

## 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/m<sup>3</sup>, mainly in the form of aerosols and can be as high as 150 ng/m<sup>3</sup> near point sources. Based on 1996 air quality data, EPA has reported average U.S. ambient air levels of 2.2 ng/m<sup>3</sup>. 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/m<sup>3</sup>.

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 and average between 2 and 4.3 µg/L. Based on these average nickel concentrations and a reference water intake of 2 L/day, the estimated average intake of nickel from drinking water ranges from 4 to 8.6 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 for adults (>18 years of age). Based on these average water and food nickel levels, a daily dose of 0.001–0.0024 mg/kg/day can be estimated using a reference body weight of 70 kg. In children, mean daily nickel intakes of 9, 39, 82, and 99 µg/day have been determined for children aged 0–6 months, 7–12 months, 1–3 years, and 4–8 years, respectively. The mean daily dietary intakes of

## 2. RELEVANCE TO PUBLIC HEALTH

nickel in children aged 9–18 years (128–137 µg/day in males and 101–109 µg/day for females) are similar to the mean intakes determined in adults (>18 years of age).

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 found mean nickel levels of 0.39 ppm, with 10% of the population having levels >1.50 ppm.

About 20–35% of the inhaled nickel that is retained in the lungs is absorbed into the blood. Absorption of nickel following oral exposure has been shown to vary (3–40%) depending on whether the nickel was in drinking water or food, with greater absorption occurring with drinking water. Fasting individuals have also been shown to absorb more nickel from the gastrointestinal tract. Most of the absorbed nickel is excreted in the urine, regardless of the route of exposure.

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

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.

### 2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to nickel via inhalation, oral, and dermal routes of exposure. Based on occupational exposure studies, reports of allergic contact dermatitis, and animal exposure studies, the primary targets of toxicity appear to be the respiratory tract following inhalation exposure, the immune system following inhalation, oral, or dermal exposure, and possibly the reproductive system and the developing organism following oral exposure.

## 2. RELEVANCE TO PUBLIC HEALTH

The most commonly reported adverse health effect associated with nickel exposure is contact dermatitis. Contact dermatitis is the result of an allergic reaction to nickel that has been reported in the general population and workers exposed via dermal contact with airborne nickel, liquid nickel solution, or prolonged contact with metal items such as jewelry and prosthetic devices that contain nickel. After an individual becomes sensitized to nickel, dermal contact with a small amount of nickel or oral exposure to fairly low doses of nickel can result in dermatitis. Approximately 10–20% of the general population is sensitized to nickel.

Adverse respiratory effects have been reported in humans and animals exposed to nickel compounds at concentrations much higher than typically found in the environment. The available data on noncancerous respiratory effects in humans are limited. In nickel workers, exposure to nickel did not result in increases in the risk of death from nonmalignant respiratory system disease. Studies examining potential nonlethal respiratory effects have not found consistent results. Animal data provide strong evidence that nickel is a respiratory toxicant; lung inflammation is the predominant effect. Evidence of lung inflammation has been observed following acute-, intermediate-, and chronic-duration exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide. Nickel sulfate was the most toxic of the three compounds and nickel oxide was the least toxic. For all three compounds, the threshold for lung effects decreased as the duration of exposure increased. Exposure to nickel sulfate or nickel subsulfide also produced damage to the nasal olfactory epithelium. Human and animal data provide strong evidence that inhalation exposure to some nickel compounds can induce lung cancer. As described in greater detail later in this section, carcinogenic responses have been observed following inhalation exposure to nickel subsulfide and nickel oxide; in the absence of exposure to other carcinogenic agents, nickel sulfate does not appear to be carcinogenic following inhalation exposure.

The potential for nickel compounds to induce reproductive effects has not been firmly established. Several animal studies have reported adverse effects in the male reproductive system following oral exposure to nickel sulfate, nickel chloride, or nickel nitrate. The observed effects included histological alterations in the epididymis and seminal vesicles, decreases in sperm concentration, motility, and abnormalities, and decreases in fertility following male exposure, but not female only exposure. However, the poor reporting of study results, particularly incidence data and statistical analysis, limits the interpretation of these studies. Additionally, other studies have not found histological alterations in the male reproductive system following long-term oral exposure or impaired fertility following oral exposure. A number of studies have reported decreases in survival of the offspring of animals exposed prior to mating and during the gestation and lactation periods. Interpretation of these data are complicated by

## 2. RELEVANCE TO PUBLIC HEALTH

maternal toxicity, particularly decreases in body weight gain, which frequently occurred at the same dose levels.

