APPENDIX A. ATSDR MINIMAL RISK LEVEL 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. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious 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.

APPENDIX A

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 S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: $1x10^{-4}$ mg Ni/m^3
Critical Effect: Bronchiole epithelial degeneration/hyperplasia
Reference: Efremenko et al. 2017a, 2017b
Point of Departure: LOAEL of 0.2244 mg Ni/m^3 ($LOAEL_{HEC}$ of 0.0403 mg Ni/m^3)
Uncertainty Factor: 300
LSE Graph Key: 3
Species: Rat

MRL Summary: An acute-duration inhalation MRL of $1x10^{-4}$ mg Ni/m^3 was derived for nickel based on bronchiole epithelial degeneration/hyperplasia in male rats exposed to 0.2244 mg Ni/m^3 as nickel sulfate hexahydrate 6 hours/day for 5 days (Efremenko et al. 2017a, 2017b). The MRL is based on a LOAEL of 0.2244 mg Ni/m^3 adjusted to continuous duration exposure and converted to a human equivalent concentration (HEC) of 0.0403 mg Ni/m^3 and divided by a total uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: Several case studies in workers who inhaled large amounts of nickel dust or fumes indicate that 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 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).

The acute inhalation toxicity of nickel sulfate, nickel subsulfide, nickel oxide, and nickel chloride has been evaluated in rats and/or mice. The available studies suggest that the respiratory tract and the immune system are the most sensitive targets of nickel toxicity; a summary of the NOAEL and LOAEL values for these endpoints is presented in Table A-1.

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

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Respiratory					
Rat (M)	5 days 6 hours/day		0.2244	Bronchiole epithelial degeneration/ hyperplasia	Efremenko et al. 2017a, 2017b (nickel sulfate hexahydrate)
Rat (M)	5 days 6 hours/day		0.44	Peribronchiolar/ perivascular inflammation and >250% increase of LDH in BALF	Efremenko et al. 2014 (nickel subsulfide)

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

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Rat (B)	12 days in 16-day period 6 hours/day		0.44	Chronic lung inflammation; olfactory epithelium atrophy	NTP 1996b (nickel subsulfide)
Rat (B)	7 days 6 hours/day		0.44	Alveolitis	Benson et al. 1995b (nickel subsulfide)
Rat (B)	12 days in 16-day period 6 hours/day		0.7 (SLOAEL)	Labored breathing, 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; olfactory epithelium atrophy	NTP 1996c (nickel sulfate hexahydrate)
Mouse (B)	12 days in 16-day period 6 hours/day	0.44	0.88	Atrophy of olfactory epithelium	NTP 1996b (nickel subsulfide)
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	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 (F)	2 hours	0.37	0.5	Increased susceptibility to Streptococcal infection	Adkins et al. 1979 (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)

[a]All concentrations are reported in mg Ni/m^3; concentrations reported in terms of the nickel compound were converted by multiplying the concentration by a ratio of the nickel compound molecular weight to nickel molecular weight.

B = both males and females; BALF = bronchoalveolar lavage fluid; F = females; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

The respiratory tract effects observed in rats and/or mice include inflammation (peribronchiolar/perivascular inflammation, chronic lung inflammation, and alveolitis), bronchiole epithelial degeneration/hyperplasia, alveolar macrophage hyperplasia, labored breathing, and atrophy of the olfactory epithelium. Rats appear to be more sensitive than mice. In the available acute-duration database, the lower respiratory and nasal effects occur at similar concentrations. For a given effect, comparisons across studies reporting respiratory effects suggest differences in the toxicity of nickel compounds, which are likely due to differences in solubility and bioavailability. For example, the lowest LOAELs for lung inflammation in rats for the three nickel compounds tested by NTP were 0.44 mg Ni/m^3 for nickel subsulfide (NTP 1996b), 0.7 mg Ni/m^3 for nickel sulfate (NTP 1996c), and 7.9 mg Ni/m^3 for nickel oxide (NTP 1996a). The 0.7 mg Ni/m^3 concentration was considered a serious LOAEL for nickel sulfate because labored breathing was also observed at this concentration; labored breathing was not observed in the rats exposed to nickel subsulfide until concentrations of 3.65 mg Ni/m^3. It is noted that a decrease in body weight of >20% was also observed in rats exposed to 0.7 mg Ni/m^3 as nickel sulfate (NTP 1996c). Efremenko et al. (2017a, 2017b) did not report labored breathing in rats exposed to a lower nickel sulfate concentration (0.2244 mg Ni/m^3). The lowest LOAEL for respiratory effects is 0.2244 mg Ni/m^3 for bronchiole epithelial degeneration/hyperplasia identified in rats exposed to nickel sulfate hexahydrate 6 hours/day for 5 days (Efremenko et al. 2017a, 2017b).

Immunological effects observed in mice exposed to inhaled nickel include impaired immune function and lymphoid hyperplasia in bronchial lymph nodes. Immunological effects were observed at concentrations of ≥0.25 mg Ni/m^3 as nickel chloride (Adkins et al. 1979; Graham et al. 1978).

The lowest LOAEL for immunological effects (0.25 mg Ni/m^3) is similar to the LOAEL of 0.2244 mg Ni/m^3 for respiratory effects; the lower respiratory tract was selected as the critical target because it has the lowest LOAEL and is well supported by other acute-duration inhalation studies with nickel sulfate and other nickel compounds.

Selection of the Principal Study: The Efremenko et al. (2017a, 2017b) study of nickel sulfate was selected as the principal study because it identified the lowest LOAEL of 0.2244 mg Ni/m^3 for bronchiole epithelial degeneration/hyperplasia.

Summary of the Principal Study:

Efremenko AY, Campbell JL, Dodd DE, et al. 2017a. Time- and concentration-dependent genomic responses of the rat airway to inhaled nickel sulfate. Environ Mol Mutagen 58(8):607-618. https://doi.org/10.1002/em.22139. https://www.ncbi.nlm.nih.gov/pubmed/28862355.

Efremenko AY, Campbell JL, Dodd DE, et al. 2017b. Supplemental material: Time- and concentration-dependent genomic responses of the rat airway to inhaled nickel sulfate. Environ Mol Mutagen 58(8):607-618. https://doi.org/10.1002/em.22139. https://www.ncbi.nlm.nih.gov/pubmed/28862355.

Groups of five male Fischer 344 rats were whole-body exposed to analytical concentrations of 0.002 (control group), 0.128, 0.246, 0.496, or 1.020 mg/m^3 nickel sulfate hexahydrate 6 hours/day for 5 days (0.0004, 0.0282, 0.0541, 0.109, and 0.2244 mg Ni/m^3) (Efremenko et al. 2017a, 2017b). The particle size distributions (average mass median aerodynamic diameter, MMAD) and geometric standard deviations were 0.82 µm (1.41), 0.88 µm (1.36), 1.00 µm (1.40), and 1.09 µm (1.42) for the 0.0282, 0.0541, 0.109, and 0.2244 mg Ni/m^3 groups, respectively. Animals were observed for overt clinical signs daily and body weight was measured at termination. At termination, groups of five animals in the control and 0.2244 mg Ni/m^3 groups underwent BALF cytology and histopathology analysis (animals were sacrificed within 24 hours of exposure termination); groups of five animals in all concentration groups underwent BALF analysis. Additional groups of eight rats underwent gene expression analysis.

Significant increases in total protein and lactate dehydrogenase were observed in the BALF at 0.109 and 0.2244 mg Ni/m^3; alkaline phosphatase levels were increased at all nickel concentrations. The toxicological significance of these findings is not known. Increases in lymphocytes and neutrophils were also increased in the BALF at 0.2244 mg Ni/m^3. Lung histopathology was only evaluated in the 0 and 0.2244 mg Ni/m^3 groups. An increase in bronchiole epithelial degeneration/hyperplasia was observed; the lesion was observed in five of five rats, as compared to zero of five controls, and the severity was graded as mild.

Selection of the Point of Departure for the MRL: The LOAEL of 0.2244 mg Ni/m^3 as nickel sulfate for bronchiole epithelial degeneration/hyperplasia in rats (Efremenko et al. 2017a, 2017b) was selected as the basis of the acute-duration inhalation MRL for nickel.

Benchmark dose (BMD) modeling was not conducted because histopathological examinations were only conducted in controls and rats exposed to 0.2244 mg Ni/m^3.

Adjustment for Intermittent Exposure: The LOAEL of 0.2244 mg Ni/m^3 was adjusted to continuous exposure using the following equation:

$$BMCL_{ADJ} = 0.2244\ mg\ Ni/m^3 \times \frac{6\ hours}{24\ hours} = 0.0561\ mg\ Ni/m^3$$

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

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

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 for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the thoracic region (combined tracheobronchial and pulmonary regions) is used to extrapolate deposited doses in rats to deposited doses in humans. The thoracic region was used since lesions were observed in bronchiolar and pulmonary tissues. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD, version 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-2. For breathing frequency and tidal volume parameter values in humans, a time-weighted average (TWA) of default values in males (ICRP 1994) was calculated based on the following activity pattern over a 24-hour exposure period: 8 hours sleeping (nasal breathing) + 8 hours at rest/sitting (nasal breathing) + 8 hours of light activity (oronasal-mouth breather). Default values in males were selected to be health protective, as males are predicted to have higher deposition fractions than females.

Table A-2. MPPD Model (Version 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	4 mL (default)	3,300 mL (default)
Upper respiratory tract	0.42 mL (default)	50 mL (default)
Inhalant properties		
Density[a]	2.07 g/cm^3	2.07 g/cm^3
Diameter, MMAD[b]	1.09 µm	1.09 µm
GSD[b]	1.47	1.47
Inhalability adjustment	On	On
Exposure condition		
Aerosol concentration ($LOAEL_{ADJ}$)	0.0561 mg Ni/m^3	0.0561 mg Ni/m^3
Breathing frequency	102 breaths/minute (default)	14.7 breaths/minute (calculated TWA)[c]
Tidal volume	2.1 mL (default)	875 mL (calculated TWA)[d]
Breathing scenario	Whole body	Nasal/oronasal breather[e]
Results		
Thoracic region deposition fraction (total tracheobronchial and pulmonary deposition fraction)	0.0846	0.1758

[a]Haynes et al. 2015, nickel sulfate.
[b]Efremenko et al. 2017a, 2017b.
[c]Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).
[d]Tidal volume is 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).
[e]Breathing scenario is 8 hours of sleep (nasal breathing, on back), 8 hours at rest (nasal breathing, upright), and 8 hours light activity (oronasal-mouth breathing, upright).

GSD = geometric standard deviation; $LOAEL_{ADJ}$ = lowest-observed-adverse-effect level adjusted for continuous exposure; MMAD = mass median aerodynamic diameter; MPPD = Multiple-Path Particle Dosimetry; TWA = time-weighted average

The deposition fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $LOAEL_{HEC}$. Table A-3 lists the values used within the equation and the source of these values. The exposure days (n) are 5 days to represent 24 hours of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure.

$$BMCL_{HEC} = 0.0561\ mg\ Ni/m^3 \times \frac{0.20\frac{m^3}{day}}{20\frac{m^3}{day}} \times \frac{0.0846}{0.1758} \times \frac{\frac{1-(1-0.289\ day^{-1})^5}{1-(1-0.289\ day^{-1})}}{\frac{1-(1-0.277\ day^{-1})^5}{1-(1-0.277\ day^{-1})}} \times \frac{1}{1.04} \times \frac{54\ m^2}{0.34\ m^2}$$

$$LOAEL_{HEC} = 0.0403\ mg\ Ni/m^3$$

Table A-3. Values Used to Calculate a Human Equivalent Concentration (HEC)

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.20 m^3/day	20 m^3/day	EPA 1994
Deposition fraction (DF)	0.0846	0.1758	Calculated using MPPD software
Clearance rate[a] (k)	0.289 day^{-1}	0.277 day^{-1}	Oller et al. 2014
Retention half-time	2.4 days	2.5 days	Oller et al. 2014
Ratio of retention half-time (RH) (to rat half-time)	1	1.04	Calculated
Thoracic surface area (SA)	0.342 m^2	54.32 m^2	EPA 1994
Exposure days (n)	5 days	5 days	Efremenko et al. 2017a, 2017b

[a]Total clearance rate = ln2/retention half-time.

HEC = human equivalent concentration; MPPD = Multiple Path Particle Dosimetry

Uncertainty Factor: The $LOAEL_{HEC}$ is divided by a total uncertainty factor of 300:

- 10 for the use of a LOAEL,
- 3 for extrapolation from rats to humans with dosimetric adjustments,
- 10 for human variability

$$Provisional\ MRL = \frac{LOAEL_{HEC}}{UFs} = \frac{0.0403\ mg\ Ni/m^3}{300}$$

$$= 1.34x10^{-4}\ mg\ Ni/m^3;\ rounded\ to\ 1x10^{-4}\ mg\ Ni/m^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a well-established target of toxicity following inhalation exposure to soluble and insoluble nickel compounds. Studies of workers exposed to nickel have reported increased respiratory symptoms, impaired lung function, and lung disease (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022). Pulmonary effects have been reported in several acute-duration studies in animals exposed to nickel sulfate, nickel subsulfide, or nickel oxide (Benson et al. 1995b; Efremenko et al. 2014, 2017a, 2017b; NTP 1996a, 1996b, 1996c).

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: $3x10^{-6}$ mg Ni/m^3
Critical Effect: Alveolitis and perivascular/peribronchiolar inflammation
Reference: Oller et al. 2023
Point of Departure: BMDL of 0.0014 mg Ni/m^3 ($BMDL_{HEC}$ of 0.0000982 mg Ni/m^3)
Uncertainty Factor: 30
LSE Graph Key: 28
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of $3x10^{-6}$ mg Ni/m^3 was derived for nickel based on alveolitis and perivascular/peribronchiolar inflammation observed in the lungs of rats exposed to ≥0.04 mg Ni/m^3 as nickel subsulfide for 6 hours/day, 5 days/week for 90 days (Oller et al. 2023). The MRL is based on a benchmark dose lower confidence limit (BMCL) of 0.0014 mg Ni/m^3 adjusted to continuous duration exposure and converted to a human equivalent concentration (HEC) of 0.0000982 mg Ni/m^3 ($9.82x10^{-5}$ mg Ni/m^3) and divided by a total uncertainty factor of 30 (3 for extrapolation from rats to humans with dosimetric adjustments 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. The available data suggest that the lower respiratory tract is the most sensitive target of toxicity following intermediate-duration inhalation exposure, with effects occurring at nickel concentrations of ≥0.04 mg Ni/m^3. A summary of the NOAEL and LOAEL values for respiratory effects is presented in Table A-4. The respiratory effects include inflammatory changes in the lungs, alveolar macrophage hyperplasia, and atrophy of the nasal olfactory epithelium. Immune effects also occur at relatively low nickel concentrations (see Table A-2); the effects include lymphoid hyperplasia in the bronchial and mediastinal lymph nodes and altered impaired immune function. Other observed effects included developmental effects (decreased fetal body weight) (Weischer et al. 1980) at 1.6 mg Ni/m^3 as nickel oxide and changes in hematological parameters (NTP 1996b; Weischer et al. 1980), which have been reported at nickel concentrations associated with lung inflammation.

