CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

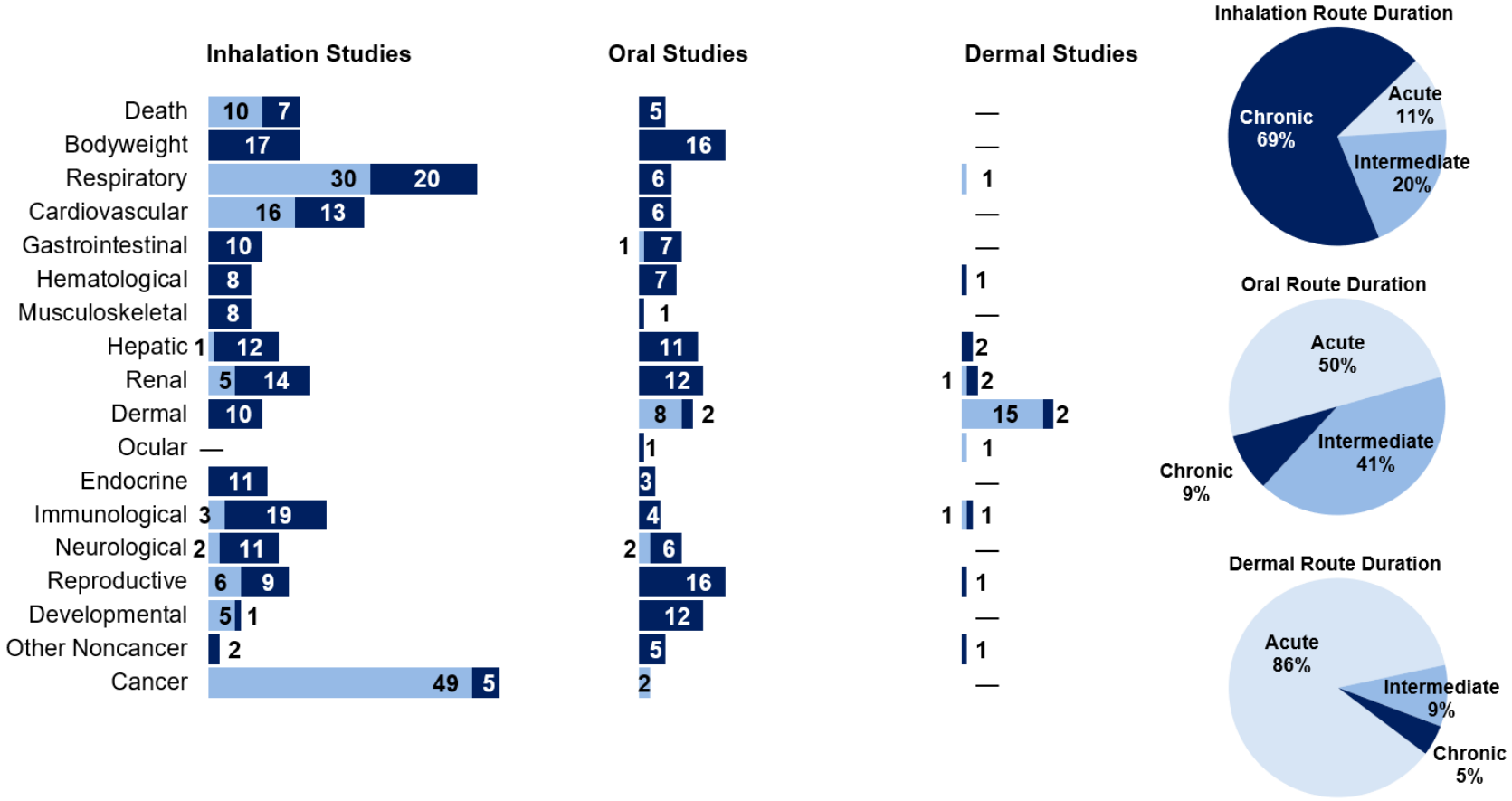
6.1 EXISTING INFORMATION ON HEALTH EFFECTS

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

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

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

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



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

6.2 IDENTIFICATION OF DATA NEEDS

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

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

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

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

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

Health Effects.

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

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

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

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

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

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

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

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

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

Biomarkers of Exposure and Effect.

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

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

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

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

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

Children's Susceptibility.

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 ONGOING STUDIES

There is no information on any ongoing studies for nickel.