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

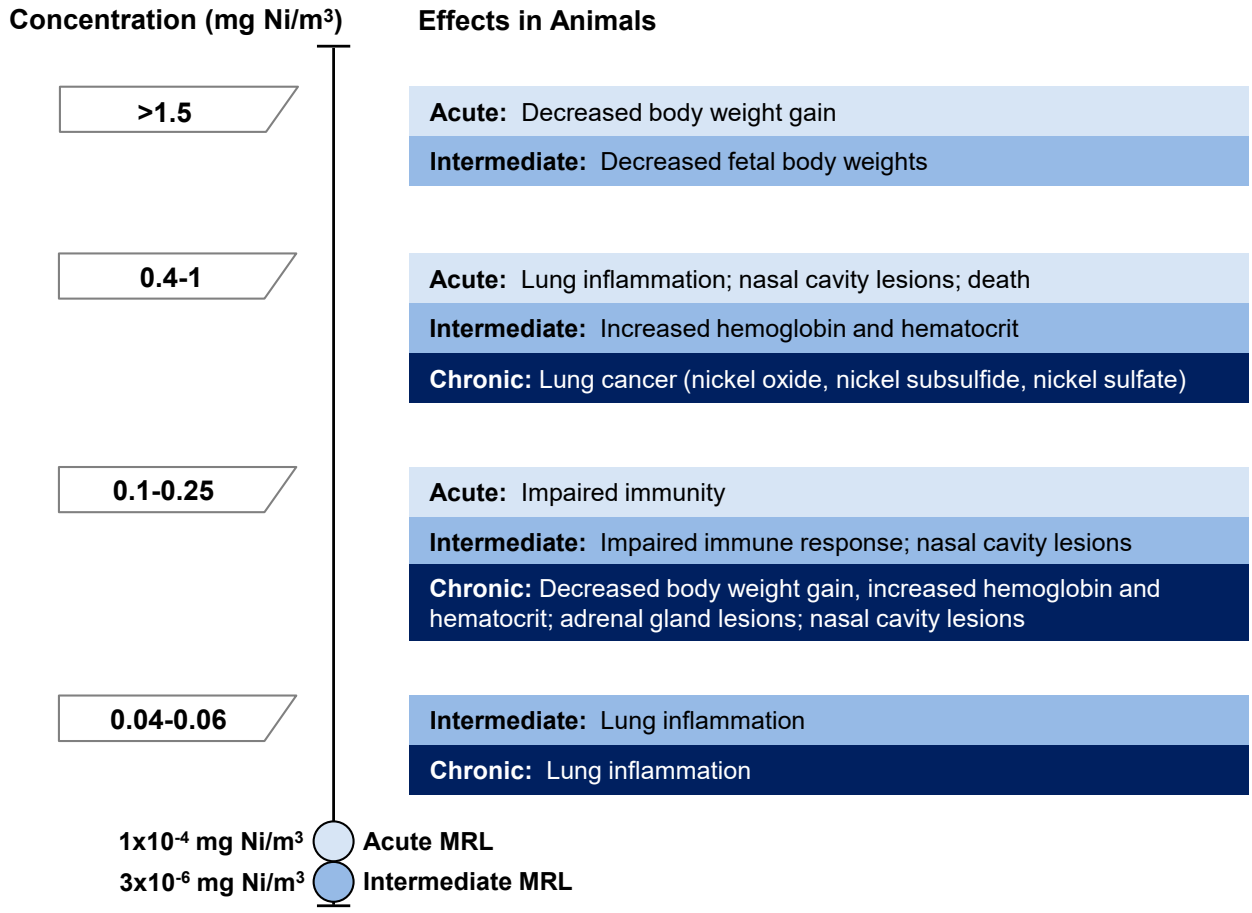
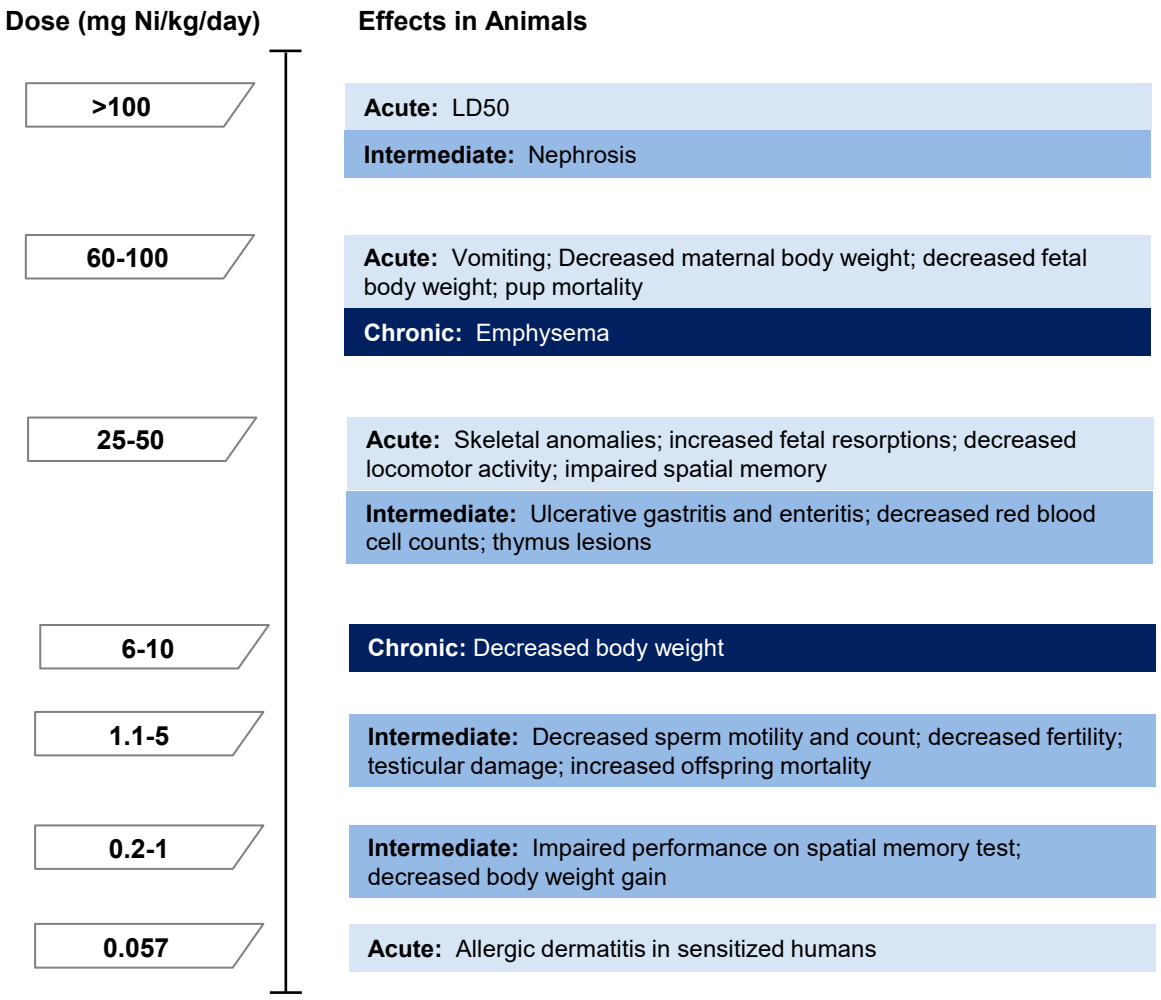


