

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO NICKEL IN THE UNITED STATES

Nickel is a very hard metal that occurs naturally in soils and volcanic dust. Nickel is used in combination with other metals to form alloys used for coins, jewelry, and stainless steel. Nickel compounds are used for electroplating, to color ceramics, and in battery production.

Nickel is released to the atmosphere by windblown dust, volcanoes, combustion of fuel oil, municipal incineration, and industries involved in nickel refining, steel production, and other nickel alloy production. The form of nickel emitted to the atmosphere is dependent upon the source. Complex nickel oxides, nickel sulfate, and metallic nickel are associated with combustion, incineration, and smelting and refining processes. Ambient air concentrations of nickel range between 7 and 12 ng/m³, mainly in the form of aerosols and can be as high as 150 ng/m³ near point sources. Based on 1996 air quality data, EPA has reported U.S. levels of 2.2 ng/m³. Ambient air levels of nickel are expected to be higher in urban air than in rural air. Concentrations of nickel in indoor air are generally <10 ng/m³.

Background levels of nickel in soils vary widely depending on local geology and anthropogenic inputs, but concentrations typically range between 4 and 80 ppm. Some areas of the United States may contain natural levels as high as 5,000 ppm. Concentrations of nickel in household dust can be high and therefore pose an increased risk to young children who have greater contact with floors. Nickel concentrations in surface water and groundwater range between 3 and 10 µg/L. Nickel levels in drinking water in the United States generally range from 0.55 to 25 µg/L (1.1 to 50 µg/day, estimated using a reference water intake of 2 L/day) and average between 2–4 µg/L (4–8 µg/day). Elevated levels of nickel may exist as a result of the corrosion and leaching of nickel alloys used in valves and faucets. For the general population, the predominant route of exposure to nickel is through food intake. Nickel intake in the United States ranges between 69 and 162 µg/day. Based on these average water and food nickel levels, a daily dose of 0.001–0.016 mg/kg/day can be estimated using a reference body weight of 70 kg.

Nickel does not bioaccumulate to a great extent in animals. There is evidence of uptake and accumulation in certain plants.

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Nickel is an essential trace element in animals, although the functional importance of nickel has not been clearly demonstrated. It is considered essential based on reports of nickel deficiency in several animal species (e.g., rats, chicks, cows, goats). Nickel deficiency is manifested primarily in the liver; effects include abnormal cellular morphology, oxidative metabolism, and increases and decreases in lipid levels. Decreases in growth and hemoglobin concentration and impaired glucose metabolism have also been observed. The essentiality of nickel in humans has not been established, and nickel dietary recommendations have not been established for humans.

A 70-kg reference man contains 10 mg of nickel, giving an average body concentration of 0.1 ppm. Reference values for nickel in healthy adults is 0.2 µg/L in serum and 1–3 µg/L in urine. A National Health and Nutritional Examination Survey II of hair from a random sample of 271 adults found mean nickel levels of 0.39 ppm, with 10% having levels >1.50 ppm.

2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to nickel via inhalation, oral, and dermal routes of exposure. The targets of toxicity appear to be similar across exposure routes with the exception of portal of entry effects. The primary targets are the respiratory tract following inhalation exposure, the reproductive system and the developing organism following inhalation and oral exposure, and the immune system following inhalation, oral, or dermal exposure.

Information on the toxicity of nickel in humans comes from occupational studies, primarily nickel refinery workers, and studies and reports of allergic contact dermatitis in nickel-sensitized individuals. Neoplastic and nonneoplastic lung and nasal effects have been found in occupational exposure studies. Exposure to other metals confounds the interpretation of these data. Nickel sensitivity has been observed in workers and the general population. The contact dermatitis is the result of an allergic reaction to nickel and has been reported following dermal contact with airborne nickel, liquid solution, or metal items such as jewelry and prosthetic devices that contain nickel as well as oral exposure to nickel compounds.

