APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide

MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MRL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL. The acute-duration inhalation database indicates respiratory toxicity as a sensitive endpoint to nickel however the lowest LOAEL for this endpoint is for serious effects. The immune endpoint was also considered however given the lack of information on the respiratory effects below the SLOAEL for forms of nickel that may be more potent, it is not known if the NOAEL value for immunotoxicity would be protective of respiratory effects.

Rationale for Not Deriving an MRL: Several case studies in workers who inhaled large amounts of nickel dust or fumes indicate the respiratory system is the most sensitive endpoint for nickel toxicity (Bowman et al. 2018; Kunimasa et al. 2011). A single case of death from adult respiratory distress syndrome (ARDS) has been reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994).

While numerous animal studies have identified the respiratory system as a sensitive endpoint of nickel, a study NOAEL to serve as a basis for MRL derivation has not been identified (Bai et al. 2013; Benson et al. 1995b; Efremenko et al. 2014; NTP 1996a, 1996b, 1996c). Several studies examining the respiratory system identified 0.4 mg Ni/m^3 as a LOAEL including endpoints considered serious effects, precluding derivation from this LOAEL value. At 0.43 mg Ni/m^3 as nickel subsulfide, Efremenko et al. (2014) reported peribronchiolar and perivascular inflammation in 5/5 rats after histological examination. The same concentration in rats resulted in elevated lactate dehydrogenase (LDH) in bronchoalveolar lavage fluid (BALF) (250%) compared to controls (Efremenko et al. 2014). Additionally, Efremenko et al. (2014) identified the lowest acute-duration respiratory NOAEL of 0.11 mg Ni/m^3 as nickel subsulfide for BALF evaluation. In Benson et al. (1995b), 0.44 mg Ni/m^3 as nickel subsulfide resulted in lung alveolitis in 6/6 rats exposed for 7 days. Similarly, NTP (1996b) identified a LOAEL of 0.44 mg Ni/m^3 for chronic lung inflammation in 10/10 rats and atrophy of the olfactory epithelium in 6/10 rats. The experiments conducted by the National Toxicology Program (NTP) observed respiratory toxicity following inhalation of nickel oxide (NTP 1996a), nickel subsulfide (NTP 1996b), and nickel sulfate hexahydrate (NTP 1996c) for 12 days, six hours per day, in both rats and mice. In mice 0.44 mg Ni/m^3 was identified as a NOAEL as neither histological changes nor clinical signs of respiratory toxicity were observed (NTP 1996b). Mice of both sexes also showed respiratory toxicity at doses ≥0.88 mg Ni/m^3 including chronic long inflammation, atrophy of the olfactory epithelium, necrotizing inflammatory lesions, edema, and vascular congestion in the lung (NTP 1996b, 1996c). Several of these studies identified lung lesions at 0.4 mg Ni/m^3 however, NTP (1996a) identified respiratory NOAELs of 3.9 mg Ni/m^3. Acute lung inflammation was observed in rats only at exposures ≥7.9 mg Ni/m^3 (NTP 1996a). Studies are summarized in Table A-1.

Two studies examined immunotoxicity in mice to nickel chloride at lower concentrations than in rat respiratory studies (Buxton et al. 2021; Graham et al. 1978) and identified a NOAEL similar to Efremenko et al. (2014). Graham et al. (1978) identified an immunological LOAEL of 0.25 mg Ni/m^3 as nickel subsulfide for impaired humoral immunity in female mice and a NOAEL of 0.1 mg Ni/m^3 in Swiss mice. Buxton et al (2021) tested lower concentrations and identified a NOAEL of 0.08 mg Ni/m^3 based

on immune response in ICR mice. Deriving a MRL based on immune effects in mice would not be protective as rats appear more sensitive to the effects of nickel, and data on immunotoxicity in rats are insufficient. Additionally, data on respiratory toxicity in mice are limited; respiratory effects are not reported in a different mouse strain (B6C3F1) exposed to 0.44 mg Ni/m^3 (NTP 1996b). Graham et al. (1978) compared immunotoxicity and showed that nickel sulfate hexahydrate is immunosuppressive at lower concentrations compared to nickel chloride. This suggests further evidence is needed on immune effects in rats at lower concentrations and in other nickel forms.

Immunotoxicity at higher concentrations has been evaluated in several other acute-duration inhalation studies. Adkins et al. (1979c) observed a concentration-related increase in susceptibility to infection resulting in increased mortality and reduced survival time in female mice exposed to concentrations up to 0.5 mg Ni/m^3 for 2 hours as nickel chloride and then exposed to Streptococcal bacteria. Mortality among mice at the highest concentration was 26% higher than controls ($p<0.05$). Mice exposed to 0.66 mg Ni/m^3 for 2 hours as nickel chloride showed a reduced ability to clear inhaled bacteria 96 hours after exposure and the incidence of mortality and sepsis was higher than controls(Adkins et al. 1979a). Exposure to a single concentration of 0.46 mg Ni/m^3 as nickel sulfate for 2 hours showed similar results indicating increased susceptibility to infection (Adkins et al. 1979b). Immune histopathological findings have also been reported. NTP (1996b) observed lymphoid hyperplasia in bronchial lymph nodes in mice of both sexes following exposure to 0.88 mg Ni/m^3 as nickel subsulfide. Likewise, female rats had hyperplasia in bronchial and mediastinal lymph nodes following exposure to 1.4 mg Ni/m^3 as nickel sulfate hexahydrate NTP (1996c).

Experimental animal studies have evaluated and observed body weight effects from acute-duration nickel inhalation exposure. Reduced body weight has been reported in rats of both sexes exposed to concentrations of 0.7 to 3.65 mg Ni/m^3 for 7 or 12 days (Benson et al. 1995b; NTP 1996b, 1996c). Weight loss or emaciation was also observed in male mice exposed 3.65 mg Ni/m^3 for 6 hours/day for 12 days (NTP 1996b). However, no exposure-related body weight changes were reported in males exposed to ≤1.83 mg Ni/m^3 and to 23.6 mg Ni/m^3 and in females exposed to 0.7 to 3.65 mg Ni/m^3 for 6 hours/day for 12 days (NTP 1996a, 1996b, 1996c).

Death occurred in rats and mice exposed to nickel via inhalation for 2 hours or 12 days. Following exposure to 1.4 or 7.3 mg Ni/m^3 for 12 days, all mice died (NTP 1996b, 1996c). All rats (5/5) exposed to 12.2 mg Ni/m^3 as nickel sulfate hexahydrate for 12 days died (NTP 1996c). Death was also reported in rats exposed for 2 hours at 36.6 mg Ni/m^3 as nickel sulfate (Hirano et al. 1994)

Multiple studies have assessed cardiovascular toxicity of acute-duration inhalation exposure to nickel oxide, nickel sulfate hexahydrate, nickel subsulfide, and nickel sulfate heptahydrate in rodents (NTP 1996a, 1996b, 1996c) and dogs (Muggenberg et al. 2003). None of these studies observed adverse cardiovascular effects, with the highest NOAEL at 23.6 mg Ni/m^3 as nickel oxide in rats and mice of both sexes (NTP 1996a). NTP studies observed no adverse dermal, endocrine, gastrointestinal, hepatic, musculoskeletal, neurological, renal, or reproductive effects following acute-duration inhalation of nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate in rats and mice (NTP 1996a, 1996b, 1996c). No hematological effects were observed for acute-duration nickel inhalation at a concentration up to 3.65 mg Ni/m^3 as nickel subsulfide in mice of both sexes (NTP 1996b). While this study did also test a concentration of 7.33 mg Ni/m^3, all animals died before hematological parameters and other examinations could be performed.

The relevant NOAEL and LOAEL values are presented in Table A-1.

Table A-1. Summary of Relevant Acute-Duration Inhalation NOAEL and LOAEL Values

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference
Respiratory					
Rat (M)	5 days 6 hours/day	0.11	0.43	Over 250% increase of LDH in BALF	Efremenko et al. 2014 (Nickel subsulfide)
Mouse (B)	12 days in 16 day period 6 hours/day	0.44	0.88	Atrophy of olfactory epithelium	NTP 1996b (Nickel subsulfide)
Rat (M)	5 days 6 hours/day		0.43	Peribronchiolar/ perivascular inflammation	Efremenko et al. 2014 (Nickel subsulfide)
Rat (B)	12 days in 16 day period 6 hours/day		0.44	Chronic lung inflammation and olfactory epithelium atrophy	NTP 1996b (Nickel subsulfide)
Rat (B)	7 days 6 hours/day		0.44*	Alveolitis in 6/6 rats	Benson et al. 1995b (Nickel subsulfide)
Rat (B)	12 days in 16 day period 6 hours/day		0.7	Increased respiration rate, chronic lung inflammation; olfactory epithelium atrophy	NTP 1996c (Nickel sulfate hexahydrate)
Mouse (B)	12 days in 16 day period 6 hours/day		0.7	Chronic lung inflammation and olfactory epithelium atrophy	NTP 1996c (Nickel sulfate hexahydrate)
Rat (B)	12 days in 16 day period 6 hours/day	3.9	7.9	Lung inflammation	NTP 1996a (Nickel oxide)
Mouse (B)	12 days in 16 day period 6 hours/day	3.9	7.9	Elevated incidence of alveolar macrophage hyperplasia	NTP 1996a (Nickel oxide)
Immunological					
Mouse (F)	24 hours	0.08		Immunosuppressive effects	Buxton et al. 2021 (Nickel chloride)
Mouse (F)	2 hours	0.1	0.25	Impaired humoral immunity	Graham et al. 1978 (Nickel chloride)
Mouse (B)	12 days in 16 day period 6 hours/day	0.44	0.88	Lymphoid hyperplasia in bronchial lymph nodes	NTP 1996b (Nickel subsulfide)

B=both; BALF=bronchoalveolar lavage fluid; HEC=human equivalent concentration; LDH=lactate dehydrogenase; M=males; NS=Not Specified
* = Serious lowest observed adverse effect level (SLOAEL)

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
MRL: 0.00003 mg Nickel/m^3 (provisional)
Critical Effect: Chronic lung inflammation
Reference: NTP 1996c
Point of Departure: NOAEL of 0.06 mg Ni/m^3 ($NOAEL_{HEC,ADJ}$ of 0.001 mg Ni/m^3)
Uncertainty Factor: 30
LSE Graph Key: 30R
Species: Rats

MRL Summary: A provisional intermediate-duration inhalation MRL of 0.00003 mg Ni/m^3 was derived for nickel based on a NOAEL of 0.06 mg Ni/m^3 accompanied by a LOAEL of 0.11 mg Ni/m^3 for chronic lung inflammation observed in female rats exposed for 6 hours per day, 5 days/week for 13 weeks (NTP 1996c). The NOAEL of 0.06 mg Ni/m^3 was adjusted for intermittent exposure and converted to a human equivalent concentration of 0.001 mg Ni/m^3. The $NOAEL_{HEC,ADJ}$ of 0.001 mg Ni/m^3 was divided by a total uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: The intermediate-duration toxicity of nickel has been assessed in several animal studies involving exposure to metallic nickel, nickel sulfate, nickel sulfate hexahydrate, nickel chloride, nickel subsulfide, and nickel oxide. Nickel is known to cause effects in the respiratory system, and these were observed at concentrations $\geq$ 0.1 mg/m^3. Researchers recorded inflammatory changes in the lungs (Benson et al. 1995a, 1995b; Horie et al. 1985; NTP 1996a, 1996b, 1996c), alveolar macrophage hyperplasia (Benson et al. 1995b; Johansson and Camner 1986; NTP 1996a, 1996b, 1996c), and atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c). Further respiratory effects were hyperplasia in the bronchial and mediastinal lymph nodes (Bingham et al. 1972, NTP 1996b, 1996c) and altered enzyme levels in bronchoalveolar lavage fluid (BALF) (Efremenko et al. 2014).

Impaired immune function was consistently observed (Section 2.14) at levels $\leq$9.2 mg Ni/m^3. Other observed effects that occurred with less dose consistency included decreased body weight gain (Benson et al. 1995b; Weischer et al. 1980), decreased sperm concentration (NTP 1996a), vascular endothelial and microcirculatory dysfunction (Xu et al. 2012; Ying et al. 2013), changes in hematological parameters (NTP 1996b; Weischer et al. 1980), urea changes (Weischer et al. 1980), and developmental toxicity (Weischer et al. 1980). A cancer effect level of 0.5 mg Ni/m^3 as nickel oxide was reported in Horie et al. (1985) for adenocarcinoma in 1 of 6 male rats.