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Respiratory					
Rat (M)	13 weeks 5 days/week 6 hours/day		0.04	Alveolitis and perivascular/ peribronchiolar inflammation and protein accumulation	Oller et al. 2023 (nickel subsulfide)

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Rat (M)	4 weeks 5 days/week 6 hours/day	0.06	0.11	Lung inflammation	Efremenko et al. 2014 (nickel subsulfide)
Rat (M)	4 weeks 5 days/week 6 hours/day	0.05412	0.1104	Alveolus inflammation	Efremenko et al. 2017a, 2017b (nickel sulfate)
Rat (M)	2–6 months 5 days/week 6 hours/day	0.03	0.11	Alveolitis	Benson et al. 1995a (nickel sulfate)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.06	0.11	Chronic active lung inflammation and interstitial infiltrates	NTP 1996c (nickel sulfate)
Rat (M)	13 weeks 5 days/week 6 hours/day	0.03	0.11	Alveolitis and perivascular/ peribronchiolar inflammation	Oller et al. 2023 (nickel sulfate)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.11	0.22	Chronic active lung inflammation	NTP 1996b (nickel subsulfide)
Rat (M)	3 weeks 5 days/week 6 hours/day	0.11	0.22	Alveolitis, perivascular inflammation, bronchiolar epithelial degeneration	Oller et al. 2023 (nickel sulfate)
Mouse (M)	2–6 months 5 days/week 6 hours/day	0.06	0.22	Interstitial pneumonia	Benson et al. 1995a (nickel sulfate)
Rat (B)	13weeks 5 days/week 6 hours/day	0.11	0.22	Olfactory epithelial atrophy	NTP 1996c (nickel sulfate)
Rat (B)	22 days 6 hours/day		0.44	Alveolitis, alveolar proteinosis; olfactory epithelium degeneration	Benson et al. 1995b (nickel subsulfide)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Olfactory epithelial atrophy	NTP 1996b (nickel subsulfide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Olfactory epithelial atrophy	NTP 1996a (nickel subsulfide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Chronic lung inflammation, fibrosis, and interstitial infiltrates	NTP 1996a (nickel sulfate)
Rat (M)	4 weeks 5 days/week 6 hours/day		0.5	Bronchial gland hyperplasia and squamous metaplasia	Horie et al. 1985 (nickel oxide)

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Rabbit (M)	4 months 5 days/week 6 hours/day		0.6	Interstitial inflammation and intraalveolar accumulation of macrophages	Johansson et al. 1988a, 1989 (nickel chloride)
Rat (M)	16 days 6 hours/day		0.64	Olfactory epithelial atrophy	Evans et al. 1995 (nickel sulfate)
Mouse (M)	2–6 months 5 days/week 6 hours/day		0.98	Interstitial pneumonia	Benson et al. 1995a (nickel oxide)
Rat (M)	2–6 months 5 days/week 6 hours/day	0.49	1.96	Moderate alveolitis	Benson et al. 1995a (nickel oxide)
Rat (B)	13 weeks 5 days/week 6 hours/day	2	3.9	Chronic active lung inflammation, granulomatous inflammation, and lung interstitial infiltrate	NTP 1996a (nickel oxide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	2 F 3.9 M	3.9 F 7.6 M	Perivascular lymphocytic infiltrates	NTP 1996a (nickel oxide)
Immunological					
Rat (M)	4 months continuous	0.025	0.145	Impaired response to sRBC exposure	Spiegelberg et al. 1984 (nickel oxide)
Rat (M)	4 weeks continuous	0.093	0.216	Impaired response to sRBC exposure	Spiegelberg et al. 1984 (nickel oxide)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.11	0.22	Lymphoid hyperplasia in bronchial and mediastinal lymph nodes	NTP 1996c (nickel sulfate)
Rat (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Lymphoid hyperplasia in bronchial and mediastinal lymph nodes	NTP 1996b (nickel subsulfide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.22	0.44	Bronchial lymph node hyperplasia	NTP 1996a (nickel sulfate)
Mouse (F)	65 days 5 days/week 6 hours/day		0.45	Decreased resistance to tumor challenge	Haley et al. 1990 (nickel sulfate)
Mouse (F)	65 days 5 days/week 6 hours/day		0.45	Decreased alveolar macrophage activity	Haley et al. 1990 (nickel subsulfide)
Mouse (F)	65 days 5 days/week 6 hours/day		0.47	Decreased alveolar macrophage activity	Haley et al. 1990 (nickel oxide)

Table A-4. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Mouse (B)	13 weeks 5 days/week 6 hours/day	0.44 F 0.88 M	0.88 F 1.83 M	Bronchial lymph node hyperplasia	NTP 1996a (nickel subsulfide)
Rat (B)	13 weeks 5 days/week 6 hours/day	2	3.9	Lymphoid hyperplasia in mediastinal lymph nodes	NTP 1996a (nickel oxide)
Mouse (B)	13 weeks 5 days/week 6 hours/day	3.9	7.9	Bronchial lymph node hyperplasia	NTP 1996a (nickel oxide)
Rat (M)	4 weeks 5 days/week 8 hours/day		9.2	Increased production of tumor necrosis factor by alveolar macrophages	Morimoto et al. 1995 (nickel oxide)

[a]All concentrations are reported in mg Ni/m^3; concentrations reported in terms of the nickel compound were converted by multiplying the concentration by a ratio of the nickel compound molecular weight to nickel molecular weight.

B = both males and females; F = females; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; sRBC = sheep red blood cell

Studies conducted by NTP (1996a, 1996b, 1996c), Oller et al. (2023), and Benson et al. (1995a, 1995b) allow for comparisons across nickel compounds and animal species. Of the three nickel compounds tested in these studies, nickel oxide was the least toxic (Benson et al. 1995a, 1995b; NTP 1996a, 1996b, 1996c). Although the results of the NTP (1996b, 1996c) and Benson et al. (1995a, 1995b) studies suggest that lung toxicity of nickel sulfate is greater than nickel subsulfide, the Oller et al. (2023) study identified a lower LOAEL for lung effects associated with nickel subsulfide than with nickel sulfate. The NTP (1996a, 1996b, 1996c) and Benson et al. (1995a, 1995b) studies also provide suggestive evidence that rats are more sensitive than mice.

Selection of the Principal Study: The Oller et al. (2023) study of nickel subsulfide was selected as the principal study because it identified the lowest LOAEL of 0.04 mg Ni/m^3 for lung effects (alveolitis, perivascular/peribronchiolar inflammation, and protein accumulation).

Summary of the Principal Study:

Oller AR, Buxton S, March TH, et al. 2023. Comparative pulmonary and genotoxic responses to inhaled nickel subsulfide and nickel sulfate in F344 rats. J Appl Toxicol 43(5):734-751. https://doi.org/10.1002/jat.4422.

Groups of 13 male F344 rats were whole-body exposed to 0, 0.05, 0.15, or 0.6 mg/m^3 nickel subsulfide (0, 0.04, 0.11, or 0.44 mg Ni/m^3) 6 hours/day, 5 days/week for 13 weeks. Additional groups of animals (13/group) were exposed to 0 or 0.22 mg Ni/m^3 for 13 weeks followed by a 13-week observation period. Actual concentrations were 0.02, 0.06, 0.15, and 0.59 mg/m^3 nickel subsulfide (0.01, 0.04, 0.11, and 0.44 mg Ni/m^3); the particle sizes (MMAD) were 1.90 µm (geometric standard deviation [GSD] of 2.28) and 1.89 µm (2.38) for the 0.11 and 0.44 Ni/m^3 concentrations, respectively; particle size was not

determined at the control or 0.04 mg Ni/m^3 concentrations. The following parameters were used to assess toxicity: clinical signs, body weight, histopathology of the lung and lung weights (n=8/group), and evaluation of bronchoalveolar lavage fluid (BALF) (n=5/group).

No clinical signs of toxicity or alterations in terminal body weights were observed. Concentration-related increased absolute lung weights were observed at ≥0.04 mg Ni/m^3 (24, 48, and 86% at 0.04, 0.11, and 0.44 mg Ni/m^3, respectively). Histological alterations in the lungs consisted of alveolitis, protein accumulation, and perivascular/peribronchiolar inflammation at ≥0.04 mg Ni/m^3. The incidences of these lesions are presented in Table A-5. Type II cell hyperplasia was also observed at 0.44 mg Ni/m^3. Alveolar septal infiltrates, histiocytosis, and type II epithelial cell hyperplasia were observed in the 0.44 mg Ni/m^3 recovery group. BALF alterations consisted of increased LDH at 0.11 mg Ni/m^3 and increased total protein, beta-glucuronidase, RBC phagocytosis, and total nucleated cell levels at 0.22 mg Ni/m^3. No BALF alterations were observed in the recovery group.

Table A-5. Incidence of Select Lung Lesions in Rats Exposed to Nickel Subsulfide for 13 Weeks via Inhalation

Concentration (mg Ni/m^3)	Alveolitis	Perivascular/peribronchiolar inflammation	Protein accumulation
0.01 (control group)	1/8 (0.1)[a]	2/8 (0.3)[a]	0/8
0.04	7/8[b] (1.1)	7/8[b] (0.9)	8/8[b] (2.0)
0.11	7/8[b] (1.6)	8/8[b] (1.8)	8/8[b] (3.1)
0.44	8/8[b] (2.1)	8/8[b] (2.3)	8/8[b] (3.5)

[a]Average severity of lesion: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.
[b]Statistically different from control group, p<0.05 (Fischer Exact test conducted by ATSDR).

Source: Oller et al. 2023

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ of 0.0014 mg Ni/m^3 for perivascular/peribronchiolar inflammation in rats (Oller et al. 2023) was selected as the basis of the intermediate-duration inhalation MRL for nickel.

Incidence data for alveolitis and perivascular/peribronchiolar inflammation (Table A-5) were fit to all dichotomous models in EPA's Benchmark Dose Software (BMDS) (version 3.3.2) using a benchmark response (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. The incidence data for protein accumulation was not modeled due to the 100% incidence at all non-control nickel concentrations.

Although several models of the alveolitis incidence data met three of the model fit criteria, the models failed the visual inspection of the dose-response curve. Most of the models of the perivascular/peribronchiolar inflammation incidence data provided adequate fit; the results are presented in Table A-6. The Multistage Degree 1 and Quantal Linear identified the lowest Akaike Information Criterion (AIC) and were selected; both models estimated a benchmark concentration (BMC) of 0.0024 mg Ni/m^3 and a BMCL of 0.0014 mg Ni/m^3. The model fit for the Multistage 1 Degree model is presented in Figure A-1.

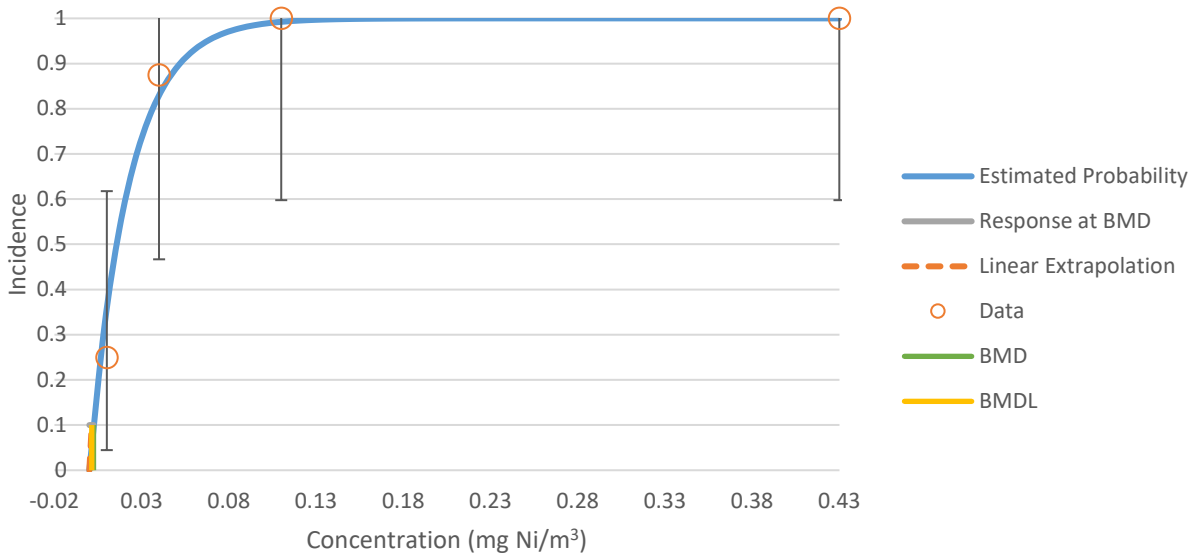
Table A-6. Results of BMD Analysis of Perivascular/Peribronchiolar Inflammation Incidence Data in Male F344 rats Exposed to Nickel Subsulfide via Inhalation 6 Hours/Day, 5 Days/Week for 13 Weeks (Oller et al. 2023)

					Scaled residuals[c]	
Model	BMC_{10}[a]	$BMCL_{10}$[a]	p-Value[b]	AIC	Dose group near BMC	Control dose group
Dichotomous Hill	0.0230	0.0020	0.9734	21.03	-7.1×10^{-5}	-7.1×10^{-5}
Gamma[d]	0.0162	0.0015	0.9966	21.03	6.19×10^{-6}	6.19×10^{-6}
Log-Logistic[e]	0.0230	0.0020	0.9734	21.03	-7.1×10^{-5}	-7.1×10^{-5}
Multistage Degree 3[f]			NA	23.03	-6.1×10^{-9}	-6.1×10^{-9}
Multistage Degree 2[f]	0.0094	0.0015	1.0000	19.03	5.11×10^{-6}	5.11×10^{-6}
Multistage Degree 1[f,g]	**0.0024**	**0.0014**	**0.9006**	**17.70**	**-0.63669**	**-0.63669**
Weibull[d]	0.0067	0.0015	0.9890	21.03	9.36×10^{-5}	9.36×10^{-5}
Logistic	0.0070	0.0035	0.9995	19.03	0.001763	0.001763
Log-Probit	0.0259	0.0018	1.0000	21.03	6.04×10^{-9}	-2.9×10^{-8}
Probit	0.0062	0.0037	0.7546	19.64	-0.50568	-0.50568
Quantal Linear[g]	**0.0024**	**0.0014**	**0.9006**	**17.70**	**-0.63669**	**-0.63669**

[a]BMC and BMCLs not providing adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Of the models providing adequate fit, the BMDLs were sufficiently close (differed by <3-fold); therefore, the models with the lowest AIC were selected (Multistage Degree 1 and Quantal Linear models).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); NA = not applicable

Figure A-1. Predicted (Frequentist Multistage 1 Degree Model) and Observed Incidence of Perivascular/Peribronchiolar Inflammation in Male Rats Exposed to Nickel Subsulfide



Two potential PODs were considered for MRL derivation: $BMCL_{10}$ of 0.0014 mg Ni/m^3 for perivascular/peribronchiolar inflammation and a LOAEL of 0.04 mg Ni/m^3 for alveolitis and protein accumulation in the lung. The $BMCL_{10}$ of 0.0014 mg Ni/m^3 was selected as the POD for the MRL because it results in the most-health protective MRL.