The animal studies support the available human data that the respiratory tract and immune systems are sensitive targets of toxicity. Additionally, animal studies suggest that the reproductive system and the developing organism may also be sensitive to nickel. Inflammatory lung effects have been observed in a number of animal studies involving exposure to nickel sulfate, nickel subsulfide, or nickel oxide; damage to the nasal olfactory epithelium has also been observed in animals exposed to nickel sulfate or nickel

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sub sulfide. Long-term exposure to less-soluble nickel compounds (nickel subsulfide or nickel oxide) resulted in lung cancer. A number of animal studies have found impaired immune function following inhalation, oral, or dermal exposure to several nickel compounds. Male reproductive effects consisting of histological alterations, sperm parameter alterations, and impaired fertility have been observed in animals following oral exposure (not tested after dermal exposure). The primary developmental effect observed in animals orally exposed to nickel is increased fetal/pup mortality or decreased survival.

A greater detailed discussion of nickel-induced respiratory effects, cancer, immunological effects, reproductive effects, and developmental effects follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Respiratory Effects. Numerous human and animal studies have identified the respiratory tract as the most sensitive target of inhaled nickel toxicity. Chronic bronchitis, emphysema, and impaired lung function have been observed in nickel welders and foundry workers. Co-exposure to other toxic metals such as uranium, iron, lead, and chromium confounds the interpretation of these studies. The predominant respiratory effect in animals exposed to nickel sulfate, nickel subsulfide, or nickel oxide is lung inflammation. Other lung effects include increased lung weight, alveolar macrophage hyperplasia, interstitial infiltrates, proteinosis, fibrosis, and impaired lung function (as evidenced by labored breathing). In addition to the pulmonary effects, nickel sulfate and nickel subsulfide exposure resulted in atrophy of the nasal olfactory epithelium; the lowest-adverse-effect level (LOAEL) values for these lesions were similar to or higher than the LOAELs for lung inflammation. Damage to the olfactory epithelium was not observed following exposure to nickel oxide.

A series of studies conducted by NTP allow for the comparison of the toxicity of nickel sulfate, nickel subsulfide, and nickel oxide in rats and mice. Following acute- or intermediate-duration exposure, the toxicity of the different nickel compounds is related to its solubility, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The difference in the toxicity across compounds is probably due to the ability of water-soluble nickel compounds to cross the cell membrane and interact with cytoplasmic proteins. In contrast, the severity of inflammatory and proliferative lesions following chronic exposure was greater in rats exposed to nickel subsulfide or nickel oxide, as compared to nickel sulfate. Additionally, parenchymal damage secondary to inflammation was evident in the rats exposed to nickel subsulfide and nickel oxide, but not nickel sulfate. For all durations and nickel compounds tested, rats appear to be more sensitive to the lung effects than mice; significant increases in the incidence of lung inflammation were observed at lower concentrations in the rats than mice.

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However, mice were more susceptible to the lethal effects (presumably from impaired lung function) than rats.

Cancer. The carcinogenic effect of nickel has been well documented in occupationally-exposed individuals. Several cohorts of workers, particularly nickel refinery workers, found significant increases in the risk and incidence of lung and nasal cancers. For most of the studies, the exact nickel compound is not known, although it is believed that nickel sulfate and the combination of nickel sulfides and oxides are the causative agents. A common limitation of the occupational studies involves co-exposure to other metals, particularly arsenic and chromium, which are also carcinogenic. Increases in the incidence of lung tumors have also been observed in animals exposed to nickel subsulfide or nickel oxide, but not after nickel sulfate exposure.

The Department of Health and Human Services has determined that metallic nickel may reasonably be anticipated to be a human carcinogen and nickel compounds are known to be human carcinogens. Similarly, IARC classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). EPA has classified nickel refinery dust and nickel subsulfide in Group A (human carcinogen). Other nickel compounds have not been classified by the EPA. Based on the occupational data, inhalation unit risk levels of $2.4 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ and $4.8 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ were derived by EPA for nickel refinery dust and nickel subsulfide, respectively.

