a decrease in the ratio of B cells to total cells at 14.4 mg Ni/kg/day. In the thymus, the changes consisted of an increase in the total number of cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; an increase in CD^{4+} T cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; a decrease in the ratio of CD^{4+} T cells to total cells at 28.8 mg Ni/kg/day; increases in CD^{8+} T cells at 5.75 and 14.4 mg Ni/kg/day and a decrease at 28.8 mg

Ni/kg/day; increases in the ratio of CD^{8+} T cells to total cells at ≥5.75 mg Ni/kg/day; and an increase in the number of B cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day. When challenged with Coxsackie virus B3, an enhanced inflammatory response was observed in the hearts of mice treated with nickel chloride in drinking water at 20.3 mg Ni/kg/day for 10–11 weeks (Ilbäck et al. 1994). Nickel treatment had no adverse effect on virus-induced lethality, spleen or thymus weights, or the number of cells in the spleen or thymus. Gross and microscopic examinations of the spleen did not reveal any adverse effects in dogs fed 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976).

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

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

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

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

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

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

2.15 NEUROLOGICAL

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

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

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

Neurological effects of giddiness and weariness were observed among 20 of 32 workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). It was estimated that the workers were exposed to 7.1–35.7 mg Ni/kg. Seven workers reported giddiness and six workers reported weariness within hours of the exposure. The contribution of boric acid to these effects is not known.

In a study designed to determine the absorption and elimination of nickel in humans, one man developed left homonymous hemianopsia (loss of sight in the same corresponding two left halves of the visual fields of both eyes) 7 hours after ingesting a single dose of 0.05 mg Ni/kg as nickel sulfate in drinking water. The condition lasted for 2 hours (Sunderman et al. 1989b). The appearance of the visual defect involving the same two left halves of the visual fields in both eyes occurred soon after the peak serum concentration of nickel was reached, leading the study authors to suspect a causal relationship between nickel exposure and the loss of sight/visual field defect. The doses given to other subjects were lowered to 0.018 and 0.012 mg Ni/kg with no adverse effects.

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

Evaluation of the potential neurotoxicity of nickel in animals has primarily focused on histopathology and overt signs of toxicity; only one study evaluated neurobehavior. Microscopic examinations did not reveal any changes in the whole brains of rats or mice exposed to nickel as nickel sulfate hexahydrate, nickel oxide, or nickel subsulfide for 12 days (6-hour/day) over 16 days (NTP 1996a, 1996b, 1996c). The maximum concentrations that did not result in deaths or changes in brain histology were 3.1, 23.6, and 7.33 mg Ni/m^3 in Fischer-344 rats for nickel sulfate hexahydrate, nickel oxide, and nickel subsulfide, respectively, and 0.7, 23.6, and 3.65 mg/m^3 in B6C3F1 mice for nickel sulfate hexahydrate, nickel oxide,

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

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

A small number of oral exposure studies evaluate neurological endpoints. In a 90-day study, lethargy, ataxia, prostration, irregular breathing, and reduce body temperature were observed in rats treated by gavage with nickel chloride (American Biogenics Corporation 1988). These effects were observed frequently at 25 mg Ni/kg/day, a dose at which all rats died, and at lower incidences at 8.6 mg Ni/kg/day, a dose at which 6/52 rats died. At the lower dose, it is not clear if the adverse neurological effects were observed only in the animals that died. No signs of neurological dysfunction were observed at 1.2 mg/kg/day. Hypoactivity and/or salivation was also observed in an unspecified number of rats administered ≥28 mg Ni/kg/day for 3 days (Oller and Erexson 2007). Microscopic examinations of whole brains did not reveal any changes in the brains of dogs treated with nickel sulfate at doses ≤62.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976). Two studies have evaluated neurobehavior. In mice administered a single dose of 50 mg Ni/kg as nickel chloride, increases in escape latency in the Morris water maze test, indicating impaired learning and spatial memory, and decreased total distance traveled in the open field test were observed (He et al. 2013). A study in rats exposed to 0.2 mg Ni/kg as nickel

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

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

2.16 REPRODUCTIVE

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

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

respectively (NTP 1996a, 1996b, 1996c). Histological changes in the testes were not observed. No effect on the length of the estrous cycle was noted in mice or rats exposed to nickel sulfate hexahydrate at ≤0.44 mg Ni/m^3, nickel oxide at ≤7.9 mg Ni/m^3, or nickel subsulfide at ≤1.83 mg Ni/m^3 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic-duration exposure of rats and mice to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, and exposure of mice to nickel oxide, nickel subsulfide, respectively, or nickel sulfate hexahydrate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the reproductive organs (NTP 1996a, 1996b, 1996c).

Several studies have examined the reproductive toxicity of nickel following oral exposure to rats, mice, or dogs. The studies have found conflicting results, with some studies identifying LOAELs for serious health effects and others identifying NOAELs at very similar dose levels. Histological alterations have been observed in male reproductive tissues in some studies. Pandey et al. (1999) reported regressed epithelium and vacuolated cells in the epididymis of mice administered 1.1 mg Ni/kg as nickel sulfate via gavage 5 days/week for 35 days (Pandey et al. 1999). In the seminiferous tubules, the damage consisted of atrophy of centrally located tubules and disturbed spermatogenesis in mice administered 1.1 mg Ni/kg as nickel sulfate (5 days/week) (Pandey et al. 1999). The significance of these findings is not known because the incidence data and statistical analysis were not reported. Additionally, interpretation of Pandey et al. (1999) is impeded by limited methodological details and possible improper tissue fixation. Käkelä et al. (1999) reported a statistically significant decrease in seminiferous tubule diameter in Wistar rats exposed to 3.6 mg Ni/kg/day as nickel chloride in drinking water for 28 or 42 days. A significant decrease in basal spermatogonia was also observed in the rats exposed for 28 days, but not in the rats exposed for 42 days. Although it was not discussed in the report, the final body weights of males exposed for 28 days appeared to be lower than control body weights; this may contribute to the histological findings in the maturing rats (Rehm et al. 2008). Toman et al. (2012) did not observe any exposure-related changes in relative testis weight in mice following 3–12 weeks of exposure to 4.5 mg Ni/kg/day as nickel chloride; however, histological alterations, including degeneration of seminiferous epithelium and empty spaces in the epithelium, indicating spermatogenesis disruption were observed (Toman et al. 2012). Other studies have not found histological alterations in male or female reproductive tissues in rats administered up to 25 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988), rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 90 days (Obone et al. 1999), rats exposed to 2.2 mg Ni/kg/day as nickel sulfate administered via gavage for 16 weeks (Springborn Laboratories 2000b), or dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976).

Significant decreases in sperm count and sperm motility and sperm abnormalities (banana and detached head; acrosome up, down, or missing; curved neck and curved, bent, round, loop, and folded tail) were observed in mice administered ≥2.2 mg Ni/kg as nickel sulfate (decreased sperm count significant at 4.5 mg Ni/kg) or 2.5 mg Ni/kg as nickel chloride 5 days/week for 35 days (Pandey and Srivastava 2000); no sperm effects were observed at 1.1 or 1.2 mg Ni/kg as nickel sulfate or nickel chloride, respectively. Although the route of administration was not reported, it is assumed that the nickel chloride and nickel sulfate were administered via gavage. The study authors reported a dose-related decrease in body weight gain and decreases in absolute and relative testes, epididymis, seminal vesicle, and prostate gland weights at the two highest dose levels (2.2 and 4.5 mg Ni/kg as nickel sulfate and 2.5 and 4.9 mg Ni/kg as nickel chloride). Similarly, Pandey et al. (1999) reported decreases in sperm count and motility in mice administered 2.2 mg Ni/kg as nickel sulfate, 5 days/week for 35 days; an increase in sperm abnormalities was also observed at 1.1 mg Ni/kg. Although Pandey et al. (1999) did not report alterations in body weight gain, significant decreases in testes, epididymis, seminal vesicle, and prostate gland weights were observed. In both studies (Pandey and Srivastava 2000; Pandey et al. 1999), there were no significant alterations in the occurrence of a particular sperm abnormality; the total number of abnormalities was increased. Toman et al. (2012) did not observe any exposure-related changes in relative testis weight following 3–12 weeks of exposure to 4.5 mg Ni/kg/day as nickel chloride; however, significant changes were observed in the testis upon histological examination. The study authors observed signs of degeneration of seminiferous epithelium and empty spaces in the epithelium indicating spermatogenesis disruption (Toman et al. 2012). Sobti and Gill (1989) reported increases in sperm head abnormalities in mice administered via gavage of 23, 28, or 43 mg Ni/kg as nickel nitrate, nickel sulfate, or nickel chloride, respectively; it should be noted that this study was poorly reported and no information on number of animals tested or the exposure duration were given. No alterations in sperm count, concentration, motility, or morphology were observed in the F0 or F1 rats administered 2.2 mg Ni/kg/day as nickel sulfate via gavage for 16–18 weeks (Springborn Laboratories 2000b).

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

fertility in rats (Käkelä et al. 1999). In a study in which male and female rats were exposed to 3.6 (males) or 4.0 (females) mg Ni/kg/day as nickel chloride in drinking water for 28–76 days, decreased fertility was observed (Käkelä et al. 1999). In contrast to these findings, better reported studies have not found effects on fertility. No adverse effects on fertility were observed in a multigeneration study in which male and female rats were exposed to doses as high as 55 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to mating (EPA 1988a, 1988b), in a 1-generation study in which rats were administered 16.8 mg Ni/kg/day as nickel sulfate via gavage for 2-weeks prior to mating, during mating, and during gestation (Springborn Laboratories 2000a), in a 2-generation study involving gavage administration of up to 2.2 mg Ni/kg/day for 10 weeks prior to mating, during mating, gestation, and lactation (Springborn Laboratories 2000b), or in a multi-litter study in which female rats were exposed to doses as high as 31.6 mg Ni/kg/day (Smith et al. 1993).

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

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

2.17 DEVELOPMENTAL

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

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

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

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

The available animal data on developmental toxicity provide suggestive evidence that the developing fetus and neonates are sensitive targets of toxicity of soluble nickel compounds; developmental toxicity has not been evaluated following oral exposure to metallic nickel or insoluble nickel compounds. The most reported endpoint was fetal loss and decreased survival observed in the rat and mouse offspring in studies involving male-only exposure, female-only exposure, and combined male and female exposure in single generation, multi-litter, and multigeneration studies. The developmental effects were often reported at maternally toxic doses. Other developmental endpoints that have been examined include body weights, gross necropsy for abnormalities, and neurodevelopmental toxicity.

Male-only exposure to 3.6 mg Ni/kg/day as nickel chloride in drinking water for 28 days resulted in decreases in the number of pups born alive (2.7/dam versus 10.2/dam in controls), the number of pups surviving until postnatal day (PND) 4 (56% versus 100% in controls), and litter size at PND 21 (1.3 pups versus 9.2 pups in controls) (Käkelä et al. 1999). However, when the male rats were exposed to

3.6 Ni/kg/day for 42 days, no significant alterations in pup viability or survival were observed (Käkelä et al. 1999). A NOAEL was not identified in this study.

Several studies that examined female-only exposure to nickel also examined fetal loss and postnatal survival (El-Sekily et al. 2020; EPA 1983; Käkelä et al. 1999; Saini et al. 2013, 2014a, 2014b; Seidenberg et al. 1986; Smith et al. 1993). Increased fetal resorption sites were observed in mice administered 46.125 mg Ni/kg/day as nickel chloride on GDs 6–18 (El-Sekily et al. 2020). The study also reported an increase in stillborn fetuses at 184 mg Ni/kg/day. Decreased number of live fetuses per dam and reduced number of implantation sites were observed in mice administered nickel chloride at 46 mg Ni/kg/day on GDs 0–5 (Saini et al. 2014a) or at 184.5 mg Ni/kg/day on GDs 6–13 (Saini et al. 2013). Similarly, nickel chloride exposure to 92.25 mg Ni/kg/day on GDs 0–5 or 184.5 mg Ni/kg/day on GDs 6–13 or 14–18 resulted in decreased average litter size per day (Saini et al. 2014b). An increase in spontaneous abortions was observed in female mice exposed to 160 mg Ni/kg/day as nickel chloride in drinking water on GDs 2–17 (EPA 1983); no effects were observed at 80 mg Ni/kg/day. In contrast, no effects on the average number of neonates per litter were observed when mouse dams were treated by gavage on GDs 8–12 with 90.6 mg Ni/kg/day as nickel chloride (a dose that resulted in a significant decrease in maternal body weight) (Seidenberg et al. 1986). Exposure of rats to 13 mg Ni/kg/day as nickel chloride in drinking water for 14 days prior to mating and during mating, gestation, and lactation resulted in decreased pup survival from birth to PND 4 (87 versus 100% in controls) and from PND 4 to 21 (52 versus 90% in controls) (Käkelä et al. 1999); no significant effects were observed at 4.0 mg Ni/kg/day. Pup mortality was also observed in a multi-litter study in which rats were exposed to nickel chloride in drinking water for 11 weeks prior to breeding and during two successive gestation and lactation periods (Smith et al. 1993). In the first litter, the percentages of dead pups per litter at PND 1 was increased at 31.6 mg Ni/kg/day; no significant alterations were observed in the number of dead pups at PND 21. In the second litter, the number of litters with dead pups at birth was increased at 31.6 mg Ni/kg/day, the percentages of dead pups per litter at PND 1 was increased at ≥1.3 mg Ni/kg/day, and the percentage of dead pups at PND 21 was increased at 31.6 mg Ni/kg/day.

Offspring mortality was also observed in studies involving combined male and female exposure (Ambrose et al. 1976; EPA 1988a, 1988b; Käkelä et al. 1999; Springborn Laboratories 2000b). Exposure of rats to 3.6–4.0 mg Ni/kg/day as nickel chloride in drinking water for 28 days prior to mating and during mating, gestation, and lactation adversely affected the litter size at PND 21 and pup survival from PND 4 to 21 (Käkelä et al. 1999). Increases in post-implantation losses were observed in the offspring of rats administered 6.7 mg Ni/kg/day as nickel sulfate via gavage for 14 days prior to mating, and during mating and gestation (Springborn Laboratories 2000b); at 16.7 mg Ni/kg/day, an increased number of

dead pups at lactation day 0 and a decreased mean litter size were observed. This study identified a NOAEL of 4.5 mg Ni/kg/day. In a multigeneration study (Ambrose et al. 1976) involving exposure of rats to nickel chloride in the diet for 11 weeks prior to mating and during mating, gestation, and lactation, a dose-related increase in the number of stillborn pups was observed. An independent statistical analysis of the data using the Fisher Exact Test found significant increases in the total number pups born dead at ≥22.5 mg Ni/kg/day for the F1a generation, 45 and 90 mg Ni/kg/day for the F1b generation, 90 mg Ni/kg/day for the F2a generation, 22.5 mg Ni/kg/day for the F2b generation, and 45 and 90 mg Ni/kg/day for the F3b generation. The study authors noted that the numbers of offspring (dead and alive) were progressively less with increasing nickel levels >45 mg/kg/day (10.3, 10.6, 9.8, and 9.0 for 0, 22.5, 45, and 90 mg/kg/day, respectively); the number of offspring weaned per litter was also decreased with increasing nickel levels (8.1, 7.2, 6.8, and 6.4 for 0, 22.5, 45, and 90 mg/kg/day, respectively). In a 2-generation study in which the P0 generation was exposed to nickel chloride in drinking water for 11 weeks before mating and during gestation and lactation, and the F1b generation animals were mated to produce the F2 generations, a reduction in live litter size was observed in the F1a, F1b, and F2a offspring of rats exposed to 55 mg Ni/kg/day (EPA 1988a, 1988b). Increases in mortality were also observed in the F1b rats on PNDs 22–42; these increases were statistically significant in males at 30 and 55 mg Ni/kg/day and in females at 55 mg Ni/kg/day. No adverse developmental effects, including no effect on litter size, were observed in the cesarean delivered F2b rats, suggesting that the nickel-induced decrease in live litter size occurred postnatally. No alterations in offspring mortality or survival were observed in another 2-generation study in which rats were administered up to 2.2 mg Ni/kg/day as nickel sulfate via gavage for 10 weeks prior to mating and during gestation and lactation (Springborn Laboratories 2000b).

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

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

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

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

2.18 OTHER NONCANCER

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

2.19 CANCER

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

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

Sunderman et al. (1989a) examined the histopathological diagnosis of 100 cases of sinonasal cancer and 259 cases of lung cancer among workers at three nickel refinery facilities. The primary sinonasal cancers were squamous cell carcinomas (48%), anaplastic and undifferentiated carcinomas (39%), and adenocarcinomas (6%). In an analysis of lung cancer, the cancers were primarily squamous cell carcinomas (67%); anaplastic, small cell, and oat cell carcinomas (15%); and adenocarcinomas (8%). The types of sinonasal and lung cancers were similar to those found in the general population, suggesting a lack of nickel-specific tumor types.

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

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

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

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

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

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

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

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

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

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

In lifetime drinking water studies in rats and mice, nickel acetate (0.6 mg Ni/kg/day for rats; 0.95 mg Ni/kg/day for mice) was found to be noncarcinogenic (Schroeder et al. 1964, 1974). The incidence of tumors was comparable to that observed in controls. Similarly, no increases in neoplastic lesions related to nickel exposure were observed in 344 rats administered doses up to 11.2 mg Ni/kg/day for 2 years (Heim et al. 2007).

The U.S. Department of Health and Human Services (NTP 2016) has determined that metallic nickel may reasonably be anticipated to be a human carcinogen and that nickel compounds are known to be human carcinogens. Similarly, IARC (1990, 2021) classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). EPA has classified nickel refinery dust and nickel subsulfide in Group A (human carcinogen) (IRIS 1987a, 1987b); other nickel compounds have not been classified by EPA.

2.20 GENOTOXICITY

A number of studies have examined the genotoxicity of nickel and nickel compounds; the results of these *in vivo* and *in vitro* tests are presented in Tables 2-7 and 2-8, respectively. The available weight of evidence suggests that nickel does not alter the frequency of gene mutations in nonmammalian organisms (Arlauskas et al. 1985; Biggart and Costa 1986; Green et al. 1976; Marzin and Phi 1985; Rasmuson 1985; Wong 1988), although some studies have found gene mutations (Ogawa et al. 1994; Pikálek and Necásek 1983; Rodríguez-Arnaiz and Ramos 1986). Mixed results for gene mutations have been found in mammalian test systems. Increases in the frequency of gene mutations have been found at the HGPRT locus in Chinese hamster V79 cells exposed to nickel (Hartwig and Beyersmann 1989; Miyaki et al. 1979; Ohshima 2003). Two studies on V79 cells (Åkerlund et al. 2018; Buxton et al. 2020) and another in Chinese hamster ovary cells (Hsie et al. 1979) failed to find evidence of gene mutations at this locus. An increase in gene mutation frequency has also been found in Chinese hamster ovary AS52 cells (hprt locus) (Fletcher et al. 1994), mouse lymphoma cells (Amacher and Paillet 1980; McGregor et al. 1988), and virus-infected mouse sarcoma cells (Biggart and Murphy 1988; Biggart et al. 1987). Kargacin et al. (1993) observed increased mutant frequencies in response to nickel exposure (crystalline nickel sulfide, nickel subsulfide, nickel oxides, and nickel chloride) in V79 cells transfected with the gpt gene from *E. coli*. Subsequent work showed that the mechanism for nickel-induced mutation in this model was epigenetic, occurring via nickel-mediated deoxyribonucleic acid (DNA) condensation and hypermethylation resulting in silencing of the gpt transgene (Klein and Costa 1997). Gene mutation frequency was not affected in transgenic mouse and rat respiratory tissue following inhalation exposure to nickel subsulfide (Mayer et al. 1998). Dominant lethal mutations were not affected by intraperitoneal exposure of nickel acetate in mice (Deknudt and Léonard 1982). Nickel acetate exposure ranging from 0.5 to 5 mg/kg was associated with increased frequency of dominant lethal mutations in germline cells of mice (Domshlak et al. 2005). Additionally, increased frequency of gene mutations was observed in pigment cells of first-generation mice at doses >1.0 mg/kg (Domshlak et al. 2005). There is evidence to suggest that nickel is clastogenic and can damage DNA. Chromosome gaps or chromosome aberrations have been reported in several studies of lymphocytes from nickel refinery workers (Deng et al. 1988; Waksvik and Boysen 1982; Waksvik et al. 1984). Welding fumes are a complex mixture of several metals including nickel and have been shown to cause cytotoxic and genotoxic effects such as DNA methylation and telomere alterations (Shoeb et al. 2017, 2021, 2024). Workers in a welding factory exposed to high concentrations of nickel (0.340–10.129 mg/m^3) showed significant increases in chromosomal aberrations relative to unexposed controls, though the controls were co-exposed to chromium and PAHs (Borská et al. 2003). *In vivo* studies show that intraperitoneal injection resulted in

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

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

Species (test system)	Endpoint	Results	Reference	Compound
Drosophila melanogaster	Gene mutation	–	Rasmuson 1985	Nickel nitrate or chloride
	Recessive lethal	+	Rodríguez-Arnaiz and Ramos 1986	Nickel sulfate
	Gene mutation (wing spot test)	(+)	Ogawa et al. 1994	Nickel chloride
Mammalian cells				
Human lymphocytes	Chromosome gaps	+	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
	Sister chromatid exchange	–	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
	Chromosome aberrations	+	Waksvik et al. 1984	Nickel
	Sister chromatid exchange	–	Waksvik et al. 1984	Nickel
	Chromosome aberrations	+	Deng et al. 1988	Nickel
	Sister chromatid exchange	+	Deng et al. 1988	Nickel
	Chromosome aberrations	+	Borská et al. 2003	Nickel
	DNA damage	+	Iarmarcovai et al. 2005	Nickel
	Micronuclei formation	+	Iarmarcovai et al. 2005	Nickel
Human blood cells	Oxidative DNA damage	+	Cheng et al. 2019	Nickel
Human umbilical cord blood	Oxidative DNA damage	+	Ni et al. 2014	Nickel
Human urine	Oxidative DNA damage	+	Kim et al. 2004	Nickel
Human plasma	Oxidative DNA damage	+	Wu et al. 2015	Nickel
Human buccal mucosa cells	DNA damage	–	Hafez et al. 2011	Nickel
Human sperm cells	DNA damage	–	Wang et al. 2016	Nickel

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

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

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

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

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

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

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

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

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
CHO AS52 cells	Gene mutation at *grp* locus	NT	+	Fletcher et al. 1994	Nickel oxide (black and green); amorphous nickel sulfide; nickel subsulfide; nickel chloride; nickel sulfate; nickel acetate
CD2F1 mouse lung and nasal mucosa cells	DNA fragmentation	NT	+	Mayer et al. 1998	Nickel subsulfide
Human diploid fibroblasts	DNA single strand breaks	NT	–	Hamilton-Koch et al. 1986	Nickel chloride
Human gastric mucosal cells	DNA damage (comet analysis)	NT	–[a]	Pool-Zobel et al. 1994	Nickel sulfate
Human HeLa cells	DNA replication	NT	+	Chin et al. 1994	Nickel chloride
Human leukemic cells	DNA damage	NT	–	Cavallo et al. 2003	Nickel sulfate
Human leukemic cells	Inhibition of DNA repair	NT	+	Cavallo et al. 2003	Nickel sulfate
Human leukemic cells	DNA fragmentation	NT	+	Jia and Chen 2008	Nickel chloride
Human lymphoblastoid TK6 cells	DNA damage	NT	+	Guillamet et al. 2008	Nickel chloride
Human B lymphoblastoid cells	DNA damage	NT	+	Lou et al. 2013	Nickel chloride
Human lymphocytes	DNA single strand breaks	NT	+	Chen et al. 2003	Nickel chloride
Human lymphocytes	DNA damage	NT	+	Rao et al. 2008	Nickel chloride
Human peripheral lymphocytes	DNA single strand breaks	NT	+	M'Bemba-Meka et al. 2005	Nickel carbonate hydroxide, nickel subsulfide, nickel oxide
Human peripheral lymphocytes	DNA single strand breaks	NT	–	M'Bemba-Meka et al. 2005	Nickel sulfate
Human alveolar epithelial cells (A549)	DNA strand breaks	NT	+	Schwerdtle and Hartwig 2006	Nickel chloride, nickel oxide
Human alveolar epithelial cells	DNA damage	NT	–	Di Pietro et al. 2009	Nickel

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

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

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

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

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

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

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

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

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

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

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

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

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

Siwicki 2018). In a study of HeLa cells, exposure to nickel adversely affected DNA replication (Chin et al. 1994). DNA single-strand breaks and damage (as assessed using comet analysis) were not found in human diploid fibroblasts (Hamilton-Koch et al. 1986) or human gastric mucosal cells (Pool-Zobel et al. 1994), respectively.

2.21 NICKEL NANOPARTICLES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.1 TOXICOKINETICS

- 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 soluble nickel is absorbed into the bloodstream. Estimates of absorption of nickel from soluble nickel compounds following oral exposure in humans range from 12–40% after fasting, and 1–37% when consumed with a meal. Absorption is much lower for ingested insoluble nickel compounds (<1%). Dermal absorption of nickel through intact skin is slow and minimal.

- 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.

- Nickel does not undergo any metabolism prior to excretion.

- Urine is the main form of excretion of absorbed nickel through all exposure routes, while unabsorbed ingested 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 >2.5 µm predominantly occurs in the nasopharyngeal area, whereas particulates <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 to 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 nickel oxide mg/m^3 for 2 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, nickel oxide 0.05 lower; and nickel subsulfide upper 0.09, nickel subsulfide 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 5 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 to 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 4 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 1–3 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 gastrointestinal 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 reported similar absorption rates of between 1 and 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) suggested that at concentrations ≤10 mg Ni/L, nickel is absorbed via active transport and facilitated diffusion; however, the carriers become saturated at concentrations >10 mg Ni/L and nickel absorption also occurred via passive diffusion. *In vitro* data also showed 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 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 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 5 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 reported that <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) reported 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 exhibited 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 that showed that nickel resorption is similar between individuals with and without nickel hypersensitivity. Fullerton et al. (1986) reported that the absorption rate depended on which form of nickel was used. Nickel ions penetrated occluded human skin *in vitro* about 50 times faster when aqueous nickel chloride was used than the absorption rate of the nickel ions when aqueous nickel sulfate was used. Fullerton et al. (1986) also reported that the absorption rate was 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 appeared 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 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 workers 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 10 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, 1988; Dunnick et al. 1989; Goodman et al. 2011; Tanaka et al. 1985). The lung burden of nickel also decreased with decreasing particle size (≤4 µm) (Kodama et al. 1985a, 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 6 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 reported 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; 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) reported that approximately 20% of the inhaled concentration of nickel oxide was retained in the lungs at the end of exposure for either 2 days, 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 6 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 varied 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 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 Ni^{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 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 GDs 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) reported 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 to 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 study authors 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- 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 3 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 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) reported 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/minute/1.73 m^2 for water and 5.8±4.3 mL/minute/1.73 m^2 for food. Nielsen et al. (1999) reported similar elimination median half-times of 19.9–26.7 hours and median clearances of 8.15–8.4 mL/minute. Patriarca et al. (1997) reported similar findings from a nickel tracer study in which 51–82% of the administered label was excreted in urine over 5 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 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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). 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 (Clewell 1995).

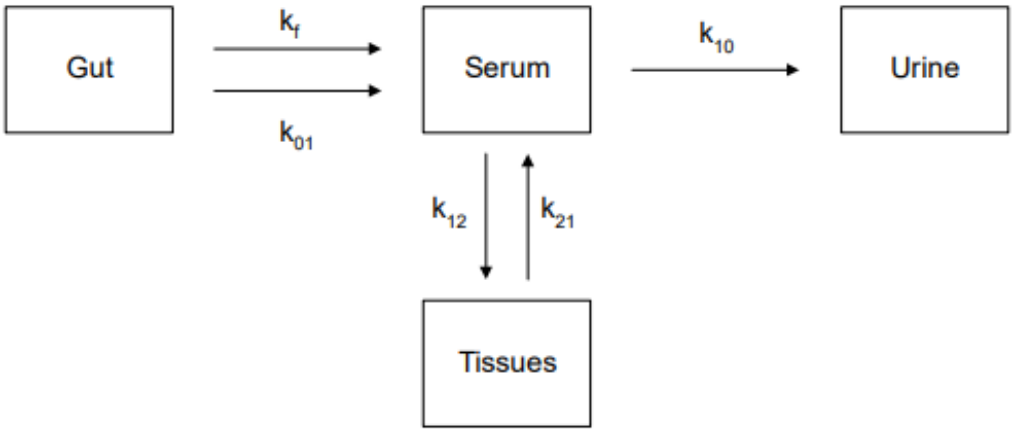
Sunderman et al. (1989b; Dede et al. 2018) Model

Sunderman et al. (1989b) developed a model to predict nickel absorption, serum levels, and excretion following oral exposure to nickel in water and food in volunteers. 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 administering 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 (Figure 3-1). 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.

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).

The model was tested using the Sunderman et al. (1989b) data as well as data from Nielsen (1990). The model predictions showed good agreement with the Sunderman et al. (1989b) data. However, the model underpredicted the cumulative urinary excretion of nickel compared to the Nielsen (1990) data. The study authors suggested 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).

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



k_{01} = first-order rate constant for intestinal absorption of nickel from oral $NiSO_4$; k_{10} = first-order rate constant for nickel excretion in urine; 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_f = zero-order rate constant for fractional absorption of dietary nickel

Source: 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)
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).
[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.

Bogen et al. (2021) Model

Bogen et al. (2021) modified the Sunderman et al. (1989b) human model. A compartment representing bone that receives nickel from the tissues compartment was added to the model. The rate coefficient for transfer of nickel from blood to urine was revised to be dependent on the concentration in the central compartment (plasma or serum).

Transfer of nickel from the tissues compartment to bone is assumed to be unidirectional (bone is a permanent sink for nickel) and governed by a unidirectional first-order rate coefficient that was optimized to be 85.15 $year^{-1}$ (see further discussion of optimization data). Transfer of nickel to urine is assumed to be governed by a concentration-dependent rate coefficient (k_u):

$$k_u = k_1 \times C/(K_M + C)$$

where k_u and k_1 are in units of $hour^{-1}$ and C and K_M are in units of μg Ni/L serum or plasma (assumed to be equivalent with respect to nickel concentration)

The value assigned to k_1 was 0.21 $hour^{-1}$ (Sunderman et al. 1989b) and the value for K_M was optimized to 2.85 μg/L based on Sunderman et al. (1989b). These assignments result in a curvilinear relationship between k_u and serum concentration with the value for k_u being half of the maximum value (0.21/2 $hour^{-1}$) at a concentration of 2.85 μg/L and 0.20 $hour^{-1}$ at a concentration of 50 μg/L, the highest concentration in studies used to optimize the model (Sunderman et al. 1989b).

The gastrointestinal absorption fraction was optimized to 30%, compared to 27% estimated by Sunderman et al. (1989b). Baseline dietary nickel uptake to blood was adjusted to predict the baseline serum nickel concentrations in the Sunderman et al. (1989b) study, 0.32 μg/L, which corresponded to an intake of 1.22 μg/day. All other parameter values remained the same as in the Sunderman et al. (1989b) model (Table 3-1).

Parameter optimization was based on data from Sunderman et al. (1989b). The optimized model was evaluated against data from Patriarca et al. (1997) and various unpublished reports of a human pharmacokinetics study described in Bogen et al. (2021) and referred to as the "NiPERA" data. In the NiPERA study, adult subjects (n=9 males, 9 females) received a single oral dose of (5, 10, or 20 μg Ni/kg) in an aqueous solution of ^{62}Ni tracer.

After optimization to the Sunderman et al. (1989b) data, the model predicted the time profiles for serum nickel following single oral doses of 12 or 18 μg/kg body weight soluble nickel (Sunderman et al. 1989b). The model substantially overestimated concentrations observed at early time points following a single dose of 50 μg/kg (<10 hours, see Figure 2 in Bogen et al. 2021). The optimized model also predicted the time profile of the cumulative excretion of nickel (fraction of dose) that were within ±1 standard error (SE) of the observed means (see Figure 1 in Bogen et al. 2021).

After further optimization of the gastrointestinal absorption fraction and baseline nickel ingestion rate to the evaluation data sets (Patriarca et al. 1997, NiPERA), and no other parameter changes, the model predicted the time profiles for plasma nickel within ±1 SE of the observed means in subjects who ingested a single dose of 5, 10, or 20 μg Ni/kg body weight. The model also predicted the time profile of cumulative urinary excretion (fraction of dose) within ±1 SE in subjects who ingested a single dose of 5 or 10 μg Ni/kg. The model overestimated cumulative urinary excretion in subjects who ingested 20 μg Ni/kg, although the predictions were within ±2 SE of observed means (see Figures 2 and 4 in Bogen et al. 2021).

In further analyses, Bogen et al. (2021) applied the model to predict urinary nickel levels expected for various occupation exposure scenarios, taking into account inter-individual variability in observed urinary nickel excretion estimated from Neilsen et al. (1999) and the NiPERA studies.

Melo and Leggett (2017) Model

Melo and Leggett (2017) developed a model of nickel biokinetics in human adults for use in radionuclide radiation dosimetry. The model includes compartments representing blood, bone, gastrointestinal tract, kidneys, liver, other soft tissues, and urinary bladder. Transfer of nickel between compartments are governed by first-order rate coefficients (day^{-1}).

The blood compartment is subdivided into plasma and red blood cells (RBCs). All transfers of nickel between blood and tissues occur through the plasma compartment. The gastrointestinal tract includes subcompartments representing the small intestine and colon. The small intestine receives nickel from the liver (biliary transfer, see below) and transfers nickel to plasma (absorption). The colon receives nickel from plasma (secretion) and transfers nickel to feces.