Intermediate-duration inhalation studies conducted by the National Toxicology Program in rats and mice indicate that the most sensitive target of nickel toxicity is the respiratory system (NTP 1996a, 1996b, 1996c). In these studies, chronic lung inflammation was observed following 13-week (6 hours/day, 5 days/week) exposures to nickel oxide (NTP 1996a), nickel subsulfide (NTP 1996b), and nickel sulfate hexahydrate (NTP 1996c). The intermediate-duration studies by NTP indicate that nickel sulfate hexahydrate is more toxic than nickel subsulfide and nickel oxide (NTP 1996a, 1996b, 1996c). In rats, the respective NOAEL and LOAEL values for chronic lung inflammation were 0.06 and 0.11 mg Ni/m^3 for

nickel sulfate (NTP 1996c), 0.11 and 0.22 mg Ni/m^3 for nickel subsulfide (NTP 1996b), and 2.0 and 3.9 mg Ni/m^3 for nickel oxide, respectively (NTP 1996a). Atrophy of the nasal olfactory epithelium was observed at 0.22 mg Ni/m^3 in males rats exposed to nickel sulfate hexahydrate (NTP 1996c). Labored breathing was observed in rats exposed to 1.83 mg Ni/m^3 as nickel subsulfide. Respiratory toxicity findings from the NTP studies are supported by findings from Efremenko et al. (2014) and Oller et al. (2022) which reported histological changes at a LOAEL of 0.11 mg Ni/m^3. Efremenko et al. (2014) observed minimal to mild alveolus inflammation characterized by prominent macrophages in alveoli with distended cytoplasm. In rats exposed to ≥0.11 mg Ni/m^3 as nickel sulfate hexahydrate, Oller et al. (2022) reported the incidence and severity of pulmonary lesions increased with increasing nickel concentration. Pulmonary lesions include perivascular and peribronchiolar lesions, and alveolitis. At 0.03 mg Ni/m^3, the incidence of lesions, inflammation, and lung weights were similar to controls. Oller et al. (2022) reported similar findings for a 13-week exposure to nickel subsulfide.

The NTP studies reported similar differential effects in mice. For nickel sulfate hexahydrate and nickel subsulfide, the LOAEL values for mice were higher than the LOAELs in rats; the LOAEL for respiratory effects following exposure to nickel oxide was the same in rats and mice for chronic inflammation and perivascular lymphocytic infiltrates, respectively.

Xu et al. (2012) only tested one concentration of 0.00017 mg Ni/m^3 as nickel sulfate and observed microcirculatory dysfunction and increased macrophages in lung and epididymal white adipose tissues (eWAT) of male apolipoprotein E deficient mice. Similarly, Ying et al. (2013) only tested 0.0004 mg Ni/m^3 metallic nickel in the same mouse strain and observed vascular endothelial dysfunction. The cardiovascular effects noted in these two studies are not corroborated by other findings in rats and mice studies. All the NTP studies examined the cardiovascular system for histological and organ weight changes and no exposure-related changes were noted (NTP 1996a, 1996b, 1996c). Additionally, no cardiovascular clinical signs were noted in any of the animals. The NOAEL and LOAEL values considered for MRL derivation are presented in Table A-2.

Table A-2. Summary of NOAEL and LOAEL Values for Considered for Derivation of an Intermediate-Duration Inhalation MRL

Species (sex)	Frequency/ Duration	NOAEL ($NOAEL_{HEC,ADJ}$) (mg Ni/m^3)	LOAEL ($LOAEL_{HEC,ADJ}$) (mg Ni/m^3)	Effect	Reference (Chemical Form)
Respiratory					
Rat (M)	13 weeks, 5 days/week, 6 hours/day	0.03 (0.0005)	0.11 (0.002)	Increased incidence and severity of lung lesions	Oller et al. 2022 (Nickel sulfate hexahydrate)
Rat (M)	2-6 months, 5 days/week 6 hours/day	0.03 (0.0005)	0.11 (0.002)	Alveolitis that persisted for 4 months after the exposure	Benson et al. 1995a (Nickel sulfate)
Rat (F)	13 weeks, 5 days/week, 6 hours/day	0.06 (0.001)	0.11 (0.003)	Chronic lung inflammation, interstitial infiltrates	NTP 1996c (Nickel sulfate hexahydrate)
Rat (M)	4 weeks, 5 days/week 6 hours/day	0.06 (0.001)	0.11 (0.002)	Minimal to mild alveolus inflammation in 5/5 rats	Efremenko et al. 2014 (Nickel subsulfide)

F=females; HEC=human equivalent concentration; M=males
Indicates study selected as the principal study

Selection of the Principal Study: NTP (1996c) was selected as the principal study. NTP (1996c) and Oller et al. (2022) both identified a respiratory LOAEL of 0.11 mg Ni/m^3 for similar histological effects. The NTP study identified a higher respiratory NOAEL value that was not examined in the Oller et al. (2022) study. Additionally, NTP (1996c) exposed rats to nickel sulfate hexahydrate, therefore, using this study would also be protective against the toxicity of other nickel compounds. The observed respiratory effects are supported by a large body of evidence indicating the lungs are a primary target of intermediate-duration exposure to inhaled nickel.

Summary of the Principal Study:
NTP 1996c. Toxicology and carcinogenesis of nickel sulfate hexahydrate (CAS No. 10101 97-0) in F344/N rats and B6C3F1 mice (inhalation studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

Groups of 10 male and 10 female F344/N rats were exposed to 0.12, 0.25, 0.5, 1.0, or 2.0 mg/m^3 nickel sulfate hexahydrate, corresponding to nickel concentrations of 0.03, 0.06, 0.11, 0.22, or 0.44 mg Ni/m^3, (as calculated by study authors). Rats were exposed for 13 weeks, 6 hours/day, 5 days/week. The mass median aerodynamic diameter (MMAD) (and sigma g) values reported in Table K1 of the paper were 2.31 (2.1), 2.11 (2.7), 3.08 (2.9), 1.81 (2.2), and 2.01 (2.0) for the 0.03, 0.06, 0.11, 0.22, and 0.44 mg Ni/m^3 concentrations, respectively. Endpoints examined included body weight gain, clinical signs, hematology, and organ weight. Furthermore, microscopic examinations of the following organs were completed: adrenal gland, bone, brain, clitoral gland, epididymis, oviduct, esophagus, heart, large intestine, small intestine, kidneys, larynx, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary, preputial gland, prostate, salivary gland, seminal vesicle, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, bladder, and uterus.

No exposure related deaths, alterations in body weight gain, or clinical signs were observed in rats. Several hematological parameters were measured in female rats. Increases in hematocrit, hemoglobin, and erythrocyte concentrations were described as minimal and appeared consistent with mild dehydration. Increased lymphocytes and segmented neutrophils could not be linked to nickel exposure and likely resulted in elevated leukocyte numbers.

Significant alterations in absolute lung weights were observed at concentrations ≥0.11 mg Ni/m^3. Lung lesions consisted of minimal alveolar macrophage hyperplasia at 0.03–0.11 mg Ni/m^3, mild to moderate macrophage hyperplasia at 0.22 and 0.44 mg Ni/m^3, interstitial infiltrates at 0.22 mg Ni/m^3 and higher in males and at 0.11 mg Ni/m^3 and higher in females. Additionally chronic active inflammation characterized by slight thickening of alveolar septa due to an increase in mononuclear inflammatory cells, and few neutrophils and fibroblasts in the interstitium was reported at 0.11 and 0.22 mg Ni/m^3 in females and males, respectively. Hyperplasia of bronchial and mediastinal lymph nodes was observed at 0.22 mg Ni/m^3 and higher. Atrophy of the olfactory epithelium was seen at 0.22 and 0.44 mg Ni/m^3. The minimal alveolar macrophage hyperplasia observed at 0.03 to 0.11 mg Ni/m^3 was not considered an adverse health effect. This is because the slight changes in the number of macrophages were part of the normal physiologic response to inhaled particles and it is not believed to compromise the lung's ability to clear foreign matter. Table A-3 presents the incidence data for chronic active lung inflammation and lung interstitial infiltrates in both sexes.

Table A-3. Incidence of Select Nonneoplastic Lung Lesions in Rats Exposed to Nickel Sulfate Hexahydrate for 13 Weeks via Inhalation (NTP 1996c)

Concentration (mg Ni/m^3)	Chronic Active Inflammation n=10/sex Incidence (Severity)[a]		Interstitial Infiltrate n=10/sex Incidence (Severity)	
	Females	Males	Females	Males
0	0	0	0	1
0.03	0	0	0	0
0.06	0	0	0	1
0.11	4* (1.0)	2 (1.0)	6* (1.0)	5 (1.0)
0.22	10* (1.3)	10* (1.5)	10* (1.0)	10* (1.0)
0.44	10* (1.0)	8* (1.3)	10* (1.0)	9* (1.1)

*Statistically significant from control group
[a]Severity stated where applicable; represents average severity of lesions in affected animals. 1=minimal, 2=mild, 3=moderate, 4=marked

Selection of the Point of Departure for the Provisional MRL:
The NOAEL of 0.06 mg/m^3 for chronic active inflammation in rats is the basis of the intermediate-duration inhalation MRL for nickel. Minimal alveolar macrophage hyperplasia was observed in rats exposed at the two lowest concentrations (0.03 and 0.06 mg Ni/m^3), however 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. Therefore, the effect was not considered adverse because it is 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^3 as nickel sulfate for 6 months. Thus, the 0.06 mg Ni/m^3 concentration was identified as a NOAEL and adjusted for intermittent exposure ($NOAEL_{ADJ}$).

Incidence data for chronic active inflammation in female rats (Table A-3) were fit to all dichotomous models in EPA's BMDS (version 3.2) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. One model was determined to have an adequate model fit and a BMDL value of 0.065 mg Ni/m^3 which is slightly higher than the study NOAEL. Therefore, the POD was defined as the NOAEL of 0.06 mg Ni/m^3 and supported by the BMD modeling.

Adjustment for Intermittent Exposure: The NOAEL of 0.06 mg Ni/m^3 was adjusted from intermittent exposure to continuous exposure using the following equation:

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

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated using the following equation from Lee et al. (2019), adopted from NIOSH (2013):

$$NOAEL_{HEC,ADJ} = NOAEL_{ADJ} \times \frac{VR_R}{VR_H} \times \frac{DF_R}{DF_H} \times \frac{\frac{1-k_R^n}{1-k_R}}{\frac{1-k_H^n}{1-k_H}} \times \frac{RH_R}{RH_H} \times \frac{SA_H}{SA_R}$$

Where VR= ventilation rate, DF = deposition fraction, k = 1-clearance rate, RH=particle retention half time, SA = alveolar surface area, n = exposure days, R = rat, and H = human. For this equation, deposition fractions and ventilation rates for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the pulmonary region is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD V 3.04) developed by Applied Research Associates, Inc. (ARA) to first calculate the deposition fraction (DF) for rats and humans. The MPPD model parameters and results for the rat and human deposition fractions are presented in Table A-4.

Table A-4. MPPD model (v 3.04) Inputs and Results for Rat and Human Models

Parameters	Rats	Humans
Airway morphometry		
Model	Asymmetric Multiple Path	Yem/Schum 5-Lobe
Functional residual capacity (FRC)	4 ml (default)	3300 ml (default)
Upper respiratory tract (URT)	0.42 ml (default)	50 ml (default)
Inhalant properties		
Density[1]	2.07	2.07
Diameter, MMAD[2]	2.11 µm	2.11 µm
GSD[2]	2.7	2.7
Exposure condition		
Aerosol concentration ($NOAEL_{ADJ}$)	0.011 mg/m^3	0.011 mg/m^3
Breathing frequency	102 breaths/min (default)	12 breaths/min (resting default)
Tidal volume	2.1 ml (default)	625 ml (resting default)
Breathing scenario	Nose only	Nasal
Results		
Alveolar region deposition fraction (Total pulmonary deposition fraction)	0.0361	0.1199

[1]PubChem, Ni Sulfate Hexahydrate
[2]From NTP (1996c), Table K1

The daily ventilation rate for rats (VR_R) was calculated using the breathing frequency and tidal volume presented in Table A-4 as follows:

$$102\ \text{min} \times 2.1\ ml = 214.2\ ml/min$$

$$214.2\frac{ml}{min} = 0.0002142\frac{m^3}{min}$$

$$\frac{0.0002142\ m^3}{1\ min} = \frac{X}{1440\ \text{min}\ \ (full\ day)}$$

$$VR_R = 0.31\ \frac{m^3}{day}$$

The daily ventilation rate for humans (VR_H) of 15.3 m^3/day is provided in ATSDR's Guidance for Inhalation Exposures (ATSDR 2021; Table A-1). The ventilation rate was calculated by applying a weighted average of adult age ranges to EPA's inhalation rates for male and female adults >21 years of age, as reported in the Exposure Factors Handbook (EPA 2011; Table 6-1).

The depositions fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $NOAEL_{HEC,ADJ}$. Table A-5 lists the values used within the equation and the source of these values. The exposure days (n) are 91 days to represent 13 weeks of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure.

$$NOAEL_{HEC,ADJ} = 0.011\ \frac{mg^3}{m} \times \frac{0.31\frac{m^3}{day}}{15.3\frac{m^3}{day}} \times \frac{0.0361}{0.1199} \times \frac{\frac{1-(1-0.00105652)^{91}}{1-(1-0.00105652)}}{\frac{1-(1-0.00002)^{91}}{1-(1-0.00002)}} \times \frac{1}{10} \times \frac{54\ m^2}{0.34\ m^2}$$

$$NOAEL_{HEC,ADJ} = 0.001\ mg/m^3$$

Table A-5. Values Used to Calculate Human Equivalent Concentration (HEC) NOAEL for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.31 m^3/day	15.3 m^3/day	Calculated daily ventilation rate
Deposition fraction (DF)	0.0361	0.1199	Calculated using MPPD software
1-clearance rate (k)	0.9989	0.99998	MPPD
Clearance rate	0.00105652	0.00002	MPPD
Ratio of retention half-time (RH)	1	10	NIOSH (2013) per Lee et al. (2019) and Oller et al. (2014)
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA (1994), Table 4-4
Exposure days (n)	91 days	91 days	NTP (1996c)

Uncertainty Factor: The $NOAEL_{HEC,ADJ}$ is divided by a total uncertainty factor of 30:

- 3 for species-to-species extrapolation with dosimetric adjustments
- 10 for human variability

$$Provisional\ MRL = \frac{NOAEL_{HEC,ADJ}}{UFs} = \frac{0.001\ mg\ Ni/m^3}{30}$$

$$= 0.00003\ mg\ Ni/m^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The proposed intermediate-duration inhalation MRL is supported by the LOAEL reported in Xu et al. (2012). In this study, only a single concentration of 0.00017 mg Ni/m^3 as nickel sulfate was tested in mice, which resulted in microcirculatory dysfunction, and increased macrophages in lung and eWAT tissues. Further, the critical effect is supported by Benson et al. (1995a), Efremenko et al. (2014), and Oller et al. (2022) which also identified LOAELs of 0.11 mg Ni/m^3 for lung lesions.

