CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

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

1.2 SUMMARY OF HEALTH EFFECTS

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

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

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

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

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

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

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

Dermal. Contact dermatitis is commonly observed in individuals allergic to nickel or who have become sensitized to it. As previously noted, adverse immune responses to airborne nickel are reported in workers. In controlled human studies, dermatitis is reported in individuals who were sensitized to nickel dermally and then ingested single oral challenges of nickel-containing solution (Burrows et al. 1981; Christensen and Möller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Hindsén et al. 2001; Jensen et

al. 2003; Kaaber et al. 1978; Veien et al. 1987). Prolonged dermal exposure to nickel, such as by wearing nickel-containing jewelry, may lead to nickel sensitization (Akasya-Hillenbrand and Ozkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widström 1985; Meijer et al. 1995; Uter et al. 2003). Increased ingestion of nickel through diet for 4 days was also found to aggravate hand eczema (dermatitis) in women already diagnosed (Nielsen et al. 1990). Patch tests with nickel sulfate on sensitive individuals indicates a concentration-response relationship between contact dermatitis severity and nickel exposure (Emmett et al. 1988; Eun and Marks 1990). Some evidence suggests that acute or intermediate exposure to nickel orally may reduce sensitization (Jordan and King 1979; van Hoogstraten et al. 1991).