The liver is divided into two subcompartments. A fast turnover compartment, liver 1, receives nickel from plasma and transfers nickel to a slower turnover compartment, liver 2, and to the small intestine (biliary secretion). Nickel is returned to the plasma from liver 2. Kinetics of return to plasma from liver 2 are slow relative to transfer from plasma to liver 1, resulting in accumulation of nickel in liver 2.

The kidneys are also divided into two subcompartments. A fast turnover compartment, kidney 1, exchanges nickel with plasma and transfers nickel to a slower turnover compartment, kidney 2, and to the urinary bladder. Nickel in the urinary bladder is transferred to urine. Nickel in kidney 2 is returned slowly to plasma.

The other soft tissues compartment is divided into fast turnover (other 1) and slow turnover (other 2) subcompartments, which independently exchange nickel with plasma.

Bone is represented with subcompartments representing cortical and trabecular bone. Both cortical and trabecular bone are further subdivided into bone surface and volume. Exchange with plasma occurs with the surface compartment. Long-term retention of nickel in bone is attributed to the bone volume compartments, which receive nickel from bone surface and return nickel slowly to plasma.

Transfer coefficients from tissues to plasma were set so that the combined rates agreed with the combined rates in the Sunderman et al. (1989b) model. Transfer rates to kidney, urinary bladder, and urine were also set to agree with the transfer rate from serum to urine in the Sunderman et al. (1989b) model. Values assigned to rate coefficients for each compartment and subcompartment were based on a variety of sources, including studies in mice, rabbits, and rats (see Melo and Leggett 2017 for references).

Melo and Leggett (2017) reported that the model reproduced the time courses for plasma nickel and urinary nickel (fraction of dose) predicted by the Sunderman et al. (1989b) model. Melo and Leggett (2017) also compared model predictions to data on uptake and retention of nickel in rats (Smith and Hackley 1968) and uptake and retention of nickel in RBCs of humans dosed with nickel tracer (Patriarca et al. 1997). However, none of these comparisons were presented in the Melo and Legget (2017) publication.

Melo and Leggett (2017) used the model to predict the distribution and retention kinetics of nickel in tissues following absorption of ^{63}Ni into blood. These predictions were used to derive tissue radiation

dose coefficients, where the dose coefficient is the radiation dose equivalent of a given tissue per unit of ^{63}Ni activity absorbed into blood (sievert/becquerel).

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 were 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.

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

		Clearance rate coefficient constant		
Species	Nickel compound	*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]Hsieh et al. (1999a).
[b]Hsieh et al. (1999b).

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, 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 study authors suggested 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.

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.

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 dosimetric model of lung burden of lung deposition and clearance of inhaled nickel (Hsieh et al. 1999a, 1999b,

1999c; Yu et al. 2001) 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) described an approach to derive human equivalent concentrations (HECs) 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 HECs to derive inhalation MRL values (see Appendix A). 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. 2000, 2002; International Committee on Nickel Carcinogenesis in Man 1990). It is not known if the apparent species differences are due to differences in carcinogenic potential, co-exposure to other nickel compounds or other metals, or differences in exposure 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.

Contact allergy to nickel has been shown to be dependent upon the human TLR4; mice expressing the human TLR4 exhibited nickel hypersensitivity, while those expressing the mouse TLR4 did not (Saito et al. 2016). This finding suggests that animals may not be good models for contact dermatitis in humans exposed to nickel.

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.

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). The study authors suggested 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; EPA 1988a, 1988b; Käkelä et al. 1999; Smith et al. 1993) and mice (EPA 1983) following oral exposure to nickel. Decreases in pup body weight have also been observed in rats following inhalation (Weischer et al. 1980) or oral (Ambrose et al. 1976; EPA 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 2006).

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 2006). 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 2006). 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 7–9 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, 1986; Novey et al. 1983). These changes were found in both sensitized (Novey et al. 1983) and non-sensitized (Bencko et al. 1983, 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; therefore, it 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 (Fischer and Rystedt 1983; Veien et al. 1987). 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 1 week before nickel treatment enhanced the nephrotoxicity and hepatotoxicity of nickel (Khandelwal and Tandon 1984). The mechanism of interaction could not be determined from these studies. Pretreatment of mice with cadmium 24 hours before nickel treatment has also been shown to decrease nickel-induced lethality and lipid peroxidation in the liver (Srivastava et al. 1995). The investigators suggested that a cadmium-induced production of ceruloplasmin, which prevented a nickel-induced reduction of ceruloplasmin, provided protection against nickel toxicity.

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

In iron-deficient rats, nickel enhanced the absorption of iron (Nielsen 1980; Nielsen and Flyvholm 1984; Nielsen et al. 1980). 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 et al. (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 and Menné (1990) suggested that vasoactive substances found in food can enhance nickel sensitivity reactions. Suggested foods 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 (Kerfoot 2012). Its outer shell of electrons has a $3d^8\,4s^2$ configuration (Haynes et al. 2015). Nickel occurs naturally in the Earth's crust. 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. Information regarding the chemical identity of nickel and nickel compounds is presented in Table 4-1.

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

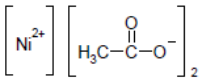
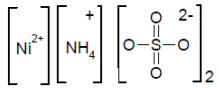
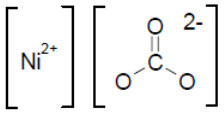
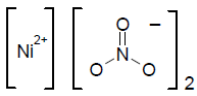
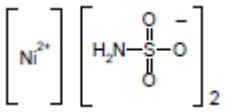
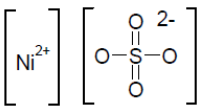
Characteristic	Nickel[a]	Nickel acetate[b]	Nickel ammonium sulfate[c]	Nickel carbonate[d]
Synonym(s) and Registered trade name(s)	CI 77775; NI 0901-S; NI 270; NI 4303T; Nickel 200; Nickel 201; Nickel 205; Nickel 207; Nickel 270; Nickel sponge; NI 0901-S (Harshaw); NP-2; Raney alloy; Raney nickel; RCH 55/5	Nickel (II) acetate; nickelous acetate; nickel diacetate; acetic acid, nickel(2+) salt; AI3-26110; nickel(2+) acetate	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)	CI 7779; Carbonic acid, nickel (2+) salt; nickel (II) carbonate; nickelous carbonate
Chemical formula	Ni	$C_4H_6NiO_4$	Ni $(NH_4)_2(SO_4)_2$[e]	$NiCO_3$
SMILES	[Ni]	CC(=O)[O-]. CC(=O)[O-].[Ni+2]	[NH4+].[NH4+]. [O-]S(=O)(=O)[O-]. [O-]S(=O)(=O) [O-].[Ni+2]	C(=O)([O-]) [O-].[Ni+2]
Chemical structure	Ni			
CAS registry number	7440-02-0	373-02-4; 14998-37-9 (EU)	15699-18-0	3333-67-3; 16337-84-1 (EU); 18195-55-6 (EU); 39380-74-0 (EU)

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

Characteristic	Nickel chloride[f]	Nickel cyanide[g]	Nickel oxide[h]	Nickel nitrate[i]
Synonym(s) and Registered trade name(s)	Nickel (2+) chloride; nickel dichloride; nickel(II) chloride; nickelous chloride	Dicyanonickel; Nickel dicyanide; Nickel (II) cyanide	Bunsenite; CI 77777; Green nickel oxide; mononickel oxide; nickel (II) oxide; nickel(2+) oxide; nickel protoxide	Nickel dinitrate; nickel (II) nitrate; nickel(2+) nitrate; nickelous nitrate; nitric acid, nickel(II) salt; nitric acid, nickel(2+) salt
Chemical formula	$NiCl_2$	C_2N_2Ni	NiO	$Ni(NO_3)_2$
SMILES	Cl[Ni]Cl	[C-]#N. [C-]#N.[Ni+2]	O=[Ni]	[N+](=O)([O-]) [O-].[N+](=O) ([O-])[O-].[Ni+2]
Chemical structure	Cl–Ni–Cl	CN–Ni–CN	Ni–O	
CAS registry number	7718-54-9; 37211-05-5 (EU and NZ)	557-19-7	1313-99-1; 34492-97-2; 11099-02-8	13138-45-9; 13478-00-7 (hexahydrate); 14216-75-2 (EU)

Characteristic	Nickel subsulfide[j]	Nickel sulfamate[k]	Nickel sulfate[l]
Synonym(s) and Registered trade name(s)	Trinickel disulfide; Heazlewoodite; nickel subsulphide; nickel sulfide; alpha-nickel sulfide (3:2) crystalline; nickel sulphide; nickel tritadisulphide	Nickel bis(sulphamidate); nickel (II) sulfamate; Aeronikl 250; Aeronikl 400; Aeronikl 575; sulfamic acid, nickel(2+) salt (2:1); Nickel aminosulfonate	NCI-C60344; Nickel (II) sulfate; nickelous sulfate; nickel(2+) sulfate; nickel sulphate; sulfuric acid, nickel(2+) salt; sulphuric acid, nickel (II) salt
Chemical formula	Ni_3S_2	$Ni(SO_3NH_2)_2$	$NiSO_4$
SMILES	[S-2].[S-2].[Ni].[Ni+2].[Ni+2]	NS(=O)(=O) [O-].NS(=O)(=O)[O-].[Ni+2]	[O-]S(=O)(=O)[O-].[Ni+2]
Chemical structure	Ni-Ni-Ni=S=S		
CAS registry number	12035-72-2	13770-89-3	7786-81-4; 15244-37-8 (EU)

[a]NLM 2024a unless otherwise specified.
[b]NLM 2024b unless otherwise specified.
[c]NLM 2024c unless otherwise specified.
[d]NLM 2024d unless otherwise specified.
[e]Haynes et al. 2015.
[f]NLM 2024e unless otherwise specified.
[g]NLM 2024f unless otherwise specified.
[h]NLM 2024g unless otherwise specified.
[i]NLM 2024h unless otherwise specified.
[j]NLM 2024i unless otherwise specified.
[k]NLM 2024j unless otherwise specified.
[l]NLM 2024k unless otherwise specified.

CAS = Chemical Abstract Service; EU = European Union; NZ = New Zealand; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Nickel 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 (Haynes et al. 2015). 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. Information regarding physical and chemical properties of nickel and nickel compounds is presented in Table 4-2.

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

Property	Nickel[a]	Nickel acetate[b]	Nickel ammonium sulfate[c]	Nickel carbonate[d]
Molecular weight	58.7	176.78	286.9	118.70
Color	Silvery white	Green	Blue-green	Green
Physical state	Solid[e]	Solid[e,f]	Solid[e]	Solid[e]
Melting point	1,455°C[e]	Decomposes at 250°C[e,f]	Decomposes at 250°C[e]	Decomposes on heating
Boiling point	2,913°C[e]	16°C[e,f]	No data	No data
Density:	8.9[e]	1.74 g/cm^3[e,f]	1.92 g/cm^3[g]	4.39 g/cm^3
Odor	Odorless	Acetic acid odor[g]	Odorless[g]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Taste threshold	No data	No data	No data	No data
Solubility:				
Water	Insoluble in H_2O[e]	Very soluble in H_2O[e,f]; 17 pounds/ 100 pounds water at 68 °F	Slightly soluble in H_2O[e]; 10.4 g/100 g H_2O[g] at 20°C; 6.5 g/100 g H_2O at 68 °F[e,g]	0.0043 g/100 g H_2O[e]; 93 mg/L at 25°C
Organic solvent(s)	Slightly soluble in dilute acid	Soluble in ethanol[e,f]	Insoluble in alcohol[g]	Soluble in dilute acid[e]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	0 mmHg (approximate)	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	Nonflammable	Nonflammable	No data
Flashpoint	No data	Nonflammable	Nonflammable	No data
Flammability limits	No data	Nonflammable	Nonflammable	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

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

Property	Nickel chloride[h]	Nickel cyanide[i]	Nickel oxide[j]	Nickel nitrate[k]
Molecular weight	129.60	110.73	74.69	182.7
Color	Yellow[e]; green[e,g]	Yellow-brown; green[e,g]	Green; black	Green
Physical state	Solid	Solid	Solid	Solid
Melting point	1,031°C[e]	>200°C	1,957°C[e]	Decomposes at 56°C[e,g]
Boiling point	Sublimation point 985°C[e]	Decomposes	No data	No data
Density	3.51 g/cm^3	2.393 g/cm^3	6.72 g/cm^{3e}	2.05 g/cm^{3e,g}
Odor	Odorless	Weak almond odor	Odorless	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Taste threshold	No data	No data	No data	No data
Solubility:				
Water	67.5 g/100 g H_2O[e]	Insoluble in H_2O	Insoluble in H_2O[e] 0.11 mg/100 mL H_2O at 20°C	99.2 g/100 g H_2O[e,g]
Organic solvent(s)	Soluble in ethanol	Soluble in aqueous alkali cyanides and other bases	Soluble in acid	Soluble in ethanol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	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	Nonflammable	No data	No data
Flashpoint	Nonflammable	Nonflammable	Flammable as dust or fume	No data
Flammability limits	Nonflammable	Nonflammable	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	No data	No data	May explode after prolonged exposure to fire or heat

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

Property	Nickel subsulfide[l]	Nickel sulfamate[m]	Nickel sulfate[n]
Molecular weight	240.21	250.87	154.76
Color	Yellow[e]	Blue-green	Greenish-yellow; blue-green[g], green[o]
Physical state	Solid[e]	Liquid	Solid
Melting point	789°C[e]	No data	Decomposes at 840°C Decomposes at 100°C[e,g]
Boiling point	No data	No data	No data
Density	5.87 g/cm^3[e]	No data	4.01 g/cm^3; 2.03 g/cm^3[g]; 1.98 g/cm^3[o]
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
Solubility: Water Organic solvent(s)	 No data No data	 Highly soluble[f,p] No data	 40.4 g/100 g H_2O[e,g,o] Insoluble in alcohol; slightly soluble[g] or soluble[o] in ethanol
Partition coefficients: Log K_{ow} Log K_{oc}	 No data No data	 No data No data	 No data No data
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
Flashpoint	No data	No data	Nonflammable
Flammability limits	No data	No data	Nonflammable
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

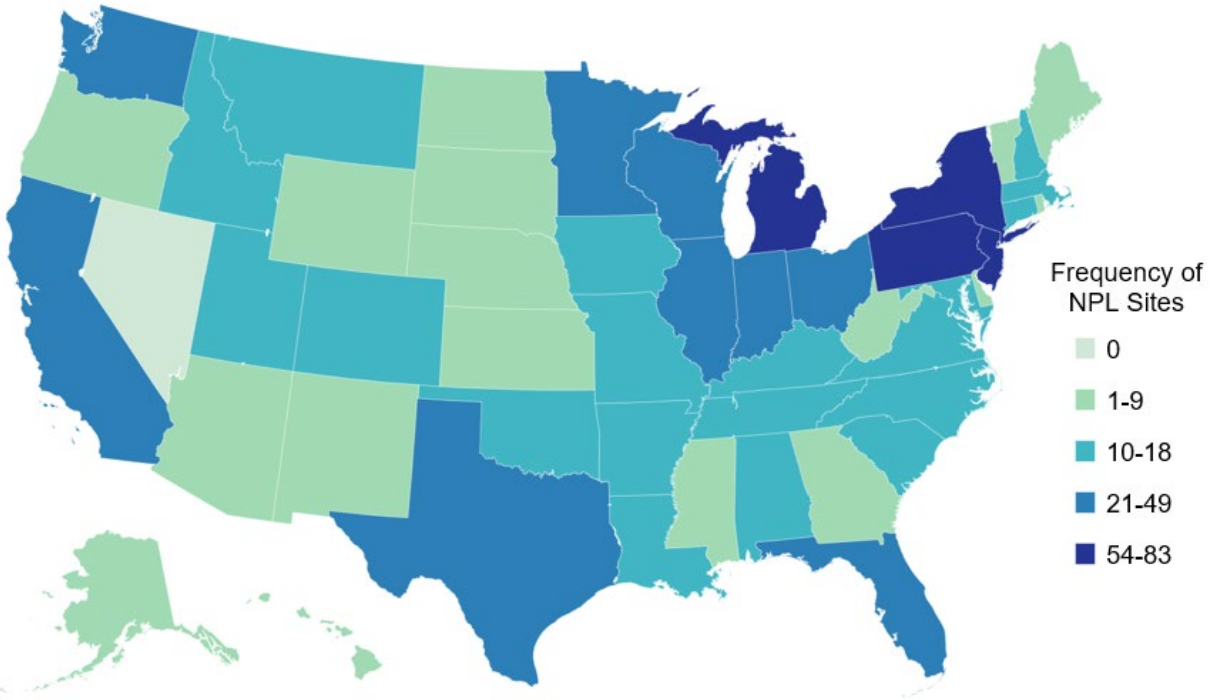
[a]NLM 2024a unless otherwise specified.
[b]NLM 2024b unless otherwise specified.
[c]NLM 2024c unless otherwise specified.
[d]NLM 2024d unless otherwise specified.
[e]Haynes et al. 2015.
[f]Data are for the tetrahydrate.
[g]Data are for the hexahydrate.
[h]NLM 2024e unless otherwise specified.
[i]NLM 2024f unless otherwise specified.
[j]NLM 2024g unless otherwise specified.
[k]NLM 2024h unless otherwise specified.
[l]NLM 2024i unless otherwise specified.
[m]NLM 2024j unless otherwise specified.
[n]NLM 2024k unless otherwise specified.
[o]Data are for the heptahydrate.
[p]Lascelles et al. 2019.

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 in which nickel and nickel compounds have been evaluated 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, 1 is located in Guam, and 4 are located in Puerto Rico (not shown).

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



Source: ATSDR 2022

- Nickel is primarily used for production of stainless, alloy steels, nonferrous alloys, superalloys, and in electroplating.

- Nickel is an element and a component of the Earth's crust. It is ubiquitous in the environment. Nickel is released to the atmosphere or water from natural sources such as soil particles and anthropogenic sources such as oil combustion. Nickel is generally present at trace levels in air and water.

- Nickel typically exists in the environment as a hexahydrate, complexed to other species, or adsorbed to particulate matter. It is dispersed in the atmosphere by wind and removed by wet and

dry deposition. Nickel typically accumulates at the surface of soils due to deposition and is strongly adsorbed by soil. Nickel does not concentrate in the food chain. Accumulation in plants has been observed due to its necessity as an essential nutrient.

- The general population may be exposed to trace amounts of nickel through inhalation of ambient air and ingestion of food and drinking water. Small increases in dietary exposure may occur through use of stainless-steel cookware under certain conditions. Exposure may also occur from consumer goods, like toys and jewelry.

- Higher exposures may occur for workers and people who smoke tobacco or e-cigarettes. 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.

Nickel and its compounds are naturally present in the Earth's crust and can be found in many minerals. In 2023, nickel in the United States was produced from one mine in Michigan (USGS 2024). The United States imports more nickel than it produces or exports. Nickel is primarily used for stainless steels, batteries, alloy steels, nonferrous alloys and superalloys, and electroplating (IEA 2023; USGS 2024). Nickel compounds have applications in catalyst synthesis, electroplating, batteries, and pigments for ceramics (Antonsen and Meshri 2005; Lascelles et al. 2019; Tundermann et al. 2013). Nickel was identified as one of the Energy Critical Materials by the Department of Energy (DOE) in 2023 (DOE 2023). Nickel is also used as an alloy in medical and dental appliances and tools, for cast iron, for chemical uses, and to make U.S. coins (Berniyanti et al. 2020; Hariyani et al. 2015; Kulkami et al. 2016; USDT 2018).

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. Nickel is an essential nutrient for plants; therefore, some uptake and accumulation is expected to occur (Brown et al.

1987; Correia et al. 2018; Wood et al. 2004). Nickel does not appear to accumulate in aquatic organisms or biomagnify in aquatic food webs (McGeer et al. 2003). 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 <3 ng/m^3 (EPA 2024). 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. 2012; Peltier and Lippmann 2010; 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 2010; Schachter et al. 2020). Dissolved nickel is present in natural waters at trace levels; 3–3.5 ppb in surface water and around 4–7 ppb in groundwater (WQP 2024). Nickel is naturally present in soil, sediment, and food. According to the U.S. FDA Total Diet Study, the average concentration of nickel in various U.S. foods ranges from 0.034 to 10.6 mg/kg (FDA 2023). Nickel is also present in cigarettes and smokeless tobacco products at concentrations ranging from 1.19 to 27.67 µg/g and in e-cigarette liquid at concentrations up to 22,600 µg/L (Aherrera et al. 2017; Arain et al. 2015; Badea et al. 2018; Hess et al. 2017; Mohammad et al. 2019).

The general population is primarily exposed to trace amounts of nickel in food and drinking water and in the ambient environment. The average daily dietary nickel intake for U.S. diets is <0.5–162 µg (Institute of Medicine 2001). Estimates from the European Union are 2.51–10.1 µg/kg body weight/day across different age groups (EFSA 2020). The general population may also be exposed to nickel from stainless steel cookware, jewelry, clothing buckles and fasteners, technology, and toys, which may leach from the products under certain conditions (Hedberg et al. 2014; Jensen et al. 2014; Kamerud et al. 2013; Thyssen and Maibach 2008; Tuchman et al. 2015; Uter and Wolter 2018).

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 (Hughson et al. 2010; Julander et al. 2010; Vuskovic et al. 2013). Populations living near these industry sites or near disposal sites may also have increased 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 (Aherrera et al. 2017; Badea et al. 2018; Kettelarij et al. 2014, 2016; Pappas et al. 2008).

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 (Kerfoot 2012). Pentlandite often occurs along with the iron mineral pyrrhotite and the copper mineral, chalcopyrite (Tundermann et al. 2013). 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 to 3% nickel. The non-sulfur addition process involves the reduction, smelting, and refining of lateritic ores to a low nickel ferronickel-like product called nickel pig iron (NPI) in a method referred to as the rotary kiln-electric furnace (RKEF) process. The process usually involves ore drying, prereduction of the ore in a rotary kiln, final reduction, and smelting in an electric arc furnace, before refining steps. NPI is suitable for stainless steel production.

Sulfide ores are processed by sequential pyrometallurgical processes: roasting, smelting, and converting (Tundermann et al. 2013). During roasting, iron is oxidized, and the sulfur is removed as sulfur dioxide. The smelting stage occurs in reverberatory or blast furnaces, or by flash smelting. Iron oxide and other oxide compounds are removed in a slag and further reduction of the sulfur content occurs, yielding an impure copper-nickel-iron-sulfur matte. During converting, the molten matte is added with silica to air to remove the remaining iron and sulfur, to yield a sulfur-deficient copper-nickel matte (Tundermann et al.

2013). After physical separation of the copper and nickel sulfides, the nickel is refined electrochemically or by a 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 (Tundermann et al. 2013).

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 (Tundermann et al. 2013). The smelting process that does not include adding sulfur produces a ferronickel alloy, containing ≤50% nickel, which can be used directly in steel production (Tundermann et al. 2013). Hydro-metallurgical techniques involve leaching with ammonia or sulfuric acid, after which the nickel is selectively precipitated (Duke 1980b; IARC 1990; Tien and Howson 1981; Warner 1984). Nickel precipitated by the acid-leaching process can be used for applications such as batteries (Tundermann et al. 2013). 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 350 million tons of nickel resources available globally (USGS 2024). Approximately 54% of these resources is in laterites and 35% is in sulfide deposits, but nickel can also be found in manganese crusts and nodules on the ocean floor (USGS 2024). Nickel has also been found in meteorites, with the content ranging from 5 to 50% (Duke 1980a; Mastromatteo 1986). In 2023, all of the 16,000 tons of nickel produced in the United States occurred at the underground Eagle Mine in Michigan (USGS 2024). 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 2024).

Simple nickel salts (nickel acetate, nickel nitrate, and nickel chloride) can be produced by the reaction of the organic acid and nickel carbonate, reaction of the acid with an aqueous nickel salt solution, or reaction of the acid with a fine nickel powder or black nickel oxide (Antonsen and Meshri 2005). Nickel carbonate can be produced by oxidation of nickel powder in ammonia and CO_2; the carbonate salt is formed as a precipitate after boiling off the ammonia (Antonsen and Meshri 2005). Double salts like nickel ammonium sulfate are produced by crystallizing the individual salts from aqueous solution (Antonsen and Meshri 2005). Nickel cyanide is produced from potassium cyanide and nickel sulfate (Antonsen and Meshri 2005). A sintered green nickel oxide is produced by smelting purified nickel matte at 1,000°C, and the powdered form is produced through desulfurization of the nickel matte. Green nickel oxide is also a product of thermal decomposition of some nickel salts (nickel carbonate and nickel nitrate)

(Antonsen and Meshri 2005). Black nickel oxide is produced from the calcination of nickel carbonate or nickel nitrate salts at 600°C. Nickel subsulfide occurs in the mineral, heazlewoodite (Antonsen and Meshri 2005). Nickel sulfamate is prepared from fine nickel powder or black nickel oxide with a hot sulfamic acid aqueous solution (Antonsen and Meshri 2005). Nickel sulfate can be prepared in a similar way with sulfuric acid, or from a gas-phase reaction of nickel carbonyl, sulfur dioxide, and oxygen at 100°C.

Table 5-1 summarizes information on companies that reported the production, import, or use of nickel and Table 5-2 summarizes information on companies that reported the production, import, or use of nickel compounds for the Toxics Release Inventory (TRI) in 2022 (TRI22 2024). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	72	0	10,000,000,000	1, 7, 8, 9, 11, 12, 13, 14
AR	42	0	999,999	2, 4, 7, 8, 11, 12, 13, 14
AZ	24	0	9,999,999	1, 5, 8, 11, 12, 14
CA	99	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14
CO	12	0	999,999	1, 2, 3, 4, 5, 7, 8, 11, 12, 14
CT	53	100	9,999,999	2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
DE	3	10,000	99,999	2, 3, 8
FL	28	100	999,999	1, 5, 7, 8, 9, 10, 12, 13, 14
GA	43	0	49,999,999	1, 2, 3, 5, 7, 8, 11, 12, 14
IA	70	100	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	9	0	999,999	1, 5, 8, 12, 14
IL	134	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
IN	161	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	49	0	9,999,999	7, 8, 9, 12, 14
KY	60	100	49,999,999	1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14
LA	29	1,000	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
MA	36	1,000	999,999	8, 9, 11, 12, 14
MD	9	0	999,999	2, 3, 4, 8, 9, 12
ME	8	1,000	999,999	2, 3, 7, 8, 9, 11, 12
MI	112	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 14

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MN	57	0	999,999	2, 7, 8, 9, 12, 13, 14
MO	58	0	9,999,999	1, 7, 8, 9, 10, 11, 12, 13, 14
MS	29	1,000	9,999,999	7, 8, 12
MT	1	10,000	99,999	7, 8, 11
NC	70	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
ND	6	1,000	99,999	8, 9, 10, 12
NE	23	1,000	999,999	1, 2, 3, 5, 8, 9, 10, 11, 14
NH	14	100	999,999	2, 3, 7, 8, 11
NJ	20	100	9,999,999	2, 3, 4, 7, 8, 9, 11, 12, 14
NM	2	10,000	999,999	2, 4, 9, 11, 12
NV	13	100	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NY	47	0	49,999,999	2, 3, 4, 7, 8, 9, 11, 12, 14
OH	219	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	73	100	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	19	100	999,999	1, 2, 3, 4, 6, 7, 8, 9, 12, 14
PA	207	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	3	10,000	9,999,999	7, 8, 11
RI	6	1,000	99,999	8, 9
SC	56	100	9,999,999	2, 3, 4, 6, 7, 8, 9, 11, 12, 14
SD	10	0	99,999	8, 14
TN	75	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
TX	170	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	15	1,000	999,999	7, 8
VA	28	1,000	999,999	1, 2, 3, 4, 5, 7, 8, 12, 14
VT	2	1,000	99,999	2, 3, 8, 9, 11, 14
WA	23	1,000	999,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 14
WI	177	0	9,999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 14

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WV	7	100	9,999,999	1, 2, 3, 5, 7, 8, 14
WY	2	1,000	99,999	2, 4, 9, 12

[a]Post office state abbreviations 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: TRI22 2024 (Data are from 2022)

Table 5-2. Facilities that Produce, Process, or Use Nickel Compounds[a]

State[b]	Number of facilities	Minimum amount on site in pounds[c]	Maximum amount on site in pounds[c]	Activities and uses[d]
AK	3	10,000	9,999,999	1, 5, 8, 12, 13, 14
AL	37	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	15	1,000	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	11	1,000	99,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13, 14
CA	43	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
CO	12	0	999,999	1, 2, 4, 5, 6, 7, 8, 10, 12, 13, 14
CT	10	1,000	999,999	1, 3, 7, 8, 9, 10, 11, 12, 13
DC	1	10,000	99,999	1, 3, 11
DE	3	100	999,999	1, 2, 3, 8, 10, 13, 14
FL	18	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	22	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	1	0	99	1, 5
IA	8	1,000	999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12
ID	7	0	999,999	1, 5, 7, 8, 11, 12, 13, 14
IL	61	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
IN	64	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	11	1,000	999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Nickel Compounds[a]

State[b]	Number of facilities	Minimum amount on site in pounds[c]	Maximum amount on site in pounds[c]	Activities and uses[d]
KY	32	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
LA	38	0	49,999,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14
MA	5	1,000	999,999	1, 3, 4, 5, 6, 7, 8
MD	13	0	999,999	1, 3, 4, 5, 7, 9, 13, 14
ME	2	0	999	1, 5, 8, 12
MI	68	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	21	0	99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MO	20	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
MS	20	1,000	9,999,999	1, 2, 5, 7, 8, 10, 11, 12, 13, 14
MT	8	1,000	9,999,999	1, 3, 4, 5, 6, 10, 11, 12, 13, 14
NC	18	100	9,999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
ND	4	1,000	999,999	1, 3, 5, 12, 13, 14
NE	9	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13
NH	4	1,000	99,999	8, 14
NJ	10	1,000	999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 14
NM	4	100	99,999	1, 3, 4, 5, 9, 10, 13, 14
NV	17	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
NY	14	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
OH	76	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	21	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
OR	4	1,000	9,999,999	1, 2, 3, 5, 7, 8, 11
PA	75	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	2	1,000	99,999	1, 3, 5, 6, 8, 12, 14
RI	4	1,000	9,999,999	7, 8, 10
SC	28	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
TN	45	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	101	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	14	1,000	49,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	6	10,000	999,999	1, 5, 8, 12
VT	1	10,000	99,999	1, 2, 3, 5, 8, 9, 11
WA	11	100	9,999,999	1, 3, 5, 7, 8, 9, 10, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Nickel Compounds[a]

State[b]	Number of facilities	Minimum amount on site in pounds[c]	Maximum amount on site in pounds[c]	Activities and uses[d]
WI	31	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
WV	13	1,000	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
WY	7	0	9,999,999	1, 3, 4, 5, 9, 10, 12, 13, 14

[a]Data are for any unique substance that contains nickel as part of that chemical's structure; specific nickel compounds are not specified by the TRI.
[b]Post office state abbreviations used.
[c]Amounts on site reported by facilities in each state.
[d]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: TRI22 2024 (Data are from 2022)

5.2.2 Import/Export

According to USGS (2024), an estimated 1 metric ton of nickel ore and concentrates, 120,000 metric tons of primary nickel, and 39,000 metric tons of secondary nickel were imported into the United States in 2023. Between 2019 and 2022, annual imports ranged from 3 to 95 metric tons of ores and concentrates, 105,000–127,000 metric tons of primary nickel, and 31,800–37,700 of secondary nickel (USGS 2024). Between 2019 and 2022, Canada, Norway, Finland, and Russia supplied 46, 9, 7, and 7% of nickel, respectively (USGS 2024). Canada, Mexico, and the United Kingdom supplied 40, 26, and 9% of nickel-containing scrap, respectively (USGS 2024). The product class with the highest quantity of imports in 2018 was unwrought cathodes, pellets, briquets, and shot at 112,000 metric tons of contained nickel, followed by stainless steel scrap at 24,800 metric tons of contained nickel (USGS 2023).

Nickel exports of ores and concentrates in the United States ranged from 13,400 to 15,200 metric tons between 2019 and 2022; primary nickel exports ranged from 11,100 to 12,800 and secondary nickel exports ranged from 29,200 to 47,800 (USGS 2024). Exports in 2023 are estimated to be 10,000 metric tons of ores and concentrates, 11,000 metric tons of primary nickel, and 58,000 metric tons of secondary nickel (USGS 2024). In 2018, stainless steel scrap was the product class with the most exports at 49,000 metric tons of contained nickel (USGS 2023). Most exports of nickel in 2018 were to Canada (35,900 metric tons) followed by Taiwan (7,790 metric tons) and Mexico (4,280 metric tons) (USGS 2023).

5.2.3 Use

Nickel is useful in many applications due to its resistance to corrosion, strength, and ability to withstand extreme temperatures. Commercial forms of nickel and their uses are reported below in Table 5-3.