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic
MRL: 0.00001 mg Nickel/m^3 (provisional)
Critical Effect: Chronic lung inflammation, fibrosis, alveolar proteinosis
Reference: NTP 1996c
Point of Departure: NOAEL of 0.03 mg Ni/m^3 ($NOAEL_{HEC,ADJ}$ of 0.00036 mg Ni/m^3)
Uncertainty Factor: 30
LSE Graph Key: 58R
Species: Rats

MRL Summary: A provisional chronic-duration inhalation MRL of 0.00001 mg Ni/m^3 was derived for nickel based on a NOAEL of 0.03 mg Ni/m^3 accompanied with a LOAEL of 0.06 mg Ni/m^3 as nickel sulfate hexahydrate for chronic lung inflammation, fibrosis, and alveolar proteinosis observed in male and female rats exposed for 6 hours per day, 5 days/week for 2 years (NTP 1996c). The NOAEL of 0.03 mg Ni/m^3 was adjusted for intermittent exposure and converted to a human equivalent concentration of 0.00036 mg Ni/m^3. The $NOAEL_{HEC,ADJ}$ of 0.00036 mg Ni/m^3 was divided by a total uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Numerous studies in workers have examined respiratory toxicity following chronic-duration exposure to nickel. Several studies have found no increased risk in death (Arena et al. 1998; Cox et al. 1981; Cragle et al. 1984; Egedahl et al. 2001; Enterline and Marsh 1982; Moulin et al. 2000; Polednak 1981; Redmond 1984; Roberts et al. 1989a; Shannon et al. 1984b; Shannon et al. 1991). However respiratory effects have been reported in workers such as welders and nickel refinery workers, these effects include reduced vital capacity, respiratory symptoms, chronic bronchitis, pulmonary fibrosis, and asthma (Berge and Skyberg 2003; Dolovich et al. 1984; Fishwick et al. 2004; Kilburn et al. 1990; Novey et al. 1983; Shirakawa et al. 1990). Two case studies of metalworkers exposed to nickel in indoor air for 5 to 6 years reported nasal septal perforation, nasal obstruction, and mild right-sided epistaxis (Bolek et al. 2017; Peric and Durdevic 2020).

Several animal studies (NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974; Takenaka et al. 1985; Tananka et al. 1988) assessed the noncarcinogenic toxicity of nickel sulfate, nickel chloride, nickel subsulfide, and nickel oxide. The respiratory system is a sensitive target of chronic-duration exposure with LOAELs ranging from 0.06 mg Ni/m^3 to 1 mg Ni/m^3. Respiratory effects observed include inflammatory changes in the lungs (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1974; Tanaka et al. 1988), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), congestion, and increased lung weight (Takenaka et al. 1985). Rats exposed to ≥0.06 to 0.2 mg Ni/m^3 as nickel oxide had decreased survival time compared to controls (Takenaka et al. 1985). Other non-cancerous health effects due to nickel exposure include evidence of renal damage (Oller et al. 2008), changes in hematological parameters (NTP 1996b; Oller et al. 2008), damage to the bronchial lymph nodes (NTP 1996a, 1996b, 1996c; Oller et al. 2008), and decreased body weight gain likely associated with impaired lung function (NTP 1996b, 1996c). Cancer effect levels of 0.4 to 2 mg Ni/m^3 were identified for pheochromocytoma, adenomas and carcinomas in the adrenal cortex and lung (NTP 1996a, 1996b; Oller et al. 2008; Ottolenghi et al. 1974).

Chronic-duration 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 resulted in chronic lung inflammation, fibrosis, bronchiolization, and alveolar proteinosis at 0.06 mg Ni/m^3 and atrophy of the olfactory epithelium at 0.11 mg Ni/m^3 (NTP 1996c); no adverse respiratory effects were observed at 0.03 mg Ni/m^3. 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^3, and atrophy of the nasal olfactory epithelium at 0.73 mg Ni/m^3. Chronic lung inflammation and alveolar epithelial hyperplasia were observed at the lowest nickel oxide concentration tested (0.5 mg Ni/m^3) (NTP 1996a). Similar effects were observed in mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 2 years; however, at LOAEL values similar to or higher than to those in rats. The respiratory NOAEL and LOAEL values considered for MRL derivation are presented in Table A-6.

Table A-6. Respiratory NOAEL and LOAEL Values Relevant to Derivation of a Chronic-Duration Inhalation MRL

Species (sex)	Frequency/ Duration	NOAEL ($NOAEL_{HEC,ADJ}$) (mg Ni/m^3)	LOAEL ($LOAEL_{HEC,ADJ}$) (mg Ni/m^3)	Effect	Reference
Rat (B)	2 years, 5 days/week, 6 hours/day	0.03 (0.00036)	0.06 (0.0009)	Chronic lung inflammation, lung fibrosis	NTP 1996c (Nickel sulfate hexahydrate)
Rat (M)	31 months, 7 days/week, 23 hours/day		0.06 (N/A)[a]	Congestion, increased lung weight, alveolar proteinosis	Takenaka et al. 1985 (Nickel oxide)

B=Both; F=females; M=males; HEC=human equivalent concentration
[a]No information on particle size was provided by the study authors; the HEC could not be modeled.
Indicates study selected as the principal study.

Selection of the Principal Study: NTP (1996c) was selected as the principal study for derivation, as it identified the highest NOAEL in the chronic-duration inhalation database below the lowest LOAEL which was identified for lung lesions in rats. Use of this study would be protective against the toxicity of other nickel compounds, and as similarly observed in the intermediate-duration database, there is substantial evidence indicating the lungs are a primary target of chronic-duration exposure to inhaled nickel. The same study tested concentrations in mice, however the lowest concentration tested was also the LOAEL (0.06 mg Ni/m^3) in the rat studies. Therefore, the rat studies are specifically selected for derivation of this MRL.

Summary of the Principal Study:
NTP 1996c. Toxicology and carcinogenesis of nickel sulfate hexahydrate (CAS No. 10101 97-0) in F344/N rats and B6C3F1 mice (inhalation studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

Groups of 10 male and 10 female F344/N rats were exposed to 0.12, 0.25, or 0.5 mg/m^3 nickel sulfate hexahydrate (0, 0.03, 0.06, or 0.11 mg Ni/m^3 as calculated by study authors) for 6 hours/day, 5 days/week for 2 years. The mean mass median aerodynamic diameter (MMAD) and sigma g values (reported in Table K2 of the paper) were 2.50 (sigma g of 2.38), 2.24 (2.21), and 2.25 (2.08) for the 0.03, 0.06, and 0.11 mg Ni/m^3 concentrations, respectively. Endpoints examined included body weight gain, clinical observations, hematology, and organ weights. Microscopic examinations of the following organs were completed: adrenal gland, bone, brain, clitoral gland, epididymis, oviduct, esophagus, heart, large

intestine, small intestine, kidneys, larynx, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary, preputial gland, prostate, salivary gland, seminal vesicle, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, bladder, and uterus.

No significant alterations in survival, body weight, or the occurrence of clinical signs were observed. The only treatment-related changes noted were in the respiratory tract. Lung lesions consisted of chronic active inflammation, hyperplasia of alveolar macrophages, alveolar proteinosis, and fibrosis at 0.06 and 0.11 mg Ni/m^3. The combined incidences of chronic active inflammation in the male and female rats were 28/106, 24/106, 91/106, and 98/107 in the 0, 0.03, 0.06, and 0.11 mg Ni/m^3 groups, respectively. The chronic inflammation consisted of multifocal, minimal to mild accumulation of macrophages, neutrophils, and cellular debris within the alveolar spaces. No significant alterations in malignant tumors were observed in the lungs. Significant increases in the incidence of lymphoid hyperplasia of the bronchial lymph nodes and atrophy of the olfactory epithelium were observed at 0.11 mg Ni/m^3. Table A-7 presents the incidence data for chronic active lung inflammation and lung interstitial infiltrates in both sexes.

Table A-7. Incidence of Select Nonneoplastic Lung Lesions in Rats Exposed to Nickel Sulfate Hexahydrate for 2 Years via Inhalation (NTP 1996c)

Concentration (mg Ni/m^3)	Chronic Active Inflammation n=53/sex Incidence (Severity)[a]		Lung Fibrosis n=53/sex Incidence (Severity)[a]	
	Females[1]	Males[2]	Females[1]	Males[2]
0	14 (1.4)	14 (1.1)	8 (1.4)	3 (1.0)
0.03	13 (1.2)	11 (1.2)	7 (1.3)	6 (1.2)
0.06	49* (2.1)	42* (1.9)	45* (1.7)	35* (1.7)
0.11	52* (2.3)	46* (2.2)	49* (1.9)	43* (1.8)

*Statistically significant from control group (p≤0.01)
[a]Severity stated where applicable; represents average severity of lesions in affected animals. 1=minimal, 2=mild, 3=moderate, 4=marked

[1]For control group, n=52; For 0.11 mg Ni/m^3 group, n=54
[2]For control group, n=54

Selection of the Point of Departure for the Provisional MRL:
The NOAEL of 0.03 mg Ni/m^3 for chronic active inflammation in rats is the basis of the chronic-duration inhalation MRL for nickel. The NOAEL from NTP (1996c) is the highest NOAEL below the lowest LOAEL in the chronic-duration inhalation database. The LOAEL of 0.06 mg Ni/m^3 is for significantly increased incidence of chronic lung inflammation and lung fibrosis in male and female rats. The concentration of 0.03 mg Ni/m^3 was selected as the POD and adjusted for intermittent exposure ($NOAEL_{ADJ}$).

Incidence data for chronic active inflammation in female rats (Table A-6) were fit to all dichotomous models in EPA's BMDS (version 3.2) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-value (p≥0.1), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. For all model tests, the BMDS recommendation was "Questionable" as none of the models provided an adequate fit for the data. Therefore, the POD was defined as the NOAEL of 0.03 mg/m^3.

Adjustment for Intermittent Exposure: The NOAEL of 0.03 mg Ni/m^3 was adjusted from intermittent exposure to a continuous exposure scenario using the following equation:

$$NOAEL_{ADJ} = 0.03\ mg\ Ni/m^3 \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.0054\ mg\ Ni/m^3$$

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated using the following equation from Lee et al. (2019), adopted from NIOSH (2013):

$$NOAEL_{HEC,ADJ} = NOAEL_{ADJ} \times \frac{VR_R}{VR_H} \times \frac{DF_R}{DF_H} \times \frac{\frac{1-k_R^n}{1-k_R}}{\frac{1-k_H^n}{1-k_H}} \times \frac{RH_R}{RH_H} \times \frac{SA_H}{SA_R}$$

Where VR= ventilation rate, DF = deposition fraction, k = 1-clearance rate, RH=particle retention half time, SA = alveolar surface area, n = exposure days, R = rat, and H = human. For this equation, deposition fractions and ventilation rates for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the pulmonary region is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD V 3.04) developed by Applied Research Associates, Inc. (ARA) to first calculate the deposition fraction (DF) for rats and humans. The MPPD model parameters and results for the rat and human deposition fractions are presented in Table A-8.

Table A-8. MPPD model (v 3.04) Inputs and Results for Rat and Human Models

Parameters	Rats	Humans
Airway morphometry		
Model	Asymmetric Multiple Path	Yem/Schum 5-Lobe
Functional residual capacity (FRC)	4 ml (default)	3300 ml (default)
Upper respiratory tract (URT)	0.42 ml (default)	50 ml (default)
Inhalant properties		
Density[1]	2.07	2.07
Diameter, MMAD[2]	2.5 µm	2.5 µm
GSD[2]	2.38	2.38
Exposure condition		
Aerosol concentration ($NOAEL_{ADJ}$)	0.0054 mg/m^3	0.0054 mg/m^3
Breathing frequency	102 breaths/min (default)	12 breaths/min (resting default)
Tidal volume	2.1 ml (default)	625 ml (resting default)
Breathing scenario	Nose only	Nasal
Results		
Alveolar region deposition fraction (Total pulmonary deposition fraction)	0.0362	0.1224

[1]PubChem, Ni Sulfate Hexahydrate
[2]From NTP (1996c), Table K1

The daily ventilation rate for rats (VR_R) was calculated using the breathing frequency and tidal volume presented in Table A-7 as follows:

$$102\ \text{min} \times 2.1\ ml = 214.2\ ml/min$$

$$214.2\frac{ml}{min} = 0.0002142\frac{m^3}{min}$$

$$\frac{0.0002142\ m^3}{1\ min} = \frac{X}{1440\ \text{min}\ \ (full\ day)}$$

$$VR_R = 0.31\ \frac{m^3}{day}$$

The daily ventilation rate for humans (VR_H) of 15.3 m^3/day is provided in ATSDR's Guidance for Inhalation Exposures (ATSDR 2021; Table A-1). The ventilation rate was calculated by applying a weighted average of adult age ranges to EPA's inhalation rates for male and female adults >21 years of age, as reported in the Exposure Factors Handbook (EPA 2011; Table 6-1).