Although the evidence is sufficient to consider less-soluble nickel compounds as carcinogens following inhalation exposure, how environmental exposure to nickel affects cancer risk is not clear. Nickel levels in the environment are much lower than those that were associated with cancer in workers. In the environment, nickel is also more likely to be in the form of a mineral lattice rather than the more active nickel refinery dust that contains nickel subsulfide, the form of nickel most consistently associated with cancer. Although soluble nickel compounds may not be directly carcinogenic, as indicated by the negative results in the nickel sulfate bioassay, inhalation of nickel sulfate did result in an inflammatory response in the lungs of animals. Because sustained tissue damage can serve to promote carcinogenesis, epidemiology studies of humans who are exposed to many substances may not be able to distinguish between the carcinogenic activity of less-soluble nickel compounds and the promoting activity of toxic concentrations of soluble nickel compounds.

Immunological Effects. The immunotoxicity of nickel has been established in human and animal studies following inhalation, oral, and dermal exposure. In humans, the immune response to nickel is

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elicited as allergic contact dermatitis, a rash that develops shortly after exposure to metallic nickel or nickel compounds. Nickel sensitization typically involves initial exposure to a large nickel dose; thereafter, much lower doses or concentrations are needed to elicit a response. Nickel-induced dermatitis is not typically seen in nonsensitized humans. A number of studies have examined the prevalence of nickel sensitization in humans. In a survey of the general population, 11% of the subjects tested positive for nickel sensitization. Somewhat higher rates (approximately 15–20%) are found in subjects undergoing patch tests to identify the cause of contact dermatitis. These studies clearly demonstrated a higher prevalence in young women; this is probably due to a higher rate of ear piercing in this segment of the population rather than increased susceptibility to sensitization. Small oral doses of nickel (0.02 mg Ni/kg) can cause a flare-up in dermatitis among nickel-sensitized individuals. Animal studies demonstrate the potential of nickel to induce immune effects in nonsensitized individuals. Alterations in parameters of nonspecific immunity (e.g., natural killer cells, tumor necrosis factor, macrophage activity) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) have been observed in animals following inhalation or oral exposure.

Reproductive Effects. The available data suggest that the male reproductive system may be a sensitive target of ingested nickel toxicity; more minor reproductive effects have also been observed following inhalation exposure. Exposure of rats and mice to relatively low oral doses (1.9 mg/kg/day) of nickel chloride or nickel sulfate resulted in histological alterations in the epididymis and seminal vesicles; although other studies in rats and dogs have not found histological alterations following oral exposure to nickel for 90 days or 2 years. Decreases in sperm concentration, motility, and abnormalities have also been reported in mice orally exposed to nickel sulfate, nickel chloride, or nickel nitrate (Pandey et al. 2000; Pandey and Srivastava 2000; Sobti and Gill 1989). Significant alterations in fertility have been observed in some, but not all studies. Decreases in fertility were observed in male rats, but not in female rats orally exposed to nickel. However, a multigeneration study involving male and female exposure to nickel chloride did not find any significant alterations in fertility in rats.

Developmental Effects. Serious developmental effects have been reported in animals. Decreases in pup survival has been consistently observed in several studies that involved exposure prior to mating and during gestation and lactation. Decreased pup survival has also been observed in a study in which nickel-exposed males were mated with unexposed females. Decreases in pup body weights have also been reported. Differences in the study designs and the method of nickel chloride administration complicates identification of the threshold for developmental effects. The lowest LOAEL values range from 1.3 to 90 mg Ni/kg/day and the highest no-observed-adverse-effect level (NOAEL) values range from 4 to

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45 mg Ni/kg/day. Interpretation of these data is also complicated by the maternal toxicity, particularly decreases in body weight gain, which frequently occurred at the same dose levels. Inhalation exposure resulted in relatively minor effects, including decreases in fetal body weight.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