Table 5-3. Commercial Forms of Nickel and Their Uses

Type	Approximate nickel content (weight %)	Uses	Reference
Electrolytic (cathode)	>99.9	Alloy production, electroplating	Tundermann et al. 2013
Electrolytic rounds	>99.9	Electroplating	
Carbonyl pellets	>99.7	Alloy production, electroplating	
Briquettes	99.9	Alloy production	
Rondelles	99.3	Alloy production	
Powder	99.74	Sintered parts, battery electrodes	
Nickel oxide sinter	76.0	Steel and ferrous alloy production	
Ferronickel	20–50	Steel and ferrous alloy production	
Nickel acetate tetrahydrate ($Ni(CH_3COO)_2 \cdot 4\ H_2O$)	23.59	Catalyst intermediate, intermediate for other nickel compounds, dye mordant, sealer for anodized aluminum, electroplating	Antonsen and Meshri 2005
Nickel ammonium sulfate		Formerly in electroplating; Dye mordant	Antonsen and Meshri 2005; Lascelles et al. 2019
Basic nickel carbonate ($2\ NiCO_3 \cdot 3\ Ni(OH)_2 \cdot 4\ H_2O$)	49.94	Catalyst intermediate, colored glass preparation, pigment manufacture, neutralizing compound in electroplating solutions	Antonsen and Meshri 2005; Lascelles et al. 2019
Nickel chloride hexahydrate ($NiCl_2 \cdot 6\ H_2O$)	24.69	Electroplating, catalyst intermediate	Antonsen and Meshri 2005; Lascelles et al. 2019; Tundermann et al. 2013
Nickel cyanide	53.01	Used in Reppe process	Antonsen and Meshri 2005

Table 5-3. Commercial Forms of Nickel and Their Uses

Type	Approximate nickel content (weight %)	Uses	Reference
Nickel oxide	76–77 (black oxide); 78.5(green oxide)	Alloy steels and stainless steels (sinter oxide); ceramic industry for frit, ferrites, and inorganic colors (green and black oxide); catalysts, nickel salt production (black oxide)	Antonsen and Meshri 2005; Lascelles et al. 2019
Nickel nitrate hexahydrate ($Ni(NO_3)_2{\cdot}6\ H_2O$)	20.18	Electroplating, catalysts; intermediate in nickel-alkaline batteries	Antonsen and Meshri 2005; Lascelles et al. 2019; Tundermann et al. 2013
Nickel sulfamate	11 (aqueous solution)	Electrolyte in electroforming systems	Lascelles et al. 2019
Nickel sulfate tetrahydrate ($NiSO_4{\cdot}6\ H_2O$)	22.33	Electroplating, catalysts; lithium-ion batteries	Tundermann et al. 2013; Lascelles et al. 2019

In 2018, 159,000 of the 230,000 metric tons of nickel consumed in the United States was for stainless and heat-resistant steel (USGS 2023). In 2023, the estimated total apparent consumption of nickel in the United States was 190,000 metric tons (USGS 2024). Total apparent consumption ranged from 200,000 to 217,000 between 2019 and 2022 (USGS 2024). The primary uses of nickel in the United States are for stainless and alloy steels, nonferrous alloys and superalloys, and electroplating (USGS 2024). More than 85% of consumption in the United States is typically accounted for by stainless and alloy steel and nickel-containing alloys (USGS 2024). 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 (USGS 2023, 2024). Nickel is used in all U.S. coins but the penny (USDT 2018).

Nickel was on the 2023 DOE Critical Materials list of materials essential for energy technology development (DOE 2023). A growing sector of nickel demand is batteries. Nickel is used in the cathodes of lithium-ion batteries, such as the lithium-nickel-cobalt-aluminum and lithium-nickel-cobalt-manganese cathode formulations (USGS 2023). The Nickel Institute estimated that 39% of lithium-ion batteries contained nickel in 2016 and estimated that this would increase to 58% in 2025 (USGS 2023). The use of batteries in electric vehicles (EVs) is part of this increased demand. In 2022, 10% of global nickel demand was for EV batteries (IEA 2023).

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 57% of nickel consumption in 2023 was derived from secondary, purchased scrap (USGS 2024). The 2022 TRI reported that 80% of the 7,456,857 pounds of nickel and 88% of the 26,369,893 pounds of nickel compounds disposed of or otherwise released are released to land (TRI22 2024). 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 (II) is poorly removed from wastewater 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 is removed from electroplating wastes by treatment with hydroxide, lime, and/or sulfide to precipitate the metal (Barakat 2011). Removal by adsorption onto activated carbon is also utilized (Barakat 2011).

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

Tables 5-4 and 5-5 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 Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to

report (EPA 2022a). 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's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022a).

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Nickel[a]

		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
AL	72	11,038	10,812	0	56,151	71,471	11,410	138,063	149,472
AZ	24	705	76	0	593,806	135	589,887	4,834	594,721
AR	41	2,626	16	0	1,163	1,490	3,016	2,279	5,295
CA	99	940	3,971	0	185,492	8,734	123,858	75,278	199,136
CO	12	43	50	0	118,594	11,455	92,044	38,098	130,142
CT	53	621	7,385	0	7,610	7,727	669	22,674	23,342
DE	3	5	0	0	698	146	5	844	849
FL	28	10,249	53	5,183	21,474	421	15,711	21,670	37,381
GA	43	1,167	51	0	24,936	44,688	22,697	48,146	70,843
ID	9	198	0	0	107,386	5,098	76,255	36,427	112,682
IL	134	4,470	1,344	2,310	57,720	14,233	5,817	74,259	80,076
IN	160	10,487	10,757	0	1,713,545	6,194	11,372	1,729,611	1,740,983
IA	68	4,029	705	0	35,205	12,020	22,273	29,686	51,959
KS	49	1,223	21	0	1,629	25,111	1,229	26,756	27,985
KY	60	6,230	307	0	752,821	1,618	6,248	754,728	760,976
LA	29	532	1,081	3,067	9,625	12	5,049	9,267	14,316
ME	8	249	34	0	1,580	3,647	264	5,246	5,510
MD	9	6	10	0	6	1,212	6	1,227	1,234
MA	36	413	932	0	52,547	31,123	1,201	83,815	85,015
MI	112	304,816	742	0	53,218	20,696	304,934	74,538	379,472
MN	57	1,861	30	0	15,690	13,016	1,862	28,736	30,597
MS	29	3,623	2,557	0	9,976	83,402	6,156	93,402	99,559
MO	58	951	541	0	103,871	106	96,229	9,240	105,469
MT	1	19	0	0	5	0	19	5	24
NE	23	731	2,468	0	15,986	3,289	731	21,744	22,475
NV	13	23	34	0	1,168,157	1,018	1,167,754	1,477	1,169,231
NH	14	46	22	0	6,608	4,059	47	10,688	10,734
NJ	20	684	98	0	116,105	2,194	691	118,389	119,080

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Nickel[a]

		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
NM	2	60	0	0	27,000	0	27,060	0	27,060
NY	47	893	1,751	0	12,474	7,151	1,038	21,230	22,268
NC	69	6,274	194	0	56,547	2,811	59,453	6,373	65,826
ND	6	252	8	0	5,119	0	265	5,114	5,380
OH	217	6,211	1,858	2,054	97,656	61,070	46,972	121,876	168,848
OK	73	1,277	67	0	52,439	1	1,305	52,480	53,786
OR	19	40,814	228	0	86,004	5,873	113,690	19,228	132,918
PA	207	12,963	1,920	0	70,299	56,006	13,875	127,313	141,189
RI	6	0	20	0	0	2,314	0	2,334	2,334
SC	56	809	370	0	33,377	16,230	1,892	48,893	50,785
SD	10	48	7	0	33	5,804	48	5,844	5,891
TN	75	11,379	117,393	0	164,468	64,383	11,508	346,115	357,623
TX	170	8,151	1,701	87,485	33,709	7,975	97,768	41,252	139,020
UT	15	322	14	0	201	0	324	213	537
VT	2	0	1	0	51	29,100	0	29,152	29,152
VA	28	479	682	0	20,624	1,172	1,010	21,947	22,957
WA	23	1,237	1,076	0	10,765	48,291	1,247	60,121	61,368
WV	6	8,748	292	0	0	7,189	8,758	7,471	16,229
WI	176	4,251	9,765	0	56,863	21,889	4,727	88,042	92,769
WY	2	21	1	0	32,337	0	32,359	0	32,359
PR	3	0	0	0	0	0	0	0	0
Total	2,476	472,173	181,445	100,099	5,991,567	711,573	2,990,732	4,466,125	7,456,857

[a]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. Data are for elemental nickel (CASRN 7440-02-0).
[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: TRI22 2024 (Data are from 2022)

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

		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
AL	37	3,713	5,715	0	600,299	20,896	374,222	256,401	630,623
AK	3	94	11	0	3,183,593	0	3,183,698	0	3,183,698
AZ	11	665	10	0	81,769	15,240	80,309	17,375	97,684
AR	15	140,172	413	0	503,512	2,970	606,034	41,034	647,068
CA	37	1,842	2,206	0	432,485	44,351	400,016	80,867	480,883
CO	12	4,767	211	0	182,341	0	157,416	29,903	187,319
CT	10	1,520	172	0	464	26,303	1,548	26,911	28,459
DE	3	127	366	0	0	1,506	493	1,506	1,998
DC	1	0	2	0	109	0	0	111	111
FL	18	3,904	4,643	0	166,197	6,824	81,613	99,956	181,569
GA	22	745	2,295	0	68,482	466,906	70,465	467,963	538,428
HI	1	15,000	1	0	21,200	0	15,001	21,200	36,201
ID	7	505	169	0	168,650	0	159,926	9,399	169,325
IL	56	10,536	21,619	280	597,894	157,658	464,085	323,902	787,987
IN	62	27,418	46,927	366	786,196	85,412	645,238	301,081	946,319
IA	7	424	151	0	9,935	0	568	9,941	10,510
KS	11	854	43,147	122	36,155	137,868	36,762	181,385	218,146
KY	32	4,371	9,911	0	447,216	162,593	324,639	299,452	624,090
LA	38	22,726	7,129	9,518	395,991	1,087	245,624	190,827	436,450
ME	2	200	212	0	1,640	0	2,052	0	2,052
MD	13	557	146	0	22,396	0	960	22,138	23,098
MA	5	1,133	32	0	4,184	15,296	1,133	19,511	20,644
MI	66	6,672	27,943	115,813	5,884,641	31,839	5,774,511	292,398	6,066,908
MN	21	856	625	0	56,717	23,904	28,630	53,472	82,102
MS	20	4,380	475	105,851	61,893	13,200	125,119	60,680	185,799
MO	20	891	407	0	98,524	5,501	64,970	40,352	105,323
MT	8	1,171	98	0	593,779	11	392,956	202,103	595,059
NE	9	1,176	1,262	0	68,559	2,061	56,410	16,648	73,058
NV	13	14,460	222	260	2,840,791	12	2,827,076	28,670	2,855,746
NH	4	0	0	0	4,058	0	0	4,058	4,058
NJ	10	256	38,529	0	13,529	8,209	641	59,883	60,524
NM	4	227	20	7	55,663	8,509	55,917	8,509	64,426
NY	14	624	679	5	10,125	16,023	625	26,831	27,456
NC	18	2,882	956	0	389,089	751	355,577	38,102	393,679
ND	3	819	1	244	71,958	0	46,214	26,808	73,022

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

		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
OH	76	52,707	8,118	37,344	1,162,019	540,489	379,098	1,421,579	1,800,677
OK	20	1,218	126	1,826	298,871	0	275,341	26,700	302,041
OR	4	83	27	0	2,340	0	114	2,336	2,451
PA	75	13,669	2,531	0	793,506	114,452	444,577	479,581	924,158
RI	4	85	4	0	0	1,689	85	1,693	1,778
SC	28	4,107	1,677	0	213,624	43,899	165,044	98,263	263,308
TN	45	2,088	12,817	0	241,731	10,357	177,079	89,914	266,993
TX	101	23,645	17,092	106,757	1,309,571	70,893	569,155	958,803	1,527,958
UT	14	2,566	334	0	613,629	10	612,075	4,465	616,540
VT	1	0	1,547	0	770	15,007	0	17,324	17,324
VA	6	225	7,914	0	22,032	6,947	22,271	14,847	37,118
WA	11	2,835	1,082	0	32,554	16	7,042	29,445	36,487
WV	12	3,121	700	0	479,498	51	420,812	62,558	483,370
WI	31	541	1,302	2,131	69,913	12,683	3,186	83,384	86,569
WY	7	986	0	0	142,799	0	124,354	19,431	143,785
PR	2	230	26	0	19,257	0	230	19,283	19,513
Total	1,050	383,795	272,003	380,524	23,262,149	2,071,422	19,780,910	6,588,984	26,369,893

[a]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. Data are for any unique substance that contains nickel as part of that chemical's structure; specific nickel compounds are not specified by the TRI.
[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: TRI22 2024 (Data are from 2022)

5.3.1 Air

Emissions also occur from industries that produce, process, and use nickel and its compounds. Estimated releases of 472,173 pounds (~214 metric tons) of nickel to the atmosphere from 2,476 domestic manufacturing and processing facilities in 2022 accounted for about 6.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-4.

Estimated releases of 383,795 pounds (~174 metric tons) of nickel compounds to the atmosphere from 1,050 domestic manufacturing and processing facilities in 2022 accounted for about 1.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-5.

Nickel is released to the air from both anthropogenic and geogenic sources. 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, transformation, and bioavailability are concerned.

Natural sources of nickel include windblown dust, volcanic ash, forest fires, meteoric dust, and sea salt spray. It is estimated that 30 million kg 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). Sokolov et al. (2023) reported atmospheric emissions of nickel from the Pechenganickel smelting facility located in Northern Russia and used these emissions data to model deposition to nearby soils, water bodies, and sediment. Atmospheric emissions rose from approximately 100 metric tons per year in the 1960s to a maximum of >500 tons per year by 1980 and decreased to <100 metric tons around 2020 before the plant was closed. A comprehensive review of atmospheric nickel releases from a wide variety of sources in Europe has been summarized in the European Union Risk Assessment Report (EU RAR) of nickel and nickel compounds (EC 2008).

EPA’s National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United

States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Nickel and nickel compound emissions estimated from the 2020 inventory are summarized in Table 5-6. Limited sectors were relevant for estimations of nickel oxide, nickel subsulfide, and nickel refinery dust emissions.

Table 5-6. National Emission Inventory (NEI) Total National Emissions for Nickel and Nickel Compounds Estimated by Sector 2020

Sector	Nickel emissions (pounds)	Nickel oxide emissions (pounds)	Nickel subsulfide emissions (pounds)	Nickel refinery dust emissions (pounds)
Industrial processes; NEC	109,409	14	24	–
Mobile; locomotives	87,367	–	–	–
Fuel combustion; electric generation; natural gas	86,871	–	–	–
Fuel combustion; commercial/ institutional; oil	46,984	–	–	–
Industrial processes; non-ferrous metals	41,483	5	-	0
Fuel combustion; electric generation; coal	40,376	–	–	–
Industrial processes; ferrous metals	38,799	2	–	–
Fuel combustion; electric generation; oil	36,039	–	–	–
Fuel combustion; industrial boilers, ICEs; oil	34,919	–	–	–
Industrial processes; petroleum refineries	29,416	–	26	–
Fuel combustion; industrial boilers, ICEs; natural gas	25,057	–	–	–
Mobile; on-road non-diesel light duty vehicles	24,955	–	–	–
Industrial processes; chemical manufacturing	24,764	26	–	1,581
Fuel combustion; industrial boilers, ICEs; coal	14,660	–	–	–
Fuel combustion; industrial boilers, ICEs; other	7,526	–	–	–
Mobile; non-road equipment; gasoline	7,314	–	–	–
Mobile; commercial marine vessels	7,204	–	–	–

Table 5-6. National Emission Inventory (NEI) Total National Emissions for Nickel and Nickel Compounds Estimated by Sector 2020

Sector	Nickel emissions (pounds)	Nickel oxide emissions (pounds)	Nickel subsulfide emissions (pounds)	Nickel refinery dust emissions (pounds)
Fuel combustion; industrial boilers, ICEs; biomass	3,375	–	–	–
Mobile; on-road diesel heavy duty vehicles	3,336	–	–	–
Solvent; industrial surface coating and solvent use	3,239	46	–	–
Industrial processes; pulp and paper	3,159	–	–	–
Industrial processes; cement manufacturing	2,670	–	–	–
Fuel combustion; commercial/ institutional; natural gas	2,472	–	–	–
Industrial processes; storage and transfer	2,050	91	0	0
Industrial processes; mining	1,350	–	–	–
Fuel combustion; residential; oil	1,183	–	–	–
Waste disposal	1,022	0	–	–
Mobile; on-road diesel light duty vehicles	1,006	–	–	–
Mobile; non-road equipment; diesel	915	–	–	–
Solvent; degreasing	805	–	–	–
Fuel combustion; electric generation; other	782	–	–	–
Fuel combustion; electric generation; biomass	446	–	–	–
Dust; construction dust	440	–	–	–
Industrial processes; oil and gas production	423	–	–	–
Mobile; on-road non-diesel heavy duty vehicles	369	–	–	–
Fuel combustion; commercial/ institutional; coal	300	–	–	–
Mobile; non-road equipment; other	243	–	–	–
Fuel combustion; commercial/ institutional; biomass	224	–	–	–
Fuel combustion; residential; wood	81	–	–	–
Fuel combustion; commercial/ institutional; other	47	–	–	–

Table 5-6. National Emission Inventory (NEI) Total National Emissions for Nickel and Nickel Compounds Estimated by Sector 2020

Sector	Nickel emissions (pounds)	Nickel oxide emissions (pounds)	Nickel subsulfide emissions (pounds)	Nickel refinery dust emissions (pounds)
Miscellaneous non-industrial NEC	13	–	–	–
Solvent; graphic arts	10	–	–	–
Bulk gasoline terminals	1	–	0	–
Fuel combustion; residential; other	0	–	–	–

Source: EPA 2020a

ICE = internal combustion engine; NEC = not elsewhere classified

Eagle Mine, in the upper peninsula of Michigan, is a nickel and copper mining site and the only active primary nickel mine in the United States. Estimated emissions, including fugitive emissions, from storage and transport on site were 2.275 pounds of nickel per year (Barr 2019). The nickel ore is sent to Humboldt Mill in Champion, Michigan, for processing. Estimated emissions from this site processes, including fugitive emissions, were 126.5 pounds of nickel per year (Barr 2023).

Nickel is present in fuel oil, natural gas, and coal. Outside of industrial processes, the other largest activities releasing nickel to the atmosphere is fuel combustion for motor vehicles or electricity generation (EPA 2020a). The nickel species present in particulate emissions from the stacks of eight residual fuel oil burning electric utility steam-generating units in New York, Hawaii, and Florida were characterized; 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 ≤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 median 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 bioavailable than embedded nickel.

Residual fuel oil combustion for residential space and water heating as a potential source of indoor air emissions has been well characterized (Habre et al. 2014; Hsu et al. 2012; Schachter et al. 2020). Nickel

has been measured in the vapor of e-cigarettes (Goniewicz et al. 2014; Pappas et al. 2020), which may also contribute to releases to indoor air.

Nickel emissions from municipal incinerators depend on the nickel content of the refuse and the design and operation of the incinerator. Emissions of 1,022 pounds of nickel were estimated from waste disposal in 2020 (EPA 2020a). 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 pounds/year and regional point sources contributed 105,660 pounds/year of the total nickel emissions (117,195 pounds/year) in Milwaukee (de Foy et al. 2012). Emissions from Milwaukee ships accounted for 145 pounds/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 (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 study authors of a long-term study of nickel in seven Korean cities between 1998 and 2010 concluded that 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

Estimated releases of 181,445 pounds (~82 metric tons) of nickel to surface water from 2,476 domestic manufacturing and processing facilities in 2022 accounted for about 2.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-4.

Estimated releases of 272,003 pounds (~123 metric tons) of nickel compounds to surface water from 1,050 domestic manufacturing and processing facilities in 2022 accounted for about 1.0% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-5.

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

Nickel emissions to water can result from industrial activities. Limited industrial effluent sampling in New Mexico of several sources between 2018 and 2019 reported a maximum of 25 µg/L nickel (dissolved fraction) at the outfall of an electricity generation site (WQP 2024). The maximum at a mining outfall was 20 µg/L nickel (dissolved fraction). Limited industrial effluent monitoring in Ohio reported a maximum of 90.8 µg/L nickel (total recoverable) at a truck, bus, and engine manufacturing site in 2018 (WQP 2024).

Recent emission estimates per sector in the United States were not located; however, robust estimates from the European Union may be comparable. In the European Union, the total emissions to surface water were 70,914 kg Ni/year from smelting/refining; 16,660 kg Ni/year from stainless steel production; 1,004 kg Ni/year from steel product manufacturing sites; 240 kg Ni/year from nickel alloy production; 34.5 kg Ni/year from steel production/foundries; 2,331 kg nickel/year from nickel chemical production companies; 290 kg Ni/year from nickel catalyst production; 1,370 kg Ni/year from plating; 13 kg nickel/year from metal product manufacturing; 463 kg Ni/year from battery production; 26 kg Ni/year from powder metallurgy production; and 5.8 kg Ni/year from recycling (EC 2008).

Nickel mining activities are expected to be another source of aquatic emissions. At Eagle Mine in the upper peninsula of Michigan, water is pumped underground for drilling, bolting, and dust suppression; this water is pumped back to the surface for storage and eventual treatment (Eagle Mine 2023). Water that has come into contact with the temporary development rock storage area is also pumped out and eventually treated. Nickel was present at 460–52,100 µg/L in water used for underground operations; 3,890–7,160 µg/L in water recovered after contact with development rock; and 22–214 µg/L in the contact water basin in 2022 (Eagle Mine 2023). Water is treated in a system that includes metals precipitation and sedimentation treatment, and final discharge is to a rapid infiltration system (MDEQ 2013). Available monitoring of the treated effluent in 2023 reported one measurement at 5.6 µg/L nickel; the remainder was below the limit of detection (2 µg/L) (CEMP 2023).

Domestic wastewater is another anthropogenic source of nickel in waterways. Maximum nickel concentrations in treated wastewater effluent were 22.9 µg/L total nickel and 6.4 µg/L dissolved nickel in

samples collected between 2018 and 2023 (WQP 2024). From a study of influent streams of a wastewater 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) accounted 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. Nickel may be removed by chemical precipitation or coagulation treatment in publicly owned treatment works, which reduces nickel releases (EPA 1981). For example, improvements in sewage treatment facilities have attributed to a reduction in the flux of nickel in wastewater effluents into the Hudson River estuary, decreasing from 518 kg/day in 1974 to 43 kg/day in 1997 (Sañudo-Wilhelmy and Gill 1999).

Nickel is a common constituent of urban and stormwater runoff. A significant source in these scenarios is from cars. Nickel can be released from diesel fuel and gasoline, lubricating oil, metal plating, and wear of the bushing or brake lining (WSDOT 2006). Use of deicers and paving asphalt can also contribute to nickel runoff. Nickel was reported at a median of 9.0 µg/L in urban stormwater runoff (EPA 2007). Runoff from highways ranged from 0 to 53.3 µg/L and runoff from parking lots ranged from 2.1 to 18 µg/L (EPA 2007).

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). Municipal solid waste landfills in the European Union had a maximum of 23.1 mg/L total nickel in leachate, with leachate means of different landfills ranging from 0.0035 to 1.25 mg/L total nickel (EC 2008).

5.3.3 Soil

Estimated releases of 5.99 million pounds (~2,700 metric tons) of nickel to soils from 2,476 domestic manufacturing and processing facilities in 2022, accounted for about 80% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 100,099 pounds (~45 metric tons), constituting about 1.3% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-4.

Estimated releases of 23.2 million pounds (~10,500 metric tons) of nickel compounds to soils from 1,050 domestic manufacturing and processing facilities in 2012, accounted for about 88% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 380,524 pounds (~173 metric tons), constituting about 1.4% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-5.

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 source of anthropogenic nickel will depend greatly on land use. The major sources of anthropogenic nickel release to soil are industrial waste materials, and to agricultural soils are lime, fertilizer, and sewage sludge (McIlveen and Negusanti 1994).

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). Sokolov et al. (2023) used emission data over a roughly 50-year period from a smelting facility in

Northern Russia to calculate atmospheric deposition rates in nearby soils, waters, and sediment. Results from the model indicated that the intensities of nickel accumulation in the soil and bottom sediments were 2.35 and 4.48 mg/(m^2 year) during the maximum deposition periods (1980–2005), whereas the model predicted a decrease in the intensity of accumulation in the bottom sediments (0.23 mg/(m^2 year)) and slow leaching from the soil (0.19 mg/(m^2 year)) after the plant was closed.

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 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. Combustion conditions can impact the speciation of nickel and size of the aerosol. In the presence of sulfur, the resulting aerosols are smaller (mean size of 34 nm); without sulfur, NiO forms as larger aerosols (mean size of 44 nm) (Wang and Biswas 2000).

Metal deposition is characterized by large temporal and spatial variability. Prehistoric periods of climate change and the industrial revolution's influence on nickel deposition has been demonstrated through analysis of the Finnish peat moss cores (Krachler et al. 2003; Rausch et al. 2005). 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). Atmospheric deposition is the primary source of nickel to the open ocean, and events like Saharan dust events, which are large-scale depositions of soil dust from the Saharan Desert, are important influxes of nickel to surface seawater (Ebling et al. 2017). 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). For the coastal ocean and waterways, fluvial input plays a bigger role in providing nickel than atmospheric deposition. The nickel that is carried into oceans in both dissolved and particulate forms through riverine input is estimated 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, competition, and complexation are processes that affect partitioning. These processes are influenced by pH, redox potential, ionic strength of the water, concentration of competing and complexing ions, and species and concentration of the metal (Doig and Liber 2007; Paquin et al. 2002; Santore et al. 2021). With respect to the complexation and adsorption of nickel, the quantity and quality of organic matter have been found to be particularly important parameters (Doig and Liber 2007). The humic acid fraction reduced dissolved nickel to a greater extent than the fulvic acid fraction when dissolved organic carbon (DOC) was comparable (Doig and Liber 2007). Sorptive removal of nickel follows kinetically controlled adsorption to settling organic particulate or transport to, and direct adsorption by, the settled organic particulate (Burton et al. 2019; Huntsman et al. 2019). Desorption from dissolved organic matter is impacted by the concentration of nickel, pH, and quality of organic matter (Wang et al. 2019). Nickel dissociated faster from the fulvic acid fraction than the humic acid fraction when pH was decreased (Wang et al. 2019). The presence of other metals such as Ca^{+2} and Mg^{+2} can result in greater dissociation of soluble nickel from DOC as well (Mandal et al. 2002).

Adsorption of nickel onto suspended particles in water is one of the main removal mechanisms of nickel from the water column. 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 adsorptivity 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 wastewater 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 also 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 in soil can accumulate from chemical weathering and migration of underlying sediments, atmospheric deposition of soil dust, or, more likely for surface soils, atmospheric deposition of anthropogenic particulate (Krachler et al. 2003). Nickel typically accumulates at the surface of soils due to deposition; however, evidence of mobility in subsurface soil prior to deposition has been reported (Krachler et al. 2003; Rausch et al. 2005). 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 (Hale et al. 2017; 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 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 to assess the potential mobility of nickel in contaminated subsoil; nickel was more mobile in soils than lead, cadmium, and zinc (LaBauve et al. 1988). The retention of nickel in 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. Mobility in soil is reduced for insoluble species of nickel, and through the initial fast adsorption followed by slow sequestration of the soluble nickel species (Hale et al. 2017).

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 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 that 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.

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 (H_2SO_4) 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. The presence of acid volatile sulfide, iron oxide, and

manganese oxide in sediment changes the speciation of nickel, which can impact mobility (Costello et al. 2016; Schlekat et al. 2016). Nickel competitively binds with iron or manganese monosulfides, precipitating out as nickel sulfide, reducing the metal's bioavailability and mobility (Schlekat et al. 2016). This reduction in aqueous availability is seen until nickel reaches 2–8 times higher concentrations than acid volatile sulfide concentrations.

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) >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 BCF for three carnivorous fish was 36. The concentrations 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) were obtained for all organisms. When the study authors also included data for exposure concentrations outside the range of 5–50 µg/L, a BCF value of 157±135 was obtained. The study 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.

The most important water chemistry parameters that control uptake in aquatic organisms are water hardness and DOC (EPA 2022b). Increased water hardness (higher Ca^{+2} and Mg^{+2} concentrations) has been associated with decreased metal toxicity. Nickel uptake occurs through Ca^{+2} and Mg^{+2} uptake pathways and the presence of these cations in hard water competitively reduces uptake of nickel (Brix et al. 2017). Nickel binds with DOC in water, therefore reducing the bioavailable portion for uptake by aquatic species in high DOC waters (EPA 2022b). Water pH plays a species-dependent role in reducing toxicity, potentially due to different species' pH-driven mechanisms of nickel bioavailability (EPA 2022b).

In soil, bioavailability is impacted by the speciation of nickel deposited and aging of the soil. A review of soil toxicity studies investigated biogeochemical drivers of bioavailability (Hale et al. 2017). Soils with nickel chloride ($NiCl_2$), a soluble species, had higher bioavailability than soils with nickel oxide (NiO), an insoluble species released during refining activities. Soil aging results in the oxidation of insoluble nickel species to potentially other equally insoluble species (as was the case with NiO), or initial fast adsorption followed by slow sequestration of the soluble nickel species; ultimately, the soil amended with the soluble species still had higher bioavailability after aging (Hale et al. 2017). The presence of acid volatile sulfide, iron oxide, and manganese oxide in sediment changes the speciation of nickel as the sediment ages, which resulted in differences in bioavailability and toxicity during this process compared to steady toxicity levels seen in sediments without these redox reagents (Costello et al. 2016).

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 (USGS 2000b, 2000c).

Uptake and accumulation of nickel into various plant species is known to occur. For example, Peralta-Videa et al. (2002) reported 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 concentrations were 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 3 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. Nickel is an essential nutrient for some crops, and deficiency can result in growth deficiencies (Brown et al. 1987; Wood et al. 2004). Therefore, uptake and accumulation in plants is expected to occur to some degree. Studies in tomato plants showed increased nickel uptake with increased nickel soil concentration; the highest detections were in the root of the plant, followed by the leaves, stem, and fruit (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 (ratios >0.1 and <1) accumulators of nickel (Correia et al. 2018). The highest reported BCF was approximately 0.36 in the roots (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. While most analytical methods provide information concerning the metal content rather than the specific compounds or species, some characterization of nickel in airborne particulate is available. In airborne dust collected near a metallurgical plant in Dortmund, Germany, nickel was identified at 48±18% in the oxidized (NiO) fraction, at 36±20% in the soluble fraction, at 11±15% in the metallic (Ni) fraction, and at 6±4% in the sulfidic (NiS) fraction (Fuichtjohann et al. 2001). In urban aerosols collected from Davie, Florida, nickel was present as 50% oxidized ($NiFe_2O_4$), 40% soluble ($NiSO_4 \cdot H_2O$) and 10% NiS (DOE 2003). The majority of nickel (78%) in the PM10 fraction (fraction absorbed to particulate matter ≤10 microns) was the soluble species. Combustion conditions can impact the speciation of nickel and size of the aerosol. In the presence of sulfur, the resulting aerosols contain a mix of $NiSO_4$ and NiO; without sulfur, NiO forms. Higher temperatures resulted in more NiO and less $NiSO_4$ formation (Wang and Biswas 2000). 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.

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.

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 5-7 shows the limit of detections typically achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-8.

Table 5-7. 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	0.18 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 5-8. Summary of Environmental Levels of Nickel

Media	Low	High	For more information
Outdoor air (ng/m^3)	0.70	72.32	Section 5.5.1
Indoor air (ng/m^3)	2.79	23.7	Section 5.5.1
Surface water (ppb)	2.2	1,200	Section 5.5.2
Groundwater (ppb)	4.38	6,110	Section 5.5.2
Drinking water (ppb)	2	48	Section 5.5.2
Ocean water (ng/L)	111	3,000	Section 5.5.2
Food (ppb)	0	10,600	Section 5.5.4
Soil (ppm)	<0.5	2,870	Section 5.5.3

Presented in Table 5-9 is a summary of the range of concentrations detected in environmental media at NPL sites.

Table 5-9. Nickel Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	188	300	12.4	426	242
Soil (ppb)	71,700	90,100	10.2	414	224
Air (ppbv)	0.0833	1.47	156	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 5-10 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 total suspended particulate (TSP) air concentrations are typically <3 ng/m^3, with a maximum mean concentration of 18 ng/m^3 in the last 5 years according to these data. The potentially respirable fraction is reflected in the PM10 concentrations, where means were generally <1.5 ng/m^3, with a maximum mean of 9.9 ng/m^3 reported for this time period. Recent studies with data on outdoor air concentrations are presented in Table 5-11. 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 m (Han et al. 2020).

Table 5-10. Percentile Distribution of Mean Nickel Concentrations Measured in Ambient Air at Locations Across the United States[a]

Year	Number of U.S. locations	Percentile				Maximum
		10th	50th	75th	95th	
Nickel total suspended particulates (ng/m^3)						
2018	43	0.87	2.12	3.27	5.88	62.4
2019	40	0.70	1.18	1.74	3.76	72.32
2020	37	0.70	1.45	2.23	3.68	26.8
2021	34	0.95	2.16	3.02	5.26	42.7
2022	43	0.73	1.46	2.13	3.75	28.9
2023[b]	29	0.73	1.37	1.96	4.46	16
Nickel PM10 (ng/m^3)						
2018	22	0.41	0.65	0.90	2.23	22.8
2019	19	0.40	0.67	0.90	2.72	41.3
2020	19	0.35	0.67	0.96	3.46	216
2021	17	0.47	0.77	1.06	2.13	34.7
2022	11	0.55	0.83	1.07	2.18	6.6
2023[b]	12	0.49	0.84	1.24	4.54	60.2

[a]At standard temperature and pressure conditions.
[b]As of October 26, 2023.

PM10 = fraction absorbed to particulate matter ≤10 microns.

Source: EPA 2024

Table 5-11. 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 5-11. 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 2010
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
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

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 2010; 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. 2012; 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. 2012; Peltier and Lippmann 2010; Rohr et al. 2014a). Peltier and Lippmann (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 5.5–24.6 ng/m^3 in winter samples and 3.0–15.1 ng/m^3 in summer samples (Peltier and Lippmann 2010). In the winter, fuel oil combustion typically increases for heating residential buildings (Schachter et al. 2020).