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

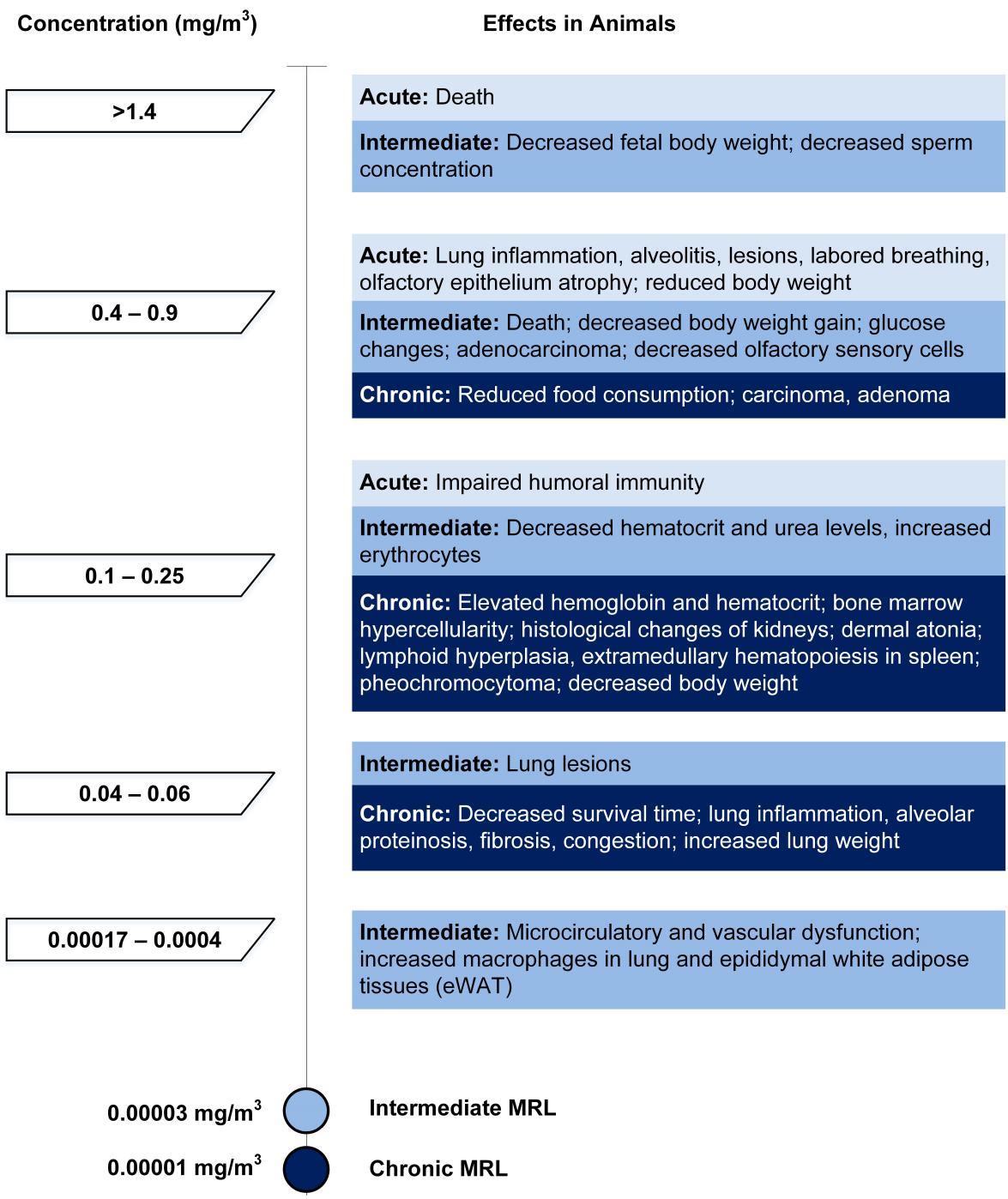
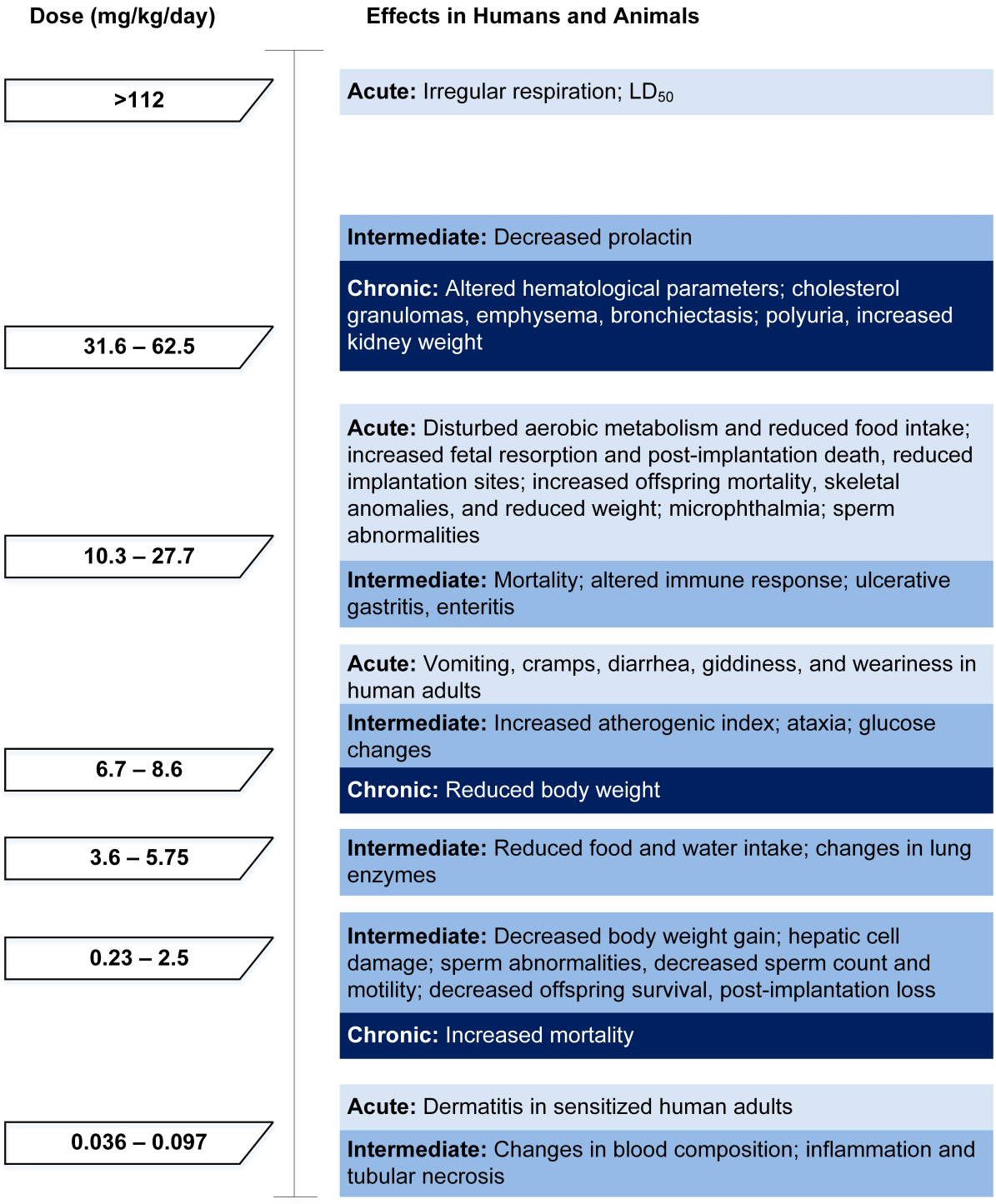


