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).

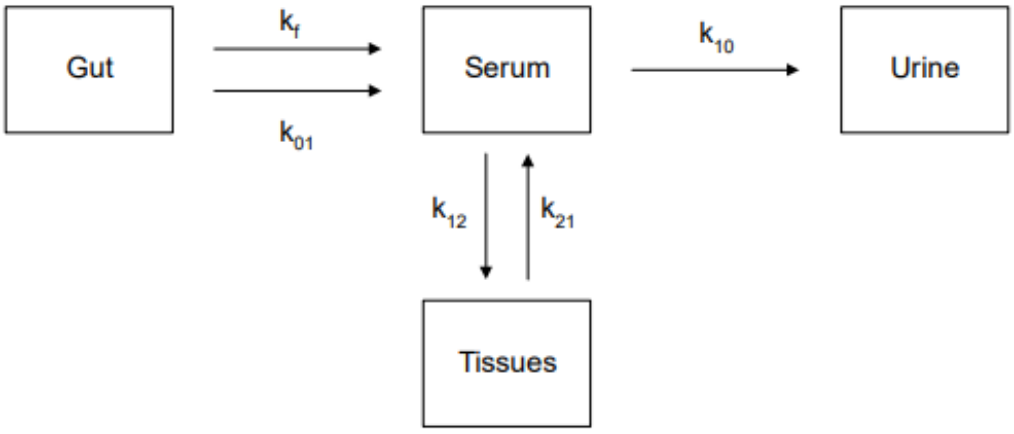
Sunderman et al. (1989b; Dede et al. 2018) Model

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.