The results of studies which monitored indoor air concentrations of nickel are presented in Table 5-12. 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 2010; 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 5.5–24.6 ng/m^3 in winter samples and 3.0–15.1 ng/m^3 in summer samples (Peltier and Lippmann 2010). 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. 2012; 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 5-12. 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

Table 5-12. Indoor Air Monitoring Data for Nickel

Location	Geographic type	Date(s)	Mean concentration	Notes	Reference
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 4.17 ng/m^3; maximum concentration 42.5 ng/m^3	Sax et al. 2006
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

Nickel is ubiquitous in the environment and is commonly detected in surface and groundwater, precipitation, and seawater. Nickel has been detected in rain and snow as a result of atmospheric washing out of particulates containing nickel. The concentration of nickel in precipitation is influenced by the back-trajectory of the air masses in which the precipitation originates. Correlation with other trace metals can help elucidate the source of the emission (Rivera-Rivera et al. 2020). Rainwater samples were collected in Mexico between 2016 and 2017. Nickel was detected at averages of 0.012 mg/L in rural area samples and 0.033 mg/L in industrial area samples (Rivera-Rivera et al. 2020). Mean concentrations of

nickel in precipitation collected near a large municipal incinerator in Claremont, New Hampshire, were 0.69 µg/L in rainwater and 0.62 µg/L in snow (Feng et al. 2000).

The distribution of nickel in the marine water column has been well characterized by GEOTRACES studies. Higher levels of nickel are found in deep seawater than in surface water: average surface water nickel concentrations in the equatorial Atlantic Ocean were 111 and 122 ng/L and the highest average was found in Antarctic bottom water at 443 ng/L (Middag et al. 2020). 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 EPA maintains a Water Quality Portal (WQP) database which aggregates air monitoring data from the National Water Information System (NWIS) and STORage and RETrieval (STORET) system. A summary of the data for ambient surface and groundwater from recent years are reported in Table 5-13 (WQP 2024). Data are reported as the dissolved fraction to reflect the potentially bioavailable fraction. Nickel is ubiquitous in the environment and was detected fairly consistently at averages around 3–3.5 ppb in surface water and at averages around 4–7 ppb in groundwater. The maximum of 6,110 µg/L observed in 2021 was recorded in Utah during drought conditions which may have impacted the results. This value is an order of magnitude higher than other measurements from that location and may be an outlier.

Table 5-13. Summary of Concentrations of Dissolved Nickel (ppb) Measured in Surface Water and Groundwater Across the United States

Year	Average	Maximum	Number of samples	Percent detected
Surface water				
2018	4.69	450	6,176	47%
2019	2.89	251	6,628	45%
2020	3.16	357	4,736	48%
2021	3.60	506	6,397	45%
2022	3.49	1,200	6,612	46%
2023	2.96	440	4,078	55%
Groundwater				
2018	6.13	262	1,472	55%
2019	6.80	206	1,353	59%
2020	5.92	443	1,074	54%
2021	18.2	6,110	1,062	58%

Table 5-13. Summary of Concentrations of Dissolved Nickel (ppb) Measured in Surface Water and Groundwater Across the United States

Year	Average	Maximum	Number of samples	Percent detected
2022	7.59	579	1,135	61%
2023	4.38	400	602	58%

Source: WQP 2024

Nickel in surface water can be geologically influenced. Surface water samples were collected between 2013 and 2015 in northern Minnesota to determine the potential influence of underlying nickel-rich mineral deposits in the bedrock (USGS 2020). Measured median values were 3.4 µg/L (total) and 3.2 µg/L (dissolved) in Filson Creek; 2.3 µg/L (total) and 2.2 µg/L (dissolved) in Keeley Creek; and 1.1 µg/L (total and dissolved) in the St. Louis River. The Filson Creek and Keeley Creek watersheds contain exposed Cu-Ni-sulfide mineralization, resulting in higher nickel concentrations near these areas; mineralization impacts were not observed for the St. Louis River due to thick glacial sediments covering the bedrock (USGS 2020).

For the USGS National Water-Quality Assessment Program, a comprehensive study of trace elements in groundwater across the United States was conducted from 1992 to 2003. In this study, the USGS collected data from 5,183 monitoring and drinking-water wells representing more than 40 principal and other aquifers in humid and dry regions and in various land-use settings (USGS 2011). Very few samples (0.23%) exceeded the human-health benchmark value of 100 µg/L. The median nickel concentration was 1.1 µg/L and the maximum was 670 µg/L (USGS 2011). Dry regions had significantly more detections (62%) than humid regions (54%) greater than the reporting level (1 µg/L). In dry regions, the percentage of detections >1 µg/L were the same for agricultural and urban land use wells (86%). In humid regions, percent detections urban land-use wells (78%) were significantly higher than in agricultural land-use wells (72%) (USGS 2011).

In a comprehensive survey of U.S. groundwater conducted between 1992 and 2003 by the USGS, 46% of drinking water wells in dry regions and 42% of drinking water wells in humid regions had nickel greater than the 1 µg/L reporting limit (USGS 2011). Nickel was detected in two bottled water samples at 2 and 7.4 ppb collected for the FDA's Total Diet Study between 2018 and 2020 (FDA 2023c). Drinking water sampled for the European Union diet study contained 2–3 ppb (EFSA 2020).

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. At the Bonita Peak Mining District Superfund Site, dissolved nickel was detected at an average of 27.1 µg/L (maximum: 820 µg/L) in groundwater in 2021 and at annual averages of 11.7–15.8 µg/L between 2018 and 2012 (overall maximum: 274 µg/L) (WQP 2024). In a monitoring study of the Upper Columbia River in Washington state, which is impacted by smelter slag pollution, medians were 0.6 µg/L (range: 0.6–17 µg/L, detected in 27% of samples) in surface water; 0.6 µg/L (range: 0.4–1 µg/L, detected in 39% of samples) in shallow pore-water; and 0.6 µg/L (range: 0.5–1 µg/L, detected in 57% of samples) (USGS 2016). At Eagle Mine, the only active primary nickel mine in the United States, groundwater monitoring wells reported one sample with 29.2 µg/L nickel; the remaining samples in 2023 were non-detects (<25.0 µg/L) (CEMP 2023). Nickel was not detected (<1.0 µg/L) in surface water near the mine in 2023. Nickel was not detected (<20.0 µg/L) in groundwater at the processing mill, and maximum surface water detections were 8.8 µg/L in 2023 (CEMP 2023).

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; a range of nickel in U.S. soil has been reported as <0.5–1,890 ppm (USGS 2012). Enrichment factors, the ratio of the measured soil concentration to the regional standard geochemical background concentration, can be calculated to elucidate anthropogenic influence (USGS 2021).

Sediment is an important sink for nickel in water. Nickel content of 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 (Suh et al. 2019). Table 5-14 shows the results of several studies measuring concentrations of nickel in soil and sediment.

Table 5-14. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
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		
Conterminous United States			USGS 2013
Surface soil (0–5 cm)			
Range	<0.5–1,890 mg/kg	4,841 samples	
Mean	17.7±45.2mg/kg		
Soil A horizon			
Range	<0.5–2,310 mg/kg	4,813 samples	
Mean	18.5±54.4 mg/kg		
Soil C horizon			
Range	<0.5–2,870 mg/kg	4,780 samples	
Mean	22.6±68.8 mg/kg		

Table 5-14. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
United States			WQP 2024
Soil			
2018			
Maximum	27.8 mg/kg	Detected in 100% of 94 samples	
Mean	7.29 mg/kg		
2019			
Maximum	180 mg/kg	Detected in 100% of 122 samples	
Mean	13.2 mg/kg		
2020			
Maximum	21,000 mg/kg	Detected in 85% of 39 samples;	
Mean	3,040 mg/kg	maximum reported from South Dakota,	
2021		possibly due to natural enrichment	
Maximum	30 mg/kg	Detected in 100% of 10 samples	
Mean	28.2 mg/kg		
2022			
Maximum	42 mg/kg	Detected in 100% of 15 samples	
Mean	17.2 mg/kg		
2023			
Range	26 mg/kg	Detected in 10% of 7 samples	
Mean	19 mg/kg		
Bonita Peak Mining Superfund Site, Colorado			WQP 20224
Soil			
2018			
Maximum	66.8 mg/kg	Detected in 99% of 97 samples	
Mean	4.3 mg/kg		
2021			
Maximum	131 mg/kg	Detected in 81% of 186 samples	
Mean	6.7 mg/kg		
United States			WQP 2024
Sediment			
2018			
Maximum	306 mg/kg	Detected in 80% of 1,467 samples	
Mean	17 mg/kg		
2019			
Maximum	169 mg/kg	Detected in 73% of 1,144 samples	
Mean	21.7 mg/kg		
2020			
Maximum	390 mg/kg	Detected in 87% of 2,197 samples	
Mean	21.6 mg/kg		
2021			
Maximum	1,170 mg/kg	Detected in 79% of 1,134 samples	
Mean	19.4 mg/kg		
2022			
Maximum	8,960 mg/kg	Detected in 65% of 500 samples	
Mean	53.5 mg/kg		
2023			
Maximum	319 mg/kg	Detected in 93% of 154 samples	
Mean	12.3 mg/kg		

Table 5-14. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
Raritan River Basin, Passaic River Basin, Rahway River Basin, and Great Egg Harbor River Basin, New Jersey		Estimated baseline nickel: 3 µg/g (coastal plain sites), 20 µg/g (non-coastal plain sites)	USGS 2000b
Stream and riverbed-sediment		Concentrations significantly related to urban industrial/commercial land use and population density	
Range	18–43 µg/g		
Northern Rockies Intermontane Basin			USGS 2000a
Stream and riverbed-sediment		0–2-cm depth; 16 samples; basin impacted by mining activities	
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		
Upper Columbia River, Washington		Area impacted by mining slag	USGS 2017
Sediment (total)			
Range	1.7–39.3 mg/kg	Total nickel	
Median	17.7 mg/kg		
Sediment (SEM)			
Range	0.293–8.63 mg/kg	Simultaneously-extracted metals, represents to bioavailable fraction.	
Median	3.2 mg/kg		
Bonita Peak Mining Superfund Site, Colorado			WQP 2024
Sediment			
2018			
Maximum	40.600 mg/kg	Detected in 100% of 122 samples	
Mean	7.148 mg/kg		

Table 5-14. Concentrations of Nickel in Soil and Sediment

Location	Concentration	Notes	Reference
Midnite Mine Superfund Site, Washington			WQP 2024
Sediment			
2018			
Maximum	472 mg/kg	Detected in 90% of 10 samples	
Mean	84.9 mg/kg		
2019			
Maximum	297 mg/kg	Detected in 90% of 10 samples	
Mean	47.2 mg/kg		
2020			
Maximum	100 mg/kg	Detected in 100% of 10 samples	
Mean	21.7 mg/kg		
2021			
Maximum	566 mg/kg	Detected in 100% of 10 samples.	
Mean	74.6 mg/kg		
2022			
Maximum	428 mg/kg	Detected in 100% of 10 samples	
Mean	75.8 mg/kg		

SEM = standard error of the mean

5.5.4 Other Media

Tables 5-15 and 5-16 and present the results of the FDA's Total Diet Study from 2018 through 2020 (FDA 2023c) for general food items and for baby food items. The Total Diet Study is conducted through Market Based Surveys in each of four geographic regions of the United States (north central, west, south, and northeast) during which foods purchased in each region for different are tested for elements, pesticides, and radionuclides. Products with the highest nickel concentrations included dairy products like cream cheese and milk; vegetables like peas and pickles; pie crust; veggie burgers; and popsicles (FDA 2023c). The European Union diet study reported the highest mean nickel concentrations in cocoa products, herbs and spices, tea leaves, and seaweed (EFSA 2020).

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Cream cheese	1	1	10,600	–
Peas, green, frozen, boiled	3	3	4,400	4,200–6,200
Pickles, dill, cucumber	22	22	3,800	2,800–5,000
Pie crust	1	1	3,200	–
Veggie burger	3	3	2,400	2,000–3,200

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Yogurt, lowfat, vanilla	7	7	2,000	1,600–2,700
Popsicle, fruit-flavored	3	3	1,600	1,300–2,000
Eggplant, fresh, peeled, boiled	3	3	1,100	1,000–1,100
Milk, reduced fat, fluid	3	3	1,000	830–1,000
Milk, chocolate, reduced fat, fluid	3	3	960	930–1,300
Beer	3	3	920	910–1,000
Milk, skim, fluid	2	2	920	910–930
Quinoa, cooked	7	7	870	700–1,200
Coffee, brewed from ground	3	3	810	640–860
Juice, lemon	3	3	670	510–-810
Pork sausage (link/patty), pan-cooked	3	3	660	620–680
Pork chop, pan-cooked with oil	3	3	650	530–800
Juice, tomato-vegetable	1	1	650	–
Almonds, shelled	8	8	590	510–800
Mixed vegetables, frozen, boiled	3	3	580	490–660
Cauliflower, fresh/frozen, boiled	3	3	540	470–570
Luncheon meat, bologna	27	27	530	380–680
Fish sticks or patty, frozen, oven-cooked	3	3	520	510–570
Eggs, hard-boiled	3	3	460	450–890
Pork and beans, canned	3	3	450	420–480
Lima beans, immature, frozen, boiled	3	3	440	400–550
Beans, black, canned, drained solids	3	3	440	350–630
Avocado, raw	27	27	390	220–500
Beans, kidney, canned, drained solids	5	5	360	260–420
Muffin, blueberry	3	3	360	360–390
Blueberries, raw	3	3	330	250–480
Granola bar	1	1	330	–
Breakfast tart/toaster pastry	8	8	325	89–600
Beans, pinto, canned, drained solids	3	3	310	310–380
Beans, white, canned, drained solids	3	3	300	200–360
Bread, white, enriched, pre-sliced	3	3	260	260–310
Crackers, cheese	1	1	250	–
Broth, chicken, cartoned	1	1	250	–
Crackers, saltine	3	3	240	220-290
Bagel, plain, toasted	3	3	230	200–270
Soup, broccoli cheese, canned, condensed, prepared with water	3	3	230	200–230
Chips, tortilla	3	3	220	140–230

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Soup, clam chowder, New England, canned, ready to serve	8	8	215	190–250
Soup, cream of mushroom, canned, condensed, prepared with water	3	3	210	120–220
Soup, cream of potato, canned, condensed, prepared with water	2	2	210	180–240
Macaroni and cheese, prepared from boxed mix	27	27	200	120–280
Soup, vegetable beef, canned, ready to serve	5	5	190	150–390
Cinnamon roll, iced	27	27	180	66–580
Peach, raw/frozen	27	27	180	140–250
Pasta, rice noodles, cooked	5	5	180	–
Soup, vegetable, canned, ready to serve	1	1	180	180–180
Cereal, shredded wheat, frosted	3	3	170	150–210
Apple, red, with peel, raw	3	3	170	140–180
Fruit cocktail, canned in light syrup, solids and liquids	8	8	155	94–190
Pasta, whole wheat, cooked	5	5	150	120–200
Pudding, ready-to-eat, chocolate	3	3	150	100–190
Syrup, pancake	27	27	140	50–280
Raisins	8	8	140	90–150
Beans, garbanzo (chickpeas), canned, drained solids	5	5	140	60–180
Grapefruit, raw	3	3	140	130–150
Lentils, dry, cooked	3	3	140	130–290
Luncheon meat, turkey	3	2	140	0–160
Green beans, canned, drained solids	8	8	135	100–180
Brussels sprouts, fresh/frozen, boiled	27	27	130	69–290
Turkey, ground, pan-cooked	27	25	130	0–240
Cookies, chocolate chip	3	3	130	120–200
Cookies, sugar	3	3	130	63–150
Frankfurter (all beef/beef and pork), boiled	3	3	130	130–140
Cucumber, peeled, raw	22	22	120	71–250
Tofu, firm, plain, drained solids	9	9	120	94–140
Lettuce, iceberg, raw	8	8	120	58–200
Doughnut, cake-type, plain	3	3	120	63–160
Luncheon meat, ham	3	3	120	89–130
Chips, potato	27	26	110	0–190
Mushrooms, canned, drained solids	3	3	110	89–140

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Potato, peeled, boiled	3	3	110	94–180
Potato, with peel, baked	3	3	110	98–130
Chili con carne with beans, canned	3	3	110	93–150
Soup, tomato, canned, condensed, prepared with water	27	23	100	0–740
Mayonnaise	8	8	96.5	67–180
Cream, half and half	8	8	91	58–130
Sugar, white, granulated	27	17	90	0–250
Beef steak, loin/sirloin, oven-roasted	3	3	90	78-91
Cake, white with white icing	3	3	88	73–110
Margarine, salted	27	26	85	0–180
Butter, salted	27	27	84	69–140
Cookies, sandwich, with creme filling	27	27	81	56–150
Broccoli, fresh/frozen, boiled	3	3	81	51–83
Pie, apple, fresh/frozen	27	27	80	54–180
Powder, protein	27	27	79	55–160
Pie, pumpkin, fresh/frozen	27	26	79	0–120
Carbonated beverage, cola, regular	3	2	76	0–170
Sorbet, fruit-flavored	27	20	75	0–270
Chicken potpie, frozen, heated	27	26	72	0–140
Gelatin dessert, strawberry	27	24	72	0–220
Cheese, American, processed	3	3	72	65–79
Potatoes, French fries, fast-food	8	8	69	42–130
Cornbread, homemade	3	3	69	63–79
Soup, chicken noodle, canned, condensed, prepared with water	27	26	67	0–140
Pepper, bell, green, raw	27	22	67	0–310
BF, pasta, tomato and beef	3	2	67	0–67
Banana, raw	27	23	64	0–110
Pear, with peel, raw	8	7	61.5	0–91
Alcohol, distilled, whiskey/scotch	6	4	60.5	0–300
Yogurt, lowfat, fruit-flavored	3	2	60	0–120
Cheese, Swiss	3	3	59	48–75
Fruit drink (5–25% juice), canned or bottled	3	3	59	56–64
Celery, raw	27	19	58	0–170
Chicken nuggets, fast-food	3	3	58	42–68
Watermelon, raw/frozen	3	2	58	0–66
English muffin, plain, toasted	27	20	57	0–110

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Corn, canned, drained solids	27	18	56	0–140
Crackers, butter-type	27	20	55	0–130
Squash, winter, fresh/frozen, boiled	27	20	54	0–90
Juice, grape, bottled	27	18	52	0–100
Cereal, granola	27	17	52	0–420
Alcohol, distilled, vodka	3	3	47	42–73
Biscuits, fast-food	3	2	47	0–58
Pretzels, hard, salted	3	2	43	0–46
Syrup, chocolate-flavored	3	3	35	22–40
Jelly, grape	3	3	34	33–71
Cake, chocolate with chocolate icing	27	13	0	0–450
Pineapple, raw/frozen	27	13	0	0–480
Tomato, raw	27	13	0	0–400
Juice, orange, bottled/cartoned	27	12	0	0–170
Cheese, Monterey jack	27	12	0	0–150
Milk shake, vanilla, fast-food	27	11	0	0–580
Ketchup, tomato	27	10	0	0–130
Corn, frozen, boiled	27	9	0	0–85
Water, bottled, mineral/spring	27	8	0	0–76
Honey	27	8	0	0–72
Oil, olive	27	7	0	0–79
Onion, mature, raw	27	7	0	0–91
Spaghetti, enriched, boiled	22	6	0	0–76
Brown gravy, canned or bottled	27	6	0	0–87
Salad dressing, Italian, regular	27	6	0	0–140
Sweet potato, baked, peel removed	27	6	0	0–100
Shrimp, pre-cooked, shells removed, no tails	27	6	0	0–71
Salsa, tomato, bottled	27	5	0	0–160
Green beans, fresh/frozen, boiled	27	5	0	0–91
Pork bacon, oven-cooked	27	5	0	0–120
Salami, dry/hard	27	4	0	0–72
Juice, apple, bottled	27	4	0	0–79
Tea, brewed from tea bag	21	4	0	0–360
Chicken thigh, oven-roasted, skin removed	27	3	0	0–290
Beans, refried, canned	27	3	0	0–90
Tortilla, flour	27	3	0	0–99
Cocoa powder	8	2	0	0–44

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Cereal, oat ring	27	2	0	0–7.4
Ice cream, chocolate	27	2	0	0–76
Beverage, coconut water	8	2	0	0–86
Beef, ground, pan-cooked	27	2	0	0–78
Cantaloupe, raw/frozen	27	2	0	0–120
Fruit drink, from powder	27	2	0	0–110
Chicken leg, fried with skin, fast-food	27	1	–	0–40
Tuna, canned in water, drained solids	27	1	–	0–43
Peanut butter, creamy	3	1	–	0–51
Soup, ramen noodles, prepared with water	3	1	–	0–55
Cod, baked	3	1	–	0–20
Bread, white roll/bun (hamburger/hotdog)	3	1	–	0–62
Grapes, seedless, red/green, raw	27	1	–	0–88
Kale, fresh, pan-cooked	3	1	–	0–56
Meal replacement, liquid ready-to-drink, vanilla	27	1	–	0–54
Cereal, oat ring, honey	27	1	–	0–48
Sauce, soy	3	1	–	0–65
Sauce, tomato, pasta	8	1	–	0–53
Sour cream	27	1	–	0–58
Ham, cured (not canned), baked	27	1	–	0–64
Rice, white, enriched, cooked	3	1	–	0–20
Strawberry, raw/frozen	27	1	–	0–46
Collards, fresh/frozen, boiled	27	1	–	0–80
Asparagus, fresh/frozen, boiled	3	1	–	0–22
Salmon, steaks/fillets, baked	3	0	–	–
Baking powder	13	0	–	–
Cottage cheese, creamed, reduced fat	27	0	–	–
Chicken breast, fried with skin, fast-food	27	0	–	–
Catfish, pan-cooked with oil	27	0	–	–
Peanuts, dry roasted, salted	3	0	–	–
Seeds, sunflower, shelled, salted, roasted	27	0	–	–
Pancakes, frozen, heated	27	0	–	–
Fruit juice blend (100% juice), canned/ bottled	3	0	–	–
Juice, cranberry cocktail, bottled	27	0	–	–
Carrot, baby, raw	3	0	–	–
Lettuce, leaf, raw	3	0	–	–

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Oatmeal, plain, quick, cooked	1	0	–	–
Candy bar, chocolate, nougat, with nuts	3	0	–	–
Popcorn, microwave, butter-flavored	27	0	–	–
Oil, vegetable	3	0	–	–
Bread, whole wheat, pre-sliced	3	0	–	–
Tilapia, baked	3	0	–	–
Cheese, mozzarella	27	0	–	–
Cereal, corn flakes	3	0	–	–
Brownie	3	0	–	–
Cereal, crisped rice	3	0	–	–
Mustard, yellow, plain	3	0	–	–
Tortilla, corn	3	0	–	–
Walnuts, shelled	3	0	–	–
Rice, brown, cooked	3	0	–	–
Pizza, cheese, fast-food	3	0	–	–
Sauce, barbecue	3	0	–	–
Cabbage, raw	27	0	–	–
Zucchini, fresh/frozen, boiled	3	0	–	–
Cereal, bran with raisins	3	0	–	–
Spinach, raw	3	0	–	–
Yogurt, frozen, vanilla	3	0	–	–
Eggplant, baked with peel	3	0	–	–
Candy bar, milk chocolate, plain	27	0	–	–
Mango, raw/frozen	3	0	–	–
Garlic, raw	3	0	–	–
Cashews, salted	3	0	–	–
Olives, black, pitted	3	0	–	–
Wine, red	3	0	–	–
Crackers, graham	3	0	–	–
Wine, white	3	0	–	–
Beverage, almond (non-dairy)	8	0	–	–
Beverage, energy	8	0	–	–
Beverage, soy (non-dairy)	3	0	–	–
Beverage, sports	27	0	–	–
Carbonated beverage, lemon-lime, regular	3	0	–	–
Candies, fruit snacks	3	0	–	–
Carbonated beverage, cola, diet	26	0	–	–

Table 5-15. Nickel Detections in Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2018–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Cereal, whole wheat, cooked	27	0	–	–
Juice, pineapple, canned	3	0	–	–
Salad dressing, ranch, low-calorie	3	0	–	–
Salad dressing, ranch, regular	3	0	–	–
Sauce, tomato, canned	3	0	–	–
Milk, whole, fluid	3	0	–	–
Cheese, cheddar (sharp/mild)	27	0	–	–
Lamb chop, pan-cooked with oil	27	0	–	–
Turkey breast, oven-roasted	3	0	–	–
Cream of wheat (farina), enriched, cooked	3	0	–	–
Corn/hominy grits, enriched, cooked	3	0	–	–
Noodles, egg, enriched, boiled	3	0	–	–
Orange, raw	27	0	–	–
Applesauce, bottled	6	0	–	–
Juice, grapefruit, bottled/cartoned	27	0	–	–
Cream substitute, non-dairy, liquid	27	0	–	–
Chicken breast, oven-roasted, skin removed	3	0	–	–
Mushrooms, raw	3	0	–	–
Ice cream, vanilla	3	0	–	–
Candy, hard	3	0	–	–
Breadcrumbs	3	0	–	–
Flour, white, all-purpose	3	0	–	–
Salt, sea	1	0	–	–
Salt, iodized	1	0	–	–

Source: FDA 2023c

Table 5-16. Nickel Detections in Baby Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2019–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Beef and broth/gravy	27	24	72	0–220
Vegetables and beef	8	8	70.5	59–140
Chicken noodle dinner	3	3	69	63–79
Vegetables and chicken	8	8	69	42–130
Green beans	27	26	67	0–140
Turkey and rice	3	3	67	64–69

Table 5-16. Nickel Detections in Baby Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2019–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Pasta, tomato and beef	3	2	67	0–67
Carrots	27	22	67	0–310
Mixed vegetables	3	3	65	47–69
Peas	27	23	64	0–110
Sweet potatoes	3	2	64	0–87
Applesauce	3	3	63	60–69
Peaches	27	27	62	39–120
Pears	8	7	61.5	0–91
Juice, apple	6	4	60.5	0–300
Bananas	3	2	23	0–25
Teething biscuits	14	7	21	0–85
Cereal, oatmeal, dry	8	0	–	–
Cereal, mixed, dry	5	2	0	0–47
Finger foods, puffed snack	27	13	0	0–450
Peas, green beans, and avocado, pouch	3	0	–	–
Cereal, oatmeal, dry, prepared with water	3	0	–	–
Squash	3	0	–	–
Peas and spinach, glass jar	3	0	–	–
Prunes	6	2	0	0–100
Infant formula, soy-based, powdered	2	0	–	–
Sweet potato, apple, and spinach, pouch	3	0	–	–
Apple and sweet potato with cinnamon, pouch	3	0	–	–
Organic pears and spinach, pouch	3	0	–	–
Banana and blueberry, pouch	3	0	–	–
Pumpkin, banana, papaya, and cardamom, bowl	8	0	–	–
Cereal, rice, dry	5	2	0	0–60
Macaroni and cheese with vegetables	27	10	0	0–130
Turkey, quinoa, apple, and sweet potato, pouch	3	1	–	0–88
Cereal, mixed, dry, prepared with water	27	1	–	0–88
Pear, blueberry, apple, and avocado, pouch	3	0	–	–
Apple, spinach, and avocado, bowl/pouch	3	1	–	0–110
Pear, mango, avocado, pouch	1	0	–	–

Table 5-16. Nickel Detections in Baby Food from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS), 2019–2020

TDS food name	Number of analyses	Number of detects	Median (µg/kg)	Range (µg/kg)
Mango, yellow zucchini, corn, and turmeric, pouch	8	1	0	0–43
Organic yogurt, apple, pumpkin, cinnamon, and quinoa, pouch	3	0	–	–
Ravioli, cheese-filled, with tomato sauce	3	0	–	–
Mango, pouch	3	0	–	–
Mango, glass jar	3	0	–	–
Banana, blackberry, and blueberry, plastic jar	3	0	–	–
Sweet potato, apple, and corn, pouch	3	0	–	–
Vegetables and turkey	27	1	–	0–80
Juice, pear	27	2	0	0–120
Infant formula, milk-based, powdered	5	1	–	0–44
Cereal, rice, dry, prepared with water	3	0	–	–
Turkey and broth/gravy	27	0	–	–
Juice, grape	27	4	0	0–79
Fruit yogurt dessert	27	0	–	–
Apples with berries	27	13	0	0–400
Apples with fruit other than berries	27	7	0	0–91
Infant formula, milk-based, powdered, prepared with water	26	0	–	–
Infant formula, soy-based, powdered, prepared with water	21	4	0	0–360
Water, baby, bottled	3	0	–	–
Banana and strawberry, glass jar	3	0	–	–
Banana, apple, and pear, plastic jar	3	0	–	–
Apple, sweet potato, and pineapple, pouch	3	1	0	0–67
Mango, carrot, and turmeric, bowl	8	2	0	0–100
Juice, mixed fruit	1	0	–	–
Yogurt, peach pear	1	0	–	–

Source: FDA 2023c

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). The concentrations of nickel in drinks (48.4–319 µg/kg), legumes (149–744 µg/kg), breakfast cereals (413–485 µg/kg), soy-based foods (281–2,389 µg/kg), dried fruits (184–1,085 µg/kg), nuts (1,061–2,649 µg/kg), and chocolate (4,114–4,785 µg/kg) were measured in Belgium (Babaahmadifooladi et al. 2021). Based on these concentrations, the mean daily exposure to nickel through the consumption of different foods ranged from 0.31 to 4.70 µg/kg body weight/day in individuals aged 3–9 years, 0.13–2.00 in individuals aged 10–17 years µg/kg body weight/day, and 0.09–1.20 µg/kg body weight/day in individuals aged 18–64 years (Babaahmadifooladi et al. 2021). The exposure decreased when considering the bioaccessible fraction and dialyzable fraction (Babaahmadifooladi et al. 2021).

Many studies have measured nickel levels in cigarettes, smokeless tobacco products, and e-cigarettes. These studies are shown in Table 5-17. According to these studies, the mean concentration of nickel ranges from 2.1 to 3.9 µg/g in traditional cigarettes, 1.19–16.8 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 5-17. 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, Georgia 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 µg/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 to 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 to 35±2.5 µg/g	Mohammad et al. 2019
Shisha	27.67±5.31 µg/g	Mean of three products from stores in the UAE; mean of each product	Mohammad et al. 2019

Table 5-17. Concentrations of Nickel in Cigarettes, Electronic Cigarettes, and Smokeless Tobacco Products

Product	Concentration	Notes	Source
		ranged from 20±3.33 to 36.6±7.4 µg/g	
Mainpuri	10.6±0.34–16.8±0.46 µg/g	Range of means of 12 brands purchased in Pakistan	Arain et al. 2013, 2015
Gutkha	1.19±0.13–2.43±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±22.4–22,600±24,400 µg/L	Range of means of five commercial brands in the United States; range across the 48 samples was 13.7–72,700 µg/L; medians for each brand ranged from 58.1 to 15,400 µg/L	Hess et al. 2017
Aerosols	490–190,000 nickel-containing particles per 10 puffs	Five brands were studied; two brands were not able to give accurate particle counts; mean particle size ranged from 55±17 to 138±23	Pappas et al. 2020
Vapor	0.11±0.06–0.29±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. 2014

[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

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). A summary of recent biota monitoring data from the WQP are presented in Table 5-18. The *Bivalvia* and *Polychaeta* samples collected in 2021 with maximum values an order of magnitude higher than typically reported for other species were collected from an oceanic dredge near the Virginia Beach, Virginia coastline (WQP 2024).

Table 5-18. Summary of Nickel (µg/kg) Measured in Biota Samples Across the United States

Year	Species	Mean	Maximum	Number of samples	Percent detected
2018		433	4,650	250	8.0%
	Ictalurus punctatus	2,410	4,650	27	7.4%
	Lepomis megalotis	467	1,240	3	100%
	Ameiurus natalis	367	611	3	67%
	Micropterus dolomieu	260	260	6	17%
	Pomoxis nigromaculatus	243	243	7	14%
	Species with the five highest average detections reported; also detected in *Micropterus salmoides*, *Morone saxatilis*, *Cyprinus carpio*, and *Oncorhynchus mykiss*				
2019		315	2,800	266	21%
	Polychaeta	1,660	2,800	3	100%
	Salvelinus confluentus	1,170	1,170	8	13%
	Amia calva	685	720	7	29%
	Bivalvia	680	1,400	3	100%
	Richardsonius balteatus	588	1,540	16	25%
	Species with the five highest average detections reported; also detected in *Ictalurus furcatus, Hybognathus nuchalis, Lepomis cyanellus, Ptychocheilus oregonensis, A. natalis, Lepomis macrochirus, M. salmoides, Catostomus commersonii, Oncorhynchus nerka, Semotilus atromaculatus, C. carpio, Mylocheilus caurinus, Catostomus macrocheilus*, and *L. megalotis*				
2020		733	24,000	248	54%
	Taxon unknown	7,090	24,000	13	85%
	O. mykiss	510	3,010	13	54%
	Micropterus punctulatus	326	393	9	33%
	Pylodictis olivaris	287	373	7	29%
	M. salmoides	206	378	20	75%
	Species with the five highest average detections reported; also detected in *I. punctatus, Sciaenops ocellatus, P. nigromaculatus, Esox niger, I. furcatus, M. saxatilis, Lepomis microlophus, A. calva, L. macrochirus, Oncorhynchus clarkia, Morone chrysops, Catostomus Catostomus, C. macrocheilus, M. caurinus*, and *P. oregonensis*				
2021		1,300	17,300	145	91%
	Bivalvia	7,610	17,300	8	100%
	Polychaeta	7,445	14,500	8	100%
	Taxon unknown	–	4,800	1	100%
	P. olivaris	–	2,000	1	100%
	Sander vitreus	–	2,000	1	100%
	Species with the five highest average detections reported; also detected in *Vertebrata, A. calva, I. furcatus, M. salmoides, L. microlophus, I. punctatus, P. nigromaculatus, M. saxatilis,*				

Table 5-18. Summary of Nickel (µg/kg) Measured in Biota Samples Across the United States

Year	Species	Mean	Maximum	Number of samples	Percent detected
	L. macrochirus, Lepomis auratus, E. niger, M. punctulatus, Coregonus clupeaformis, A. natalis, M. dolomieu, and *C. commersonii*				
2022		952	4,610	52	88%
	C. commersonii x Catostomus latipinnis	1,820	2,310	2	100%
	Salmo trutta	1,680	2,660	2	100%
	C. latipinnis	1,490	4,610	9	100%
	Pantosteus discobolus	1,270	2,090	7	100%
	C. commersonii x Catostomus discobolus	–	1,260	1	100%
	Species with the five highest average detections reported; also detected in *C. commersonii, O. mykiss, M. salmoides, I. punctatus, M. dolomieu, L. microlophus, P. nigromaculatus,* and *A. calva*				
2023		515	1,080	8	100%
	P. discobolus	766	1,080	4	100%
	C. commersonii	–	510	1	100%
	S. trutta	213	311	2	100%
	O. mykiss	–	122	1	100%

Source: WQP 2024

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, water, and food.