Figure 1-2. Health Effects Found in Humans* and Animals Following Oral Exposure to Nickel



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

1.3 MINIMAL RISK LEVELS (MRLS)

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

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

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

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

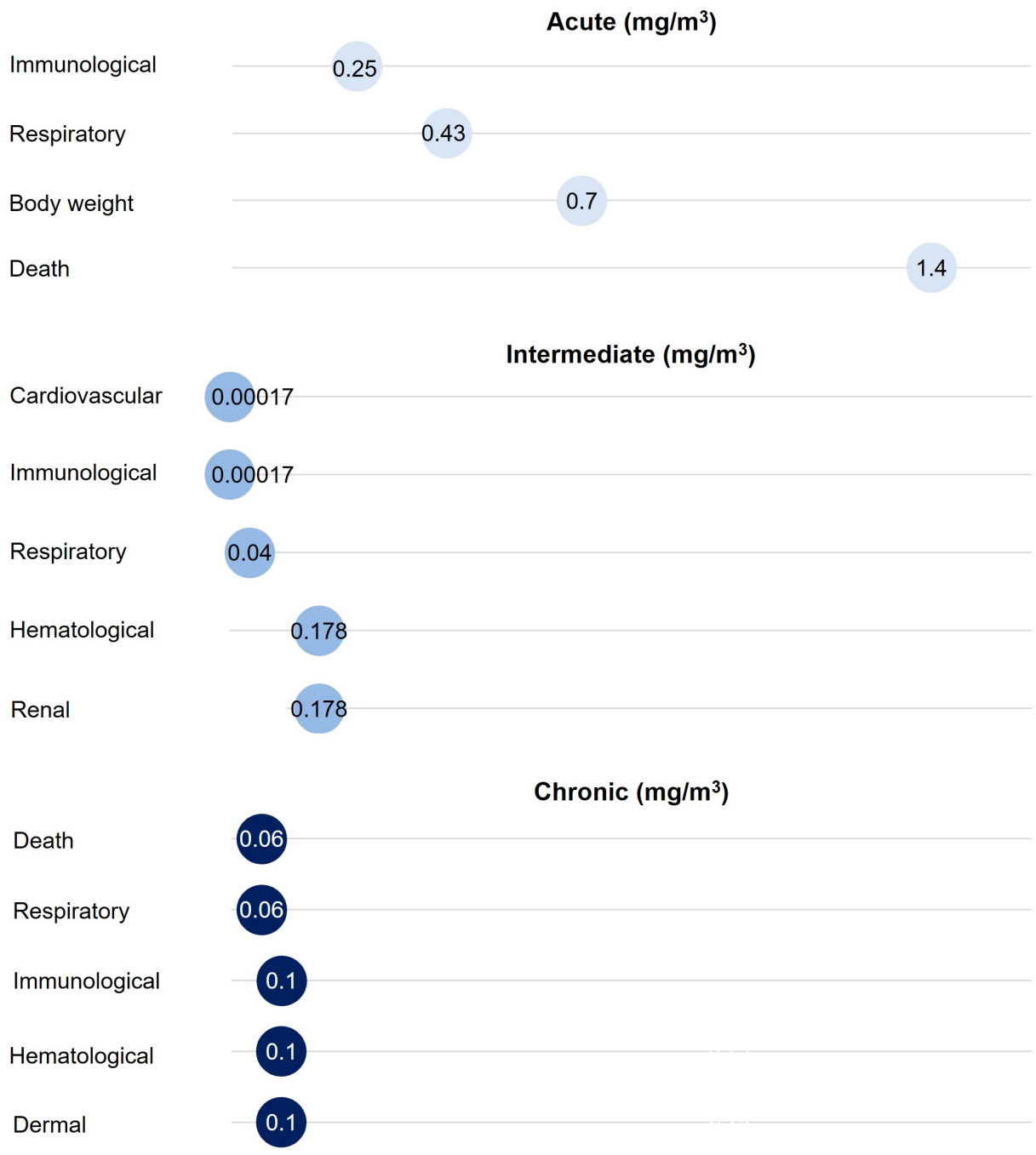