The deposition fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $NOAEL_{HEC,ADJ}$. Table A-9 lists the values used within the equation and the source of these values. The exposure days (n) are 91 days to represent 13 weeks of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure.

$$NOAEL_{HEC,ADJ} = 0.0054\ \frac{mg^3}{m} \times \frac{0.31\frac{m^3}{day}}{15.3\frac{m^3}{day}} \times \frac{0.0362}{0.1224} \times \frac{\frac{1-(1-0.00105652)^{730}}{1-(1-0.00105652)}}{\frac{1-(1-0.00002)^{730}}{1-(1-0.00002)}} \times \frac{1}{10} \times \frac{54\ m^2}{0.34\ m^2}$$

$$NOAEL_{HEC,ADJ} = 0.00036\ mg/m^3$$

Table A-9. Values Used to Calculate Human Equivalent Concentration (HEC) NOAEL for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.31 m^3/day	15.3 m^3/day	Calculated daily ventilation rate
Deposition fraction (DF); calculated using MPPD software	0.0362	0.1224	Calculated using MPPD software
1-clearance rate (k)	0.9989	0.99998	MPPD
Clearance rate	0.00105652	0.00002	MPPD
Ratio of retention half-time (RH)	1	10	NIOSH 2013 per Lee et al. 2019 and Oller et al. 2014
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA 1994, Table 4-4
Exposure days (n)	730 days	730 days	NTP (1996c)

Uncertainty Factor: The $NOAEL_{HEC,ADJ}$ is divided by a total uncertainty factor of 30:

- 3 for interspecies extrapolation with dosimetric adjustments
- 10 for human variability

$$Provisional\ MRL = \frac{NOAEL_{HEC,ADJ}}{UFs} = \frac{0.00036\ mg\ Ni/m^3}{30}$$

$$= 0.000012\ mg\ Ni/m^3\ (Rounded\ to\ 0.00001\ mg\ Ni/m^3)$$

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL. Data in humans are limited by small sample sizes and not appropriate for extrapolation to a large population. Data from animals in the acute-duration oral database does not provide sufficient information to derive an MRL because serious health effects are seen at the lowest doses tested for critical endpoints in animals.

Rationale for Not Deriving an MRL: Several studies in humans (Gawkrodger et al. 1986; Hindsén et al. 2001; Jensen et al. 2003) examined allergic dermatitis at various challenge doses. These studies were not considered for MRL development as sample sizes for doses tested were no more than 10 individuals in any study, and Jensen et al. (2003) noted that extrapolation of these results to larger populations would not be statistically correct. Jensen et al. (2003) calculated that a sample size of 36 individuals per dose would be required to reach statistical significance. In nickel-sensitized individuals, allergic dermatitis occurred from ingesting a single challenge dose ≥0.058 mg Ni/kg as nickel sulfate (Gawkrodger et al. 1986; Hindsén et al. 2001; Jensen et al. 2003). Sunderman et al. (1988) was the only human study to observe non-dermal effects. However, this resulted from worker exposure to a solution containing nickel sulfate and nickel chloride and exposure could only be estimated.

Several animal studies report serious development and reproductive toxicity at the lowest doses tested thus precluding MRL derivation from these end points due to the ATSDR policy of not deriving MRLs from serious LOAELs. As Table A-10 shows, the severity of development and reproductive effects at 10.3 mg Ni/kg/day varies, including no developmental effects reported (Saini et al. 2014b). Since the database is inconclusive on the potential toxicity at 10.3 mg Ni/kg/day, deriving an MRL based on this value would not be protective, and further data on toxicity at lower doses is needed. At 10.29 mg Ni/kg, pregnant mice showed reduced gestation index (percent of pregnancies resulting in live litter) (Saini et al. 2014b). In the same study, the offspring of exposed dams showed a bodyweight reduction of 14% compared to controls when observed on gestation days 6 through 13 (Saini et al. 2014b). While Saini et al. (2014b) observed no effects for developmental effects at 10.29 mg Ni/kg, this was due to no abnormalities observed in offspring on gestation days 0 through 5 and days 14 through 18. At higher doses, pregnant dams showed reduced litter size, greater offspring body weight loss, and offspring mortality (Saini et al. 2014b). In a separate study, the offspring of dams exposed to 10.29 mg Ni/kg showed skeletal abnormalities including delayed ossification of skull bone, vertebrate, and sternum (El Sekily et al. 2020). The incidence of these abnormalities increased with dose. High fetal resorption and a significantly decreased number of live-birth offspring was reported at all doses (El Sekily et al. 2020). Two studies in mice report serious skeletal anomalies and post-implantation loss at 11.4 mg Ni/kg (Saini et al. 2013, 2014a), and sperm abnormalities in exposed males at 23 to 43 mg Ni/kg (Sobti and Gill 1989).

Only two studies examined neurotoxicity and due to limited evidence, the end point cannot be identified as a critical effect. Mice exposed to a single dose of 12.34 mg Ni/kg showed disturbances to aerobic metabolism, reduced spatial memory performance, and reduced locomotor activity. No effects were seen in mice exposed to 1.2 mg Ni/kg (He et al. 2013). Oller and Erexson (2008) reported neurological effects, as hypoactivity and increased salivation in rats exposed to 27.91 mg Ni/kg/day.

Other adverse effects have been observed in rats, mice, and dogs at doses ranging from 11.35 to 111.6 mg Ni/kg (Ambrose et al. 1976; Haro et al. 1968; He et al. 2013; Oller and Erexson 2007; RTI 1988a, 1988b; Saini et al. 2013, 2014a; Seidenberg et al. 1986; Singla et al. 2006, Sobti and Gill 1989). Haro et al. (1968) calculated LD_{50} values for rats and mice of both sexes following exposure to single doses of nickel acetate. Among rats the LD_{50} values were 116 and 120 mg/kg/day for females and males, respectively. Among mice the LD_{50} values were 139 and 136 mg/kg/day for females and males, respectively (Haro et al. 1968). Exposure-related death was observed at doses ≥140 mg/kg/day in rats (Oller and Erexson 2007; RTI 1988a, 1988b). The relevant NOAEL and LOAEL values are presented in Table A-10.

Table A-10. Effect levels for Select Acute-Duration Oral Exposure to Nickel Studies

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Developmental					
Mouse (NS)	8 days Daily		10.29*	Significant increase in fetal resorption and skeletal anomalies	El Sekily et al. 2020 (Nickel chloride hexahydrate)
Mouse (F)	GD 0-5 Daily	10.29	41.19*	11.75% offspring mortality	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (F)	GD 14-18 Daily	10.29	20.59*	11.11% offspring mortality	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (F)	GD 6-13 Daily		10.29	14% less offspring bodyweight at birth	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (B)	GD 0-5 Daily		11.35	12% fetuses with skeletal defect	Saini et al. 2014a (Nickel chloride hexahydrate)
Reproductive					
Mouse (F)	GD 0-5 Daily		10.29	Reduced gestation index (75%)	Saini et al. 2014b (Nickel chloride hexahydrate)
Mouse (F)	GD 0-5 Daily		11.35*	Decreased implantation sites/dam and number of live fetuses/dams	Saini et al. 2014a (Nickel chloride hexahydrate)
Mouse (F)	GD 6-13 Daily		11.38*	4.16% embryos resorbed/post-implantation death	Saini et al. 2013 (Nickel chloride hexahydrate)
Dermal					
Human (F)	Once	0.014	0.057	Dermatitis in nickel sensitive subjects	Hindsen et al. 2001 (Nickel sulfate)
Human (F)	Once	0.014	0.057	Dermatitis in nickel sensitive subjects	Jensen et al. 2003 (Nickel sulfate)
Human (NS)	2 days 2 times/day	0.03			Burrows et al. 1981 (Nickel sulfate)
Human (F)	2 days Once/day	0.043	0.097	Allergic dermatitis in sensitized individuals	Gawkrodger et al. 1986 (Nickel sulfate)

B=Both; F=females; GD=gestation day; M=males; NS=Not Specified
* = Serious lowest observed adverse effect level (SLOAEL)

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL as a NOAEL has not been identified in the database and the lowest LOAEL is associated with serious effects, precluding MRL derivation.

Rationale for Not Deriving an MRL: An MRL cannot be derived from human studies as only one study examined effects of intermediate-duration oral nickel exposure. No dermal reactions were reported among 8 women exposed to oral doses of 0.02 mg/kg/day (Santucci et al. 1994).

Among experimental animal studies, Dahdouh et al. (2016) observed serious renal effects at the lowest LOAEL in the intermediate-duration oral database precluding derivation of an intermediate-duration oral MRL that is health protective. Dahdouh et al. (2016) tested the lowest dose in the intermediate-duration oral database for animals, observing adverse hematological and renal effects in male mice exposed to 0.036 mg Ni/kg/day as nickel sulfate. Hematological effects included reduced red blood cells and hemoglobin, and elevated white blood cells; renal effects included proximal tubule degeneration with tubular necrosis and inflammation (Dahdouh et al. 2016). The relevant exposure doses are summarized in Table A-11.

Developmental toxicity data from a two-generation (Springborn Labs 2000a) and a one-generation (Springborn Labs 2000b) rat study were considered for MRL derivation, but a resulting MRL would not be health protective. Springborn Laboratories (2000b) observed significantly increased incidence of stillborn offspring in rats exposed to ≥6.7 mg Ni/kg/day as nickel sulfate hexahydrate starting on postnatal day 22 for 1, 2, or 3 weeks, and in utero. Developmental effects did not appear significant at doses ≤4.5 mg Ni/kg/day (Springborn Laboratories 2000b). At 6.7 mg Ni/kg/day, there was also significant post-implantation loss indicative of reproductive toxicity (Springborn Laboratories 2000b). Both studies provided data on post-implantation loss incidence for each exposed dam and controls. While neither study identified a LOAEL for developmental effects, the data were amenable to benchmark dose modeling. Multiple other studies also report serious developmental effects in rats and mice at doses ranging from 1.3 to 160 mg Ni/kg/day including decreased pup survival, structural abnormalities, and spontaneous abortion (Berman and Rehnberg 1983; Kakela et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). In mice, post-implantation loss is reported at 2.2 mg Ni/kg/day (Pandey et al. 1999). Male reproductive toxicity is observed in several mouse studies at doses of 1.1 to 4.53 mg Ni/kg/day and included sperm abnormalities, changes in sperm motility, concentration, and count, and histological changes (Pandey et al. 1999; Pandey and Srivastava 2000; Toman et al. 2012).

The BMDL values from Springborn Laboratories (2000a, 2000b) are higher than the serious LOAEL identified by Dahdouh et al. (2016), thus these values would not be health protective nor suitable for MRL derivation. BMD modeling was conducted to identify a potential POD for incidence of litter-specific post-implantation loss. The data were fitted to all available dichotomous nested models in EPA's Benchmark Software (BMDS version 3.2). A BMR of 10% was selected in the absence of data that would support a lower BMR. Adequate model fit is judged by four criteria: chi squared goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, BMDLs <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among all of

the models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) is selected as the POD when the difference between the BMDLs estimated from these models was <3-fold; otherwise, the lowest BMDL was chosen. The recommended BMDLs were 3.34 mg Ni/kg/day from the Springborn Laboratories (2000b) data, and 2.01 mg Ni/kg/day from the Springborn Laboratories (2000a) data. Use of the lower BMDL from Springborn Laboratories (2000a) would not be protective since it is higher than the lowest LOAEL in the database where a SLOAEL of 0.036 mg/kg/day for renal effects in mice is identified. Additionally, Smith et al. (1993) identified a developmental SLOAEL of 1.3 mg/kg/day.

Table A-11. Summary of NOAEL, LOAEL, and SLOAEL Values for Intermediate-Duration Oral Exposure to Nickel, Excluding Death Effects

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference
Hematological					
Mouse (M)	28 days Daily		0.036	Changes in blood chemistry (reduced RBCs and hemoglobin; increased WBCs)	Dahdouh et al. 2016 (Nickel sulfate)
Rat (M)	28 days Daily	0.23	0.49	Increased leukocytes (36%)	Weischer et al. 1980 (Nickel chloride)
Renal					
Mouse (M)	28 days Daily		0.036*	Proximal tubule degeneration with tubular necrosis and inflammation	Dahdouh et al. 2016 (Nickel sulfate)
Rat (M)	28 days Daily		0.23	Decreased urea (15%)	Weischer et al. 1980 (Nickel chloride)
Developmental					
Rat (F)	11 weeks (breeding-lactation) 2 litters		1.3*	Decreased pup survival	Smith et al. 1993 (Nickel chloride)
Rat (B)	18 weeks daily	2.2		Post-implantation loss	Springborn Laboratories 2000a (Nickel sulfate hexahydrate)
Rat (F)	F1 generation began on PND 22 for 1, 2, or 3 weeks	4.5	6.7	Significantly increased incidence of stillborn pup	Springborn Laboratories 2000b (Nickel sulfate hexahydrate)

B=Both; F=Female; M=Male; RBCs=red blood cells; WBCs=white blood cells
* = Serious lowest observed adverse effect level (SLOAEL)

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: August 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL as the database indicates that serious adverse health effects are associated with the lowest levels of exposure, and no critical effect can be identified as the basis of an MRL.