Adjustment for Intermittent Exposure: The $BMCL_{10}$ of 0.0014 mg Ni/m^3 was adjusted from intermittent exposure to continuous exposure using the following equation:

$$BMCL_{ADJ} = 0.0014\ mg\ Ni/m^3 \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.0025\ mg\ Ni/m^3$$

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

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

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 for rats and humans must be calculated. The RDDR for the thoracic region (combined tracheobronchial and pulmonary regions) is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using ARA MPDD Model (version 3.04) 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-7. For breathing frequency and tidal volume parameter values in humans, a TWA of default values in males

(ICRP 1994) was calculated based on the following activity pattern over a 24-hour exposure period: 8 hours sleeping (nasal breathing) + 8 hours at rest/sitting (nasal breathing) + 8 hours of light activity (oronasal-mouth breather). Default values in males were selected to be health protective, as males are predicted to have higher deposition fractions than females.

Table A-7. MPPD Model (Version 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	4 mL (default)	3,300 mL (default)
Upper respiratory tract	0.42 mL (default)	50 mL (default)
Inhalant properties		
Density[a]	5.87 g/cm^3	5.87 g/cm^3
Diameter, MMAD[b]	1.90 µm	1.90 µm
GSD[b]	2.28	2.28
Inhalability adjustment	On	On
Exposure condition		
Aerosol concentration ($BMCL_{ADJ}$)	0.0025 mg Ni/m^3	0.0025 mg Ni/m^3
Breathing frequency	102 breaths/minute (default)	14.7 breaths/minute (calculated TWA)[c]
Tidal volume	2.1 mL (default)	875 mL (calculated TWA)[d]
Breathing scenario	Whole body	Nasal/oronasal breather[e]
Results		
Thoracic region deposition fraction (total tracheobronchial and pulmonary deposition fraction)	0.0610	0.2273

[a]Haynes et al. (2015), nickel subsulfide.
[b]Oller et al. (2023).
[c]Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).
[d]Tidal volume is 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).
[e]Breathing scenario is 8 hours of sleep (nasal breathing, on back), 8 hours at rest (nasal breathing, upright), and 8 hours light activity (oronasal-mouth breathing, upright).

$BMCL_{ADJ}$ = lower 95% confidence interval of the benchmark concentration adjusted for continuous exposure; GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter; MPPD = Multiple-Path Particle Dosimetry; TWA = time-weighted average

The deposition fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the $BMCL_{HEC}$. Table A-8 lists the values used within the equation and the source of these values. The exposure days (n) are 91 days to represent 24 hours of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure. Clearance data are not available for nickel subsulfide but are available for nickel oxide and nickel sulfate (Oller et al. 2014). Although nickel subsulfide and nickel oxide are both less soluble compounds, pulmonary clearance data for these three nickel compounds suggest that nickel subsulfide toxicokinetic properties may be more similar to nickel sulfate than nickel oxide. As reviewed by NTP (1996b), pulmonary clearance half-times in rats following intratracheal administration were 5 days for nickel subsulfide,

120 days for nickel oxide, and 1–3 days for nickel sulfate. Nickel subsulfide and nickel sulfate were distributed to extrarespiratory tissues, whereas nickel oxide was not distributed to extrarespiratory tissues. Using the clearance rates for nickel sulfate over those for nickel oxide is supported by the lung burden data from the NTP studies. The lung burdens in male rats exposed to approximately 0.4 mg Ni/m^3 for 13 weeks (6 hours/day, 5 days/week) were 7 µg Ni/g lung for nickel subsulfide (NTP 1996b), 3.348 µg Ni/g lung for nickel sulfate (NTP 1996c), and 80 µg Ni/g lung for nickel oxide (NTP 1996a). ICRP (1994) assigned nickel sulfate and nickel subsulfide to the same dissolution/absorption class F (fast, absorption half-time <10 days) based on a review of literature on retention kinetics of inhaled nickel sulfate and nickel subsulfide in cynomolgus monkeys and rats.

$$BMCL_{HEC} = 0.0025\ mg/m^3 \times \frac{0.20\frac{m^3}{day}}{20\frac{m^3}{day}} \times \frac{0.0610}{0.2273} \times \frac{\frac{1-(1-0.289\ day^{-1})^{91}}{1-(1-0.289\ day^{-1})}}{\frac{1-(1-0.277\ day^{-1})^{91}}{1-(1-0.277\ day^{-1})}} \times \frac{1}{1.04} \times \frac{54\ m^2}{0.34\ m^2}$$

$$BMCL_{HEC} = 0.0000982\ mg/m^3$$

Table A-8. Values Used to Calculate a Human Equivalent Concentration (HEC) for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.20 m^3/day	20 m^3/day	EPA 1994
Deposition fraction (DF)	0.0456	0.1647	Calculated using MPPD software
Clearance rate[a] (k)	0.289 day^{-1}	0.277 day^{-1}	Oller et al. 2014
Ratio of retention half-time (RH) (to rat half-time)	1	1.04	Calculated
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA 1994
Exposure days (n)	91 days	91 days	Oller et al. 2023

[a]Total clearance rate = ln2/retention half-time.

HEC = human equivalent concentration; MPPD = Multiple Path Particle Dosimetry

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

- 3 for extrapolation from rats to humans with dosimetric adjustments
- 10 for human variability

$$MRL = \frac{BMCL_{HEC}}{UFs} = \frac{0.0000982\ mg\ Ni/m^3}{30}$$

$$= 3.3x10^{-6}\ mg\ Ni/m^3, \text{ rounded to } 3x10^{-6}\ mg\ Ni/m^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a well-established target of toxicity following inhalation exposure to soluble and insoluble nickel compounds. Studies of workers exposed to nickel have reported increased respiratory symptoms, impaired lung function, and lung disease (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022). Lung inflammation has been reported in a number of intermediate-duration studies in animals exposed to nickel subsulfide, nickel sulfate, nickel chloride, or nickel oxide (Benson et al. 1995a, 1995b; Efremenko et al. 2014, 2017a, 2017b; Johansson et al. 1988a;

NTP 1996a, 1996b, 1996c; Oller et al. 2023). Olfactory epithelial atrophy has also been observed in rats and mice exposed to nickel sulfate or nickel subsulfide (NTP 1996b, 1996c).

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: A chronic-duration inhalation MRL was not derived for nickel. Although several chronic-duration inhalation studies are available, an MRL based on the study with the lowest LOAEL resulted in an MRL that was higher than the intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: Numerous studies in workers have examined respiratory tract toxicity following chronic-duration exposure to nickel. Several studies of workers such as welders and nickel refinery workers have reported respiratory effects, which include reduced vital capacity, respiratory symptoms, chronic bronchitis, pulmonary fibrosis, and asthma (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022).

Several animal studies (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1975; Takenaka et al. 1985; Tanaka et al. 1988) assessed the toxicity of nickel sulfate, nickel chloride, nickel subsulfide, nickel oxide, and metallic nickel. The respiratory system is a sensitive target of chronic-duration exposure with LOAELs ranging from 0.06 to 1.0 mg Ni/m^3. Respiratory effects observed include inflammatory changes in the lungs (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1975; Tanaka et al. 1988), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), congestion, and increased lung weight (Takenaka et al. 1985). A summary of the NOAEL and LOAEL values for respiratory effects is presented in Table A-9. Rats exposed to ≥0.06–0.2 mg Ni/m^3 as nickel oxide had decreased survival time compared to controls (Takenaka et al. 1985). Other noncancerous health effects due to nickel exposure include evidence of changes in hematological parameters (increased hemoglobin, hematocrit, and erythrocytes) at ≥0.1 mg Ni/m^3 (NTP 1996b; Oller et al. 2008), lymphoid hyperplasia in bronchial lymph nodes at ≥0.1 mg Ni/m^3 (NTP 1996a, 1996b, 1996c; Oller et al. 2008), and decreased body weight gain at ≥0.1 mg Ni/m^3 (NTP 1996b, 1996c). The hematological and body weight effects were likely secondary to the lung damage. The available chronic-duration inhalation database provides strong support for identifying the respiratory tract, in particular the lungs, as the critical effect for deriving an MRL.

Table A-9. Summary of Relevant Chronic-Duration Inhalation NOAEL and LOAEL Values for Respiratory Effects in Animals Exposed to Nickel[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Respiratory					
Rat (B)	2 years 5 days/week 6 hours/day	0.03	0.06	Chronic lung inflammation, fibrosis, alveolar proteinosis	NTP 1996c (nickel sulfate)

Table A-9. Summary of Relevant Chronic-Duration Inhalation NOAEL and LOAEL Values for Respiratory Effects in Animals Exposed to Nickel[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Mouse (F)	2 years 5 days/week 6 hours/day		0.06	Chronic lung inflammation and bronchiolization	NTP 1996c (nickel sulfate)
Rat (M)	31 months 7 days/week 23 hours/day		0.06	Increased lung weight, congestion, alveolar proteinosis	Takenaka et al. 1985 (nickel oxide)
Rat (B)	2 years 5 days/week 6 hours/day		0.1 (SLOAEL)	Labored breathing, alveolar proteinosis, histiocytosis, chronic lung inflammation, bronchiolar alveolar hyperplasia (females)	Oller et al. 2008 (metallic nickel)
Rat (B)	2 years 5 days/week 6 hours/day		0.11 (SLOAEL)	Rapid shallow breathing, chronic lung inflammation, lung fibrosis	NTP 1996b (nickel subsulfide)
Mouse (M)	2 years 5 days/week 6 hours/day	0.06	0.11	Chronic lung inflammation and bronchiolization	NTP 1996c (nickel sulfate)
Mouse (M)	2 years 5 days/week 6 hours/day	0.06	0.11	Atrophy of olfactory epithelium	NTP 1996c (nickel sulfate)
Rat (B)	2 years 5 days/week 6 hours/day	0.06	0.11	Atrophy of olfactory epithelium	NTP 1996c (nickel sulfate)
Rat	12 months 5 days/week 7 hours/day		0.235 (SLOAEL)	Pneumonia, increased lung weight	Tanaka et al. 1988 (nickel oxide)
Mouse (B)	2 years 5 days/week 6 hours/day		0.44	Chronic lung inflammation and bronchiolization, alveolar proteinosis, fibrosis Atrophy of olfactory epithelium	NTP 1996b (nickel subsulfide)
Rat (B)	2 years 5 days/week 6 hours/day		0.5	Chronic lung inflammation and lung alveolus pigmentation	NTP 1996a (nickel oxide)
Rat (B)	78–80 weeks 5 days/week 6 hours/day		0.63 (SLOAEL)	Pneumonitis, bronchitis, emphysema, hyperplasia	Ottolenghi et al. 1975 (nickel sulfide)
Rat (B)	2 years 5 days/week 6 hours/day	0.11	0.73	Atrophy of olfactory epithelium	NTP 1996b (nickel subsulfide)

Table A-9. Summary of Relevant Chronic-Duration Inhalation NOAEL and LOAEL Values for Respiratory Effects in Animals Exposed to Nickel[a]

Species (sex)	Frequency/ duration	NOAEL (mg Ni/m^3)	LOAEL (mg Ni/m^3)	Effect	Reference (chemical form)
Mouse (B)	2 years 5 days/week 6 hours/day		1.0	Chronic lung inflammation, bronchiolization, and alveolar proteinosis	NTP 1996a (nickel oxide)

[a]All concentrations are reported in mg Ni/m^3; concentrations reported in terms of the nickel compound were converted by multiplying the concentration by a ratio of the nickel compound molecular weight to nickel molecular weight.

B = both males and females; F = females; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

The NTP (1996c) rat and mouse studies and the Takenaka et al. (1985) rat study identified the lowest LOAEL value (0.06 mg Ni/m^3) for lung effects. The NTP (1996c) rat study was selected as the principal study over the other two studies. The rat study was selected over the mouse study since it identified a NOAEL; the available data suggest that the rat is more sensitive than the mouse; thus, derivation of an MRL based on the rat NOAEL should be protective. The NTP (1996c) study was selected over the Takenaka et al. (1985) study because the latter study is poorly reported and the $LOAEL_{ADJ}$ (0.057 mg Ni/m^3) is higher than the $LOAEL_{ADJ}$ for the NTP (1996c) study (0.011 mg Ni/m^3).

Incidence data for chronic active inflammation and lung fibrosis (presented in Table A-10) were fit to all dichotomous models in EPA's BMDS (version 3.3.2) 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, BMCL <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. None of the models provided adequate fit. Therefore, the NOAEL of 0.03 mg Ni/m^3 was selected as the point of departure (POD) for the MRL.