Table 5-19 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 (1.22 µg/g creatinine).

Table 5-19. Geometric Mean and Selected Percentiles of Urinary Nickel for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles				Sample size
			50th	75th	90th	95th	
Urinary nickel (µg/L)							
Total	2017–2018	1.11 (1.03–1.20)	1.16	1.95	3.03	4.23	2,791
Age group							
3–5 years	2017–2018	1.36 (1.17–1.56)		1.50	2.55	4.19 5.59	399
6–11 years	2017–2018	1.55 (1.37–1.76)		1.70	2.54	4.23 5.02	328
12–19 years	2017–2018	1.30 (1.20–1.40)	1.30	2.30	3.57	4.17	362
≥20 years	2017–2018	1.04 (0.953–1.14)	1.07	1.75	2.82	3.95	1,702
Sex							
Males	2017–2018	1.14 (1.04–1.25)	1.19	1.89	3.00	4.31	1,376
Females	2017–2018	1.09 (0.97–1.22)	1.12	2.00	3.08	4.15	1,415
Race/ethnicity							
Mexican American	2017–2018	1.15 (1.05–1.26)	1.17	2.08	3.06	3.85	434
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
All Hispanic	2017–2018	1.13 (1.02–1.24)	1.14		2.01	3.02 3.98	675
Non-Hispanic Asian	2017–2018	1.14 (0.949–1.38)	1.22	1.97	3.39	4.56	362
Urinary nickel (creatinine corrected) (µg/g creatinine)							
Total	2017–2018	1.22 (1.15–1.30)			1.20	1.88 2.87 3.84	2,789
Age group							
3-5 years	2017–2018	2.81 (2.58–3.07)			2.71	4.07 6.29 7.79	399
6-11 years	2017–2018	2.17 (1.99–2.36)			2.03	3.15 4.81 6.08	327
12–19 years	2017–2018	1.17 (1.07–1.28)			1.17	1.75 2.73 3.03	362
≥20 years	2017–2018	1.11 (1.04–1.19)			1.10	1.69 2.53 3.23	1,701
Sex							
Males	2017–2018	1.06 (0.991–1.14)			1.04	1.60 2.61 3.59	1,375
Females	2017–2018	1.40 (1.30–1.51)			1.38	2.17 3.08 4.04	1,414
Race/ethnicity							
Mexican American	2017–2018	1.24 (1.16–1.33)			1.16	1.91 2.75 3.65	432

Table 5-19. Geometric Mean and Selected Percentiles of Urinary Nickel for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles				Sample size
			50th	75th	90th	95th	
Non-Hispanic White	2017–2018	1.25 (1.14–1.37)	1.22	1.94	2.90	3.84	908
Non-Hispanic Black	2017–2018	1.01 (0.937–1.09)	0.979	1.65	2.53	3.05	637
All Hispanic	2017–2018	1.22 (1.14–1.30)	1.14	1.80	2.73	3.78	673
Non-Hispanic Asian	2017–2018	1.50 (1.25–1.80)	1.57	2.41	3.66	5.51	362

CI = confidence interval

Source: CDC 2024

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 5-15). The Tolerable Upper Intake Level for nickel by life stage group is shown in Table 5-20. More recently, the European Food Safety Authority (EFSA) derived a tolerable daily intake of 13 µg/kg body weight/day (EFSA 2020).

Table 5-20. Tolerable Upper Intake Levels for Nickel

Life stage group	UL (µg/day)
0–12 months old	ND[a]
1–3 years old	200
4–8 years old	300
9–13 years old	600
14–18 years old	1,000
≥19 years old	1,000
Pregnant females, 14–18 years old	1,000
Pregnant females, 19–50 years old	1,000
Lactating females, 14–18 years old	1,000
Lactating females, 19–50 years old	1,000

[a]Data are insufficient to determine a UL.

ND = not determined; UL = Tolerable Upper Intake Level

Source: Institute of Medicine 2001

Daily nickel intake calculations using the most recent Total Diet Study results (reported in Tables 5-15 and 5-16) were not available. Using data for the 1991–1997 Total Diet Study and the 1988–1994 NHANES, the Institute of Medicine (2001) estimated that the nickel intake from food for the general population is <0.5 mg/day and that supplements provide 9.6–15 µg/day. 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.

More recent dietary intake estimates are available from data outside of the United States, which are presented in Table 5-21. EFSA published daily intake estimates as part of their comprehensive risk assessment of nickel in food and drinking water (EFSA 2020). These estimates considered multiple market studies and dietary surveys within the European Union and are expected to be comparable to dietary exposure in the United States. Dietary exposure estimates based on consumption of cucumbers and bell peppers in Iran are expected to be comparable to expected exposures in the United States based on similar nickel contents of the produce. The mean concentrations of nickel measured in cucumbers and bell peppers in Iran were 0.18 and 0.08 µg/g, respectively (Khoshgoftarmanesh et al. 2009), which are comparable to those for cucumbers (120 µg/kg or 0.120 µg/g) and raw sweet green peppers (67 µg/kg or 0.067 µg/g) in the U.S. Total Diet Study (FDA 2023c). Nickel intake was estimated from measured concentrations in products from the Belgian marked; the potential exposure decreased when considering the bioaccessible fraction and dialyzable fraction (Babaahmadifooladi et al. 2021). 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 (<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).

Table 5-21. Nickel Dietary Intake Estimates from Outside of the United States

Life stage group	Dietary exposure (µg/kg body weight/day)	Notes	Reference
<12 months old	4.40–6.14	Median lower bound and upper bound; based on data from the European market	EFSA 2020
≥12–<36 months old	8.52–10.1		
≥36 months–<10 years old	7.05–8.16		
≥10–<18 years old	3.58–4.27		
≥18–<65 years old	2.90–3.41		

Table 5-21. Nickel Dietary Intake Estimates from Outside of the United States

Life stage group	Dietary exposure (µg/kg body weight/day)	Notes	Reference
≥65–<75 years old	2.51–2.99		
≥75 years old	3.05–3.55		
Children	0.06–0.17	Based on intake from cucumbers and bell peppers in Iran; 0.07–0.24 µg/kg body weight/day average exposure	Khoshgoftarmanesh et al. 2009
≥55 years old	0.03–0.19		
3–9 years old	0.31–4.70	Based on drinks, legumes, breakfast cereals, soy-based foods, dried fruits, nuts, and chocolate from the Belgian market	Babaahmadifooladi et al. 2021
10–17 years old	0.13–2.00		
18–64 years old	0.09–1.20		
Not specified	12.2±8.41	Exposure from rice grown in soil naturally enriched in nickel	Li et al. 2020a
Not specified	0.84±0.40	Exposure from wheat grown in soil naturally enriched in nickel	

There is evidence that stainless steel pots and utensils may release nickel into acid solution (IARC 1990). 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. 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). Another study found that nickel leaching did not correlate with the nickel content of the stainless steel, but reduced leaching was observed when there was an increased chromium oxide layer on the product, which helps prevent corrosion (Kamerud et al. 2013). The initial nickel content of the tomato sauce tested prior to cooking was 90–244 µg/kg; an average of 698 µg/kg nickel was reported after the 10th 6-hour cooking cycle in stainless steel cookware. This is equivalent to 88 µg nickel per 126 g serving of tomato, which is below the ULs reported in Table 5-16 (Kamerud et al. 2013). A standardized citric acidic leaching study of several grades of stainless steel (204, 201, 316L, 304, and LDX 2101) showed decreased nickel release in tests up to 240 hours heating citric acid at 40°C after the initial 2-hour trial heating citric acid at 70°C (Hedberg et al. 2014). None of the products released nickel in excess of its corresponding release limit set by the

Council of Europe (0.14 µg/cm^2). 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 1990). 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. These studies indicate that while the general population is expected to be exposed to nickel in food, dietary exposure may slightly increase if an individual uses stainless steel cookware to prepare acidic foods for prolonged cook times.

Nickel is a common allergen, and the general population may be exposed to nickel in jewelry. The European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) has set allergy protective thresholds for nickel release at 0.35 µg/cm^2/week for piercing posts and 0.88 µg/cm^2/week for other items in direct and prolonged contact with the skin (Uter and Wolter 2018). 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, California. 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. After being immersed in artificial sweat for a week, nickel release was detected in 79 of the 96 jewelry samples at a rate ranging from 0.01 to 598 µg/cm^2/week (Hamann et al. 2015). The prevalence of samples that exceeded the REACH criteria was not discussed; however, data for five samples exceeding the criteria (1.6–598 µg/cm^2/week) were reported by the study authors (Hamann et al. 2015).

Children may be exposed to nickel in jewelry, clothing buckles and fasteners, and technology (Tuchman et al. 2015). Jensen et al. (2014) described children's toys as another potential source of nickel exposure. To evaluate nickel release from children's toys, 63 toys were purchased from toy and thrift shops in the United States and an online retailer and 149 toys from 8 toy stores in Denmark. Of the toys in the United States, 50.8% tested positive for nickel release with a dimethylglyoxime (DMG) screening test compared to 27.5% of the toys from Denmark (Jensen et al. 2014). This study did not quantify nickel release from

the toys and limited dermal contact considerations were discussed. Other sources of nickel exposure in children are food consumption and accidental ingestion of soil containing nickel. Nickel concentrations in baby food in the United States ranged from 0 (not detected) to 450 µg/kg (FDA 2023c). 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 was 1.12 µg/kg body weight for 6-month-old children, 2.76 µg/kg body weight for 1-year-old children, and 3.13 µg/kg body weight for 2-year-old children (Pereira et al. 2020). Wittsiepe et al. (2009) estimated that the daily dietary intake rate for 4–7-year-old children in Germany was 12–560 µg/day based on concentrations in food samples or 35–1,050 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 body weight/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 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 study 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 were 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 0.0051–10 μg/cm^2/week and from dental alloys in the range of 0.0046–0.024 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 that 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 handwashing (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 concentrations of nickel in blood were 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 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, Kulkami 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 to 769.8 ng/m^3 and decreased to levels similar to background concentrations at 600 meters away (Han et al. 2020). Han et al. (2020) estimated that the cancer risks due to inhalation of nickel were 0.21–14 cases per million at the fence line, 0.03–1.1 cases per million in near neighborhoods, and 0.21–0.47 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 and ash mixture), the average nickel concentration among 17 commercially available brands is 2.28 µg/g. Using artificial saliva, the study authors found that 20–46% 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 intakes were 10.6–25.9 µg/10 g of gutkha (chewing tobacco mixture), 75.6–141 µg/10 g of moist snuff (finely ground or pulverized tobacco leaves), and 103–173 µg/10 g of mainpuri (chewing tobacco mixture). Whole blood and scalp hair nickel concentrations of people who do not consume smokeless tobacco products were 2–3 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 5–6 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

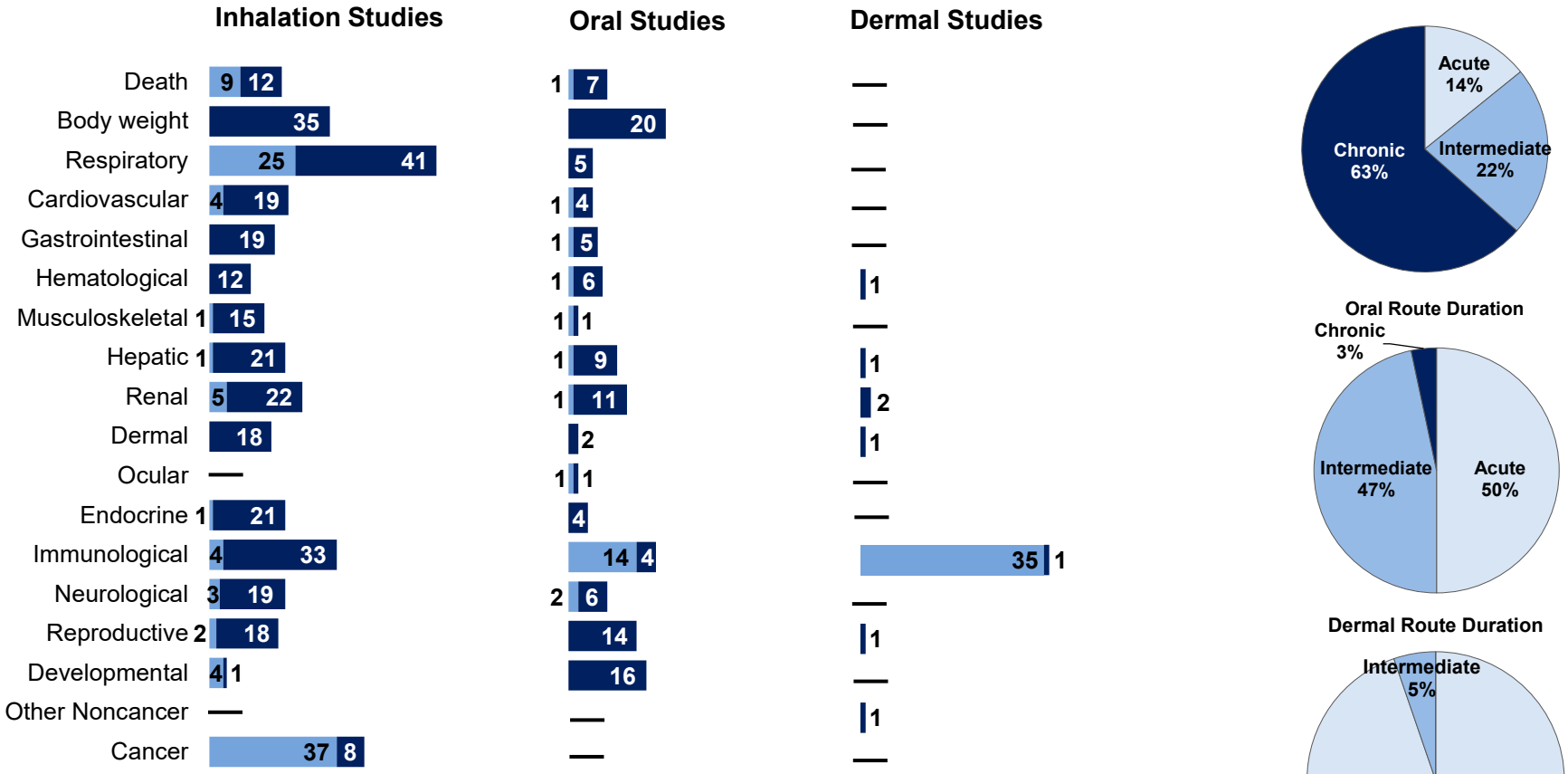
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to nickel that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of nickel. The number of human and animal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

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.

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

Potential body weighty, respiratory, and renal effects were the most studied endpoints
The majority of the studies examined oral 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.

Acute-Duration MRLs. The acute-duration inhalation animal database was adequate for the derivation of an acute-inhalation MRL. No human studies adequately reporting exposure levels following acute-duration inhalation exposure were identified. A number of studies in animals evaluated the respiratory system, identifying lung inflammation and nasal olfactory epithelium atrophy as sensitive endpoints of nickel toxicity. Studies have also examined the immunotoxicity of nickel, finding alterations in immune function and histological alterations in lymph nodes. Studies evaluating the lung following exposure to lower concentrations of nickel in rats would be useful to establish a concentration-response relationship. Few studies in humans examining oral exposure to nickel have reported allergic dermatitis; however, these studies examined nickel-sensitized individuals and the small sample sizes do not allow for adequate statistical extrapolation to a larger population. 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 suggested reproductive and developmental toxicity following oral exposure; however, serious developmental effects were observed at the lowest doses tested. 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-duration 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. The intermediate-duration oral database was not adequate for the derivation of an oral MRL. Several studies reported developmental and reproductive effects in rats and mice. However, serious health effects were observed at some of the lowest doses tested. 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 insufficient for the derivation of a chronic-duration inhalation MRL. Several chronic-duration exposures studies in workers indicate that the respiratory system is a sensitive target of nickel toxicity. Animal studies also evaluated the chronic toxicity of several nickel compounds. These studies clearly identified the lungs as sensitive targets of toxicity. Derivation of an MRL from the available studies resulted in a value that is higher than the intermediate-duration inhalation MRL. Additional chronic-duration studies would be useful for

establishing a concentration-response between nickel and lung toxicity. Studies evaluating multiple nickel compounds would also be useful for comparing toxicity across compounds. The chronic-duration oral database was not adequate for the derivation of an oral MRL. No studies in humans examined chronic-duration oral exposure to nickel. A limited number of studies in animals suggest that chronic-duration exposure results in body weight changes in rats; however, this is not likely a direct effect of nickel. Additional studies would be useful to identify the sensitive endpoints of nickel toxicity.

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. Numerous studies have evaluated the immunotoxicity of nickel in humans following dermal exposure, generally by use of patch testing in individuals with contact dermatitis or studies designed to assess the occurrence of nickel sensitivity in the general population. Animal studies demonstrated that nickel can induce immunological effects in nonsensitized individuals. Alterations in nonspecific immunity (e.g., macrophage activity) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) have been observed in animals following inhalation or oral exposure. A dermal exposure study examined the exposure-response relationship for nickel sensitization in mice. Studies designed to assess the dose-response relationship for contact dermatitis and dermatitis following oral exposure are needed. Additionally, studies that examine whether tolerance to nickel can develop and assess cross sensitization of nickel with other metals would also be useful.

Neurological. There are limited data on the neurotoxicity of nickel in humans and animals. No histological alterations were observed in the central nervous system following inhalation or oral exposure of rats and mice. Although histological damage to the nasal olfactory epithelium was observed in animals following inhalation exposure to nickel sulfate or nickel subsulfide, functional changes were not noted. Neurological signs (lethargy, hypoactivity, ataxia, prostration) were observed in dying rats treated with nickel for 3 months and in rats exposed for 3 days; these effects were probably associated with overall toxicity. Impaired performance in spatial memory tests have been reported in animals exposed to nickel chloride. No animal dermal exposure studies examined neurological endpoints. 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 are limited to a few studies of women working at a nickel hydrometallurgy refining plant; interpretation of the study results is limited by conflicting results. Conflicting results were also observed in oral exposure animal studies examining male reproductive toxicity. Several of the studies finding effects were poorly reported or had methodological deficiencies, which limits the interpretation of results and comparisons with studies finding no reproductive effects. Reproductive effects have also been examined in inhalation studies, with one study reporting alterations in sperm parameters following intermediate-duration exposure to nickel oxide. Additional studies, particularly by the oral route, are needed to establish dose response relationships for male reproductive endpoints (e.g., sperm parameters and fertility).

Developmental. There are limited data on the potential developmental toxicity of nickel in humans. In general, the studies of women working at a nickel hydrometallurgy refining plant did not find associations with adverse birth outcomes. Animal studies have reported decreased fetal body weight following inhalation exposure to nickel oxide and fetal loss, decreased survival, and skeletal abnormalities following oral exposure to soluble nickel compounds. Developmental toxicity studies utilizing several dose levels would provide useful information in establishing the dose-response relationships for nickel, especially testing lower doses than are 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, nickel sensitivity following oral exposure, or dermal exposure. As nickel exposure levels in the occupational environments have been reduced, continued health monitoring of populations occupationally exposed to nickel would be useful to determine if more subtle adverse health effects occur in humans at lower concentrations. Continued monitoring of nickel sensitization in the general population to identify trends and differences in exposure risk behaviors (such as increased popularity of body piercing with nickel-containing jewelry) 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 (Bell et al. 2010; Ebisu and Bell 2012; Pedersen et al. 2016; Vaktskjold et al. 2008a) 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. Nickel is a naturally occurring component of the diet and can be detected in hair, blood, urine, and feces. Positive qualitative correlations have been found between air concentrations of nickel and nickel levels in the feces and urine 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.

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, gastrointestinal tract, and skin. Food greatly decreases the absorption of nickel from the gastrointestinal tract. Following absorption from the lungs and the gastrointestinal tract, nickel is excreted in the urine. Increased levels of nickel were found in the lungs, nasal septum, liver, and kidneys of workers inhaling nickel. 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. 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. 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. The toxicokinetics of both inhaled and ingested nickel have been examined in several species of animals (rats, mice, dogs, hamsters). Dermal studies have been performed in guinea pigs and rabbits. 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, 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. 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. 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 United States are reported to the TRI. However, only certain facilities are required to report, and this is not an exhaustive list.

Environmental Fate. Nickel is an element and is therefore cycled through biogeochemical processes in the environment. In assessing human exposure, the form of nickel and its bioavailability must be considered. This information is site specific. There are some data available on the forms of nickel present in air, water, sediment, and soil (Cahill 1989; Fuichtjohann et al. 2001; Galbreath 2003; Poulton et al. 1988; Rai and Zachara 1984; Sadiq and Enfield 1984a; Schroeder et al. 1987; Wang and Biswas 2000). Detailed information on the environmental transformations that may occur, transformation rates, and conditions that facilitate these transformations would be helpful in assessing the environmental fate of nickel.

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. Factors influencing the bioavailability of nickel from water and sediment/soil have been elucidated (Burton et al. 2019; Hale et al. 2017; Huntsman et al. 2019; Mandal et al. 2002; Wang et al. 2019). Additional studies quantifying the oral bioavailability of nickel in soil would provide information on the potential of such environmental exposure.

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; 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). Nickel does not appear to biomagnify in food webs, but quantitative data are 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 United States are monitored by the FDA (FDA 2023c), and nickel levels in air and water are monitored by EPA (EPA 2024; WQP 2024). 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 exposed populations living in the vicinity of hazardous waste sites. Also, few data are available regarding nickel levels at contaminated or hazardous waste sites (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 United States. More recent information on dietary intake in the United States 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 al. 1999), including data for various age ranges of children (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 are not specific 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

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database, which tracks projects funded by NIH.

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 2006
	Nickel subsulfide	Not evaluated	IRIS 2002
WHO	Air quality guidelines		WHO 2000
	Incremental risk for 1 µg/m^3 nickel in air	3.8X10^{-4}	
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	Nickel		
	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	
	Lifetime health advisory	0.1 mg/L	
	National primary drinking water regulations	Not listed	EPA 2009
	RfD		
	Nickel, soluble salts	0.02 mg/kg/day	IRIS 1994
	Nickel refinery dust	Not evaluated	IRIS 2006
	Nickel subsulfide	Not evaluated	IRIS 2002
WHO	Guideline value		WHO 2022
	Nickel	0.07 mg/L	
FDA	Substances added to food (formerly EAFUS)		
	Nickel	GRAS	FDA 2023a
		Permitted as a component of	FDA 2023b

Table 7-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
		paper/paperboard in contact with dry food	
	Allowable level of nickel in bottled water	0.1 mg/L	FDA 2022
	Cancer		
HHS	Carcinogenicity classification		NTP 2021
	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[a]	IRIS 2006
	Nickel subsulfide	A[a]	IRIS 2002
	Inhalation unit risk		
	Nickel refinery dust	0.00024 $(\mu g/m^3)^{-1}$	IRIS 2006
	Nickel subsulfide	0.00048 $(\mu g/m^3)^{-1}$	IRIS 2002
IARC	Carcinogenicity classification		
	Nickel compounds	Group 1[c]	IARC 2012
	Nickel, metallic	Group 2B[d]	IARC 1990
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, construction, and shipyards		OSHA 2021a, 2021b, 2021c
	Nickel, metal, and insoluble compounds (as Ni)	1 mg/m^3	
	Nickel, soluble compounds (as Ni)	1 mg/m^3	
NIOSH	REL (up to 10-hour TWA)		
	Nickel metal and other compounds (as Ni)	0.015 mg/m^3 [e]	NIOSH 2019
	Emergency Criteria		
NIOSH	IDLH		
	Nickel metal and other compounds (as Ni)	10 mg/m^3 [e]	NIOSH 2019
EPA	AEGLS-air[f]	No data	EPA 2018b
DOE	PACs-air[h]		DOE 2018a
	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	

Table 7-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
	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]A: human carcinogen.
[b]B2: probable human carcinogen.
[c]Group 1: carcinogenic to humans.
[d]Group 2B: possibly carcinogenic to humans
[e]Potential occupational carcinogen.
[f]Definitions of AEGL terminology are available from EPA (2018c).
[g]Not recommended due to insufficient data.
[h]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; 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 = U.S. Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; 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 LEVEL 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. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious 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.

APPENDIX A

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 S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: $1x10^{-4}$ mg Ni/m^3
Critical Effect: Bronchiole epithelial degeneration/hyperplasia
Reference: Efremenko et al. 2017a, 2017b
Point of Departure: LOAEL of 0.2244 mg Ni/m^3 ($LOAEL_{HEC}$ of 0.0403 mg Ni/m^3)
Uncertainty Factor: 300
LSE Graph Key: 3
Species: Rat

MRL Summary: An acute-duration inhalation MRL of $1x10^{-4}$ mg Ni/m^3 was derived for nickel based on bronchiole epithelial degeneration/hyperplasia in male rats exposed to 0.2244 mg Ni/m^3 as nickel sulfate hexahydrate 6 hours/day for 5 days (Efremenko et al. 2017a, 2017b). The MRL is based on a LOAEL of 0.2244 mg Ni/m^3 adjusted to continuous duration exposure and converted to a human equivalent concentration (HEC) of 0.0403 mg Ni/m^3 and divided by a total uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: Several case studies in workers who inhaled large amounts of nickel dust or fumes indicate that 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 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).

The acute inhalation toxicity of nickel sulfate, nickel subsulfide, nickel oxide, and nickel chloride has been evaluated in rats and/or mice. The available studies suggest that the respiratory tract and the immune system are the most sensitive targets of nickel toxicity; a summary of the NOAEL and LOAEL values for these endpoints is presented in Table A-1.

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

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Respiratory					
Rat (M)	5 days 6 hours/day		0.2244	Bronchiole epithelial degeneration/ hyperplasia	Efremenko et al. 2017a, 2017b (nickel sulfate hexahydrate)
Rat (M)	5 days 6 hours/day		0.44	Peribronchiolar/ perivascular inflammation and >250% increase of LDH in BALF	Efremenko et al. 2014 (nickel subsulfide)

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

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Rat (B)	12 days in 16-day period 6 hours/day		0.44	Chronic lung inflammation; olfactory epithelium atrophy	NTP 1996b (nickel subsulfide)
Rat (B)	7 days 6 hours/day		0.44	Alveolitis	Benson et al. 1995b (nickel subsulfide)
Rat (B)	12 days in 16-day period 6 hours/day		0.7 (SLOAEL)	Labored breathing, 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; olfactory epithelium atrophy	NTP 1996c (nickel sulfate hexahydrate)
Mouse (B)	12 days in 16-day period 6 hours/day	0.44	0.88	Atrophy of olfactory epithelium	NTP 1996b (nickel subsulfide)
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	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 (F)	2 hours	0.37	0.5	Increased susceptibility to Streptococcal infection	Adkins et al. 1979 (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)

[a]All concentrations are reported in mg Ni/m^3; concentrations reported in terms of the nickel compound were converted by multiplying the concentration by a ratio of the nickel compound molecular weight to nickel molecular weight.

B = both males and females; BALF = bronchoalveolar lavage fluid; F = females; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

The respiratory tract effects observed in rats and/or mice include inflammation (peribronchiolar/perivascular inflammation, chronic lung inflammation, and alveolitis), bronchiole epithelial degeneration/hyperplasia, alveolar macrophage hyperplasia, labored breathing, and atrophy of the olfactory epithelium. Rats appear to be more sensitive than mice. In the available acute-duration database, the lower respiratory and nasal effects occur at similar concentrations. For a given effect, comparisons across studies reporting respiratory effects suggest differences in the toxicity of nickel compounds, which are likely due to differences in solubility and bioavailability. For example, the lowest LOAELs for lung inflammation in rats for the three nickel compounds tested by NTP were 0.44 mg Ni/m^3 for nickel subsulfide (NTP 1996b), 0.7 mg Ni/m^3 for nickel sulfate (NTP 1996c), and 7.9 mg Ni/m^3 for nickel oxide (NTP 1996a). The 0.7 mg Ni/m^3 concentration was considered a serious LOAEL for nickel sulfate because labored breathing was also observed at this concentration; labored breathing was not observed in the rats exposed to nickel subsulfide until concentrations of 3.65 mg Ni/m^3. It is noted that a decrease in body weight of >20% was also observed in rats exposed to 0.7 mg Ni/m^3 as nickel sulfate (NTP 1996c). Efremenko et al. (2017a, 2017b) did not report labored breathing in rats exposed to a lower nickel sulfate concentration (0.2244 mg Ni/m^3). The lowest LOAEL for respiratory effects is 0.2244 mg Ni/m^3 for bronchiole epithelial degeneration/hyperplasia identified in rats exposed to nickel sulfate hexahydrate 6 hours/day for 5 days (Efremenko et al. 2017a, 2017b).

Immunological effects observed in mice exposed to inhaled nickel include impaired immune function and lymphoid hyperplasia in bronchial lymph nodes. Immunological effects were observed at concentrations of ≥0.25 mg Ni/m^3 as nickel chloride (Adkins et al. 1979; Graham et al. 1978).

The lowest LOAEL for immunological effects (0.25 mg Ni/m^3) is similar to the LOAEL of 0.2244 mg Ni/m^3 for respiratory effects; the lower respiratory tract was selected as the critical target because it has the lowest LOAEL and is well supported by other acute-duration inhalation studies with nickel sulfate and other nickel compounds.

Selection of the Principal Study: The Efremenko et al. (2017a, 2017b) study of nickel sulfate was selected as the principal study because it identified the lowest LOAEL of 0.2244 mg Ni/m^3 for bronchiole epithelial degeneration/hyperplasia.

Summary of the Principal Study:

Efremenko AY, Campbell JL, Dodd DE, et al. 2017a. Time- and concentration-dependent genomic responses of the rat airway to inhaled nickel sulfate. Environ Mol Mutagen 58(8):607-618. https://doi.org/10.1002/em.22139. https://www.ncbi.nlm.nih.gov/pubmed/28862355.

Efremenko AY, Campbell JL, Dodd DE, et al. 2017b. Supplemental material: Time- and concentration-dependent genomic responses of the rat airway to inhaled nickel sulfate. Environ Mol Mutagen 58(8):607-618. https://doi.org/10.1002/em.22139. https://www.ncbi.nlm.nih.gov/pubmed/28862355.

Groups of five male Fischer 344 rats were whole-body exposed to analytical concentrations of 0.002 (control group), 0.128, 0.246, 0.496, or 1.020 mg/m^3 nickel sulfate hexahydrate 6 hours/day for 5 days (0.0004, 0.0282, 0.0541, 0.109, and 0.2244 mg Ni/m^3) (Efremenko et al. 2017a, 2017b). The particle size distributions (average mass median aerodynamic diameter, MMAD) and geometric standard deviations were 0.82 µm (1.41), 0.88 µm (1.36), 1.00 µm (1.40), and 1.09 µm (1.42) for the 0.0282, 0.0541, 0.109, and 0.2244 mg Ni/m^3 groups, respectively. Animals were observed for overt clinical signs daily and body weight was measured at termination. At termination, groups of five animals in the control and 0.2244 mg Ni/m^3 groups underwent BALF cytology and histopathology analysis (animals were sacrificed within 24 hours of exposure termination); groups of five animals in all concentration groups underwent BALF analysis. Additional groups of eight rats underwent gene expression analysis.

Significant increases in total protein and lactate dehydrogenase were observed in the BALF at 0.109 and 0.2244 mg Ni/m^3; alkaline phosphatase levels were increased at all nickel concentrations. The toxicological significance of these findings is not known. Increases in lymphocytes and neutrophils were also increased in the BALF at 0.2244 mg Ni/m^3. Lung histopathology was only evaluated in the 0 and 0.2244 mg Ni/m^3 groups. An increase in bronchiole epithelial degeneration/hyperplasia was observed; the lesion was observed in five of five rats, as compared to zero of five controls, and the severity was graded as mild.

Selection of the Point of Departure for the MRL: The LOAEL of 0.2244 mg Ni/m^3 as nickel sulfate for bronchiole epithelial degeneration/hyperplasia in rats (Efremenko et al. 2017a, 2017b) was selected as the basis of the acute-duration inhalation MRL for nickel.

Benchmark dose (BMD) modeling was not conducted because histopathological examinations were only conducted in controls and rats exposed to 0.2244 mg Ni/m^3.

Adjustment for Intermittent Exposure: The LOAEL of 0.2244 mg Ni/m^3 was adjusted to continuous exposure using the following equation:

$$BMCL_{ADJ} = 0.2244\ mg\ Ni/m^3 \times \frac{6\ hours}{24\ hours} = 0.0561\ mg\ Ni/m^3$$

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

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

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 for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the thoracic region (combined tracheobronchial and pulmonary regions) is used to extrapolate deposited doses in rats to deposited doses in humans. The thoracic region was used since lesions were observed in bronchiolar and pulmonary tissues. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD, version 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-2. For breathing frequency and tidal volume parameter values in humans, a time-weighted average (TWA) of default values in males (ICRP 1994) was calculated based on the following activity pattern over a 24-hour exposure period: 8 hours sleeping (nasal breathing) + 8 hours at rest/sitting (nasal breathing) + 8 hours of light activity (oronasal-mouth breather). Default values in males were selected to be health protective, as males are predicted to have higher deposition fractions than females.