Rationale for Not Deriving an MRL: No studies were located that exposed humans to nickel for chronic durations. Animal toxicity data following chronic-duration oral exposure to nickel are limited to a few studies that report serious LOAELs at the lowest doses tested. Thus, no exposure levels can be used to derive an MRL value. At the lowest dose tested in animals, 2.2 mg Ni/kg/day, 33% mortality was seen in female rats (20/60 died) (Heim et al. 2007). Heim et al. (2007) also observed increased leukocytes in female rats exposed to 2.2 mg Ni/kg/day as nickel sulfate hexahydrate, and reduced bodyweight in male rats exposed to 6.7 mg Ni/kg/day as nickel sulfate hexahydrate. Kidney, lung, blood effects and exposure-related body weight changes were observed in dogs following exposure to 62.5 mg Ni/kg/day as nickel sulfate (Ambrose et al. 1976).

The EPA derived an oral reference dose of 0.02 mg Ni/kg/day for nickel based on a rat study by Ambrose et al. (1976). This study was not used to derive an oral chronic-duration MRL as authors noted high mortality among all groups especially controls of both sexes and males at the highest dose. In the chronic-duration rat study, groups of 25 males and 25 females were exposed to doses of 0, 7.5, 75, 187.5 mg Ni/kg/day as nickel sulfate in their diet for 2 years. The exposure-related body weight and organ weight changes were the basis of EPA's oral reference dose (Ambrose et al. 1976). Body weight reductions in male and female rats exposed to 187.5 and 75 mg Ni/kg/day, respectively were significant compared to controls. The EPA also reported increased relative heart weights and decreased relative liver weights as critical effects. In the rat study by Ambrose et al. (1976), through the 2-year study poor survival was observed among control groups for both sexes (44/50 controls died) and was significantly higher than for any of the exposure groups. The study quality was deemed insufficient for derivation of a MRL by ATSDR as the high mortality among controls does not allow for accurate interpretation of the results. The EPA's derivation of the oral reference dose similarly states concerns with interpreting results from this study due to the high mortality. The relevant NOAEL and LOAEL doses are summarized in Table A-12.

Table A-12. Summary of Relevant NOAEL and LOAEL Values for Chronic-Duration Oral Exposure to Nickel, Excluding Death Effects

Species (sex)	Frequency/ Duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference
Hematological					
Rat (F)	2 years Daily	11.2			Heim et al. 2007 (Nickel sulfate hexahydrate)
Bodyweight					
Rat (F)	2 years Daily	7.5	75*	34% less body weight compared to controls through 104 weeks of exposure	Ambrose et al. 1976[1] (Nickel sulfate)
Rat (M)	2 years Daily	75	187.5*	up to 35% less body weight compared to controls through 78 weeks of exposure	Ambrose et al. 1976[1] (Nickel sulfate)
Rat (M)	2 years Daily	2.2	6.7	11% reduced bodyweight	Heim et al. 2007 (Nickel sulfate hexahydrate)
Dog (NS)	2 years Daily	25	62.5	10% decrease in body weight gain	Ambrose et al. 1976 (Nickel sulfate)

F=females; M=males; NS=Not Specified

*= Serious lowest observed adverse effect level (SLOAEL)

[1]The chronic-duration rat study by Ambrose et al. (1976) is not included in Table 2-2 or **Figure 2-22. Levels of Significant Exposure to Nickel – Oral**Figure 2-22, as it was excluded from the LSE database due to poor study quality.

Agency Contact (Chemical Managers): Custodio Muianga, PhD, MPH; Franco Scinicariello, MD, M.P.H.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR NICKEL

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to nickel.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for nickel. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of nickel have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of nickel are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion

Table B-1. Inclusion Criteria for the Literature Search and Screen

PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for nickel (ATSDR 2005); thus, the literature search was restricted to studies published between 2003 to 2020. The following main databases were searched in October 2020:

- Science Direct
- PubMed
- Medline
- SCOPUS

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for nickel. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to nickel were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date search hits	Query string
PubMed	
10/2020	TI/AB((Nickel OR “CI 777775” OR Alnico) OR RN(7440-02-0))
8,752 hits	AND
	(MeSH Terms (“Death”[MeSH Terms] OR “Body Weight”[MeSH Terms] OR “respiratory system”[MeSH Terms] OR “cardiovascular diseases”[MeSH Terms] OR “gastrointestinal diseases” [MeSH Terms] OR “hematologic diseases” [MeSH Terms] OR “musculoskeletal diseases” [MeSH Terms] OR “hepatic infraction” [MeSH Terms] OR “renal insufficiency” [MeSH Terms] OR dermatology [MeSH Terms] OR “endocrine system” [MeSH Terms] OR neurology[MeSH Terms] OR “reproductive health” [MeSH Terms] OR “developmental disabilities” [MeSH Terms] OR “psychology, developmental” [MeSH Terms] OR Neoplasms[MeSH Terms] OR “DNA Damage” [MeSH Terms])
	OR
	TI/AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (tiab(“nickel acetate” OR “Acetic acid” OR “Nickel di(acetate)” OR “Nickel diacetate” OR “Nickel(2+) acetate” OR “Nickel(2+) diacetate” OR “Nickel(2+) salt” OR “Nickel(cento) acetate” OR “Nickel(II) acetate” OR “Nickelous acetate”) OR RN(“373-02-4”))
	AND
	(MeSH Terms (“Death”[MeSH Terms] OR “Body Weight”[MeSH Terms] OR “respiratory system”[MeSH Terms] OR “cardiovascular diseases”[MeSH Terms] OR “gastrointestinal diseases” [MeSH Terms] OR “hematologic diseases” [MeSH Terms] OR “musculoskeletal diseases” [MeSH Terms] OR “hepatic infraction” [MeSH Terms] OR “renal insufficiency” [MeSH Terms] OR dermatology [MeSH Terms] OR “endocrine system” [MeSH Terms] OR neurology[MeSH Terms] OR “reproductive health” [MeSH Terms] OR “developmental disabilities” [MeSH Terms] OR “psychology, developmental” [MeSH Terms] OR Neoplasms[MeSH Terms] OR “DNA Damage” [MeSH Terms])
	OR
	TI/AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (tiab(“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	"Nickel ammonium sulfate" OR "Nickel(II) ammonium sulfate" OR "Sulfuric acid") OR RN("7785-20-8"))
	AND
	(MeSH Terms ("Death"[MeSH Terms] OR "Body Weight"[MeSH Terms] OR "respiratory system"[MeSH Terms] OR "cardiovascular diseases"[MeSH Terms] OR "gastrointestinal diseases" [MeSH Terms] OR "hematologic diseases" [MeSH Terms] OR "musculoskeletal diseases" [MeSH Terms] OR "hepatic infraction" [MeSH Terms] OR "renal insufficiency" [MeSH Terms] OR dermatology [MeSH Terms] OR "endocrine system" [MeSH Terms] OR neurology[MeSH Terms] OR "reproductive health" [MeSH Terms] OR "developmental disabilities" [MeSH Terms] OR "psychology, developmental" [MeSH Terms] OR Neoplasms[MeSH Terms] OR "DNA Damage" [MeSH Terms])
	OR
	TI/AB (Death OR "Body weight" OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR "health effects"))
MEDLINE	
10/2020	(Nickel OR "CI 777775" OR Alnico) OR RN ("7440-02-0")
5,186 hits	AND
	((MH Death OR "Body Weight" OR "respiratory system" OR "cardiovascular diseases" OR "gastrointestinal diseases" OR "hematologic diseases" OR "musculoskeletal diseases" OR "hepatic infraction" OR "renal insufficiency" OR dermatology OR "endocrine system" OR neurology OR "reproductive health" OR "developmental disabilities" OR "psychology, developmental" OR Neoplasms OR "DNA Damage") OR AB (Death OR "Body weight" OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR "health effects")) ("nickel acetate" OR "Acetic acid" OR "Nickel di(acetate)" OR "Nickel diacetate" OR "Nickel(2+) acetate" OR "Nickel(2+) diacetate" OR "Nickel(2+) salt" OR "Nickel(cento) acetate" OR "Nickel(II) acetate" OR "Nickelous acetate") OR RN ("373-02-4")
	AND
	((MH Death OR "Body Weight" OR "respiratory system" OR "cardiovascular diseases" OR "gastrointestinal diseases" OR "hematologic diseases" OR "musculoskeletal diseases" OR "hepatic infraction" OR "renal insufficiency" OR dermatology OR "endocrine system" OR neurology OR "reproductive health" OR "developmental disabilities" OR "psychology, developmental" OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR “Nickel ammonium sulfate” OR “Nickel(II) ammonium sulfate” OR “Sulfuric acid”) OR RN(“7785-20-8”) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”))
Science Direct 10/2020 547 hits	(Nickel OR “CI 777775” OR Alnico OR “7440-02-0”) AND 547 ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel acetate” OR “Acetic acid” OR “Nickel di(acetate)” OR “Nickel diacetate” OR “Nickel(2+) acetate” OR “Nickel(2+) diacetate” OR “Nickel(2+) salt” OR “Nickel(cento) acetate” OR “Nickel(II) acetate” OR “Nickelous acetate” OR “373-02-4”) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR “Nickel ammonium sulfate” OR “Nickel(II) ammonium sulfate” OR “Sulfuric acid” OR “7785-20-8”) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”))
Scopus 10/2020 3,520 hits	Title Abstract(Nickel OR “CI 777775” OR Alnico OR 7440-02-0) AND Title Abstract ((Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR “health effects”)) (“nickel acetate” OR “Acetic acid” OR “Nickel di(acetate)” OR “Nickel diacetate” OR “Nickel(2+) acetate” OR “Nickel(2+) diacetate” OR “Nickel(2+) salt” OR “Nickel(cento) acetate” OR “Nickel(II) acetate” OR “Nickelous acetate” OR “373-02-4”) AND Title Abstract (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR “health effects”) (“nickel ammonium sulfate” OR “Ammonium disulfatonickelate(II)” OR “Ammonium nickel sulfate” OR “Ammonium nickel(2+ sulfate)” OR “Ammonium nickel(2+) salt” OR “Dammonium nickel bis(sulphate)” OR

Table B-2. Database Query Strings

Database search date search hits	Query string
	"Nickel ammonium sulfate" OR "Nickel(II) ammonium sulfate" OR "Sulfuric acid" OR "7785-20-8") AND Title Abstract (Death OR "Body weight" OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR "health effects")

The October 2020 results were:

- Number of records identified from Science Direct, PubMed, Medline, and SCOPUS (after duplicate removal): 10,739
- Number of records identified from other strategies: 6
- Total number of records to undergo literature screening: 10,745

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on nickel:

- Title and abstract screen
- Full text screen

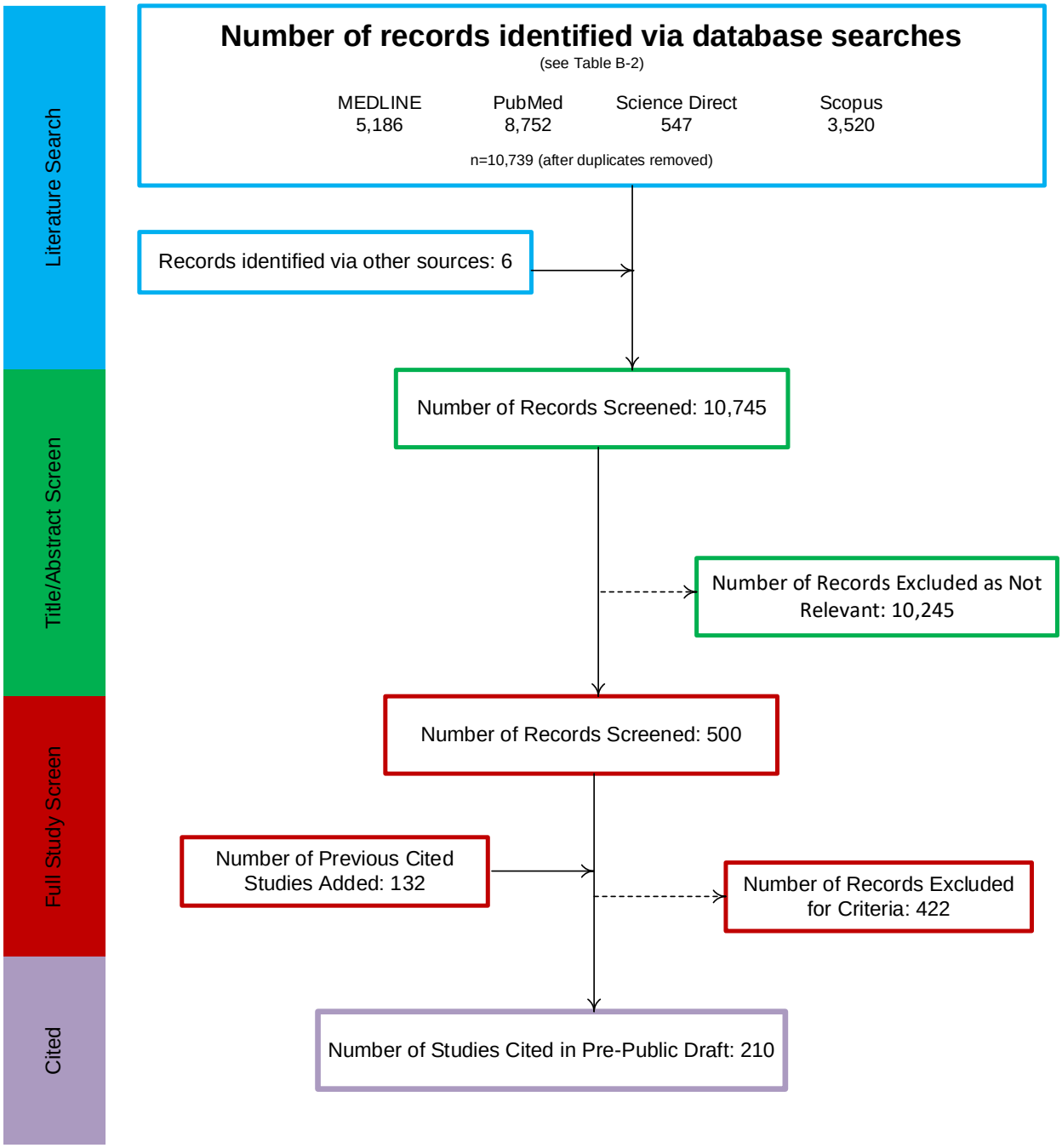
Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 10,745
- Number of studies considered relevant and moved to the next step: 500

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 500
- Number of studies cited in the pre-public draft of the toxicological profile: 78
- Total number of studies cited in the profile: 210

Figure B-1. October 2020 Literature Search Results and Screen for Nickel



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR NICKEL

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to nickel, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to nickel:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, and dermal exposure to nickel. The inclusion criteria used to identify relevant studies examining the health effects of nickel are presented in Table B-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of nickel. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the literature search to update the existing toxicological profile for nickel (ATSDR 2005) was restricted to studies published between 2003 and 2020. See Appendix B for the databases searched and the strategy.

A total of 10,739 records relevant to the health effects section of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in APPENDIX B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of nickel.

Title and Abstract Screen. In the Title and Abstract Screen step, 10,745 records were reviewed; 500 studies were considered to meet the health effects inclusion criteria in Table B-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 500 health effects studies identified in the update literature was performed. Of these studies, 422 did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanism of action or were relevant to other sections of the toxicological profile. Additionally, 132 studies cited in the LSE tables for the existing profile were included in the full study screen bringing the total number of studies for the qualitative review to 210.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-1. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

A summary of the extracted data for each study is presented in the Supplemental Documents for nickel and overviews of the results of the inhalation, oral and dermal exposure studies are presented in Sections 2.2 - 2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Table 2-1, Table 2-2, and Table 2-3, respectively).

Table C-1. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for nickel identified in human and animal studies are presented in Tables C-2 and C-3, respectively.

Human studies evaluating noncancerous effects are primarily cohort studies of occupational exposure that examined respiratory effects. Several other studies were conducted at the population level to examine associations between exposure to nickel in air and respiratory and/or cardiovascular mortality. Most studies in humans analyzed the increased risk of various types of cancer both among general and occupational populations. Taken together, studies in humans indicate that the respiratory system is a target of nickel toxicity particularly through the inhalation route. Inhalation and oral animal studies have examined a wide range primarily focusing on the respiratory and immunological system and a majority of these studies indicated an adverse health effect. Dermal studies in humans focused on examining dermal effects while dermal studies in animals were limited to examining a few endpoints. The respiratory system is considered the target of nickel toxicity and given that effects were seen at low doses in animals, intermediate- and chronic-duration inhalation MRL were derived. Additionally, nickel allergy is commonly examined in humans through dermal patch testing, and many animal studies indicate nickel has some effect on immune function. Studies examining the respiratory and immune endpoints were carried through Steps 4–8 of the systematic review.

Table C-2. Overview of the Health Outcomes for Nickel Evaluated in Human Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Cohort	0	20	5	1	0	0	1	2	0	0	0	3	0	1	3	0	36
	0	7	0	0	0	0	1	2	0	0	0	3	0	1	3	0	20
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	5
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2
Population	0	5	11	0	0	0	0	0	0	0	0	0	1	5	1	0	9
	0	5	9	0	0	0	0	0	0	0	0	0	1	1	1	0	3
Case series	0	4	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
	0	4	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Oral Studies																	
Cohort	0	0	0	1	0	0	0	0	13	0	0	0	1	0	0	0	0
	0	0	0	1	0	0	0	0	9	0	0	0	1	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
Case series	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermal Studies																	
Cohort	0	1	0	0	0	0	0	1	15	0	0	1	0	0	0	0	0
	0	1	0	0	0	0	0	0	14	0	0	1	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

Table C-3. Overview of the Health Outcomes for Nickel Evaluated in Experimental Animal Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Acute-duration	5	6	4	3	1	3	3	3	3	0	3	6	3	3	0	0	0
	3	6	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0
Intermediate-duration	8	13	5	3	3	3	4	5	3	0	4	10	4	3	1	1	1
	2	13	2	0	2	0	0	1	0	0	0	10	1	1	1	1	1
Chronic-duration	6	7	4	4	4	2	5	6	4	0	4	5	4	3	0	1	4
	3	7	0	0	2	0	0	1	1	0	2	4	0	0	0	1	4
Oral Studies																	
Acute-duration	1	1	0	2	0	0	0	0	0	0	0	0	3	5	5	3	0
	1	1	0	2	0	0	0	0	0	0	0	0	2	4	4	3	0
Intermediate-duration	12	4	4	3	5	0	9	10	1	1	2	3	2	9	6	2	0
	7	3	1	1	5	0	4	7	0	0	1	3	1	5	6	2	0
Chronic-duration	2	1	1	1	2	1	1	1	1	0	1	1	1	1	0	0	0
	2	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
Dermal Studies																	
Acute-duration	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Intermediate-duration	0	0	0	0	1	0	2	2	1	0	0	0	0	1	0	1	0
	0	0	0	0	0	0	2	1	1	0	0	0	0	1	0	1	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies and animal experimental studies are presented in C-4, C-5, and C-6, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-4. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-5. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational epidemiological studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational epidemiological studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of nickel health effects studies (observational epidemiology and animal experimental studies) are presented in Table C-7 and C-8, respectively.

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables? *	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization? *	Detection bias — Is there confidence in the outcome assessment? *	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory							
Cohort Studies Inhalation							
Arena et al. 1998	++	+	++	-	-	++	Second
Bell et al. 2009	+	-	+	-	+	++	Second
Bell et al. 2014	-	-	+	-	+	++	Second
Berge and Skyberg 2003	+	+	-	-	-	++	Second
Cornell and Landis 1984	+	+	+	-	-	++	Second
Cox et al. 1981	+	-	+	-	-	+	Third
Cragle et al. 1984	+	-	+	-	-	+	Third
Dolovich et al.1984	-	+	+	-	+	+	Second

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables? ***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization? ***	Detection bias — **Is there confidence in the outcome assessment? ***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Egedahl et al. 2001	-	+	+	-	+	++	Second
Enterline and Marsh 1982	-	-	+	-	+	++	Second
Fishwick et al. 2004	++	+	+	-	-	++	Second
Gehring et al. 2015	+	+	+	--	-	+	Second
Kilburn et al. 1990	+	-	+	-	+	++	Second
Moulin et al. 2000	+	+	-	-	+	+	Second
Muir et al. 1993	+	+	-	-	+	+	Second
Patel et al. 2009	+	-	+	-	-	++	Third
Polednak 1981	-	-	+	+	+	+	Second
Redmond 1984	+	+	-	-	+	+	Second

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables? *	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization? *	Detection bias — Is there confidence in the outcome assessment? *	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Roberts et al. 1989a	+	-	+	-	+	+	Second
Rosa et al. 2016	+	+	+	-	-	+	Second
Schachter et al. 2020	-	+	+	-	+	+	Second
Shannon et al. 1984a	+	+	-	-	-	+	Second
Shannon et al. 1984b	+	-	-	--	-	+	Third
Shannon et al. 1991	+	-	+	+	-	+	Second
Shirakawa et al. 1990	-	+	+	-	+	+	Second
Outcome: Immunological							
Cohort Studies Inhalation							
Bencko et al. 1983	--	-	+	-	-	++	Third

Table C-7. Summary of Risk of Bias Assessment for Nickel—Observational Epidemiology Studies

	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
Reference	Were the comparison groups appropriate?	**Did the study design or analysis account for important confounding and modifying variables? ***	Were outcome data complete without attrition or exclusion from analysis?	**Is there confidence in the exposure characterization? ***	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
Bencko et al. 1986	++	+	+	-	+	++	Second
Shirakawa et al. 1990	-	+	+	-	+	+	Second
Cohort Studies Dermal							
Mozzanica et al. 1990	+	-	+	+	-	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory									
Inhalation Acute Exposure									
Benson et al. 1995b (Rat)	-	-	+	-	+	++	+	+	First
Efremenko et al. 2014 (Rat)	++	-	+	-	+	+	++	+	First
Inhalation Intermediate Exposure									
Benson et al. 1995a (Rat)	-	-	+	-	+	++	+	+	First
Benson et al. 1995a (Rat)	-	-	+	-	+	++	+	+	First
Benson et al. 1995a (Mice)	-	-	+	-	+	++	+	+	First
Benson et al. 1995a (Mice)	-	-	+	-	+	++	+	+	First
Benson et al. 1995b (Rat)	-	-	+	-	+	++	+	+	First
Bingham et al. 1972 (Rat)	-	-	+	-	+	-	+	+	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
Bingham et al. 1972 (Rat)	-	-	+	-	+	-	+	+	Second
Efremenko et al. 2014 (Rat)	++	-	+	-	+	+	++	+	First
Evans et al. 1995 (Rat)	-	-	++	-	+	+	++	++	First
Horie et al. 1985 (Rat)	-	-	+	-	+	-	-	+	Second
Johansson and Camner 1986 (Rabbit)	-	-	-	-	+	-	-	+	Third
NTP 1996a (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 16 D	-	-	+	-	++	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
NTP 1996b (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
Oller et al. 2022 (Rat) 13 Wk	++	+	+	+	++	++	+	+	First
Oller et al. 2022 (Rat) 13 Wk	++	+	+	+	++	++	+	+	First
Weischer et al. 1980 (Rat)	-	-	+	-	+	-	+	+	Second
Inhalation Chronic Exposure									
NTP 1996a (Rat)	-	-	+	-	++	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
NTP 1996a (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice)	-	-	+	-	++	++	++	++	First
Oller et al. 2008 (Rat)	++	-	+	-	+	++	++	++	First
Ottolenghi et al. 1974 (Rat)	-	-	+	-	+	-	+	+	Second
Takenaka et al. 1985 (Rat)	-	-	++	-	+	-	+	+	Second
Oral Intermediate Exposure									
American Biogenics Corp 1988 (Rat)	++	-	+	-	+	++	+	+	First
Obone et al. 1999 (Rat)	-	-	+	-	++	+	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
RTI 1988a, 1988b (Rat)	+	-	+	-	+	-	+	+	First
Springborn Laboratories 2002 (Rat)	++	-	+	-	++	++	++	++	First
Oral Chronic Exposure									
Ambrose et al. 1976 (Rat)	-	-	+	-	+	-	+	+	Second
Ambrose et al. 1976 (Dog)	-	-	+	-	+	-	+	+	Second
Outcome: Immunological									
Inhalation Acute Exposure									
Adkins et al. 1979a (Mice)	-	-	+	-	+	-	+	+	Second
Adkins et al. 1979b (Mice)	-	-	+	-	+	-	+	+	Second
Adkins et al. 1979c (Mice)	-	-	+	-	+	-	+	+	Second
Buxton et al. 2021 (Mice)	++	-	++	-	+	+	+	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Graham et al. 1978 (Mice)	-	-	+	-	+	-	+	+	Second
Inhalation Intermediate Exposure									
Haley et al. 1990 (Mice)	+	-	+	-	+	++	++	++	First
Haley et al. 1990 (Mice)	+	-	+	-	+	++	++	++	First
Haley et al. 1990 (Mice)	+	-	+	-	+	++	++	++	First
Johansson et al. 1980 (Rabbit)	-	-	+	-	++	-	+	+	Second
Johansson et al. 1987 (Rabbit)	-	-	+	-	+	-	+	+	Second
Johansson et al. 1988 (Rabbit)	-	-	+	-	+	-	+	+	Second
Johansson et al. 1989 (Rabbit)	-	-	+	-	+	-	+	+	Second
Morimoto et al. 1995 (Rat)	-	-	+	-	+	+	+	+	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
NTP 1996a (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996a (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice) 16 D	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat) 13 Wk	-	-	+	-	++	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: **Is there confidence in the outcome assessment? ***	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
NTP 1996c (Mice) 13 Wk	-	-	+	-	++	++	++	++	First
Spiegelberg et al. 1984 (Rat)	-	-	+	-	+	-	+	+	Second
Xu et al. 2012 (Mice)	+	-	+	-	+	-	++	++	First
Inhalation Chronic Exposure									
NTP 1996a (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996a (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996b (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996b (Mice)	-	-	+	-	++	++	++	++	First
NTP 1996c (Rat)	-	-	+	-	++	++	++	++	First
NTP 1996c (Mice)	-	-	+	-	++	++	++	++	First
Oller et al. 2008 (Rat)	++	-	+	-	+	++	++	++	First