Table A-10. Incidence of Select Nonneoplastic Lung Lesions in Rats Exposed to Nickel Sulfate Hexahydrate for 2 Years via Inhalation

Concentration (mg Ni/m^3)	Incidence (severity)[a]			
	Chronic active inflammation		Lung fibrosis	
	Females	Males	Females	Males
0	14/52 (1.4)	14/54 (1.1)	8/52 (1.4)	3/54 (1.0)[b]
0.03	13/53 (1.2)	11/53 (1.2)	7 53(1.3)	6/53 (1.2)
0.06	49/53[b] (2.1)	42/53[b] (1.9)	45/53[b] (1.7)	35/53[b] (1.7)
0.11	52/54[b] (2.3)	46/53[b] (2.2)	49/54[b] (1.9)	43/53[b] (1.8)

[a]Average severity of lesions in affected animals: 1=minimal; 2=mild; 3=moderate; and 4=marked.
[b]Statistically different from control group ($p \leq 0.01$).

Source: NTP 1996c

The NOAEL of 0.03 mg Ni/m^3 was adjusted for continuous exposure (6 hours/24 hours; 5 days/7 days) to a $NOAEL_{ADJ}$ of 0.0053 mg Ni/m^3 and converted to a $NOAEL_{HEC}$ of 0.0033 mg Ni/m^3 using the

methodology and equations shown in the intermediate-duration MRL section and the values shown in Tables A-11 and A-12. Using the $NOAEL_{HEC}$ of 0.0033 mg Ni/m^3 as the final POD and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) would result in a chronic-duration inhalation MRL of 0.0001 mg Ni/m^3 ($1x10^{-4}$ mg Ni/m^3). However, this value is higher than the intermediate-duration inhalation MRL of $3x10^{-6}$ mg Ni/m^3. A comparison of the intermediate and chronic inhalation databases offers an explanation for why the intermediate MRL is lower than the chronic-duration MRL. The intermediate-duration MRL is based on a study that identified a LOAEL of 0.04 mg Ni/m^3 as nickel subsulfide (Oller et al. 2023); this LOAEL is lower than the intermediate-duration LOAELs for other nickel compounds. In the chronic-duration MRL database, the lowest LOAEL is 0.06 mg Ni/m^3 (NOAEL of 0.03 mg Ni/m^3) as nickel sulfate; for nickel subsulfide, the lowest LOAEL is 0.11 mg Ni/m^3, a NOAEL was not identified. The intermediate-duration MRL was considered more protective and thus, a chronic-duration inhalation MRL was not derived.

Table A-11. MPPD Model (Version 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	4 mL (default)	3,300 mL (default)
Upper respiratory tract	0.42 mL (default)	50 mL (default)
Inhalant properties		
Density[a]	2.07 g/cm^3	2.07 g/cm^3
Diameter, MMAD[b]	2.5 µm	2.5 µm
GSD[b]	2.38	2.38
Inhalability adjustment	On	On
Exposure condition		
Aerosol concentration ($NOAEL_{ADJ}$)	0.0053 mg Ni/m^3	0.0053 mg Ni/m^3
Breathing frequency	102 breaths/minute (default)	14.7 breaths/minute (calculated TWA)[c]
Tidal volume	2.1 mL (default)	875 mL (calculated TWA)[d]
Breathing scenario	Whole body	Nasa/oronasal breather[e]
Results		
Alveolar region deposition fraction (total pulmonary deposition fraction)	0.0330	0.1419

[a]NLM (2024l), nickel sulfate hexahydrate.
[b]NTP (1996c), Table K1.
[c]Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).
[d]Tidal volume is 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).
[e]Breathing scenario is assumed nasal with sleep and at rest and oronasal-mouth with light activity.

GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter; MPPD = Multiple-Path Particle Dosimetry; $NOAEL_{ADJ}$ = no-observed-adverse-effect level adjusted for continuous exposure; TWA = time-weighted average

Table A-12. Values Used to Calculate a Human Equivalent Concentration (HEC) for Nickel

Variable	Rat value (R)	Human value (H)	Source
Ventilation rate (VR)	0.3616 m^3/day	20 m^3/day	EPA 1994
Deposition fraction (DF)	0.0330	0.1419	Calculated using MPPD software
Clearance rate[a] (k)	0.289 day^{-1}	0.277 day^{-1}	Oller et al. 2014
Ratio of retention half-time (RH) (to rat half-time)	1	1.04	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

[a]Total clearance rate = ln2/retention half-time.

MPPD = Multiple Path Particle Dosimetry; NOAEL = no-observed-adverse-effect level

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
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 are 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 in nickel sensitized subjects 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 adequate. 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) reported nausea and abdominal cramps in approximately half of the workers ingesting water contaminated with nickel sulfate, nickel chloride, and boric acid; estimated exposure was 7.1–35.7 mg Ni/kg.

Developmental, reproductive, and neurological effects have been observed at the lowest doses tested in acute-duration oral animal studies. A summary of the NOAEL and LOAEL values for the sensitive targets of toxicity is presented in Table A-13. The observed developmental effects include increased resorptions, decreased litter size, increased pup mortality, decreased pup body weight, and skeletal abnormalities. The lowest LOAEL is approximately 46 mg Ni/kg/day as nickel chloride. Two studies reported serious effects at this dose level (increased resorptions/decreased implantation site and decreased number of live fetuses) (El-Sekily et al. 2020; Saini et al. 2014a); skeletal abnormalities have also been observed at this dose level (Saini et al. 2013, 2014a). However, a series of studies conducted by Saini et al. (2014b) reported no developmental effects at 46.125 mg Ni/kg/day in mice administered nickel chloride on GDs 0–5, 6–13, or 14–18; increased mortality and decreased birth weight were observed at the next highest dose tested (92.25 mg Ni/kg/day). Neurological effects (alterations in memory and decreased activity) were observed in mice following a single dose of 50 mg Ni/kg/day as nickel chloride.

Table A-13. 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 (F)	GDs 0–5		46	Skeletal abnormalities	Saini et al. 2014a (nickel chloride hexahydrate)

Table A-13. 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)
Mouse (F)	GDs 6–13		46.125	Skeletal abnormalities	Saini et al. 2013 (nickel chloride hexahydrate)
Mouse (F)	GDs 6–13		46.125 (SLOAEL)	Increased resorption sites; incomplete skeletal and limb ossification; and supernumerary ribs	El-Sekily et al. 2020 (nickel chloride hexahydrate)
Mouse (F)	GDs 0–5	46.125	92.25 (SLOAEL)	Decreased litter size/dam	Saini et al. 2014b (nickel chloride hexahydrate)
Mouse (F)	GDs 14–18	46.125	92.25 (SLOAEL)	Offspring mortality (11.11%) and decreased birth weight (16%)	Saini et al. 2014b (nickel chloride hexahydrate)
Mouse (F)	GDs 6–13	46.125	92.25 (SLOAEL)	Increased offspring mortality (9.52%) and decreased birth weight (16%)	Saini et al. 2014b (nickel chloride hexahydrate)
Mouse (F)	GDs 8–12	45.3		No alteration in locomotor activity in offspring	Gray et al. 1986 (nickel chloride)
Reproductive					
Mouse (F)	GDs 0–5		46 (SLOAEL)	Decreased number of implantation sites and number of live fetuses/dam	Saini et al. 2014a (nickel chloride hexahydrate)
Neurological					
Mouse (M)	Once	5	50	Reduced spatial memory performance; reduced locomotor activity	He et al. 2013 (nickel chloride hexahydrate)

F = females; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

Several animal studies reported serious developmental and reproductive effects at the lowest doses tested (46 mg Ni/kg/day). This precludes MRL derivation from these endpoints due to the ATSDR practice of not deriving MRLs from serious LOAELs. The conflicting results reported in studies testing 46 mg Ni/kg/day may be indicative that the dose is near the NOAEL/LOAEL boundary. Deriving an MRL on this value may not be health protective for the serious developmental effects, and further data on developmental toxicity at lower doses are needed.

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
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 eight women sensitized to nickel and exposed to oral doses of 0.02 mg Ni/kg/day as nickel sulfate (Santucci et al. 1994).

Among experimental animal studies, neurological, body weight, reproductive, and developmental effects have been observed at the lowest doses tested. A summary of studies evaluating these endpoints is presented in Table A-14. Alterations in sperm parameters (decreased sperm motility and count and increased sperm abnormalities) and decreased fertility have been reported in male rats and mice exposed to ≥1.1 mg Ni/kg/day as nickel sulfate or nickel chloride (Käkelä et al. 1999; Pandey and Srivastava 2000; Pandey et al. 1999). Decreased fertility was also observed in a study in which males and females were exposed to 3.6 mg Ni/kg/day as nickel chloride for 28–76 days (Käkelä et al. 1999) but was not observed when only females were exposed to doses up to 13 mg Ni/kg/day as nickel chloride (Käkelä et al. 1999). Developmental effects have been observed at similar doses. Decreased pup survival, increased post-implantation loss, and decreased litter size were observed at doses of ≥1.3 mg Ni/kg/day as nickel chloride or nickel sulfate. The developmental effects were considered to be serious health effects. Other effects observed at higher doses included decreased body weight gain at ≥7.6 mg Ni/kg/day (Adeyemi et al. 2017; American Biogenics Corporation 1988; Dieter et al. 1988; Mahmoud et al. 2011; Springborn Laboratories 2002; Whanger 1973) and histological alterations in the kidneys and/or alterations in function parameters (plasma creatinine and urea, blood urea nitrogen, urine volume) at ≥7.6 mg Ni/kg/day (Adeyemi and Elebiyo 2014; Dahdouh et al. 2016; Dieter et al. 1988; Obone et al. 1999).

Table A-14. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to Nickel

Species (sex)	Frequency/ duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Neurological					
Rat (M)	90 days 3 days/week		0.2	Impaired performance on test of learning and spatial memory	Anyachor et al. 2023
Body weight					
Rat (M)	28 days		0.23 (SLOAEL)	Decreased body weight gain (20%)	Weischer et al. 1980

Table A-14. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to Nickel

Species (sex)	Frequency/ duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Reproductive					
Mouse (M)	35 days 5 days/week		1.1	Decreased sperm motility and sperm count; increased sperm abnormalities	Pandey et al. 1999 (nickel sulfate)
Mouse (M)	35 days 5 days/week	1.1	2.2	Decreased sperm count and motility, increased sperm abnormalities	Pandey and Srivastava 2000 (nickel sulfate)
Mouse (M)	35 days 5 days/week	1.2	2.5	Decreased sperm count and motility, increased sperm abnormalities	Pandey and Srivastava 2000 (nickel chloride)
Rat (M)	10 weeks prior to mating	2.2		No alteration in sperm count, concentration, or motility	Springborn Laboratories 2000b (nickel sulfate)
Rat (B)	10 weeks prior to mating	2.2		No effect on fertility	Springborn Laboratories 2000b (nickel sulfate)
Rat (M)	28 or 42 days before mating		3.6 (SLOAEL)	Decreased fertility	Käkelä et al. 1999 (nickel chloride)
Rat (B)	28–76 days		3.6 (SLOAEL)	Decreased fertility	Käkelä et al. 1999 (nickel chloride)
Mouse (M)	3–12 weeks		4.5	Degeneration of seminiferous epithelium	Toman et al. 2012 (nickel chloride)
Rat (B)	2 weeks prior to mating	16.8		No effect on fertility	Springborn Laboratories 2000a (nickel sulfate)
Rat (F)	11 weeks prior to mating	31.6		No effect on fertility	Smith et al. 1993 (nickel chloride)
Rat (B)	11 weeks prior to mating	40 (M) 55 (F)		No effect on fertility	EPA 1988a, 1988b (nickel chloride)
Developmental					
Rat (F)	11 weeks (breeding through lactation); two litters		1.3 (SLOAEL)	Decreased pup survival	Smith et al. 1993 (nickel chloride)
Mouse (M)	35 days 5 days/week		2.2 (SLOAEL)	Increased post-implantation loss	Pandey et al. 1999 (nickel sulfate)

Table A-14. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to Nickel

Species (sex)	Frequency/ duration	NOAEL (mg Ni/kg/day)	LOAEL (mg Ni/kg/day)	Effect	Reference (nickel compound)
Rat (M)	28 or 42 days before mating		3.6 (SLOAEL)	Decreased number of pups born alive per dam, decreased litter size	Käkelä et al. 1999 (nickel chloride)
Rat (B)	28–76 days		3.6 (SLOAEL)	Decreased number of pups born alive per dam, decreased litter size	Käkelä et al. 1999 (nickel chloride)
Rat (F)	2 weeks prior to mating and during gestation and lactation	4.5	6.7 (SLOAEL)	Increased post-implantation loss	Springborn Laboratories 2000a (nickel sulfate hexahydrate)
Rat (B)	2-generation study, 10 weeks prior to mating and during gestation and lactation	2.2		No developmental effects	Springborn Laboratories 2000b (nickel sulfate hexahydrate)

B = both males and females; F = females; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

The available intermediate-duration data are not considered suitable for MRL derivation because serious body weight and developmental effects were observed at some of the lowest doses tested. Although a slightly lower less serious LOAEL was identified for neurological effects, this dose of 0.2 mg Ni/kg/day is only slightly lower than the serious LOAEL of 0.23 mg Ni/kg/day. Therefore, deriving an MRL based on the neurological effects may not be protective of the developmental effects. It is noted that the neurological effects data from the Anyachor et al. (2023) study is not amenable to BMD modeling because only one dose was tested.

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., M.P.H.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Nickel
CAS Numbers: 7440-02-0
Date: October 2024
Profile Status: Final
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 duration. Two animal studies have evaluated the chronic oral toxicity of nickel sulfate. A study in rats (Heim et al. 2007) reported increased mortality in females and decreased terminal body weights in males administered via gavage 6.7 mg Ni/kg/day as nickel sulfate for 2 years; the NOAEL for body weight effects in females was 2.2 mg Ni/kg/day. No other biologically relevant adverse effects were reported in the study. In the second chronic-duration study, body weight, respiratory (cholesterol granulomas, emphysema, and bronchiolectasis), and renal effects (polyuria) were observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet (Ambrose et al. 1976). The database also includes a 2-year study in rats conducted by Ambrose et al. (1976), which reported a 34% decrease in terminal body weights in female rats exposed to 75 mg Ni/kg/day as nickel sulfate in the diet; however, the study quality is considered poor due to the high mortality in the control group.