Figure 1-2. Health Effects Found in Humans* and Animals Following Oral Exposure to Nickel



*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.

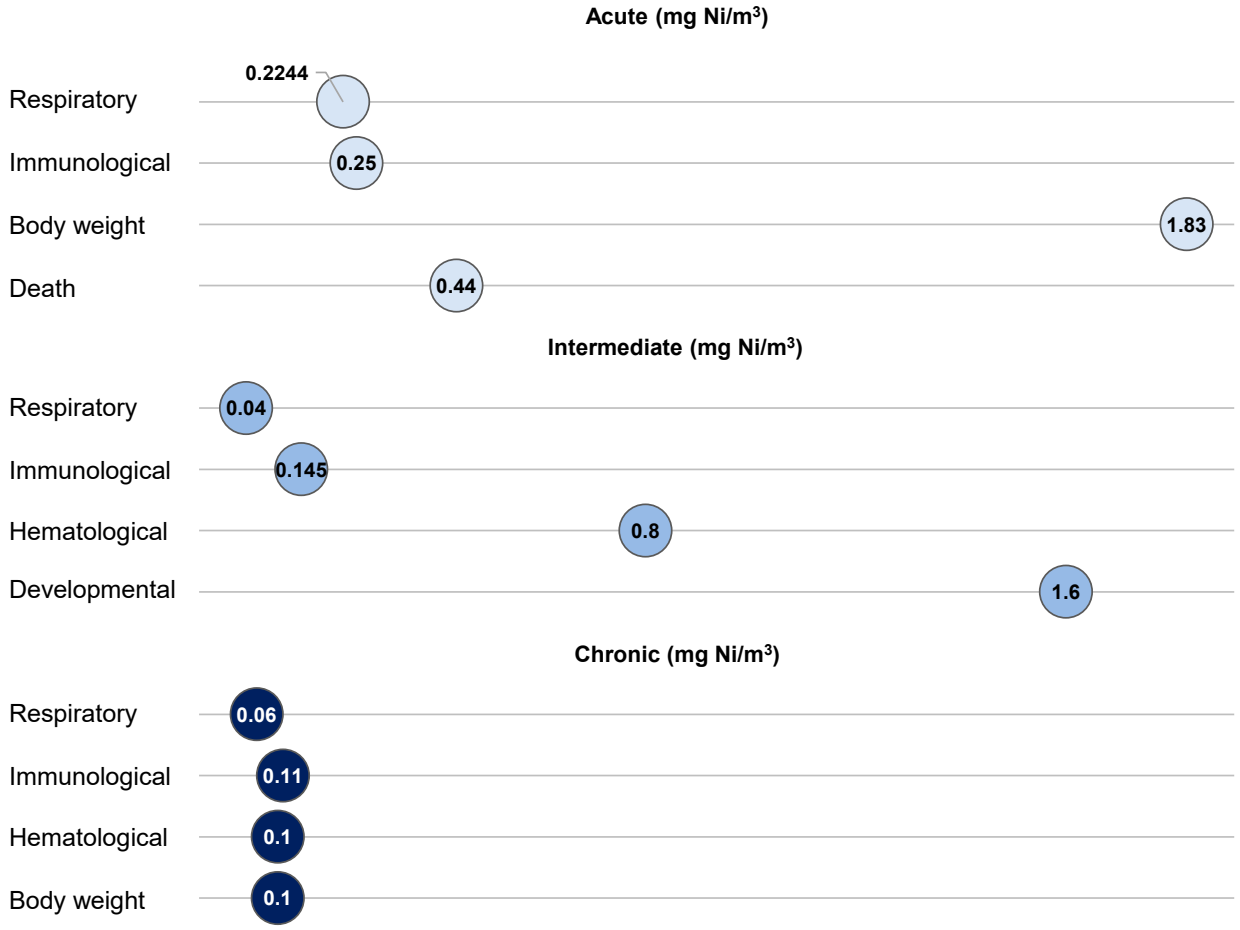


Figure 1-4. Summary of Sensitive Targets of Nickel – Oral

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.