The acute toxicity of nickel has been assessed in several animal studies involving exposure to nickel sulfate (Evans et al. 1995; NTP 1996c), nickel chloride (Adkins et al. 1979; Graham et al. 1978), nickel subsulfide (Benson et al. 1995b; NTP 1996b), and nickel oxide (NTP 1996a). The observed effects include inflammatory changes in the lungs (Benson et al. 1995a; NTP 1996a, 1996b, 1996c), atrophy of the nasal olfactory epithelium (Evans et al. 1995; NTP 1996b, 1996c), hyperplasia in the bronchial and mediastinal lymph nodes (NTP 1996b, 1996c), impaired immune function (Adkins et al. 1979; Graham et al. 1978), and decreases in body weight gain (NTP 1996b, 1996c), which are probably secondary to the lung damage. NOAEL values for respiratory tract effects were not established for nickel sulfate or nickel subsulfide. In studies by the National Toxicology Program (NTP 1996b, 1996c) (6 hours/day for 12 days in a 16-day period), chronic lung inflammation and atrophy of the nasal olfactory epithelium were observed at the lowest tested nickel sulfate (0.7 mg Ni/m³) and nickel subsulfide (0.44 mg Ni/m³) concentrations. At 0.7 and 3.65 mg Ni/m³ as nickel sulfate and nickel subsulfide, respectively, the inflammation was accompanied by labored breathing, suggestive of impaired lung function. Alveolitis was also observed in rats exposed to 0.22 mg Ni/m³ as nickel subsulfide 6 hours/day for 7 days (Benson et al. 1995b). In mice, the LOAELs for chronic lung inflammation were 0.7 and 1.83 mg Ni/m³ for nickel sulfate and nickel subsulfide, respectively. Nickel oxide was less toxic than the other two nickel compounds. The NOAEL and LOAEL values for acute lung inflammation were 3.9 and 7.9 mg Ni/m³ in rats, respectively; in mice, the highest concentration tested (23.6 mg Ni/m³) was a NOAEL for respiratory effects. Based on these data and data from longer-term studies (NTP 1996a, 1996b, 1996c), nickel sulfate appears to be the most toxic to the respiratory tract of the three nickel compounds tested by NTP. The higher degree of toxicity is probably related to its solubility and increased ability to cross the cell membrane and interact with cytoplasmic proteins. Although the acute-duration nickel subsulfide study used lower concentrations than the nickel sulfate study, there is some evidence to suggest that the nickel sulfate effects were more severe. At 0.7 mg Ni/m³ as nickel sulfate, the chronic lung inflammation was given a severity score of 1.2–1.8 (minimal to mild) and was accompanied by labored breathing and a 28% decrease in body weight. The lung inflammation in rats exposed to 0.44 or 0.88 mg Ni/m³ as nickel

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sub sulfide was scored as minimal (1.0) and was not accompanied by altered respiration or body weight effects.

These acute-duration studies provide strong evidence that the respiratory tract is the most sensitive target of nickel toxicity. The three NTP (1996a, 1996b, 1996c) studies demonstrate that nickel sulfate is more toxic to the lungs than nickel subsulfide or nickel oxide. Because the lowest concentration tested in the nickel sulfate study (0.7 mg Ni/m³) was a serious LOAEL for respiratory and body weight effects, this study cannot be used for MRL derivation. An immunotoxicity study by Graham et al. (1978) established a lower LOAEL (0.25 mg Ni/m³) for a soluble nickel compound, nickel chloride; the NOAEL was 0.1 mg Ni/m³. This study was not selected as the basis for MRL because the respiratory tract was not examined and it is not known if the NOAEL for immunotoxicity would also be a NOAEL for respiratory effects.

- An MRL of 0.0002 mg Ni/m³ has been derived for intermediate-duration exposure to nickel.

The intermediate-duration toxicity of nickel has been assessed in several animal studies involving exposure to metallic nickel, nickel sulfate, nickel chloride, nickel subsulfide, and nickel oxide. The observed effects include inflammatory changes in the lungs (Benson et al. 1995b; Horie et al. 1985; NTP 1996a, 1996b, 1996c), alveolar macrophage hyperplasia (Benson et al. 1995b; Johansson and Camner 1986; NTP 1996a, 1996b, 1996c), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), hyperplasia in the bronchial and mediastinal lymph nodes (NTP 1996b, 1996c), impaired immune function (Adkins et al. 1979; Graham et al. 1978; Haley et al. 1990; Johansson et al. 1980, 1987, 1988a, 1989; Johansson and Camner 1986; Morimoto et al. 1995; Spiegelberg et al. 1984), decreases in body weight gain (NTP 1996b, 1996c; Weischer et al. 1980), which are probably secondary to the lung damage, decreased sperm concentration (NTP 1996a), and developmental toxicity (Weischer et al. 1980).