The database was not considered suitable for derivation of a chronic-duration oral MRL. The rat (Heim et al. 2007) and dog (Ambrose et al. 1976) were not considered suitable principal studies because increased mortality was observed at the lowest adverse effect level. Although the Heim et al. (2007) study identified a NOAEL for body weight effects at 2.2 mg/kg/day, alterations in body weight are not considered primary effects of nickel and are likely secondary effects; therefore, the Heim et al. (2007) was not considered suitable as the basis for MRL derivation.

Agency Contact (Chemical Managers): Custodio Muianga, Ph.D., 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 were 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. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. 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

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

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
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 Draft Toxicological Profile for Nickel released for public comment in 2023; thus, the literature search was restricted to studies published between January 2020 and October 2023. The following main databases were searched in October 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

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	Query string
PubMed	
10/2023	(((7440-02-0[rn] OR 373-02-4[rn] OR 7718-54-9[rn] OR 1313-99-1[rn] OR 7786-81-4[rn] OR 13138-45-9[rn] OR 15699-18-0[rn] OR 3333-67-3[rn] OR ("Dicyanonickel"[tw] OR "Nickel cyanide"[tw]) OR 13770-89-3[rn]) AND ((("NICKEL/toxicity"[mh] OR "NICKEL/adverse effects"[mh] OR "NICKEL/poisoning"[mh] OR "NICKEL/pharmacokinetics"[mh] OR "environmental exposure"[mh] OR ci[sh] OR toxicokinetics[mh:noexp] OR "NICKEL/blood"[mh] OR "NICKEL/cerebrospinal fluid"[mh] OR "NICKEL/urine"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh]) OR "NICKEL/antagonists and inhibitors"[mh] OR ("NICKEL/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "NICKEL/pharmacology"[majr] OR ("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]) OR (Nickel[mh] AND (indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) OR "Sulfonic Acids"[mh] OR "Organometallic Compounds"[mh]) AND (2020:3000[mhda]))) OR (((((("(Oxido)nickel"[tw] OR "Ammonium disulfatonickelate(II)"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Bunsenite"[tw] OR "Dicyanonickel"[tw] OR "Mononickel oxide"[tw] OR "Ni 210"[tw] OR "Nickel"[tw] OR "Nickelacetat"[tw] OR "Nickelcarbonat"[tw] OR "Nickelchlorid"[tw] OR "Nickeldi(acetat)"[tw] OR "Nickeldichlorid"[tw] OR "Nickelmonoxid"[tw] OR "Nickelous acetate"[tw] OR "Nickelous carbonate"[tw] OR "Nickelous chloride"[tw] OR "Nickelous nitrate"[tw] OR "Nickelous oxide"[tw] OR "Nickelous sulfate"[tw] OR "Nickelous sulphate"[tw] OR "Nickelsulfat"[tw] OR "Raney Ni"[tw] OR "Carbonyl 255"[tw] OR "Carbonyl Ni 123"[tw] OR "Carbonyl Ni 283"[tw] OR "Celmet"[tw] OR "Cerac N 2003"[tw] OR "Fine Emerald"[tw] OR "Inco 210"[tw] OR "Incofoam"[tw] OR "Melbright EF 2201"[tw] OR "MG-Ni 50"[tw] OR "MG-Ni 600"[tw] OR "Ni 006021"[tw] OR "Ni 0901-S"[tw] OR "NI 0901-S (harshaw)"[tw] OR "NI 110104"[tw] OR "NI 123"[tw] OR "Ni 123J"[tw] OR "Ni 123T"[tw] OR "Ni 255"[tw] OR "NI 255AC"[tw] OR "NI 255T"[tw] OR "NI 255T280"[tw] OR "Ni 270"[tw] OR "NI 287"[tw] OR "NI 313324"[tw] OR "NI 313463"[tw] OR "NI 313551"[tw] OR "Ni 4303T"[tw] OR "NI 525"[tw] OR "Ni Celmet"[tw] OR "Ni Powder CuLox 5100A"[tw] OR "Niccolum metallicum"[tw] OR "Nichel(II) chloride"[tw] OR "Nicobraz LM BNI2"[tw] OR "Nicrobraz LM:BNi 2"[tw] OR "NiFL 5"[tw] OR "NiFLA 10"[tw] OR "Ni-Flake 95"[tw] OR "Ni-J 20"[tw] OR "Nikko 255"[tw] OR "Nikko Rica 123"[tw] OR "NiO-D"[tw] OR "NiO-FP"[tw] OR "NiO-G 39"[tw] OR "NiS 10"[tw] OR "Novamet 123"[tw] OR "Novamet 4SP"[tw] OR "Novamet 4SP10"[tw] OR "Novamet 525"[tw] OR "Novamet CNS 400"[tw] OR "Novamet HCA 1"[tw] OR "Novamet NI 255"[tw] OR "Raney 2400"[tw] OR "Raney 2486"[tw] OR "Raney 2800"[tw] OR "Raney 3110"[tw] OR "Raney 3202"[tw] OR "Raney 4200"[tw] OR "Raney 5831"[tw] OR "Raney 5886"[tw] OR "Raney alloy"[tw] OR "SF-Ni"[tw] OR "SFR-Ni"[tw] OR "Sun Ti-Ni"[tw] OR "Top Seal DX 300"[tw] OR "Top Seal H 298"[tw]) NOT medline[sb])) AND 2020:3000[dp] AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR respiratory OR "pulmonary edema" OR "pulmonary effect" OR "pulmonary system" OR "pulmonary function" OR "pulmonary organ" OR "pulmonary toxicity" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR cardiovascular OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory organ" OR "circulatory toxicity" OR "cardiac arrest" OR "cardiac palpitation" OR "cardiac arrhythmia" OR "cardiac edema" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heart beat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR "digestive system" OR "digestive function" OR "digestive effect" OR "digestive organ" OR "Intestinal system" OR "intestinal function" OR "intestinal microbiota" OR "intestinal effect" OR "intestinal organ" OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR stomach OR intestine OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR

Table B-2. Database Query Strings

Database search date	Query string
	hepatotox* OR renal OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR bun OR nephropathy OR nephrotox* OR dermal OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin exposure" OR "skin contact" OR acanthosis OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR endocrine OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR fertility OR "maternal toxicity" OR developmental OR "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mechanism of absorption"[tiab:~0] OR "mechanism of distribution"[tiab:~0] OR "mechanism of excretion"[tiab:~0] OR "mechanism of metabolism"[tiab:~0] OR "mechanism of toxic effect"[tiab:~0] OR "mechanism of toxicity" OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "human health" OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR "National Health and Nutrition Examination Survey" OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR

Table B-2. Database Query Strings

Database search date	Query string
	leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish)))
NTRL	
10/2023	Limited to 2020 to present; terms searched in title or keyword "Nickel" OR "(Oxido)nickel" OR "Ammonium disulfatonickelate(II)" OR "Bunsenite" OR "Dicyanonickel" OR "Mononickel oxide" OR "Ni 210" OR "Nickelacetat" OR "Nickelcarbonat" OR "Nickelchlorid" OR "Nickeldi(acetat)" OR "Nickeldichlorid" OR "Nickelmonoxid" OR "Nickelous acetate" OR "Nickelous carbonate" OR "Nickelous chloride" OR "Nickelous nitrate" OR "Nickelous oxide" OR "Nickelous sulfate" OR "Nickelous sulphate" OR "Nickelsulfat" OR "Raney Ni"
Toxcenter	
10/2023	FILE 'TOXCENTER' ENTERED AT 10:29:54 ON 24 OCT 2023 L1 187783 SEA 7440-02-0 OR 373-02-4 OR 7718-54-9 OR 1313-99-1 OR 7786-81-4 OR 13138-45-9 OR 15699-18-0 OR 3333-67-3 OR 557-19-7 OR 13770-89-3 L2 33611 SEA L1 AND PY>2019 L3 28623 SEA L2 NOT PATENT/DT ACT TOXQUERY/Q --------- L4 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L5 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L6 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L7 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L8 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L9 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L10 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L11 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L12 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L13 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L14 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L15 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)

Table B-2. Database Query Strings

Database search date	Query string
	L16 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L17 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L18 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L19 QUE (ENDOCRIN? AND DISRUPT?)
	L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L26 QUE (NEPHROTOX? OR HEPATOTOX?)
	L27 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L28 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L29 QUE L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28
	L30 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L31 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L32 QUE L29 OR L30 OR L31
	L33 QUE (NONHUMAN MAMMALS)/ORGN
	L34 QUE L32 OR L33
	L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L36 QUE L34 OR L35

	L38 11491 SEA L3 AND L32
	L41 752 SEA L38 AND MEDLINE/FS
	L42 2371 SEA L38 AND BIOSIS/FS
	L43 8356 SEA L38 AND CAPLUS/FS
	L44 10143 DUP REM L41 L42 L43 (1336 DUPLICATES REMOVED)
	L*** DEL 752 S L38 AND MEDLINE/FS
	L*** DEL 752 S L38 AND MEDLINE/FS
	L45 750 SEA L44

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 2371 S L38 AND BIOSIS/FS L*** DEL 2371 S L38 AND BIOSIS/FS L46 2217 SEA L44 L*** DEL 8356 S L38 AND CAPLUS/FS L*** DEL 8356 S L38 AND CAPLUS/FS L47 7176 SEA L44 L48 9393 SEA (L45 OR L46 OR L47) NOT MEDLINE/FS

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2023	Compounds searched: 7440-02-0; 373-02-4; 7718-54-9; 1313-99-1; 7786-81-4; 13138-45-9; 3333-67-3; 13770-89-3; 557-19-7; 15699-18-0
NTP	
10/2023	7440-02-0 7786-81-4 1313-99-1 373-02-4 7718-54-9 3333-67-3 "Bunsenite" "Mononickel oxide" "Nickelous chloride" "Nickelous oxide" "Nickelous sulfate" "Nickelous sulphate" 15699-18-0 557-19-7 13770-89-3 13138-45-9 "Ammonium disulfatonickelate(II)" "Dicyanonickel" "Ni 210" "Nickelacetat" "Nickelcarbonat" "Nickelous acetate" "Nickelchlorid" "Nickeldi(acetat)" "Nickeldichlorid" "Nickelmonoxid" "Nickelous carbonate" "Nickelous nitrate" "Nickelsulfat" "(Oxido)nickel" "Raney Ni"
Regulations.gov	
10/2023	"Nickel" "Bunsenite" "Mononickel oxide" "Nickelous chloride" "Nickelous oxide" "Nickelous sulfate" "Nickelous sulphate" "Ammonium disulfatonickelate(II)" "Dicyanonickel" "Ni 210" "Nickelacetat" "Nickelcarbonat" "Nickelous acetate" "Nickelchlorid" "Nickeldi(acetat)" "Nickeldichlorid" "Nickelmonoxid" "Nickelous carbonate" "Nickelous nitrate" "Nickelsulfat" "(Oxido)nickel"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Raney Ni" "7440-02-0" "373-02-4" "7718-54-9" "1313-99-1" "7786-81-4" "13138-45-9" "15699-18-0" "3333-67-3" "557-19-7" "13770-89-3"
NIH RePORTER	
03/2024	Fiscal Year: Active Projects; Text Search: "(Oxido)nickel" OR "Ammonium disulfatonickelate(II)" OR "Bunsenite" OR "Dicyanonickel" OR "Mononickel oxide" OR "Ni 210" OR "Nickel" OR "Nickelacetat" OR "Nickelcarbonat" OR "Nickelchlorid" OR "Nickeldi(acetat)" OR "Nickeldichlorid" OR "Nickelmonoxid" OR "Nickelous acetate" OR "Nickelous carbonate" OR "Nickelous chloride" OR "Nickelous nitrate" OR "Nickelous oxide" OR "Nickelous sulfate" OR "Nickelous sulphate" OR "Nickelsulfat" OR "Raney Ni" OR "Carbonyl 255" OR "Carbonyl Ni 123" OR "Carbonyl Ni 283" OR "Celmet" OR "Cerac N 2003" OR "Fine Emerald" OR "Inco 210" OR "Incofoam" OR "Melbright EF 2201" OR "MG-Ni 50" OR "MG-Ni 600" OR "Ni 006021" OR "Ni 0901-S" OR "NI 0901-S (harshaw)" OR "NI 110104" OR "NI 123" OR "Ni 123J" OR "Ni 123T" OR "Ni 255" OR "NI 255AC" OR "NI 255T" OR "NI 255T280" OR "Ni 270" OR "NI 287" OR "NI 313324" OR "NI 313463" OR "NI 313551" OR "Ni 4303T" OR "NI 525" OR "Ni Celmet" OR "Ni Powder CuLox 5100A" OR "Niccolum metallicum" OR "Nichel(II) chloride" OR "Nicobraz LM BNI2" OR "Nicrobraz LM:BNi 2" OR "NiFL 5" OR "NiFLA 10" OR "Ni-Flake 95" OR "Ni-J 20" OR "Nikko 255" OR "Nikko Rica 123" OR "NiO-D" OR "NiO-FP" OR "NiO-G 39" OR "NiS 10" OR "Novamet 123" OR "Novamet 4SP" OR "Novamet 4SP10" OR "Novamet 525" OR "Novamet CNS 400" OR "Novamet HCA 1" OR "Novamet NI 255" OR "Raney 2400" OR "Raney 2486" OR "Raney 2800" OR "Raney 3110" OR "Raney 3202" OR "Raney 4200" OR "Raney 5831" OR "Raney 5886" OR "Raney alloy" OR "SF-Ni" OR "SFR-Ni" OR "Sun Ti-Ni" OR "Top Seal DX 300" OR "Top Seal H 298" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 10,701
- Number of records identified from other strategies: 146
- Total number of records to undergo literature screening: 10,847

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.

