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

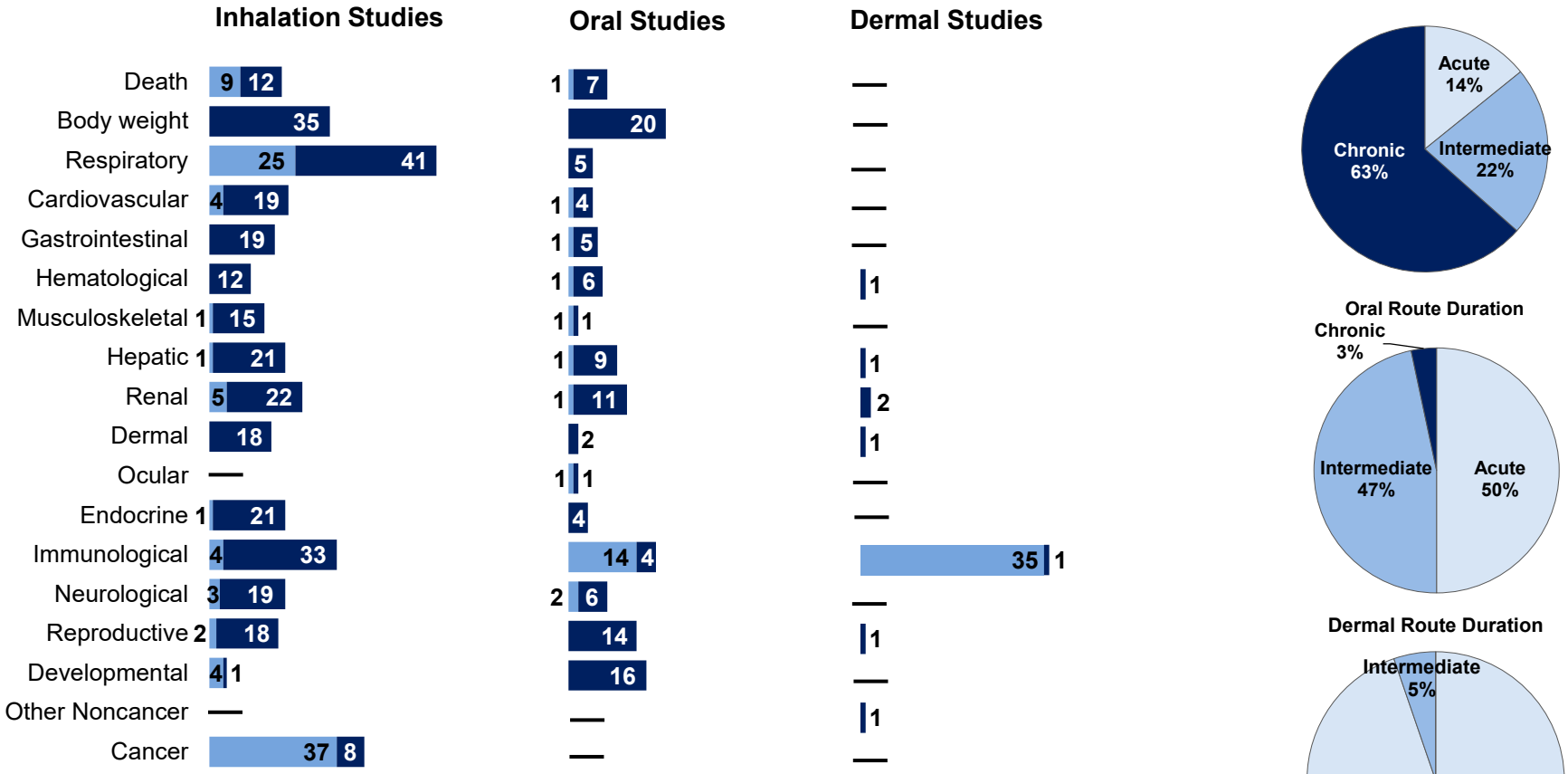
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to nickel that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of nickel. The number of human and animal 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.