The most consistently reported adverse effects resulting from exposure to nickel are contact dermatitis and respiratory effects, including cancer; a more detailed discussion of these 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.

**Contact Dermatitis.** Nickel sensitivity is a form of delayed hypersensitivity that is found in 10–20% of the general population. The prevalence of nickel sensitivity is higher among young women than any other segment of the population, which is probably the result of higher rates of ear and other types of body piercing rather than increased susceptibility to sensitization. There is some evidence of a genetic susceptibility factor that may predispose certain individuals to the development of nickel sensitivity. A significant increase in human leukocyte antigen (HLA)-DRw6 antigens were found among individuals with nickel contact dermatitis compared to individuals with no history of atopy or contact dermatitis. The relative risk of individuals with the HLA-DRw6 allele developing nickel sensitivity was estimated to be 3.3.

Nickel sensitization typically involves initial prolonged contact with nickel or exposure to a very large nickel dose. In the general population, the initial nickel contact often comes from body piercing with jewelry that releases large amount of nickel ions. The resulting dermatitis, which is an inflammatory reaction mediated by type IV hypersensitivity, typically occurs beneath the metal object. With repeated exposure, the area of sensitization can spread to other locations, particularly the hands. Shorter contact with nickel items, such as nickel-plated coins or door handles, does not result in nickel sensitization. After an individual becomes sensitized to nickel, much lower concentrations are needed to elicit a response. There is limited information on nickel levels resulting in sensitization. One study found that the sensitizing nickel level was 100–1,000 times higher than the level eliciting dermatitis in a previously sensitized individual. Among sensitized individuals, a direct relationship between nickel exposure level and severity of the dermatitis has been found. A weak reaction has been reported in individuals exposed to nickel alloys that release nickel ions at a rate of  $<0.5 \mu\text{g}/\text{cm}^2/\text{week}$ ; a strong reaction was observed for nickel alloys that release  $>1 \mu\text{g}/\text{cm}^2/\text{week}$ . No reaction was seen in nickel-sensitized subjects undergoing patch testing with 0.01% nickel as nickel sulfate in petrolatum; however, exposure to 0.03% nickel resulted in dermatitis. Similarly, an oral challenge dose of 0.02 mg Ni/kg can induce dermatitis in a small percentage of nickel-sensitized individuals, whereas exposure to higher doses (0.06 mg Ni/kg) will often

## 2. RELEVANCE TO PUBLIC HEALTH

result in dermatitis in most nickel-sensitized individuals. Exposure to these nickel concentrations will not result in dermatitis in nonsensitized individuals.

**Respiratory Effects.** Both noncancerous and cancerous respiratory effects have been observed in humans and animals exposed to airborne nickel compounds. Chronic bronchitis, emphysema, pulmonary fibrosis, and impaired lung function have been observed in nickel welders and foundry workers. These effects were not consistently seen across studies, and co-exposure to other toxic metals such as uranium, iron, lead, and chromium confounds the interpretation of the results. Studies examining the risk of death from nonmalignant respiratory disease among nickel workers have not found significant increases; however, many studies found that the number of observed deaths were significantly lower than expected, suggesting a healthy worker effect.

In animals, the predominant noncancerous effect is lung inflammation following exposure to nickel sulfate, nickel subsulfide, and nickel oxide. The toxicity of nickel in the respiratory tract appears to be related to the solubility of the individual nickel compounds, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The pulmonary toxicity appears to be related to exposure concentration rather than nickel lung burden. It has been postulated that the higher toxicity of soluble nickel is due to the higher concentrations of free nickel ions, which can diffuse across the cell membrane and interact with cytoplasmic proteins. In contrast, insoluble nickel compounds are phagocytized and a smaller amount of nickel ions interact with cytoplasmic proteins. Following an intermediate-duration exposure, the respective no-observed-adverse effect level (NOAEL) and lowest-observed-adverse effect level (LOAEL) values for lung inflammation were 0.06 and 0.11 mg Ni/m<sup>3</sup> for nickel sulfate, 0.11 and 0.22 mg Ni/m<sup>3</sup> for nickel subsulfide, and 2 and 3.9 mg Ni/m<sup>3</sup> for nickel oxide. At approximately 0.4 mg Ni/m<sup>3</sup> as nickel sulfate, nickel subsulfide, and nickel oxide, the lung burdens following a 13-week exposure were 6, 7, and 80 µg Ni/g lung, respectively. 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. However, mice were more susceptible to the lethal effects (presumably from impaired lung function) than rats. In addition to the pulmonary effects, atrophy of the nasal olfactory epithelium was observed in rats exposed to nickel sulfate or nickel subsulfide for acute, intermediate, and chronic durations; nasal effects were not observed following exposure to nickel oxide.