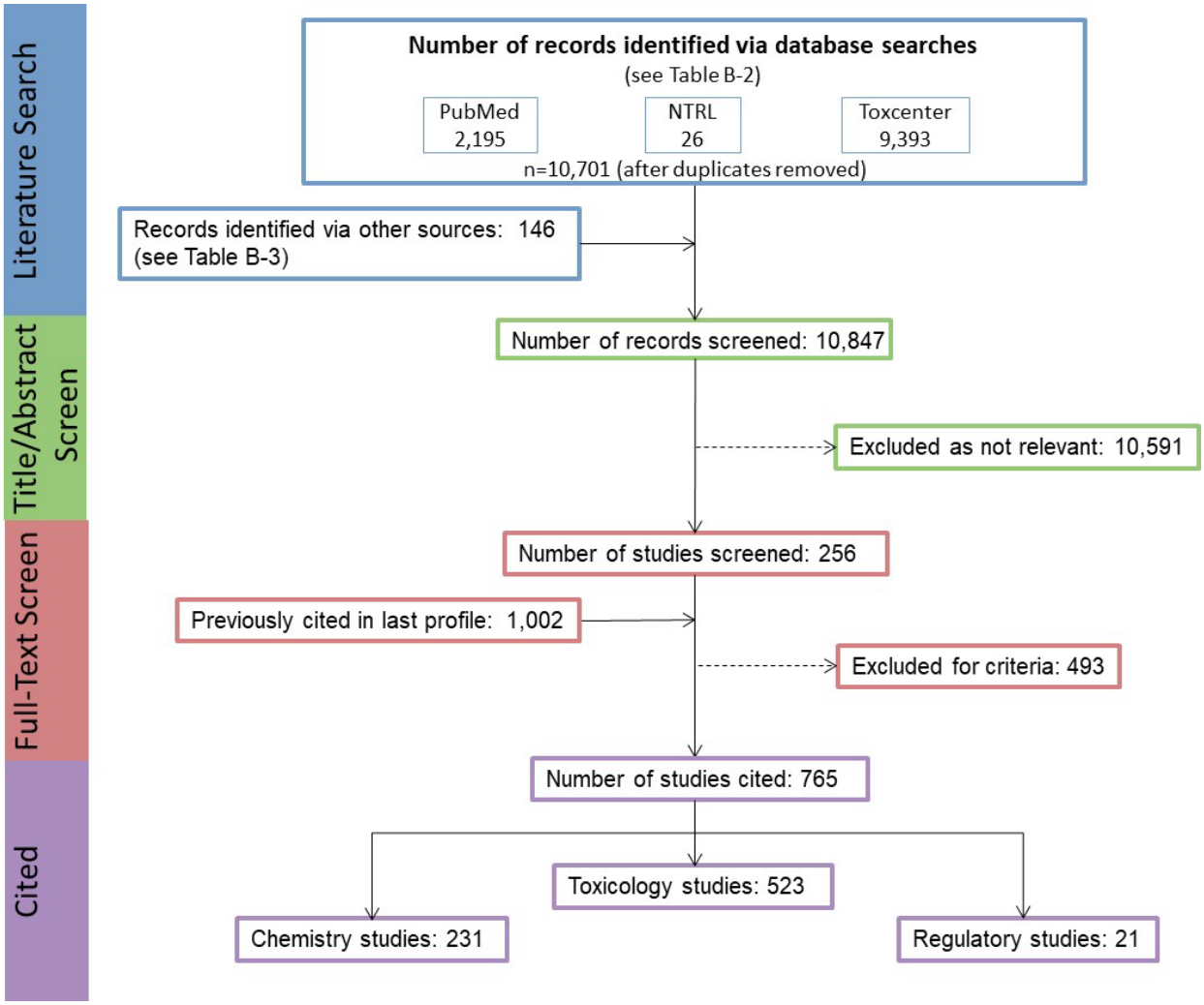
- Number of titles and abstracts screened: 10,847
- Number of studies considered relevant and moved to the next step: 256

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: 256
- Number of studies cited in the pre-public draft of the toxicological profile: 1,002
- Total number of studies cited in the profile: 766

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. October 2023 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, or dermal/ocular exposure to nickel. The inclusion criteria used to identify relevant studies examining the health effects of nickel are presented in Table C-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.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

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

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

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

Prioritization of Human Data. Human studies of exposure to nickel include case reports/case series, controlled oral exposure studies, epidemiological studies of occupational exposures, and epidemiological studies of general population exposures to nickel as a constituent of ambient particulate matter. All controlled exposure studies were included. Case reports and case series were included in the profile if there was clear evidence of exposure primarily to nickel. Epidemiology studies included in this profile were restricted to those of populations with known exposure above background levels (e.g., occupational exposure).

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were 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 current literature search was intended to update the Draft Toxicological Profile for Nickel released for public comment in 2023. See Appendix B for the databases searched and the search strategy.

A total of 10,847 records relevant to all sections 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, 10,847 records were reviewed; 23 documents were considered to meet the health effects inclusion criteria in Table C-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 189 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 189 documents (231 studies), 60 documents (93 studies) were included in the qualitative review.

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-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. 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

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 (Tables 2-1, 2-2, and 2-3, respectively).

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-3 and C-4, respectively.

Human studies evaluating noncancerous effects are primarily cohort studies of occupational exposure that examined mortality from respiratory effects.

Animal studies examined a wide range of endpoints following inhalation, oral, and dermal exposure and reported body weight, respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, reproductive, developmental, and cancer effects. Of the consistently observed effects, respiratory effects following inhalation exposure, immunological effects, reproductive, and developmental effects were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). There were 93 studies (published in 60 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. 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	Caner
Inhalation studies																	
Cohort		14 3	4 0			1 0	1 1	4 2			1 1	3 3	1 0	2 1	4 0		28 11
Case control																	8 1
Cross-sectional		4 3											1 1				
Case series		7 7	1 1	1 1	1 1	1 1	1 1	2 2		1 1		1 1	3 3				1 1
Controlled																	
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Controlled												16 16					
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Controlled												33 33					

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

APPENDIX C

Table C-4. 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[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	8	10	6	6		3	6	6	6		6	11	6	6			
	3	10	0	0		0	0	0	0		0	6	0	0			
Intermediate-duration	17	23	6	6	5	6	6	7	6		7	14	6	6	1		
	2	23	0	0	2	0	0	0	0		0	14	0	1	1		
Chronic-duration	10	10	7	7	7	6	8	8	6		8	8	7	6			8
	4	10	0	0	3	0	0	0	0		4	7	0	0			4
Acute-duration	3			1									1	1	7		
	3			1									1	1	5		
Intermediate-duration	15	4	3	3	4		8	10	1	1	3	3	4	12	9		
	8	3	0	1	2		2	5	0	0	1	3	2	2	8		
Chronic-duration	2	1	1	1	2	1	1	1	1		1	1	1				
	2	1	0	0	1	0	0	1	0		0	0	0				
Acute-duration												1					
												1					
Intermediate-duration					1		1	2	1					1		1	
					0		1	1	1					1		1	
Chronic-duration																	

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	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

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 Tables C-5, C-6, and C-7, 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-5. 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-6. 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-7. 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 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 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 Tables C-8 and C-9, respectively.

Table C-8. 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							
Berge and Skyberg 2003	+	+	–	–	–	++	Second
Syurin and Vinnikov 2022	–	+	+	–	– –	++	Second
Cross-sectional							
Fishwick et al. 2004	++	+	+	–	–	++	Second
Kilburn et al. 1990	+	–	+	–	+	++	Second
Muir et al. 1993	+	+	–	–	+	+	Second
Wu et al. 2022	+	++	+	+	+	++	First
Outcome: Immunological							
Cohort studies inhalation							
Bencko et al. 1983	– –	–	+	–	–	++	Third
Bencko et al. 1986	++	+	+	–	+	++	Second

APPENDIX C

Table C-8. 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: Reproductive							
Cohort studies inhalation							
Chashschin et al. 1994	–	–	–	–	–	++	Third
Case-Control studies							
Chashschin et al. 1994	–	–	–	–	–	++	Third
Vaktskjold et al. 2008b	+	+	+	+	+	++	First
Outcome: Developmental							
Cohort studies inhalation							
Chashschin et al. 1994	–	–	–	–	–	++	Third
Vaktskjold et al. 2006	+	+	+	+	+	++	First
Vaktskjold et al. 2007	+	+	+	+	+	++	First
Vaktskjold et al. 2008a	+	+	+	+	+	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; *Key question used to assign risk of bias tier

Table C-9. 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
Outcome: Respiratory									
Inhalation acute exposure									
Benson et al. 1995b (rat)	+	+	+	+	+	++	+	+	First
Efremenko et al. 2014 (rat)	++	+	+	+	+	+	++	+	First
Efremenko et al. 2017a, 2017b (rat)	++	+	+	+	+	++	++	+	First
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Benson et al. 1995a (rat, nickel sulfate)	+	+	+	+	+	++	+	+	First
Benson et al. 1995a (rat, nickel oxide)	+	+	+	+	+	++	+	+	First
Benson et al. 1995a (mouse, nickel sulfate)	+	+	+	+	+	++	+	+	First
Benson et al. 1995a (mouse, nickel oxide)	+	+	+	+	+	++	+	+	First
Benson et al. 1995b (rat)	+	+	+	+	+	++	+	+	First

APPENDIX C

Table C-9. 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
Efremenko et al. 2014 (rat)	++	–	+	–	+	+	++	+	First
Efremenko et al. 2017a, 2017b (rat)	++	+	+	+	+	++	++	+	First
Evans et al. 1995 (rat)	–	–	++	–	+	+	++	++	First
Horie et al. 1985 (rat)	–	–	+	–	+	–	–	+	Second
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Oller et al. 2023 (rat, nickel subsulfide)	++	+	+	+	++	++	+	+	First
Oller et al. 2023 (rat, nickel sulfate)	++	+	+	+	++	++	+	+	First
Weischer et al. 1980 (rat)	–	–	+	–	+	–	+	+	Second
Inhalation chronic exposure									
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First

Table C-9. 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 (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Oller et al. 2008 (rat)	++	-	+	–	+	++	++	++	First
Ottolenghi et al. 1975 (rat)	–	–	+	–	+	–	+	+	Second
Takenaka et al. 1985 (rat)	–	–	++	–	+	–	+	+	Second
Tanaka et al. 1988 (rat)	–	+	+	+	+	+	+	+	First
Oral intermediate exposure									
American Biogenics Corporation 1988 (rat)	++	–	+	–	+	++	+	+	First
Obone et al. 1999 (rat)	–	–	+	–	++	+	++	++	First
EPA 1988a, 1988b (rat)	+	–	+	–	+	–	+	+	First
Springborn Laboratories 2002 (rat)	++	–	+	–	++	++	++	++	First
Oral intermediate exposure									
Ambrose et al. 1976 (dog)	–	–	+	–	+	–	+	+	Second
Outcome: Immunological									
Inhalation acute exposure									
Adkins et al. 1979 (mouse, bacteria clearance)	–	–	+	–	+	–	+	+	Second
Adkins et al. 1979 (mouse, nickel chloride)	–	–	+	–	+	–	+	+	Second

Table C-9. 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
Adkins et al. 1979 (mouse, nickel sulfate)	–	–	+	–	+	–	+	+	Second
Buxton et al. 2021 (mouse)	++	–	++	–	+	+	+	++	First
Graham et al. 1978 (mouse)	–	–	+	–	+	–	+	+	Second
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Haley et al. 1990 (mouse, nickel oxide)	+	–	+	–	+	++	++	++	First
Haley et al. 1990 (mouse, nickel subsulfide)	+	–	+	–	+	++	++	++	First
Haley et al. 1990 (mouse, nickel sulfate)	+	–	+	–	+	++	++	++	First
Johansson et al. 1987 (rabbit)	–	–	+	–	+	–	+	+	Second
Johansson et al. 1988a, 1989 (rabbit)	–	–	+	–	+	–	+	+	Second
Morimoto et al. 1995 (rat)	–	–	+	–	+	+	+	+	First
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First

APPENDIX C

Table C-9. 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 (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Spiegelberg et al. 1984 (rat)	–	–	+	–	+	–	+	+	Second
Inhalation chronic exposure									
NTP 1996a (rat)	–	–	+	–	++	++	++	++	First
NTP 1996a (mouse)	–	–	+	–	++	++	++	++	First
NTP 1996b (rat)	–	–	+	–	++	++	++	++	First
NTP 1996b (mouse)	–	–	+	–	++	++	++	++	First
NTP 1996c (rat)	–	–	+	–	++	++	++	++	First
NTP 1996c (mouse)	–	–	+	–	++	++	++	++	First
Oller et al. 2008 (rat)	++	–	+	–	+	++	++	++	First
Ottolenghi et al. 1975 (rat)	–	–	+	–	+	–	+	+	Second
Oral intermediate exposure									
Dieter et al. 1988 (mouse)	–	–	+	–	+	–	+	+	Second
Ilbäck et al. 1994 (mouse)	+	–	+	–	+	–	+	+	First
Obone et al. 1999 (rat)	–	–	+	–	++	+	++	++	First
Oral chronic exposure									
Ambrose et al. 1976 (dog)	–	–	+	–	+	–	+	+	Second

Table C-9. 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
Dermal acute exposure									
Siller and Seymour 1994 (mouse)	–	–	+	–	+	–	+	+	Second
Outcome: Reproductive									
Inhalation acute exposure									
NTP 1996a (rat)	+	+	+	+	+	++	++	+	First
NTP 1996a (mouse)	+	+	+	+	+	++	++	+	First
NTP 1996b (rat)	+	+	+	+	+	++	++	+	First
NTP 1996b (mouse)	+	+	+	+	+	++	++	+	First
NTP 1996c (rat)	+	+	+	+	+	++	++	+	First
NTP 1996c (mouse)	+	+	+	+	+	++	++	+	First
Inhalation intermediate exposure									
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Inhalation chronic exposure									
NTP 1996a (rat)	+	+	+	+	++	++	++	++	First
NTP 1996a (mouse)	+	+	+	+	++	++	++	++	First

Table C-9. 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 1996b (rat)	+	+	+	+	++	++	++	++	First
NTP 1996b (mouse)	+	+	+	+	++	++	++	++	First
NTP 1996c (rat)	+	+	+	+	++	++	++	++	First
NTP 1996c (mouse)	+	+	+	+	++	++	++	++	First
Oral acute exposure									
Saini et al. 2013 (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014a (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014b (mouse, GDs 0–5)	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (mouse, GDs 6–13)	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (mouse, GDs 14–18)	–	+	+	+	+	+	++	+	First
Seidenberg et al. 1986 (mouse)	–	+	+	+	+	–	+	+	First
Sobti and Gill 1989 (mouse, nickel sulfate)	–	+	+	+	–	–	–	+	Second
Sobti and Gill 1989 (mouse, nickel nitrate)	–	+	+	+	–	–	–	+	Second
Sobti and Gill 1989 (mouse, nickel chloride)	–	+	+	+	–	–	–	+	Second