Table A-2. MPPD Model (Version 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	4 mL (default)	3,300 mL (default)
Upper respiratory tract	0.42 mL (default)	50 mL (default)
Inhalant properties		
Density[a]	2.07 g/cm^3	2.07 g/cm^3
Diameter, MMAD[b]	1.09 µm	1.09 µm
GSD[b]	1.47	1.47
Inhalability adjustment	On	On
Exposure condition		
Aerosol concentration ($LOAEL_{ADJ}$)	0.0561 mg Ni/m^3	0.0561 mg Ni/m^3
Breathing frequency	102 breaths/minute (default)	14.7 breaths/minute (calculated TWA)[c]
Tidal volume	2.1 mL (default)	875 mL (calculated TWA)[d]
Breathing scenario	Whole body	Nasal/oronasal breather[e]
Results		
Thoracic region deposition fraction (total tracheobronchial and pulmonary deposition fraction)	0.0846	0.1758

[a]Haynes et al. 2015, nickel sulfate.
[b]Efremenko et al. 2017a, 2017b.
[c]Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).
[d]Tidal volume is 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).
[e]Breathing scenario is 8 hours of sleep (nasal breathing, on back), 8 hours at rest (nasal breathing, upright), and 8 hours light activity (oronasal-mouth breathing, upright).

GSD = geometric standard deviation; $LOAEL_{ADJ}$ = lowest-observed-adverse-effect level adjusted for continuous exposure; MMAD = mass median aerodynamic diameter; MPPD = Multiple-Path Particle Dosimetry; TWA = time-weighted average

The deposition fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $LOAEL_{HEC}$. Table A-3 lists the values used within the equation and the source of these values. The exposure days (n) are 5 days to represent 24 hours of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure.

$$BMCL_{HEC} = 0.0561\ mg\ Ni/m^3 \times \frac{0.20\frac{m^3}{day}}{20\frac{m^3}{day}} \times \frac{0.0846}{0.1758} \times \frac{\frac{1-(1-0.289\ day^{-1})^5}{1-(1-0.289\ day^{-1})}}{\frac{1-(1-0.277\ day^{-1})^5}{1-(1-0.277\ day^{-1})}} \times \frac{1}{1.04} \times \frac{54\ m^2}{0.34\ m^2}$$

$$LOAEL_{HEC} = 0.0403\ mg\ Ni/m^3$$

Table A-3. Values Used to Calculate a Human Equivalent Concentration (HEC)

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.20 m^3/day	20 m^3/day	EPA 1994
Deposition fraction (DF)	0.0846	0.1758	Calculated using MPPD software
Clearance rate[a] (k)	0.289 day^{-1}	0.277 day^{-1}	Oller et al. 2014
Retention half-time	2.4 days	2.5 days	Oller et al. 2014
Ratio of retention half-time (RH) (to rat half-time)	1	1.04	Calculated
Thoracic surface area (SA)	0.342 m^2	54.32 m^2	EPA 1994
Exposure days (n)	5 days	5 days	Efremenko et al. 2017a, 2017b

[a]Total clearance rate = ln2/retention half-time.

HEC = human equivalent concentration; MPPD = Multiple Path Particle Dosimetry

Uncertainty Factor: The $LOAEL_{HEC}$ is divided by a total uncertainty factor of 300:

- 10 for the use of a LOAEL,
- 3 for extrapolation from rats to humans with dosimetric adjustments,
- 10 for human variability

$$Provisional\ MRL = \frac{LOAEL_{HEC}}{UFs} = \frac{0.0403\ mg\ Ni/m^3}{300}$$

$$= 1.34x10^{-4}\ mg\ Ni/m^3;\ rounded\ to\ 1x10^{-4}\ mg\ Ni/m^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a well-established target of toxicity following inhalation exposure to soluble and insoluble nickel compounds. Studies of workers exposed to nickel have reported increased respiratory symptoms, impaired lung function, and lung disease (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022). Pulmonary effects have been reported in several acute-duration studies in animals exposed to nickel sulfate, nickel subsulfide, or nickel oxide (Benson et al. 1995b; Efremenko et al. 2014, 2017a, 2017b; NTP 1996a, 1996b, 1996c).

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: $3x10^{-6}$ mg Ni/m^3
Critical Effect: Alveolitis and perivascular/peribronchiolar inflammation
Reference: Oller et al. 2023
Point of Departure: BMDL of 0.0014 mg Ni/m^3 ($BMDL_{HEC}$ of 0.0000982 mg Ni/m^3)
Uncertainty Factor: 30
LSE Graph Key: 28
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of $3x10^{-6}$ mg Ni/m^3 was derived for nickel based on alveolitis and perivascular/peribronchiolar inflammation observed in the lungs of rats exposed to ≥0.04 mg Ni/m^3 as nickel subsulfide for 6 hours/day, 5 days/week for 90 days (Oller et al. 2023). The MRL is based on a benchmark dose lower confidence limit (BMCL) of 0.0014 mg Ni/m^3 adjusted to continuous duration exposure and converted to a human equivalent concentration (HEC) of 0.0000982 mg Ni/m^3 ($9.82x10^{-5}$ mg Ni/m^3) and divided by a total uncertainty factor of 30 (3 for extrapolation from rats to humans with dosimetric adjustments 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. The available data suggest that the lower respiratory tract is the most sensitive target of toxicity following intermediate-duration inhalation exposure, with effects occurring at nickel concentrations of ≥0.04 mg Ni/m^3. A summary of the NOAEL and LOAEL values for respiratory effects is presented in Table A-4. The respiratory effects include inflammatory changes in the lungs, alveolar macrophage hyperplasia, and atrophy of the nasal olfactory epithelium. Immune effects also occur at relatively low nickel concentrations (see Table A-2); the effects include lymphoid hyperplasia in the bronchial and mediastinal lymph nodes and altered impaired immune function. Other observed effects included developmental effects (decreased fetal body weight) (Weischer et al. 1980) at 1.6 mg Ni/m^3 as nickel oxide and changes in hematological parameters (NTP 1996b; Weischer et al. 1980), which have been reported at nickel concentrations associated with lung inflammation.

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Respiratory					
Rat (M)	13 weeks 5 days/week 6 hours/day		0.04	Alveolitis and perivascular/ peribronchiolar inflammation and protein accumulation	Oller et al. 2023 (nickel subsulfide)

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Rat (M)	4 weeks 5 days/week 6 hours/day	0.06	0.11	Lung inflammation	Efremenko et al. 2014 (nickel subsulfide)
Rat (M)	4 weeks 5 days/week 6 hours/day	0.05412	0.1104	Alveolus inflammation	Efremenko et al. 2017a, 2017b (nickel sulfate)
Rat (M)	2–6 months 5 days/week 6 hours/day	0.03	0.11	Alveolitis	Benson et al. 1995a (nickel sulfate)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.06	0.11	Chronic active lung inflammation and interstitial infiltrates	NTP 1996c (nickel sulfate)
Rat (M)	13 weeks 5 days/week 6 hours/day	0.03	0.11	Alveolitis and perivascular/ peribronchiolar inflammation	Oller et al. 2023 (nickel sulfate)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.11	0.22	Chronic active lung inflammation	NTP 1996b (nickel subsulfide)
Rat (M)	3 weeks 5 days/week 6 hours/day	0.11	0.22	Alveolitis, perivascular inflammation, bronchiolar epithelial degeneration	Oller et al. 2023 (nickel sulfate)
Mouse (M)	2–6 months 5 days/week 6 hours/day	0.06	0.22	Interstitial pneumonia	Benson et al. 1995a (nickel sulfate)
Rat (B)	13weeks 5 days/week 6 hours/day	0.11	0.22	Olfactory epithelial atrophy	NTP 1996c (nickel sulfate)
Rat (B)	22 days 6 hours/day		0.44	Alveolitis, alveolar proteinosis; olfactory epithelium degeneration	Benson et al. 1995b (nickel subsulfide)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Olfactory epithelial atrophy	NTP 1996b (nickel subsulfide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Olfactory epithelial atrophy	NTP 1996a (nickel subsulfide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Chronic lung inflammation, fibrosis, and interstitial infiltrates	NTP 1996a (nickel sulfate)
Rat (M)	4 weeks 5 days/week 6 hours/day		0.5	Bronchial gland hyperplasia and squamous metaplasia	Horie et al. 1985 (nickel oxide)

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Rabbit (M)	4 months 5 days/week 6 hours/day		0.6	Interstitial inflammation and intraalveolar accumulation of macrophages	Johansson et al. 1988a, 1989 (nickel chloride)
Rat (M)	16 days 6 hours/day		0.64	Olfactory epithelial atrophy	Evans et al. 1995 (nickel sulfate)
Mouse (M)	2–6 months 5 days/week 6 hours/day		0.98	Interstitial pneumonia	Benson et al. 1995a (nickel oxide)
Rat (M)	2–6 months 5 days/week 6 hours/day	0.49	1.96	Moderate alveolitis	Benson et al. 1995a (nickel oxide)
Rat (B)	13 weeks 5 days/week 6 hours/day	2	3.9	Chronic active lung inflammation, granulomatous inflammation, and lung interstitial infiltrate	NTP 1996a (nickel oxide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	2 F 3.9 M	3.9 F 7.6 M	Perivascular lymphocytic infiltrates	NTP 1996a (nickel oxide)
Immunological					
Rat (M)	4 months continuous	0.025	0.145	Impaired response to sRBC exposure	Spiegelberg et al. 1984 (nickel oxide)
Rat (M)	4 weeks continuous	0.093	0.216	Impaired response to sRBC exposure	Spiegelberg et al. 1984 (nickel oxide)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.11	0.22	Lymphoid hyperplasia in bronchial and mediastinal lymph nodes	NTP 1996c (nickel sulfate)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Lymphoid hyperplasia in bronchial and mediastinal lymph nodes	NTP 1996b (nickel subsulfide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Bronchial lymph node hyperplasia	NTP 1996a (nickel sulfate)
Mouse (F)	65 days 5 days/week 6 hours/day		0.45	Decreased resistance to tumor challenge	Haley et al. 1990 (nickel sulfate)
Mouse (F)	65 days 5 days/week 6 hours/day		0.45	Decreased alveolar macrophage activity	Haley et al. 1990 (nickel subsulfide)
Mouse (F)	65 days 5 days/week 6 hours/day		0.47	Decreased alveolar macrophage activity	Haley et al. 1990 (nickel oxide)

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.44 F 0.88 M	0.88 F 1.83 M	Bronchial lymph node hyperplasia	NTP 1996a (nickel subsulfide)
Rat (B)	13 weeks 5 days/week 6 hours/day	2	3.9	Lymphoid hyperplasia in mediastinal lymph nodes	NTP 1996a (nickel oxide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	3.9	7.9	Bronchial lymph node hyperplasia	NTP 1996a (nickel oxide)
Rat (M)	4 weeks 5 days/week 8 hours/day		9.2	Increased production of tumor necrosis factor by alveolar macrophages	Morimoto et al. 1995 (nickel oxide)

[a]All concentrations are reported in mg Ni/m^3; concentrations reported in terms of the nickel compound were converted by multiplying the concentration by a ratio of the nickel compound molecular weight to nickel molecular weight.

B = both males and females; F = females; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; sRBC = sheep red blood cell

Studies conducted by NTP (1996a, 1996b, 1996c), Oller et al. (2023), and Benson et al. (1995a, 1995b) allow for comparisons across nickel compounds and animal species. Of the three nickel compounds tested in these studies, nickel oxide was the least toxic (Benson et al. 1995a, 1995b; NTP 1996a, 1996b, 1996c). Although the results of the NTP (1996b, 1996c) and Benson et al. (1995a, 1995b) studies suggest that lung toxicity of nickel sulfate is greater than nickel subsulfide, the Oller et al. (2023) study identified a lower LOAEL for lung effects associated with nickel subsulfide than with nickel sulfate. The NTP (1996a, 1996b, 1996c) and Benson et al. (1995a, 1995b) studies also provide suggestive evidence that rats are more sensitive than mice.

Selection of the Principal Study: The Oller et al. (2023) study of nickel subsulfide was selected as the principal study because it identified the lowest LOAEL of 0.04 mg Ni/m^3 for lung effects (alveolitis, perivascular/peribronchiolar inflammation, and protein accumulation).

Summary of the Principal Study:

Oller AR, Buxton S, March TH, et al. 2023. Comparative pulmonary and genotoxic responses to inhaled nickel subsulfide and nickel sulfate in F344 rats. J Appl Toxicol 43(5):734-751. https://doi.org/10.1002/jat.4422.

Groups of 13 male F344 rats were whole-body exposed to 0, 0.05, 0.15, or 0.6 mg/m^3 nickel subsulfide (0, 0.04, 0.11, or 0.44 mg Ni/m^3) 6 hours/day, 5 days/week for 13 weeks. Additional groups of animals (13/group) were exposed to 0 or 0.22 mg Ni/m^3 for 13 weeks followed by a 13-week observation period. Actual concentrations were 0.02, 0.06, 0.15, and 0.59 mg/m^3 nickel subsulfide (0.01, 0.04, 0.11, and 0.44 mg Ni/m^3); the particle sizes (MMAD) were 1.90 µm (geometric standard deviation [GSD] of 2.28) and 1.89 µm (2.38) for the 0.11 and 0.44 Ni/m^3 concentrations, respectively; particle size was not

determined at the control or 0.04 mg Ni/m^3 concentrations. The following parameters were used to assess toxicity: clinical signs, body weight, histopathology of the lung and lung weights (n=8/group), and evaluation of bronchoalveolar lavage fluid (BALF) (n=5/group).

No clinical signs of toxicity or alterations in terminal body weights were observed. Concentration-related increased absolute lung weights were observed at ≥0.04 mg Ni/m^3 (24, 48, and 86% at 0.04, 0.11, and 0.44 mg Ni/m^3, respectively). Histological alterations in the lungs consisted of alveolitis, protein accumulation, and perivascular/peribronchiolar inflammation at ≥0.04 mg Ni/m^3. The incidences of these lesions are presented in Table A-5. Type II cell hyperplasia was also observed at 0.44 mg Ni/m^3. Alveolar septal infiltrates, histiocytosis, and type II epithelial cell hyperplasia were observed in the 0.44 mg Ni/m^3 recovery group. BALF alterations consisted of increased LDH at 0.11 mg Ni/m^3 and increased total protein, beta-glucuronidase, RBC phagocytosis, and total nucleated cell levels at 0.22 mg Ni/m^3. No BALF alterations were observed in the recovery group.

Table A-5. Incidence of Select Lung Lesions in Rats Exposed to Nickel Subsulfide for 13 Weeks via Inhalation

Concentration (mg Ni/m^3)	Alveolitis	Perivascular/peribronchiolar inflammation	Protein accumulation
0.01 (control group)	1/8 (0.1)[a]	2/8 (0.3)[a]	0/8
0.04	7/8[b] (1.1)	7/8[b] (0.9)	8/8[b] (2.0)
0.11	7/8[b] (1.6)	8/8[b] (1.8)	8/8[b] (3.1)
0.44	8/8[b] (2.1)	8/8[b] (2.3)	8/8[b] (3.5)

[a]Average severity of lesion: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.
[b]Statistically different from control group, p<0.05 (Fischer Exact test conducted by ATSDR).

Source: Oller et al. 2023

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ of 0.0014 mg Ni/m^3 for perivascular/peribronchiolar inflammation in rats (Oller et al. 2023) was selected as the basis of the intermediate-duration inhalation MRL for nickel.

Incidence data for alveolitis and perivascular/peribronchiolar inflammation (Table A-5) were fit to all dichotomous models in EPA's Benchmark Dose Software (BMDS) (version 3.3.2) using a benchmark response (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. The incidence data for protein accumulation was not modeled due to the 100% incidence at all non-control nickel concentrations.

Although several models of the alveolitis incidence data met three of the model fit criteria, the models failed the visual inspection of the dose-response curve. Most of the models of the perivascular/peribronchiolar inflammation incidence data provided adequate fit; the results are presented in Table A-6. The Multistage Degree 1 and Quantal Linear identified the lowest Akaike Information Criterion (AIC) and were selected; both models estimated a benchmark concentration (BMC) of 0.0024 mg Ni/m^3 and a BMCL of 0.0014 mg Ni/m^3. The model fit for the Multistage 1 Degree model is presented in Figure A-1.

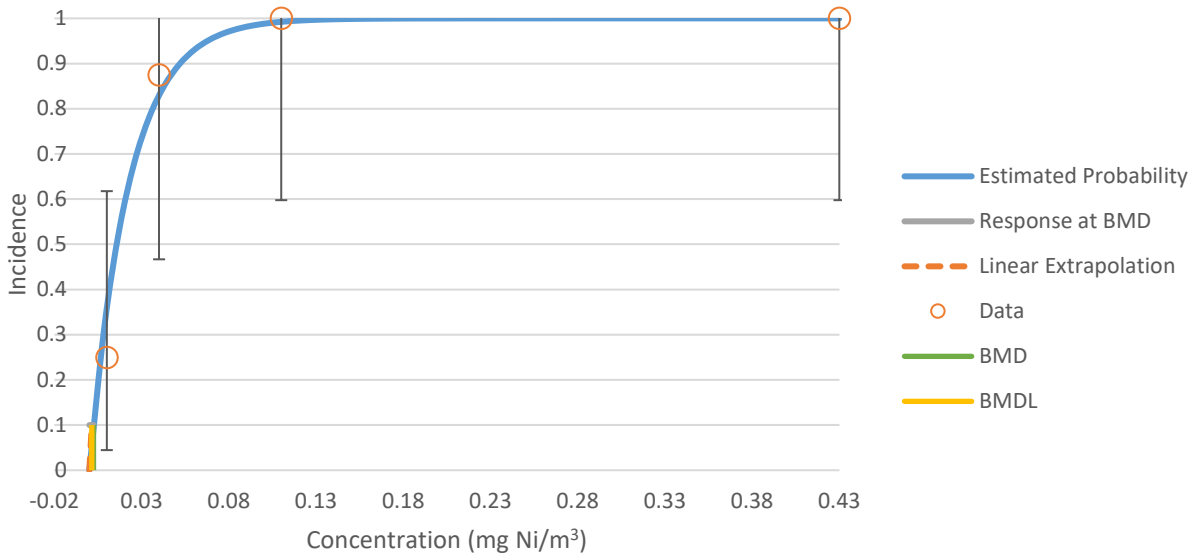
Table A-6. Results of BMD Analysis of Perivascular/Peribronchiolar Inflammation Incidence Data in Male F344 rats Exposed to Nickel Subsulfide via Inhalation 6 Hours/Day, 5 Days/Week for 13 Weeks (Oller et al. 2023)

					Scaled residuals[c]	
Model	BMC_{10}[a]	$BMCL_{10}$[a]	p-Value[b]	AIC	Dose group near BMC	Control dose group
Dichotomous Hill	0.0230	0.0020	0.9734	21.03	-7.1×10^{-5}	-7.1×10^{-5}
Gamma[d]	0.0162	0.0015	0.9966	21.03	6.19×10^{-6}	6.19×10^{-6}
Log-Logistic[e]	0.0230	0.0020	0.9734	21.03	-7.1×10^{-5}	-7.1×10^{-5}
Multistage Degree 3[f]			NA	23.03	-6.1×10^{-9}	-6.1×10^{-9}
Multistage Degree 2[f]	0.0094	0.0015	1.0000	19.03	5.11×10^{-6}	5.11×10^{-6}
Multistage Degree 1[f,g]	**0.0024**	**0.0014**	**0.9006**	**17.70**	**-0.63669**	**-0.63669**
Weibull[d]	0.0067	0.0015	0.9890	21.03	9.36×10^{-5}	9.36×10^{-5}
Logistic	0.0070	0.0035	0.9995	19.03	0.001763	0.001763
Log-Probit	0.0259	0.0018	1.0000	21.03	6.04×10^{-9}	-2.9×10^{-8}
Probit	0.0062	0.0037	0.7546	19.64	-0.50568	-0.50568
Quantal Linear[g]	**0.0024**	**0.0014**	**0.9006**	**17.70**	**-0.63669**	**-0.63669**

[a]BMC and BMCLs not providing adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Of the models providing adequate fit, the BMDLs were sufficiently close (differed by <3-fold); therefore, the models with the lowest AIC were selected (Multistage Degree 1 and Quantal Linear models).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); NA = not applicable

Figure A-1. Predicted (Frequentist Multistage 1 Degree Model) and Observed Incidence of Perivascular/Peribronchiolar Inflammation in Male Rats Exposed to Nickel Subsulfide



Two potential PODs were considered for MRL derivation: $BMCL_{10}$ of 0.0014 mg Ni/m^3 for perivascular/peribronchiolar inflammation and a LOAEL of 0.04 mg Ni/m^3 for alveolitis and protein accumulation in the lung. The $BMCL_{10}$ of 0.0014 mg Ni/m^3 was selected as the POD for the MRL because it results in the most-health protective MRL.

Adjustment for Intermittent Exposure: The $BMCL_{10}$ of 0.0014 mg Ni/m^3 was adjusted from intermittent exposure to continuous exposure using the following equation:

$$BMCL_{ADJ} = 0.0014\ mg\ Ni/m^3 \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.0025\ mg\ Ni/m^3$$

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

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

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 for rats and humans must be calculated. The RDDR for the thoracic region (combined tracheobronchial and pulmonary regions) is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using ARA MPDD Model (version 3.04) 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-7. For breathing frequency and tidal volume parameter values in humans, a TWA of default values in males

(ICRP 1994) was calculated based on the following activity pattern over a 24-hour exposure period: 8 hours sleeping (nasal breathing) + 8 hours at rest/sitting (nasal breathing) + 8 hours of light activity (oronasal-mouth breather). Default values in males were selected to be health protective, as males are predicted to have higher deposition fractions than females.

Table A-7. MPPD Model (Version 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	4 mL (default)	3,300 mL (default)
Upper respiratory tract	0.42 mL (default)	50 mL (default)
Inhalant properties		
Density[a]	5.87 g/cm^3	5.87 g/cm^3
Diameter, MMAD[b]	1.90 µm	1.90 µm
GSD[b]	2.28	2.28
Inhalability adjustment	On	On
Exposure condition		
Aerosol concentration ($BMCL_{ADJ}$)	0.0025 mg Ni/m^3	0.0025 mg Ni/m^3
Breathing frequency	102 breaths/minute (default)	14.7 breaths/minute (calculated TWA)[c]
Tidal volume	2.1 mL (default)	875 mL (calculated TWA)[d]
Breathing scenario	Whole body	Nasal/oronasal breather[e]
Results		
Thoracic region deposition fraction (total tracheobronchial and pulmonary deposition fraction)	0.0610	0.2273

[a]Haynes et al. (2015), nickel subsulfide.
[b]Oller et al. (2023).
[c]Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).
[d]Tidal volume is 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).
[e]Breathing scenario is 8 hours of sleep (nasal breathing, on back), 8 hours at rest (nasal breathing, upright), and 8 hours light activity (oronasal-mouth breathing, upright).

$BMCL_{ADJ}$ = lower 95% confidence interval of the benchmark concentration adjusted for continuous exposure; GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter; MPPD = Multiple-Path Particle Dosimetry; TWA = time-weighted average

The deposition fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $BMCL_{HEC}$. Table A-8 lists the values used within the equation and the source of these values. The exposure days (n) are 91 days to represent 24 hours of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure. Clearance data are not available for nickel subsulfide but are available for nickel oxide and nickel sulfate (Oller et al. 2014). Although nickel subsulfide and nickel oxide are both less soluble compounds, pulmonary clearance data for these three nickel compounds suggest that nickel subsulfide toxicokinetic properties may be more similar to nickel sulfate than nickel oxide. As reviewed by NTP (1996b), pulmonary clearance half-times in rats following intratracheal administration were 5 days for nickel subsulfide,

120 days for nickel oxide, and 1–3 days for nickel sulfate. Nickel subsulfide and nickel sulfate were distributed to extrarespiratory tissues, whereas nickel oxide was not distributed to extrarespiratory tissues. Using the clearance rates for nickel sulfate over those for nickel oxide is supported by the lung burden data from the NTP studies. The lung burdens in male rats exposed to approximately 0.4 mg Ni/m^3 for 13 weeks (6 hours/day, 5 days/week) were 7 µg Ni/g lung for nickel subsulfide (NTP 1996b), 3.348 µg Ni/g lung for nickel sulfate (NTP 1996c), and 80 µg Ni/g lung for nickel oxide (NTP 1996a). ICRP (1994) assigned nickel sulfate and nickel subsulfide to the same dissolution/absorption class F (fast, absorption half-time <10 days) based on a review of literature on retention kinetics of inhaled nickel sulfate and nickel subsulfide in cynomolgus monkeys and rats.

$$BMCL_{HEC} = 0.0025\ mg/m^3 \times \frac{0.20\frac{m^3}{day}}{20\frac{m^3}{day}} \times \frac{0.0610}{0.2273} \times \frac{\frac{1-(1-0.289\ day^{-1})^{91}}{1-(1-0.289\ day^{-1})}}{\frac{1-(1-0.277\ day^{-1})^{91}}{1-(1-0.277\ day^{-1})}} \times \frac{1}{1.04} \times \frac{54\ m^2}{0.34\ m^2}$$

$$BMCL_{HEC} = 0.0000982\ mg/m^3$$

Table A-8. Values Used to Calculate a Human Equivalent Concentration (HEC) for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.20 m^3/day	20 m^3/day	EPA 1994
Deposition fraction (DF)	0.0456	0.1647	Calculated using MPPD software
Clearance rate[a] (k)	0.289 day^{-1}	0.277 day^{-1}	Oller et al. 2014
Ratio of retention half-time (RH) (to rat half-time)	1	1.04	Calculated
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA 1994
Exposure days (n)	91 days	91 days	Oller et al. 2023

[a]Total clearance rate = ln2/retention half-time.

HEC = human equivalent concentration; MPPD = Multiple Path Particle Dosimetry

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

- 3 for extrapolation from rats to humans with dosimetric adjustments
- 10 for human variability

$$MRL = \frac{BMCL_{HEC}}{UFs} = \frac{0.0000982\ mg\ Ni/m^3}{30}$$

$$= 3.3x10^{-6}\ mg\ Ni/m^3, \text{ rounded to } 3x10^{-6}\ mg\ Ni/m^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a well-established target of toxicity following inhalation exposure to soluble and insoluble nickel compounds. Studies of workers exposed to nickel have reported increased respiratory symptoms, impaired lung function, and lung disease (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022). Lung inflammation has been reported in a number of intermediate-duration studies in animals exposed to nickel subsulfide, nickel sulfate, nickel chloride, or nickel oxide (Benson et al. 1995a, 1995b; Efremenko et al. 2014, 2017a, 2017b; Johansson et al. 1988a;

NTP 1996a, 1996b, 1996c; Oller et al. 2023). Olfactory epithelial atrophy has also been observed in rats and mice exposed to nickel sulfate or nickel subsulfide (NTP 1996b, 1996c).

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: A chronic-duration inhalation MRL was not derived for nickel. Although several chronic-duration inhalation studies are available, an MRL based on the study with the lowest LOAEL resulted in an MRL that was higher than the intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: Numerous studies in workers have examined respiratory tract toxicity following chronic-duration exposure to nickel. Several studies of workers such as welders and nickel refinery workers have reported respiratory effects, which include reduced vital capacity, respiratory symptoms, chronic bronchitis, pulmonary fibrosis, and asthma (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022).

Several animal studies (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1975; Takenaka et al. 1985; Tanaka et al. 1988) assessed the toxicity of nickel sulfate, nickel chloride, nickel subsulfide, nickel oxide, and metallic nickel. The respiratory system is a sensitive target of chronic-duration exposure with LOAELs ranging from 0.06 to 1.0 mg Ni/m^3. Respiratory effects observed include inflammatory changes in the lungs (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1975; Tanaka et al. 1988), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), congestion, and increased lung weight (Takenaka et al. 1985). A summary of the NOAEL and LOAEL values for respiratory effects is presented in Table A-9. Rats exposed to ≥0.06–0.2 mg Ni/m^3 as nickel oxide had decreased survival time compared to controls (Takenaka et al. 1985). Other noncancerous health effects due to nickel exposure include evidence of changes in hematological parameters (increased hemoglobin, hematocrit, and erythrocytes) at ≥0.1 mg Ni/m^3 (NTP 1996b; Oller et al. 2008), lymphoid hyperplasia in bronchial lymph nodes at ≥0.1 mg Ni/m^3 (NTP 1996a, 1996b, 1996c; Oller et al. 2008), and decreased body weight gain at ≥0.1 mg Ni/m^3 (NTP 1996b, 1996c). The hematological and body weight effects were likely secondary to the lung damage. The available chronic-duration inhalation database provides strong support for identifying the respiratory tract, in particular the lungs, as the critical effect for deriving an MRL.

Table A-9. Summary of Relevant Chronic-Duration Inhalation NOAEL and LOAEL Values for Respiratory Effects in Animals Exposed to Nickel[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Respiratory					
Rat (B)	2 years 5 days/week 6 hours/day	0.03	0.06	Chronic lung inflammation, fibrosis, alveolar proteinosis	NTP 1996c (nickel sulfate)

Table A-9. Summary of Relevant Chronic-Duration Inhalation NOAEL and LOAEL Values for Respiratory Effects in Animals Exposed to Nickel[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Mouse (F)	2 years 5 days/week 6 hours/day		0.06	Chronic lung inflammation and bronchiolization	NTP 1996c (nickel sulfate)
Rat (M)	31 months 7 days/week 23 hours/day		0.06	Increased lung weight, congestion, alveolar proteinosis	Takenaka et al. 1985 (nickel oxide)
Rat (B)	2 years 5 days/week 6 hours/day		0.1 (SLOAEL)	Labored breathing, alveolar proteinosis, histiocytosis, chronic lung inflammation, bronchiolar alveolar hyperplasia (females)	Oller et al. 2008 (metallic nickel)
Rat (B)	2 years 5 days/week 6 hours/day		0.11 (SLOAEL)	Rapid shallow breathing, chronic lung inflammation, lung fibrosis	NTP 1996b (nickel subsulfide)
Mouse (M)	2 years 5 days/week 6 hours/day	0.06	0.11	Chronic lung inflammation and bronchiolization	NTP 1996c (nickel sulfate)
Mouse (M)	2 years 5 days/week 6 hours/day	0.06	0.11	Atrophy of olfactory epithelium	NTP 1996c (nickel sulfate)
Rat (B)	2 years 5 days/week 6 hours/day	0.06	0.11	Atrophy of olfactory epithelium	NTP 1996c (nickel sulfate)
Rat	12 months 5 days/week 7 hours/day		0.235 (SLOAEL)	Pneumonia, increased lung weight	Tanaka et al. 1988 (nickel oxide)
Mouse (B)	2 years 5 days/week 6 hours/day		0.44	Chronic lung inflammation and bronchiolization, alveolar proteinosis, fibrosis Atrophy of olfactory epithelium	NTP 1996b (nickel subsulfide)
Rat (B)	2 years 5 days/week 6 hours/day		0.5	Chronic lung inflammation and lung alveolus pigmentation	NTP 1996a (nickel oxide)
Rat (B)	78–80 weeks 5 days/week 6 hours/day		0.63 (SLOAEL)	Pneumonitis, bronchitis, emphysema, hyperplasia	Ottolenghi et al. 1975 (nickel sulfide)
Rat (B)	2 years 5 days/week 6 hours/day	0.11	0.73	Atrophy of olfactory epithelium	NTP 1996b (nickel subsulfide)

Table A-9. Summary of Relevant Chronic-Duration Inhalation NOAEL and LOAEL Values for Respiratory Effects in Animals Exposed to Nickel[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Mouse (B)	2 years 5 days/week 6 hours/day		1.0	Chronic lung inflammation, bronchiolization, and alveolar proteinosis	NTP 1996a (nickel oxide)

[a]All concentrations are reported in mg Ni/m^3; concentrations reported in terms of the nickel compound were converted by multiplying the concentration by a ratio of the nickel compound molecular weight to nickel molecular weight.

B = both males and females; F = females; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

The NTP (1996c) rat and mouse studies and the Takenaka et al. (1985) rat study identified the lowest LOAEL value (0.06 mg Ni/m^3) for lung effects. The NTP (1996c) rat study was selected as the principal study over the other two studies. The rat study was selected over the mouse study since it identified a NOAEL; the available data suggest that the rat is more sensitive than the mouse; thus, derivation of an MRL based on the rat NOAEL should be protective. The NTP (1996c) study was selected over the Takenaka et al. (1985) study because the latter study is poorly reported and the $LOAEL_{ADJ}$ (0.057 mg Ni/m^3) is higher than the $LOAEL_{ADJ}$ for the NTP (1996c) study (0.011 mg Ni/m^3).

Incidence data for chronic active inflammation and lung fibrosis (presented in Table A-10) were fit to all dichotomous models in EPA's BMDS (version 3.3.2) 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, BMCL <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. None of the models provided adequate fit. Therefore, the NOAEL of 0.03 mg Ni/m^3 was selected as the point of departure (POD) for the MRL.

Table A-10. Incidence of Select Nonneoplastic Lung Lesions in Rats Exposed to Nickel Sulfate Hexahydrate for 2 Years via Inhalation

Concentration (mg Ni/m^3)	Incidence (severity)[a]			
	Chronic active inflammation		Lung fibrosis	
	Females	Males	Females	Males
0	14/52 (1.4)	14/54 (1.1)	8/52 (1.4)	3/54 (1.0)[b]
0.03	13/53 (1.2)	11/53 (1.2)	7 53(1.3)	6/53 (1.2)
0.06	49/53[b] (2.1)	42/53[b] (1.9)	45/53[b] (1.7)	35/53[b] (1.7)
0.11	52/54[b] (2.3)	46/53[b] (2.2)	49/54[b] (1.9)	43/53[b] (1.8)

[a]Average severity of lesions in affected animals: 1=minimal; 2=mild; 3=moderate; and 4=marked.
[b]Statistically different from control group ($p \leq 0.01$).