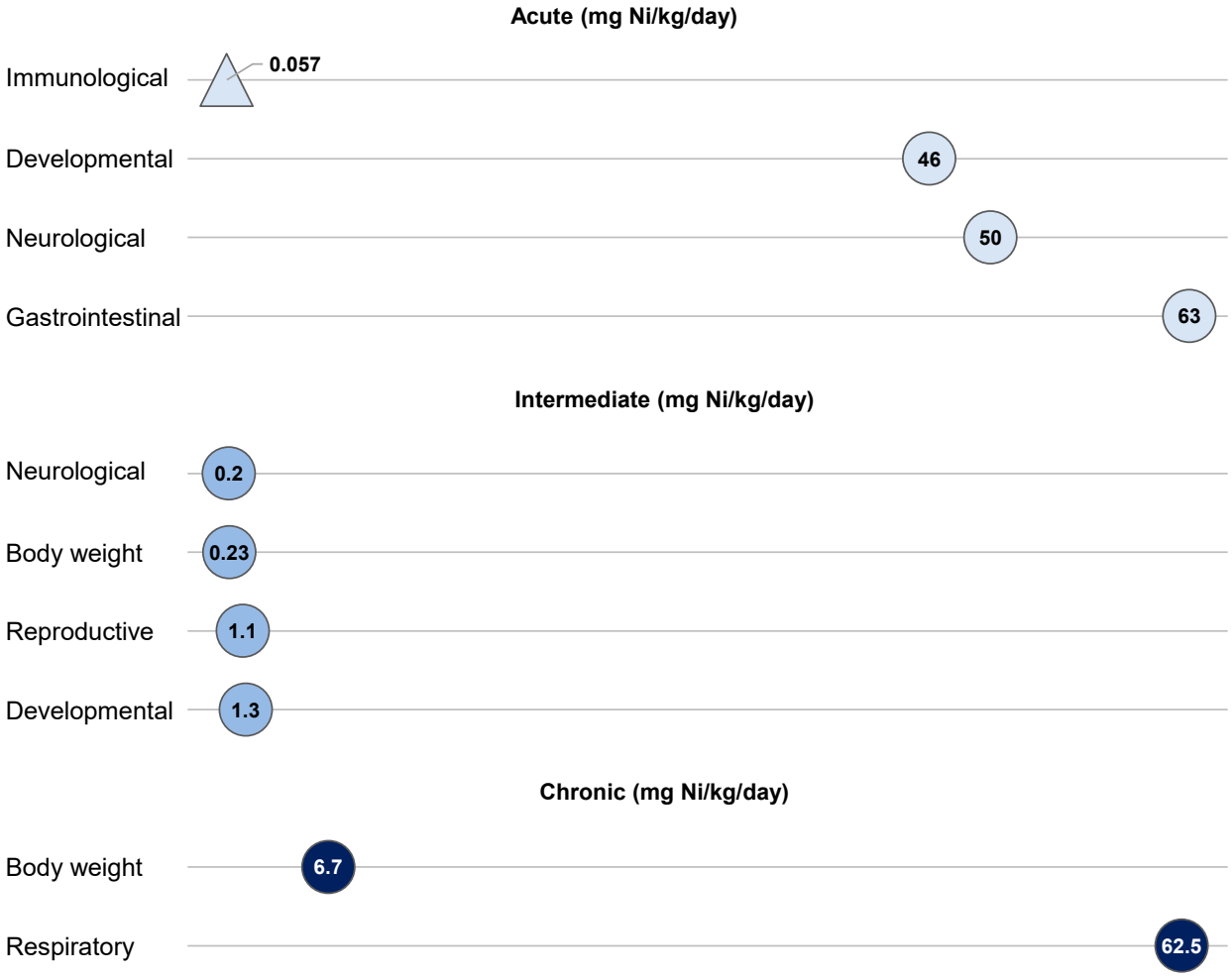


Table 1-1. Minimal Risk Levels (MRLs) for Nickel[a]

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