Figure 1-4. Summary of Sensitive Targets of Nickel – Oral

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

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

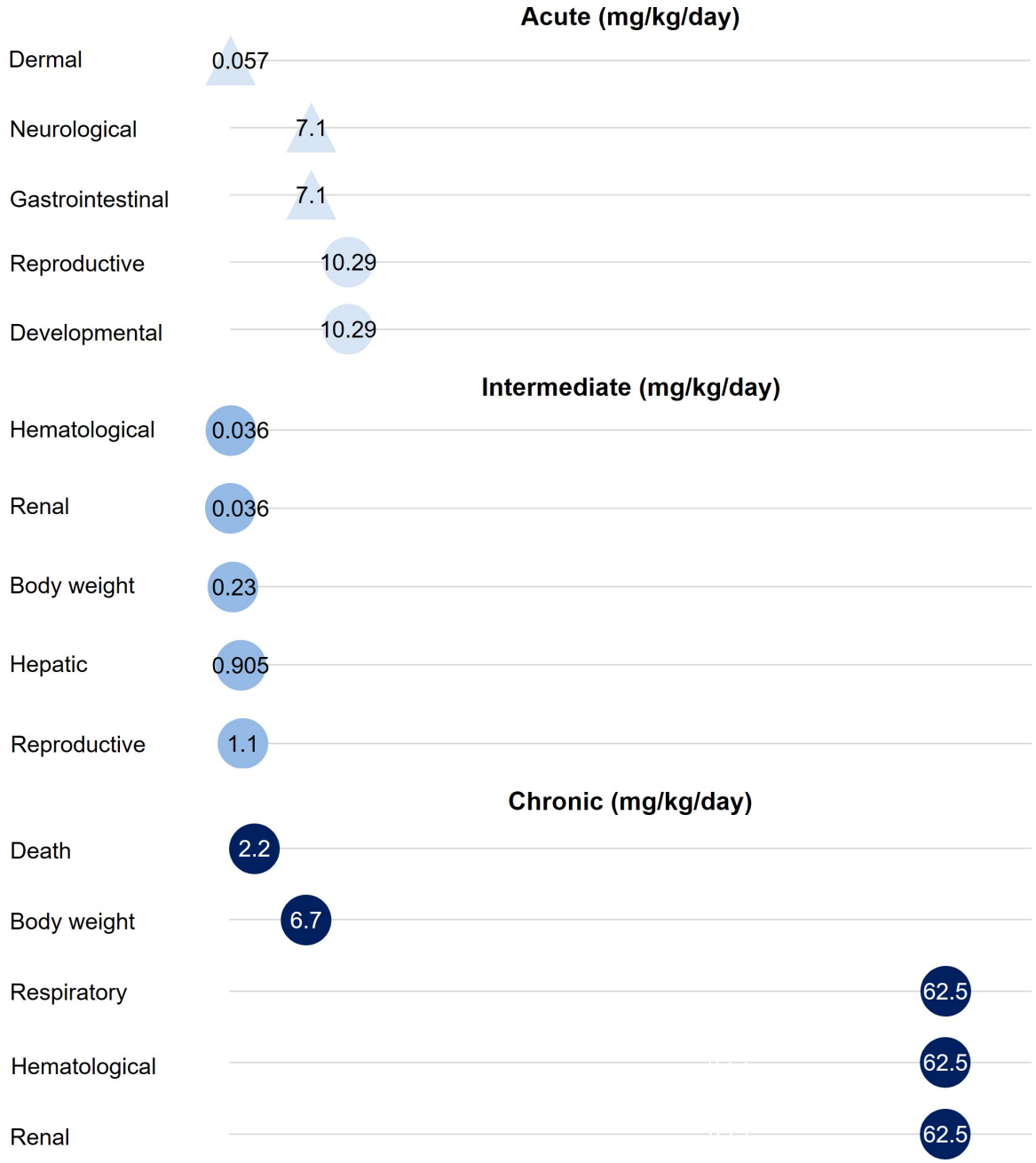


Table 1-1. Minimal Risk Levels (MRLs) for Chemical Nickel[a]

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

[a]See Appendix A for additional information.

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