As with the acute-duration studies, the most sensitive target of nickel toxicity is the lungs. Chronic lung inflammation was observed at the lowest-adverse-effect levels following 13-week (6 hours/day, 5 days/week) exposures to nickel sulfate, nickel subsulfide, or nickel oxide (NTP 1996a, 1996b, 1996c). Intermediate-duration studies clearly demonstrate that nickel sulfate is more toxic than nickel subsulfide and nickel oxide. In rats, the respective NOAEL and LOAEL values for chronic lung inflammation were 0.06 and 0.11 mg Ni/m³ for nickel sulfate (NTP 1996c), 0.11 and 0.22 mg Ni/m³ for nickel subsulfide (NTP 1996b), and 2.0 and 3.9 mg Ni/m³ for nickel oxide (NTP 1996a). Atrophy of the nasal olfactory epithelium was observed at 0.22 and 0.44 mg Ni/m³ as nickel sulfate (NTP 1996c) and nickel subsulfide (NTP 1996b), respectively. Similar effects were observed in mice. For nickel sulfate and nickel subsulfide, the LOAEL values for mice were higher than the LOAELs identified in rats; the LOAEL for

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chronic inflammation following exposure to nickel oxide was the same in rats and mice. The LOAEL values for immunotoxicity, reproductive toxicity, and developmental toxicity were higher than the LOAEL values for respiratory effects in rats exposed to nickel sulfate.

Derivation of an intermediate-duration MRL based on the NTP study of nickel sulfate (NTP 1996c) would be protective against the toxicity of other nickel compounds. In the nickel sulfate study, alveolar macrophage hyperplasia was observed in rats exposed at the two lowest concentrations (0.03 and 0.06 mg Ni/m³). NTP noted that when lung effects only consisted of alveolar macrophage hyperplasia, there was only a slight increase in the number of alveolar macrophages and the differences between controls and nickel-exposed animals were subtle; the severity score for the alveolar macrophage hyperplasia was 1.0 (minimal). The minimal alveolar macrophage hyperplasia was not considered adverse because it is considered to be part of the normal physiologic response to inhaled particles and it is not believed to compromise the lung's ability to clear foreign matter. This is supported by the Benson et al. (1995a) study, which found no effect on the clearance of a nickel sulfate tracer in animals exposed to 0.03 or 0.11 mg Ni/m³ as nickel sulfate for 6 months. Thus, the 0.06 mg Ni/m³ concentration was identified as a NOAEL and adjusted for intermittent exposure (NOAEL_{ADJ}).

The intermediate-duration inhalation MRL of 0.0002 mg Ni/m³ was derived by dividing the NOAEL_{HEC} of 0.0052 mg Ni/m³ by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability). The NOAEL_{HEC} was calculated using the following equations:

$$\begin{aligned} \text{NOAEL}_{\text{ADJ}} &= 0.06 \text{ mg Ni/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} = 0.011 \text{ mg Ni/m}^3 \\ \text{NOAEL}_{\text{HEC}} &= \text{NOAEL}_{\text{ADJ}} \times \text{RDDR} = 0.011 \text{ mg Ni/m}^3 \times 0.474 = 0.0052 \text{ mg Ni/m}^3 \end{aligned}$$

The regional deposited dose ratio (RDDR) for the pulmonary region was used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using EPA software and the following parameters: particle size (MMAD) of 2.11 μm with a geometric standard deviation (sigma g) of 2.7 (as reported in Table K1 of NTP 1996c); default human body weight (70 kg), minute volume (13 L), and pulmonary surface area (54 m²); and default female F344 rat body weight (0.124 kg), minute volume (101.3 mL), and pulmonary surface area (0.34 m²).