The carcinogenicity of nickel has been well documented in occupationally-exposed individuals. Significant increases in the risk of mortality from lung or nasal cancers were observed in several cohorts

## 2. RELEVANCE TO PUBLIC HEALTH

of nickel refinery workers. Studies of workers in other nickel industries, including nickel mining and smelting, nickel alloy production, stainless steel production, or stainless steel welding, which typically involve exposure to lower concentrations of nickel, have not found significant increases in cancer risks. In most of the occupational exposure studies, the workers were exposed to several nickel species, thus making it difficult to compare carcinogenic potential across nickel species. An extensive re-evaluation of the studies published prior to 1990 found the strongest evidence of carcinogenicity for sulfidic nickel; exposure to high concentrations ( $>10 \text{ mg Ni/m}^3$ ) resulted in increased lung cancer risks. There is weaker evidence that high concentrations ( $>10 \text{ mg Ni/m}^3$ ) of oxidic nickel, particularly when there is co-exposure to soluble nickel, is also carcinogenic. Soluble nickel does not appear to be carcinogenic in the absence of exposure to other carcinogenic agents. There is no evidence that exposure to low levels of nickel is carcinogenic in humans. The conclusions drawn from the occupational exposure studies are supported by animal inhalation studies. Significant increases in the incidence of lung tumors were observed in rats chronically exposed to nickel subsulfide or nickel oxide. The carcinogenic response was stronger for nickel subsulfide compared to nickel oxide. In contrast, no increases in lung tumor incidences were observed in rats exposed to nickel sulfate; however, the highest concentration tested ( $0.11 \text{ mg Ni/m}^3$ ) was lower than the cancer effect levels for nickel subsulfide ( $0.73 \text{ mg Ni/m}^3$ ) or nickel oxide ( $1 \text{ mg Ni/m}^3$ ).

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.

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

## 2. RELEVANCE TO PUBLIC HEALTH

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.

### 2.3 MINIMAL RISK LEVELS

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for nickel. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs may be revised.

#### *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

## 2. RELEVANCE TO PUBLIC HEALTH

observed at the lowest tested nickel sulfate ( $0.7 \text{ mg Ni/m}^3$ ) and nickel subsulfide ( $0.44 \text{ mg Ni/m}^3$ ) concentrations. At  $0.7$  and  $3.65 \text{ mg Ni/m}^3$  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  $0.22 \text{ mg Ni/m}^3$  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  $1.83 \text{ mg Ni/m}^3$  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  $7.9 \text{ mg Ni/m}^3$  in rats, respectively; in mice, the highest concentration tested ( $23.6 \text{ mg Ni/m}^3$ ) 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. 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  $0.7 \text{ mg Ni/m}^3$  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  $0.88 \text{ mg Ni/m}^3$  as nickel subsulfide 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 following inhalation exposures. 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 ( $0.7 \text{ mg Ni/m}^3$ ) 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 ( $0.25 \text{ mg Ni/m}^3$ ) for a soluble nickel compound, nickel chloride; the NOAEL was  $0.1 \text{ mg Ni/m}^3$ . 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  $0.0002 \text{ mg Ni/m}^3$  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),



## 2. RELEVANCE TO PUBLIC HEALTH

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 which are probably secondary to the lung damage (NTP 1996b, 1996c; Weischer et al. 1980), 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/m<sup>3</sup> for nickel sulfate (NTP 1996c), 0.11 and 0.22 mg Ni/m<sup>3</sup> for nickel subsulfide (NTP 1996b), and 2.0 and 3.9 mg Ni/m<sup>3</sup> for nickel oxide (NTP 1996a). Atrophy of the nasal olfactory epithelium was observed at 0.22 and 0.44 mg Ni/m<sup>3</sup> 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 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/m<sup>3</sup>). 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/m<sup>3</sup> as nickel sulfate for 6 months. Thus, the 0.06 mg Ni/m<sup>3</sup> concentration was identified as a NOAEL and adjusted for intermittent exposure (NOAEL<sub>ADI</sub>).