Table C-8. Summary of Risk Bias Assessment for Nickel – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment? ***	Were all measured outcomes reported?	Risk of bias tier
Ottolenghi et al. 1974 (Rat)	-	-	+	-	+	-	+	+	Second
Oral Intermediate Exposure									
Dieter et al. 1988 (Mice)	-	-	+	-	+	-	+	+	Second
Ilback et al. 1994 (Mice)	+	-	+	-	+	-	+	+	First
Obone et al. 1999 (Rat)	-	-	+	-	++	+	++	++	First
Oral Chronic Exposure									
Ambrose et al. 1976 (Rat)	-	-	+	-	+	-	+	+	Second
Ambrose et al. 1976 (Dog)	-	-	+	-	+	-	+	+	Second
Dermal Acute Exposure									
Siller and Seymour 1994 (Mice)	-	-	+	-	+	-	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to nickel and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence**: the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence**: the true effect may be reflected in the apparent relationship
- **Low confidence**: the true effect may be different from the apparent relationship
- **Very low confidence**: the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study, observation epidemiology, human-controlled exposures, and experimental animals. Unless there was a clear need for delineation in the confidence for a particular outcome, confidence assessments were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to nickel and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key study design features was determined for individual studies using four "yes or no" questions which were customized for observational epidemiology, human-controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human-controlled exposure studies, and experimental animal studies are presented in C-9, C-10, and C-11, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence**: Studies in which the responses to the four questions were "yes."
- **Moderate Initial Confidence**: Studies in which the responses to only three of the questions were "yes."
- **Low Initial Confidence**: Studies in which the responses to only two of the questions were "yes."
- **Very Low Initial Confidence**: Studies in which the response to one or none of the questions was "yes."

Table C-9. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-10. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested (i.e., 10 or more subjects)
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-11. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested (i.e., 3 or more animals for acute exposure, 10-20 animals for intermediate exposure, 50 or more animals for chronic exposure)
Appropriate parameters used to assess a potential adverse effect (i.e., clinical, gross, and histopathological outcomes were assessed. If an endpoint was not amendable to a clinical assessment then we did not downgrade the confidence in a study for not including it)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis (i.e., the statistical procedures used were presented in the paper and they were appropriate for the data)

The presence or absence of the key features and the initial confidence levels for studies examining respiratory and immunological effects observed in observational epidemiology and animal experimental studies are presented in Tables C-12 and C-13, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-14.

Table C-12. Presence of Key Features of Study Design for Nickel—Observational Epidemiology Studies

Reference	Key features: Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	Initial study confidence
Outcome: Respiratory Effects					
Cohort Inhalation Studies					
Arena et al. 1998	No	Yes	No	Yes	Low
Bell et al. 2009	No	Yes	No	Yes	Low
Bell et al. 2014	No	Yes	No	Yes	Low
Berge and Skyberg 2003	No	No	Yes	Yes	Low
Cornell and Landis 1984	No	Yes	Yes	Yes	Moderate
Cox et al. 1981	No	Yes	Yes	Yes	Moderate
Cragle et al. 1984	No	Yes	Yes	Yes	Moderate
Dolovich et al.1984	No	Yes	Yes	Yes	Moderate
Egedahl et al. 2001	No	Yes	Yes	Yes	Moderate
Enterline and Marsh 1982	No	Yes	Yes	Yes	Moderate
Fishwick et al. 2004	No	Yes	Yes	Yes	Moderate
Gehring et al. 2015	No	No	Yes	Yes	Low
Kilburn et al. 1990	No	Yes	Yes	Yes	Moderate
Moulin et al. 2000	No	Yes	Yes	Yes	Moderate
Muir et al. 1993	No	Yes	Yes	Yes	Moderate
Patel et al. 2009	No	Yes	Yes	Yes	Moderate
Polednak 1981	No	Yes	Yes	Yes	Moderate
Redmond 1984	No	Yes	Yes	Yes	Moderate
Roberts et al. 1989a	No	Yes	Yes	Yes	Moderate
Rosa et al. 2016	No	Yes	Yes	Yes	Moderate
Schachter et al. 2020	No	Yes	Yes	No	Low
Shannon et al. 1984a	No	Yes	Yes	Yes	Moderate
Shannon et al. 1984b	No	Yes	Yes	No	Low
Shannon et al. 1991	No	Yes	Yes	Yes	Moderate
Shirakawa et al. 1990	No	Yes	Yes	Yes	Moderate
Outcome: Immunological Effects					
Cohort Inhalation Studies					
Bencko et al. 1983	No	Yes	Yes	Yes	Moderate

Table C-12. Presence of Key Features of Study Design for Nickel—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	
Bencko et al. 1986	No	Yes	Yes	Yes	Moderate
Shirakawa et al. 1990	No	Yes	Yes	Yes	Moderate
Cohort Dermal Studies					
Mozzanica et al. 1990	No	Yes	Yes	Yes	Moderate

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Respiratory Effects					
Inhalation Acute Exposure					
Benson et al. 1995b (Rat)	Yes	Yes	Yes	Yes	High
Efremenko et al. 2014 (Rat)	Yes	Yes	Yes	Yes	High
Inhalation Intermediate Exposure					
Benson et al. 1995a (Rat)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (Rat)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (Mice)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (Mice)	Yes	Yes	Yes	Yes	High
Benson et al. 1995b (Rat)	Yes	Yes	Yes	Yes	High
Bingham et al. 1972 (Rat)	Yes	Yes	Yes	No	Moderate
Bingham et al. 1972 (Rat)	Yes	Yes	Yes	No	Moderate
Efremenko et al. 2014 (Rat)	Yes	Yes	Yes	Yes	High

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Evans et al. 1995 (Rat)	Yes	Yes	Yes	Yes	High
Horie et al. 1985 (Rat)	Yes	No	Yes	No	Low
Johansson and Camner 1986 (Rabbit)	No	No	Yes	No	Very Low
NTP 1996a (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
Oller et al. 2022 (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
Weischer et al. 1980 (Rat)	Yes	Yes	Yes	Yes	High
Inhalation Chronic Exposure					
NTP 1996a (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (Rat)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (Rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1974 (Rat)	Yes	Yes	Yes	Yes	High
Takenaka et al. 1985 (Rat)	Yes	No	Yes	No	Low
Tanaka et al. 1988 (Rat)	Yes	No	Yes	No	Low
Oral Intermediate Exposure					

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features: Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
American Biogenics Corp 1988 (Rat)	Yes	Yes	Yes	Yes	High
Obone et al. 1999 (Rat)	Yes	No	Yes	Yes	Moderate
RTI 1988a, 1988b (Rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2002 (Rat)	Yes	Yes	Yes	Yes	High
Oral Chronic Exposure					
Ambrose et al. 1976 (Rats)	Yes	No	Yes	No	Low
Ambrose et al. 1976 (Dogs)	Yes	No	Yes	No	Low
Outcome: Immunological Effects					
Inhalation Acute Exposure					
Adkins et al. 1979a (Mice)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979b (Mice)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979c (Mice)	Yes	Yes	Yes	Yes	High
Buxton et al. 2021 (Mice)	Yes	Yes	Yes	Yes	High
Graham et al. 1978 (Mice)	Yes	Yes	Yes	Yes	High
Inhalation Intermediate Exposure					
Haley et al. 1990 (Mice)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (Mice)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (Mice)	Yes	Yes	Yes	Yes	High
Johansson et al. 1980 (Rabbit)	Yes	No	Yes	No	Low
Johansson et al. 1987 (Rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1988(Rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1989 (Rabbit)	Yes	No	Yes	Yes	Moderate
Morimoto et al. 1995 (Rat)	Yes	No	Yes	Yes	Moderate
NTP 1996a (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996a (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat) 13 Wk	Yes	Yes	Yes	Yes	High

Table C-13. Presence of Key Features of Study Design for Nickel – Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
NTP 1996b (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 16 D	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat) 13 Wk	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice) 13 Wk	Yes	Yes	Yes	Yes	High
Spiegelberg et al. 1984 (Rat)	Yes	Yes	Yes	Yes	High
Xu et al. 2012 (Mice)	Yes	No	Yes	Yes	Moderate
Inhalation Chronic Exposure					
NTP 1996a (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996b (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (Mice)	Yes	Yes	Yes	Yes	High
NTP 1996c (Rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (Mice)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (Rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1974 (Rat)	Yes	Yes	Yes	Yes	High
Oral Intermediate Exposure					
Dieter et al. 1988 (Mice)	Yes	Yes	Yes	Yes	High
Ilback et al. 1994 (Mice)	Yes	No	Yes	Yes	Moderate
Obone et al. 1999 (Rat)	Yes	No	Yes	Yes	Moderate
Oral Chronic Exposure					
Ambrose et al. 1976 (Rats)	Yes	No	Yes	No	Low
Ambrose et al. 1976 (Dogs)	Yes	No	Yes	No	Low
Dermal Acute Exposure					
Siller and Seymour 1994 (Mice)	Yes	No	Yes	Yes	Moderate

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory Effects		
Inhalation Exposure		
Human Cohort Studies		
Arena et al. 1998	Low	Moderate
Bell et al. 2009	Low	
Bell et al. 2014	Low	
Berge and Skyberg 2003	Low	
Cornell and Landis 1984	Moderate	
Cox et al. 1981	Moderate	
Cragle et al. 1984	Moderate	
Dolovich et al.1984	Moderate	
Egedahl et al. 2001	Moderate	
Enterline and Marsh 1982	Moderate	
Fishwick et al. 2004	Moderate	
Gehring et al. 2015	Low	
Kilburn et al. 1990	Moderate	
Moulin et al. 2000	Moderate	
Muir et al. 1993	Moderate	
Patel et al. 2009	Moderate	
Polednak 1981	Moderate	
Redmond 1984	Moderate	
Roberts et al. 1989a	Moderate	
Rosa et al. 2016	Moderate	
Shachter et al. 2020	Low	
Shannon et al. 1984a	Moderate	
Shannon et al. 1984b	Low	
Shannon et al. 1991	Moderate	
Shirakawa et al. 1990	Moderate	
Animal Inhalation Acute Exposure		
Benson et al. 1995b (Rat)	High	High
Efremenko et al. 2014 (Rat)	High	
Animal Inhalation Intermediate Exposure		
Benson et al. 1995a (Rat)	High	High
Benson et al. 1995a (Rat)	High	
Benson et al. 1995a (Mice)	High	
Benson et al. 1995a (Mice)	High	
Benson et al. 1995b (Rat)	High	
Bingham et al. 1972 (Rat)	Moderate	
Bingham et al. 1972 (Rat)	Moderate	

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Efremenko et al. 2014 (Rat)	High	
Evans et al. 1995 (Rat)	High	
Horie et al. 1985 (Rat)	Low	
Johansson and Camner 1986 (Rabbit)	Very Low	
NTP 1996a (Rat) 16 D	High	
NTP 1996a (Mice) 16 D	High	
NTP 1996a (Rat) 13 Wk	High	
NTP 1996a (Mice) 13 Wk	High	
NTP 1996b (Rat) 16 D	High	
NTP 1996b (Mice) 16 D	High	
NTP 1996b (Rat) 13 Wk	High	
NTP 1996b (Mice) 13 Wk	High	
NTP 1996c (Rat) 16 D	High	
NTP 1996c (Mice) 16 D	High	
NTP 1996c (Rat) 13 Wk	High	
NTP 1996c (Mice) 13 Wk	High	
Oller et al. 2022 (Rat) 13 Wk	High	
Oller et al. 2022 (Rat) 13 Wk	High	
Weischer et al. 1980 (Rat)	High	
Animal Inhalation Chronic Exposure		
NTP 1996a (Rat)	High	High
NTP 1996a (Mice)	High	
NTP 1996b (Rat)	High	
NTP 1996b (Mice)	High	
NTP 1996c (Rat)	High	
NTP 1996c (Mice)	High	
Oller et al. 2008 (Rat)	High	
Ottolenghi et al. 1974 (Rat)	High	
Takenaka et al. 1985 (Rat)	Low	
Tanaka et al. 1988 (Rat)	Low	
Oral Exposure		
Animal Oral Intermediate Exposure		
American Biogenics Corp 1988 (Rat)	High	High
Obone et al. 1999 (Rat)	Moderate	
RTI 1988a, 1988b (Rat)	High	
Springborn Laboratories 2002 (Rat)	High	
Animal Oral Chronic Exposure		
Ambrose et al. 1976 (Rats)	Low	Low
Ambrose et al. 1976 (Dogs)	Low	