- An MRL of 9x10⁻⁵ mg Ni/m³ has been derived for chronic-duration exposure to nickel.

One human study (Vyskocil et al. 1994a) and several animal studies (NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974; Takenaka et al. 1985; Tananka et al. 1988) assessed the noncarcinogenic toxicity

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of nickel sulfate, nickel chloride, nickel subsulfide, and nickel oxide. These studies found inflammatory changes in the lungs (NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974; Tanaka et al. 1988), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), evidence of renal damage (Vyskocil et al. 1994a), adverse adrenal effects (NTP 1996a), decreased body weight gain, which was probably associated with impaired lung function (NTP 1996b, 1996c; Takenaka et al. 1985), and damage to the bronchial lymph nodes (NTP 1996a, 1996b, 1996c).

As with the acute- and intermediate-duration exposures, chronic exposure to nickel sulfate, nickel subsulfide, or nickel oxide resulted in chronic active lung inflammation. A 2-year exposure (6 hours/day, 5 days/week) to nickel sulfate (NTP 1996c) resulted in chronic lung inflammation and bronchialization at 0.06 mg Ni/m³ and atrophy of the olfactory epithelium at 0.11 mg Ni/m³; no adverse respiratory effects were observed at 0.03 mg Ni/m³. A similar exposure to nickel subsulfide (NTP 1996b) resulted in chronic inflammation, alveolar epithelium hyperplasia, fibrosis, and rapid and shallow breathing at 0.11 mg Ni/m³, and atrophy of the nasal olfactory epithelium at 0.73 mg Ni/m³. Chronic lung inflammation and alveolar epithelial hyperplasia were observed at the lowest nickel oxide concentration tested (0.5 mg Ni/m³) (NTP 1996a). Similar effects were observed in mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 2 years; however, the LOAEL values were higher than for rats. The NTP (1996c) study of nickel sulfate identified the lowest LOAEL for respiratory effects (0.06 mg Ni/m³); the NOAEL of 0.03 mg Ni/m³ associated with this LOAEL was used to derive a chronic-duration inhalation MRL for nickel.

The chronic-duration inhalation MRL of 9×10^{-5} mg Ni/m³ was derived by dividing the NOAEL_{HEC} of 0.0027 mg Ni/m³ by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability). The NOAEL_{HEC} was calculated using the following equations:

$$\begin{aligned} \text{NOAEL}_{\text{ADJ}} &= 0.03 \text{ mg Ni/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} = 0.0054 \text{ mg Ni/m}^3 \\ \text{NOAEL}_{\text{HEC}} &= \text{NOAEL}_{\text{ADJ}} \times \text{RDDR} = 0.0054 \text{ mg Ni/m}^3 \times 0.506 = 0.0027 \text{ mg Ni/m}^3 \end{aligned}$$

The RDDR for the pulmonary region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate the RDDR: mean particle size (MMAD) of 2.5 μm with a geometric standard deviation (sigma g) of 2.38 (as reported in Table K1 of NTP 1996c); default human body weight (70 kg), minute volume (13 L), and pulmonary surface area (54 m²); and default female F344 rat body weight (0.229 kg), minute volume (167.3 mL), and pulmonary surface area (0.34 m²).