Source: NTP 1996c

The NOAEL of 0.03 mg Ni/m^3 was adjusted for continuous exposure (6 hours/24 hours; 5 days/7 days) to a $NOAEL_{ADJ}$ of 0.0053 mg Ni/m^3 and converted to a $NOAEL_{HEC}$ of 0.0033 mg Ni/m^3 using the

methodology and equations shown in the intermediate-duration MRL section and the values shown in Tables A-11 and A-12. Using the $NOAEL_{HEC}$ of 0.0033 mg Ni/m^3 as the final POD and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) would result in a chronic-duration inhalation MRL of 0.0001 mg Ni/m^3 ($1x10^{-4}$ mg Ni/m^3). However, this value is higher than the intermediate-duration inhalation MRL of $3x10^{-6}$ mg Ni/m^3. A comparison of the intermediate and chronic inhalation databases offers an explanation for why the intermediate MRL is lower than the chronic-duration MRL. The intermediate-duration MRL is based on a study that identified a LOAEL of 0.04 mg Ni/m^3 as nickel subsulfide (Oller et al. 2023); this LOAEL is lower than the intermediate-duration LOAELs for other nickel compounds. In the chronic-duration MRL database, the lowest LOAEL is 0.06 mg Ni/m^3 (NOAEL of 0.03 mg Ni/m^3) as nickel sulfate; for nickel subsulfide, the lowest LOAEL is 0.11 mg Ni/m^3, a NOAEL was not identified. The intermediate-duration MRL was considered more protective and thus, a chronic-duration inhalation MRL was not derived.

Table A-11. MPPD Model (Version 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	4 mL (default)	3,300 mL (default)
Upper respiratory tract	0.42 mL (default)	50 mL (default)
Inhalant properties		
Density[a]	2.07 g/cm^3	2.07 g/cm^3
Diameter, MMAD[b]	2.5 µm	2.5 µm
GSD[b]	2.38	2.38
Inhalability adjustment	On	On
Exposure condition		
Aerosol concentration ($NOAEL_{ADJ}$)	0.0053 mg Ni/m^3	0.0053 mg Ni/m^3
Breathing frequency	102 breaths/minute (default)	14.7 breaths/minute (calculated TWA)[c]
Tidal volume	2.1 mL (default)	875 mL (calculated TWA)[d]
Breathing scenario	Whole body	Nasa/oronasal breather[e]
Results		
Alveolar region deposition fraction (total pulmonary deposition fraction)	0.0330	0.1419

[a]NLM (2024l), nickel sulfate hexahydrate.
[b]NTP (1996c), Table K1.
[c]Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).
[d]Tidal volume is 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).
[e]Breathing scenario is assumed nasal with sleep and at rest and oronasal-mouth with light activity.

GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter; MPPD = Multiple-Path Particle Dosimetry; $NOAEL_{ADJ}$ = no-observed-adverse-effect level adjusted for continuous exposure; TWA = time-weighted average

Table A-12. Values Used to Calculate a Human Equivalent Concentration (HEC) for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.3616 m^3/day	20 m^3/day	EPA 1994
Deposition fraction (DF)	0.0330	0.1419	Calculated using MPPD software
Clearance rate[a] (k)	0.289 day^{-1}	0.277 day^{-1}	Oller et al. 2014
Ratio of retention half-time (RH) (to rat half-time)	1	1.04	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

[a]Total clearance rate = ln2/retention half-time.

MPPD = Multiple Path Particle Dosimetry; NOAEL = no-observed-adverse-effect level

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
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 are 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 in nickel sensitized subjects 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 adequate. 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) reported nausea and abdominal cramps in approximately half of the workers ingesting water contaminated with nickel sulfate, nickel chloride, and boric acid; estimated exposure was 7.1–35.7 mg Ni/kg.

Developmental, reproductive, and neurological effects have been observed at the lowest doses tested in acute-duration oral animal studies. A summary of the NOAEL and LOAEL values for the sensitive targets of toxicity is presented in Table A-13. The observed developmental effects include increased resorptions, decreased litter size, increased pup mortality, decreased pup body weight, and skeletal abnormalities. The lowest LOAEL is approximately 46 mg Ni/kg/day as nickel chloride. Two studies reported serious effects at this dose level (increased resorptions/decreased implantation site and decreased number of live fetuses) (El-Sekily et al. 2020; Saini et al. 2014a); skeletal abnormalities have also been observed at this dose level (Saini et al. 2013, 2014a). However, a series of studies conducted by Saini et al. (2014b) reported no developmental effects at 46.125 mg Ni/kg/day in mice administered nickel chloride on GDs 0–5, 6–13, or 14–18; increased mortality and decreased birth weight were observed at the next highest dose tested (92.25 mg Ni/kg/day). Neurological effects (alterations in memory and decreased activity) were observed in mice following a single dose of 50 mg Ni/kg/day as nickel chloride.

Table A-13. 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 (F)	GDs 0–5		46	Skeletal abnormalities	Saini et al. 2014a (nickel chloride hexahydrate)

Table A-13. 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)
Mouse (F)	GDs 6–13		46.125	Skeletal abnormalities	Saini et al. 2013 (nickel chloride hexahydrate)
Mouse (F)	GDs 6–13		46.125 (SLOAEL)	Increased resorption sites; incomplete skeletal and limb ossification; and supernumerary ribs	El-Sekily et al. 2020 (nickel chloride hexahydrate)
Mouse (F)	GDs 0–5	46.125	92.25 (SLOAEL)	Decreased litter size/dam	Saini et al. 2014b (nickel chloride hexahydrate)
Mouse (F)	GDs 14–18	46.125	92.25 (SLOAEL)	Offspring mortality (11.11%) and decreased birth weight (16%)	Saini et al. 2014b (nickel chloride hexahydrate)
Mouse (F)	GDs 6–13	46.125	92.25 (SLOAEL)	Increased offspring mortality (9.52%) and decreased birth weight (16%)	Saini et al. 2014b (nickel chloride hexahydrate)
Mouse (F)	GDs 8–12	45.3		No alteration in locomotor activity in offspring	Gray et al. 1986 (nickel chloride)
Reproductive					
Mouse (F)	GDs 0–5		46 (SLOAEL)	Decreased number of implantation sites and number of live fetuses/dam	Saini et al. 2014a (nickel chloride hexahydrate)
Neurological					
Mouse (M)	Once	5	50	Reduced spatial memory performance; reduced locomotor activity	He et al. 2013 (nickel chloride hexahydrate)

F = females; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

Several animal studies reported serious developmental and reproductive effects at the lowest doses tested (46 mg Ni/kg/day). This precludes MRL derivation from these endpoints due to the ATSDR practice of not deriving MRLs from serious LOAELs. The conflicting results reported in studies testing 46 mg Ni/kg/day may be indicative that the dose is near the NOAEL/LOAEL boundary. Deriving an MRL on this value may not be health protective for the serious developmental effects, and further data on developmental toxicity at lower doses are needed.

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
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 eight women sensitized to nickel and exposed to oral doses of 0.02 mg Ni/kg/day as nickel sulfate (Santucci et al. 1994).

Among experimental animal studies, neurological, body weight, reproductive, and developmental effects have been observed at the lowest doses tested. A summary of studies evaluating these endpoints is presented in Table A-14. Alterations in sperm parameters (decreased sperm motility and count and increased sperm abnormalities) and decreased fertility have been reported in male rats and mice exposed to ≥1.1 mg Ni/kg/day as nickel sulfate or nickel chloride (Käkelä et al. 1999; Pandey and Srivastava 2000; Pandey et al. 1999). Decreased fertility was also observed in a study in which males and females were exposed to 3.6 mg Ni/kg/day as nickel chloride for 28–76 days (Käkelä et al. 1999) but was not observed when only females were exposed to doses up to 13 mg Ni/kg/day as nickel chloride (Käkelä et al. 1999). Developmental effects have been observed at similar doses. Decreased pup survival, increased post-implantation loss, and decreased litter size were observed at doses of ≥1.3 mg Ni/kg/day as nickel chloride or nickel sulfate. The developmental effects were considered to be serious health effects. Other effects observed at higher doses included decreased body weight gain at ≥7.6 mg Ni/kg/day (Adeyemi et al. 2017; American Biogenics Corporation 1988; Dieter et al. 1988; Mahmoud et al. 2011; Springborn Laboratories 2002; Whanger 1973) and histological alterations in the kidneys and/or alterations in function parameters (plasma creatinine and urea, blood urea nitrogen, urine volume) at ≥7.6 mg Ni/kg/day (Adeyemi and Elebiyo 2014; Dahdouh et al. 2016; Dieter et al. 1988; Obone et al. 1999).

Table A-14. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to Nickel

Species (sex)	Frequency/ duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Neurological					
Rat (M)	90 days 3 days/week		0.2	Impaired performance on test of learning and spatial memory	Anyachor et al. 2023
Body weight					
Rat (M)	28 days		0.23 (SLOAEL)	Decreased body weight gain (20%)	Weischer et al. 1980

Table A-14. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to Nickel

Species (sex)	Frequency/ duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Reproductive					
Mouse (M)	35 days 5 days/week		1.1	Decreased sperm motility and sperm count; increased sperm abnormalities	Pandey et al. 1999 (nickel sulfate)
Mouse (M)	35 days 5 days/week	1.1	2.2	Decreased sperm count and motility, increased sperm abnormalities	Pandey and Srivastava 2000 (nickel sulfate)
Mouse (M)	35 days 5 days/week	1.2	2.5	Decreased sperm count and motility, increased sperm abnormalities	Pandey and Srivastava 2000 (nickel chloride)
Rat (M)	10 weeks prior to mating	2.2		No alteration in sperm count, concentration, or motility	Springborn Laboratories 2000b (nickel sulfate)
Rat (B)	10 weeks prior to mating	2.2		No effect on fertility	Springborn Laboratories 2000b (nickel sulfate)
Rat (M)	28 or 42 days before mating		3.6 (SLOAEL)	Decreased fertility	Käkelä et al. 1999 (nickel chloride)
Rat (B)	28–76 days		3.6 (SLOAEL)	Decreased fertility	Käkelä et al. 1999 (nickel chloride)
Mouse (M)	3–12 weeks		4.5	Degeneration of seminiferous epithelium	Toman et al. 2012 (nickel chloride)
Rat (B)	2 weeks prior to mating	16.8		No effect on fertility	Springborn Laboratories 2000a (nickel sulfate)
Rat (F)	11 weeks prior to mating	31.6		No effect on fertility	Smith et al. 1993 (nickel chloride)
Rat (B)	11 weeks prior to mating	40 (M) 55 (F)		No effect on fertility	EPA 1988a, 1988b (nickel chloride)
Developmental					
Rat (F)	11 weeks (breeding through lactation); two litters		1.3 (SLOAEL)	Decreased pup survival	Smith et al. 1993 (nickel chloride)
Mouse (M)	35 days 5 days/week		2.2 (SLOAEL)	Increased post-implantation loss	Pandey et al. 1999 (nickel sulfate)

Table A-14. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to Nickel

Species (sex)	Frequency/ duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Rat (M)	28 or 42 days before mating		3.6 (SLOAEL)	Decreased number of pups born alive per dam, decreased litter size	Käkelä et al. 1999 (nickel chloride)
Rat (B)	28–76 days		3.6 (SLOAEL)	Decreased number of pups born alive per dam, decreased litter size	Käkelä et al. 1999 (nickel chloride)
Rat (F)	2 weeks prior to mating and during gestation and lactation	4.5	6.7 (SLOAEL)	Increased post-implantation loss	Springborn Laboratories 2000a (nickel sulfate hexahydrate)
Rat (B)	2-generation study, 10 weeks prior to mating and during gestation and lactation	2.2		No developmental effects	Springborn Laboratories 2000b (nickel sulfate hexahydrate)

B = both males and females; F = females; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

The available intermediate-duration data are not considered suitable for MRL derivation because serious body weight and developmental effects were observed at some of the lowest doses tested. Although a slightly lower less serious LOAEL was identified for neurological effects, this dose of 0.2 mg Ni/kg/day is only slightly lower than the serious LOAEL of 0.23 mg Ni/kg/day. Therefore, deriving an MRL based on the neurological effects may not be protective of the developmental effects. It is noted that the neurological effects data from the Anyachor et al. (2023) study is not amenable to BMD modeling because only one dose was tested.

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
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 duration. Two animal studies have evaluated the chronic oral toxicity of nickel sulfate. A study in rats (Heim et al. 2007) reported increased mortality in females and decreased terminal body weights in males administered via gavage 6.7 mg Ni/kg/day as nickel sulfate for 2 years; the NOAEL for body weight effects in females was 2.2 mg Ni/kg/day. No other biologically relevant adverse effects were reported in the study. In the second chronic-duration study, body weight, respiratory (cholesterol granulomas, emphysema, and bronchiolectasis), and renal effects (polyuria) were observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet (Ambrose et al. 1976). The database also includes a 2-year study in rats conducted by Ambrose et al. (1976), which reported a 34% decrease in terminal body weights in female rats exposed to 75 mg Ni/kg/day as nickel sulfate in the diet; however, the study quality is considered poor due to the high mortality in the control group.

The database was not considered suitable for derivation of a chronic-duration oral MRL. The rat (Heim et al. 2007) and dog (Ambrose et al. 1976) were not considered suitable principal studies because increased mortality was observed at the lowest adverse effect level. Although the Heim et al. (2007) study identified a NOAEL for body weight effects at 2.2 mg/kg/day, alterations in body weight are not considered primary effects of nickel and are likely secondary effects; therefore, the Heim et al. (2007) was not considered suitable as the basis for MRL derivation.

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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 were 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. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. 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

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
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 Draft Toxicological Profile for Nickel released for public comment in 2023; thus, the literature search was restricted to studies published between January 2020 and October 2023. The following main databases were searched in October 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

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	Query string
PubMed	
10/2023	(((7440-02-0[rn] OR 373-02-4[rn] OR 7718-54-9[rn] OR 1313-99-1[rn] OR 7786-81-4[rn] OR 13138-45-9[rn] OR 15699-18-0[rn] OR 3333-67-3[rn] OR ("Dicyanonickel"[tw] OR "Nickel cyanide"[tw]) OR 13770-89-3[rn]) AND ((("NICKEL/toxicity"[mh] OR "NICKEL/adverse effects"[mh] OR "NICKEL/poisoning"[mh] OR "NICKEL/pharmacokinetics"[mh] OR "environmental exposure"[mh] OR ci[sh] OR toxicokinetics[mh:noexp] OR "NICKEL/blood"[mh] OR "NICKEL/cerebrospinal fluid"[mh] OR "NICKEL/urine"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh]) OR "NICKEL/antagonists and inhibitors"[mh] OR ("NICKEL/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "NICKEL/pharmacology"[majr] OR ("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]) OR (Nickel[mh] AND (indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) OR "Sulfonic Acids"[mh] OR "Organometallic Compounds"[mh]) AND (2020:3000[mhda]))) OR (((((("(Oxido)nickel"[tw] OR "Ammonium disulfatonickelate(II)"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Bunsenite"[tw] OR "Dicyanonickel"[tw] OR "Mononickel oxide"[tw] OR "Ni 210"[tw] OR "Nickel"[tw] OR "Nickelacetat"[tw] OR "Nickelcarbonat"[tw] OR "Nickelchlorid"[tw] OR "Nickeldi(acetat)"[tw] OR "Nickeldichlorid"[tw] OR "Nickelmonoxid"[tw] OR "Nickelous acetate"[tw] OR "Nickelous carbonate"[tw] OR "Nickelous chloride"[tw] OR "Nickelous nitrate"[tw] OR "Nickelous oxide"[tw] OR "Nickelous sulfate"[tw] OR "Nickelous sulphate"[tw] OR "Nickelsulfat"[tw] OR "Raney Ni"[tw] OR "Carbonyl 255"[tw] OR "Carbonyl Ni 123"[tw] OR "Carbonyl Ni 283"[tw] OR "Celmet"[tw] OR "Cerac N 2003"[tw] OR "Fine Emerald"[tw] OR "Inco 210"[tw] OR "Incofoam"[tw] OR "Melbright EF 2201"[tw] OR "MG-Ni 50"[tw] OR "MG-Ni 600"[tw] OR "Ni 006021"[tw] OR "Ni 0901-S"[tw] OR "NI 0901-S (harshaw)"[tw] OR "NI 110104"[tw] OR "NI 123"[tw] OR "Ni 123J"[tw] OR "Ni 123T"[tw] OR "Ni 255"[tw] OR "NI 255AC"[tw] OR "NI 255T"[tw] OR "NI 255T280"[tw] OR "Ni 270"[tw] OR "NI 287"[tw] OR "NI 313324"[tw] OR "NI 313463"[tw] OR "NI 313551"[tw] OR "Ni 4303T"[tw] OR "NI 525"[tw] OR "Ni Celmet"[tw] OR "Ni Powder CuLox 5100A"[tw] OR "Niccolum metallicum"[tw] OR "Nichel(II) chloride"[tw] OR "Nicobraz LM BNI2"[tw] OR "Nicrobraz LM:BNi 2"[tw] OR "NiFL 5"[tw] OR "NiFLA 10"[tw] OR "Ni-Flake 95"[tw] OR "Ni-J 20"[tw] OR "Nikko 255"[tw] OR "Nikko Rica 123"[tw] OR "NiO-D"[tw] OR "NiO-FP"[tw] OR "NiO-G 39"[tw] OR "NiS 10"[tw] OR "Novamet 123"[tw] OR "Novamet 4SP"[tw] OR "Novamet 4SP10"[tw] OR "Novamet 525"[tw] OR "Novamet CNS 400"[tw] OR "Novamet HCA 1"[tw] OR "Novamet NI 255"[tw] OR "Raney 2400"[tw] OR "Raney 2486"[tw] OR "Raney 2800"[tw] OR "Raney 3110"[tw] OR "Raney 3202"[tw] OR "Raney 4200"[tw] OR "Raney 5831"[tw] OR "Raney 5886"[tw] OR "Raney alloy"[tw] OR "SF-Ni"[tw] OR "SFR-Ni"[tw] OR "Sun Ti-Ni"[tw] OR "Top Seal DX 300"[tw] OR "Top Seal H 298"[tw]) NOT medline[sb])) AND 2020:3000[dp] AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR respiratory OR "pulmonary edema" OR "pulmonary effect" OR "pulmonary system" OR "pulmonary function" OR "pulmonary organ" OR "pulmonary toxicity" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR cardiovascular OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory organ" OR "circulatory toxicity" OR "cardiac arrest" OR "cardiac palpitation" OR "cardiac arrhythmia" OR "cardiac edema" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heart beat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR "digestive system" OR "digestive function" OR "digestive effect" OR "digestive organ" OR "Intestinal system" OR "intestinal function" OR "intestinal microbiota" OR "intestinal effect" OR "intestinal organ" OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR stomach OR intestine OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR

Table B-2. Database Query Strings

Database search date	Query string
	hepatotox* OR renal OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR bun OR nephropathy OR nephrotox* OR dermal OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin exposure" OR "skin contact" OR acanthosis OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR endocrine OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR fertility OR "maternal toxicity" OR developmental OR "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mechanism of absorption"[tiab:~0] OR "mechanism of distribution"[tiab:~0] OR "mechanism of excretion"[tiab:~0] OR "mechanism of metabolism"[tiab:~0] OR "mechanism of toxic effect"[tiab:~0] OR "mechanism of toxicity" OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "human health" OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR "National Health and Nutrition Examination Survey" OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR

Table B-2. Database Query Strings

Database search date	Query string
	leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish)))
NTRL	
10/2023	Limited to 2020 to present; terms searched in title or keyword "Nickel" OR "(Oxido)nickel" OR "Ammonium disulfatonickelate(II)" OR "Bunsenite" OR "Dicyanonickel" OR "Mononickel oxide" OR "Ni 210" OR "Nickelacetat" OR "Nickelcarbonat" OR "Nickelchlorid" OR "Nickeldi(acetat)" OR "Nickeldichlorid" OR "Nickelmonoxid" OR "Nickelous acetate" OR "Nickelous carbonate" OR "Nickelous chloride" OR "Nickelous nitrate" OR "Nickelous oxide" OR "Nickelous sulfate" OR "Nickelous sulphate" OR "Nickelsulfat" OR "Raney Ni"
Toxcenter	
10/2023	FILE 'TOXCENTER' ENTERED AT 10:29:54 ON 24 OCT 2023 L1 187783 SEA 7440-02-0 OR 373-02-4 OR 7718-54-9 OR 1313-99-1 OR 7786-81-4 OR 13138-45-9 OR 15699-18-0 OR 3333-67-3 OR 557-19-7 OR 13770-89-3 L2 33611 SEA L1 AND PY>2019 L3 28623 SEA L2 NOT PATENT/DT ACT TOXQUERY/Q --------- L4 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L5 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L6 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L7 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L8 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L9 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L10 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L11 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L12 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L13 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L14 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L15 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)

Table B-2. Database Query Strings

Database search date	Query string
	L16 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L17 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L18 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L19 QUE (ENDOCRIN? AND DISRUPT?)
	L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L26 QUE (NEPHROTOX? OR HEPATOTOX?)
	L27 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L28 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L29 QUE L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28
	L30 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L31 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L32 QUE L29 OR L30 OR L31
	L33 QUE (NONHUMAN MAMMALS)/ORGN
	L34 QUE L32 OR L33
	L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L36 QUE L34 OR L35

	L38 11491 SEA L3 AND L32
	L41 752 SEA L38 AND MEDLINE/FS
	L42 2371 SEA L38 AND BIOSIS/FS
	L43 8356 SEA L38 AND CAPLUS/FS
	L44 10143 DUP REM L41 L42 L43 (1336 DUPLICATES REMOVED)
	L*** DEL 752 S L38 AND MEDLINE/FS
	L*** DEL 752 S L38 AND MEDLINE/FS
	L45 750 SEA L44

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 2371 S L38 AND BIOSIS/FS L*** DEL 2371 S L38 AND BIOSIS/FS L46 2217 SEA L44 L*** DEL 8356 S L38 AND CAPLUS/FS L*** DEL 8356 S L38 AND CAPLUS/FS L47 7176 SEA L44 L48 9393 SEA (L45 OR L46 OR L47) NOT MEDLINE/FS

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2023	Compounds searched: 7440-02-0; 373-02-4; 7718-54-9; 1313-99-1; 7786-81-4; 13138-45-9; 3333-67-3; 13770-89-3; 557-19-7; 15699-18-0
NTP	
10/2023	7440-02-0 7786-81-4 1313-99-1 373-02-4 7718-54-9 3333-67-3 "Bunsenite" "Mononickel oxide" "Nickelous chloride" "Nickelous oxide" "Nickelous sulfate" "Nickelous sulphate" 15699-18-0 557-19-7 13770-89-3 13138-45-9 "Ammonium disulfatonickelate(II)" "Dicyanonickel" "Ni 210" "Nickelacetat" "Nickelcarbonat" "Nickelous acetate" "Nickelchlorid" "Nickeldi(acetat)" "Nickeldichlorid" "Nickelmonoxid" "Nickelous carbonate" "Nickelous nitrate" "Nickelsulfat" "(Oxido)nickel" "Raney Ni"
Regulations.gov	
10/2023	"Nickel" "Bunsenite" "Mononickel oxide" "Nickelous chloride" "Nickelous oxide" "Nickelous sulfate" "Nickelous sulphate" "Ammonium disulfatonickelate(II)" "Dicyanonickel" "Ni 210" "Nickelacetat" "Nickelcarbonat" "Nickelous acetate" "Nickelchlorid" "Nickeldi(acetat)" "Nickeldichlorid" "Nickelmonoxid" "Nickelous carbonate" "Nickelous nitrate" "Nickelsulfat" "(Oxido)nickel"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Raney Ni" "7440-02-0" "373-02-4" "7718-54-9" "1313-99-1" "7786-81-4" "13138-45-9" "15699-18-0" "3333-67-3" "557-19-7" "13770-89-3"
NIH RePORTER	
03/2024	Fiscal Year: Active Projects; Text Search: "(Oxido)nickel" OR "Ammonium disulfatonickelate(II)" OR "Bunsenite" OR "Dicyanonickel" OR "Mononickel oxide" OR "Ni 210" OR "Nickel" OR "Nickelacetat" OR "Nickelcarbonat" OR "Nickelchlorid" OR "Nickeldi(acetat)" OR "Nickeldichlorid" OR "Nickelmonoxid" OR "Nickelous acetate" OR "Nickelous carbonate" OR "Nickelous chloride" OR "Nickelous nitrate" OR "Nickelous oxide" OR "Nickelous sulfate" OR "Nickelous sulphate" OR "Nickelsulfat" OR "Raney Ni" OR "Carbonyl 255" OR "Carbonyl Ni 123" OR "Carbonyl Ni 283" OR "Celmet" OR "Cerac N 2003" OR "Fine Emerald" OR "Inco 210" OR "Incofoam" OR "Melbright EF 2201" OR "MG-Ni 50" OR "MG-Ni 600" OR "Ni 006021" OR "Ni 0901-S" OR "NI 0901-S (harshaw)" OR "NI 110104" OR "NI 123" OR "Ni 123J" OR "Ni 123T" OR "Ni 255" OR "NI 255AC" OR "NI 255T" OR "NI 255T280" OR "Ni 270" OR "NI 287" OR "NI 313324" OR "NI 313463" OR "NI 313551" OR "Ni 4303T" OR "NI 525" OR "Ni Celmet" OR "Ni Powder CuLox 5100A" OR "Niccolum metallicum" OR "Nichel(II) chloride" OR "Nicobraz LM BNI2" OR "Nicrobraz LM:BNi 2" OR "NiFL 5" OR "NiFLA 10" OR "Ni-Flake 95" OR "Ni-J 20" OR "Nikko 255" OR "Nikko Rica 123" OR "NiO-D" OR "NiO-FP" OR "NiO-G 39" OR "NiS 10" OR "Novamet 123" OR "Novamet 4SP" OR "Novamet 4SP10" OR "Novamet 525" OR "Novamet CNS 400" OR "Novamet HCA 1" OR "Novamet NI 255" OR "Raney 2400" OR "Raney 2486" OR "Raney 2800" OR "Raney 3110" OR "Raney 3202" OR "Raney 4200" OR "Raney 5831" OR "Raney 5886" OR "Raney alloy" OR "SF-Ni" OR "SFR-Ni" OR "Sun Ti-Ni" OR "Top Seal DX 300" OR "Top Seal H 298" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 10,701
- Number of records identified from other strategies: 146
- Total number of records to undergo literature screening: 10,847

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.

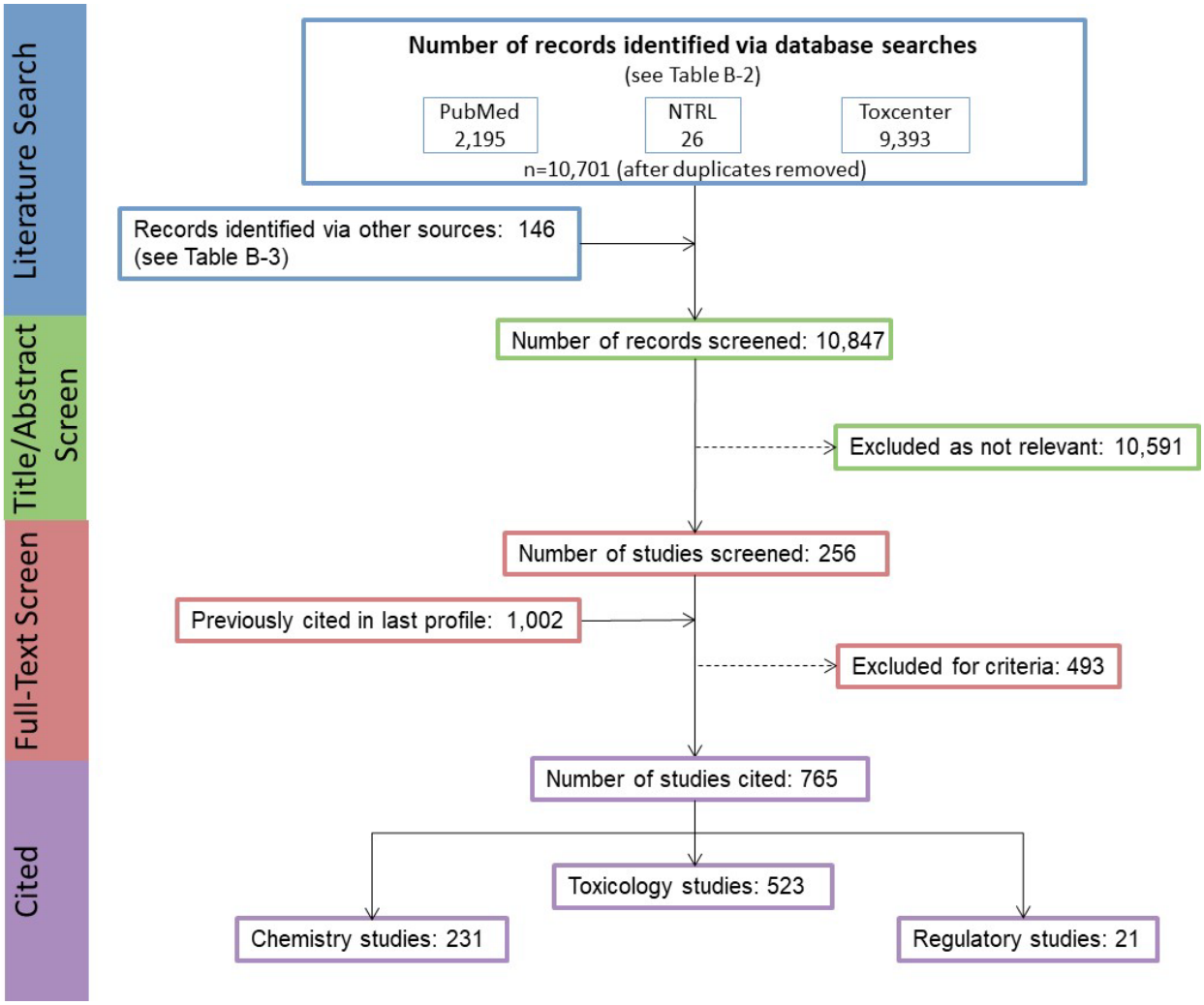
- Number of titles and abstracts screened: 10,847
- Number of studies considered relevant and moved to the next step: 256

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: 256
- Number of studies cited in the pre-public draft of the toxicological profile: 1,002
- Total number of studies cited in the profile: 766

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. October 2023 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, or dermal/ocular exposure to nickel. The inclusion criteria used to identify relevant studies examining the health effects of nickel are presented in Table C-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.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

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

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

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

Prioritization of Human Data. Human studies of exposure to nickel include case reports/case series, controlled oral exposure studies, epidemiological studies of occupational exposures, and epidemiological studies of general population exposures to nickel as a constituent of ambient particulate matter. All controlled exposure studies were included. Case reports and case series were included in the profile if there was clear evidence of exposure primarily to nickel. Epidemiology studies included in this profile were restricted to those of populations with known exposure above background levels (e.g., occupational exposure).

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were 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 current literature search was intended to update the Draft Toxicological Profile for Nickel released for public comment in 2023. See Appendix B for the databases searched and the search strategy.

A total of 10,847 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, 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, 10,847 records were reviewed; 23 documents were considered to meet the health effects inclusion criteria in Table C-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 189 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 189 documents (231 studies), 60 documents (93 studies) were included in the qualitative review.

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-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. 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

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 (Tables 2-1, 2-2, and 2-3, respectively).

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-3 and C-4, respectively.

Human studies evaluating noncancerous effects are primarily cohort studies of occupational exposure that examined mortality from respiratory effects.

Animal studies examined a wide range of endpoints following inhalation, oral, and dermal exposure and reported body weight, respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, reproductive, developmental, and cancer effects. Of the consistently observed effects, respiratory effects following inhalation exposure, immunological effects, reproductive, and developmental effects were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). There were 93 studies (published in 60 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

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Table C-3. 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	Caner
Inhalation studies																	
Cohort		14 3	4 0			1 0	1 1	4 2			1 1	3 3	1 0	2 1	4 0		28 11
Case control																	8 1
Cross-sectional		4 3											1 1				
Case series		7 7	1 1	1 1	1 1	1 1	1 1	2 2		1 1		1 1	3 3				1 1
Controlled																	
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Controlled												16 16					
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Controlled												33 33					

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

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Table C-4. 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[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	8	10	6	6		3	6	6	6		6	11	6	6			
	3	10	0	0		0	0	0	0		0	6	0	0			
Intermediate-duration	17	23	6	6	5	6	6	7	6		7	14	6	6	1		
	2	23	0	0	2	0	0	0	0		0	14	0	1	1		
Chronic-duration	10	10	7	7	7	6	8	8	6		8	8	7	6			8
	4	10	0	0	3	0	0	0	0		4	7	0	0			4
Acute-duration	3			1									1	1	7		
	3			1									1	1	5		
Intermediate-duration	15	4	3	3	4		8	10	1	1	3	3	4	12	9		
	8	3	0	1	2		2	5	0	0	1	3	2	2	8		
Chronic-duration	2	1	1	1	2	1	1	1	1		1	1	1				
	2	1	0	0	1	0	0	1	0		0	0	0				
Acute-duration												1					
												1					
Intermediate-duration					1		1	2	1					1		1	
					0		1	1	1					1		1	
Chronic-duration																	

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	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

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 Tables C-5, C-6, and C-7, 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-5. 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-6. 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-7. 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 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 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 Tables C-8 and C-9, respectively.