APPENDIX C

Table C-9. 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
Oral intermediate exposure									
Ambrose et al. 1976 (rat)	–	+	+	+	+	–	+	+	First
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	–	+	+	+	+	–	+	+	First
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	–	+	+	+	++	–	+	+	First
Käkelä et al. 1999 (rat, 28–76 days)	–	+	+	+	+	–	+	+	First
Obone et al. 1999 (rat)	–	+	+	+	++	+	++	++	First
Pandey and Srivastava 2000 (mouse, nickel chloride)	–	+	+	+	++	–	+	+	First
Pandey and Srivastava 2000 (mouse, nickel sulfate)	–	+	+	+	++	–	+	+	First
Pandey et al. 1999 (mouse, one dose group)	–	+	+	+	++	+	+	+	First
Pandey et al. 1999 (mouse, two dose groups)	–	+	+	+	+	+	+	+	First
EPA 1988a, 1988b (rat)	+	+	+	+	+	–	+	+	First
Smith et al. 1993 (rat)	+	+	+	+	+	–	+	+	First
Springborn Laboratories 2000a (rat)	++	+	+	+	++	++	+	++	First

Table C-9. 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
Springborn Laboratories 2000b (rat)	++	+	+	+	++	++	+	++	First
Toman et al. 2012 (mouse)	–	+	+	+	++	–	+	+	First
Oral chronic exposure									
Ambrose et al. 1976 (dog)	–	+	+	+	++	–	+	+	First
Outcome: Developmental									
Oral acute exposure									
Saini et al. 2013 (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014a (mouse)	–	+	+	+	+	–	++	+	First
Saini et al. 2014b (mouse, GDs 0–5)	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (mouse, GDs 6–13	–	+	+	+	+	+	++	+	First
Saini et al. 2014b (Mouse, GDs 14–18)	–	+	+	+	+	+	++	+	First
Seidenberg et al. 1986 (mouse)	–	+	+	+	+	–	+	+	First
Oral intermediate exposure									
Ambrose et al. 1976 (rat)	–	+	+	+	+	–	+	+	First
EPA 1983 (mouse)	+	+	–	+	–	–	+	+	First
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	–	+	+	+	+	–	+	+	First

APPENDIX C

Table C-9. 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
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	–	+	+	+	++	–	+	+	First
Käkelä et al. 1999 (rat, 28–76 days)	–	+	+	+	+	–	+	+	First
EPA 1988a, 1988b (rat)	+	+	+	+	+	–	+	+	First
Smith et al. 1993 (rat)	+	+	+	+	+	–	+	+	First
Springborn Laboratories 2000a (rat)	++	+	+	+	++	++	+	++	First
Springborn Laboratories 2000b (rat)	++	+	+	+	++	++	+	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; *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 HHS, 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: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome 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 features of study design was determined for individual studies using four "yes or no" questions, which were customized for 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, and experimental animal studies are presented in Tables C-10, C-11, and C-12, 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-10. 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-11. 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
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-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory and immunological effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. 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					
Berge and Skyberg 2003	No	No	Yes	Yes	Low
Syurin and Vinnikov 2022	No	Yes	Yes	Yes	Moderate

Table C-13. 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	
Cross-sectional studies					
Fishwick et al. 2004	No	Yes	Yes	Yes	Moderate
Kilburn et al. 1990	No	Yes	Yes	Yes	Moderate
Muir et al. 1993	No	Yes	Yes	Yes	Moderate
Wu et al. 2022	No	Yes	Yes	Yes	Moderate
Outcome: Immunological effects					
Cohort inhalation studies					
Bencko et al. 1983	No	Yes	Yes	Yes	Moderate
Bencko et al. 1986	No	Yes	Yes	Yes	Moderate
Outcome: Reproductive effects					
Cohort inhalation studies					
Chashschin et al. 1994	No	Yes	Yes	Yes	Moderate
Case-Control studies					
Vaktskjold et al. 2008b	No	Yes	Yes	Yes	Moderate
Outcome: Developmental effects					
Cohort inhalation studies					
Chashschin et al. 1994	No	Yes	Yes	Yes	Moderate
Vaktskjold et al. 2006	No	Yes	Yes	Yes	Moderate
Vaktskjold et al. 2007	No	Yes	Yes	Yes	Moderate
Vaktskjold et al. 2008a	No	Yes	Yes	Yes	Moderate

Table C-14. 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
Efremenko et al. 2017a, 2017b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Benson et al. 1995a (rat, nickel sulfate)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (rat, nickel oxide)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Benson et al. 1995a (mouse, nickel oxide)	Yes	Yes	Yes	Yes	High
Benson et al. 1995b (rat)	Yes	Yes	Yes	Yes	High
Efremenko et al. 2014 (rat)	Yes	Yes	Yes	Yes	High
Efremenko et al. 2017a, 2017b (rat)	Yes	Yes	Yes	Yes	High
Evans et al. 1995 (rat)	Yes	Yes	Yes	Yes	High
Horie et al. 1985 (rat)	Yes	No	Yes	No	Low
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Oller et al. 2023 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Oller et al. 2023 (rat)	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 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1975 (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					
American Biogenics Corporation 1988 (rat)	Yes	Yes	Yes	Yes	High
Obone et al. 1999 (rat)	Yes	No	Yes	Yes	Moderate
EPA 1988a, 1988b (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2002 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Ambrose et al. 1976 (dog)	Yes	No	Yes	No	Low
Outcome: Immunological effects					
Inhalation acute exposure					
Adkins et al. 1979 (mouse, bacteria clearance)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979 (mouse, nickel chloride)	Yes	Yes	Yes	Yes	High
Adkins et al. 1979 (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Buxton et al. 2021 (mouse)	Yes	Yes	Yes	Yes	High
Graham et al. 1978 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Haley et al. 1990 (mouse, nickel oxide)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (mouse, nickel subsulfide)	Yes	Yes	Yes	Yes	High
Haley et al. 1990 (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Johansson et al. 1987 (rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1988a, 1989 (rabbit)	Yes	No	Yes	Yes	Moderate
Morimoto et al. 1995 (rat)	Yes	No	Yes	Yes	Moderate
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Spiegelberg et al. 1984 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Oller et al. 2008 (rat)	Yes	Yes	Yes	Yes	High
Ottolenghi et al. 1975 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Oral intermediate exposure					
Dieter et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Ilbäck et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Obone et al. 1999 (rat)	Yes	No	Yes	Yes	Moderate
Oral chronic exposure					
Ambrose et al. 1976 (dog)	Yes	No	Yes	No	Low
Dermal acute exposure					
Siller and Seymour 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Outcome: Reproductive effects					
Inhalation acute exposure					
NTP 1996a (rat)	Yes	Yes	Yes	No	Moderate
NTP 1996a (mouse)	Yes	Yes	Yes	No	Moderate
NTP 1996b (rat)	Yes	Yes	Yes	No	Moderate
NTP 1996b (mouse)	Yes	Yes	Yes	No	Moderate
NTP 1996c (rat)	Yes	Yes	Yes	No	Moderate
NTP 1996c (mouse)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1996a (rat)	Yes	Yes	Yes	Yes	High
NTP 1996a (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996b (rat)	Yes	Yes	Yes	Yes	High
NTP 1996b (mouse)	Yes	Yes	Yes	Yes	High
NTP 1996c (rat)	Yes	Yes	Yes	Yes	High
NTP 1996c (mouse)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Oral acute exposure					
Saini et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014a (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 0–5)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 6–13)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 14–18)	Yes	Yes	Yes	Yes	High
Seidenberg et al. 1986 (mouse)	Yes	Yes	Yes	Yes	High
Sobti and Gill 1989 (mouse, nickel sulfate)	Yes	No	No	Yes	Low
Sobti and Gill 1989 (mouse, nickel nitrate)	Yes	No	No	Yes	Low
Sobti and Gill 1989 (mouse, nickel chloride)	Yes	No	No	Yes	Low
Oral intermediate exposure					
Ambrose et al. 1976 (rat)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat; male 28 or 42 days prior to mating)	Yes	No	Yes	Yes	Moderate
Käkelä et al. 1999 (rat, female; 14 or 100 days prior to mating)	Yes	No	Yes	Yes	Moderate
Käkelä et al. 1999 (rat, Male and female; 28–76 days)	Yes	No	Yes	Yes	Moderate
Obone et al. 1999 (rat)	Yes	Yes	Yes	No	Moderate
Pandey and Srivastava 2000 (mouse, nickel chloride)	Yes	Yes	Yes	Yes	High
Pandey and Srivastava 2000 (mouse, nickel sulfate)	Yes	Yes	Yes	Yes	High
Pandey et al. 1999 (mouse, one dose group)	Yes	Yes	Yes	Yes	High
Pandey et al. 1999 (mouse, two dose groups)	Yes	Yes	Yes	Yes	High
EPA 1988a, 1988b (rat)	Yes	Yes	Yes	Yes	High
Smith et al. 1993 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. 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	
Springborn Laboratories 2000a (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2000b (rat)	Yes	Yes	Yes	Yes	High
Toman et al. 2012 (mouse)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Ambrose et al. 1976 (dog)	Yes	Yes	Yes	No	Moderate
Outcome: Developmental effects					
Oral acute exposure					
Saini et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014a (mouse)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 0–5)	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (mouse, GDs 6–13	Yes	Yes	Yes	Yes	High
Saini et al. 2014b (Mouse, GDs 14–18)	Yes	Yes	Yes	Yes	High
Seidenberg et al. 1986 (mouse)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Ambrose et al. 1976 (rat)	Yes	Yes	Yes	Yes	High
EPA 1983 (mouse)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	Yes	Yes	Yes	Yes	High
Käkelä et al. 1999 (rat, 28–76 days)	Yes	Yes	Yes	Yes	High
EPA 1988a, 1988b (rat)	Yes	Yes	Yes	Yes	High
Smith et al. 1993 (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2000a (rat)	Yes	Yes	Yes	Yes	High
Springborn Laboratories 2000b (rat)	Yes	Yes	Yes	Yes	High

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-15.

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation exposure		
Human cohort studies		
Berge and Skyberg 2003	Low	Moderate
Human cross-sectional studies		
Fishwick et al. 2004	Moderate	Moderate
Kilburn et al. 1990	Moderate	
Muir et al. 1993	Moderate	
Wu et al. 2022	Moderate	
Animal acute exposure		
Benson et al. 1995b (rat)	High	High
Efremenko et al. 2014 (rat)	High	
Efremenko et al. 2017a, 2017b (rat)	High	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Animal intermediate exposure		
Benson et al. 1995a (rat, nickel sulfate)	High	High
Benson et al. 1995a (rat, nickel oxide)	High	
Benson et al. 1995a (mouse, nickel sulfate)	High	
Benson et al. 1995a (mouse, nickel oxide)	High	
Benson et al. 1995b (rat)	High	
Bingham et al. 1972 (rat)	Moderate	
Efremenko et al. 2014 (rat)	High	
Efremenko et al. 2017a, 2017b (rat)	High	
Evans et al. 1995 (rat)	High	
Horie et al. 1985 (rat)	Low	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oller et al. 2023 (rat, nickel sulfate)	High	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Oller et al. 2023 (rat, nickel subsulfide)	High	
Weischer et al. 1980 (rat)	High	
Animal chronic exposure		
NTP 1996a (rat)	High	High
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oller et al. 2008 (rat)	High	
Ottolenghi et al. 1975 (rat)	High	
Takenaka et al. 1985 (rat)	Low	
Tanaka et al. 1988 (rat)	Low	
Oral exposure		
Animal intermediate exposure		
American Biogenics Corporation 1988 (rat)	High	High
Obone et al. 1999 (rat)	Moderate	
EPA 1988a, 1988b (rat)	High	
Springborn Laboratories 2002 (rat)	High	
Animal chronic exposure		
Ambrose et al. 1976 (dog)	Low	
Outcome: Immunological effects		
Inhalation exposure		
Human cohort studies		
Bencko et al. 1983	Moderate	Moderate
Bencko et al. 1986	Moderate	
Animal acute exposure		
Adkins et al. 1979 (mouse, bacteria clearance)	High	High
Adkins et al. 1979 (mouse, nickel chloride)	High	
Adkins et al. 1979 (mouse, nickel sulfate)	High	
Buxton et al. 2021 (mouse)	High	
Graham et al. 1978 (mouse)	High	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Animal intermediate exposure		
Haley et al. 1990 (mouse, nickel oxide)	High	High
Haley et al. 1990 (mouse, nickel subsulfide)	High	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
Haley et al. 1990 (mouse, nickel sulfate)	High	
Johansson et al. 1987 (rabbit)	Moderate	
Johansson et al. 1988a, 1989 (rabbit)	Moderate	
Morimoto et al. 1995 (rat)	Moderate	
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Spiegelberg et al. 1984 (rat)	High	
Animal chronic exposure		
NTP 1996a (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	High
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oller et al. 2008 (rat)	High	
Ottolenghi et al. 1975 (rat)	High	
Oral exposure		
Animal intermediate exposure		
Dieter et al. 1988 (mouse)	High	
Ilbäck et al. 1994 (mouse)	Moderate	Moderate
Obone et al. 1999 (rat)	Moderate	
Animal chronic exposure		
Ambrose et al. 1976 (dog)	Low	
Dermal exposure		
Animal acute exposure		
Siller and Seymour 1994 (mouse)	Moderate	Moderate
Outcome: Reproductive Effects		
Human cohort studies		
Chashschin et al. 1994	Moderate	Moderate
Human case-control studies		
Vaktskjold et al. 2008b	Moderate	Moderate
Inhalation exposure		
Animal acute exposure		
NTP 1996a (rat)	Moderate	
NTP 1996a (mouse)	Moderate	
NTP 1996b (rat)	Moderate	Moderate
NTP 1996b (mouse)	Moderate	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1996c (rat)	Moderate	
NTP 1996c (mouse)	Moderate	
Animal intermediate exposure		
NTP 1996a (rat)	High	High
NTP 1996b (rat)	High	
NTP 1996a (mouse)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Animal chronic exposure		
NTP 1996a (rat)	High	High
NTP 1996a (mouse)	High	
NTP 1996b (rat)	High	
NTP 1996b (mouse)	High	
NTP 1996c (rat)	High	
NTP 1996c (mouse)	High	
Oral exposure		
Animal acute exposure		
Saini et al. 2013 (mouse)	High	High
Saini et al. 2014a (mouse)	High	
Saini et al. 2014b (mouse, GDs 0–5)	High	
Saini et al. 2014b (mouse, GDs 6–13)	High	
Saini et al. 2014b (mouse, GDs 14–18)	High	
Seidenberg et al. 1986 (mouse)	High	
Sobti and Gill 1989 (mouse, nickel sulfate)	Low	
Sobti and Gill 1989 (mouse, nickel nitrate)	Low	
Sobti and Gill 1989 (mouse, nickel chloride)	Low	
Animal intermediate exposure		
Ambrose et al. 1976 (rat)	High	High
Käkelä et al. 1999 (rat; male 28 or 42 days prior to mating)	Moderate	
Käkelä et al. 1999 (rat, female; 14 or 100 days prior to mating)	Moderate	
Käkelä et al. 1999 (rat, Male and female; 28–76 days)	Moderate	
Obone et al. 1999 (rat)	Moderate	
Pandey and Srivastava 2000 (mouse, nickel chloride)	High	
Pandey and Srivastava 2000 (mouse, nickel sulfate)	High	
Pandey et al. 1999 (mouse, one dose group)	High	
Pandey et al. 1999 (mouse, two dose groups)	High	