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Immunological Effects		
Inhalation Exposure		
Human Cohort Studies		
Bencko et al. 1983	Moderate	Moderate
Bencko et al. 1986	Moderate	
Shirakawa et al. 1990	Moderate	
Animal Inhalation Acute Exposure		
Adkins et al. 1979a (Mice)	High	High
Adkins et al. 1979b (Mice)	High	
Adkins et al. 1979c (Mice)	High	
Buxton et al. 2021 (Mice)	High	
Graham et al. 1978 (Mice)	High	
Animal Inhalation Intermediate Exposure		
Haley et al. 1990 (Mice)	High	High
Haley et al. 1990 (Mice)	High	
Haley et al. 1990 (Mice)	High	
Johansson et al. 1980 (Rabbit)	Low	
Johansson et al. 1987 (Rabbit)	Moderate	
Johansson et al. 1988(Rabbit)	Moderate	
Johansson et al. 1989 (Rabbit)	Moderate	
Morimoto et al. 1995 (Rat)	Moderate	
NTP 1996a (Rat) 16 D	High	
NTP 1996a (Mice) 16 D	High	
NTP 1996a (Rat) 13 Wk	High	
NTP 1996a (Mice) 13 Wk	High	
NTP 1996b (Rat) 16 D	High	
NTP 1996b (Mice) 16 D	High	
NTP 1996b (Rat) 13 Wk	High	
NTP 1996b (Mice) 13 Wk	High	
NTP 1996c (Rat) 16 D	High	
NTP 1996c (Mice) 16 D	High	
NTP 1996c (Rat) 13 Wk	High	
NTP 1996c (Mice) 13 Wk	High	
Spiegelberg et al. 1984 (Rat)	High	
Xu et al. 2012 (Mice)	Moderate	
Animal Inhalation Chronic Exposure		
NTP 1996a (Rat)	High	High
NTP 1996a (Mice)	High	
NTP 1996b (Rat)	High	

Table C-14. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1996b (Mice)	High	
NTP 1996c (Rat)	High	
NTP 1996c (Mice)	High	
Oller et al. 2008 (Rat)	High	
Ottolenghi et al. 1974 (Rat)	High	
Oral Exposure		
Animal Oral Intermediate Exposure		
Dieter et al. 1988 (Mice)	High	Moderate
Ilback et al. 1994 (Mice)	Moderate	
Obone et al. 1999 (Rat)	Moderate	
Animal Oral Chronic Exposure		
Ambrose et al. 1976 (Rats)	Low	Low
Ambrose et al. 1976 (Dogs)	Low	
Dermal Exposure		
Human Cohort Studies		
Mozzanica et al. 1990	Moderate	Moderate
Animal Dermal Acute Exposure		
Siller and Seymour 1994 (Mice)	Moderate	Moderate

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for neurological effects are presented in Table C-13. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with nickel exposure is presented in Table C-14.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-4, Table C-5, and Table C-6). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below

are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:

- No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
- Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
- Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% Cis for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.

- Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response, and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

The results of this assessment are presented in Table C-15, and the final confidence in the body of literature for the neurological endpoint is presented in Table C-16.

Table C-15. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Human studies	Moderate	-1 Risk of bias +1 Direction	Moderate
Animal studies	High	+1 Direction	High
Outcome: Immunological effects			
Human studies	Moderate	-1 Risk of bias	Low
Animal studies	High	None	High

Table C-16. Confidence in the Body of Evidence for Nickel

	Confidence in body of evidence	
Outcome	Human Studies	Animal Studies

Respiratory effects	Moderate	High
Immunological effects	Low	High

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for nickel, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence**: High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence**: Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence**: Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect**: High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence**: Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome or very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for nickel is presented in C-17.

Table C-17. Level of Evidence of Health Effects for Nickel

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human Studies			
Respiratory effects	Moderate	Health Effect	Moderate
Immunological effects	Low	Health Effect	Low
Animal Studies			
Respiratory effects	High	Health Effect	High
Immunological effects	High	Health Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

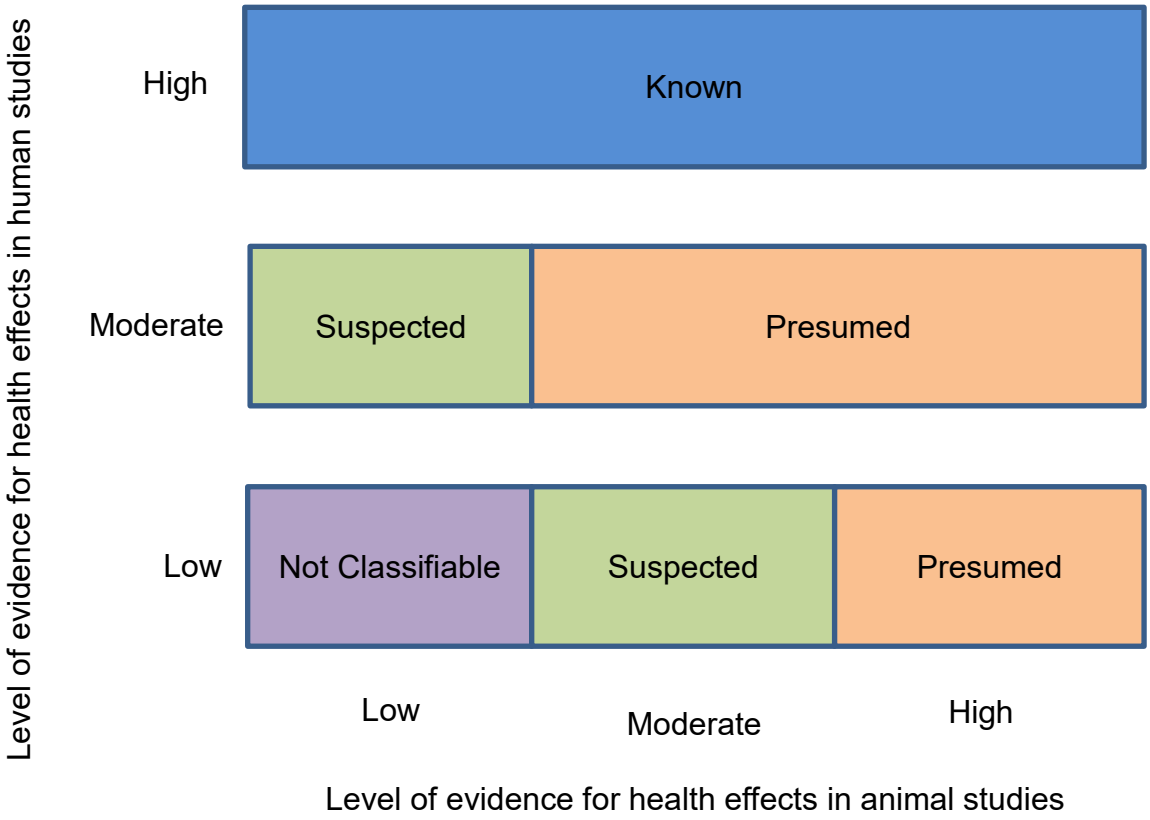
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known**: A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected**: A health effect in this category would have
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable**: A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used.

The hazard identification conclusions for nickel are listed below and summarized in C-18.

Presumed Health Effects

- Respiratory effects following inhalation and oral exposure.
  - Moderate level of evidence from human studies of occupational cohorts exposed via inhalation (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. 1989a; Shannon et al. 1984b; Shannon et al. 1991).

  - Moderate level of evidence from population level studies of exposure to nickel in air (Bell et al. 2009; Bell et al. 2014; Patel et al. 2009; Rosa et al. 2016; Schachter et al. 2020.
  - High level of evidence in rats and mice from acute-duration exposure to nickel (Bai et al. 2013; Benson et al. 1995b; Efremenko et al. 2014; Horie et al. 1985; NTP 1996b, 1996c), intermediate-duration exposure to nickel (Benson et al. 1995a; Bingham et al. 1972; NTP 1996a, 1996b, 1996c; Oller et al. 2022), and chronic-duration exposure to nickel (NTP 1996b, 1996c ; Ottolenghi et al. 1975; Takenaka et al. 1985).
  - High level of evidence in rats following acute-, intermediate-, and chronic-duration oral exposure (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Oller and Erexson 2007; RTI 1988a, 1988b).
- Immunological effects following inhalation, oral, and dermal exposure.
  - Low evidence from human inhalation studies due to the lack of controls and lack of confidence in the exposures (Bencko et al. 1983; Bencko et al. 1986; Shirakawa et al. 1990).
  - Low evidence from a limited number of dermal studies (Kapsenberg et al. 1988; Mozzanica et al. 1990).
  - High level of evidence in rats, mice, and rabbits from inhalation exposure to nickel (Adkins et al. 1979a, 1979b, 1979c; Bingham et al. 1972; Goutet et al. 2000; Haley et al. 1990; Johansson et al. 1980; Johansson et al. 1987; Johansson et al. 1988; Johansson et al. 1989; Morimoto et al. 1995; Oller et al. 2008; Xu et al. 2012).
  - High level of evidence in mice and rats from oral exposure to nickel (Dieter et al. 1988; Ilbäck et al. 1994; Obone et al. 1999), and in dogs (Ambrose et al. 1976).

Table C-18. Hazard Identification Conclusions for Nickel

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Immunological effects	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance

specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this

case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

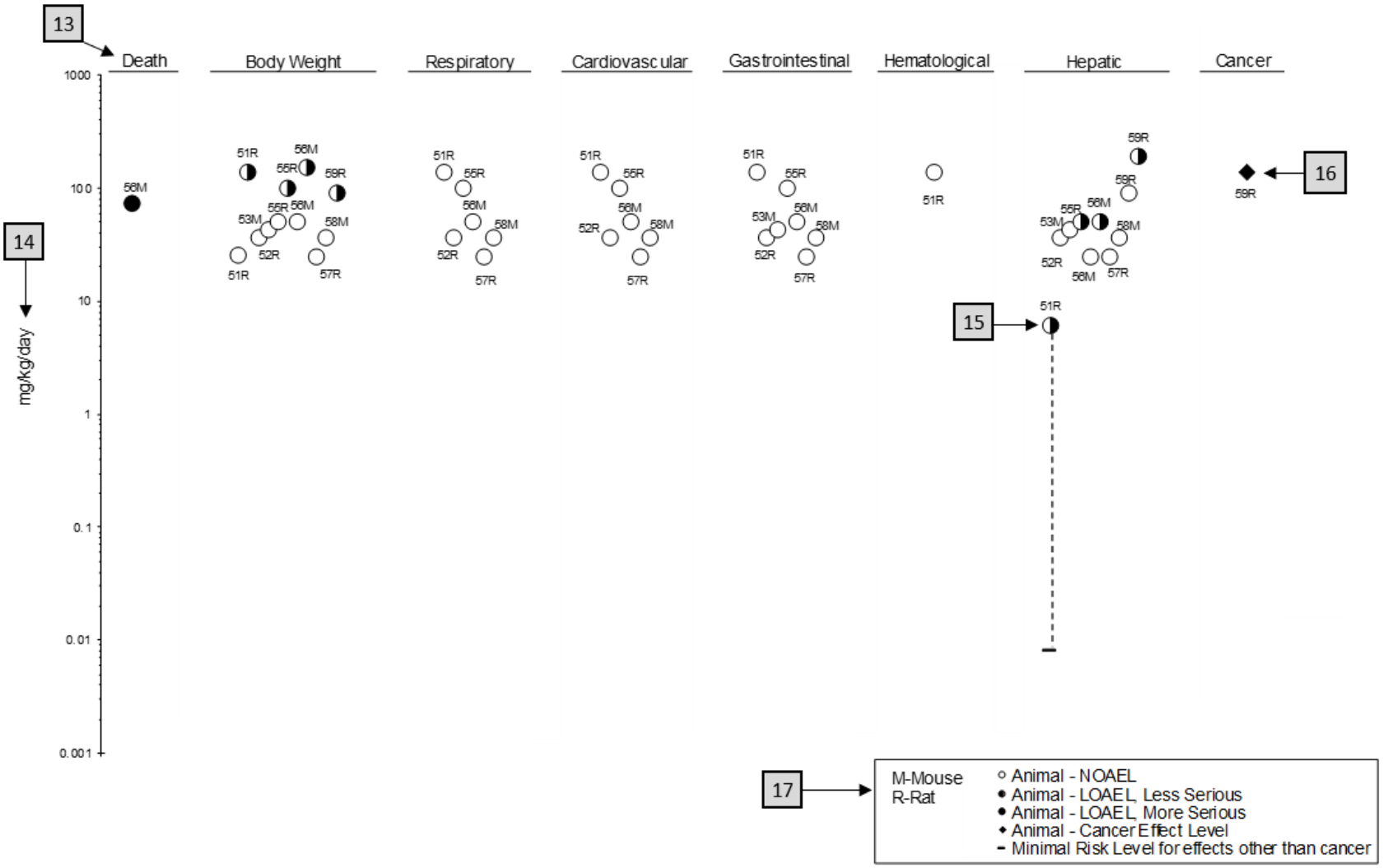
Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

(11)
[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc. gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with

realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_x	dose that produces a X% change in response rate of an adverse effect
$BMDL_x$	95% lower confidence limit on the BMD_x
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration

FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram

NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture

USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q1*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result