Table C-8. 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							
Berge and Skyberg 2003	+	+	–	–	–	++	Second
Syurin and Vinnikov 2022	–	+	+	–	– –	++	Second
Cross-sectional							
Fishwick et al. 2004	++	+	+	–	–	++	Second
Kilburn et al. 1990	+	–	+	–	+	++	Second
Muir et al. 1993	+	+	–	–	+	+	Second
Wu et al. 2022	+	++	+	+	+	++	First
Outcome: Immunological							
Cohort studies inhalation							
Bencko et al. 1983	– –	–	+	–	–	++	Third
Bencko et al. 1986	++	+	+	–	+	++	Second

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Table C-8. 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: Reproductive							
Cohort studies inhalation							
Chashschin et al. 1994	–	–	–	–	–	++	Third
Case-Control studies							
Chashschin et al. 1994	–	–	–	–	–	++	Third
Vaktskjold et al. 2008b	+	+	+	+	+	++	First
Outcome: Developmental							
Cohort studies inhalation							
Chashschin et al. 1994	–	–	–	–	–	++	Third
Vaktskjold et al. 2006	+	+	+	+	+	++	First
Vaktskjold et al. 2007	+	+	+	+	+	++	First
Vaktskjold et al. 2008a	+	+	+	+	+	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; *Key question used to assign risk of bias tier

Table C-9. 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
Outcome: Respiratory									
Inhalation acute exposure									
Benson et al. 1995b (rat)	+	+	+	+	+	++	+	+	First
Efremenko et al. 2014 (rat)	++	+	+	+	+	+	++	+	First
Efremenko et al. 2017a, 2017b (rat)	++	+	+	+	+	++	++	+	First
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Benson et al. 1995a (rat, nickel sulfate)	+	+	+	+	+	++	+	+	First
Benson et al. 1995a (rat, nickel oxide)	+	+	+	+	+	++	+	+	First
Benson et al. 1995a (mouse, nickel sulfate)	+	+	+	+	+	++	+	+	First
Benson et al. 1995a (mouse, nickel oxide)	+	+	+	+	+	++	+	+	First
Benson et al. 1995b (rat)	+	+	+	+	+	++	+	+	First

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Table C-9. 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
Efremenko et al. 2014 (rat)	++	–	+	–	+	+	++	+	First
Efremenko et al. 2017a, 2017b (rat)	++	+	+	+	+	++	++	+	First
Evans et al. 1995 (rat)	–	–	++	–	+	+	++	++	First
Horie et al. 1985 (rat)	–	–	+	–	+	–	–	+	Second
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Oller et al. 2023 (rat, nickel subsulfide)	++	+	+	+	++	++	+	+	First
Oller et al. 2023 (rat, nickel sulfate)	++	+	+	+	++	++	+	+	First
Weischer et al. 1980 (rat)	–	–	+	–	+	–	+	+	Second
Inhalation chronic exposure									
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First

Table C-9. 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 (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Oller et al. 2008 (rat)	++	-	+	–	+	++	++	++	First
Ottolenghi et al. 1975 (rat)	–	–	+	–	+	–	+	+	Second
Takenaka et al. 1985 (rat)	–	–	++	–	+	–	+	+	Second
Tanaka et al. 1988 (rat)	–	+	+	+	+	+	+	+	First
Oral intermediate exposure									
American Biogenics Corporation 1988 (rat)	++	–	+	–	+	++	+	+	First
Obone et al. 1999 (rat)	–	–	+	–	++	+	++	++	First
EPA 1988a, 1988b (rat)	+	–	+	–	+	–	+	+	First
Springborn Laboratories 2002 (rat)	++	–	+	–	++	++	++	++	First
Oral intermediate exposure									
Ambrose et al. 1976 (dog)	–	–	+	–	+	–	+	+	Second
Outcome: Immunological									
Inhalation acute exposure									
Adkins et al. 1979 (mouse, bacteria clearance)	–	–	+	–	+	–	+	+	Second
Adkins et al. 1979 (mouse, nickel chloride)	–	–	+	–	+	–	+	+	Second

Table C-9. 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
Adkins et al. 1979 (mouse, nickel sulfate)	–	–	+	–	+	–	+	+	Second
Buxton et al. 2021 (mouse)	++	–	++	–	+	+	+	++	First
Graham et al. 1978 (mouse)	–	–	+	–	+	–	+	+	Second
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Haley et al. 1990 (mouse, nickel oxide)	+	–	+	–	+	++	++	++	First
Haley et al. 1990 (mouse, nickel subsulfide)	+	–	+	–	+	++	++	++	First
Haley et al. 1990 (mouse, nickel sulfate)	+	–	+	–	+	++	++	++	First
Johansson et al. 1987 (rabbit)	–	–	+	–	+	–	+	+	Second
Johansson et al. 1988a, 1989 (rabbit)	–	–	+	–	+	–	+	+	Second
Morimoto et al. 1995 (rat)	–	–	+	–	+	+	+	+	First
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First

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Table C-9. 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 (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Spiegelberg et al. 1984 (rat)	–	–	+	–	+	–	+	+	Second
Inhalation chronic exposure									
NTP 1996a (rat)	–	–	+	–	++	++	++	++	First
NTP 1996a (mouse)	–	–	+	–	++	++	++	++	First
NTP 1996b (rat)	–	–	+	–	++	++	++	++	First
NTP 1996b (mouse)	–	–	+	–	++	++	++	++	First
NTP 1996c (rat)	–	–	+	–	++	++	++	++	First
NTP 1996c (mouse)	–	–	+	–	++	++	++	++	First
Oller et al. 2008 (rat)	++	–	+	–	+	++	++	++	First
Ottolenghi et al. 1975 (rat)	–	–	+	–	+	–	+	+	Second
Oral intermediate exposure									
Dieter et al. 1988 (mouse)	–	–	+	–	+	–	+	+	Second
Ilbäck et al. 1994 (mouse)	+	–	+	–	+	–	+	+	First
Obone et al. 1999 (rat)	–	–	+	–	++	+	++	++	First
Oral chronic exposure									
Ambrose et al. 1976 (dog)	–	–	+	–	+	–	+	+	Second

Table C-9. 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
Dermal acute exposure									
Siller and Seymour 1994 (mouse)	–	–	+	–	+	–	+	+	Second
Outcome: Reproductive									
Inhalation acute exposure									
NTP 1996a (rat)	+	+	+	+	+	++	++	+	First
NTP 1996a (mouse)	+	+	+	+	+	++	++	+	First
NTP 1996b (rat)	+	+	+	+	+	++	++	+	First
NTP 1996b (mouse)	+	+	+	+	+	++	++	+	First
NTP 1996c (rat)	+	+	+	+	+	++	++	+	First
NTP 1996c (mouse)	+	+	+	+	+	++	++	+	First
Inhalation intermediate exposure									
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Inhalation chronic exposure									
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First

Table C-9. 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 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Oral acute exposure									
Saini et al. 2013 (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014a (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014b (mouse, GDs 0–5)	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (mouse, GDs 6–13)	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (mouse, GDs 14–18)	–	+	+	+	+	+	++	+	First
Seidenberg et al. 1986 (mouse)	–	+	+	+	+	–	+	+	First
Sobti and Gill 1989 (mouse, nickel sulfate)	–	+	+	+	–	–	–	+	Second
Sobti and Gill 1989 (mouse, nickel nitrate)	–	+	+	+	–	–	–	+	Second
Sobti and Gill 1989 (mouse, nickel chloride)	–	+	+	+	–	–	–	+	Second

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Table C-9. 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
Oral intermediate exposure									
Ambrose et al. 1976 (rat)	–	+	+	+	+	–	+	+	First
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	–	+	+	+	+	–	+	+	First
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	–	+	+	+	++	–	+	+	First
Käkelä et al. 1999 (rat, 28–76 days)	–	+	+	+	+	–	+	+	First
Obone et al. 1999 (rat)	–	+	+	+	++	+	++	++	First
Pandey and Srivastava 2000 (mouse, nickel chloride)	–	+	+	+	++	–	+	+	First
Pandey and Srivastava 2000 (mouse, nickel sulfate)	–	+	+	+	++	–	+	+	First
Pandey et al. 1999 (mouse, one dose group)	–	+	+	+	++	+	+	+	First
Pandey et al. 1999 (mouse, two dose groups)	–	+	+	+	+	+	+	+	First
EPA 1988a, 1988b (rat)	+	+	+	+	+	–	+	+	First
Smith et al. 1993 (rat)	+	+	+	+	+	–	+	+	First
Springborn Laboratories 2000a (rat)	++	+	+	+	++	++	+	++	First

Table C-9. 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
Springborn Laboratories 2000b (rat)	++	+	+	+	++	++	+	++	First
Toman et al. 2012 (mouse)	–	+	+	+	++	–	+	+	First
Oral chronic exposure									
Ambrose et al. 1976 (dog)	–	+	+	+	++	–	+	+	First
Outcome: Developmental									
Oral acute exposure									
Saini et al. 2013 (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014a (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014b (mouse, GDs 0–5)	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (mouse, GDs 6–13	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (Mouse, GDs 14–18)	–	+	+	+	+	+	++	+	First
Seidenberg et al. 1986 (mouse)	–	+	+	+	+	–	+	+	First
Oral intermediate exposure									
Ambrose et al. 1976 (rat)	–	+	+	+	+	–	+	+	First
EPA 1983 (mouse)	+	+	–	+	–	–	+	+	First
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	–	+	+	+	+	–	+	+	First

APPENDIX C

Table C-9. 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
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	–	+	+	+	++	–	+	+	First
Käkelä et al. 1999 (rat, 28–76 days)	–	+	+	+	+	–	+	+	First
EPA 1988a, 1988b (rat)	+	+	+	+	+	–	+	+	First
Smith et al. 1993 (rat)	+	+	+	+	+	–	+	+	First
Springborn Laboratories 2000a (rat)	++	+	+	+	++	++	+	++	First
Springborn Laboratories 2000b (rat)	++	+	+	+	++	++	+	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; *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 HHS, 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: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome 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 features of study design was determined for individual studies using four "yes or no" questions, which were customized for 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, and experimental animal studies are presented in Tables C-10, C-11, and C-12, 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-10. 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-11. 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
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-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory and immunological effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. 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					
Berge and Skyberg 2003	No	No	Yes	Yes	Low
Syurin and Vinnikov 2022	No	Yes	Yes	Yes	Moderate

Table C-13. 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	
Cross-sectional studies					
Fishwick et al. 2004	No	Yes	Yes	Yes	Moderate
Kilburn et al. 1990	No	Yes	Yes	Yes	Moderate
Muir et al. 1993	No	Yes	Yes	Yes	Moderate
Wu et al. 2022	No	Yes	Yes	Yes	Moderate
Outcome: Immunological effects					
Cohort inhalation studies					
Bencko et al. 1983	No	Yes	Yes	Yes	Moderate
Bencko et al. 1986	No	Yes	Yes	Yes	Moderate
Outcome: Reproductive effects					
Cohort inhalation studies					
Chashschin et al. 1994	No	Yes	Yes	Yes	Moderate
Case-Control studies					
Vaktskjold et al. 2008b	No	Yes	Yes	Yes	Moderate
Outcome: Developmental effects					
Cohort inhalation studies					
Chashschin et al. 1994	No	Yes	Yes	Yes	Moderate
Vaktskjold et al. 2006	No	Yes	Yes	Yes	Moderate
Vaktskjold et al. 2007	No	Yes	Yes	Yes	Moderate
Vaktskjold et al. 2008a	No	Yes	Yes	Yes	Moderate

Table C-14. 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
Efremenko et al. 2017a, 2017b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Benson et al. 1995a (rat, nickel sulfate)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (rat, nickel oxide)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (mouse, nickel oxide)	Yes	Yes	Yes	Yes	High
Benson et al. 1995b (rat)	Yes	Yes	Yes	Yes	High
Efremenko et al. 2014 (rat)	Yes	Yes	Yes	Yes	High
Efremenko et al. 2017a, 2017b (rat)	Yes	Yes	Yes	Yes	High
Evans et al. 1995 (rat)	Yes	Yes	Yes	Yes	High
Horie et al. 1985 (rat)	Yes	No	Yes	No	Low
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Oller et al. 2023 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Oller et al. 2023 (rat)	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 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1975 (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					
American Biogenics Corporation 1988 (rat)	Yes	Yes	Yes	Yes	High
Obone et al. 1999 (rat)	Yes	No	Yes	Yes	Moderate
EPA 1988a, 1988b (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2002 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Ambrose et al. 1976 (dog)	Yes	No	Yes	No	Low
Outcome: Immunological effects					
Inhalation acute exposure					
Adkins et al. 1979 (mouse, bacteria clearance)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979 (mouse, nickel chloride)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979 (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Buxton et al. 2021 (mouse)	Yes	Yes	Yes	Yes	High
Graham et al. 1978 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Haley et al. 1990 (mouse, nickel oxide)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (mouse, nickel subsulfide)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Johansson et al. 1987 (rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1988a, 1989 (rabbit)	Yes	No	Yes	Yes	Moderate
Morimoto et al. 1995 (rat)	Yes	No	Yes	Yes	Moderate
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Spiegelberg et al. 1984 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1975 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Oral intermediate exposure					
Dieter et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Ilbäck et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Obone et al. 1999 (rat)	Yes	No	Yes	Yes	Moderate
Oral chronic exposure					
Ambrose et al. 1976 (dog)	Yes	No	Yes	No	Low
Dermal acute exposure					
Siller and Seymour 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Outcome: Reproductive effects					
Inhalation acute exposure					
NTP 1996a (rat)	Yes	Yes	Yes	No	Moderate
NTP 1996a (mouse)	Yes	Yes	Yes	No	Moderate
NTP 1996b (rat)	Yes	Yes	Yes	No	Moderate
NTP 1996b (mouse)	Yes	Yes	Yes	No	Moderate
NTP 1996c (rat)	Yes	Yes	Yes	No	Moderate
NTP 1996c (mouse)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Oral acute exposure					
Saini et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014a (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 0–5)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 6–13)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 14–18)	Yes	Yes	Yes	Yes	High
Seidenberg et al. 1986 (mouse)	Yes	Yes	Yes	Yes	High
Sobti and Gill 1989 (mouse, nickel sulfate)	Yes	No	No	Yes	Low
Sobti and Gill 1989 (mouse, nickel nitrate)	Yes	No	No	Yes	Low
Sobti and Gill 1989 (mouse, nickel chloride)	Yes	No	No	Yes	Low
Oral intermediate exposure					
Ambrose et al. 1976 (rat)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat; male 28 or 42 days prior to mating)	Yes	No	Yes	Yes	Moderate
Käkelä et al. 1999 (rat, female; 14 or 100 days prior to mating)	Yes	No	Yes	Yes	Moderate
Käkelä et al. 1999 (rat, Male and female; 28–76 days)	Yes	No	Yes	Yes	Moderate
Obone et al. 1999 (rat)	Yes	Yes	Yes	No	Moderate
Pandey and Srivastava 2000 (mouse, nickel chloride)	Yes	Yes	Yes	Yes	High
Pandey and Srivastava 2000 (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Pandey et al. 1999 (mouse, one dose group)	Yes	Yes	Yes	Yes	High
Pandey et al. 1999 (mouse, two dose groups)	Yes	Yes	Yes	Yes	High
EPA 1988a, 1988b (rat)	Yes	Yes	Yes	Yes	High
Smith et al. 1993 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Springborn Laboratories 2000a (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2000b (rat)	Yes	Yes	Yes	Yes	High
Toman et al. 2012 (mouse)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Ambrose et al. 1976 (dog)	Yes	Yes	Yes	No	Moderate
Outcome: Developmental effects					
Oral acute exposure					
Saini et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014a (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 0–5)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 6–13	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (Mouse, GDs 14–18)	Yes	Yes	Yes	Yes	High
Seidenberg et al. 1986 (mouse)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Ambrose et al. 1976 (rat)	Yes	Yes	Yes	Yes	High
EPA 1983 (mouse)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat, 28–76 days)	Yes	Yes	Yes	Yes	High
EPA 1988a, 1988b (rat)	Yes	Yes	Yes	Yes	High
Smith et al. 1993 (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2000a (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2000b (rat)	Yes	Yes	Yes	Yes	High

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-15.

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation exposure		
Human cohort studies		
Berge and Skyberg 2003	Low	Moderate
Human cross-sectional studies		
Fishwick et al. 2004	Moderate	Moderate
Kilburn et al. 1990	Moderate	
Muir et al. 1993	Moderate	
Wu et al. 2022	Moderate	
Animal acute exposure		
Benson et al. 1995b (rat)	High	High
Efremenko et al. 2014 (rat)	High	
Efremenko et al. 2017a, 2017b (rat)	High	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Animal intermediate exposure		
Benson et al. 1995a (rat, nickel sulfate)	High	High
Benson et al. 1995a (rat, nickel oxide)	High	
Benson et al. 1995a (mouse, nickel sulfate)	High	
Benson et al. 1995a (mouse, nickel oxide)	High	
Benson et al. 1995b (rat)	High	
Bingham et al. 1972 (rat)	Moderate	
Efremenko et al. 2014 (rat)	High	
Efremenko et al. 2017a, 2017b (rat)	High	
Evans et al. 1995 (rat)	High	
Horie et al. 1985 (rat)	Low	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oller et al. 2023 (rat, nickel sulfate)	High	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Oller et al. 2023 (rat, nickel subsulfide)	High	
Weischer et al. 1980 (rat)	High	
Animal chronic exposure		
NTP 1996a (rat)	High	High
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oller et al. 2008 (rat)	High	
Ottolenghi et al. 1975 (rat)	High	
Takenaka et al. 1985 (rat)	Low	
Tanaka et al. 1988 (rat)	Low	
Oral exposure		
Animal intermediate exposure		
American Biogenics Corporation 1988 (rat)	High	High
Obone et al. 1999 (rat)	Moderate	
EPA 1988a, 1988b (rat)	High	
Springborn Laboratories 2002 (rat)	High	
Animal chronic exposure		
Ambrose et al. 1976 (dog)	Low	
Outcome: Immunological effects		
Inhalation exposure		
Human cohort studies		
Bencko et al. 1983	Moderate	Moderate
Bencko et al. 1986	Moderate	
Animal acute exposure		
Adkins et al. 1979 (mouse, bacteria clearance)	High	High
Adkins et al. 1979 (mouse, nickel chloride)	High	
Adkins et al. 1979 (mouse, nickel sulfate)	High	
Buxton et al. 2021 (mouse)	High	
Graham et al. 1978 (mouse)	High	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Animal intermediate exposure		
Haley et al. 1990 (mouse, nickel oxide)	High	High
Haley et al. 1990 (mouse, nickel subsulfide)	High	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Haley et al. 1990 (mouse, nickel sulfate)	High	
Johansson et al. 1987 (rabbit)	Moderate	
Johansson et al. 1988a, 1989 (rabbit)	Moderate	
Morimoto et al. 1995 (rat)	Moderate	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Spiegelberg et al. 1984 (rat)	High	
Animal chronic exposure		
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	High
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oller et al. 2008 (rat)	High	
Ottolenghi et al. 1975 (rat)	High	
Oral exposure		
Animal intermediate exposure		
Dieter et al. 1988 (mouse)	High	
Ilbäck et al. 1994 (mouse)	Moderate	Moderate
Obone et al. 1999 (rat)	Moderate	
Animal chronic exposure		
Ambrose et al. 1976 (dog)	Low	
Dermal exposure		
Animal acute exposure		
Siller and Seymour 1994 (mouse)	Moderate	Moderate
Outcome: Reproductive Effects		
Human cohort studies		
Chashschin et al. 1994	Moderate	Moderate
Human case-control studies		
Vaktskjold et al. 2008b	Moderate	Moderate
Inhalation exposure		
Animal acute exposure		
NTP 1996a (rat)	Moderate	
NTP 1996a (mouse)	Moderate	
NTP 1996b (rat)	Moderate	Moderate
NTP 1996b (mouse)	Moderate	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1996c (rat)	Moderate	
NTP 1996c (mouse)	Moderate	
Animal intermediate exposure		
NTP 1996a (rat)	High	High
NTP 1996b (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Animal chronic exposure		
NTP 1996a (rat)	High	High
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oral exposure		
Animal acute exposure		
Saini et al. 2013 (mouse)	High	High
Saini et al. 2014a (mouse)	High	
Saini et al. 2014b (mouse, GDs 0–5)	High	
Saini et al. 2014b (mouse, GDs 6–13)	High	
Saini et al. 2014b (mouse, GDs 14–18)	High	
Seidenberg et al. 1986 (mouse)	High	
Sobti and Gill 1989 (mouse, nickel sulfate)	Low	
Sobti and Gill 1989 (mouse, nickel nitrate)	Low	
Sobti and Gill 1989 (mouse, nickel chloride)	Low	
Animal intermediate exposure		
Ambrose et al. 1976 (rat)	High	High
Käkelä et al. 1999 (rat; male 28 or 42 days prior to mating)	Moderate	
Käkelä et al. 1999 (rat, female; 14 or 100 days prior to mating)	Moderate	
Käkelä et al. 1999 (rat, Male and female; 28–76 days)	Moderate	
Obone et al. 1999 (rat)	Moderate	
Pandey and Srivastava 2000 (mouse, nickel chloride)	High	
Pandey and Srivastava 2000 (mouse, nickel sulfate)	High	
Pandey et al. 1999 (mouse, one dose group)	High	
Pandey et al. 1999 (mouse, two dose groups)	High	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
EPA 1988a, 1988b (rat)	High	
Smith et al. 1993 (rat)	High	
Springborn Laboratories 2000a (rat)	High	
Springborn Laboratories 2000b (rat)	High	
Toman et al. 2012 (mouse)	High	
Animal chronic exposure		
Ambrose et al. 1976 (dog)	Moderate	Moderate
Outcome: Developmental Effects		
Human cohort studies		
Chashschin et al. 1994	Moderate	Moderate
Vaktskjold et al. 2006	Moderate	
Vaktskjold et al. 2007	Moderate	
Vaktskjold et al. 2008a	Moderate	
Oral exposure		
Animal acute exposure		
Saini et al. 2013 (mouse)	High	High
Saini et al. 2014a (mouse)	High	
Saini et al. 2014b (mouse, GDs 0–5)	High	
Saini et al. 2014b (mouse, GDs 6–13	High	
Saini et al. 2014b (Mouse, GDs 14–18)	High	
Seidenberg et al. 1986 (mouse)	High	
Animal intermediate exposure		
Ambrose et al. 1976 (rat)	High	High
EPA 1983 (mouse)	High	
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	High	
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	High	
Käkelä et al. 1999 (rat, 28–76 days)	High	
EPA 1988a, 1988b (rat)	High	
Smith et al. 1993 (rat)	High	
Springborn Laboratories 2000a (rat)	High	
Springborn Laboratories 2000b (rat)	High	

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-16. 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-17.

Table C-16. 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	Low
Animal studies	High	+1 Consistency	High
Outcome: Immunological effects			
Human studies	Moderate	-1 Risk of bias	Low
Animal studies	High		High
Outcome: Reproductive effects			
Human studies	Moderate	-1 Inconsistency	Low
Animal studies	High	-2 Inconsistency	Low
Outcome: Developmental effects			
Human studies	Moderate	-1 Inconsistency	Low
Animal studies	High		High

Table C-17. 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
Reproductive effects	Low	Low
Developmental effects	Low	High

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-8 and C-9). 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

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 Table C-18.

Table C-18. 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
Reproductive effects	Low	Uncertain	Low
Developmental effects	Low	Health effect	Low
Animal studies			
Respiratory effects	High	Health effect	High
Immunological effects	High	Health effect	High
Reproductive effects	Low	Uncertain	High
Developmental 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:

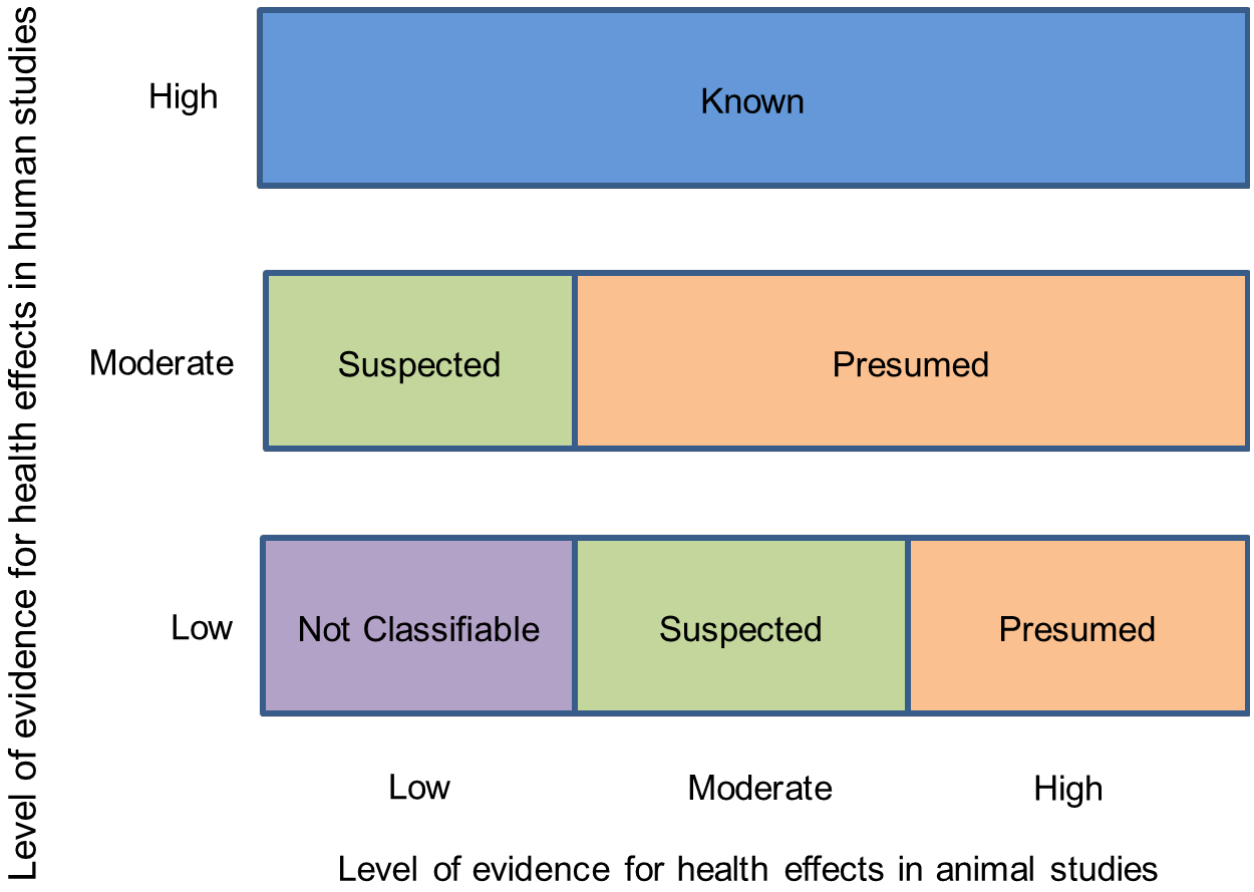
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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

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.

Figure C-1. Hazard Identification Scheme



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. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for nickel are listed below and summarized in Table C-19.

Presumed Health Effects

- Respiratory effects
  - Low level of evidence from human studies of occupational cohorts exposed via inhalation (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022).
  - High level of evidence in rats and mice from acute-duration exposure to nickel (Benson et al. 1995b; Efremenko et al. 2014, 2017a, 2017b; NTP 1996a, 1996b, 1996c), intermediate-duration exposure to nickel (Benson et al. 1995a, 1995b; Efremenko et al. 2014, 2017a, 2017b; Evans et al. 1995; Horie et al. 1985; NTP 1996a, 1996b, 1996c; Oller et al. 2023 Weischer et al. 1980), and chronic-duration exposure to nickel (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1975; Takenaka et al. 1985; Tanaka et al. 1988).
  - High level of evidence in rats following acute-, intermediate-, and chronic-duration oral exposure (Ambrose et al. 1976; American Biogenics Corporation 1988; EPA 1988a, 1988b; Obone et al. 1999; Springborn Laboratories 2002).
- Immunological effects
  - Low evidence from human inhalation studies due to the lack of controls and lack of confidence in the exposures (Bencko et al. 1983, 1986).
  - High level of evidence in rats, mice, and rabbits from inhalation exposure to nickel (Adkins et al. 1979; Graham et al. 1978; Haley et al. 1990; Johansson et al. 1987, 1988a, 1989; Morimoto et al. 1995; Oller et al. 2008).
  - 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).
- Developmental effects
  - Low evidence from human studies due to the small number of studies and inconsistencies of the findings (Chashschin et al. 1994; Vaktskjold et al. 2006, 2007, 2008a).
  - High level of evidence from animal inhalation (Weischer et al. 1980) studies and oral studies (Ambrose et al. 1976; El-Sekily et al. 2020; EPA 1983, 1988a, 1988b; Käkelä et al. 1999; Saini et al. 2013, 2014a, 2014b; Seidenberg et al. 1986; Smith et al. 1993; Springborn Laboratories 2000b).

Not Classifiable

- Reproductive effects
  - Low evidence from human studies due to the inconsistency of the findings (Chashschin et al. 1994; Vaktskjold et al. 2008b).
  - Low level of evidence from animal studies. Male reproductive effects were observed in rats exposed via inhalation to nickel oxide (NTP 1996a) but not after exposure to nickel subsulfide or nickel sulfate (NTP 1996b, 1996c). There was a high degree of inconsistency among the oral exposure studies examining male reproductive effects, with some studies finding effects (Käkelä et al. 1999; Pandey and Srivastava 2000; Pandey et al. 1999; Sobti and Gill 1989) and other studies finding no effects (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Smith et al. 1993; Springborn Laboratories 2000b; Toman et al. 2012).

Table C-19. Hazard Identification Conclusions for Nickel

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Immunological effects	Presumed health effect
Reproductive effects	Not classifiable
Developmental 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), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), 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.

(17) 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									

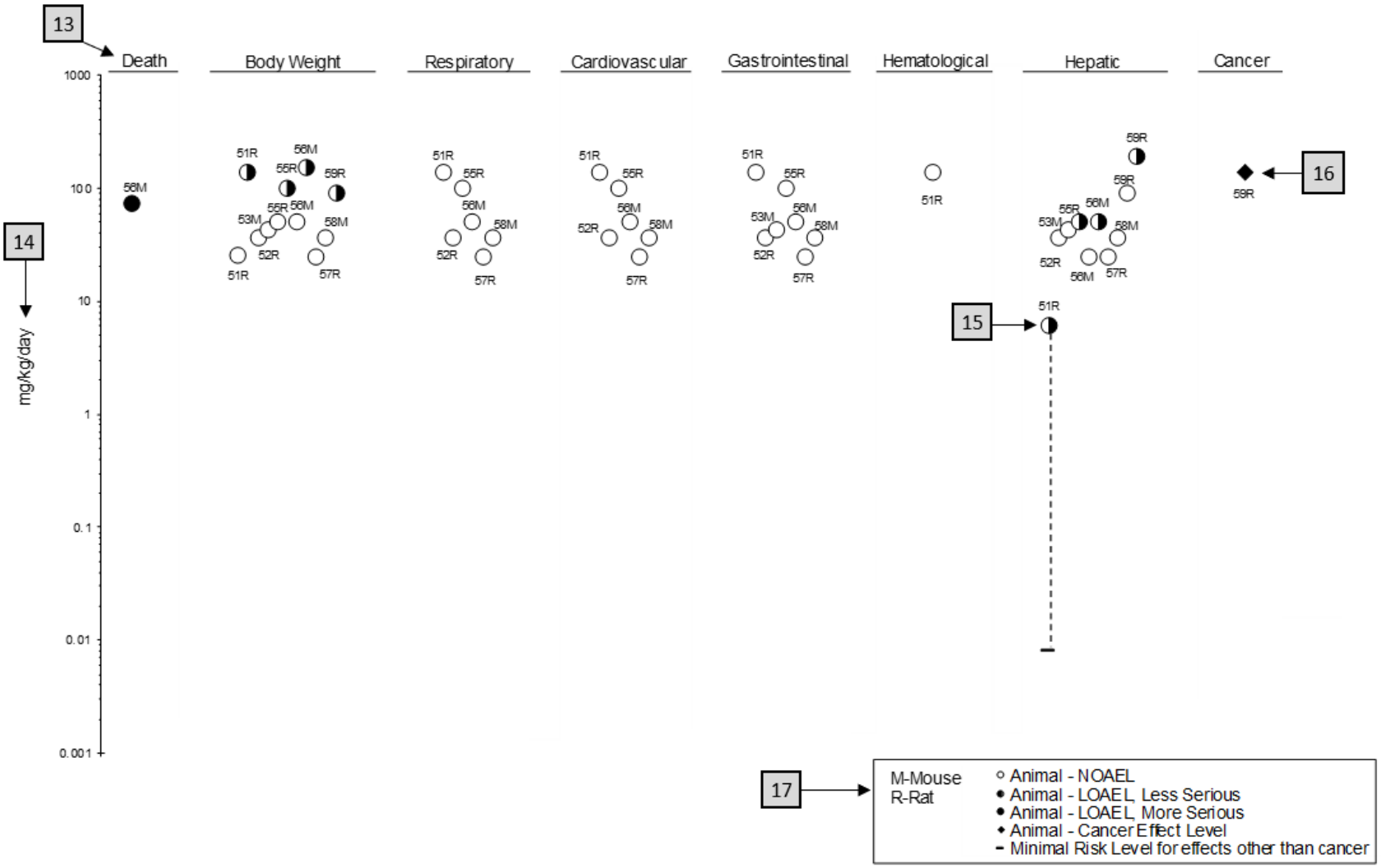
[a]The number corresponds to entries in Figure 2-x.

(11) [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).

APPENDIX D

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:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a 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.html).

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, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • 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 malignant 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 LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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 exposure level 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 exposure level, 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/m^3 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.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

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
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 Substances 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 limit
REL-C	recommended exposure limit-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
SLOAEL	serious lowest-observed-adverse-effect level
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
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result