## 2. RELEVANCE TO PUBLIC HEALTH

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

$$\text{NOAEL}_{\text{ADJ}} = 0.06 \text{ mg Ni/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} = 0.011 \text{ mg Ni/m}^3$$

$$\text{NOAEL}_{\text{HEC}} = \text{NOAEL}_{\text{ADJ}} \times \text{RDDR} = 0.011 \text{ mg Ni/m}^3 \times 0.474 = 0.0052 \text{ mg Ni/m}^3$$

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 (mass median aerodynamic diameter, MMAD) of  $2.11 \mu\text{m}$  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 ( $54 \text{ m}^2$ ); and default female F344 rat body weight (0.124 kg), minute volume (101.3 mL), and pulmonary surface area ( $0.34 \text{ m}^2$ ).

No intermediate-duration human inhalation exposure studies were identified; a number of chronic exposure studies have examined the potential of nickel and nickel compounds to induce respiratory effects in workers. Most of these studies are cohort mortality studies that did not find significant increases in the number of deaths from nonmalignant respiratory system disease (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Redmond 1984; Roberts et al. 1989b; Shannon et al. 1984b, 1991). A few studies have examined workers for possible nonlethal respiratory effects. Two studies examined chest x-rays of workers: one found an increased risk of moderate pulmonary fibrosis (Berge and Skyberg 2003) and the other did not find any significant alterations (Muir et al. 1993). Although most of occupational exposure studies did not report exposure levels, workers were typically exposed to nickel levels that far exceed levels found in ambient air.

- An MRL of  $9 \times 10^{-5} \text{ mg Ni/m}^3$  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; Tanaka et al. 1988) assessed the noncarcinogenic toxicity 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

## 2. RELEVANCE TO PUBLIC HEALTH

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/m<sup>3</sup> and atrophy of the olfactory epithelium at 0.11 mg Ni/m<sup>3</sup>; no adverse respiratory effects were observed at 0.03 mg Ni/m<sup>3</sup>. 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/m<sup>3</sup>, and atrophy of the nasal olfactory epithelium at 0.73 mg Ni/m<sup>3</sup>. Chronic lung inflammation and alveolar epithelial hyperplasia were observed at the lowest nickel oxide concentration tested (0.5 mg Ni/m<sup>3</sup>) (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/m<sup>3</sup>); the NOAEL of 0.03 mg Ni/m<sup>3</sup> associated with this LOAEL was used to derive a chronic-duration inhalation MRL for nickel.

The chronic-duration inhalation MRL of  $9 \times 10^{-5}$  mg Ni/m<sup>3</sup> was derived by dividing the NOAEL<sub>HEC</sub> of 0.0027 mg Ni/m<sup>3</sup> by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability). The NOAEL<sub>HEC</sub> 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 m<sup>2</sup>); and default female F344 rat body weight (0.229 kg), minute volume (167.3 mL), and pulmonary surface area (0.34 m<sup>2</sup>).

As discussed for the intermediate-duration inhalation MRL, the potential of nickel to induce nonmalignant respiratory tract effects has been examined in a number of cohort mortality studies. In general, these studies did not find significant increases in the risk of dying from nonmalignant respiratory

## 2. RELEVANCE TO PUBLIC HEALTH

system disease (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Redmond 1984; Roberts et al. 1989b; Shannon et al. 1984b, 1991). Mixed results have been found in the few studies examining nonlethal respiratory tract effects. Two studies examined chest x-rays of nickel workers: one found an increased risk of moderate pulmonary fibrosis (Berge and Skyberg 2003) and the other did not find any significant alterations (Muir et al. 1993). Although most of occupational exposure studies did not report exposure levels, workers were typically exposed to nickel levels that far exceed levels found in ambient air.

***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 a single challenge dose of greater than 0.01 mg Ni/kg as nickel sulfate (Hindsén et al. 2001; Jensen et al. 2003; Menne and Maibach 1987). 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), nickel acetate (Hanger 1973), or nickel sulfate (Dieter et al. 1988). Other systemic effects included 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 Biogenic Corporation 1988; RTI 1988b). Inconsistent results have been reported for the reproductive toxicity of nickel. Decreased sperm motility and count and sperm

## 2. RELEVANCE TO PUBLIC HEALTH

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 multigeneration studies of rats orally exposed to nickel sulfate or nickel chloride (RTI 1988a, 1988b; Springborn Laboratories 2000a). There is stronger evidence that prenatal 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; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993; Springborn Laboratories 2000b). 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 in rats; 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 2.2 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.

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  $\geq 1.3$  mg Ni/kg/day (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993; Springborn Laboratories 2000b).