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Oral MRLs

Information on the acute oral toxicity of nickel in humans comes from reports of accidental exposures and studies of nickel-sensitized individuals. Gastrointestinal upset (vomiting, cramps, diarrhea) and neurological symptoms (giddiness, headache, weariness) were observed in workers accidentally ingesting water containing approximately 7.1–35.7 mg Ni/kg as nickel sulfate and nickel chloride; boric acid was also present in the water (Sunderman et al. 1988). Allergic dermatitis was observed in previously nickel-sensitized individuals ingesting 0.01–0.97 mg Ni/kg as nickel sulfate (Burrows et al. 1981; Christensen and Moller 1975; Cronin et al. 1980; Gawkrödger et al. 1986; Kaaber et al. 1978). Reliable data on the acute oral toxicity of nickel in animals is limited to two studies that examined a limited number of end points. A reproductive toxicity study in mice found significant increases in sperm head abnormalities in mice exposed to a single gavage dose of 23 mg Ni/kg as nickel nitrate (Sobti and Gill 1989). No developmental effects were observed in the offspring of mice exposed via gavage to 90.6 mg Ni/kg/day as nickel chloride on gestational days 8–12 (Seidenberg et al. 1986). Intermediate-duration studies suggest that the developing organism may be a sensitive target of nickel toxicity; however, this end point has not been adequately examined following acute-duration exposure; thus, an acute-duration oral MRL for nickel has not been derived.

A number of animal studies have assessed the toxicity of nickel following intermediate-duration oral exposure. Significant decreases in body weight and organ weight (liver, kidney, pituitary) were consistently observed in rats exposed to 8.6 mg Ni/kg/day and higher as nickel chloride (American Biogenics Corporation 1988; RTI 1988a, 1988b; Weischer et al. 1980), nickel acetate (Whanger 1973), or nickel sulfate (Dieter et al. 1988). Other systemic effects included changes in blood glucose levels at 8.6 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988) and 0.38 mg Ni/kg/day as nickel chloride (Weischer et al. 1980), kidney damage (minimal convoluted tubular damage) at 108 mg Ni/kg/day as nickel sulfate (Dieter et al. 1988), and adverse lung effects at 8.6 and 20 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988; RTI 1988b). A number of reproductive and developmental toxicity studies provide suggestive evidence that the reproductive system and the developing organism are sensitive targets of nickel toxicity in animals. Inconsistent results have been reported for the reproductive toxicity of nickel. Decreased sperm motility and count and sperm abnormalities were observed at 1.9 mg Ni/kg/day and higher as nickel sulfate (Pandey and Srivastava 2000; Pandey et al. 1999) and decreased fertility was observed in studies in which males and females were exposed to 3.6 mg Ni/kg/day as nickel chloride (Käkelä et al. 1999). However, impaired reproduction has not been observed in a multigeneration study of rats exposed to nickel chloride in

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drinking water (RTI 1988a, 1988b). There is stronger evidence that perinatal exposure to nickel results in decreased survival, as measured by live litter size and neonatal mortality, in pups of rat dams exposed to nickel chloride in drinking water prior to mating and during gestation and lactation (Ambrose et al. 1976; Käkälä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). Interpretation and comparison of the studies is complicated by differences in study design and maternal toxicity, which often occurs at the same dose levels as the developmental effects. The available data are not sufficient to establish a threshold for developmental effects to nickel chloride; the lowest LOAEL values identified in the studies range from 1.3 to 90 mg Ni/kg/day and the highest NOAEL values range from 4 to 45 mg Ni/kg/day. Because decreased pup survival is considered a serious LOAEL and a NOAEL for developmental effects has not been clearly identified, an intermediate-duration oral MRL was not derived for nickel.

The essentiality of nickel in humans has not been established (IOM 2002). In the U.S., dietary intake of nickel ranges from 69 to 162 µg/day (Pennington and Jones 1987) and average drinking water intakes range from 2 to 4 µg/L (4–8 µg/day, estimated using a reference water intake of 2 L/day). Based on these water and food nickel levels, a daily dose of 0.001–0.016 mg/kg/day can be estimated using a reference water intake of 2 L/day and body weight of 70 kg.

Data on the chronic toxicity of ingested nickel are limited to one animal study that found significant decreases in body weight and liver weights in rats exposed to 75 mg Ni/kg/day as nickel sulfate in the diet and decreases in body weight, increases in liver weight, and adverse renal and lung effects in dogs 62.5 mg Ni/kg/day (Ambrose et al. 1976). The available chronic-duration database was considered inadequate for MRL derivation because intermediate-duration studies found significant decreases in survival of the offspring of rats exposed to ≥ 1.3 mg Ni/kg/day (Ambrose et al. 1976; Käkälä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993).