Table C-15. Initial Confidence Rating for Nickel Health Effects Studies

	Initial study confidence	Initial confidence rating
EPA 1988a, 1988b (rat)	High	
Smith et al. 1993 (rat)	High	
Springborn Laboratories 2000a (rat)	High	
Springborn Laboratories 2000b (rat)	High	
Toman et al. 2012 (mouse)	High	
Animal chronic exposure		
Ambrose et al. 1976 (dog)	Moderate	Moderate
Outcome: Developmental Effects		
Human cohort studies		
Chashschin et al. 1994	Moderate	Moderate
Vaktskjold et al. 2006	Moderate	
Vaktskjold et al. 2007	Moderate	
Vaktskjold et al. 2008a	Moderate	
Oral exposure		
Animal acute exposure		
Saini et al. 2013 (mouse)	High	High
Saini et al. 2014a (mouse)	High	
Saini et al. 2014b (mouse, GDs 0–5)	High	
Saini et al. 2014b (mouse, GDs 6–13	High	
Saini et al. 2014b (Mouse, GDs 14–18)	High	
Seidenberg et al. 1986 (mouse)	High	
Animal intermediate exposure		
Ambrose et al. 1976 (rat)	High	High
EPA 1983 (mouse)	High	
Käkelä et al. 1999 (rat, 28 or 42 days prior to mating)	High	
Käkelä et al. 1999 (rat, 14 or 100 days prior to mating)	High	
Käkelä et al. 1999 (rat, 28–76 days)	High	
EPA 1988a, 1988b (rat)	High	
Smith et al. 1993 (rat)	High	
Springborn Laboratories 2000a (rat)	High	
Springborn Laboratories 2000b (rat)	High	

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-16. 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-17.

Table C-16. 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	Low
Animal studies	High	+1 Consistency	High
Outcome: Immunological effects			
Human studies	Moderate	-1 Risk of bias	Low
Animal studies	High		High
Outcome: Reproductive effects			
Human studies	Moderate	-1 Inconsistency	Low
Animal studies	High	-2 Inconsistency	Low
Outcome: Developmental effects			
Human studies	Moderate	-1 Inconsistency	Low
Animal studies	High		High

Table C-17. 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
Reproductive effects	Low	Low
Developmental effects	Low	High

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-8 and C-9). 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

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 Table C-18.

Table C-18. 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
Reproductive effects	Low	Uncertain	Low
Developmental effects	Low	Health effect	Low
Animal studies			
Respiratory effects	High	Health effect	High
Immunological effects	High	Health effect	High
Reproductive effects	Low	Uncertain	High
Developmental 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:

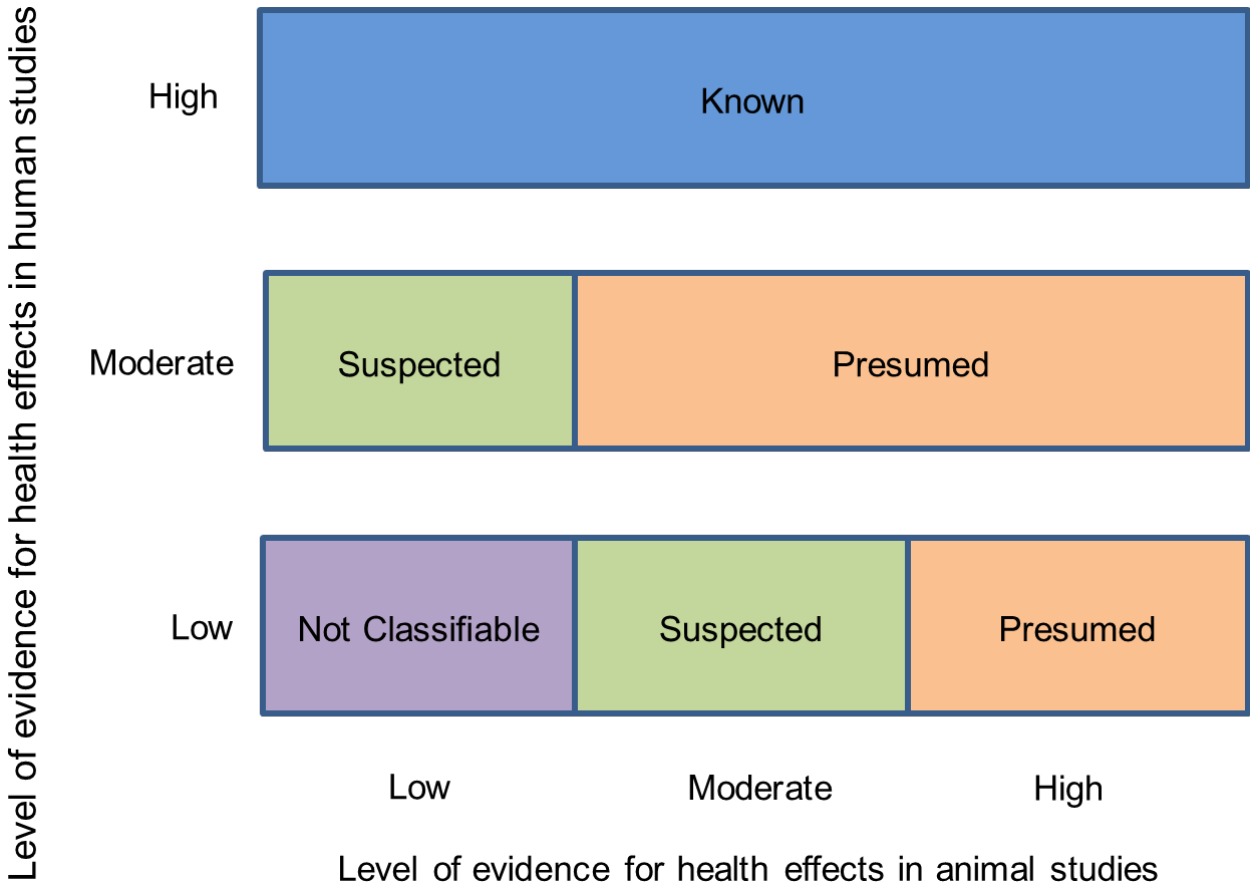
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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

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.

Figure C-1. Hazard Identification Scheme



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. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for nickel are listed below and summarized in Table C-19.

Presumed Health Effects

- Respiratory effects
  - Low level of evidence from human studies of occupational cohorts exposed via inhalation (Berge and Skyberg 2003; Fishwick et al. 2004; Kilburn et al. 1990; Syurin and Vinnikov 2022; Wu et al. 2022).
  - High level of evidence in rats and mice from acute-duration exposure to nickel (Benson et al. 1995b; Efremenko et al. 2014, 2017a, 2017b; NTP 1996a, 1996b, 1996c), intermediate-duration exposure to nickel (Benson et al. 1995a, 1995b; Efremenko et al. 2014, 2017a, 2017b; Evans et al. 1995; Horie et al. 1985; NTP 1996a, 1996b, 1996c; Oller et al. 2023 Weischer et al. 1980), and chronic-duration exposure to nickel (NTP 1996a, 1996b, 1996c; Oller et al. 2008; Ottolenghi et al. 1975; Takenaka et al. 1985; Tanaka et al. 1988).
  - High level of evidence in rats following acute-, intermediate-, and chronic-duration oral exposure (Ambrose et al. 1976; American Biogenics Corporation 1988; EPA 1988a, 1988b; Obone et al. 1999; Springborn Laboratories 2002).
- Immunological effects
  - Low evidence from human inhalation studies due to the lack of controls and lack of confidence in the exposures (Bencko et al. 1983, 1986).
  - High level of evidence in rats, mice, and rabbits from inhalation exposure to nickel (Adkins et al. 1979; Graham et al. 1978; Haley et al. 1990; Johansson et al. 1987, 1988a, 1989; Morimoto et al. 1995; Oller et al. 2008).
  - 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).
- Developmental effects
  - Low evidence from human studies due to the small number of studies and inconsistencies of the findings (Chashschin et al. 1994; Vaktskjold et al. 2006, 2007, 2008a).
  - High level of evidence from animal inhalation (Weischer et al. 1980) studies and oral studies (Ambrose et al. 1976; El-Sekily et al. 2020; EPA 1983, 1988a, 1988b; Käkelä et al. 1999; Saini et al. 2013, 2014a, 2014b; Seidenberg et al. 1986; Smith et al. 1993; Springborn Laboratories 2000b).

Not Classifiable

- Reproductive effects
  - Low evidence from human studies due to the inconsistency of the findings (Chashschin et al. 1994; Vaktskjold et al. 2008b).
  - Low level of evidence from animal studies. Male reproductive effects were observed in rats exposed via inhalation to nickel oxide (NTP 1996a) but not after exposure to nickel subsulfide or nickel sulfate (NTP 1996b, 1996c). There was a high degree of inconsistency among the oral exposure studies examining male reproductive effects, with some studies finding effects (Käkelä et al. 1999; Pandey and Srivastava 2000; Pandey et al. 1999; Sobti and Gill 1989) and other studies finding no effects (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Smith et al. 1993; Springborn Laboratories 2000b; Toman et al. 2012).

Table C-19. Hazard Identification Conclusions for Nickel

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Immunological effects	Presumed health effect
Reproductive effects	Not classifiable
Developmental 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), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), 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.

(17) 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									

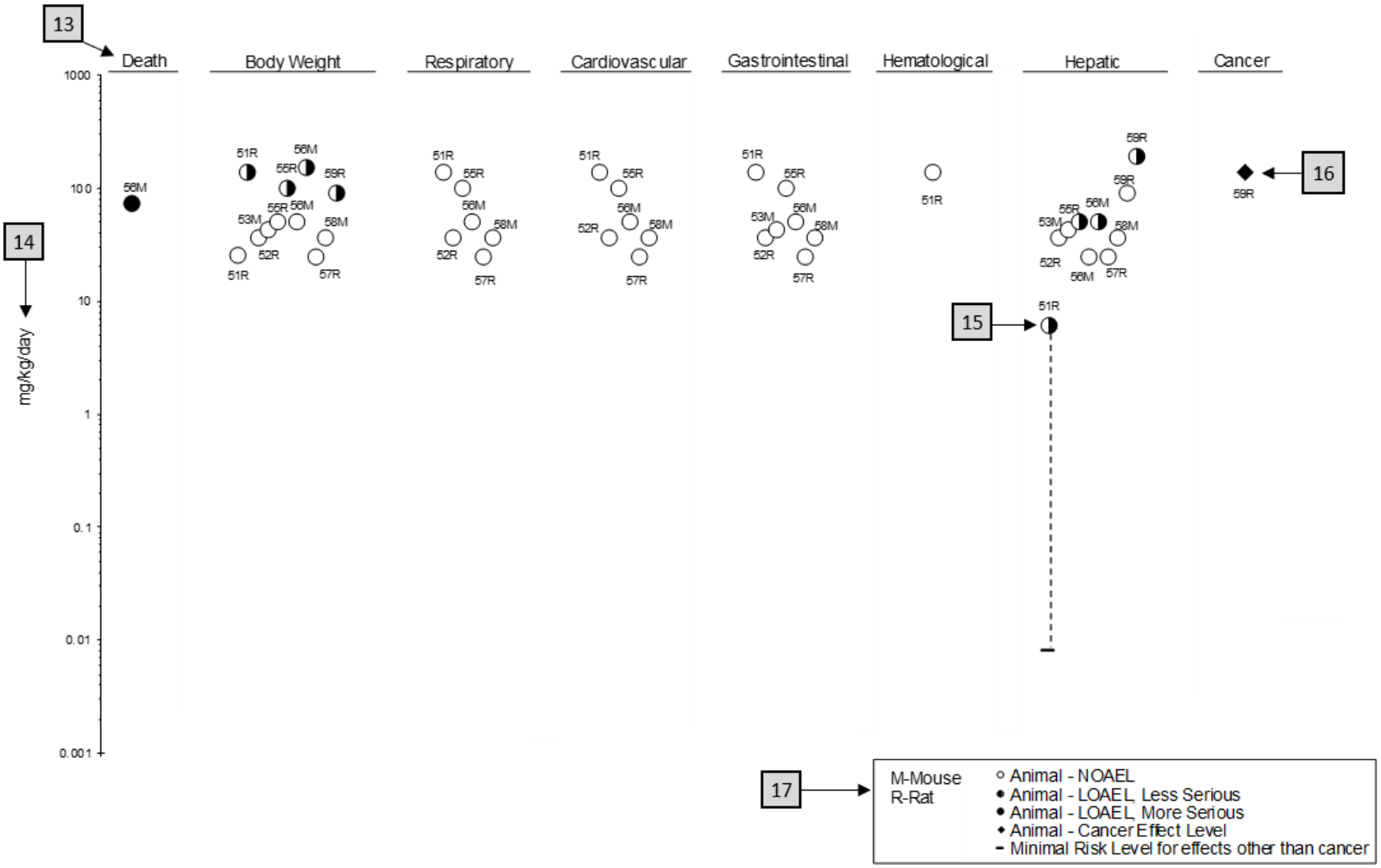
[a]The number corresponds to entries in Figure 2-x.

(11) [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).

APPENDIX D

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:

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

Managing Hazardous Materials Incidents is a 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.html).

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, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • 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 malignant 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 LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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 exposure level 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 exposure level, 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/m^3 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.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

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
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 Substances 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 limit
REL-C	recommended exposure limit-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
SLOAEL	serious lowest-observed-adverse-effect level
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
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result